Bu_3SnH-mediated cyclopropyl radical cyclizations onto indole-3-carbaldehyde

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Abstract

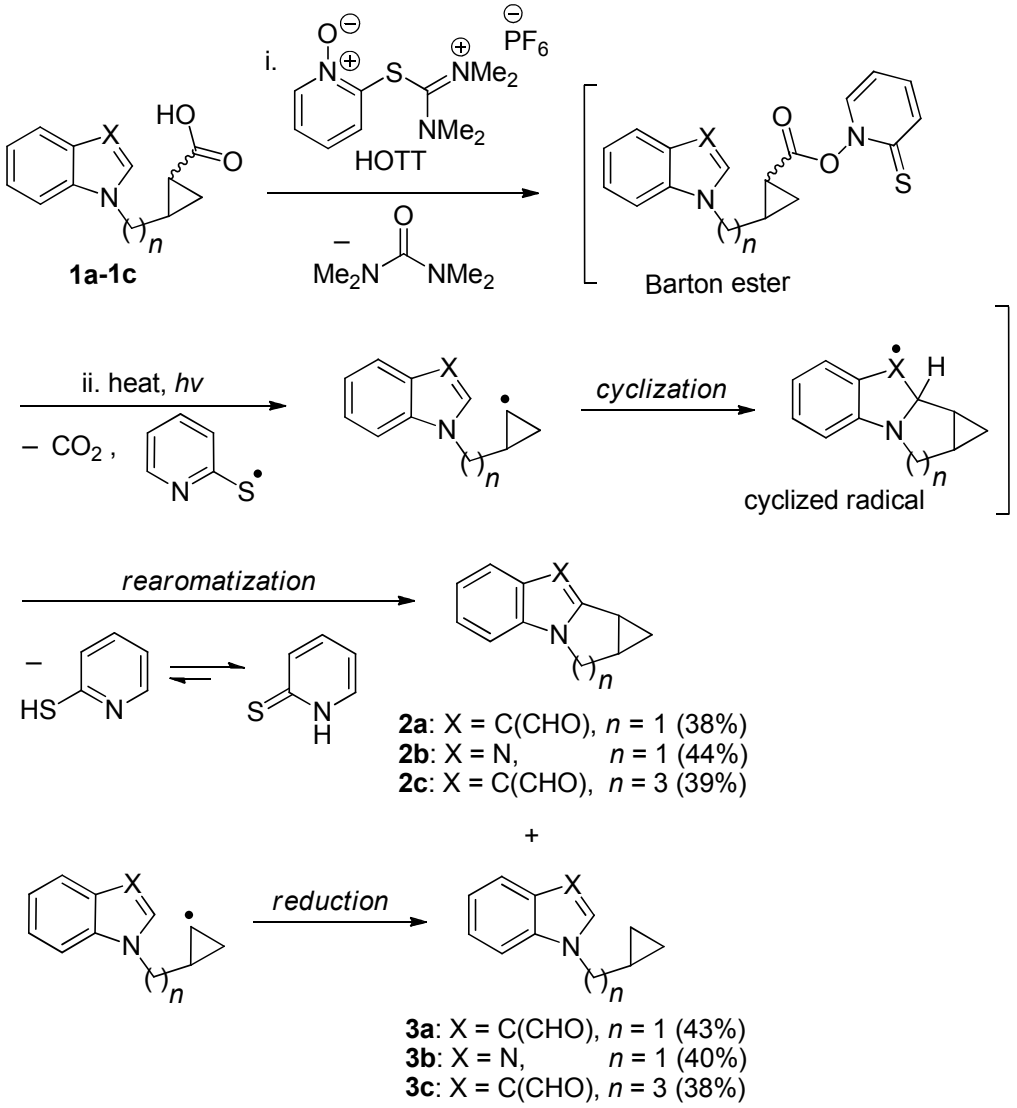
1-[ω-(2-Bromocyclopropyl)alkyl]-1*H*-indole-3-carbaldehydes and benzimidazole analogues were obtained in ~80% yield via the decomposition of Barton ester intermediates. The bromo-indolecarbaldehydes were precursors for Bu_3SnH-mediated five- and seven-membered cyclopropyl radical intramolecular aromatic substitutions giving cyclopropane-fused adducts in ~55% yields. The cyclization yields are greater than via the direct decomposition of the Barton esters. X-ray crystal structures of 1-[(2-bromocyclopropyl)-*trans*-methyl]-1*H*-benzimidazole, 1,1*a*,2,8*b*-tetrahydrocyclopropa[3,4]pyrrolo[1,2-*a*]indole-8-carbaldehyde and 1,1*a*,2,3,4,10*b*-hexahydrocyclopropa[3,4]azepino[1,2-*a*]indole-10-carbaldehyde are included

Keywords: Aromatic substitution, Barton esters, cyclopropane, radicals, mitomycins

Introduction

Recently, we reported the first radical cyclizations to give cyclopropane-fused heterocycles, as shown in Scheme 1.[1] Initiator-free intramolecular aromatic substitutions of nucleophilic alkyl and cyclopropyl radicals onto the 2-position of indole-3-carbaldehyde, indole-3-carbonitrile, and benzimidazoles were accomplished. The radicals were generated via the combined thermal and photochemical decomposition of Barton ester {pyridine-2-thione-*N*-oxycarbonyl (PTOC) or *O*-acyl thiohydroxamate}[2] intermediates formed from carboxylic acids using the Garner coupling reagent, HOTT (*S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium hexafluorophosphate).[3] All six-membered radical cyclizations were high yielding (~80%), but the more challenging five and seven-membered cyclizations were found to give lower yields (<50%), with the exception of (i) the five-membered alkyl and cyclopropyl radical cyclizations onto indole-3-carbonitrile, which occurred in 75 and 78% yields respectively, and (ii) the seven-membered alkyl radical cyclization onto indole-3-carbonitrile gave a 61% yield. The structures of the indole five-membered cyclization adducts correspond to the skeleton of Moody's cyclopropamitosene, a hypoxic tumor cell selective cytotoxin,[4] which was previously prepared using intramolecular 1,3-

