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Copper-Catalyzed Photoinduced Radical Domino Cyclization of Ynamides and Cyanamides: A Unified Entry to Rosettacin, Luotonin A, and Deoxyvasicinone

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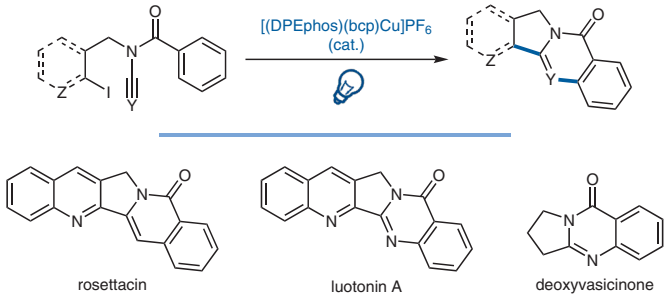

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Abstract A general and efficient procedure for the copper-catalyzed photoinduced radical domino cyclization of ynamides and cyanamides providing an efficient access to complex tri-, tetra- and pentacyclic nitrogen heterocycles is reported. Upon visible light irradiation in the presence of catalytic amounts of [(DPEphos)(bcp)Cu]PF_6 and an amine, a range of unactivated aryl and alkyl iodides were shown to be smoothly transformed to the corresponding radical species, initiating the radical domino cyclization. This procedure provides a unified entry to rosettacin, luotonin A, and deoxyvasicinone that could be efficiently prepared in a limited number of steps.

Key words copper catalysis, photocatalysis, radical cyclization, ynamides, cyanamides, rosettacin, luotonin A, deoxyvasicinone

Since the discovery of the triphenylmethyl and methyl radicals by Gomberg in 1900[1] and Paneth and Hofeditz in 1929,[2] respectively, radical chemistry has considerably evolved – with tremendous developments in the 1980s – and continuously reinvents itself.[3] Among the arsenal of reactions based on organic radical chemistry, radical cyclizations are amid the most efficient and the most commonly used. They indeed rely in most cases on readily available acyclic starting materials, the reactivity of radical species renders them less sensitive to steric hindrance compared to related polar cyclizations, they are compatible with a range of functional groups – therefore saving protection/deprotection steps – the rate constants of many of such reactions are available[4] and their regioselectivity can be generally predicted by the Beckwith rules.[5] If their synthetic usefulness has been demonstrated with the total synthesis of various natural products[6] – iconic examples being the Bakuzis' total syntheses of sativene and copacamphene,[7] Pattenden's total synthesis of alliacolide,[8] Stork's synthesis of norseychellanone,[9] and Curran's total synthesis of hirsutene[10] – the number of radical cyclizations in total synthesis is still quite in the low range, especially when put in perspective with their unrivaled efficiency. This can be attributed to some preconceived ideas on radical chemistry many synthetic chemists still have, radical reactions being often associated to poorly controlled processes hampered by competitive dimerization or polymerization. Moreover, the use of tin hydrides, which have been for years the reagents of choice in radical chemistry, has considerably reduced the attractiveness of radical cyclization in total synthesis.

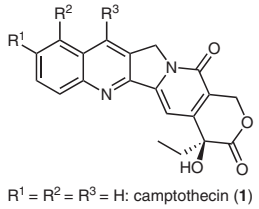
Recent developments in the catalysis of radical reactions, however, clearly bring new perspectives in radical chemistry and on its impact in natural product synthesis.[11] Among all strategies reported, the use of photocatalysis has probably been the most prolific one since it enables the generation of a range of radical species under mild, safe, and environmentally-friendly conditions.[12] While applications of photoinduced/-catalyzed radical reactions in total synthesis are still scarce, they have clearly highlighted their efficiency, their functional group tolerance and their impact in natural product synthesis for which they evidently enable new and original bond disconnections.[13] This field has been largely dominated by ruthenium or iridium complexes that combine strong absorption in the visible, high oxidation and reduction potentials, and long-lived excited states. The cost of such complexes and the search for alternative photocatalysts have stimulated numerous efforts, which recently culminated in the development of efficient organic[14] and copper-based photocatalysts.[15,16] Based on our long-standing interest in copper-catalyzed reactions[17] and our recently initiated research program on copper-catalyzed radical reactions,[18] we recently reported a broadly applicable copper catalyst, [(DPEphos)(bcp)Cu]PF_6, for photoredox transformations of organic halides: upon visible light irradiation in the presence of an amine, a range of unactivated aryl and alkyl halides were shown to be smoothly

activated, through a rare Cu(I)/Cu(I)*/Cu(0) catalytic cycle, and this complex was shown to efficiently catalyze a series of radical processes including reductions, cyclizations, and direct arylation of arenes.[19] We now report in this manuscript the use of this complex for the catalysis of domino radical cyclizations and the use of such processes for the total synthesis of rosettacin and luotonin A as well as its extension to the synthesis of deoxyvasicinone.

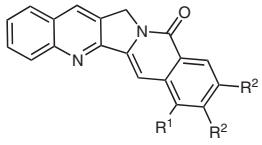
These synthetic and natural products are excellent inhibitors of topoisomerase I, an enzyme that is a good target for cancer chemotherapy[20] since it was shown to be crucial for DNA replication and transcription, preferentially expressed in the S-phase of the cell cycle and it has been found in high levels in several human tumors.[21] In 1966, an especially potent topoisomerase I inhibitor, camptothecin (**1**), was isolated from the Chinese tree *Camptotheca acuminata* (Figure 1).[22] This eventually paved the way for the design of analogues with improved solubility and potency, and resulted in the development of irinotecan (**2**) (trade name Camptosar®) by Yakult Honsha Co.,[23] topotecan (**3**) (trade name Hycamtin®) by GSK,[24] and belotecan (**4**) (trade name Camtobell®) by Chong Kun Dang Pharmaceuticals[25] for the treatment of various cancers. Despite the clinical success of camptothecin derivatives, they, however, still suffer from limited solubilities, dose-limiting toxicities, reversible complexation to the DNA-topoisomerase cleavage complex and in vivo opening of the lactone yielding to the corresponding secoacid that has a high affinity for human serum albumin.[20c] In an effort to address these problems and based on the success met with some indenoisoquinolines[26] for the inhibition of topoisomerase I, stable hybrids of camptothecin and indenoisoquinolines were developed: these synthetic compounds with a benzo[6,7]indolizino[1,2-*b*]quinolin-11-one skeleton were named 'aromathecins', with the unsubstituted core being named 'rosettacin' (**5**).[27] While initial efforts for the development of these aromathecins mostly focused on rosettacin (**5**), its dimethoxy derivative **6** and on naturally occurring 22-hydroxyacuminatine (**7**)[28] these compounds were found to be weak topoisomerase I poisons. This eventually led to the study of substituted analogues: some of them are remarkably efficient and are still under development, clearly highlighting the need for efficient and modular syntheses of such heterocyclic systems.[29]

