C–H Coupling

A Direct C–H/Ar–H Coupling Approach to Oxindoles, Thio-oxindoles, 3,4-Dihydro-1*H*-quinolin-2-ones, and 1,2,3,4-Tetrahydroquinolines

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Abstract: A copper(II)-catalysed approach to oxindoles, thio-oxindoles, 3,4-dihydro-1*H*-quinolin-2-ones, and 1,2,3,4-tetrahydroquinolines via formal C–H, Ar–H coupling is described. In a new variant, copper(II) 2-ethylhexanoate has been identified as an inexpensive and efficient catalyst for this transformation, which utilises atmospheric oxygen as the re-oxidant.

Introduction

Nitrogen-containing heterocycles represent an important class of biologically active molecules. In particular, the oxindole unit is a common structural feature in both natural products and pharmaceuticals,[1] such as the anticancer agent sunitinib[2] (**1**, US sales in excess of $1 bn in 2012) and the vasopressin V_2 receptor antagonist satavaptan[3] (**2**, Figure 1). Remarkably, the thio-oxindole ammosamide A (**3**) has been isolated from a marine-derived *Streptomyces* strain.[4] The 3,4-dihydro-1*H*-quinolin-2-one ring system has been shown to exhibit varied and potent biological activities.[5] Some structurally diverse examples include the dopamine agonist aripiprazole (**4**, US sales of $5.9 bn in 2012), the spirocyclic alkaloid trigolutesin A[6] (**5**), and the monoterpenoid alkaloid meloscine[7] (**6**). The extensive bioactivity of 1,2,3,4-tetrahydroquinolines, including antitumour, antiviral, antibacterial, antimalarial, and antifungal activity is well documented.[8] The 1,2,3,4-tetrahydroquinoline moiety is also present in many synthetic and naturally occurring compounds, for example the potent thrombin inhibitor argatroban[9] (**7**) and the complex alkaloid strychnochromine[10] (**8**). The development of efficient procedures for the preparation of these important heterocycles is therefore of considerable interest.

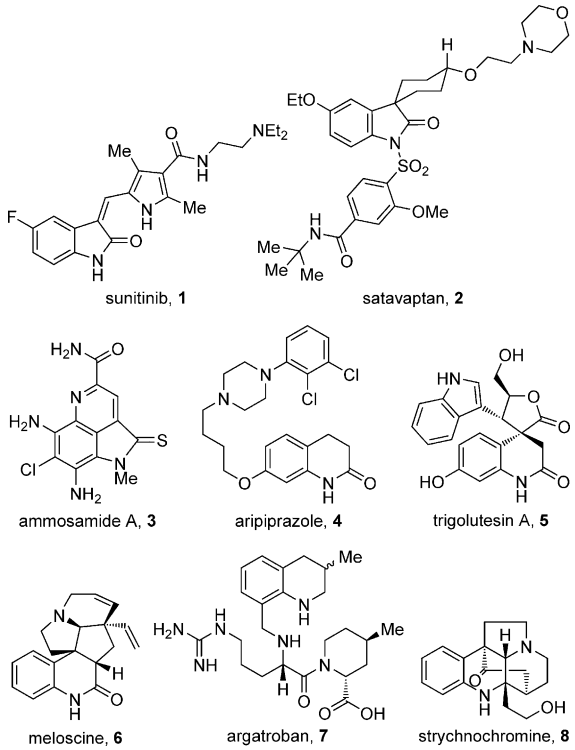

Figure 1. Examples of synthetic and naturally occurring oxindoles, thio-oxindoles, 3,4-dihydro-1*H*-quinolin-2-ones, and 1,2,3,4-tetrahydroquinolines.

Transition-metal-catalysed formation of the C3–C3a bond has emerged as a key method for the synthesis of 3,3-disubstituted oxindoles.[1a,11] In particular, cyclisation reactions of prefunctionalised anilides have predominated in this area.[12] A range of more recent metal-catalysed[13] and metal-free[14] approaches have also been reported.

