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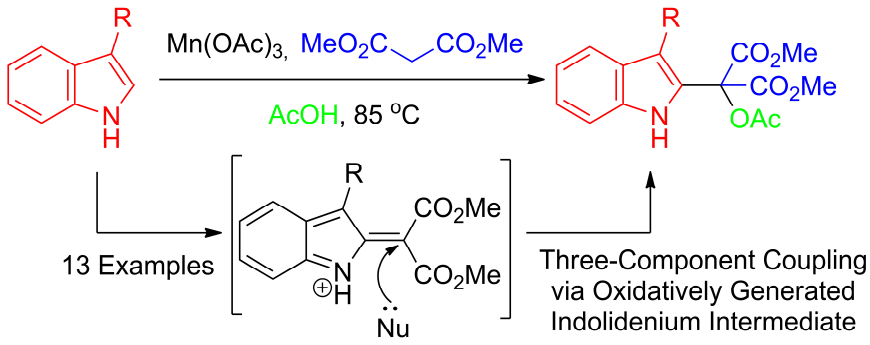

Formation and Trapping of Azafulvene Intermediates Derived from Manganese-Mediated Oxidative Malonate Coupling

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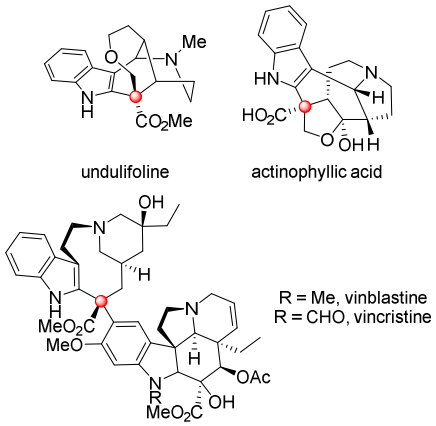
Abstract The one-pot, three-component, coupling reaction of indoles/pyrroles, dimethyl malonate, and acetic acid was performed using Mn(III) acetate as an oxidant. In the presence of $Mn(OAc)_3$, indole-2, and indole-3-carbonyl compounds were alkylated at the 3- and 2- positions, respectively, with subsequent oxidation and nucleophilic capture occurring at the newly formed benzylic carbon. In contrast, oxidation of 2- and 3-indole carboxylic acids afforded the corresponding 2-oxindol-3-ylidenes and 3-oxindol-2-ylidenes. The reaction conditions, scope, and mechanism are discussed herein.

1. Introduction

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**).

Figure 1. Stuctures of indole alkaloid natural products with C2 quaternary centers



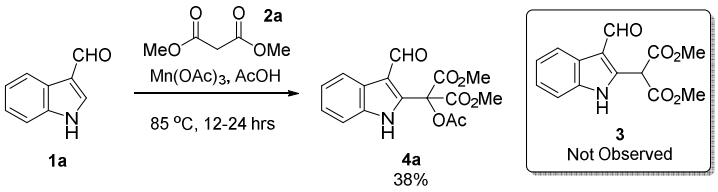
We initially proposed that the congested C2 substituent in many of these natural products could be derived from the coupling of indole with versatile malonate derivatives using Mn(III). Manganese(III) acetate is a single-electron oxidant commonly used in radical-mediated annulations, cyclizations, as well as in the coupling of 1,3-dicarbonyl compounds to alkenes and aromatic systems.[5] Oxidative radical cyclizations mediated by Mn(III) are well established and have been employed as key steps in the synthesis of natural products such as mersicarpine[6] and phloroglucinol.[7] Additionally, in the efforts towards the synthesis of tronocarpine, Kerr and co-workers were able to achieve oxidative cyclization of a wide variety of *N*-tethered dimethyl malonates of indoles, pyrroles, and indolines.[8a,8b-c] Conversely, there exist a limited number of reports involving *inter*molecular arene functionalization utilizing the radical chemistry of Mn(III), most notable being the seminal publications of Citterio and Santi, and Chuang.[9] We herein expand the scope of $Mn(OAc)_3$-mediated arene functionalization to include the successful coupling of unprotected indoles and pyrroles to dimethyl malonate.

2. Results and discussion

Initial efforts focused on accessing oxidatively coupled product **3** via the reaction of dimethyl malonate with indole-3-carboxaldehyde using $Mn(OAc)_3$ (**Scheme 1**). Interestingly, over oxidized, alkylated indole **4a**, derived from nucleophilic capture of the azafulvene indolidenium ion by acetic acid, was isolated in 38% yield with no detectable traces of **3**. Initial reports of malonate radical coupling with arenes describe the identification of over oxidized products, although the application to indole scaffolds has been relatively unexplored.[10] Previous oxidative,

and Lewis acid mediated generation of similar indolidenium intermediates have proven valuable in the synthesis of a number of indole alkaloids.[3f,4l,11]

Scheme 1. Attempted alkylation of indole-3-carboxaldehyde **1a**

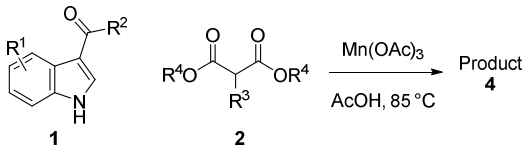


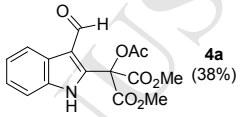
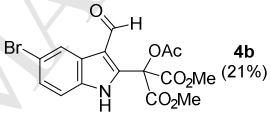
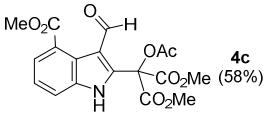
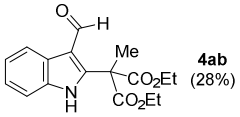
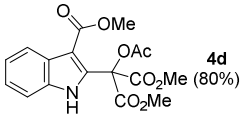
We attempted to further optimize the oxidative coupling reaction by investigating the effects of solvent, temperature, concentration, order of substrate addition, as well as the addition of co-oxidants; however, all attempts failed to significantly improve the overall yield. The best results were obtained from slow and simultaneous addition of substrates **1a** and **2a** over a period of 4–6 hours to a slurry of $Mn(OAc)_3$ in AcOH at 85 °C.[12] Full conversion of the indole starting material is observed after an additional 12 hours of stirring; however, undesirable by-products such as malonate dimers are also formed during the extended reaction time.