Interestingly, these aromathecins also bear similarity to the naturally occurring pyrrolo[2,1-*b*]quinolino[2′,3′:3,4]quinazolin-11-ones, luotonins A, B,[30] and E[31] (**8**–**10**), which were also shown to be topoisomerase I poisons.[32] As with the aromathecins, a series of analogues with greater antiproliferative activities, including 14-azacamptothecin (**11**),[27b] has been developed.[33]

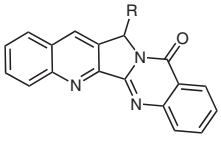
The potency of these natural or synthetic heterocycles naturally generated immediate interest from synthetic chemists to develop efficient and divergent accesses to benzo[6,7]indolizino[1,2-*b*]quinolin-11-ones and pyrrolo[2,1-*b*]quinolino[2′,3′:3,4]quinazolin-11-ones, including rosettacin and the luotonins. Syntheses of the former indeed include approaches based on a Friedländer condensation,[34] cyclization of a pyrroloquinoleine with a chlorinated benzofuranone,[35] domino N-amidoacylation/aldol-type condensation,[36] rhodium-catalyzed intramolecular annulations of alkynyl (*N*-alkoxy)benzamides[37] and its intermolecular variant,[38] aryl radical cyclization into an enamide,[39] or gold-catalyzed domino intramolecular alkyne hydroamination/lactamization.[40] As for luotonin A, total syntheses reported to date[41] feature the condensation of a oxopyrroloquinoline with 2-sulfinylaminobenzoyl chloride,[42] a biomimetic cyclization of vasicinone with anthranilic acid equivalents,[43] a Friedländer condensation,[44] an intramolecular CH arylation of a quinazolinone,[45] a palladium-catalyzed cyanation/cyclization/N-arylation domino sequence,[46] and a radical cyclization of an *N*-benzoylcyanamide.[47]



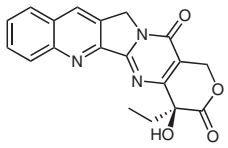
$R^1 = R^2 = R^3 = H$: camptothecin (**1**)
R^1 = OCOPipPip, $R^2 = H$, R^3 = Et: irinotecan (**2**)
R^1 = OH, $R^2 = CH_2NMe_2$, $R^3 = H$: topotecan (**3**)
$R^1 = R^2 = H$, $R^3 = CH_2CH_2NHiPr$: belotecan (**4**)



$R^1 = R^2 = H$: rosettacin (**5**)
$R^1 = H$, R^2 = OMe: 21,22-dimethoxyrosettacin (**6**)
$R^1 = CH_2OH$, $R^2 = H$: 22-hydroxyacuminatine (**7**)



R = H: luotonin A (**8**)
R = OH: luotonin B (**9**)
R = OMe: luotonin E (**10**)

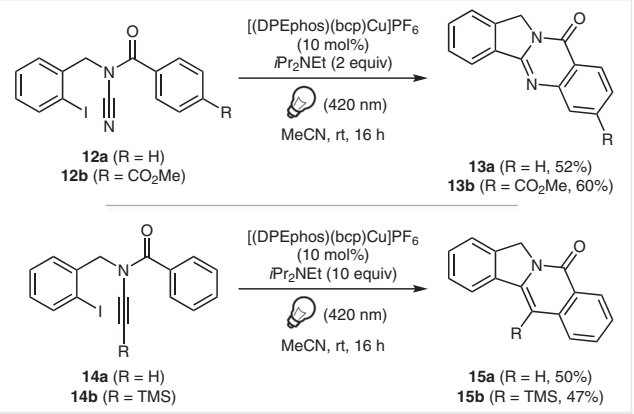


14-azacamptothecin (**11**)

Figure 1 Camptothecin, aromathecin, and luotonin derivatives: potent topoisomerase I inhibitors

Based on our combined interest in copper-based photocatalysts[19] and ynamides[48] and inspired by the most elegant work of Courillon and Malacria on radical cyclizations of *N*-benzoylynamines[49] and cyanamides,[47] we envisioned that the classical tin-based conditions used for the generation of the radical species involved in these cyclizations might be conveniently replaced by a photoactivatable copper complex and visible light. We report herein the use of such copper-catalyzed, photoinduced radical domino cyclizations for the development of a unified route to both rosettacin and luotonin A as well as its extension to the total synthesis of deoxyvasicinone.

To test this hypothesis, the radical domino cyclization of readily available *N*-benzoyl-*N*-(*o*-iodobenzyl)cyanamides **12** and ynamines **14** – whose challenging cyclization to the corresponding complex tetracyclic molecular scaffolds **13** and **15** was previously reported under tin-mediated conditions[47,49] and by photoredox activation using the highly reducing iridium catalyst *fac*-Ir(ppy)$_3$[50] – was evaluated under our previously reported conditions. Upon reaction with 10 mol% of heteroleptic copper(I) complex [(DPEphos)(bcp)Cu]PF$_6$ in the presence of 2 equivalents of Hünig's base as the sacrificial reductant in the first case and 10 equivalents in the second one under irradiation at 420 nm in acetonitrile at room temperature for 16 hours, the cyclization was found to proceed smoothly, affording the corresponding cyclized products **13** and **15** in fair to good yields and with efficiencies that compared well with previously reported procedures (Scheme 1). In all cases, minor amounts of hydrodeiodinated by-products resulting from the competing reduction of the intermediate aryl radical species by the diisopropylethylamine-derived radical cation were observed.[51]