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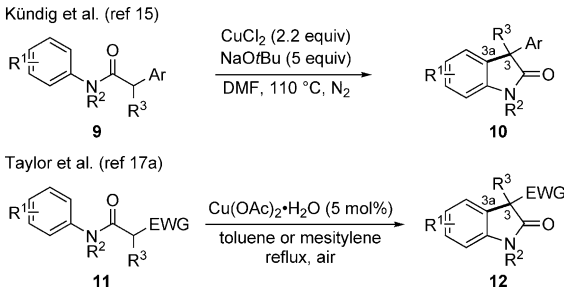
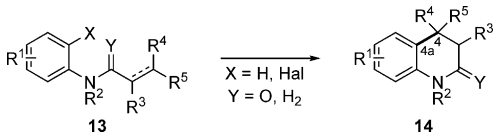


Scheme 1. Previous copper(II)-mediated approaches to oxindoles by direct C–H, Ar–H coupling.

In 2009, the research groups of Kündig[15] and Taylor[16] independently reported the cyclisation of linear anilides by direct C–H, Ar–H coupling, obviating the need for pre-functionalised substrates, using inexpensive copper salts as stoichiometric oxidants ($CuCl_2$ and $Cu(OAc)_2{\cdot}H_2O$, respectively, Scheme 1). This efficient procedure was further improved by the research group of Taylor with the discovery that catalytic $Cu(OAc)_2{\cdot}H_2O$ may be used with air serving as the terminal re-oxidant.[17] A mechanism involving deprotonation, radical formation, and homolytic aromatic substitution was proposed, initially supported by deuterium labelling[15] and radical-clock experiments,[16] and subsequently by DFT calculations carried out by the research group of Kündig.[18]

3,4-Dihydro-1*H*-quinolin-2-ones have also attracted much attention from synthetic organic chemists. With respect to disconnection of the C4–C4a bond (Scheme 2), 3,4-dihydro-1*H*-quinolin-2-ones have been prepared by Pd^{II}-catalysed Heck reactions,[19] Pd^0-catalysed cyclopropane ring expansions,[20] through multi-component reactions,[21] and from olefinated *N*-nitrosamines.[22] Transition-metal-catalysed conjugate addition/cyclisation strategies have also proved effective for the synthesis of 3,4-dihydro-1*H*-quinolin-2-ones.[23] Of particular relevance to this work, free-radical cyclisation of linear anilides has been demonstrated by several groups.[24] Notably, the majority of classical methods rely on the use of pre-functionalised substrates, while direct activation of aromatic C–H bonds is less common.



Scheme 2. Generalised approach to the synthesis of 3,4-dihydro-1*H*-quinolin-2-ones and 1,2,3,4-tetrahydroquinolines by formation of the C4–C4a bond.

1,2,3,4-Tetrahydroquinolines have also been the subject of considerable interest, and their synthesis has been recently reviewed.[8] In terms of formation of the C4–C4a bond, some recent representative examples include Pd^0-catalysed cyclopropane C–H activation,[25] Povarov reaction,[26] intramolecular Heck reaction,[27] Ni^0-mediated reductive cross-coupling,[28] Bi^{III}-catalysed Friedel–Crafts cyclisation,[29] domino reaction from benzyl azide and enamides,[30] and intramolecular radical cyclisation.[31] Although many of these methods involve a C–H activation event in one of the coupling partners,[26a–c, 29–31] the synthesis of 1,2,3,4-tetrahydroquinolines by the direct coupling of two C–H bonds remains a challenge.

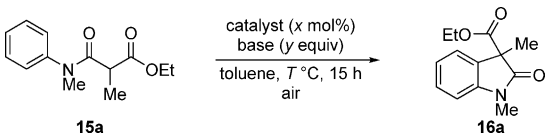
As part of our ongoing interest in the development of new approaches for the synthesis of biologically relevant heterocycles, we sought to establish a general method for the synthesis of a range of nitrogen-containing heterocycles. We now disclose Cu(2-ethylhexanoate)$_2$ as a new and efficient catalyst for the synthesis of 3,3-disubstituted oxindoles, thio-oxindoles, and related 6-membered ring systems—3,4-dihydro-1*H*-quinolin-2-ones and 1,2,3,4-tetrahydroquinolines—by direct C–H, Ar–H coupling.

