Published in final edited form as:

Tetrahedron. 2018 June 28; 74(26): 3246–3252. doi:10.1016/j.tet.2018.04.053.

Lithium bis-catechol borate as an effective reductive quencher in photoredox catalysis

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Abstract

The use of lithium bis-catechol borate (LiB(cat)_2) as a reductive quencher for the photoredox mediated intermolecular C–H functionalization of various heteroaromatics with bromopyrroloindolines is described. LiB(cat)_2 offers a financial benefit over state-of-the-art quenchers currently in use while eliminating the side reactions that typically plague these couplings. The advantage of this methodology is highlighted by the synthesis of C3–C2' (–) gliocladin C. Furthermore, additional examples of reactivity with various bromopyrroloindolines sets the stage for expedient routes towards other pharmaceutically active hexahydropyrroloindoline alkaloids and their analogues.

Graphical abstract

1. Introduction

In recent years, visible light-mediated catalysis has been extensively studied to develop an array of novel organic transformations.^{1–3} Of the myriad methods centered around photo-induced single electron transfer (SET) chemistry, our research program has been particularly interested in the reduction of activated and unactivated C–X bonds.^{4,5} Using a photoredox catalyst, an efficient method for the intramolecular radical arylation of electron-rich heterocycles was developed.⁶ Traditionally, chemists have employed trialkyl amines as

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Supplementary data

Copies of ^1H and ^{13}C NMR spectra for all products. Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/xxxxxxxxxxxxxx>.

sacrificial reductive quenchers for photocatalytic reactions. However, several unavoidable side reactions can limit the potential of photocatalysis. Of these undesired pathways, hydrogen atom abstraction from trialkyl amine **1** by radicals (**2**) lead to premature reduction of activated halides (**3**) (Figure 1). Importantly, the rate of unwanted hydrogen atom transfer is competitive with the desired trapping with a heterocycle or activated alkene. In the case of bromopyrroloindolines, which our group has been interested in coupling with heterocycles for natural product syntheses, trialkyl amines reactivity had so far limited their use.

This undesired reactivity initially hampered our efforts to develop redox neutral coupling protocol. We, therefore, introduced commercially available 4-methoxy-*N,N*-diphenylaniline **4** as a novel reductive quencher in photoredox catalysis.⁷ In the absence of α -protons, the formed *N*-centered radical cation is unable to act as a hydrogen atom donor. Due to the high cost of this reductive quencher,⁸ we envisioned employing a less expensive alternative that still avoided the deleterious side reactions seen with trialkyl amines. Similar to trialkyl amines, the redox potential of the novel quencher would have to be in the electrochemical window required for reductive quenching of photocatalysts such as $\text{Ru}(\text{bpy})_3^{2+}$ ($E_{1/2}^{\text{II}^*/\text{I}} = +0.77 \text{ V vs SCE}$)⁹ as well as be inexpensively procured. Finally, the new reductive quencher and its oxidized state need to be innocent species in the desired reaction.

The indole aromatic scaffold is ubiquitous in both bioactive natural products and pharmaceuticals,¹ and tremendous effort has been expended to develop methods for the robust and efficient functionalization of the heteroaromatic skeleton. In the same vein, reliable investigation of the bioactivity of the natural frameworks has often relied upon *de novo* synthesis to supply the necessary quantities for study. Indole alkaloids functionalized at both the 2- and 3-carbons of the aromatic scaffold, such as undulifoline,² actinophyllic acid,³ vinblastine and vincristine,⁴ piqued our interest into radical indole alkylation as they pose both strategic and methodological challenges (Figure 1).

2. Results and discussion

Given the previous success of tertiary amines as reductive quenchers, we began looking for other commercially available amines capable of undergoing reductive SET without resulting in premature reduction. Our search proved unfruitful; no amine unable to undergo H-atom donation was financially competitive or a productive quencher. In 2006, lithium bis-catechol borate **5** ($\text{LiB}(\text{cat})_2$) was reported as a reductive quencher of photoexcited ruthenium polypyridyl complexes (Figure 2).¹⁰

Although not directly available for purchase, borate complexes can readily be synthesized from abundantly-available commodity chemicals: boric acid and catechol. Furthermore, once oxidized, the borate complex is no longer ionic and thus can easily diffuse from the iridium or ruthenium photocatalyst, inhibiting the unproductive back electron transfer process.¹¹ Detailed herein, this low-cost, inert sacrificial reductant has been shown to operate effectively in our reductive, formal C–H functionalization of electron-rich heterocycles while also enabling a universal method to couple bromopyrroloindolines with electron-rich or electron-poor heterocycles.

The reaction conditions can be varied based on the availability of either coupling partner. If the heterocycle is more precious than the reagents, an excess of halide can be used. Using less than two equivalents of diethyl bromomalonate led to slow reactions and/or poor conversions to the product. Moderate to good yields were observed for electron-rich and electron-poor indoles (Scheme 1, **6–8**). Pyrroles and even azaindole were also compatible with this method (**9–10**). The starting material was fully consumed within 3 hours. It should be noted that in the case of more electron rich heterocycles such as thianaphthene, only decomposition of starting materials was observed (**11**).

