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Note

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A Low–Temperature, Transition Metal–Free Cross Dehydrogenative Coupling Protocol for the Synthesis of 3,3–Disubstituted Oxindoles

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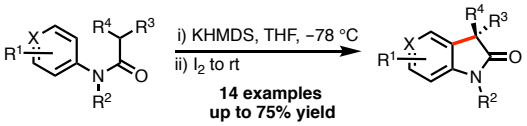
Abstract



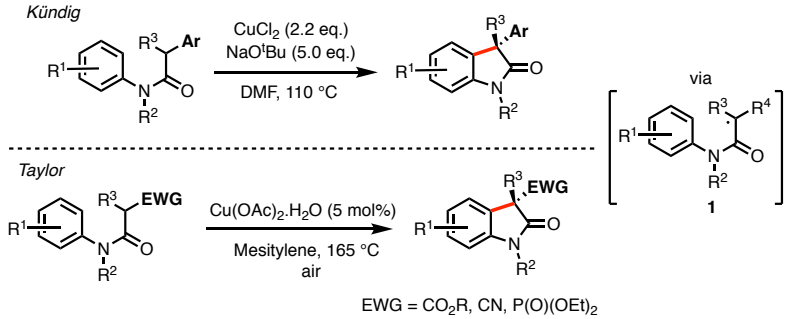
A new low–temperature procedure for the synthesis of 3,3-disubstituted 2-oxindoles via cross dehydrogenative coupling (CDC) is reported. The use of a strong, non-reversible base in these reactions has been found to effect a dramatic drop in reaction temperature (to room temperature) relative to the current state-of-the-art (>100 °C). When employing iodine as an 'oxidant', new evidence suggests that this transformation may occur via a transiently stable iodinated intermediate rather than by direct single–electron oxidation.

The remarkable biological properties of oxindoles, particularly 3,3-disubstituted 2-oxindoles, has made this class of small molecules very attractive targets for synthesis and medicinal chemistry research programs.[1] These heterocyclic scaffolds also feature in many structurally complex natural products[2,3] and therefore inspire the development of new, creative and mechanistically interesting methods for their construction.

Of the methods available for their synthesis, which include functionalization of mono-substituted 3-oxindoles[4] and isatin derivatives,[5] transition metal catalyzed arylations,[6] radical additions to *N*-acrylamides,[7] reactions of indoles[8] and oxidation of indolenines,[9] one of the most versatile and straightforward approaches is through the use of oxidative cross dehydrogenative coupling (CDC) reactions.[10-16] This approach, which proceeds via a key

intramolecular homolytic aromatic substitution of an amidyl radical **1**, was pioneered independently by Kündig et al.[10] as well as our own group[11] and utilizes easily prepared acyclic starting materials, offering a broad functional group scope and avoiding the need for expensive catalysts and ligands (Scheme 1). Bisai later extended this to a metal free variant by employing DDQ, iodine, NIS or ICl as oxidants, again at elevated temperatures.[13]

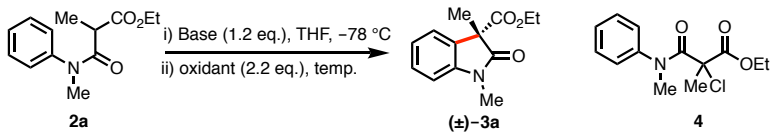
Scheme 1. Independent reports from the Kündig and Taylor groups of the CDC approach to oxindoles.



Despite the many methods to choose from for the synthesis of the 2-oxindole framework, including those in Scheme 1, the overwhelming majority of these methods require high reaction temperatures. This therefore precludes thermally–sensitive substrates and/or products and makes developing asymmetric variants of these reactions particularly challenging. Furthermore, these temperatures are often well above the flash points, but perhaps more worryingly, also above the fire points of the solvents they are carried out in.[17] Therefore, particularly when carrying out these reactions in the presence of air/oxygen, there is a pressing urgency to develop safer, lower temperature protocols. In a notable recent example, Wu and Xu reported the synthesis of a variety of heat-sensitive C3-fluorinated oxindoles using a CDC approach under electrochemical conditions at operational temperatures between –30 °C and 0 °C.[18] While this is an enormous step forward in offering a safer alternative, it requires specialized equipment and has only been demonstrated in the synthesis of C3-fluorinated products. Herein we report low–temperature conditions for the synthesis of a diverse range of 3,3-disubstituted oxindoles via cross dehydrogenative coupling as a complementary and safer addition to the current literature.

The oxidative generation of α-carbonyl radicals using a strong base and a suitable oxidant at low temperature is well documented (particularly in applications to the synthesis of 1,4-diketones)[19] and we proposed that these conditions might similarly generate the requisite α-carbonyl amidyl radical intermediate **1** (Scheme 1), which could subsequently cyclize to afford 3,3-disubstituted 2-oxindoles at safer operating temperatures. Traditionally, the oxidative generation of α-carbonyl radicals utilizes a lithium amide base and a copper(II) salt and this was used as a basis for the reaction design, with room temperature envisaged as the upper reaction temperature limit. In the event, model anilide **2a** was subjected to various conditions, the results of which are summarized in Table 1.

Table 1. Optimization of low temperature CDC of anilide **2a**.[a]



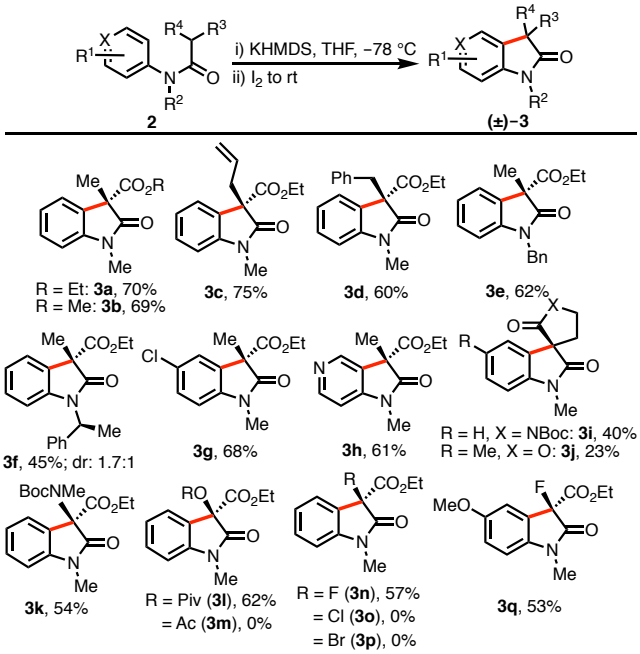
Entry	Base	Temperature[b] (°C)	Oxidant	Yield (%)[c]
1	LiHMDS	–78	$CuCl_2$	15[d]
2	LiHMDS	rt	Cu(II) 2-ethylhexanoate	48[e]
3	KHMDS	–78	$CuCl_2$	54[f]
4	KHMDS	–78 to rt	Cu(II) 2-ethylhexanoate	30[g,h]
5	KHMDS	rt	$Cu(OTf)_2$	23[e,g]
6	KHMDS	rt	$Cu(OAc)_2$	0[e,g]
7	KHMDS	–78	DDQ	16
8	LiHMDS	–78 to rt	I_2[h]	52
9	LDA	–78 to rt	I_2[h]	56
10	**KHMDS**	**–78 to rt**	**I_2**[h]	**70**