Results and Discussion

Optimisation

The initial aim was to further optimise our previously established[17a] conditions for the copper(II)-catalysed synthesis of oxindoles from linear anilides, and then apply this catalyst to a range of nitrogen-containing heterocycles. Repetition of the cyclisation of anilide **15a** with 10 mol% $Cu(OAc)_2{\cdot}H_2O$ in toluene at 120 °C for 15 h under an atmosphere of air gave desired oxindole **16a** in 85% yield (Table 1, entry 1). After a brief screen of copper salts (entries 2–4), commercially available

Table 1. Optimisation of the formation of oxindoles using catalytic copper salts.[a]



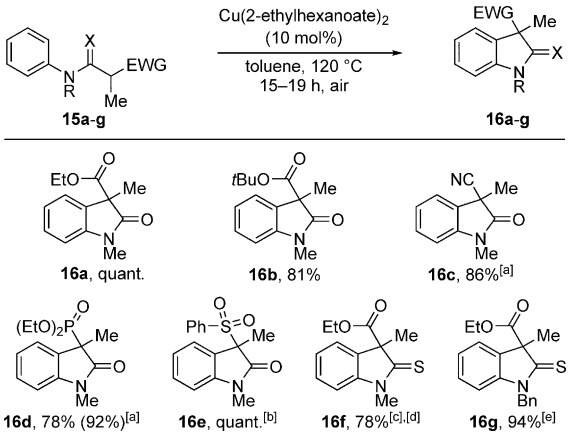
Entry	Catalyst	*x* [mol%]	Base	*y* [equiv]	*T* [°C]	Yield[d] [%]
1	$Cu(OAc)_2{\cdot}H_2O$	10	–	–	120	85
2	$Cu(2\text{-}PC)_2$	10	–	–	120	46
3	$CuOTf(MeCN)_4$	10	–	–	120	73
4	**Cu(2-ethylhexanoate)$_2$**	**10**	**–**	**–**	**120**	**quant.**[b]
5	Cu(2-ethylhexanoate)$_2$	1	–	–	120	71
6	Cu(2-ethylhexanoate)$_2$	0.1	–	–	120	16
7[c]	Cu(2-ethylhexanoate)$_2$	10	–	–	100	34
8[c]	Cu(2-ethylhexanoate)$_2$	10	NaH	2	100	(5)
9[c]	Cu(2-ethylhexanoate)$_2$	10	piperidine	10	100	45
10[c]	Cu(2-ethylhexanoate)$_2$	10	DBU	2	100	(22)
11[c]	**Cu(2-ethylhexanoate)$_2$**	**10**	**DIPEA**	**2**	**100**	**89**
12[c]	Cu(2-ethylhexanoate)$_2$	10	DIPEA	2	80	35

[a] reactions were performed using 0.4 mmol of **15a** at a concentration of 0.05 M. [b] other solvents were also examined: DMF (37%), MeCN (trace), 1,4-dioxane (trace), DMSO (trace). [c] 40 h reaction time. [d] Yields were determined upon isolation; values in parentheses represent yields determined from the ^{1}H NMR spectrum of the crude reaction mixture using 1,1,2,2-tetrachloroethane as internal standard. 2-PC = 2-pyrazinecarboxylate. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. DIPEA = diisopropylethylamine, Tf = trifluoromethanesulfonyl.

$Cu(2\text{-ethylhexanoate})_2$ was identified as a superior catalyst, giving **16a** in quantitative yield (entry 4). Other solvents (DMF, MeCN, dioxane, DMSO) were found to be unsuitable, giving poor conversions. Reduction in the catalyst loading to 1 mol% gave a lower but still synthetically useful 71% yield of the desired oxindole (entry 5), although 0.1 mol% catalyst was not as efficient (entry 6). Lowering the temperature to 100 °C significantly reduced the yield to 34%, even after an extended reaction time (entry 7). Addition of bases was therefore examined in an attempt to increase the yield at this lower temperature (entries 8–11). DIPEA was found to be the best base, giving 89% yield of **16a** at 100 °C (entry 11). However, a relatively long reaction time (40 h) was still required. Lowering the temperature still further to 80 °C led to a poor yield of product, even with the addition of base (entry 12). After extensive screening, the optimum conditions with respect to catalyst loading, temperature, and time are therefore: $Cu(2\text{-ethylhexanoate})_2$ (10 mol%), toluene, 120 °C, 15 h; or, if lower temperature is required then $Cu(2\text{-ethylhexanoate})_2$ (10 mol%), DIPEA (2.0 equiv), toluene, 100 °C, 40 h.