The radical coupling with bromopyrroloindolines with various heterocycles was also attempted (Scheme 2). Coupling with indole **12** occurred in 60% isolated yield. The use of LiB(cat)₂ enabled a shorter reaction time and a reduced excess of indole compared to trialkyl amine quenchers which was critical to achieve a 50% improvement in yield as the product was prone to decomposition under reaction conditions (Figure 3). Notably, indole-2-carbaldehyde, **13**, led to isolation of the product in 91% yield, a significant improvement of the key step towards the synthesis of the natural product (+)-gliocladin C. Previous efforts required five equivalents of indole, longer reaction times and resulted in a lower yield (Figure 3).¹² N-Boc tryptophan was isolated in good yields (**14**, 57%). Pyrrole (**15**) and furan (**16**) were also compatible with our optimized reaction protocol. Lastly, quenching the bromopyrroloindolines radical with butyl vinyl ether afforded the target aldehyde in good yields (**17**, 71%). The resulting aldehyde provides a simple yet useful handle for further transformation. For example, this aldehyde could be used to revisit syntheses of (–)-flustramine B and (+)-nocardiozines.¹³ Interestingly, we did not observe poor mass recovery in cases with electron-rich heterocycles, a dramatic improvement compared to our coupling of di-ethyl bromomalonate with said substrates.

Having demonstrated the versatility of the new reductive quencher, we decided to apply this method towards the synthesis of a gliocladin C analogue. Natural gliocladin C is a hexahydropyrroloindoline alkaloid¹⁴ containing a C3-C3' bisindole motif. Along other natural products of this class of alkaloids, gliocladin C exhibits potent cytotoxic properties against lymphocytic leukemia cell lines (ED₅₀ = 240 ng mL⁻¹).¹⁵ Novel analogues of gliocladin C are highly desired due to their potential as new anti-cancer therapy leads. Given our previous report,¹² we sought to synthesize the C3-C2' gliocladin C, **18**, in a quick and efficient manner (Scheme 3). Starting from bromopyrrolindoline **19**, C3-C2' coupling with indole proceeded smoothly with the catechol borate quencher to isolate **12** in good yield (60 %). Boc-deprotection with TMSI followed by N-acylation led to the desired triketopiperazine **20** after an unexpected second N-acylation occurring during silica gel chromatography. Finally, Pd/C dehydrogenation provided **21** and a Lewis acid-mediated deprotection delivered the C3-C2' unnatural gliocladin C (**18**) in 97% yield.

We propose that a reductive quenching cycle is occurring in this reaction (Figure 4). Ir(III) is excited by visible light irradiation to form Ir(III)*, which is then reductively quenched by LiB(cat)₂ to form the highly reducing Ir(II) species and **22**. Reductive dehalogenation regenerates Ir(III) and malonyl radical **23** that adds to the desired heterocycle, such as 3-methyl indole (**24**). Multiple mechanisms can be suggested for the re-aromatization of **25** to form product **6**. We propose **23** can oxidize **25**, which after deprotonation would yield **6**.

With re-aromatization as a potent driving force to **6**, deprotonation occurring before electron-transfer cannot be excluded. Given the short reaction times of this protocol, a chain propagation mechanism in which **25** is deprotonated is also possible.¹⁶

3. Conclusions

In summary, we have introduced a novel reductive quencher, catechol borate, that can be synthesized on scale in a single step from inexpensive commercial reagents. Employing LiB(cat)₂ as a quencher in reductive photoredox dehalogenation was found to eliminate undesired hydrogen atom abstraction observed with trialkylamines. The protocol can accommodate cases in which either substrates may be used in excess, lending desired flexibility in multistep routes towards a chemical agent. Notably, this method achieves a long-standing goal of using photoredox catalysis with non-commercially available and precious bromopyrroloindolines which thus far had not shown to be universally compatible or reactive in photoredox methods. Access to this reactivity unlocks new routes towards hexahydropyrroloindoline alkaloids and their analogues, as shown in our synthesis of unnatural C3–C2' (–)-gliocladin C, which was prepared in **6** steps (11% overall yield).

4. Experimental Section

4.1. General experimental methods

Chemicals were used as received. All reactions were performed using common inert atmosphere techniques. Reactions were monitored by TLC and visualized by a dual short wave/long wave UV lamp and stained with an ethanolic solution of potassium permanganate or *p*-anisaldehyde. Flash column chromatography was performed using 230–400 mesh silica gel. NMR spectra were recorded on Varian Unity Plus 400, Varian MR400, Varian vnmrs 500, Varian Inova 500, Varian Mercury 500, and Varian vnmrs 700 spectrometers. Chemical shifts for ¹H NMR were reported as δ, parts per million, relative to the signal of CHCl₃ at 7.26 ppm or CD₃OD at 4.78 ppm. Chemical shifts for ¹³C NMR were reported as δ, parts per million, relative to the center line signal of the CDCl₃ triplet at 77.0 ppm or the center line signal of the CD₃OD septet at 49.15 ppm. Chemical shifts for ¹⁹F NMR were reported as δ, parts per million, relative to the center line signal of the C₆H₅CF₃ triplet at –63.78 ppm. The abbreviations s, br. s, d, dd, br. d, ddd, t, q, br. q, qi, m, and br. m stand for the resonance multiplicity singlet, broad singlet, doublet, doublet of doublets, broad doublet, doublet of doublet of doublets, triplet, quartet, broad quartet, quintet, multiplet and broad multiplet, respectively. IR spectra were recorded on a Perkin-Elmer Spectrum BX FT-IR spectrometer. Mass spectra were recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Michigan in Ann Arbor, MI on an Agilent Q-TOF HPLC-MS with ESI high resolution mass spectrometer. UV/Visible spectra were recorded at the Analytical Instruments Facility at the Department of Chemistry of the University of Michigan in Ann Arbor, MI on a Shimadzu UV-1601 UV-Vis spectrometer. Concentration refers to removal of solvent under reduced pressure (house vacuum at ca. 20 mmHg). LED lights and the requisite power box and cables were purchased from Creative Lighting Solutions (<http://www.creativelightings.com>) with the following item codes: CL-FRS5050-12WP-12V (4.4W blue LED light strip), CL-FRS5050WPDD-5M-12V-BL (72 W

LED strip), CL-PS94670-25W (25 W power supply), CL-PS16020-150W (150 W power supply), CL-PC6FT-PCW (power cord), CL-TERMBL-5P (terminal block). The 300 W 2500 lumen white LED work light was purchased from Home Depot Model # WL2540LP.