[a]Reactions were stopped after complete conversion of the starting material (by TLC) unless otherwise stated (typically 2 – 8 hours). [b]Temperature after addition of the oxidant. [c]Isolated yield. [d]55% of C-Chlorination. [e]Reaction left overnight. [f]34% yield of C-chlorinated product. [g] All starting material recovered. [h]1.2 eq. of I_2.

Treating **2a** with LiHMDS and $CuCl_2$ at –78 °C afforded **3a** in 15% yield with the α-chlorinated anilide (**4**) isolated as the major product in 55% yield after 2 h at –78 °C (entry

1). It was suspected that poor the solubility of $CuCl_2$ in THF was negatively affecting the reaction but unfortunately no conversion was observed at –78 °C using the more soluble Cu(II) 2-ethylhexanoate. On carrying out the reaction at room temperature, however, oxindole **3a** was formed in 48% yield (entry 2). Switching to KHMDS, $CuCl_2$ afforded the desired oxindole in an improved yield of 54% after 2 h along with the undesired *C*-chlorinated product (**4**) in 34% yield (entry 3), whereas Cu(II) 2-ethylhexanoate gave **3a** in a disappointing 30% yield (entry 4). Neither copper(II) trifluoromethanesulfonate nor $Cu(OAc)_2$ was able to effect the reaction at room temperature (entries 5 and 6) while the organic oxidant DDQ gave **3a** in a poor yield of 16% (entry 7). A breakthrough was achieved when iodine was employed as the oxidant. Introducing iodine (1.2 eq.) to the enolate at –78 °C and subsequently warming to room temperature afforded **3a** in 52% and 56% yields when using LiHMDS and LDA (entries 8 and 9), respectively, while KHMDS provided optimal conditions, affording **3a** in 70% yield (entry 10). The use of *N*-iodosuccinimide as well as other solvents, including diethyl ether, DMSO, CH_3CN and DMF were also tested but I_2 and THF was found to be the best combination for this transformation. This optimized low temperature protocol was then applied to the synthesis of a range of 3,3-disubstituted 2-oxindoles in order to explore the substrate scope (Scheme 2).

Scheme 2. Substrate scope.



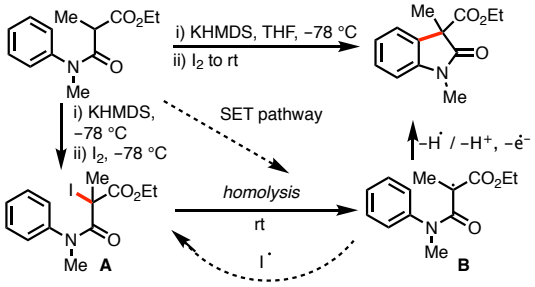
Variation of the ester group had little effect on the efficiency of the reaction and changes to the alkyl group at the methylene position were also well tolerated and afforded oxindole products **3b** – **3d** in 60 – 75% yields. Variation of the protecting group on nitrogen is possible, for example *N*-benzyl oxindole **3e** was produced in 62% yield. A key drawback of the typical high temperature CDC methods to access 2-oxindoles is in applications for stereoselective synthesis and we were interested to investigate the potential of a diastereoselective cyclization under the new room temperature conditions. Unfortunately, when the process was performed on anilide **2f**, oxindole **3f** was produced in 45% yield with a dr of 1.7:1. A similar dr was obtained using $CuCl_2$, even at –78 °C and investigations to develop stereoselective applications are currently ongoing. Substitution on the aromatic ring as well as variation to a pyridine ring was also possible giving **3g** and **3h** in 68% and 61% yields, respectively. Spirocyclic oxindoles have gained considerable interest due to their promising therapeutic potential as anticancer and antiviral agents[1b,1c] and these new conditions were found to be appropriate for the construction of these frameworks, affording nitrogen containing spiro-oxindole **3i** in 40% yield and the oxygen containing variant **3j** in 23% yield, both under the standard conditions. It should be noted that these low temperature conditions cannot be used to prepare 3-aryl oxindoles and anilides with a free N-H also did not provide oxindole formation (however these are easily accessed by deprotection of **3e**).

Oxindoles bearing heteroatoms at the 3-position are highly sought–after targets and we were interested to see whether the low temperature conditions would be amenable to their synthesis. In the event, we were delighted that oxindoles **3k** – **3q**, bearing nitrogen, oxygen as well as fluorine at the 3-position could be also be synthesized at room temperature in 53 – 62% yield. For 3-hydroxy-oxindoles synthesis, *O*–protection with a non-enolizable group was essential; thus, the OPiv substituted **3k** was obtained in 62% yield whereas the acetate protected analog was not suitable for the cyclization reaction. Interestingly, fluorine was the

only halogen compatible with the methodology affording 3-fluoro-oxindoles **3n** and **3q** in 57% and 53% yield, respectively, while neither chloride, bromide nor iodide variants were found to be suitable for this transformation. The utility of this low temperature procedure is perhaps best highlighted with respect to compounds **3n** and **3q**. 3–Fluoro-oxindoles have very encouraging therapeutic properties but their exploration has been limited due to challenges in their synthesis as they are susceptible to base–mediated decomposition above temperatures as low as –30 °C,[18] which therefore makes most CDC approaches challenging. The current method however offers a viable alternative for their synthesis without the need for specialized electrochemistry equipment[18] or transition metal catalysts.[20]