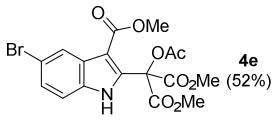
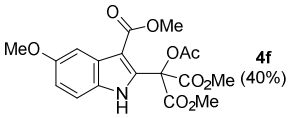
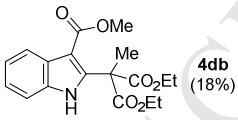
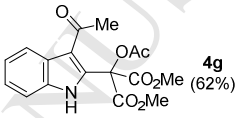
Exploring the scope of indole substitution, the optimized conditions were applied to a number of 4- and 5-substituted indole-3-carboxaldehyde compounds (**Table 1**, entries 1–3). In general, substitution lowered the yield and resulted in the formation of multiple unidentified side products. The scope of the dicarbonyl compound was also explored by reacting **1a** with diethyl methyl malonate **2b** (entry 4) providing the 2-quaternary-substituted indole **4ab** in 28% yield. We were pleased to observe a significantly improved yield of 80% when 3-carbomethoxy substituted indole **1d** was used (**Table 1**, entry 5). Again, substitution on the indole benzene unit was tolerated for compounds **1e–f** but did not provide better overall results (entries 6–7). When ester-substituted indole **1d** was reacted with tertiary malonate **2b** there was a decrease in yield similar to that observed previously with the aldehyde-substituted substrate **1a** (entry 8) as the oxidative coupling adduct (**4db**) was isolated in a modest 18% yield. It is interesting to note that nitrogen protection of indoles **1d–f** with a pivaloyl group did not increase the conversion to oxidatively coupled products and instead resulted in 80% recovery of deprotected starting

material. Finally, the reaction of 3-acetylindole also gave good yields of the oxidatively coupled product, (**4g**, **Table 1**, entry 9).

Table 1. Scope of Mn(III)-mediated oxidative coupling with 3-indole (**1**)[a]



Entry	**1** (R^1, R^2)	**2** (R^3, R^4)	Product (% Yield)[b]
1	**1a** (H, H)	**2a** (H, Me)	 **4a** (38%)
2	**1b** (5-Br, H)	**2a** (H, Me)	 **4b** (21%)
3	**1c** (4-CO_2Me, H)	**2a** (H, Me)	 **4c** (58%)
4	**1a** (H, H)	**2b** (Me, Et)	 **4ab** (28%)
5	**1d** (H, OMe)	**2a** (H, Me)	 **4d** (80%)

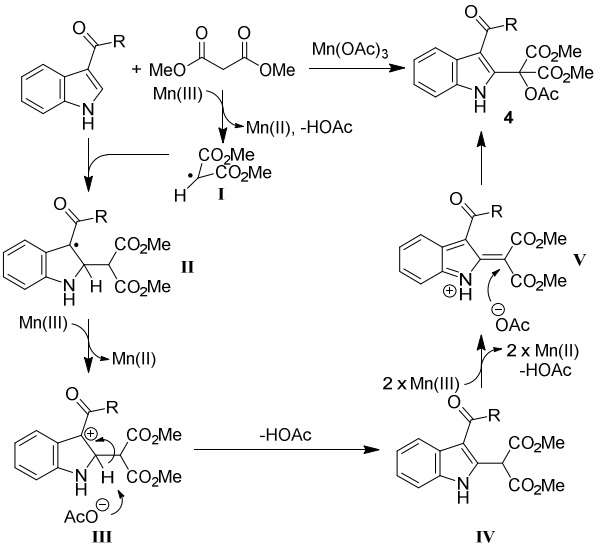
6	**1e** (5-Br, OMe)	**2a** (H, Me)	 **4e** (52%)
7	**1f** (5-OMe, OMe)	**2a** (H, Me)	 **4f** (40%)
8	**1d** (H, OMe)	**2b** (Me, Et)	 **4db** (18%)
9	**1g** (H, Me)	**2a** (H, Me)	 **4g** (62%)

[a] Reactions were performed by tandem slow addition of indoles **1**(1 equiv.) and malonates **2** (2 equiv.) over 5 h to a stirred slurry of $Mn(OAc)_3 \bullet 2H_2O$ (6 equiv.) in AcOH at 85 °C.

[b] Isolated yield.

A proposed mechanism for the formation of indole coupled products **4** is illustrated in **Scheme 2**. First, the Mn(III) enolate formed with the 1,3-dicarbonyl compound undergoes a one-electron oxidation to generate a doubly stabilized radical (**I**). Addition occurs preferentially to the least sterically hindered, non-substituted carbon of the indole 2,3-unsaturation. Subsequent oxidation by Mn(III) and acetate-mediated proton transfer rearomatizes the indole scaffold. The dialkyl arylmalonate product can again undergo rapid Mn(III)-mediated enolization and oxidation affording an indolidenium intermediate (**V**) that is ultimately trapped by acetate, furnishing the observed products, **4**.