Synthesis of oxindoles and thio-oxindoles

With the optimised conditions established, a series of representative oxindoles **16a–e** were prepared to test the scope of this new catalyst system (Scheme 3). As expected, various activating groups were well tolerated in the reaction, and the yields obtained were similar or better than those obtained under the previous $Cu(OAc)_2{\cdot}H_2O$ conditions. In some cases (EWG = CN, $P(O)(OEt)_2$), switching the solvent to mesitylene and increasing the temperature to 170 °C was required to obtain oxindoles **16c,d** in high yield. Cyclisation of an anilide bearing a sulfone (EWG = SO_2Ph) proved somewhat sluggish by using the standard conditions. However, quantitative yield of **16e** was obtained by increasing the amount of copper salt to 2 equivalents, with the addition of DIPEA, at elevated temperature. Importantly, poor conversion to **16e** was observed when $Cu(OAc)_2{\cdot}H_2O$ was used as catalyst, clearly demonstrating the superiority of the $Cu(2\text{-ethylhexanoate})_2$ system.

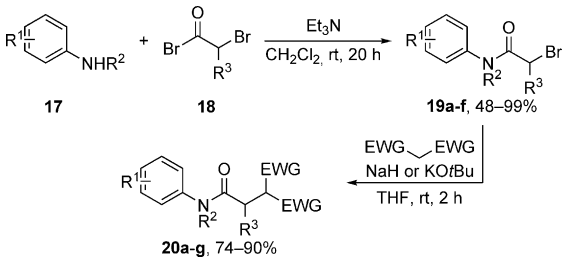


Scheme 3. Synthesis of oxindoles **16a–e** and thio-oxindoles **16f–g**. Reactions were performed using 0.285 mmol of **15** with 10 mol% catalyst at a concentration of 0.05 M unless otherwise stated. [a] Mesitylene was used as solvent at 170 °C for 3 h. [b] 2 equiv $Cu(2\text{-ethylhexanoate})_2$ and 5 equiv DIPEA were used in mesitylene at 170 °C for 19 h. [c] 2×10 mol% catalyst and 2.4 equiv DIPEA were used for 48 h. [d] Reaction was conducted on 13.9 mmol scale. [e] 2.4 equiv DIPEA was added.

Although less common than oxindoles, thio-oxindoles are useful synthetic intermediates.[32] Typically, they are prepared from pre-formed oxindoles on treatment with Lawesson's reagent. We sought to extend our methodology by applying it to the de novo construction of the thio-oxindole motif. In the event, treatment of linear thioanilides **15f,g** with 10–20 mol% catalyst delivered thio-oxindoles **16f,g** in excellent yield, providing new access to this class of heterocycle. It is noteworthy that the cyclisation to give **16f** was conducted on multi-gram scale.