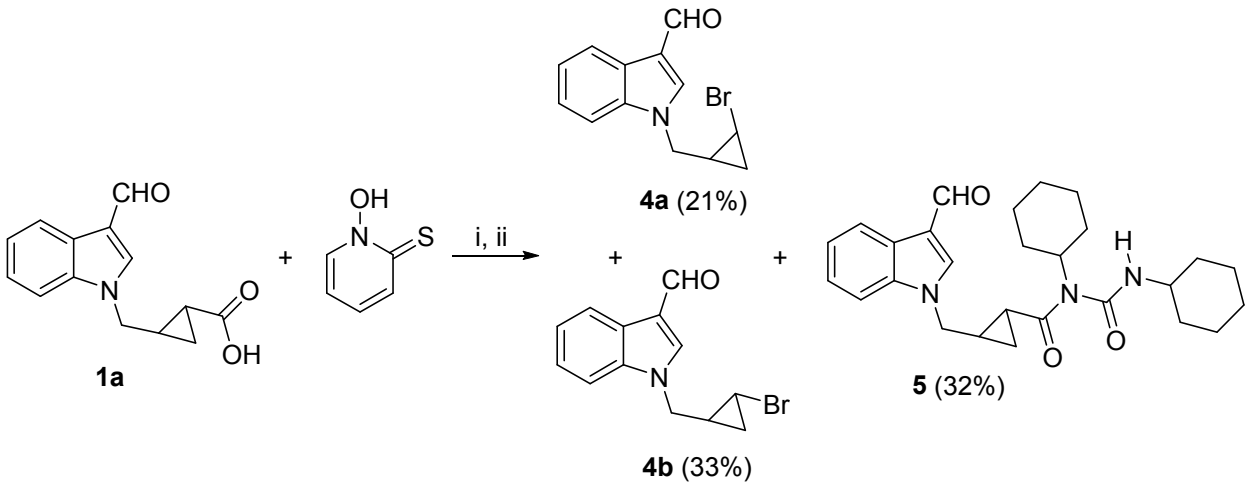
dipolar [3+2] cycloaddition methodology.[5] In this article, we disclose that yields for formation of five- and seven-membered rings using cyclopropyl radical cyclizations onto indole-3-carbaldehyde are greater when using the conventional Bu_3SnH and AIBN (2,2'-azobis(2-methylpropionitrile)) protocol for intramolecular aromatic substitutions from bromide precursors.[6,7] The synthesis of new cyclopropyl bromide radical precursors formed via the decomposition of Barton esters is detailed, as well as our initial investigations into optimizing the conversions of carboxylic acids **1** to Barton esters.



Scheme 1. One-pot Barton ester formation and initiator-free radical cyclizations; only yields for constrained cyclopropyl radical cyclizations of concern to this article are shown. *Reagents & conditions*: i, HOTT (1.5 equiv.), Et_3N (3 equiv.), THF-MeCN 3:1 (0.1 M), rt, dark, 40 min; ii, MeCN (0.01 M), reflux, 2 x 100 W, 6 h. DMAP (0.1 equiv.) & camphorsulfonic acid (4 equiv.) added to cyclizations onto benzimidazole **1b**.[1]

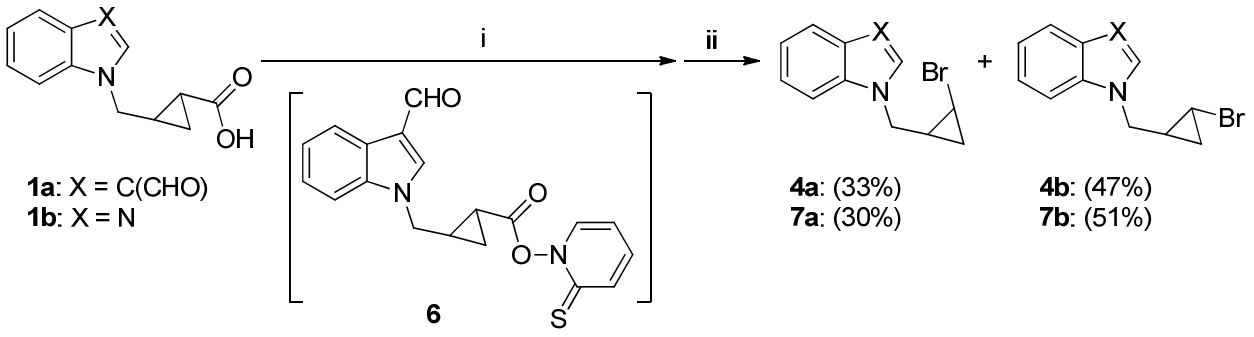
Results and Discussion

The inherent light and hydrolytic sensitivity of the required Barton esters led to difficulty in the clean isolation of these intermediates. As the starting carboxylic acid can be recovered upon inefficient decarboxylation and subsequent hydrolysis of the intermediate Barton ester, it was decided to test the efficiency of the Barton ester formation and radical decarboxylation by carrying out reactions in the presence of a large excess of bromotrichloromethane (~50 equiv.). The resulting cyclopropyl bromides were then utilized as precursors for investigating the Bu_3SnH-mediated five- and seven-membered radical cyclization reactions onto indole-3-carbaldehyde and benzimidazole. Many of the established methods for forming Barton esters were surveyed including generating the acid chloride and mixed anhydride,[8] and the Bu_3P and 2,2'-dithiopyridine *N*-oxide method reported for other three-membered radical cyclizations onto indole.[9] However, only two methods were found to be successful in allowing reasonable conversion of the carboxylic acid into the Barton ester. The first method was the traditional DCC-mediated coupling, which allowed acid **1a** to react with *N*-hydroxy-2-pyridinethione (in the absence of light) followed by the trapping of the generated intermediate radical with excess $BrCCl_3$, as shown in Scheme 2. It should be noted that elevated temperatures (chloroform under reflux) were required to facilitate the decarboxylation to cyclopropyl radicals, in agreement with reported slow decarboxylations of Barton esters to high energy aromatic and vinyl radicals.[8] Separable bromide isomers **4a** and **4b** were isolated in 54% overall yield, however *N*-acylurea **5** from the rearrangement of the intermediate *O*-acylisourea was also obtained in 32% yield. The attempted DCC-mediated reaction on the analogous benzimidazole carboxylic acid **1b** using the same conditions (shown in Scheme 2) was unsuccessful, leading to recovery of starting material.