Scheme 2. Proposed mechanism for the formation of **4**

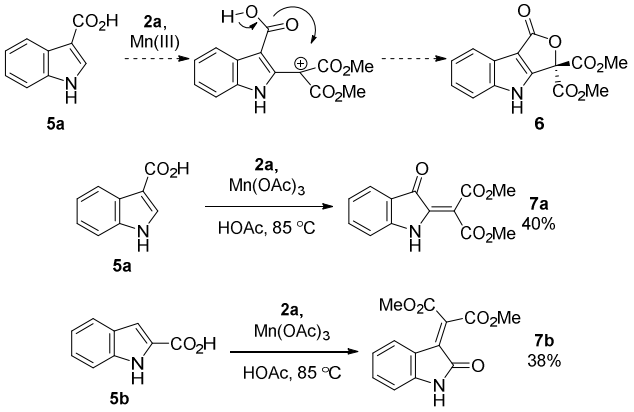


Overall, the ease of product formation seems to correlate with the ability of each substrate to stabilize the benzylic radical intermediate (**II**, **Scheme 2**). This is evidenced by the difference in yield that occurs when the 3-substituent on the indole decreases in electron-withdrawing ability, proceeding from the 3-formyl- (**4a**, 38%), to the 3-acetyl- (**4g**, 62%), to the 3-methylcarboxy- (**4d**, 80%) substituted indole. Substitution on the indole carbocycle seems to have a lesser effect, with no clear trend progressing from electron deficient to electron rich indole substrates.

During the course of the reaction, as outlined in **Scheme 2**, over oxidation occurs at the benzylic carbon, which is subsequently trapped by an external acetate nucleophile. Given this sequence of events, it was postulated that oxidative cyclization may compete with acetoxylation on a substrate such as indole-3-carboxylic acid (**5a**), which contains a pendant oxygen nucleophile able to form lactone **6** (**Scheme 3**). Surprisingly, upon the reaction of carboxylic acid **5a** and malonate **2a** in the presence of $Mn(OAc)_3$, no traces of cyclized product were detected and instead 3-oxindole-2-ylidene **7a** was obtained in 40% yield. Gribble and co-workers recently reported a similar transformation in which $Mn(OAc)_3$-mediated oxidative coupling of 2-nitroindole and dimethyl malonate led to the formation of the corresponding 2-oxoindolin-3-ylidene (**7b**) via an in situ Nef reaction.[13] Interestingly, the authors report failing to observe the 3-oxoindolin-2-ylidene (**7a**) when 3-nitroindole was used as substrate, rationalizing this result as the lack of a captodative stabilizing effect at C3 of the radical intermediate of 3-nitroindole. Testing the developed oxidative $Mn(OAc)_3$ coupling conditions with indole-2-carboxylic acid

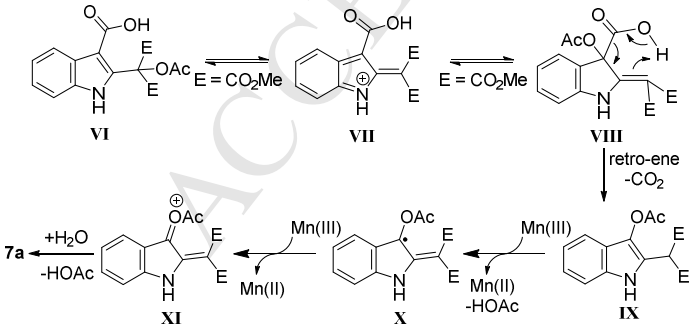
(**5b**) we observed the formation of the same 2-oxindolin-3-ylidene **7b** reported by Gribble and coworkers in 38% yield.

Scheme 3. Oxidative cyclization of **5** to oxindolinylidenes **7**.



The postulated mechanism occurs similarly to that suggested for the formation of **4**, such that the reaction of **5a** and **2a** should first give the directly coupled product with acetate incorporation at the benzylic carbon (**VI**, **Scheme 4**). However, this intermediate can likely undergo a formal [1,3]-acetate migration via nitrogen lone pair-assisted elimination/acetate addition to the indole 3-position. Decarboxylation can then occur via a retro-ene-type mechanism to form a rearomatized acetoxy indole intermediate. Subsequent Mn(III)-mediated oxidations gives the acetyl oxocarbenium ion, which upon water or acetate-mediated cleavage forms product **7a**.

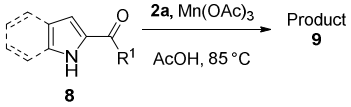
Scheme 4. Proposed mechanism for the formation of **7a**

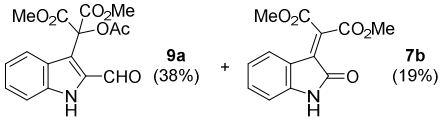
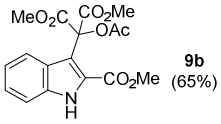
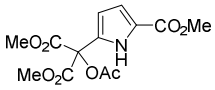
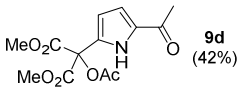


The electronic environment of the intermediate adduct radical (**II**, **Scheme 2**) was further perturbed in order to investigate Gribble's mechanistic hypothesis. Towards this end, the Mn(III)

conditions were applied to a series of heteroaromatic-2-carbonyl compounds **8a–d** (**Table 2**). Gratifyingly, in addition to the functionalization of 2-formyl- and 2-methylcarboxyindole, the reaction conditions were amenable to the oxidative coupling of pyrrole-2-carbonyl derivatives similar to the tertiary malonate coupled products reported by Baciocchi and coworkers.[9e] Both methyl 2-pyrrolecarboxylate and 2-acetylpyrrole gave the 5-alkylated product in good to moderate yields. Neither the 3- or 4-substituted regioisomers were detected by inspection of the ^{1}H NMR. Similar to the previously described indole-3-carbonyl derivatives, the yield of oxidative coupling products correlates to the electron-stabilizing effect of the substituent on C2 of the heteroaromatic moiety.

Table 2. Oxidative coupling with indole- and pyrrole-2-carbonyl compounds (**8**)[a]



Entry	**8** (heteroaromatic, R^1)	Product (Yield %)[b]
1	**8a** (indole, R^1 = H)	 **9a** (38%) + **7b** (19%)
2	**8b** (indole, R^1 = OMe)	 **9b** (65%)
3	**8c** (pyrrole, R^1 = OMe)	 **9c** (78%)
4	**8d** (pyrrole, R^1 = Me)	 **9d** (42%)

[a] Reactions were performed by tandem slow addition of indoles **8** (1 equiv.) and malonates **2** (2 equiv.) over 5 h to a stirred slurry of $Mn(OAc)_3 \cdot 2H_2O$ (6 equiv.) in AcOH at 85 °C.