Synthesis of lithium bis-catechol borate—To a 100 mL round bottom flask equipped with rubber septum and magnetic stir bar was added catechol (17.8 g, 162 mmol, 2.0 equiv) and methanol (35 mL). Lithium hydroxide monohydrate (3.40 g, 81 mmol, 1.0 equiv) was added and the reaction was stirred until homogeneous (mild heat can be used to speed up the process). Boric acid (5.00 g, 81 mmol, 1.0 equiv) was added and the reaction was allowed to stir at 60 °C for 1 hour. Methanol was removed via rotary evaporation and the reaction mixture was dissolved in THF (80 mL). Stir bar was removed and hexanes (~100 mL) was slowly added to precipitate the desired product. Crystals were collected via vacuum filtration and washed with hexanes, then ether until white. Product was further dried overnight over phosphorus pentoxide under reduced pressure. Spectroscopic data in agreement with previous report.¹

Note: Lithium bis-catechol borate should be kept in a desiccator checked for quality if stored for a period longer than one month. To check for decomposition, dissolve a sample of LiBCat₂ in THF. If a green color is observed, the batch should be discarded. Cause of green color is hypothesized to be semi-quinone species generated via partial O₂ oxidation.

Couplings with diethyl bromomalonate

General Procedure A: A flame dried 25 mL round bottom flask equipped with a rubber septum and magnetic stir bar was charged with Ir(ppy)₂(dtbbpy)PF₆ (0.01 equiv), diethyl bromomalonate (0.5–2.0 equiv), bis-catechol borate lithium salt (2.0 equiv) and corresponding indole or olefin (1 equiv). The flask was purged with a stream of argon and dry DMSO was added. The resultant mixture was degassed by argon sparging for 20 min and placed at a distance of ~2 cm from a blue LED strip. After the reaction was complete (as judged by TLC analysis), the mixture was poured into a separatory funnel containing 75 mL of EtOAc and 75 mL of sat. Na₂CO₃ (aq). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried (over Na₂SO₄) and concentrated. The residue was purified by chromatography on SiO₂, using the solvent system indicated, to afford the desired product.

Diethyl 2-(3-methyl-1H-indol-2-yl)malonate (6)—According to General Procedure A, 3-methyl indole (70 mg, 0.53 mmol), LiB(cat)₂ (0.26 g, 1.1 mmol), diethyl bromomalonate (182 μL, 1.1 mmol, 2.0 equiv) and Ir(ppy)₂(dtbbpy)PF₆ (4.9 mg, 10.0 mol) in dry DMSO (5.0 mL) afforded **6** (105 mg, 68%) as a white solid after purification by chromatography on SiO₂ (10-35% EtOAc/hexanes) (3 h reaction time). Spectroscopic data in agreement with previous report.² ¹H NMR (400 MHz): δ_H 8.93 (br. s., 1 H), 7.55 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.42-7.30 (m, 1H), 7.23- 7.16 (m, 1 H), 7.16-7.04 (m, 1 H), 4.38-4.13 (m, 4 H), 2.39- 2.21 (m, 3 H), 1.36-1.20 (m, 6 H).

Diethyl 2-(2-(methoxycarbonyl)-1-methyl-1H-indol-3-yl)malonate (7)—According to General Procedure A, 1-methylindole-2-carboxylate (175 mg, 1.0 mmol), LiB(cat)₂ (0.47

g, 2.0 mmol), diethyl bromomalonate (0.36 μ L, 5.0 mmol, 5.0 equiv) and $\text{Ir}(\text{ppy})_2(\text{dtbbpy})\text{PF}_6$ (9.1 mg, 10.0 μ mol) in dry DMSO (10.0 mL) afforded **7** (0.22 g, 42%) as a white solid after purification by chromatography on SiO_2 (10-35% EtOAc/hexanes) (3 h reaction time). Spectroscopic data in agreement with previous report.² ^1H NMR (400 MHz): δ_{H} 7.78-7.64 (m, 1 H), 7.43-7.30 (m, 2 H), 7.20-7.10 (m, 1 H), 5.75 (s, 1 H), 4.32-4.15 (m, 4 H), 4.02 (s, 3 H), 3.94 (s, 3 H), 1.24 (t, J = 7.1 Hz, 6 H).