Mechanistically, these new reaction conditions raised interesting questions, since in a related protocol, Bisai's group reported that when using KO^{t}Bu and I_2 the reaction required heating to 110 °C in order to obtain high yields and when performed at room temperature the desired oxindole was produced in 30 – 39% yields only when using NIS or ICl.[13] The mechanism proposed by Bisai features a single–electron oxidation of the enolate by I_2 (or iodine source) to form the α-carbonyl radical, followed by a cyclization, and it was therefore somewhat surprising that variation of the base could have such a dramatic difference in the yield at room temperature. In monitoring our reaction, it was found that when iodine was introduced to the preformed enolate at –78 °C, complete formation of the *C*-iodinated anilide (**A**) was observed (^{1}H-NMR and HRMS evidence) and upon warming to room temperature, this intermediate slowly decomposed to the desired oxindole (Scheme 3).

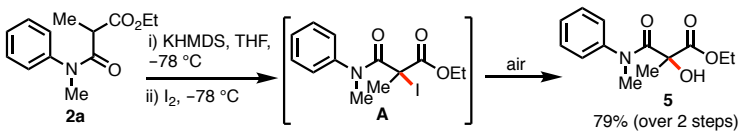
Scheme 3. Proposed mechanism for the low temperature metal–free CDC protocol.



In Bisai's report it was suggested that their high reaction temperatures (110 °C) may have prevented the observation of this transient iodide, which we can now confirm, but do not rule out the proposed direct iodine single-electron transfer oxidation mechanism at elevated temperatures. In fact, reconciling with Bisai's mechanism, it is possible that at low temperature the enolate is indeed oxidized to radical **B** but is quickly intercepted by the iodine atom (I•) to form **A** rather than undergoing cyclization (as shown by the dotted SET pathway in Scheme 4). On warming to rt, the iodide slowly undergoes thermal homolysis (since exclusion of light did not inhibit product formation) back to the α-carbonyl radical **B**, presumably facilitated by halogen-bond activation with the solvent and/or HMDS,[21] and cyclizes to afford the oxindole.

To probe the homolysis, we thought that it might be possible to trap radical **B** with O_2, by exposing the iodinated intermediate formed in situ, to air. In the event, alcohol **5** was obtained in 79% (over 2 steps) following work-up with $Na_2S_2O_3$ and therefore affords evidence in support of the proposed radical intermediate (Scheme 4).

Scheme 4. Radical trapping with O_2 to form tertiary alcohol **5**.



Similar homolyses have been proposed by Miao and Yang[22] as well as the Itoh group in their iodine–catalyzed CDC of thiophenes[23] with carbonyl compounds and our mechanistic studies and analytical data are in agreement with this report.

In summary, we have developed a mild, low–temperature and scalable set of conditions for the synthesis of a diverse range of 3,3-disubstituted 2-oxindoles via cross dehydrogenative coupling, in yields up to 75%. The significantly lower reaction temperatures described, compared to existing methods, offer conditions more appropriate for stereoselective synthesis and asymmetric CDC routes to 2-oxindoles, and these are currently being investigated. New mechanistic insight into the iodine mediated CDC reaction suggests that at temperatures below or up to rt, this process proceeds via the formation and subsequent homolysis of a transiently stable tertiary-iodide intermediate. This work, together with the report from the Itoh group,[23] highlights the scope for application of these tertiary iodides as masked radical synthons that can be activated under very mild and metal–free conditions and is currently being explored in our group.

Experimental Section

General information

Except where stated, all reagents were purchased from commercial sources and used without further purification. THF was freshly distilled from sodium-benzphenone ketyl and all other solvents were dried on an Innovative Technology Inc. PureSolv Solvent Purification System. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL ECX400 or JEOL ECS400 spectrometer, operating at 400 MHz and 100 MHz, respectively. All spectral data was acquired at 295 K. Chemical shifts are reported in parts per million (ppm, δ), downfield from tetramethylsilane (TMS, δ = 0.00 ppm) and are referenced to residual solvent ($CDCl_3$, δ =

7.26 ppm (^{1}H) and 77.16 ppm (^{13}C)). Coupling constants (*J*) are reported in Hertz (Hz). The multiplicity abbreviations used are: br broad, s singlet, d doublet, t triplet, q quartet, m multiplet, app. apparent. Signal assignment was achieved by analysis of DEPT, COSY, HMBC and HSQC experiments where required. Infrared (IR) spectra were recorded on a PerkinElmer UATR 2 spectrometer, either as a compressed solid or a thin film dispersed from CH_2Cl_2 or $CDCl_3$. High-resolution mass-spectra were obtained by the University of York Mass Spectrometry Service, using electrospray ionisation (ESI) on a Bruker Daltonics, Micro-tof spectrometer. Melting points were determined using Gallenkamp apparatus. Thin layer chromatography was carried out on Merck silica gel $60F_{254}$ pre-coated aluminium foil sheets and visualized using UV light (254 nm) and stained with basic aqueous potassium permanganate.

Synthesis of novel anilides (2):[24]

Ethyl 2-methyl-3-(methyl(pyridin-4-yl)amino)-3-oxopropanoate (2h). To a solution of 4-(methylamino)pyridine (0.379 g, 3.51 mmol), 3-ethoxy-2-methyl-3-oxopropanoic acid (0.466 g, 3.19 mmol) and DIPEA (1.67 mL, 9.57 mmol) in DCM (30 mL) at 0 °C was added dropwise T3P (50 % w/w in EtOAc, 2.64 g, 4.15 mmol) and the solution allowed to warm to rt. After 3 h sat. aq. $NaHCO_3$ (50 mL) was added and the aqueous phase extracted with DCM (2 x 30 mL). The combined organic extracts were dried with $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude material was purified by flash chromatography (3% MeOH in DCM) to afford **2i** as a yellow oil (0.752 g, quant.). $\mathbf{R_f}$ 0.24 (5% MeOH/DCM); **IR** (film, ν_{max}/cm^{-1}) 2984, 1838, 1662, 1585, 1497, 1400, 1191; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ (ppm) 8.63 (app. d, *J* = 6.2 Hz, 2H), 7.19 (app. d, *J* = 6.2 Hz, 2H), 4.14-4.01 (m, 2H), 3.47 (q, *J* = 7.0 Hz, 1H), 3.28 (s, 3H), 1.29 (d, *J* = 7.0 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (100

MHz, $CDCl_3$) δ (ppm) 170.2, 169.6, 151.6, 151.0, 121.7, 61.5, 43.8, 37.2, 14.2, 14.1; **HRMS (ESI$^+$)** *m/z* calcd. for $C_{12}H_{16}N_2NaO_3$ [M+Na$^+$] 259.1053, found 259.1046.