[b] Isolated yield.

In addition to the arylation/acetoxylation product of the reaction involving indole-2-carboxaldehyde, a 19% yield of 2-oxindol-3-ylidene (**7b**) was observed. We speculate that **7b** forms from the *in situ* oxidation of the aldehyde to the carboxylic acid and the product is therefore prone to further oxidation pathways as proposed previously (**Scheme 3**). Given the highly colored side products observed during purification, it is likely the oxindolylidenes are a common by-product in the reaction of all the indole-carboxaldehyde derivatives studied.

Minimal differences in the yields were obtained from 2- and 3-carbonyl-substituted indoles, though there is a notable disparity in yield between ester-substituted compounds **9b** and **4d**. Whereas Gribble and coworkers found 3-nitroindole to be unaffected by Mn(III) and dimethyl malonate,[13] we found that the less electron withdrawing carbonyl substituents provided the three-component coupling products in moderate to good yields when substituted at C2 or C3 of the indole scaffold. Likely the 3-nitro-substituent significantly impedes the nucleophilicity of the indole core.

3. Conclusions

In summary, we have reported the $Mn(OAc)_3$-mediated oxidative three-component coupling of indole-2-carbonyl, indole-3-carbonyl, and pyrrole-2-carbonyl compounds to dimethyl malonate in acetic acid in moderate to good yields. These oxidative coupling conditions complement the previously reported photoredox-mediated reductive alkylation of indole with bromomalonate derivatives, being tolerant to functional groups sensitive to electron-transfer mediated reduction.[14] The congested indole products formed could be applied further in the synthesis of indole alkaloid products bearing C2 quaternary centers through reversible indolidenium ions and nucleophilic capture.**4. Experimental Section4.1. General experimental methods**

The chemicals and reagents were purchased from Sigma-Aldrich, Merck, Combi-Blocks Inc., Chem-Impex Int'l, AK Scientific, Inc., Strem Chemicals Inc. (Manganese (III) acetate) and used without further purification. Infrared spectra were recorded on a Perkin Elmer BX FT-IR fitted with an ATR accessory. Absorptions are given in wavenumbers (cm-1). High resolution mass spectra were obtained at the University of Michigan Mass Spectrometry Centre on a Waters®

Micromass® AutoSpec Ultima™ high resolution mass spectrometer. Reactions that were monitored by TLC were visualized by a dual short wave/long wave UV lamp and stained with an ethanolic solution of potassium permanganate. Column flash chromatography was performed using 230-400 mesh silica gel or via automated column chromatography. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise noted. ^{1}H and ^{13}C NMR spectra were recorded in both 300 MHz NMR spectrophotometer (Bruker, AVANCE) and a 400 MHz spectrophotometer (JEOL, JNM ECS) in $CDCl_3$ using tetramethylsilane (TMS) as the internal standard and coupling constants are expressed in Hertz. Chemical shifts are reported in ppm.**4.2. Synthetic methods**

All compounds were synthesized according to a general procedure described herein: $Mn(OAc)_3$ (6 mmol) was added to a 250 mL round bottom flask with a 1" magnetic stirbar. The flask was then purged with nitrogen gas. The aromatic heterocycle (1 mmol) and malonate (2 mmol) were weighed out separately and subsequently dissolved in 7 mL of acetic acid (glacial), (If the aromatic heterocycle was slow to dissolve the vial was sonicated to facilitate a homogenous solution). Glacial acetic acid (10 mL) was added to the flask containing $Mn(OAc)_3$ and the purge needle was removed. The flask containing the solution of $Mn(OAc)_3$ was heated to 85 °C using a heating block. Once the target temperature was achieved the two solutions of malonate and heterocycle were added to the manganese solution via syringe pump over the course of 5 hours. Once the addition was complete the solution was heated for a further 12-18 hours until the starting material had been consumed as deemed by TLC.

The solution was cooled to room temperature and the acetic acid was removed on a rotary evaporator. To the brown solid was added water (100 mL) and ethyl acetate (50 mL). The two layers were separated and the aqueous phase was further extracted with ethyl acetate. The

organic phase was washed with water (x2) and brine (x1), dried over Na_2SO_4, filtered, concentrated, and subjected to flash column chromatography. Specifics of characterization and purification are described for each compound.**4.3. Physical and spectroscopic data**

Dimethyl 2-acetoxy-2-(3-formyl-1H-indol-2-yl)malonate 4a (Table 1, entry 1)

Using a gradient eluent from 5% → 40% ethyl acetate in hexanes, 126.6 mg of a white solid was obtained, 38 % yield; R_f: 0.46 (1:1, hexanes:ethyl acetate)

ν max (ATR)/cm^{-1}: 3302, 3180, 2957, 1753, 1636, 1222;

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.87 (1H, s), 10.47 (1 H, s), 8.38 (1H, d, *J* = 7.5 Hz), 7.46 (1H, d, *J* = 7.5 Hz), 7.32 (2H, m), 3.86 (6H, s) and 2.22 (3 H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ 186.2, 169.3, 165.1, 138.4, 134.5, 125.4, 124.9, 123.5, 122.5, 116.2, 111.9, 77.6, 54.4, 20.7.

m/z: (ESI+) HRMS [M+Na] $C_{16}H_{15}NO_7Na^+$: found: 356.0741; calcd: 356.0741.