Scheme 2. *Reagents & conditions*: i, DCC, DMAP, $CHCl_3$, rt, dark, 24 h; ii, $BrCCl_3$, $CHCl_3$, reflux, 4 h.

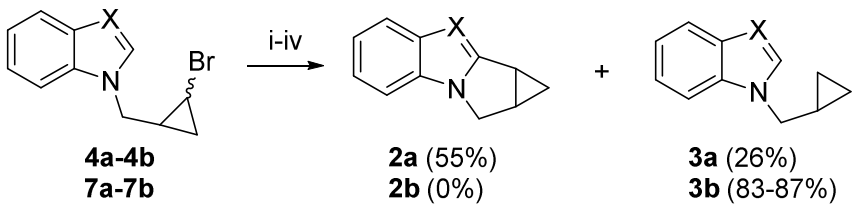
HOTT allowed for easier conversion of carboxylic acids into the Barton esters.[3] Prior to the heating (radical initiation) step, a sample of the **1a** HOTT-reaction was taken as evidence for Barton ester intermediate **6** formation (Scheme 3), and shown to have NMR signals consistent with literature Barton esters (see Experimental Section and Supplementary Material).[10] HOTT allowed the formation of isomeric bromides of indole-3-carbaldehyde **4a** and **4b**, and benzimidazole **7a** and **7b** in superior overall yields (~80%, Scheme 3). The efficiency of Barton ester formation from benzimidazole acid **1b** was optimized by addition of a catalytic amount of DMAP. The *trans*-isomers **4b** and **7b** were found to be the major products, as confirmed using the X-ray crystal structure of the benzimidazole bromide **7b** (Supplementary Material, Figure S1).



Scheme 3. *Reagents & conditions*: i, HOTT, Et_3N, THF-MeCN (3:1), rt, dark, 40 min;[a] ii, $BrCCl_3$, $CHCl_3$, reflux, 4 h.
[a] DMAP (0.1 equiv.) was added to the reaction of **1b**.

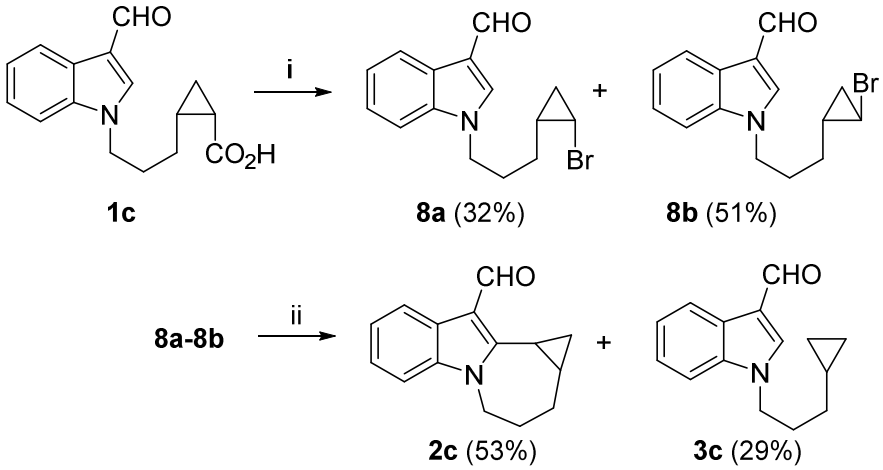
Homolytic aromatic substitutions carried out in the presence of Bu_3SnH and azo-initiator are now thought to proceed via a non-chain mechanism requiring excess initiator.[6] Aromatic substitutions are often improved by exposure to air (oxygen),[7] although no improvements in yield were observed in this case when a non-inert atmosphere was used. After attempting several conditions, we found that cyclization conditions similar to the reported Bu_3SnH-mediated substitution of alkyl radicals onto indole-3-carbaldehyde,[11] provided optimal yields of cyclopropapyrrolo[1,2-*a*]indole-3-carbaldehyde **2a** of 55% along with 26% yield of Bu_3SnH-reduced adduct **3a**, as shown in Scheme 4. This compares favorably to the yield of **2a** derived from the protocol in Scheme 1, where **2a** and **3a** were obtained in 38% and 43% yields respectively,[1] although it should be noted that the Scheme 1 protocol is a direct route from the carboxylic acid **1a**, requiring no prior bromide radical precursor synthesis. The Bu_3SnH-mediated radical cyclization using the benzimidazole analogue bromides **7a**-**7b** was however unsuccessful, although cyclopropapyrrolo[1,2-*a*]benzimidazole **2b** could be obtained via the Scheme 1 protocol in 44% yield together with 40% yield of reduced product **3b**.[1] Radical reduction through hydrogen-abstraction from the reaction solvent is the most likely explanation

for **3b** in the absence of Bu_3SnH. The presence of camphorsulfonic acid (CSA) is necessary to protonate the *N*-3 of the imidazole ring, so activating it towards constrained radical cyclizations.



Scheme 4. *Reagents & conditions* for the steps in the one-pot cyclization protocol: i. Bu_3SnH (1.2 equiv.), AIBN (1 equiv.) added over 15 min, toluene, reflux; ii. reflux, 3 h; iii, Bu_3SnH (0.4 equiv.), AIBN (0.3 equiv.) added over 5 min, toluene, reflux; iv, reflux, 15 min. For benzimidazole bromides **7a-7b**, the reaction was carried out with and without added CSA; in both cases only **3b** was recovered in 83-87% yield.