N-Methyl-2-oxo-N-(p-tolyl)tetrahydrofuran-3-carboxamide (2j). To a solution of *N*-methyl-*p*-toluidine (0.695 g, 5.73 mmol), 2-oxotetrahydrofuran-3-carboxylic acid[25] (0.626 g, 4.81 mmol), 2-chloro-1-methylpyridinium iodide (1.59 g, 6.21 mmol) in DCM (50 mL) at 0 °C was added NEt_3 (2.0 mL, 14.3 mmol) and the reaction warmed to rt and left to stir for 18 h. A solution of HCl in water (10%, 30 mL) and after the layers were separated, the aqueous phase extracted two more times with DCM (2 x 30 mL). The combined DCM extracts were washed with sat. aq. $NaHCO_3$ (60 mL), dried with $MgSO_4$, filtered and the solvent removed *in vacuo*. Purification of the crude material by flash silica gel chromatography (1:5->1:1 EtOAc:hexanes) afforded the title compound as a white solid (0.615 g, 55%). $\mathbf{R_f}$ 0.21 (2:3 EtOAc:hexanes); **M.P.** 74–76 °C; **IR** (film, ν_{max}/cm^{-1}) 2921, 1762, 1650, 1512, 1374, 1156, 1121; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.22 (s, 4H), 4.46 (td, *J* = 8.5 Hz, 4.4 Hz, 1H), 4.13 (q, *J* = 8.5 Hz, 1H), 3.53 (t, *J* = 8.6 Hz, 1H), 3.28 (s, 3H), 2.69 (dq, *J* = 12.7 Hz, 8.6 Hz, 1H), 2.36 (s, 3H), 2.28-2.17 (m, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ (ppm) 174.1, 167.9, 140.6, 138.5, 130.6, 127.2, 67.4, 43.4, 37.9, 27.4, 21.1; **HRMS (ESI$^+$)** *m/z* calcd. for $C_{13}H_{15}NNaO_3$ [M+Na$^+$] 256.0944, found 256.0947.

Ethyl 2-(benzyl(methyl)amino)-3-(methyl(phenyl)amino)-3-oxopropanoate. A mixture of ethyl 2-bromo-3-(methyl(phenyl)amino)-3-oxopropanoate[26] (0.467 g, 1.56 mmol), *N*-benzylmethylamine (0.60 mL, 4.7 mmol) and DIPEA (0.81 mL, 4.67 mmol) in CH_3CN (30 mL) was heated overnight at 70 °C under an Ar atmosphere. The solvent was removed *in vacuo* and the crude material purified by flash silca gel chromatography eluting with 1:9 EtOAc:hexanes to afford the title compound as a yellow oil (0.337 g, 64%). $\mathbf{R_f}$ 0.36 (1:9 EtOAc:hexanes); **IR** (film, ν_{max}/cm^{-1}) 2979, 1745, 1659, 1595, 1495, 1184; **^{1}H-NMR** (400

MHz, $CDCl_3$) δ (ppm) 7.38-7.30 (m, 3H), 7.37-7.15 (m, 7H), 4.27-4.10 (m, 3H), 3.84 (d, *J* = 13.7 Hz, 1H), 3.73 (d, *J* = 13.7 Hz, 1H), 3.31 (s, 3H), 2.35 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ (ppm) 168.9, 167.7, 143.4, 139.6, 129.8, 128.9, 128.3, 128.1, 127.4, 127.0, 66.5, 61.1, 58.5, 38.9, 37.7, 14.4; **HRMS (ESI$^+$)** *m/z* calcd. for $C_{20}H_{24}N_2NaO_3$ [M+Na$^+$] 363.1679, found 363.1666.

Ethyl 2-((tert-butoxycarbonyl)(methyl)amino)-3-(methyl(phenyl)amino)-3-oxopropanoate (2k). A slurry of 10 % Pd/C (0.094 g, 0.09 mmol) and ethyl 2-(benzyl(methyl)amino)-3-(methyl(phenyl)amino)-3-oxopropanoate (0.300 g, 0.88 mmol) in EtOAc (25 mL) pre-purged with N_2 was equipped with a H_2 balloon and stirred at rt for 3 h. The mixture was then filtered through Celite®, washing with EtOAc (3 x 30 mL) and the solvent removed *in vacuo*. The crude material was then dissolved in THF (20 mL) and sat. aq. $NaHCO_3$ (20 mL) and $(Boc)_2O$ (0.269 g, 1.23 mmol) added and the mixture stirred overnight. The reaction mixture was then extracted with EtOAc (3 x 20 mL), dried with $MgSO_4$ and the solvent removed *in vacuo*. Flash silica gel chromatography of the crude material afforded anilide **2m** as colorless oil (0.224 g, 73%, over 2 steps). **R_f** 0.51 (1:3 EtOAc:hexanes); **IR** (film, ν_{max}/cm^{-1}) 2977, 1753, 1695, 1664, 1366, 1312, 1144; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ (ppm) (rotamers) 7.45-7.29 (m, 3H), 7.25-7.19 (m, 2H), 5.51-5.22 (2 x s, 1H), 4.29-4.06 (m, 2H), 3.29 (s, 3H), 2.93-2.89 (2 x s, 3H), 1.33 (s, 5H), 1.28-1.20 (2 x t, *J* = 7.1 Hz, 3H), 1.16 (s, 4H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ (ppm) (rotamers) 168.1, 168.0, 166.7, 165.9, 142.8, 142.4, 130.1, 130.0, 128.6, 128.5, 127.3, 127.1, 80.5, 80.3, 61.7, 61.6, 61.0, 59.8, 38.0, 32.2, 31.6, 28.3, 28.1, 14.3, 14.2; **HRMS (ESI$^+$)** *m/z* calcd. for $C_{18}H_{26}N_2NaO_5$ [M+Na$^+$] 373.1734, found 373.1736.