Dimethyl 2-acetoxy-2-(5-bromo-3-formyl-1H-indol-2-yl)malonate 4b (Table 1, entry 2)

Using a gradient eluent from 5% → 40% ethyl acetate in hexanes, 86.7 mg of a white solid was obtained, 28% yield; R_f: 0.45 (1:1, hexanes:ethyl acetate)

ν max (ATR)/cm^{-1}: 3119, 3068, 3030, 2956, 2850, 2728, 1756, 1631, 1210;

^{1}H NMR (700 MHz, $CDCl_3$) δ 10.97 (1H, s), 10.41 (1H, s), 8.52 (1H, d, *J* = 1.3 Hz), 7.40 (2H, dd, *J* = 8.6, 1.8 Hz), 7.32 (1H, d, *J* = 8.6 Hz), 3.86 (6H, s) and 2.21 (3 H, s).

^{13}C NMR (176 MHz, $CDCl_3$) δ 186.0, 169.3, 164.9, 139.3, 133.2, 127.9, 126.9, 125.1, 117.1, 115.5, 113.4, 77.4, 54.6, 20.7.

m/z: (ESI+) HRMS [M+Na] $C_{16}H_{14}BrNO_7Na^+$: found: 433.9844; calcd: 433.9846.

Dimethyl 2-acetoxy-2-(3-formyl-4-(methoxycarbonyl)-1H-indol-2-yl)malonate 4c (Table 1, entry 3)

Using a gradient eluent from 5% → 40% ethyl acetate in hexanes, 227.0 mg of a white solid was obtained, 58 % yield; R_f: 0.43 (1:1, hexanes:ethyl acetate)

ν max (ATR)/cm^{-1}: 3209, 3023, 2955, 2848, 1765, 1747, 1714, 1642, 1237;

^{1}H NMR (500 MHz, $CDCl_3$) δ 11.02 (1H, s), 10.46 (1H, s), 7.64 (1H, dd, *J* = 7.4, 0.9 Hz), 7.61 (1H, dd, *J* = 8.2, 0.9 Hz), 7.35 (1H, d, *J* = 8.2, 7.5 Hz), 3.98 (3H, s) 3.86 (6H, s) and 2.15 (3 H, s).

^{13}C NMR (176 MHz, $CDCl_3$) δ 186.8, 169.7, 169.2, 165.1, 138.5, 135.1, 126.1, 124.4, 123.8, 121.9, 115.7, 115.6, 77.6, 54.4, 52.3, 20.6.

m/z: (ESI+) HRMS [M+Na] $C_{18}H_{17}NO_9Na^+$: found: 414.0797; calcd: 414.0796.

Diethyl 2-(3-formyl-1H-indol-2-yl)-2-methylmalonate 4ab (Table 1, entry 4)

Using a gradient eluent from 0% → 30% ethyl acetate in hexanes, 88.5 mg of a light orange colored solid was obtained, 28 % yield; R_f: 0.30 (7:3, hexane:ethyl acetate)

ν max (ATR)/cm^{-1}: 3220, 2985, 2940, 1733, 1627, 1201, 1165;

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.75 (1H, s), 10.20 (1H, s), 8.28-8.19 (1H, m), 7.49-7.40 (1H, m), 7.34-7.27 (2H, m), 4.32 and 4.29 (**AB**X_3, 4H, *J* = 10.5, 7.5 Hz), 2.02 (3H, s) and 1.28 (6H, dd, *J* = 7.5 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 184.4, 170.1, 143.6, 133.9, 126.6, 123.8, 123.0, 120.8, 113.8, 111.6, 62.8, 54.2, 25.6, 13.8.

m/z: (ESI+) HRMS [M+Na] $C_{17}H_{19}NO_5Na^+$: found: 340.1158; calcd: 340.1155.

Dimethyl 2-acetoxy-2-(3-(methoxycarbonyl)-1H-indol-2-yl)malonate 4d (Table 1, entry 5)

Using a gradient eluent from 5% → 40% ethyl acetate in hexanes, 290.5 mg of a yellow foam was obtained, 80 % yield; R_f: 0.41 (1:1, hexanes:ethyl acetate)

ν max (ATR)/cm^{-1}: 3353, 2954, 1763, 1748, 1690, 1223;

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.54 (1H, s), 8.11 (1H, d, *J* = 7.8 Hz), 7.44 (1H, d, *J* = 7.7 Hz), 7.27 (2H, m), 3.91 (3H, s), 3.86 (6H, s) and 2.11 (3 H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 165.6, 164.9, 136.8, 133.9, 125.8, 124.0, 122.3, 121.8, 112.0, 105.8, 78.0, 54.2, 51.1, 20.7.

m/z: (ESI+) HRMS [M+Na] $C_{17}H_{17}NO_8Na^+$: found: 386.0846; calcd: 386.0847.

Dimethyl 2-acetoxy-2-(5-bromo-3-(methoxycarbonyl)-1H-indol-2-yl)malonate 4e (Table 1, entry 6)

Using a gradient eluent from 5% → 40% ethyl acetate in hexanes, 230.0 mg of a white solid was obtained, 52 % yield; R_f: 0.41 (1:1, hexanes:ethyl acetate)

ν max (ATR)/cm^{-1}: 3354, 2953, 1763, 1747, 1734, 1697, 1196;

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.59 (1H, s), 8.25 (1H, d, *J* = 1.8 Hz), 7.39 (1H, dd, *J* = 8.7, 1.8 Hz), 7.33 (1H, d, *J* = 8.7 Hz), 3.91 (3H, s), 3.87 (6H, s) and 2.11 (3 H, s).

^{13}C NMR (176 MHz, $CDCl_3$) δ 170.1, 165.5, 164.4, 137.9, 132.4, 127.3, 127.1, 124.5, 115.9, 113.5, 105.4, 77.7, 54.3, 51.3, 20.7.

m/z: (ESI+) HRMS [M+Na] $C_{17}H_{16}BrNO_8Na^+$: found: 453.9952; calcd: 463.9952.