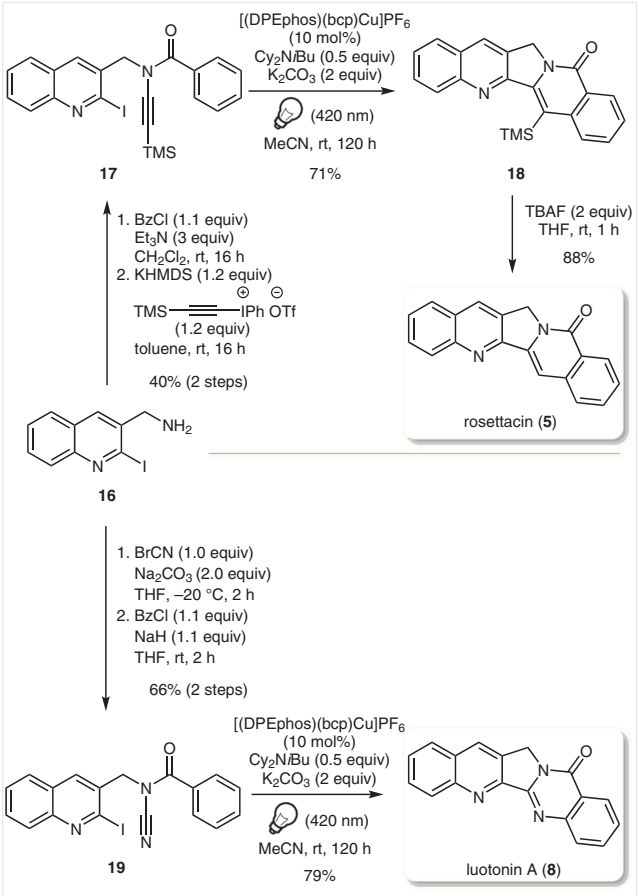


Scheme 1 Copper-catalyzed photoredox domino radical cyclization of *N*-benzoyl-*N*-(*o*-iodobenzyl)cyanamides and ynamines

Having demonstrated the feasibility of the copper-catalyzed photoinduced radical domino cyclizations envisioned as key steps for the total synthesis of rosettacin and luotonin A, we next focused our efforts on these targets. With this goal in mind, previously reported 2-iodo-3-aminomethylquinoline (**16**), prepared in five steps from commercially available 2-chloroquinoline-3-carbaldehyde,[47] was first submitted to a benzoylation followed by a subsequent alkynylation using the Witulski's procedure[52] to yield the corresponding *N*-benzoylynamine **17** required for the key radical cyclization (Scheme 2). While the use of our optimized conditions for the copper-catalyzed photoinduced cyclization provided the desired pentacyclic product **18**, its yield (45%) was, however, in the low range, especially in the context of a multi-step total synthesis. In an effort to optimize this step and minimize the competitive reduction of the starting halide, we evaluated the replacement of diisopropylethylamine by a less powerful reducing agent, dicyclohexylisobutylamine, a reducing agent initially reported by the Weaver group[53] and which we found to be especially convenient for challenging copper-catalyzed photoinduced reactions.[19] To our delight, using 0.5 equivalent of Cy$_2$N*i*-Bu and 2 equivalents of potassium carbonate in acetonitrile at room temperature for 120 hours afforded the cyclized product **18** in 71% yield without competing reduction of the starting aryl iodide **17**. Further cleavage of the TMS group with TBAF finally gave rosettacin whose spectral data were in good agreement with previously reported ones.[36] Notably, the cyclization can also be performed with blue LEDs with a slightly reduced efficiency (67%) and desilylation of **17** prior to its cyclization resulted in extensive degradation.

The success met for the synthesis of rosettacin based on this approach encouraged us to extend our strategy to the total synthesis of luotonin A. 2-Iodo-3-aminomethylquinoline (**16**) was therefore smoothly converted to *N*-benzoylcyanamide **19** by cyanation with cyanogen bromide in the presence of potassium carbonate followed by benzoylation after deprotonation of the intermediate cyanamide with sodium hydride. Reversing the order of these two steps, as originally reported by Courillon and Malacria, led to a much less efficient sequence.[47] The radical domino cyclization of **19** actually turned out to be even more efficient than the one performed from **17**, luotonin A (**8**), whose spectral data were also in good agreement with reported ones,[47] being isolated in 79% yield.

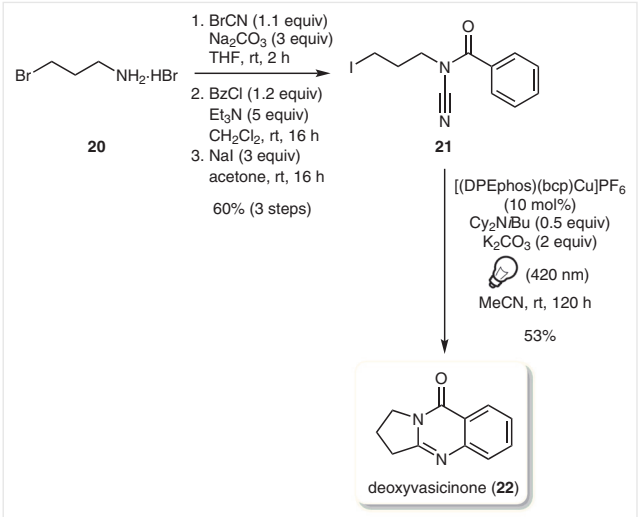
Knowing that [(DPEphos)(bcp)Cu]PF$_6$ is not only able to catalyze radical processes from aryl halides but also from alkyl halides,[19] we finally briefly envisioned extending our strategy to the total synthesis of deoxyvasicinone (**22**),[54] a naturally occurring tricyclic quinazolinone that has been reported to possess antimicrobial, anti-inflammatory, and antidepressant activities[55] and for which a number of synthetic routes,[56] including a domino radical cyclization of a *N*-benzoyl-*N*-phenylselenopropylcyanamide,[56n] have been reported. With this goal in mind, acyclic iodinated precursor **21** required for the key radical domino cyclization was readily prepared by a cyanation, benzoylation, and Finkelstein sequence from commercially available bromopropyl-



Scheme 2 Total synthesis of rosettacin and luotonin A

amine hydrobromide (**20**) (Scheme 3). Upon reaction under our standard conditions, although with an extended reaction time due to a more sluggish cyclization in this case, **21** smoothly cyclized to deoxyvasicinone (**22**) that could be isolated in 53% yield (32% overall yield for the four-step sequence from commercially available bromopropylamine). In sharp contrast, the cyclization from the corresponding bromide turned out to be much more troublesome.