Ethyl 3-(methyl(phenyl)amino)-3-oxo-2-(pivaloyloxy)propanoate (2l). Cesium hydroxide hydrate (0.587 g, 3.50 mmol) was added to a solution of pivalic acid (0.357 g, 0.402 mL, 3.50 mmol) in DMF (1.2 mL) and stirred at rt for 5 min. The resulting solution was then added to

ethyl 2-bromo-3-(methyl(phenyl)amino)-3-oxopropanoate[26] (0.350 g, 1.17 mmol), and the reaction stirred at rt for 16 h. The reaction was then diluted with water (10 mL), extracted with EtOAc (3 x 20 mL) and the combined organic extracts dried with $MgSO_4$, filtered and the solvent removed *in vacuo*. Purification of the crude material by flash silica gel chromatography (3:7 EtOAc:hexanes) afforded the title compound as a colorless oil (0.372 g, 99%). **R_f** 0.43 (2:3 EtOAc:hexanes); **IR** (film, ν_{max}/cm^{-1}) 2924, 1668, 1595, 1478, 1373, 1303, 1291, 1138, 1080; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.43-7.27 (m, 5H), 5.44 (s, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.30 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.19 (s, 9 H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ (ppm) 177.0, 165.5, 164.4, 142.3, 129.9, 128.7, 127.6, 69.9, 62.1, 38.7, 38.1, 27.0, 14.0; **HRMS (ESI$^+$)** *m/z* calcd. for $C_{17}H_{23}NNaO_5$ [M+Na^+] 344.1468, found 344.1465.

Ethyl 2-fluoro-3-(methyl(phenyl)amino)-3-oxopropanoate (2n). Prepared according to the literature procedure[18] using ethyl 3-(methyl(phenyl)amino)-3-oxopropanoate (0.300 g, 1.36 mmol), NaO^{t}Bu (0.287 g, 2.98 mmol), $ZnCl_2$ solution in diethyl ether (1 M, 2.98 mL, 2.98 mmol) and Selectfluor® (0.720 g, 2.03 mmol) to afford the title compound as a clear, colorless oil (0.285 g, 88%). **R_f** 0.23 (3:7 EtOAc:hexanes); **IR** (film, ν_{max}/cm^{-1}) 2985, 1766, 1742, 1595, 1496, 1211, 1093; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.48-3.37 (m, 3H), 7.32-7.27 (m, 2H), 5.21 (d, $J_{H\text{-}F}$ = 48.1 Hz, 1H), 4.28-4.19 (m, 2H), 3.34 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ (ppm) 165.3 (d, $J_{C\text{-}F}$ = 24.2 Hz), 163.7 (d, $J_{C\text{-}F}$ = 20.9 Hz), 141.9, 130.1, 128.9, 127.6, 83.5 (d, $J_{C\text{-}F}$ = 189.9 Hz), 62.4, 38.1, 14.1; **HRMS (ESI$^+$)** *m/z* calcd. for $C_{12}H_{14}FNNaO_3$ [M+Na^+] 262.0850, found 262.0854.

Ethyl 3-fluoro-5-methoxy-1-methyl-2-oxoindoline-3-carboxylate (2q). Prepared according to the literature procedure[18] using ethyl 3-((4-methoxyphenyl)(methyl)amino)-3-oxopropanoate (0.688 g, 2.74 mmol), NaO^{t}Bu (0.579 g, 6.02 mmol), $ZnCl_2$ solution in diethyl ether (1 M, 6.02 mL, 6.02 mmol) and Selectfluor® (1.45 g, 4.11 mmol) to afford the title

compound as a clear, colorless oil (0.435 g, 59%). **R_f** 0.35 (2:3 EtOAc:hexanes); **IR** (film, ν_{max}/cm^{-1}) 2983, 1766, 1742, 1668, 1510, 1247, 1025; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.22-7.17 (m, 2H), 6.95-6.90 (m, 2H), 5.22 (d, J_{H-F} = 48.2 Hz, 1H), 4.28-4.18 (m, 2H), 3.81 (m, 3H), 3.29 (app s, 3H), 1.28 (t, J = 7.2 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ (ppm) 165.4 (d, J_{C-F} = 24.2 Hz), 163.9 (d, J_{C-F} = 21.0 Hz), 159.7, 134.5, 128.8, 115.1, 83.5 (d, J_{C-F} = 189.5 Hz), 62.4, 55.6, 38.2, 14.1; **HRMS (ESI$^+$)** *m/z* calcd. for $C_{13}H_{16}FNNaO_4$ [M+Na$^+$] 292.0956, found 292.0967.

***Synthesis of 3,3-disubstituted 2-oxindoles (3) via I_2 mediated CDC*:**

General procedure:

KHMDS (1.0 M, 1.2 eq.) was added dropwise to a solution of anilide **2** (1.0 eq.) in THF (approx. 20 mL / 0.150 g) under an Ar atmosphere, cooled to –78 °C and the reaction mixture stirred at this temperature for 15 min. A solution of iodine (1.2 eq.) in THF (3 – 5 mL) was added and the reaction held at this temperature until complete formation of the C-iodinated intermediate was observed by TLC (approx. 15 min). The reaction was then removed from the cooling bath and stirred for the specified amount of time. Once the reaction was complete (by TLC), sat. aq. $Na_2S_2O_3$ (25 mL) was added and once the mixture was decolorised it was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried with $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude material was purified by flash silica gel chromatography eluting with 1:9->1:4 EtOAc/hexanes (unless otherwise stated) to afford oxindole **3**.

***Ethyl 1,3-dimethyl-2-oxoindoline-3-carboxylate* (3a).**[11b] Using anilide **2a**[11b] (0.200 g, 0.85 mmol) in THF (25 mL), KHMDS (1.02 mL, 1.02 mmol) and I_2 (0.261 g) in THF (4 mL) to afford title compound as a colourless oil (0.140 g, 70%). **R_f** 0.32 (1:9 EtOAc:hexanes); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.30 (td, J = 7.8 Hz, 1.2 Hz, 1H), 7.25-7.21 (m, 1H), 7.07-

7.01 (m, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 4.17-4.03 (m, 2H), 3.23 (s, 3H), 1.63 (s, 3H), 1.12 (t, *J* = 7.1 Hz, 3H). All recorded data were in accordance with those previously reported.