Dimethyl 2-acetoxy-2-(5-methoxy-3-(methoxycarbonyl)-1H-indol-2-yl)malonate 4f (Table 1, entry 7)

Using a gradient eluent from 5% → 40% ethyl acetate in hexanes, 157.4 mg of a white solid was obtained, 40 % yield; R_f: 0.42 (1:1, hexane:ethyl acetate)

ν max (ATR)/cm^{-1}: 3387, 3337, 2952, 1760, 1732, 1701, 1166;

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.46 (1H, s), 7.57 (1H, d, *J* = 2.3 Hz), 7.33 (1H, d, *J* = 8.9 Hz), 6.94 (1H, dd, *J* = 8.9, 2.4 Hz), 3.89 (3H, s), 3.86 (3H, s) 3.85 (6H, s) and 2.10 (3 H, s).

^{13}C NMR (176 MHz, $CDCl_3$) δ 169.9, 165.6, 164.8, 156.0, 136.6, 129.0, 126.8, 114.9, 112.9, 105.4, 102.8, 78.0, 55.7, 54.2, 50.9, 20.7.

m/z: (ESI+) HRMS [M+Na] $C_{18}H_{19}NO_9Na^+$: found: 416.0953; calcd: 416.0952.

Diethyl 2-(3-(methoxycarbonyl)-1H-indol-2-yl)-2-methylmalonate 4db (Table 1, entry 8)

Using a gradient eluent from 0% → 30% ethyl acetate in hexanes, 68.3 mg of a light yellow colored oil was obtained, 18 % yield; R_f: 0.53 (7:3, hexane:ethyl acetate)

ν max (ATR)/cm^{-1}: 3361, 2987, 1730, 1692, 1527, 1441, 1188;

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.46 (1H, s), 8.16-8.09 (1H, m), 7.44-7.38 (1H, m), 7.28-7.22 (2H, m), 4.28 (4H, q, *J* = 7.1 Hz), 3.88 (3H, s), 1.98 (3H, s, *J* = 7.5 Hz), 1.26 (6H, t, *J* = 7.1 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 165.3, 142.7, 133.7, 126.8, 123.0, 122.0, 121.7, 111.5, 104.2, 62.4, 55.3, 50.8, 23.9, 13.9;

m/z: (EI+) HRMS [M+] $C_{18}H_{21}NO_6^+$: found: 347.1375; calcd: 347.1369.

Dimethyl 2-acetoxy-2-(3-acetyl-1H-indol-2-yl)malonate 4g (Table 1, entry 9)

Using a gradient eluent from 5% → 40% ethyl acetate in hexanes, 216.0 mg of a slightly orange colored solid was obtained, 62 % yield; R_f: 0.35 (1:1, hexanes:ethyl acetate)

ν max (ATR)/cm^{-1}: 3328, 2955, 2848, 1752, 1720, 1655, 1224, 1182;

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.70 (1H, s), 7.92-7.84 (1H, m), 7.52-7.45 (1H, m), 7.33-7.24 (2H, m), 3.85 (6H, s), 2.70 (3H, s) 3.85 (6H, s) and 2.09 (3 H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ 194.0, 170.2, 165.6, 136.4, 134.2, 125.1, 123.7, 122.5, 120.7, 114.9, 112.7, 78.4, 54.1, 31.1, 20.7.

m/z: (ESI+) HRMS [M+Na] $C_{17}H_{17}NO_7Na^+$: found: 370.0896; calcd: 370.0897.

Dimethyl 2-(3-oxoindolin-2-ylidene)malonate 7a (Scheme 3)

Using a gradient eluent from 0% → 50% diethyl ether in hexanes, 104.5 mg of bright red colored crystals were obtained, 40 % yield; R_f: 0.26 (1:1, hexane:diethyl ether)

ν max (ATR)/cm^{-1}: 3343, 2990, 2958, 2840, 1744, 1681, 1597, 1188;

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.17 (1H, s), 7.63 (1H, d, *J* = 7.6 Hz), 7.49 (1H, app t, *J* = 7.7 Hz), 6.99 (1H, app t, *J* = 7.5 Hz), 6.92 (1H, d, *J* = 8.0 Hz), 3.92 (3H, s), and 3.83 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ 185.6, 166.4, 165.3, 152.1, 142.8, 137.6, 125.7, 122.3, 119.8, 111.9, 101.3, 53.1, 52.6.

m/z: (ESI+) HRMS [M+Na] $C_{13}H_{11}NO_5Na^+$: found: 284.0530; calcd: 284.0529.

Dimethyl 2-(2-oxoindolin-3-ylidene)malonate 7b (Scheme 3)

Using a gradient eluent from 0% → 50% diethyl ether in hexanes, 99.0 mg of an orange crystalline solid was obtained, 38 % yield; R_f: 0.27 (1:1, hexane:diethyl ether)

ν max (ATR)/cm^{-1}: 3194, 3163, 3091, 3032, 2948, 2838, 1737, 1713, 1609, 1249;

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (1H, s), 8.35 (1H, d, *J* = 7.9 Hz), 7.32 (1H, app t, *J* = 7.9 Hz), 7.01 (1H, app t, *J* = 7.8 Hz), 6.83 (1H, d, *J* = 7.8 Hz), 3.94 (3H, s) and 3.91 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7, 166.0, 163.2, 143.6, 135.4, 133.4, 129.1, 128.6, 122.9, 119.5, 110.4, 53.2, 53.1.

m/z: (ESI+) HRMS [M+Na] $C_{13}H_{11}NO_5Na^+$: found: 284.0530; calcd: 284.0529.