The success of the five-membered cyclopropyl radical cyclization onto indole-3-carbaldehyde led us to investigate the seven-membered analogue, as shown in Scheme 5. Separable bromides **8a** and **8b** were obtained in 83% combined yield from carboxylic acid **1c** via efficient HOTT-mediated Barton ester formation. Using the cyclization conditions in Scheme 4, bromides **8a-8b** were converted into novel cyclopropane-fused adduct 1,1*a*,2,3,4,10*b*-hexahydrocyclopropa[3,4]azepino[1,2-*a*]indole-10-carbaldehyde (**2c**) in 53% yield with 29% reduced cyclopropane **3c** obtained. This compares favorably with yields of 39% and 38% of **2c** and **3c** obtained from carboxylic acid **1c** using the one-pot Barton ester, and radical cyclization protocol in Scheme 1. X-ray crystal structures of cyclopropane-fused adducts **2a** and **2c** show *exo*-diastereomers; the crystal structure of azepino[1,2-*a*]indole **2c** is shown in Figure 1.



Scheme 5. *Reagents & conditions*: i, HOTT, Et_3N, then $BrCCl_3$, $CHCl_3$, reflux (see Scheme 3 for conditions); (ii) Bu_3SnH and AIBN (see Scheme 4 for conditions).

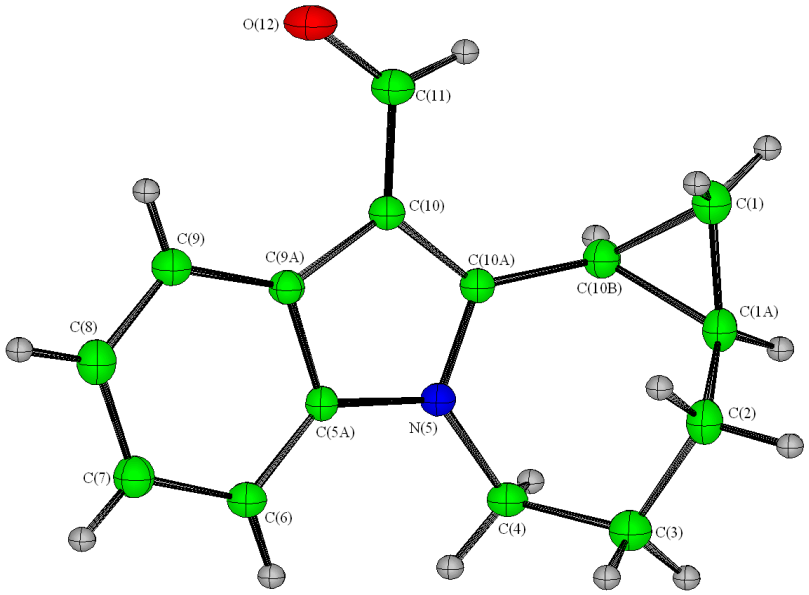


Figure 1. X-ray crystal structure of 1,1*a*,2,3,4,10*b*-hexahydrocyclopropa[3,4]azepino[1,2-*a*]indole-10-carbaldehyde* (**2c**).

The reasons for improved yields using the Bu_3SnH-mediated protocol for radical cyclizations onto indole-3-carbaldehyde remain unclear, and the use of different solvents and temperatures for reactions with and without initiators, makes the drawing of definitive explanations difficult. It is however well-documented that the addition-step of homolytic aromatic substitution (in this case the cyclization) is slow and reversible,[12] and it is plausible that initiator-derived radicals may intercept (or oxidize) the cyclized radical intermediate leading to higher yields of the aromatic substitution product, in comparison to the non-cyclized reduced product. It is noteworthy that the initiators had to be added over a relatively short-time of 5-15 minutes, in order to give the optimized cyclized yields reported. This supports the involvement of azo-initiator derived radicals in the aromatization process due to the rapid breakdown of AIBN at this reaction temperature (AIBN, $t_{1/2} < 2$ min in toluene at 110 °C).[13] The AIBN derived 2-cyano-2-propyl radical may be involved either in hydrogen abstraction from the cyclized radical to give directly the aromatic substitution product (oxidation) and/or via thermal breakdown of cyclized non-aromatic intermediates trapped by the 2-cyano-2-propyl radical.[14] The latter may account for the requirement of prolonged (3 hour) heating of the reaction mixture in toluene under reflux after the addition of most of the initiators was completed, as previously observed in our related radical cyclizations.[7]

Conclusions

To conclude, this work shows that five- and seven-membered cyclopropyl radical cyclizations can be used to access the cyclopropamitosene skeleton, and the ring expanded azepino[1,2-

a]indole analogue in respectable yields. The transformations are another example of "oxidative" aromatic substitutions mediated by the "reductant" Bu_3SnH. Included is a first report of a crystal structure of the cyclopropane-fused azepino[1,2-*a*]indole heterocyclic system. Overall, our radical cyclization pathways via Barton esters compare favorably with alternative cycloaddition protocols to these cyclopropane-fused heterocyclic systems.