***Methyl 1,3-dimethyl-2-oxoindoline-3-carboxylate* (3b).**[13a] Using anilide **2b**[13a] (0.167 g, 0.75 mmol) in THF (20 mL), KHMDS (0.91 mL, 0.91 mmol) and I_2 (0.232 g, 0.91 mmol) in THF (3 mL) to afford the title compound as a colorless solid (0.114 g, 69%). $\mathbf{R_f}$ 0.42 (2:3 EtOAc:hexanes); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.32 (td, *J* = 7.7 Hz, 1.2 Hz, 1H), 7.27-7.23 (m, 1H), 7.07 (td, *J* = 7.7 Hz, 0.9 Hz, 1H), 6.87 (d, *J* = 7.7 Hz, 1H), 3.65 (s, 3H), 3.25 (s, 3H), 1.66 (s, 3H). All recorded data were in accordance with those previously reported.

***Ethyl 3-allyl-1-methyl-2-oxoindoline-3-carboxylate* (3c).**[13a] Using anilide **2c**[13a] (0.357 g, 1.37 mmol) in THF (30 mL), KHMDS (1.64 mL, 1.64 mmol) and I_2 (0.419 g, 1.64 mmol) in THF (5 mL) to afford the title compound as a light yellow solid (0.267 g, 75%). $\mathbf{R_f}$ 0.41 (3:7 EtOAc:hexanes); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.29 (td, *J* = 7.7 Hz, 1.2 Hz, 1H), 7.26-7.23 (m, 1H), 7.04 (td, 7.7 Hz, 1.0 Hz, 1H), 6.82 (d, 7.7 Hz, 1H), 5.41-5.28 (m, 1H), 5.00 (dq, *J* = 17.0 Hz, 1.3 Hz, 1H), 4.91-4.87 (m, 1H), 4.18-4.04 (m, 2H), 3.20 (s, 3H), 2.98 (dd, *J* = 13.8 Hz, 6.7 Hz, 1H), 2.91 (dd, *J* = 13.8 Hz, 7.8 Hz, 1H), 1.14 (t, *J* = 7.1 Hz, 3H). All recorded data were in accordance with those previously reported.

***Ethyl 3-benzyl-1-methyl-2-oxoindoline-3-carboxylate* (3d).**[11b] Using anilide **2d**[11b] (0.424 g, 1.36 mmol) in THF (35 mL), KHMDS (1.63 mL, 1.63 mmol) and I_2 (0.418 g, 1.63 mmol) in THF (5 mL) to afford the title compound as a colorless solid (0.254 g, 60%). $\mathbf{R_f}$ 0.31 (3:7 EtOAc:hexanes); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.32 (ddd, *J* = 7.6 Hz, 1.2 Hz, 0.5 Hz, 1H), 7.21 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.05 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.04-6.97 (m, 3H), 6.86-6.81 (m, 2H), 6.56 (d, *J* = 7.6 Hz, 1H), 4.26-4.09 (m, 2H), 3.56 (d, *J* = 13.7 Hz,

1H), 3.52 (d, *J* = 13.7 Hz, 1H), 2.93 (s, 3H), 1.19 (s, 3H). All recorded data were in accordance with those previously reported.

***Ethyl 1-benzyl-3-methyl-2-oxoindoline-3-carboxylate* (3e).**[11b] Using anilide **2e**[11b] (0.148 g, 0.48 mmol) in THF (15 mL), KHMDS (0.57 mL, 0.57 mmol) and I_2 (0.146 g, 0.57 mmol) in THF (3 mL) to afford the title compound as a colourless solid (0.91 g, 62%). $\mathbf{R_f}$ 0.31 (3:7 EtOAc:hexanes); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.35-7.22 (m, 6H), 7.18 (td, *J* = 7.8 Hz, 1.3 Hz, 1H), 7.02 (td, *J* = 7.8 Hz, 1.0 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 5.19 (d, *J* = 15.8 Hz, 1H), 4,73 (d, *J* = 15.8 Hz, 1H), 4.24-4.04 (m, 2H), 1.72 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H). All recorded data were in accordance with those previously reported.

Ethyl 3-methyl-2-oxo-1-((S)-1-phenylethyl)indoline-3-carboxylate (3f).[11d] Using anilide **2f**[11d] (0.180 g, 0.55 mmol) in THF (15 mL), KHMDS (0.66 mL, 0.66 mmol) and I_2 (0.170 g, 0.66 mmol) in THF (3 mL) to afford the title compound as a colorless oil (0.080 g, 45%) in a 1.7:1 mixture of inseparable diastereomers. $\mathbf{R_f}$ 0.28 (1:4 EtOAc:hexanes); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.42-7.39 (m, 1H), 7.37-7.22 (m, 5H), 7.09-7.01 (m, 1H), 7.00-6.94 (m, 1H), 6.53-6.44 (2 x ddd, *J* = 7.8 Hz, 1.1 Hz, 0.6 Hz, 1H), 5.97-5.81 (2 x q, *J* = 7.2 Hz, 1H), 4.26-4.02 (m, 2H), 1.88-1.81 (2 x d, *J* = 7.2 Hz, 3H), 1.74-1.71 (2 x s, 3H), 1.23-1.14 (2 x t, *J* = 7.1 Hz, 3H). All recorded data were in accordance with those previously reported.

Ethyl 5-chloro-1,3-dimethyl-2-oxoindoline-3-carboxylate (3g).[16] Using anilide **2g**[16] (0.225 g, 0.83 mmol) in THF (20 mL), KHMDS (1.0 mL, 1.00 mmol) and I_2 (0.256 g, 1.00 mmol) in THF (5 mL) to afford the title compound as a colorless oil (0.151 g, 68%). $\mathbf{R_f}$ 0.43 (3:7 EtOAc:hexanes); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.28 (dd, *J* = 8.3 Hz, 2.1 Hz, 1H), 7.22 (d, *J* = 2.1 Hz, 1H), 6.78 (d, *J* = 8.3 Hz, 1H), 4.20-4.05 (m, 2H), 3.22 (s, 3H), 1.64 (s,

3H), 1.16 (d, *J* = 7.2 Hz, 3H). All recorded data were in accordance with those previously reported.