Dimethyl 2-acetoxy-2-(2-formyl-1H-indol-3-yl)malonate 9a (Table 2, entry 1)

Using a gradient eluent from 5% → 40% ethyl acetate in hexanes, 126.5 mg of a white crystalline solid was obtained 38 % yield; R_f: 0.55 (1:1, hexanes:ethyl acetate)

ν max (ATR)/cm^{-1}: 3367, 2952, 1745, 1642, 1223;

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.36 (1H, s), 9.72 (1H, s), 7.88 (1H, d, *J* = 8.4 Hz), 7.45 (1H, d, *J* = 8.4 Hz), 7.37 (1H, app t, *J* = 7.6 Hz), 7.18 (1H, app t, *J* = 7.6 Hz), 3.80 (6H, s) and 2.35 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ 183.8, 169.5, 166.2, 136.4, 132.9, 127.1, 125.0, 122.5, 122.0, 116.0, 112.6, 81.3, 53.7, 20.8.

m/z: (ESI+) HRMS [M+Na] $C_{16}H_{15}NO_7Na^+$: found: 356.0741; calcd: 356.0741.

Dimethyl 2-acetoxy-2-(2-(methoxycarbonyl)-1H-indol-3-yl)malonate 9b (Table 2, entry 2)

Using a gradient eluent from 5% → 40% ethyl acetate in hexanes, 236.4 mg of a yellow crystalline solid was obtained, 65 % yield; R_f: 0.40 (1:1, hexanes:ethyl acetate)

ν max (ATR)/cm^{-1}: 3384, 3054, 2998, 2953, 1773, 1726, 1208;

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.35 (1H, s), 7.74 (1H, d, *J* = 8.3 Hz), 7.38 (1H, d, *J* = 8.2 Hz), 7.29 (1H, app t, *J* = 7.5 Hz), 7.15 (1H, app t, *J* = 7.5 Hz), 3.83 (6H, s) 3.82 (3H, s) and 2.22 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 166.7, 160.7, 135.1, 126.2, 125.5, 124.4, 122.3, 121.4, 114.7, 112.2, 81.4, 53.4, 52.1, 20.9.

m/z: (ESI+) HRMS [M+Na] $C_{17}H_{17}NO_8Na^+$: found: 386.0847; calcd: 386.0846.

Dimethyl 2-acetoxy-2-(5-(methoxycarbonyl)-1H-pyrrol-2-yl)malonate 9c (Table 2, entry 3)

Using a gradient eluent from 5% → 40% ethyl acetate in hexanes, 244.9 mg of a yellow oil was obtained, 78 % yield; R_f: 0.5 (1:1, hexane:ethyl acetate)

ν max (ATR)/cm^{-1}: 3429, 3313, 3006, 2956, 1748, 1705, 1206;

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.99 (1H, s), 6.79 (1H, dd, *J* = 3.8, 2.8 Hz), 6.27 (1H, dd, *J* = 3.8, 2.7 Hz), 3.82 (3H, s), 3.80 (6H, s) and 2.18 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.6, 165.2, 160.9, 128.2, 123.8, 115.0, 110.3, 78.2, 53.8, 51.6, 20.7.

m/z: (ESI+) HRMS [M+Na] $C_{13}H_{15}NO_8Na^+$: found: 336.0691; calcd: 336.0690.

Dimethyl 2-acetoxy-2-(5-acetyl-1H-pyrrol-2-yl)malonate 9d (Table 2, entry 4)

Using a gradient eluent from 5% → 40% ethyl acetate in hexanes, 124.5 mg of a yellow oil was obtained, 42 % yield; R_f: 0.45 (1:1, hexane:ethyl acetate)

ν max (ATR)/cm^{-1}: 3429, 3252, 3012, 2957, 1746, 1649, 1206;

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.99 (1H, s), 6.80 (1H, dd, *J* = 3.9, 2.6 Hz), 6.33 (1H, dd, *J* = 3.9, 2.7 Hz), 3.83 (6H, s), 2.41 (3H, s) and 2.23 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ 187.8, 169.4, 165.0, 132.8, 129.7, 115.9, 110.3, 78.3, 53.9, 25.4, 20.7.

m/z: (ESI+) HRMS [M+Na] $C_{13}H_{15}NO_7Na^+$: found: 320.0739; calcd: 320.0741.

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Supplementary data

Copies of ^{1}H 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/xxxxxxxxxxxxxxxx.

References and Notes

1. (a) Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A. K.; Choi, E. H. *Molecules* **2013**, *18*, 6620–6662; (b) O'Connor, S. E.; Maresh, J. J. *Nat. Prod. Rep.*, **2006**, *23*, 532–547.
2. Massiot, G.; Boumedjel, A.; Nuzillard, J.-M.; Richard, B.; Le Men-Olivier, L.; David, B.; Hadi, H. A. *Phytochemistry* **1992**, ***31***, 1078–1079.
3. (a) Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 7568–7569; (b) Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc*. **2010**, *132*, 4894–4906; (c) Vaswani, R. G.; Day, J. J.; Wood, J. L. *Org. Lett.* **2009**, *11*, 4532–4535; (d) Zaimoku, H.; Taniguchi, T.; Ishibashi, H. *Org. Lett*. **2012**, *14*, 1656–1658; (e) Galicia, I. Z.; Maldonado, L. A. *Tetrahedron Lett.* **2013**, *54*, 2180–2182; (f) Granger, B. A.; Jewett, I. T.; Butler, J. D.; Hua, B.; Knezevic, C. E.; Parkinson, E. I.; Hergenrother, P. J.; Martin, S. F. *J. Am. Chem. Soc.* **2013**, *135*, 12984–12986.
4. (a) Potier, P. *J. Nat. Prod.* **1980**, *43*, 72−86; (b) Langlois, N.; Gueritte, F.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1976**, *98*, 7017−7024; (c) Kutney, J. P.; Hibino, T.; Jahngen, E.; Okutani, T.; Ratcliffe, A. H.; Treasurywala, A. M.; Wunderly, S. *Helv. Chim. Acta* **1976**, *59*, 2858−2882; (d) Kuehne, M. E.; Matson, P. A.; Bornmann, W. G. *J. Org. Chem.* **1991**, *56*, 513−528; (e) Bornmann, W. G.; Kuehne, M. E. *J. Org. Chem.* **1992**, *57*, 1752−1760; (f) Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 2137−2139; (g) Kuboyama, T.; Yokoshima, S.; Tokuyama, H.; Fukuyama, T. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11966−11970; (h) Magnus, P.; Stamford, A.; Ladlow, M. *J. Am. Chem. Soc.* **1990**, *112*, 8210−8212; (i) Ishikawa, H.; Colby, D. A.; Seto, S.; Va, P.; Tam, A.; Kakei, H.; Rayl, T. J.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2009**, *131*, 4904−4916; (j) Ishikawa, H.; Elliott, G. I.; Velcicky, J.; Choi, Y.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 10596−10612; (k) Choi, Y.; Ishikawa, H.; Velcicky, J.; Elliott, G. I.; Miller, M. M.; Boger, D. L. *Org. Lett.* **2005**, *7*, 4539−4542; (l) Ishikawa, H.; Colby, D. A.; Seto, S.; Va, P.; Tam, A.; Kakei, H.; Rayl, T. J.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2009**, *131*, 4904–4916.
5. For comprehensive reviews on Mn(III)-mediated transformations, see: (a) De Klein. W. J. In *Organic Syntheses by Oxidation with Metal Compounds*; Mijs, W. J., De Jonge, C. R. H. I., Eds.; Plenum Press: New York, **1986**; 261–314; (b) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339–364; (c) Melikyan, G. G. *Synthesis* **1993**, 833–850.