Diethyl (S)-2-(3-(2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-1H-indol-2-yl)malonate (8)—According to General Procedure A, methyl (2S)-2-(tert-butoxycarbonylamino)-3-(1H-indol-3-yl)propanoate (0.200 g, 0.63 mmol), $\text{LiB}(\text{cat})_2$ (0.308 g, 1.3 mmol), diethyl bromomalonate (214 μ L, 1.3 mmol, 2.0 equiv) and $\text{Ir}(\text{ppy})_2(\text{dtbbpy})\text{PF}_6$ (5.7 mg, 6.0 mol) in dry DMSO (10.0 mL) afforded **8** (0.14 g, 47%) as a beige solid after purification by chromatography on SiO_2 (10-35% EtOAc/hexanes) (3 h reaction time). Spectroscopic data in agreement with previous report.² ^1H NMR (400 MHz): δ_{H} 8.93 (br. s., 1 H), 7.52 (d, J = 8.0 Hz, 1 H), 7.33 (d, J = 8.0 Hz, 1 H), 7.17 (td, J = 7.5, 1.2 Hz, 1 H), 7.12-7.04 (m, 1 H), 5.24 (d, J = 8.0 Hz, 1 H), 4.96 (s, 1 H), 4.70-4.57 (m, 1 H), 4.33-4.13 (m, 4 H), 3.59 (s, 3 H); 3.26 (d, J = 5.9 Hz, 2 H), 1.39 (s, 6 H), 1.27 (td, J = 7.1, 1.5 Hz, 6 H).

Diethyl 2-(3-acetyl-1-methyl-1H-pyrrol-2-yl)malonate (9)—According to General Procedure A, 1-(1-methylpyrrol-3-yl)ethanone (88 mg, 0.711 mmol), $\text{LiB}(\text{cat})_2$ (0.17 g, 0.71 mmol), diethyl bromomalonate (53.5 μ L, 0.36 mmol, 2.0 equiv) and $\text{Ir}(\text{ppy})_2(\text{dtbbpy})\text{PF}_6$ (3.2 mg, 4.0 mol) in dry DMSO (3.5 mL) afforded **9** (100 mg, 57%) as a white solid after purification by chromatography on SiO_2 (15% EtOAc/hexanes) (16 h reaction time). Spectroscopic data in agreement with previous report.² ^1H NMR (300 MHz): δ_{H} 6.61 (s, 1 H), 6.53 (dd, J = 15.3, 2.9 Hz, 1 H), 4.38-4.05 (m, 4 H), 3.63 (s, 3 H), 2.40 (s, 3 H), 1.27 (t, J = 7.1 Hz, 6 H).

Diethyl 2-(5-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)malonate (10)—According to General Procedure A, 5-bromo-1-methyl-pyrrolo[2,3-b]pyridine (75 mg, 0.36 mmol), $\text{LiB}(\text{cat})_2$ (0.175 g, 0.74 mmol), diethyl bromomalonate (121 μ L, 0.71 mmol, 2.0 equiv) and $\text{Ir}(\text{ppy})_2(\text{dtbbpy})\text{PF}_6$ (3.2 mg, 4.0 mol) in dry DMSO (5.7 mL) afforded **10** (55 mg, 42%) as a yellow oil after purification by chromatography on SiO_2 (10-35% EtOAc/hexanes) (3 h reaction time). Spectroscopic data in agreement with previous report.² ^1H NMR (500 MHz): δ_{H} 8.25 (d, J = 2.2 Hz, 1 H), 7.89 (dd, J = 2.2, 0.5 Hz, 1 H), 6.44 (s, 1 H), 4.84 (s, 1 H), 4.30 – 4.11 (m, 4 H), 3.73 (s, 3 H), 1.22 (t, J = 7.1 Hz, 6 H).

Couplings with bromopyrroloindolines

General Procedure B: A flame dried 25 mL round bottom flask equipped with a rubber septum and magnetic stir bar was charged with $\text{Ir}(\text{ppy})_2(\text{dtbbpy})\text{PF}_6$ (10 μ mol, 0.01 equiv), the corresponding bromopyrroloindoline (1.0 mmol, 1.0 equiv), bis-catecholborate lithium salt (2.0 mmol, 2.0 equiv) and corresponding indole or olefin (2.0–10.0 equiv). The flask was purged with a stream of argon and 10 mL of dry DMSO was added. The resultant mixture was degassed by argon sparging for 20 min and placed at a distance of ~2 cm from a blue LED strip. After the reaction was complete (as judged by TLC analysis), the mixture

was poured into a separatory funnel containing 75 mL of EtOAc and 75 mL of sat. Na_2CO_3 (aq). The layers were separated and the aqueous layer was extracted with EtOAc (2×50 mL). The combined organic layers were dried (over Na_2SO_4) and concentrated. The residue was purified by chromatography on SiO_2 , using the solvent system indicated, to afford the desired product.

(2R,3aR,8aS)-8-benzyl-1-tert-butyl-3a-(1H-indol-2-yl)-2-(methylcarbamoyl)-3,3a-dihydropyrrolo[2,3-b]indole-1,8(2H,8aH)-dicarboxylate (12)—According to General Procedure B, bromopyrroloindoline **19** (0.53 g, 1.0 mmol), $\text{LiB}(\text{cat})_2$ (0.47 g, 2.0 mmol), indole (1.2 g, 10.0 mmol, 10.0 equiv) and $\text{Ir}(\text{ppy})_2(\text{dtbbpy})\text{PF}_6$ (9.1 mg, 10.0 mol) in dry DMSO (10.0 mL) afforded **12** (0.34 g, 60%) as a white solid after purification by chromatography on SiO_2 (1:1 hexanes/EtOAc) (3 h reaction time). Excess indole was recovered upon purification and re-used. R_f (1:1 hexanes/EtOAc): 0.32; $[\alpha]_{\text{D}}^{25} = -45.3^\circ$ (c