Ethyl 1,3-dimethyl-2-oxo-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine-3-carboxylate (3h). Using anilide **2h** (0.171 g, 0.72 mmol) in THF (20 mL), KHMDS (0.87 mL, 0.87 mmol) and I_2 (0.222 g, 0.87 mmol) in THF (5 mL). Purification by flash chromatography using alumina gel eluting with 1:20->1:4 EtOAc:hexanes afforded the title compound as a colorless oil (0.106 g, 61%). **R_f** 0.27 (2:3 hexanes/EtOAc); **IR** (film, ν_{max}/cm^{-1}) 2985, 1722, 1603, 1496, 1340, 1236, 1218, 1123; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ (ppm) 8.49 (d, *J* = 5.3 Hz, 1H), 8.35 (s, 1H), 6.82 (d, *J* = 5.3 Hz, 1H), 4.20-4.05 (m, 2H), 3.23 (s, 3H), 1.68 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ (ppm) 174.9, 168.8, 151.0, 150.8, 143.3, 126.1, 104.3, 62.4, 53.7, 26.7, 20.0,14.0; **HRMS (ESI$^+$)** *m/z* calcd. for $C_{12}H_{15}N_2O_3$ [M+H$^+$] 235.1077, found 235.1067.

Tert-butyl 1-methyl-2,2'-dioxospiro[indoline-3,3'-pyrrolidine]-1'-carboxylate (3i).[11f] Using anilide **2i**[11d] (0.200 g, 0.628 mmol) in THF (20 mL), KHMDS (0.754 mL, 0.754 mmol) and I_2 (0.191 g, 0.754 mmol) in THF (3 mL). Purification of the crude material by flash silica gel chromatography (3:7 EtOAc:hexanes) afforded the title compound as a colorless solid (0.079 g, 40%). **R_f** 0.34 (1:1 hexanes/EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.33 (t, *J* = 7.7 Hz, 1H), 7.20 (d, *J* = 7.7 Hz, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.86 (d, *J* = 7.7 Hz, 1H), 4.19 (ddd, *J* = 10.8, 8.0, 7.0 Hz, 1H), 3.98 (ddd, *J* = 10.8, 8.4, 4.6 Hz, 1H), 3.22 (s, 3H), 2.63 (ddd, J = 13.0, 8.0, 4.6 Hz, 1H), 2.37 (ddd, *J* = 13.0, 8.4, 7.0 Hz, 1H), 1.54 (s, 9H); **HRMS (ESI$^+$)** *m/z* calcd. for $C_{17}H_{20}N_2NaO_4$ [M+Na$^+$] 339.1315, found 339.1311. All recorded data were in accordance with those previously reported.

1',5'-Dimethyl-4,5-dihydro-2H-spiro[furan-3,3'-indoline]-2,2'-dione (3j). Using anilide **2j** (0.200 g, 0.86 mmol) in THF (25 mL), KHMDS (1.03 mL, 1.03 mmol) and I_2 (0.263 g, 1.03 mmol) in THF (5 mL) to afford the title compound as a colorless solid (0.046 g, 23%). $\mathbf{R_f}$ 0.49 (9:11 hexanes/EtOAc); **M.P.** 162–164 °C; **IR** (film, ν_{max}/cm^{-1}) 2921, 1767, 1702, 1621, 1603, 1500, 1358, 1161, 1022; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.15 (app. d, *J* = 8.0 Hz, 1H), 7.04 (app. s, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 4.80 (dt, *J* = 8.8 Hz, 7.6 Hz, 1H), 4.60 (ddd, *J* = 8.8 Hz, 8.2 Hz, 5.0 H), 3.21 (s, 3H), 2.92-2.83 (m, 1H), 2.70-2.59 (m, 1H), 2.33 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ (ppm) 173.3, 173.3 142.0, 133.3, 130.0, 127.8, 123.9, 108.8, 66.9, 55.7, 33.6, 26.8, 21.2; **HRMS (ESI$^+$)** *m/z* calcd. for $C_{13}H_{13}NNaO_3$ [M+Na$^+$] 254.0788, found 254.0789.

Ethyl 3-((tert-butoxycarbonyl)(methyl)amino)-1-methyl-2-oxoindoline-3-carboxylate (3k). Using anilide **2k** (0.181 g, 0.52 mmol) in THF (20 mL), KHMDS (0.62 mL, 0.62 mmol) and I_2 (0.159 g, 0.62 mmol) in THF (4 mL) to afford the title compound as a yellow oil (0.095 g, 61%). $\mathbf{R_f}$ 0.38 (3:7 hexanes/EtOAc); **IR** (film, ν_{max}/cm^{-1}) 2979, 1747, 1726, 1698, 1608, 1472, 1365, 1341, 1239, 1151, 1089; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.47 (d, *J* = 7.7 Hz, 1H), 7.34 (td, *J* = 7.7 Hz, 1.3 Hz, 1H), 7.08 (td, *J* = 7.7 Hz, 1.0 Hz, 1H), 6.82 (d, *J* = 7.7 Hz, 1H), 4.23-4.15 (m, 2H), 3.21 (s, 3H), 2.71 (s, 3H), 1.43 (s, 9H), 1.21 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ (ppm) (rotamers) 171.3, 166.7, 156.0, 144.0, 130.4, 130.1 126.8, 125.8, 125.4, 123.2, 108.7, 81.7, 71.5, 62.3, 32.9, 28.2, 26.7, 13.9; **HRMS (ESI$^+$)** *m/z* calcd. for $C_{18}H_{24}N_2NaO_5$ [M+Na$^+$] 371.1577, found 371.1579.

Ethyl 1-methyl-2-oxo-3-(pivaloyloxy)indoline-3-carboxylate (3l). Using anilide **2l** (0.199 g, 0.62 mmol) in THF (20 mL), KHMDS (0.74 mL, 0.74 mmol) and I_2 (0.190 g, 0.74 mmol) in THF (4 mL) to afford the title compound as a yellow oil (0.095 g, 61%). $\mathbf{R_f}$ 0.55 (3:7 hexanes/EtOAc); **IR** (film, ν_{max}/cm^{-1}) 2973, 1739, 1611, 1471, 1347, 1236, 1135, 1068; **^{1}H-**

NMR (400 MHz, $CDCl_3$) δ (ppm) 7.36 (td, *J* = 7.7 Hz, 1.2 Hz, 1H), 7.31-7.28 (m, 1H), 7.03 (td, *J* = 7.7 Hz, 1.0 Hz, 1H), 6.86 (d, *J* = 7.7 Hz, 1H), 4.27-4.10 (m, 2H), 3.26 (s, 3H), 1.23 (s, 9H), 1.17 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ (ppm) (rotamers) 176.4, 170.2, 165.1, 164.4, 145.1, 131.0, 129.9, 128.7, 127.6, 124.7, 123.6, 123.2, 108.9, 79.9, 70.0, 62.7, 62.1, 38.9, 38.1, 26.9, 13.9; **HRMS (ESI$^+$)** *m/z* calcd. for $C_{17}H_{21}NNaO_5$ [M+Na$^+$] 342.1312, found 342.1308.