Experimental Section

General. All materials were obtained from Sigma-Aldrich. Solvents were purified and dried prior to use according to conventional methods. All reactions were carried out under a nitrogen atmosphere. NaH was obtained as 60% dispersion in oil and used without further purification. Et_3N was distilled over CaH_2 before use. Monitoring of reactions by thin layer chromatography (TLC) was carried out on aluminium-backed plates coated with silica gel (Merck Kieselgel 60 F_{254}). Column chromatography was carried out using Merck Kieselgel silica gel 60 (particle size 0.040-0.063 mm). Melting points were determined on a Stuart Scientific melting point apparatus SMP3. IR spectra were obtained using a Perkin-Elmer Spectrum 1000 FT-IR spectrophotometer with ATR accessory. NMR spectra were recorded using a JEOL GXFT 400 MHz instrument equipped with a DEC AXP 300 computer workstation. Chemical shifts are reported relative to Me_4Si as internal standard and NMR assignments were supported by DEPT and ^1H-^{13}C NMR correlation 2D spectra. Coupling constants (*J*) are expressed in Hertz (Hz). High resolution mass spectra (HRMS) for all compounds were carried out using electrospray ionization (ESI) on a Waters LCT Premier XE spectrometer by manual peak matching. The precision of all accurate mass measurements is better than 5 ppm. The synthesis of 2'-[(3-formyl-1*H*-indol-1-yl)methyl]-*trans*-cyclopropanecarboxylic acid (**1a**), 2'-(1*H*-benzimidazol-1-ylmethyl)-*trans*-cyclopropane carboxylic acid (**1b**), 1,1*a*,2,8*b*-tetrahydrocyclopropa[3,4]pyrrolo[1,2-*a*]indole-8-carbaldehyde (**2a**), 1-(cyclopropylmethyl)-1*H*-indole-3-carbaldehyde (**3a**), 1,1*a*,8,8*a*-tetrahydrocyclopropa [3,4]pyrrolo[1,2-*a*]benzimidazole (**2b**), and 1-(cyclopropylmethyl)-1*H*-benzimidazole (**3b**) are described in our recent publication.[1] The method of Dappen *et al.* using $CuSO_4$-catalyzed decomposition of ethyl diazoacetate in cyclohexane under reflux converted 5-bromopent-1-ene quantitatively to *cis*- and *trans*-isomers of ethyl 2-(3-bromopropyl)cyclopropanecarboxylates, which were separated by column chromatography.[15] HOTT is commercially available, however we preferred to access it using the literature procedure,[3] which in our hands yielded almost 10 g of HOTT in 65% yield from tetramethylchloroformamidinium hexafluorophosphate and *N*-hydroxy-2-pyridinethione.

2′-[3-(3-Formyl-1*H*-indol-1-yl)propyl]-*cis*-cyclopropanecarboxylic acid (1c). Indole-3-carbaldehyde (1.234 g, 8.5 mmol) and NaH (0.224 g, 9.35 mmol) in DMF (25 mL) were heated at 100 °C for 30 min. A solution of ethyl 2-*cis*-(3-bromopropyl)cyclopropanecarboxylate (2.197 g, 9.35 mmol) in DMF (10 mL) was added, and the mixture stirred at room temperature for 16 h.

The mixture was evaporated, dissolved in $CHCl_3$ (50 mL), and washed with water (3 x 25 mL). The organic extract was dried (Na_2SO_4), evaporated and the residue purified by column chromatography using silica gel as adsorbent with a gradient elution of hexanes and EtOAc to yield ethyl *cis*-2′-[3-(3-formyl-1*H*-indol-1-yl)propyl]cyclopropanecarboxylate (1.840 g, 72%) as a yellow oil. R_f 0.51 (hexanes-EtOAc 3:2); IR (ν_{max}, neat/cm^{-1}) 2933, 2249, 1718 (C=O ester), 1659 (C=O aldehyde), 1615, 1578, 1533, 1468, 1402, 1389, 1178, 1136, 1095, 1048. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.92 (1H, ddd, *J* 4.6, 6.9, 6.9, 3′-H), 1.03 (1H, ddd, *J* 4.6, 8.2, 8.2, 3′-H), 1.20 (3H, t, *J* 7.1, CH_3), 1.23-1.26 (1H, m, 2′-H), 1.55-1.71 (3H, m), 1.82-2.00 (2H, m), 4.02-4.08 (2H, m, OCH_2), 4.15 (2H, t, *J* 7.3, NCH_2), 7.29-7.33 (3H, m), 7.69 (1H, s, 2-H), 8.27-8.29 (1H, m, 4-H), 9.97 (1H, s, CHO). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 13.6 (3′-CH_2), 14.4 (CH_3), 18.1, 21.1 (1′,2′-CH), 24.5, 29.9 (CH_2), 47.1 (NCH_2), 60.5 (OCH_2), 110.1 (7-CH), 118.2 (C), 122.2 (4-CH), 123.0, 124.0 (5,6-CH), 125.6 (C), 137.2 (3-C), 138.3 (2-CH), 172.9 (COOEt), 184.6 (CHO). HRMS (ESI) *m/z* (M+H$^+$) calcd for $C_{18}H_{22}NO_3$ 300.1600, found 300.1598. A mixture of the latter ethyl ester (1.734 g, 5.8 mmol) and NaOH (2.5 M, 3.5 mL) in EtOH (30 mL) was refluxed for 4 h. The solution was evaporated, dissolved in water (20 mL), and washed with EtOAc (2 x 100 mL) to remove traces of unreacted ester. The aqueous solution was acidified with HCl (2.8 M) to pH 4, extracted with EtOAc (2 x 30 mL), dried (Na_2SO_4), and evaporated to give the *title compound* **1c** (1.231 g, 78%), as a brown oil. IR ($\nu_{max,}$ neat/cm^{-1}) 1689 (C=O acid), 1651 (C=O aldehyde), 1613, 1575, 1527, 1459, 1396, 1388, 1171, 1133, 1070, 1042. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.94-0.99 (1H, m, 3′-H), 1.11 (1H, ddd, *J* 4.6, 8.0, 8.0, 3′-H), 1.26-1.32 (1H, m), 1.59-1.75 (3H, m), 1.87-1.98 (2H, m), 4.11 (2H, t, *J* 7.3, NCH_2), 7.25-7.33 (3H, m), 7.67 (1H, s, 2-H), 8.26-8.28 (1H, m, 4-H), 9.90 (1H, s, CHO), 10.90 (1H, bs, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.6 (3′-CH_2), 18.0, 22.1 (1′,2′-CH), 24.4, 29.7 (CH_2), 47.0 (NCH_2), 110.2 (7-CH), 118.0 (C), 122.2, 123.1, 124.1 (all CH), 125.5 (C), 137.3 (C), 138.9 (2-CH), 178.9 (COOH), 185.0 (CHO). HRMS (ESI) *m/z* (M+H$^+$) calcd for $C_{16}H_{18}NO_3$ 272.1287, found 272.1284.