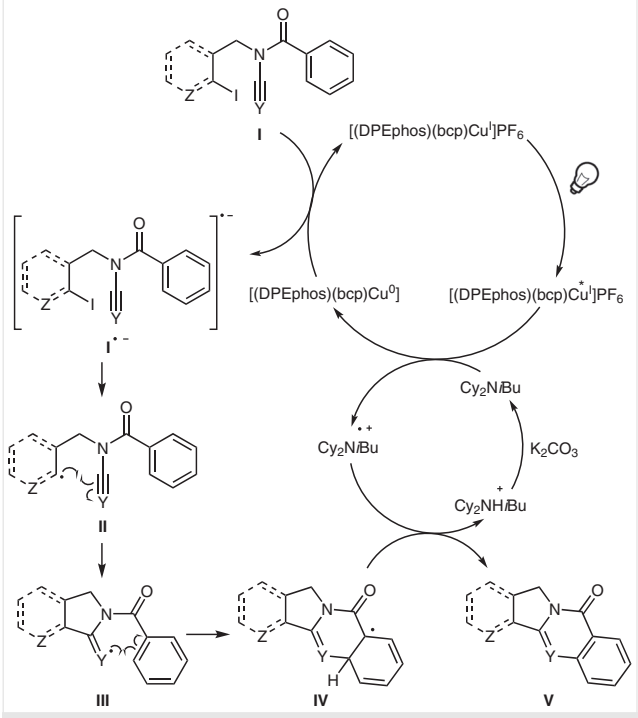
Based on our previously reported mechanistic studies on the activation of aryl halides with [(DPEphos)(bcp)Cu]PF_6,[19] the mechanism shown in Scheme 4 can be proposed for the radical domino cyclizations of **I** to **V**. The reaction would be initiated by reduction of the photoexcited complex, [(DPEphos)(bcp)Cu]PF_6*, with Cy_2Ni-Bu generating a transient copper(0) complex [(DPEphos)(bcp)Cu] and an amine radical cation. Reduction of the starting C–I bond in **I** by this copper(0) complex would regenerate the copper(I) catalyst and initiate the generation of radical intermediate **II** whose 5-*exo*-dig cyclization to the C≡C or C≡N triple bond would afford an intermediate vinylic or iminyl radical **III** that would cyclize to the arene through a 6-*endo*-trig process. Subsequent aromatization of **IV** to **V** would finally generate



Scheme 3 Total synthesis of deoxyvasicinone

Cy_2N^+Hi-Bu that would then react with potassium carbonate to regenerate Cy_2Ni-Bu, thereby accounting for the use of substoichiometric amounts of this amine.

In conclusion, we have reported a general and efficient procedure for the copper-catalyzed photoinduced radical domino cyclization of ynamides and cyanamides providing an efficient access to complex tri-, tetra-, and pentacyclic nitrogen heterocycles. This procedure provides a unified



Scheme 4 Mechanistic proposal for the copper-catalyzed photoinduced radical domino cyclizations

entry to rosettacin, luotonin A, and deoxyvasicinone that could be efficiently prepared in a limited number of steps and should be easily amenable to the preparation of analogues in a diversity-oriented approach. All together, these results further highlight the efficiency of [(DPEphos)(bcp)Cu]PF_6 as a photocatalyst and as a remarkable and readily available alternative to iridium and ruthenium complexes. Compared to related domino radical cyclizations based on tin-based methods for the generation of radical species previously reported, photoinduced processes with photoactivatable copper complexes clearly represent an attractive alternative that should contribute to the growing interest for radical chemistry. Further applications of photocatalysis of radical reactions and cyclizations with well-defined copper complexes are under study in our group and will be reported in due time.

All reactions were carried out in oven-dried glassware under an argon atmosphere employing standard techniques in handling air-sensitive materials. All solvents were reagent grade. THF was freshly distilled from Na and benzoquinone under argon. CH_2Cl_2 was freshly distilled from CaH_2 under argon. Anhyd toluene was purchased from ACROS. MeCN was freshly distilled from CaH_2 under argon and degassed by freeze-pump-thaw cycles. *N*,*N*′-Diisopropylethylamine was distilled from KOH under argon and stored away from light. All other reagents were used as supplied. [(DPEphos)(bcp)Cu]PF_6 was prepared according to our previously reported procedure.[19] Cy_2Ni-Bu was prepared according to a previously reported procedure.[57]

Reactions were magnetically stirred and monitored by TLC using Merck Kiesegel 60F_{254} plates. Flash chromatography was performed with silica gel 60 (particle size 35–70 µm) supplied by Merck. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. Photoinduced copper-catalyzed reactions were performed in a Luzchem CCP-4V photoreactor using 420 nm light tubes supplied by Luzchem.

^{1}H NMR spectra were recorded using an internal deuterium lock at ambient temperature on Bruker 300 MHz, Jeol 400 MHz, or Varian 600 MHz spectrometers. Internal reference of δ_H 7.26 was used for $CDCl_3$. Data are presented as follows: chemical shift (in ppm on the δ scale relative to δ_{TMS} = 0), multiplicity (standard abbreviations), coupling constant (*J*/Hz), and integration. Resonances that are either partially or fully obscured are denoted obscured (obs). ^{13}C NMR spectra were recorded at 75 MHz, 100 MHz, or 150 MHz using $CDCl_3$ (δ_C 77.16) as internal reference. Melting points were recorded on a Stuart Scientific Analogue SMP11. IR spectra were recorded on a Bruker Alpha (ATR). High-resolution mass spectra were obtained on an Agilent Technologies QTOF 6520 spectrometer.