Ethyl 3-fluoro-1-methyl-2-oxoindoline-3-carboxylate (3n).[20] Using anilide **2n** (0.221 g, 0.92 mmol) in THF (25 mL), KHMDS (1.11 mL, 1.11 mmol) and I_2 (0.236 g, 1.11 mmol) in THF (5 mL) to afford the title compound as a colourless solid (0.124 g, 57%). **R_f** 0.26 (1:3 hexanes/EtOAc); **M.P.** 79–81 °C; **IR** (film, ν_{max}/cm^{-1}) 2985, 1763, 1729, 1613, 1471, 1494, 1252, 1226, 1071; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.46-7.41 (m, 1H), 7.40-7.36 (m, 1H), 7.13-7.08 (m, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 4.33-4.18 (m, 2H), 3.23 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ (ppm) 168.7 (d, $J_{C\text{-}F}$ = 21.2 Hz), 165.4 (d, $J_{C\text{-}F}$ = 31.0 Hz), 145.3 (d, $J_{C\text{-}F}$ = 5.1 Hz), 132.5 (d, $J_{C\text{-}F}$ = 3.1 Hz), 124.8 (d, $J_{C\text{-}F}$ = 1.2 Hz), 123.7 (d, $J_{C\text{-}F}$ = 2.7 Hz), 123.1 (d, $J_{C\text{-}F}$ = 19.0 Hz), 109.4 (d, $J_{C\text{-}F}$ = 1.4 Hz), 90.2 (d, $J_{C\text{-}F}$ = 200.5 Hz), 62.9, 26.7, 14.0; **HRMS (ESI$^+$)** *m/z* calcd. for $C_{12}H_{12}FNNaO_3$ [M+Na$^+$] 260.0693, found 260.0693.

Ethyl 3-fluoro-5-methoxy-1-methyl-2-oxoindoline-3-carboxylate (3q). Using anilide **2q** (0.340 g, 1.26 mmol) in THF (30 mL), KHMDS (1.52 mL, 1.52 mmol) and I_2 (0.388 g, 1.52 mmol) in THF (5 mL) to afford the title compound as a colorless solid (0.178 g, 53%). **R_f** 0.34 (3:7 hexanes/EtOAc); **M.P.** 101–103 °C; **IR** (film, ν_{max}/cm^{-1}) 2941, 1761, 1725, 1605, 1497, 1471, 1287, 1233, 1070, 1028; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.00-6.97 (m, 1H), 6.96-6.92 (m, 1H), 6.79 (dd, *J* = 8.5 Hz, 1.1 Hz, 1H), 4.33-4.17 (m, 2H), 3.77 (s, 3H), 3.20 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ (ppm) 168.4 (d, *J* =

21.3 Hz), 165.4 (d, *J* = 30.9 Hz), 156.6 (d, *J* = 2.9 Hz,), 138.4 (d, *J* = 5.2 Hz), 124.0 (d, *J* = 18.7 Hz), 117.0 (d, *J* = 3.0 Hz), 111.6 (d, *J* = 1.1 Hz), 110.0 (d, *J* = 1.4 Hz), 90.4 (d, *J* = 200.9 Hz), 63.0, 56.0, 26.8, 14.0; **HRMS (ESI$^+$)** *m/z* calcd. for $C_{13}H_{14}FNNaO_4$ [M+Na$^+$] 290.0799, found 290.0809.

Ethyl 2-iodo-2-methyl-3-(methyl(phenyl)amino)-3-oxopropanoate (A). Modified from the general procedure. Using **2a** (0.100 g, 0.43 mmol), KHMDS (0.51 mL, 0.51 mmol) and I_2 (0.130 g, 0.51 mmol). After formation of the iodide (by TLC), aq. NH_4Cl was added (20 mL) and extracted with EtOAc (2 x 20 mL), dried with $MgSO_4$ and the solvent removed *in vacuo*. The crude material was then subjected to flash chromatography (1:9 EtOAc:hexanes) and quickly transferred for ^{1}H-NMR and HRMS analysis. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.52-7.14 (m, 5H), 4.25-3.67 (m, 2H), 3.27 (s, 3H), 2.30 (s, 3H), 1.28-1.16 (m, 3H); **HRMS (ESI$^+$)** *m/z* calcd. for $C_{13}H_{16}INNaO_3$ [M+Na$^+$] 384.0067, found 384.0067.

Ethyl 2-hydroxy-2-methyl-3-(methyl(phenyl)amino)-3-oxopropanoate (5). Modified from the general procedure. Using **2a** (0.127 g, 0.54 mmol), KHMDS (0.65 mL, 0.65 mmol) and I_2 (0.166 g, 0.65 mmol). After formation of the iodide (by TLC), the reaction flask was opened to the air and stirred at rt for 18 hr. The reaction was worked–up as per the general procedure to afford **6** as a colorless oil (0.107 g, 79%). **IR** (film, ν_{max}/cm^{-1}) 3386, 2986, 2939, 1732, 1643, 1595, 1247, 1104; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.41-7.33 (m, 3H), 7.21-7.14 (m, 2H), 4.31-3.88 (m, 3H), 3.29 (s, 3H), 1.39 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ (ppm) 171.9, 170.1, 141.8, 138.6, 129.5, 128.9, 76.0, 62.2, 40.3, 24.1, 13.9; **HRMS (ESI$^+$)** *m/z* calcd. for $C_{13}H_{18}NO_4$ [M+H$^+$] 252.1230, found 252.1239.

Supporting Information

The supporting information is available free of charge on the ACS publication website at DOI:.

NMR spectra of products and new anilides (PDF).

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Notes

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