DCC-mediated esterification of indole-3-carbaldehyde 1a (Preparation of bromides 4a and 4b). Acid **1a** (0.530 g, 2.18 mmol), DCC (1.100 g, 5.33 mmol), *N*-hydroxy-2-thiopyridone (0.277 g, 2.18 mmol) and DMAP (50 mg, 0.41 mmol) in $CHCl_3$ (10 mL) were stirred in the absence of light for 24 h. The by-product dicyclohexylurea was removed by filtration and to the yellow filtrate $BrCCl_3$ (10 mL, 0.101 mol) in $CHCl_3$ (80 mL) was added. The mixture was heated under reflux for 4 h. The cooled solution was evaporated and purified by column chromatography using silica gel as adsorbent with a gradient elution of hexanes and Et_2O to yield 1-[(2′-bromocyclopropyl)-*cis*-methyl]-1*H*-indole-3-carbaldehyde **(4a)** (0.132 g, 21%), as a yellow oil. R_f 0.43 (Et_2O); IR ($\nu_{max,}$ neat/cm^{-1}) 1651 (C=O), 1612, 1576, 1528, 1485, 1467, 1448, 1399, 1382, 1259, 1174, 1133, 1040. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.87-0.92 (1H, m, 3′-H), 1.40–1.46 (1H, m), 1.47-1.55 (1H, m), 3.18-3.23 (1H, m, 2′-H), 4.27 (1H, dd, *J* 8.3, 14.6, NCH*H*), 4.45 (1H, dd, *J* 5.3, 14.6, NC*H*H), 7.33-7.37 (2H, m), 7.44-7.46 (1H, m, 7-H), 7.95 (1H, s, 2-H), 8.31-8.33 (1H, m, 4-H), 10.01 (1H, s, CHO). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.3 (3′-CH_2), 16.3, 21.8 (1′, 2′-CH), 48.1 (NCH_2), 110.0 (7-CH), 118.5 (C), 122.4 (4-CH), 123.1, 124.2

(5,6-CH), 125.5, 137.4 (C), 138.4 (2-CH), 184.7 (CHO). HRMS (ESI) *m/z* ($M+H^+$) calcd for $C_{13}H_{13}{}^{79}BrNO$ 278.0181, found 278.0171. The second fraction eluted was 1-[(2′-bromocyclopropyl)-*trans*-methyl]-1*H*-indole-3-carbaldehyde **(4b)** (0.198 g, 33%), as a white solid, mp 78-80 ˚C. R_f 0.33 (Et_2O); IR (ν_{max}, neat/cm^{-1}) 1649 (C=O), 1610, 1577, 1528, 1487, 1470, 1444, 1395, 1380, 1307, 1244, 1223, 1168, 1136, 1032. ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.09-1.14 (1H, m, 3′-H), 1.25-1.30 (1H, m, 3′-H), 1.79–1.87 (m, 1H), 2.85 (1H, ddd, *J* 3.9, 3.9, 7.8, 2′-H), 4.14 (2H, d, *J* 6.9, NCH_2), 7.32-7.37 (3H, m), 7.80 (1H, s, 2-H), 8.32-8.34 (1H, m, 4-H), 10.03 (1H, s, CHO). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 15.3 (3′-CH_2), 17.3 (1′-CH), 21.9 (2′-CH), 48.9 (NCH_2), 109.8 (7-CH), 118.7 (C), 122.4 (4-CH), 123.3, 124.3 (5,6-CH), 125.5, 137.4 (C), 137.5 (2-CH), 184.7 (CHO). HRMS (ESI) *m/z* ($M+H^+$) calcd for $C_{13}H_{13}{}^{79}BrNO$ 278.0181, found 278.0174. The third fraction eluted was *N*-cyclohexyl-*N*-[(cyclohexylamino)carbonyl]-2′-*trans*-[(3-formyl-1*H*-indol-1-yl)methyl]cyclopropanecarboxamide **(5)**. (0.314 g, 32%), as a white solid, mp 164-165 ˚C. R_f 0.25 (Et_2O); IR (ν_{max}, neat/cm^{-1}) 3298 (NH), 3050, 2930, 2854, 1692 (C=O amide), 1642 (C=O aldehyde), 1528, 1487, 1466, 1450, 1390, 1340, 1264, 1227, 1179, 1135, 1079. ^1H NMR (400 MHz, $CDCl_3$) δ_H 0.88 (1H, ddd, *J* 4.7, 6.1, 8.4, 3′-H), 1.06-1.38 (9H, m), 1.58-1.90 (13H, m), 1.97-2.05 (1H, m), 3.60-3.67 (1H, m), 3.99-4.04 (1H, m), 4.16 (2H, d, *J* 6.4, NCH_2), 6.62 (1H, bs, NH), 7.27-7.36 (3H, m), 7.78 (1H, s, 2-H), 8.26-8.28 (1H, m, 4-H), 9.96 (1H, s, CHO). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.6 (3′-CH_2), 20.3, 21.5 (1′, 2′-CH), 24.8, 25.4, 25.5, 26.1, 26.2, 31.1, 31.2, 32.7, 32.8 (CH_2), 48.7 (NCH_2), 50.1, 55.6 (NCH), 110.0 (7-CH), 118.5 (C), 122.2 (4-CH), 123.2, 124.3 (5,6-CH), 125.4, 137.5 (C), 137.8 (2-CH), 154.0, 171.4 (C=O), 184.7 (CHO). HRMS (ESI) *m/z* ($M+H^+$) calcd for $C_{27}H_{36}N_3O_3$ 450.2757, found 450.2761.