0.7, CHCl_3); IR (neat): 3359, 2975, 1715, 1667, 1555, 1482, 1456, 1407, 1366, 1323, 1283, 1216, 1157, 1026, 914, 750 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ_{H} 7.69 (d, $J = 7.69$ Hz, 1 H), 7.33 - 7.45 (m, 5 H), 7.14 - 7.23 (m, 7 H), 7.06 (t, $J = 7.05$ Hz, 1 H), 6.30 (br. s., 2 H), 5.94 (br. s., 1 H), 5.32 (d, $J = 12.47$ Hz, 1 H), 5.10 (d, $J = 12.47$ Hz, 1 H), 4.28 (br. s., 1 H), 2.98 (dd, $J = 4.89$ Hz, 1 H), 2.92 (d, $J = 4.89$ Hz, 3 H), 2.81 - 2.85 (m, 1 H), 1.41 (s, 9 H); ^{13}C NMR (126 MHz, cdcl_3) δ 173.34, 153.54, 141.36, 138.44, 137.16, 135.96, 129.35, 128.60, 128.14, 127.75, 127.54, 124.71, 124.63, 122.21, 120.43, 119.82, 118.04, 111.40, 101.99, 82.52, 81.86, 67.69, 60.84, 56.22, 38.21, 28.38, 28.30, 28.24, 26.66, 26.52; HRMS (ESI) m/z calculated for $\text{C}_{33}\text{H}_{34}\text{N}_4\text{NaO}_5^+$ ($[\text{M}+\text{Na}]^+$) 589.2427, found 589.2424.

(2R,3aR,8aS)-8-benzyl-1-tert-butyl-3a-(2-formyl-1H-indol-3-yl)-2-(methylcarbamoyl)-3,3a-dihydropyrrolo[2,3-b]indole-1,8(2H,8aH)-dicarboxylate (13)—According to General Procedure B, bromopyrroloindoline **19** (0.53 g, 1.0 mmol), $\text{LiB}(\text{cat})_2$ (0.47 g, 2.0 mmol), indole-2-carboxaldehyde (0.29 g, 2.0 mmol, 2.0 equiv) and $\text{Ir}(\text{ppy})_2(\text{dtbbpy})\text{PF}_6$ (9.1 mg, 10.0 mol) in dry DMSO (10.0 mL) afforded **13** (0.54 g, 91%) as a white solid after purification by chromatography on SiO_2 (7:3 hexanes/acetone) (6 h reaction time). R_f (3:2 hexanes/acetone): 0.30. Spectroscopic data in agreement with previous report.³ ^1H NMR (CDCl_3 , 400 MHz) δ_{H} 9.32 (s, 1 H), 8.22 (s, 1 H), 8.05 (d, $J = 6.8$ Hz, 1 H), 7.71 (br. s, 1 H), 7.42-7.34 (m, 4 H), 7.21-7.04 (m, 7 H), 6.64 (s, 1 H), 6.06 (s, 1 H), 5.25 (d, $J = 12.4$ Hz, 1 H), 4.97 (d, $J = 12.0$ Hz, 1 H), 4.00 (dd, $J = 9.6, 7.2$ Hz, 1 H), 3.40 (dd, $J = 12.8, 10.0$ Hz, 1 H), 2.95 (dd, $J = 12.8, 6.8$ Hz, 1 H), 2.86 (d, $J = 4.8$ Hz, 3 H), 1.37 (s, 9 H).

(2R,3aR,8aS)-8-benzyl-1-tert-butyl-2-methyl-3a-(3-((S)-2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-1H-indol-2-yl)-3,3a-dihydropyrrolo[2,3-b]indole-1,2,8(2H,8aH)-tricarboxylate (14)—According to General Procedure B, bromopyrroloindoline **19** (1.1 g, 2.0 mmol), $\text{LiB}(\text{cat})_2$ (0.93 g, 4.0 mmol), Boc-tryptophan methyl ester (6.3 g, 20 mmol, 10 equiv) and $\text{Ir}(\text{ppy})_2(\text{dtbbpy})\text{PF}_6$ (18 mg, 20 μmol) in dry DMSO (20.0 mL) afforded **14** (0.88 g, 57%) as a white solid after purification by chromatography on SiO_2 (0:100 $\rightarrow$ 1:99 MeOH/ CH_2Cl_2) (12 h reaction time). R_f (8:2, hexanes/EtOAc): 0.16; $[\alpha]_{\text{D}}^{25} = +1.3^\circ$ (c 0.0048, CHCl_3); IR (neat): 3385, 3360,

2980, 1719, 1482, 1456, 1437, 1409, 1367, 1332, 1285, 1214, 1156, 1064, 1021, 752 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ_H 7.81 (br. s., 1 H), 7.64 (d, *J* = 7.6 Hz, 1 H), 7.59 (br. s., 1 H), 7.53 (d, *J* = 7.3 Hz, 1 H), 7.48 (t, *J* = 7.7 Hz, 1 H), 7.16–7.35 (m, 9 H), 6.58 (s, 1 H), 5.45 (d, *J* = 12.5 Hz, 1 H), 5.15 (d, *J* = 8.1 Hz, 2 H), 4.69 (d, *J* = 7.6 Hz, 1 H), 4.16 (m, 1 H), 3.90 (s, 3 H), 3.63 (s, 3 H), 3.27–3.35 (m, 2 H), 3.14 (dd, *J* = 12.7, 6.6 Hz, 1 H), 3.01 (d, *J* = 10.8 Hz, 1 H), 1.47 (d, *J* = 31.8 Hz, 18 H); ¹³C NMR (126 MHz) δ_C 172.95, 172.47, 154.94, 153.23, 141.51, 134.63, 130.05, 129.33, 128.44, 128.02, 127.49, 124.05, 122.41, 119.90, 119.03, 110.94, 107.72, 82.50, 81.56, 79.70, 67.71, 60.39, 59.80, 54.17, 52.40, 52.15, 38.09, 28.57, 28.21, 21.03, 14.20; HRMS (ESI) *m/z* calculated for C₄₂H₄₈N₄NaO₁₀⁺ ([M+Na]⁺) 791.3268, found 791.3254.