Synthesis of 3,4-dihydro-1*H*-quinolin-2-ones

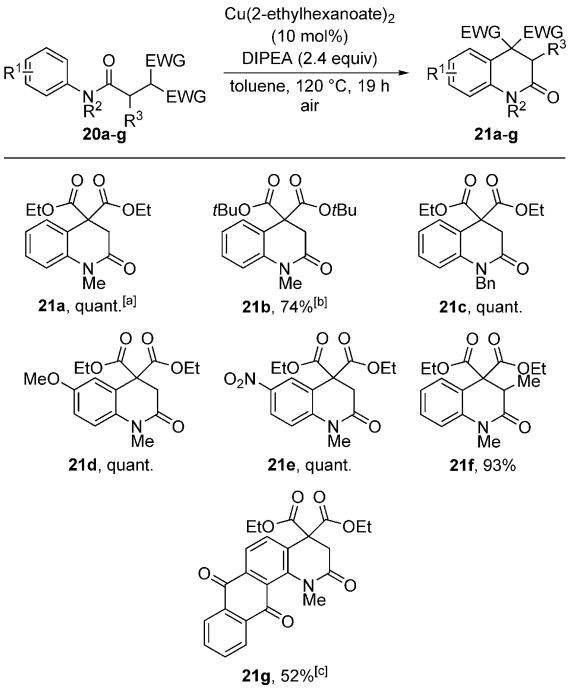
Having successfully established an improved catalyst system for the synthesis of oxindoles, preparation of the corresponding 3,4-dihydro-1*H*-quinolin-2-ones was next examined. The required linear anilides, **20a–g**, were rapidly accessed in 2 steps from commercially available anilines **17** by acylation followed by alkylation with an activated methylene compound, generally in high yield (Scheme 4).



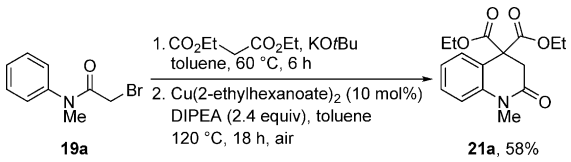
Scheme 4. Synthesis of 3,4-dihydro-1*H*-quinolin-2-one cyclisation precursors **20a–g**.

Tsubusaki and Nishino have previously demonstrated the cyclisation of anilides to give 3,4-dihydro-1*H*-quinolin-2-ones in high yield using manganese(III) acetate as the oxidant.[24d] However, stoichiometric amounts (3–10 equiv) of $Mn(OAc)_3$ were required in refluxing acetic acid as solvent, potentially limiting the scalability and substrate scope. Cyclisation of model substrate **20a** under our milder catalytic conditions [10 mol% $Cu(2\text{-ethylhexanoate})_2$, toluene, 120 °C, 19 h] led to a disappointing 46% conversion to desired 3,4-dihydro-1*H*-quinolin-2-one **21a** (Scheme 5). Pleasingly, cyclisation of **20a** with added base delivered **21a** in quantitative yield.

The scope of this copper(II)-catalysed synthesis of 3,4-dihydro-1*H*-quinolin-2-ones was next investigated. As may be expected from the results obtained with the corresponding oxindoles, a *tert*-butyl ester activating group could be utilised in the reaction to give **21b** in 74% yield. A benzyl protecting group on the nitrogen atom and electron-donating and electron-withdrawing groups on the aromatic ring were also well



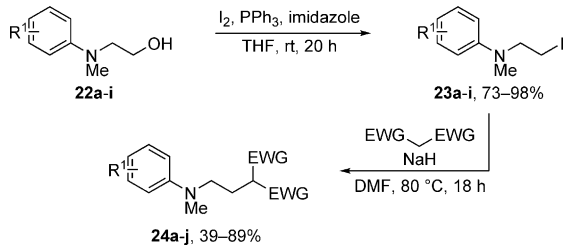
Scheme 5. Synthesis of 3,4-dihydro-1*H*-quinolin-2-ones **21 a**–**g**. Reactions were performed by using 0.165 mmol of **20** with 10 mol% catalyst and 2.4 equiv DIPEA at a concentration of 0.04 M unless otherwise stated. [a] In the absence of DIPEA, 46% conversion was observed based on the ratio of anilide to product in the ^{1}H NMR spectrum of the crude reaction mixture. [b] Mesitylene was used as solvent at 165 °C for 2 h. [c] Reaction was conducted on 0.500 mmol scale with 1 equiv of Cu(2-ethylhexanoate)$_2$ in mesitylene at 165 °C for 21 h.



Scheme 6. One-pot synthesis of 3,4-dihydro-1*H*-quinolin-2-one **21 a**.

Synthesis of tetrahydroquinolines

Having demonstrated the efficient synthesis of oxindoles and 3,4-dihydro-1*H*-quinolin-2-ones, attention turned to application of the copper(II) catalyst system to the preparation of 1,2,3,4-tetrahydroquinolines. The required cyclisation precursors **24 a**–**j** were readily accessible in 2 steps from 2-((aryl)methylamino)alcohols **22 a**–**i** by simple conversion to the iodide followed by alkylation (Scheme 7).