General procedure for the HOTT-mediated formation of bromides. Et_3N (0.32 mL, 2.30 mmol) in THF (5.7 mL) was added to a mixture of acid **1a-1c** (0.76 mmol) and HOTT (0.424 g, 1.14 mmol) (and DMAP 9.8 mg, 0.08 mmol included for **1b**) in MeCN (1.9 mL). The solution was stirred at room temperature in the absence of light for 40 min. The formation of Barton ester intermediate **6** from the HOTT-mediated coupling with **1a** was confirmed by sampling the mixture also containing 1,1,3,3-tetramethylurea and reaction solvents; ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.27-1.32 (1H, m, 3′-H), 1.71 (1H, ddd, *J* 4.6, 4.6, 9.5, 3′-H), 2.07 (1H, ddd, *J* 4.6, 4.6, 8.7, 1′-H), 2.32-2.41 (1H, m), 4.22 (1H, dd, *J* 6.9, 14.6, NCH*H*), 4.33 (1H, dd, *J* 6.2, 14.6, NC*H*H), 6.63 (1H, dt, *J* 1.7, 6.9, Pyr-5-H), 7.19-7.23 (1H, m), 7.32-7.41 (3H, m), 7.56 (1H, d, *J* 6.9, Pyr-6-H), 7.68 (1H, dd, *J* 1.7, 8.7, Pyr-4-H), 8.01 (1H, s, 2-H), 8.30-8.34 (1H, m, 4-H), 10.06 (1H, s, CHO). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 15.3, 17.7, 23.1, 48.5, 109.7, 112.8 (CH), 118.8 (C), 122.4, 123.2, 124.3, (all CH), 125.3 (C), 133.6 (CH), 137.3 (C), 137.3, 137.5, 137.8 (all CH), 168.4 (C=O), 175.4 (C=S), 184.8 (CHO). $BrCCl_3$ (3.7 mL, 38.00 mmol) in $CHCl_3$ (40 mL) was added, and the solution was heated under reflux for 4 h. The solution was evaporated, dissolved in CH_2Cl_2 (10 mL) and washed with H_2O (2 x 10 mL). The organic extract was evaporated and purified by column chromatography using silica gel as adsorbent with a gradient elution of hexanes and Et_2O.

1-[(2′-Bromocyclopropyl)-*cis*-methyl]-1*H*-benzimidazole (7a) and 1-[(2′-bromocyclo propyl)-*trans*-methyl]-1*H*-benzimidazole (7b) via HOTT-mediated esterification. The *title compound* **7a** (57 mg, 30%) was isolated as a white solid, mp 86-88 °C. R_f 0.39 (Et_2O); IR (ν_{max}, neat/cm^{-1}) 1614, 1494, 1457, 1364, 1330, 1287, 1260, 1214, 1136, 1041. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.87-0.91 (1H, m, 3′-H), 1.39-1.55 (2H, m), 3.16-3.21 (1H, m, 2′-H), 4.32 (1H, dd, *J* 7.8, 14.7, NCH*H*), 4.41 (1H, dd, *J* 5.6, 14.7, NC*H*H), 7.28-7.35 (2H, m), 7.47-7.49 (1H, m, 7-H), 7.82-7.84 (1H, m, 4-H), 8.14 (1H, s, 2-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.4 (3′-CH_2), 16.4, 21.6 (1′, 2′-CH), 46.4 (NCH_2), 109.7 (7-CH), 120.5 (4-CH), 122.4, 123.2 (5,6-CH), 133.8 (C), 143.0 (2-CH), 143.6 (C). HRMS (ESI) *m/z* ($M+H^+$) calcd for $C_{11}H_{12}{}^{79}BrN_2$ 251.0184, found 251.0179. The second fraction eluted was the *title compound* **7b** (97 mg, 51%), as a colorless solid, mp 91-93 °C. R_f 0.29 (Et_2O); IR (ν_{max}, neat/cm^{-1}) 1613, 1491, 1461, 1442, 1393, 1359, 1335, 1270, 1241, 1133, 1042. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.06-1.11 (1H, m, 3′-H), 1.21-1.26 (1H, m), 1.78-1.86 (1H, m, 1′-H), 2.84 (1H, ddd, *J* 3.9, 3.9, 7.7, 2′-H), 4.10 (1H, dd, *J* 6.8, 14.6, NCH*H*), 4.18 (1H, dd, *J* 6.8, 14.6, NC*H*H), 7.28-7.35 (2H, m), 7.40 (1H, d, *J* 7.3, 7-H), 7.83 (1H, d, *J* 7.1, 4-H), 7.95 (1H, s, 2-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 15.3 (3′-CH_2), 17.3, 22.1 (1', 2′-CH), 47.0 (NCH_2), 109.6 (7-CH), 120.6 (4-CH), 122.5, 123.3 (5,6-CH), 133.9 (C), 142.5 (2-CH), 143.9 (C). HRMS (ESI) *m/z* ($M+H^+$) calcd for $C_{11}H_{12}{}^{79}BrN_2$ 251.0184, found 251.0181.