(2R,3aR,8aS)-8-benzyl-1-tert-butyl-3a-(3-acetyl-1-methyl-1H-pyrrol-2-yl)-2-(methylcarbamoyl)-3,3a-dihydropyrrolo[2,3-*b*]indole-1,8(2H,8aH)-dicarboxylate (15)—According to General Procedure B, bromopyrroloindoline **19** (0.53 g, 1.0 mmol), LiB(cat)₂ (0.47 g, 2.0 mmol), 1-methyl-3-acetylpyrrole (0.59 L, 5.0 mmol, 5.0 equiv) and Ir(ppy)₂(dtbbpy)PF₆ (9.1 mg, 10.0 μmol) in dry DMSO (10.0 mL) afforded **15** (0.34 g, 60%) as a white solid after purification by chromatography on SiO₂ (1:1 hexanes/EtOAc) (12 h reaction time). *R_f* (1:1 hexanes/EtOAc): 0.16; [α]_D²⁵ = −83.1° (*c* 0.0081, CHCl₃); IR (neat):

3393, 2978, 2930, 1710, 1645, 1547, 1483, 1406, 1378, 1359, 1324, 1284, 1263, 1213, 1151, 1134, 1080, 1065, 1021, 926, 864, 750 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ_H 7.59 (br. s., 1 H), 7.32–7.37 (m, 2 H), 7.06–7.19 (m, 4 H), 6.55 (br. s., 1 H), 6.42 (s, 1 H), 6.21 (br. s., 1 H), 5.30 (d, *J* = 12.2 Hz, 1 H), 5.04 (br. s., 1 H), 3.83 (t, *J* = 7.8 Hz, 1 H), 2.81–2.84 (m, 4 H), 2.69–2.73 (m, 1 H), 2.66 (s, 3 H), 2.41 (s, 3 H), 1.30 (s, 9 H); ¹³C NMR (126 MHz, cdcl₃) δ 194.84, 173.50, 153.33, 142.55, 136.56, 134.35, 132.53, 130.48, 128.65, 128.53, 128.36, 127.90, 127.44, 126.92, 125.34, 124.26, 122.61, 118.69, 112.69, 83.93, 81.07, 67.43, 63.69, 39.11, 29.82, 29.50, 28.35, 28.30, 26.25; HRMS (ESI) *m/z* calculated for C₃₂H₃₆N₄NaO₆⁺ ([M+Na]⁺) 595.2533, found 595.2537.

(2R,3aS,8aS)-8-benzyl-1-tert-butyl-3a-(furan-2-yl)-2-(methylcarbamoyl)-3,3a-dihydropyrrolo[2,3-*b*]indole-1,8(2H,8aH)-dicarboxylate (16)—According to General Procedure B, bromopyrroloindoline **19** (0.53 g, 1.0 mmol), LiB(cat)₂ (0.47 g, 2.0 mmol), furan (0.36 μL, 5.0 mmol, 5.0 equiv) and Ir(ppy)₂(dtbbpy)PF₆ (9.1 mg, 10.0 mol) in dry DMSO (10.0 mL) afforded **16** (0.22 g, 42%) as a white solid after purification by chromatography on SiO₂ (7:3, hexanes/acetone) (5 h reaction time). *R_f* (7:3, hexanes/acetone): 0.27; [α]_D²⁵ = +9.6° (*c* 0.0065, CHCl₃); IR (neat): 3309, 2980, 1713, 1664, 1562,

1481, 1464, 1407, 1367, 1353, 1327, 1287, 1269, 1215, 1157, 1081, 1052, 1028, 980, 910, 857, 750 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ_H 7.60 (br. s., 1 H), 7.23–7.30 (m, 8 H), 7.05–7.08 (m, 1 H), 6.40 (s, 1 H), 6.15 (s., 2H), 5.77 (s, 1 H), 5.38 (d, *J* = 12.5 Hz, 1 H), 5.11 (d, *J* = 12.5 Hz, 1 H), 3.84–3.87 (m, *J* =, 1 H), 2.75 (s, *J* = 4.9 Hz, 5 H), 1.35 (s, 9 H); ¹³C NMR (126 MHz, cdcl₃) δ 172.22, 153.47, 152.70, 142.76, 141.54, 136.05, 133.03, 129.29, 128.47, 128.03, 127.71, 124.37, 123.72, 118.03, 110.20, 107.05, 81.24, 80.88, 67.59, 61.35, 55.32, 37.10, 28.17, 28.12, 26.30, 26.26; HRMS (ESI) *m/z* calculated for C₂₉H₃₁N₃NaO₆⁺ ([M+Na]⁺) 540.2111, found 540.2109.