N-(2-Iodobenzyl)-*N*-[(trimethylsilyl)ethynyl]benzamide (14b)

To a solution of *N*-(2-iodobenzyl)benzamide[47] (674 mg, 2.00 mmol) in anhyd toluene (25 mL) under argon was added KHMDS (0.5 M solution in toluene, 4.8 mL, 2.40 mmol) at 0 °C. The mixture was stirred at this temperature for 2 h and [(trimethylsilyl)ethynyl]phenyliodonium triflate (1.1 g, 2.40 mmol) was added. The mixture was then stirred at r.t. overnight and filtered through a pad of Celite (rinsed with a solution of toluene/Et_2O: 4:1). After concentration under vacuum, the residue was purified by column chromatography over silica gel (PE/EtOAc, 90:10 to 70:30) to afford **14b** (400 mg, 0.92 mmol, 46%) as a yellow solid; mp 59–61 °C.

IR (ATR): 2960, 2170, 1675, 1440, 1367, 1288, 1016, 982, 847 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91–7.85 (m, 3 H), 7.50 (t, *J* = 7.3 Hz, 1 H), 7.45–7.33 (m, 4 H), 7.02 (m, 1 H), 4.91 (s, 2 H), –0.05 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.7, 139.7, 138.1, 133.2, 131.7, 130.1, 129.7, 129.2 (2 C), 128.4, 127.8 (2 C), 99.5, 97.4, 56.9, –0.2 (3 C).

ESI-HRMS: *m*/*z* calcd for $C_{19}H_{21}INOSi$ [M + H]$^+$: 434.0432; found: 434.0447.

N-Ethynyl-*N*-(2-iodobenzyl)benzamide (14a)

To a solution of **14b** (300 mg, 0.69 mmol) in anhyd THF (7 mL) was added TBAF (1 M solution in THF, 1.40 mL, 1.40 mmol) at –10 °C. The mixture was stirred at the same temperature for 5 min and was then allowed to warm up to r.t. over 1 h. The reaction was quenched with sat. aq NH_4Cl (3 mL). The aqueous phase was extracted with Et_2O (3 ×) and the combined organic layers were washed with brine, dried (over Na_2SO_4), filtered, and concentrated under vacuum. The residue was purified by column chromatography over silica gel (PE/EtOAc, 95:5) to afford **14a** (250 mg, 0.69 mmol, 99%) as an off-white solid; mp 60–62 °C.

IR (ATR): 2142, 1664, 1293, 1015, 742 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91–7.85 (m, 3 H), 7.52 (t, *J* = 7.4 Hz, 1 H), 7.46–7.36 (m, 4 H), 7.03 (app dt, *J* = 8.1, 4.5 Hz, 1 H), 4.93 (s, 2 H), 2.69 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.0, 139.9, 137.9, 133.1, 131.9, 129.7, 129.5, 129.0 (2 C), 128.5, 128.1 (2 C), 99.0, 78.2, 62.0, 57.0.

ESI-HRMS: *m*/*z* calcd for $C_{16}H_{12}INO$ [M + H]$^+$: 362.0036; found: 362.0040.

Copper-Catalyzed Photoredox Cyclization of *N*-Benzoyl-*N*-(*o*-iodobenzyl)cyanamides 12; General Procedure 1

An oven-dried quartz vial was charged with [(DPEphos)(bcp)Cu]PF_6 (22 mg, 0.02 mmol) and the corresponding cyanamide **12** (0.20 mmol). The vial was evacuated under high vacuum, backfilled with argon, and sealed with a rubber septum. MeCN (2 mL) and *i*-Pr_2NEt (70 µL, 0.40 mmol) were next added and the reaction mixture was stirred in a photoreactor under 420 nm wavelength irradiation for 16 h. The mixture was filtered through a pad of Celite (rinsed with Et_2O) and concentrated under vacuum. The residue was then purified by flash column chromatography over silica gel to afford the corresponding pure product **13**.

Isoindolo[1,2-*b*]quinazolin-10(12*H*)-one (13a)

Following general procedure 1; solvent system for flash column chromatography: PE/EtOAc (80:20 to 60:40); yield: 26 mg (52%, 0.10 mmol); pale yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.36 (d, *J* = 7.2 Hz, 1 H), 8.15 (d, *J* = 7.4 Hz, 1 H), 7.83–7.74 (m, 2 H), 7.64–7.46 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.8, 155.1, 149.7, 139.8, 134.4, 132.9, 132.5, 129.0, 127.5, 126.6, 126.5, 123.7, 123.6, 120.8, 49.9.

The spectroscopic data correspond to those previously reported.[47]

7-Methoxycarbonylisoindolo[1,2-*b*]quinazolin-10(12*H*)-one (13b)

Following general procedure 1; solvent system for flash column chromatography: PE/EtOAc (80:20 to 60:40); yield: 35 mg (60%, 0.12 mmol); white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.52 (app s, 1 H), 8.44 (d, *J* = 8.3 Hz, 1 H), 8.20 (d, *J* = 10.5 Hz, 1 H), 8.09 (dd, *J* = 9.9, 1.6 Hz, 1 H), 7.71–7.58 (m, 3 H), 5.19 (s, 2 H), 4.00 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4, 160.3, 155.8, 149.6, 139.8, 135.6, 132.8, 132.6, 129.5, 129.2, 127.0, 126.6, 123.9, 123.7, 52.8, 50.1.

The spectroscopic data correspond to those previously reported.[47]

Copper-Catalyzed Photoredox Cyclization of *N*-Benzoyl-*N*-(*o*-iodobenzyl)ynamides 14; General Procedure 2

An oven-dried quartz vial was charged with [(DPEphos)(bcp)Cu]PF_6 (22 mg, 0.02 mmol) and the corresponding ynamide **14** (0.20 mmol). The vial was evacuated under high vacuum, backfilled with argon and sealed with a rubber septum. MeCN (2 mL) and *i*-Pr_2NEt (350 µL, 2.00 mmol) were next added and the reaction mixture was stirred in a photoreactor under 420 nm wavelength irradiation for 16 h. The mixture was filtered through a pad of Celite (rinsed with Et_2O) and concentrated under vacuum. The residue was then purified by flash column chromatography over silica gel to afford the corresponding pure product **15**.