6. Kerr, M.A.; Magolan, J. *Org. Lett.* **2006**, *8*, 4561–4564.
7. Kraus, G.A.; Dneprovskaia, E.; Nguyen, T. H.; Jeon, I. *Tetrahedron* **2003**, *59*, 8975–8978.
8. (a) Kerr, M.A.; Magolan, J. *Org. Lett.* **2008**, *10*, 1437–1440; for more recent examples see also: (b) Oisaki, K.; Abe, J.; Kanai, M. *Org. Biomol. Chem.* **2013**, *11*, 4569–4572; (c) Lee, H. S.; Kim, S. H.; Kim, Y. M.; Kim, J. N. *Tetrahedron Lett.* **2010**, *51*, 5071–5075.
9. Some notable examples: (a) Nishino, H.; Cong, Z. *Synthesis* **2008**, *17*, 2686–2694; (b) Tsai, A.-I.; Lin, C.-H.; Chuang, C.-P. *Heterocycles* **2005**, *65*, 2381–2394; (c) Wang, S-F.; Chuang, C-P. *Heterocycles* **1997**, *45*, 347–359; (d) Chuang, C.-P.; Wang, S.-F. *Tetrahedron Lett.* **1994**, *35*, 1283–1284; (e) Baciocchi, E.; Muraglia, E. *J. Org. Chem.* **1993**, *58*, 7610–7612; (f) Citterio, A.; Santi. R.; Fiorani, T.; Strologo, S. *J. Org. Chem.* **1989**, *54*, 2703–2712.
10. Related coupling processes achived using copper: Bao, Y.-H.; Zhu, J.-Y.; Qin, W.-B.; Kong, U.-B.; Chen, Z.-W.; Tang, S.-B.; Liu, L.-X. *Org. Biomol. Chem.* **2013**, *11*, 7938–7945.
11. (a) Levinson, A. M. *Org. Lett.* **2014**, *16*, 4904–4907; (b) Jiricek, J.; Blechert, S. *J. Am. Chem. Soc.* **2004**, *126*, 3534–3538; (c) Zhong, X.; Li, Y.; Han, F.-S. *Chem. Eur. J.* **2012**, *18*, 9784–9788; (d) Zhong, X.; Li, Y.; Zhang, J.; Han, F.-S. *Org. Lett.* **2015**, *17*, 720–723.
12. *General procedure*: $Mn(OAc)_3$ (6 mmol) was added to a 250 mL round bottom flask with a 1" magnetic stirbar and purged with nitrogen gas. The aromatic heterocycle (1 mmol) and malonate (2 mmol) were weighed out separately and subsequently dissolved in 7 mL of acetic acid (glacial), (if the aromatic heterocycle was slow to dissolve the vial was sonicated to facilitate formation of a homogeneous solution). Glacial acetic acid (10 mL) was added to the flask containing $Mn(OAc)_3$ and the purge needle was removed. The flask containing the solution of $Mn(OAc)_3$ was heated to 85 °C using a heating block. Once the target temperature was achieved the two solutions of malonate and heterocycle were added to the manganese solution via syringe pump over the course of 5 hours. Once the addition was complete the solution was heated for a further 12–24 hours until the starting material had been consumed as deemed by TLC. The solution was cooled to room temperature and the acetic acid was removed on a rotary evaporator. To the brown solid was added water (100 mL) and ethyl acetate (50 mL). The two layers were separated and the aqueous phase was further extracted with ethyl acetate. The organic phase was washed with water (x2), washed with brine (x1), dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatagraphy provided compounds **4a–g**, **7a–b**, and **9a–d**.

13. Gribble, G.W., Kishbaugh, T.L.S., Adrosov, D.A., *Tetrahedron Lett.* **2008**, *49*, 6621–6623.
14. (a) Tucker, J. W.; Narayanam, J. M. R.; Krabbe, S. W.; Stephenson, C. R. J. *Org. Lett.* **2010**, *12*, 368–371; (b) Furst, L.; Matsuura, B. S.; Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *Org. Lett.* **2010**, *12*, 3104–3107; (d) Devery, III, J. J.; Douglas, J. J.; Nguyen, J. D.; Cole, K. P.; Flowers, II, R. A.; Stephenson, C. R. J. *Chem. Sci.* **2015**, *6*, 537-541; (c) Swift, E. C.; Williams, T. M.; Stephenson, C. R. J. *Synlett* **2015**, *accepted.*