1-[3-(2′-Bromocyclopropyl)-*cis*-propyl]-1*H*-indole-3-carbaldehyde (8a) and 1-[3-(2′-bromocyclopropyl)-*trans*-propyl]-1*H*-indole-3-carbaldehyde (8b). These bromides were prepared using the general HOTT-mediated esterification procedure, which yielded the *title compound* **8a** (74 mg, 32%), as a yellow oil. R_f 0.74 (Et_2O); IR (ν_{max}, neat/cm^{-1}) 2934, 1653 (C=O), 1614, 1576, 1533, 1486, 1469, 1402, 1390, 1258, 1173, 1135. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.50-0.54 (1H, m, 3′-H), 0.79–0.89 (1H, m, 1′-H), 1.16-1.22 (1H, m, 3′-H), 1.48-1.55 (1H, m), 1.56-1.66 (1H, m), 1.98-2.16 (2H, m, CH_2), 3.03-3.08 (1H, m, 2′-H), 4.21-4.25 (2H, m, NCH_2), 7.29-7.41 (3H, m), 7.74 (1H, s, 2-H), 8.29-8.31 (1H, m, 4-H), 9.99 (1H, s, CHO). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 15.1 (3′-CH_2), 16.2 (2′-CH), 23.4 (1′-CH), 28.6, 29.2 (CH_2), 47.1 (NCH_2), 110.1 (7-CH), 118.2 (C), 122.3 (4-CH), 123.0, 124.1 (5,6-CH), 125.5, 137.3 (C), 138.2 (2-CH), 184.6 (CHO). HRMS (ESI) *m/z* ($M+H^+$) calcd for $C_{15}H_{17}{}^{79}BrNO$ 306.0494, found 306.0504. The second fraction eluted was the *title compound* **8b** (0.118 g, 51%), as a yellow oil. R_f 0.70 (Et_2O); IR (ν_{max}, neat/cm^{-1}) 2931, 1656 (C=O), 1614, 1577, 1532, 1469, 1401, 1389, 1245, 1173, 1134, 1037. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.74-0.79 (1H, m, 3′-H), 1.03 (1H, ddd, *J* 3.7, 6.2, 9.8, 3′-H), 1.18-1.26 (1H, m, 1′-H), 1.31-1.37 (2H, m, CH_2), 2.00–2.08 (2H, m, CH_2), 2.56 (1H, ddd, *J* 3.7, 3.7, 7.4, 2′-H), 4.19-4.24 (2H, m, NCH_2), 7.29-7.40 (3H, m), 7.71 (1H, s, 2-H), 8.29-8.32 (1H, m, 4-H), 10.00 (1H, s, CHO). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.0 (3′-CH_2), 19.3 (2′-CH), 22.3 (1′-CH), 29.1, 30.0 (CH_2), 46.8 (NCH_2), 110.1 (7-CH), 118.3 (C), 122.3 (4-CH), 123.1, 124.1 (5,6-CH), 125.6, 137.2 (C), 138.0 (2-CH), 184.6 (CHO). HRMS (ESI) *m/z* ($M+H^+$) calcd for $C_{15}H_{17}{}^{79}BrNO$ 306.0494, found 306.0493.

General procedure for Bu_3SnH-mediated radical cyclizations. Preparation of 1,1a,2,3,4,10*b*-hexahydrocyclopropa[3,4]azepino[1,2-*a*]indole-10-carbaldehyde (2c). A

solution of Bu_3SnH (0.116 mL, 0.431 mmol) and AIBN (60 mg, 0.360 mmol) in toluene (4.6 mL) was added to a solution of bromides **8a-8b** (0.110 g, 0.360 mmol) in toluene (3.4 mL) under reflux using a syringe pump over 15 min (**8a-8b** contained an isomeric ratio of **8a** and **8b** identical to the preceding HOTT-mediated esterification). The reaction was stirred under reflux for 3 h, and a further portion of Bu_3SnH (38 μL, 0.141 mmol) and AIBN (20 mg, 0.120 mmol) in toluene (2 mL) was added over 5 min. The reaction was stirred under reflux for 15 min, and the cooled solution evaporated. EtOAc (5 mL), water (5 mL), and excess KF were added, and the mixture stirred overnight. The organic extract was evaporated and purified by column chromatography using silica gel as adsorbant with gradient elution of hexanes and EtOAc to yield the *title compound* **2c** (43 mg, 53%), as a yellow solid, mp 124-125 ^{o}C. R_f 0.29 (hexane-EtOAc 3:7); IR (ν_{max}, neat/cm^{-1}) 1638 (C=O), 1608, 1573, 1535, 1459, 1428, 1368, 1328, 1282, 1252, 1211, 1188, 1168, 1125, 1077. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.32-0.47 (1H, m), 0.68 (1H, q, *J* 5.0, 1-H), 1.23-1.34 (1H, m), 1.45-1.51 (1H, m, 1-H), 1.79-1.94 (2H, m), 2.16-2.27 (2H, m), 4.37-4.53 (2H, m, 4-H), 7.23-7.31 (3H, m), 8.27-8.31 (1H, m, 9-H), 10.31 (1H, s, CHO). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 9.4, 11.6 (CH), 15.6 (1-CH_2), 23.5, 26.7 (CH_2), 41.0 (4-CH_2), 108.8 (6-CH), 115.6 (C), 121.7 (9-CH), 122.5, 123.3 (7,8-CH), 125.2, 135.3, 150.9 (all C), 185.6 (CHO). HRMS (ESI) *m/z* (M+H$^+$) calcd for $C_{15}H_{16}NO$ 226.1232, found 226.1231. The second fraction eluted was *1-(3-cyclopropylpropyl)-1H-indole-3-carbaldehyde* **(3c)** (24 mg, 29%), as a yellow oil. R_f 0.36 (hexane-EtOAc 3:7); IR (ν_{max}, neat/cm^{-1}) 1656 (C=O), 1611, 1605, 1578, 1532, 1467, 1398, 1388, 1257, 1170, 1133. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (-0.01)-0.01 (2H, m), 0.42-0.47 (2H, m), 0.62-0.73 (1H, m), 1.23-1.28 (2H, m), 1.96-2.04 (2H, m), 4.19 (2H, t, *J* 7.3, NCH_2), 7.28-7.38 (3H, m), 7.71 (1H, s, 2-H), 8.28-8.31 (1H, m, 4-H), 9.99 (1H, s, CHO). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 4.5 (2 x CH_2), 10.3 (CH), 29.8, 31.8 (CH_2), 47.0 (NCH_2), 110.0 (7-CH), 118.0 (C), 122.1, 122.8, 123.9 (all CH), 125.5, 137.2 (C), 138.1 (2-CH), 184.5 (CHO). HRMS (ESI) *m/z* (M+H$^+$) calcd for $C_{15}H_{18}NO$ 228.1388, found 228.1380.

Supporting Information available. It contains the X-ray crystal structures of **7b** and **2a**, as well as ^{1}H NMR and ^{13}C NMR spectra of all new compounds. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-936653 for (**7b**), CCDC-936652 for (**2a**), and CCDC-936651 for (**2c**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

We thank the Irish Research Council for Science Engineering and Technology funded by the National Development Plan for awarding an Embark Scholar Award to Karen Fahey, and the College of Science, National University of Ireland Galway for a Postgraduate Scholarship for Robert Coyle.

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