(2R,3aS,8aS)-8-benzyl-1-tert-butyl-2-(methylcarbamoyl)-3a-(2-oxoethyl)-3,3a-dihydropyrrolo[2,3-b]indole-1,8(2H,8aH)-dicarboxylate (17)—According to the General Procedure B, bromopyrroloindoline **19** (0.53 g, 1.0 mmol), LiB(cat)₂ (0.47 g, 2.0 mmol), butyl vinyl ether (0.65 μ L, 5.0 mmol, 5.0 equiv) and Ir(ppy)₂(dtbbpy)PF₆ (9.1 mg, 10.0 μ mol) in dry DMSO (10.0 mL) afforded **17** (0.35 g, 71%) as a white solid after purification by chromatography on SiO₂ (7:3, hexanes/acetone) (12 h reaction time). *R_f*(7:3, hexanes/acetone): 0.17; [α]_D²⁵ = +33.9° (*c* 0.0073, CHCl₃); IR (neat): 3347, 2980, 2930,

1716, 1559, 1481, 1464, 1409, 1355, 1330, 1269, 1213, 1154, 1035, 912, 752 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ _H 9.59 (s, 1 H), 7.60 (d, *J* = 7 Hz, 1 H), 7.35 (d, *J* = 7.2 Hz, 2 H), 7.33-7.39 (m, 4 H), 7.24-7.28 (m, 4 H), 7.07 (t, *J* = 7.5 Hz, 1 H), 6.17 (s, 1 H), 5.77 (br. s., 1 H), 5.41 (d, *J* = 12.2 Hz, 1 H), 5.22 (d, *J* = 12.0 Hz, 1 H), 3.81 (dd, *J* = 9.7, 7.0 Hz, 1 H), 2.77-2.89 (m, 3 H), 2.32 (dd, *J* = 13.0, 10.0 Hz, 1 H), 1.37 (s, 9 H); ¹³C NMR (126 MHz, cdcl₃) δ 199.14, 172.84, 153.61, 141.06, 136.04, 134.35, 129.20, 128.65, 128.60, 128.41, 128.31, 128.10, 124.39, 123.98, 117.77, 81.36, 67.96, 61.31, 52.32, 49.84, 37.71, 28.25, 26.34; HRMS (ESI) *m/z* calculated for C₂₇H₃₁N₃NaO₆⁺ ([M+Na]⁺) 516.2111, found 516.2108.

C3–C2' (–)-gliocladin C Synthesis (5aS,10bR,11aR)-benzyl-10b-(1H-indol-2-yl)-2-methyl-1,3,4-trioxo-3,4,5a,10b,11,11a-hexahydro-1H-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-6(2H)-carboxylate (20)—Trimethylsilyl iodide (0.19 mL, 1.4 mmol, 2.0 equiv) was added dropwise to a solution of **19** (0.37 g, 0.68 mmol, 1.0 equiv) in MeCN (10 mL) at 0 °C. The reaction mixture was stirred for 45 min at 0 °C and then quenched with sat NaHCO₃(aq) and stirred for an additional 0.5 h at 23 °C, followed by extraction with CH₂Cl₂ (3 $\times$ 25 mL). Combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and were concentrated under reduced pressure. The residue was purified by flash column chromatography on SiO₂ (3:7 hexanes/EtOAc) to yield the 2° amine (300 mg, 95%) as yellow solid. *R_f*(1:1, hexanes/EtOAc): 0.17. The 2° amine (0.33 g, 0.71 mmol, 1.0 equiv) was dissolved in CH₂Cl₂ and cooled to 0 °C. To this was added Et₃N (0.3 mL, 2.1 mmol, 3.0 equiv) and ClCOCO₂Et (0.16 mL, 1.4 mmol, 2.0 equiv). The mixture was stirred 1 h before quenching with 10 mL 1 N HCl. The mixture was extracted 4 X with CH₂Cl₂ and the combined organic phases were washed with 40 mL sat. NaHCO₃ (aq), dried over anhydrous Na₂SO₄, filtered, and were concentrated. Two major products are observed on TLC (6:4 hexanes/EtOAc), a non-polar compound (*R_f* = 0.31) and a polar compound (*R_f* = 0.06). Upon flash chromatography on SiO₂ (6:4 hexanes/EtOAc) the polar compound converts to the more non-polar compound to yield **20** (0.21 g, 57%) as a yellow solid upon one additional flash. [α]_D²⁵ = +120.0° (*c* 0.00027, CHCl₃); IR (neat): 3346,

3058, 2917, 2849, 1691, 1600, 1482, 1455, 1417, 1396, 1366, 1316, 1277, 1205, 1149, 1051, 1024, 752 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ _H 8.69 (br. s., 1 H), 7.84 (d, *J* = 7.83 Hz, 1 H), 7.747 (d, *J* = 7.63 Hz, 1 H), 7.29 - 7.38 (m, 3 H), 7.16-7.26 (m, 5H), 7.02-7.10 (m, 3H), 6.83 (s, 1 H), 6.28 (s, 1 H), 5.18 (d, *J* = 11.93 Hz, 1 H), 5.03 (d, *J* = 11.93 Hz, 1 H), 4.37 (dd, *J* = 10.76, 6.46 Hz, 1 H), 3.23 (s, 3 H), 3.09 - 3.12 (m, 2 H); ¹³C NMR (126 MHz, cdcl₃) δ 166.89, 157.72, 152.55, 151.00, 142.45, 137.10, 136.96, 135.58, 130.71, 130.44, 128.91, 128.73, 128.59, 128.48, 127.78, 124.93, 124.91, 122.73, 120.68, 120.38, 116.36,

111.33, 101.67, 81.49, 68.41, 59.73, 54.38, 43.40, 27.51; HRMS (ESI) m/z calculated for $C_{30}H_{24}N_4NaO_5^+$ ($[M+Na]^+$) 543.1644, found 543.1652.