Isoindolo[2,1-*b*]isoquinolin-5(7*H*)-one (15a)

Following general procedure 2;solvent system for flash column chromatography: PE/EtOAc (80:20); yield: 23 mg (50%, 0.10 mmol); yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 8.8 Hz, 1 H), 7.82–7.76 (m, 1 H), 7.65 (obs dd, *J* = 7.3, 1.3 Hz, 1 H), 7.65 (d, *J* = 1.3 Hz, 1 H), 7.60–7.55 (m, 1 H), 7.51–7.43 (m, 3 H), 7.02 (s, 1 H), 5.19 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.7, 142.7, 138.5, 138.2, 164.6, 132.7, 130.4, 128.9, 128.0, 126.9, 126.7, 125.3, 124.0, 121.6, 98.6, 52.6.

The spectroscopic data correspond to those previously reported.[58]

12-(Trimethylsilyl)isoindolo[2,1-*b*]isoquinolin-5(7*H*)-one (15b)

Following general procedure 2; solvent system for flash column chromatography: PE/EtOAc (75:25); yield: 29 mg (47%, 0.10 mmol); pale yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 8.0 Hz, 1 H), 7.95–7.86 (m, 2 H), 7.67–7.54 (m, 2 H), 7.51–7.43 (m, 2 H), 5.20 (s, 2 H), 0.56 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$,): δ = 161.2, 148.8, 142.2, 139.3, 135.5, 131.0, 129.7, 128.4, 127.3, 126.5, 125.8, 124.7, 123.3, 108.6, 52.1, 3.5.

The spectroscopic data correspond to those previously reported.[49]

***N*-[(2-Iodoquinolin-3-yl)methyl]benzamide**

To a solution of 2-iodo-3-aminomethylquinoline (**16**;[47] 380 mg, 1.34 mmol) in anhyd CH_2Cl_2 (13 mL) was added Et_3N (559 µL, 4.01 mmol) at 0 °C. After 5 min, benzoyl chloride (171 µL, 1.47 mmol) was added dropwise and the reaction mixture was stirred at r.t. for 16 h. The resulting mixture was quenched with sat. aq NH_4Cl and extracted with CH_2Cl_2 (2 ×). The combined organic layers were washed with sat. aq $NaHCO_3$ (2 ×) and brine (1 ×), dried ($MgSO_4$), filtered, and concentrated under vacuum to afford *N*-[(2-iodoquinolin-3-yl)methyl]benzamide as an off-white solid (520 mg, 1.34 mmol, quant).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (s, 1 H), 8.00 (d, *J* = 8.4 Hz, 1 H), 7.83–7.80 (m, 2 H), 7.75 (d, *J* = 7.8 Hz, 1 H), 7.71–7.65 (m, 1 H), 7.57–7.40 (m, 4 H), 7.03 (br t, 1 H), 4.74 (d, *J* = 6.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3, 148.8, 136.5, 134.1, 133.9, 132.0, 130.5, 128.9 (2 C), 128.5, 127.9, 127.7, 127.3, 127.1 (2 C), 124.2, 47.1.

The spectroscopic data correspond to those previously reported.[47]

***N*-[(2-Iodoquinolin-3-yl)methyl]-*N*-[(trimethylsilyl)ethynyl]benzamide (17)**

To a solution of *N*-[(2-iodoquinolin-3-yl)methyl]benzamide (809 mg, 2.08 mmol) in anhyd toluene (50 mL) was added KHMDS (0.5 M in toluene, 5 mL, 2.50 mmol) at 0 °C. After 2 h, [(trimethylsilyl)ethynyl]phenyliodonium triflate (1.1 g, 2.5 mmol) was added and the reaction mixture was stirred at r.t. for 16 h. The resulting mixture was filtered through a pad of Celite (rinsed with CH_2Cl_2) and concentrated under vacuum. The crude residue was then purified by flash column chromatography over silica gel (PE/EtOAc 80:20) to afford **17** as a dark yellow solid (399 mg, 0.82 mmol, 40%); mp 76–81 °C.

IR (ATR): 2927, 2166, 1684, 1328, 1247, 1128, 977, 845, 753, 704 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 8.4 Hz, 1 H), 8.01 (s, 1 H), 7.92 (d, *J* = 6.9 Hz, 2 H), 7.82 (d, *J* = 8.4 Hz, 1 H), 7.76–7.70 (m, 1 H), 7.62–7.49 (m, 2 H), 7.45–7.39 (m, 2 H), 5.04 (s, 2 H), –0.10 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6, 148.9, 136.6, 132.8, 132.0, 130.7, 130.6, 129.2, 129.0, 128.7, 127.8, 127.7, 127.6, 127.1, 123.9, 97.0, 55.3, –0.3 (3 C), the two Csp carbon atoms were not observed.

ESI-HRMS: *m*/*z* calcd for $C_{22}H_{21}IN_2OSi$ $[M + H]^+$: 485.0541; found: 485.0542.

6-(Trimethylsilyl)rosettacin (18)

An oven-dried vial containing **17** (48 mg, 0.10 mmol), [(DPEphos)(bcp)Cu]PF_6 (11 mg, 0.01 mmol), Cy_2Ni-Bu (12 mg, 0.05 mmol), and K_2CO_3 (28 mg, 0.20 mmol) was evacuated under high vacuum, backfilled with argon and sealed with a rubber septum. MeCN (2 mL) was added and the reaction mixture was stirred at r.t. in a photoreactor under 420 nm wavenlength irradiation for 120 h. The resulting mixture was filtered through a pad of Celite (rinsed with CH_2Cl_2) and concentrated under vacuum. The crude residue was then purified by flash column chromatography over silica gel (PE/EtOAc 60:40) to afford **18** as a light yellow solid (24 mg, 0.07 mmol, 71%); mp 163–171 °C.

IR (ATR): 3904, 3650, 2928, 1652, 1470, 1406, 1369, 1022, 860, 761, 732, 688, 606 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.64 (d, *J* = 9.3 Hz, 1 H), 8.30 (s, 1 H), 8.24–8.17 (m, 2 H), 7.91 (d, *J* = 7.8 Hz, 1 H), 7.82–7.76 (m, 1 H), 7.73–7.67 (m, 1 H), 7.65–7.62 (m, 1 H), 7.59–7.53 (m, 1 H), 5.38 (s, 2 H), 0.70 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.5, 154.8, 148.0, 145.5, 141.8, 131.5, 129.9 (2 C), 129.6, 129.2, 129.0, 127.9, 127.6, 127.5, 127.4, 126.7, 125.8, 113.3, 49.5, 4.3 (3 C).