(5aS,10bR)-benzyl-10b-(1H-indol-2-yl)-2-methyl-1,3,4-trioxo-3,4,5a,10b-tetrahydro-1H-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-6(2H)-carboxylate (21)—

Triketopiperazine **20** (0.11 g, 0.22 mmol, 1.0 equiv) and 10 wt.% Pd/C (0.11 g) were refluxed in toluene (3.0 mL) for 5 d. The mixture was filtered over Celite and purified by flash chromatography on SiO_2 (6:4 hexanes/EtOAc) to yield **21** (63 mg, 56%) as a white solid. R_f (8:2, hexanes/EtOAc): 0.32; $[\alpha]_{25}^D = -57.5^\circ$ (c 0.0007, $CHCl_3$); IR (neat): 3338,

3063, 2925, 2852, 1719, 1685, 1599, 1480, 1455, 1409, 1335, 1309, 1230, 1155, 1083, 1052, 1027, 752 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ_H 7.95 d, $J = 8.22$ Hz, 1H), 7.85 (br. s., 1 H), 7.55 (d, $J = 7.9$ Hz, 1 H), 7.39 - 7.43 (m, 3 H), 7.27-7.30 (m, 3 H), 7.10-7.24 (m, 5 H), 6.84 (s, 2H), 6.37 (s, 1H), 5.25-5.36 (m, 2 H), 3.33 (s, 3 H); ^{13}C NMR (176 MHz, $cdcl_3$) δ 156.90, 156.28, 152.87, 149.40, 141.64, 136.79, 135.31, 135.00, 132.87, 130.54, 130.36, 129.13, 128.70, 128.66, 128.06, 125.29, 124.75, 124.35, 123.29, 121.03, 120.84, 117.85, 111.36, 102.61, 102.60, 84.61, 69.22, 59.16, 27.65; HRMS (ESI) m/z calculated for $C_{30}H_{22}N_4O_5^+$ ($[M+H]^+$) 519.1668, found 519.1663.

(5aR,10bR)-10b-(1H-indol-2-yl)-2-methyl-5a,6-dihydro-1H-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,3,4(2H,10bH)-trione (C3-C2' (-)-gliocladin C, (18)—

Cbz-amine **22** (50 mg, 96 μmol , 1.0 equiv) was placed in a flame dried round bottom flask, dissolved in CH_2Cl_2 (19 mL), and cooled to -78°C . To this solution was added a solution of 1M BCl_3 in CH_2Cl_2 (0.29 mL 0.29 mmol, 3.0 equiv). The reaction mixture was stirred for 12 h (during the reaction time the flask was allowed to warm to room temperature) and then quenched with sat. $NaHCO_3$ (aq). To this solution was added 75 mL of $CHCl_3$ and the mixture was stirred for an additional 12 h at rt. The suspension was extracted ($2 \times 25\text{ mL } CHCl_3$) and washed with brine, dried over anhydrous Na_2SO_4 , filtered and was concentrated under reduced pressure. The residue was purified by flash column chromatography on SiO_2 (7:3 hexanes/EtOAc), providing **18** (37 mg, 97%) as yellow solid. R_f (1:1, hexanes/EtOAc): 0.35; $[\alpha]_{25}^D = -17.0^\circ$ (c 0.005, $CHCl_3$); IR (neat): 3340, 2958, 1735, 1682, 1638, 1602, 1483,

1455, 1429, 1345, 1310, 1250, 1144, 1113, 1066, 1023, 748 cm^{-1} ; 1H NMR (500 MHz, acetone- d_6) δ_H 10.18 (br. s., 1 H), 7.51 (d, $J = 7.83$ Hz, 1 H), 7.31 (dd, $J = 14.06, 7.95$ Hz, 2 H), 7.14 (t, $J = 7.58$ Hz, 1 H), 7.08 (t, $J = 7.46$ Hz, 1 H), 6.96 - 7.04 (m, 1 H), 6.90 (s, 1 H), 6.73 - 6.85 (m, 2 H), 6.58 (br. s., 1 H), 6.34 (dd, $J = 10.88, 2.08$ Hz, 2 H), 3.25 (s, 3 H); ^{13}C NMR (101 MHz, acetone- d_6) δ_C 158.5, 158.0, 150.8, 150.3, 139.5, 138.3, 133.7, 130.3, 129.2, 129.1, 125.8, 125.0, 122.7, 121.2, 120.5, 120.0, 112.2, 111.0, 101.3, 84.8, 61.8, 27.2; HRMS (ESI) m/z calculated for $C_{22}H_{16}N_4O_3^+$ ($[M+H]^+$) 385.1301, found 385.1311.

Supplementary Material

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Acknowledgments

The authors thank Dr. Joel Beatty, and Dr. Irene Bosque for their helpful discussions and suggestions. This work was partially funded by the Boston University Undergraduate Research Opportunities Program. Financial support for this research from the NIH-NIGMS (R01-GM096129), the Camille Dreyfus Scholar Award Program, Eli Lilly, Novartis, Boston University and the University of Michigan is gratefully acknowledged.

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Figure 1.
Off-cycle reactivity with trialkyl amine reductive quenchers

Figure 2.
Comparison of reductive quenchers

Figure 3.
Improved key step towards gliocladin C and its analogues

Figure 4.
Proposed mechanism

Scheme 1.
Malonate coupling scope

Scheme 2.
Bromopyrroloindoline coupling scope

Scheme 3.
Total synthesis of C3-C2' unnatural gliocladin C 18