ESI-HRMS: *m*/*z* calcd for $C_{22}H_{20}N_2OSi$ $[M + H]^+$: 357.1418; found: 357.1422.

Rosettacin (5)

To a solution of **18** (22 mg, 0.06 mmol) in THF (1.4 mL) was slowly added TBAF (1 M in THF, 120 µL, 0.12 mmol) at 0 °C and the reaction mixture was stirred for 1 h at r.t. The resulting mixture was quenched with sat. aq NH_4Cl and extracted with EtOAc (3 ×). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under vacuum. The crude residue was then purified by flash column chromatography over silica gel (PE/EtOAc 60:40) to afford rosettacin (**5**) as a light yellow solid (15 mg, 0.05 mmol, 88%); mp 285–290 °C.

IR (ATR): 3355, 2924, 2853, 1661, 1604, 1450, 1399, 1331, 1026, 919, 844, 752, 727, 687 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 7.8 Hz, 1 H), 8.27 (s, 1 H), 8.19 (d, *J* = 8.4 Hz, 1 H), 7.86 (d, *J* = 7.8 Hz, 1 H), 7.78–7.74 (m, 2 H), 7.70 (t, *J* = 7.8 Hz, 1 H), 7.62 (s, 1 H), 7.60–7.54 (m, 2 H), 5.32 (s, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 161.2, 153.7, 149.0, 140.1, 137.7, 132.6, 130.8, 130.3, 129.6, 128.9, 128.2, 128.1, 127.6 (2 C), 127.4 (2 C), 126.2, 101.3, 49.6.

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{12}N_2O$: 285.1022; found: 285.1019.

The spectroscopic data correspond to those previously reported.[36]

N-[(2-Iodoquinolin-3-yl)methyl]cyanamide

To a solution of CNBr (106 mg, 1.0 mmol) in anhyd THF (1.5 mL) at –20 °C was added Na_2CO_3 (212 mg, 2.0 mmol) and a solution of 2-iodo-3-aminomethylquinoline (**16**;[47] 284 mg, 1.0 mmol) in THF (2.5 mL). The reaction mixture was stirred at –20 °C for 2 h. The mixture was then filtered through a pad of Celite (rinsed with CH_2Cl_2) and concentrated under vacuum. The crude residue was purified by flash column chromatography over silica gel (PE/EtOAc 80:20) to afford *N*-[(2-iodoquinolin-3-yl)methyl]cyanamide as an off-white solid (169 mg, 0.55 mmol, 55%); mp 104–107 °C.

IR (ATR): 3800, 3406, 2917, 2236, 1680, 1586, 1557, 1395, 1329, 1133, 1002, 777, 725, 659 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08–8.05 (m, 2 H), 7.84 (d, *J* = 8.1 Hz, 1 H), 7.76 (t, *J* = 8.4, 1 H), 7.62 (t, *J* = 8.4 Hz, 1 H), 4.40 (d, *J* = 6.3 Hz, 2 H), 4.32 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.2, 136.3, 132.0, 131.1, 128.7, 128.1, 128.0, 127.0, 123.0, 114.8, 53.3.

ESI-HRMS: *m*/*z* calcd for $C_{11}H_8IN_3$ [M + H]$^+$: 309.9836; found: 309.9837.

N-Cyano-*N*-[(2-iodoquinolin-3-yl)methyl]benzamide (19)

To a solution of *N*-[(2-iodoquinolin-3-yl)methyl]cyanamide (50 mg, 0.16 mmol) in THF (1.6 mL) was added NaH (60% in mineral oil, 7 mg, 0.18 mmol) at 0 °C. After 10 min, benzoyl chloride (21 µL, 0.18 mmol) was added dropwise and the reaction mixture was stirred at r.t. for 2 h. The resulting mixture was quenched with sat. aq NH_4Cl and extracted with CH_2Cl_2 (2 ×). The combined organic layers were washed with sat. aq $NaHCO_3$ (2 ×) and brine (1 ×), dried ($MgSO_4$), filtered, and concentrated under vacuum to afford **19** as a light yellow solid (67 mg, 0.16 mmol, quant).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (obs s, 1 H), 8.07 (obs d, *J* = 7.2 Hz, 1 H), 7.90 (d, *J* = 7.5 Hz, 2 H), 7.83–7.73 (m, 2 H), 7.61–7.57 (m, 2 H), 7.50 (t, *J* = 7.8 Hz, 2 H), 5.07 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.2, 149.3, 138.0, 134.6, 133.8, 131.4, 130.7, 130.4, 129.8, 129.1, 128.9, 128.8, 128.1, 128.0, 126.8, 122.8, 110.5, 54.1.

The spectroscopic data correspond to those previously reported.[47]

Luotonin A (8)

An oven-dried vial containing **19** (37 mg, 0.09 mmol), [(DPEphos)(bcp)Cu]PF_6 (9 mg, 9.0 µmol), Cy_2Ni-Bu (11 mg, 0.04 mmol), and K_2CO_3 (25 mg, 0.18 mmol) was evacuated under high vacuum, backfilled with argon and sealed with a rubber septum. MeCN (2 mL) was added and the reaction mixture was stirred at r.t. in a photoreactor under 420 nm wavenlength irradiation for 120 h. The resulting mixture was filtered through a pad of Celite (rinsed with CH_2Cl_2) and concentrated under vacuum. The crude residue was then purified by flash column chromatography over silica gel (PE/EtOAc 60:40) to afford luotonin A (**8**) as an orange/pink solid (20 mg, 0.07 mmol, 79%); mp 265–270 °C.

IR (ATR): 3708, 2927, 2854, 1681, 1633, 1466, 840, 770, 737, 695, 665 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.49–8.41 (m, 3 H), 8.12 (d, *J* = 7.8 Hz, 1 H), 7.95 (d, *J* = 7.5 Hz, 1 H), 7.89–7.82 (m, 2 H), 7.71–7.66 (m, 1 H), 7.58 (t, *J* = 8.1 Hz, 1 H), 5.34 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.8, 152.7, 151.3, 149.5 (2 C), 134.7, 131.6, 130.8 (2 C), 129.5, 128.9 (2 C), 128.6, 128.0, 127.5, 126.5, 121.4, 47.4.

ESI-HRMS: *m*/*z* calcd for $C_{18}H_{11}N_3O$ [M + H]$^+$: 286.0975; found: 286.0969.

The spectroscopic data correspond to those previously reported.[47]

N-(3-Bromopropyl)cyanamide

To a solution of CNBr (722 mg, 6.8 mmol) in anhyd THF (6 mL) cooled to –20 °C was added in one portion Na_2CO_3 (2.14 g, 20.4 mmol) followed by a solution of 3-bromopropylamine hydrobromide (**20**; 1.5 g, 6.8 mmol) in anhyd THF (8 mL). The resulting solution was stirred for 2 h at –20 °C and then allowed to warm up to 0 °C. The reaction mixture was then filtered over a pad of Celite (rinsed with Et_2O) and the filtrate was concentrated under vacuum. The crude residue was then purified by flash column chromatography over silica gel (PE/EtOAc 60:40) to afford *N*-(3-bromopropyl)cyanamide as a light yellow oil (1.1 g, 6.8 mmol, quant).

IR (ATR): 3205, 2906, 2239, 1436, 1262, 1164, 751, 667 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.98 (s, 1 H), 3.49 (t, *J* = 6.2 Hz, 2 H), 3.49 (app q, *J* = 6.5 Hz, 2 H), 2.14 (app quint, *J* = 6.3 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 115.7, 44.2, 31.8, 29.5.

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_4H_7{}^{81}BrN_2$: 164.9845; found: 164.9841.

N-(3-Bromopropyl)-*N*-cyanobenzamide

To a solution of *N*-(3-bromopropyl)cyanamide (1 g, 6.1 mmol) in anhyd THF (60 mL) was added NaH (60% in mineral oil, 162 mg, 6.7 mmol) at 0 °C. After 10 min, benzoyl chloride was added dropwise and the resulting solution was stirred overnight at r.t. The reaction mixture was quenched with sat. aq NH_4Cl, the aqueous layer was extracted with CH_2Cl_2 (2 ×) and the combined organic layers were washed with sat. aq $NaHCO_3$ (3 ×) and brine (1 ×), then dried ($MgSO_4$), filtered, and concentrated under vacuum. The crude residue was then purified by flash column chromatography over silica gel (PE/EtOAc 90:10 to 80:20) to afford *N*-(3-bromopropyl)-*N*-cyanobenzamide as a white solid (970 mg, 3.7 mmol, 60%); mp 43–45 °C.

IR (ATR): 2225, 1701, 1436, 1339, 1181, 1022, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82–7.79 (m, 2 H), 7.62–7.58 (m, 1 H), 7.51–7.46 (m, 2 H), 3.94 (t, *J* = 6.9 Hz, 2 H), 3.49 (app t, *J* = 6.4 Hz, 2 H), 2.36 (app quint, *J* = 6.5 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3, 133.4, 130.7, 128.7, 110.9, 46.7, 30.5, 28.8.

ESI-HRMS: *m*/*z* calcd for $C_{11}H_{11}{}^{81}BrN_2O$ [M + H]$^+$: 269.0180; found: 269.0100.

N-(3-Iodopropyl)-*N*-cyanobenzamide (21)

To a solution of *N*-(3-bromopropyl)-*N*-cyanobenzamide (150 mg, 0.56 mmol) in acetone (5 mL) was added NaI (251 mg, 1.67 mmol). The resulting mixture was stirred at r.t. for 16 h, filtered over a pad of Celite (rinsed with EtOAc), and concentrated under vacuum. The crude resi-

due was then purified by flash column chromatography over silica gel (PE/EtOAc 80:20) to afford **21** as a colorless oil (168 mg, 0.56 mmol, quant).

IR (ATR): 2364, 1703, 1447, 1272, 1110, 790, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.82–7.79 (m, 2 H), 7.62–7.58 (m, 1 H), 7.51–7.46 (m, 2 H), 3.88 (t, *J* = 6.9 Hz, 2 H), 3.24 (app t, *J* = 6.9 Hz, 2 H), 2.33 (app quint, *J* = 6.9 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3, 133.4, 130.7, 128.7, 110.9, 48.5, 31.2, 0.9.

ESI-HRMS: *m*/*z* calcd for $C_{11}H_{11}IN_2O$ $[M + H]^+$: 314.9989; found: 314.9987.

Deoxyvasicinone (22)

An oven-dried vial containing **21** (62.6 mg, 0.20 mmol), [(DPEphos)(bcp)Cu]PF_6 (22 mg, 0.02 mmol), Cy_2Ni-Bu (25 mg, 0.1 mmol), and K_2CO_3 (55 mg, 0.40 mmol) was evacuated under high vacuum, backfilled with argon, and sealed with a rubber septum. MeCN (2 mL) was added and the reaction mixture was stirred at r.t. in a photoreactor under 420 nm wavenlength irradiation for 120 h. The resulting mixture was filtered through a pad of Celite (rinsed with CH_2Cl_2) and concentrated under vacuum. The crude residue was then purified by trituration in pentane to afford deoxyvasicinone (**22**) as a light yellow solid (21.2 mg, 0.11 mmol, 53%); mp 107–109 °C.

IR (ATR): 2960, 2924, 1670, 1485, 1425, 771, 690 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.82–7.79 (m, 2 H), 7.62–7.58 (m, 1 H), 7.51–7.46 (m, 2 H), 3.88 (t, *J* = 6.9 Hz, 2 H), 3.24 (app t, *J* = 6.9 Hz, 2 H), 2.33 (app quint, *J* = 6.9 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1, 159.5, 149.3, 134.2, 126.8, 126.5, 126.2, 120.5, 46.5, 32.6, 19.5.

ESI-HRMS *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{10}N_2O$: 187.0866; found: 187.0862.

The spectroscopic data correspond to those previously reported.[56g]

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Supporting Information

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