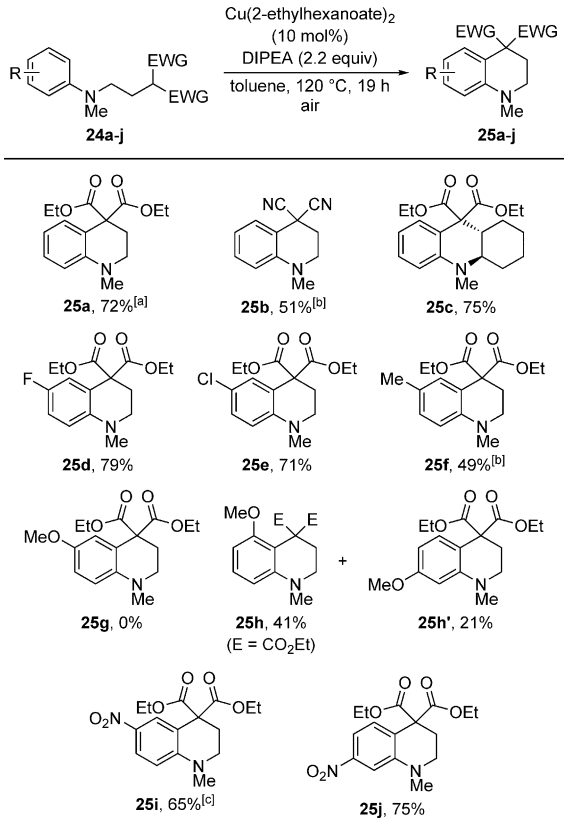


Scheme 7. Synthesis of 1,2,3,4-tetrahydroquinoline cyclisation precursors **24 a**–**j**.

tolerated (**21 c**–**e**). Introduction of an alkyl group at C-3 (R^3 = Me) was shown to hinder the reaction under the previous $Mn(OAc)_3$ conditions, delivering **21 f** in 61% yield along with 28% yield of an over-oxidation by-product. However, a much improved yield of 93% was obtained by using our copper(II)-catalysed transformation. A more complex substrate based on the 1-aminoanthraquinone scaffold was also successfully cyclised to give tetracycle **21 g** in 52% yield, with the lower than expected yield owing to competing hydrolysis of the amide during the reaction. Notably, for those 3,4-dihydro-1*H*-quinolin-2-ones previously prepared by Nishino's stoichiometric $Mn(OAc)_3$ procedure (**21 a**, **21 c**–**f**), equal or superior yields were obtained using the copper(II) method, which uses only catalytic amounts of transition-metal salt under much milder reaction conditions.

We have previously demonstrated a telescoped alkylation/cyclisation sequence for the synthesis of oxindoles.[16a] It was anticipated that a similar strategy could be applied to the one-pot synthesis of 3,4-dihydro-1*H*-quinolin-2-ones. In the event, treatment of **19 a** with diethyl malonate and KO*t*Bu in toluene at 60 °C for 6 h, followed by addition of copper(II) 2-ethylhexanoate and DIPEA and heating at 120 °C for a further 18 h delivered 3,4-dihydro-1*H*-quinolin-2-one **21 a** in 58% unoptimised yield (Scheme 6).

In general, cyclisation of the aniline-derived substrates **24** was slightly lower yielding than the corresponding anilides **20**. For example, treatment of model substrate **24 a** with 10 mol% copper(II) 2-ethylhexanoate gave 1,2,3,4-tetrahydroquinoline **25 a** in 72% yield after 19 h (Scheme 8). Once again, improved conversion to the desired product was observed on addition of DIPEA. Likewise, $Cu(OAc)_2{\cdot}H_2O$ proved an inferior catalyst, with only 40% conversion observed in the same timeframe. In the case of nitrile **25 b**, 1 equivalent of the copper salt was required to obtain a modest 51% yield. Substitution in the aliphatic chain was well tolerated, giving access to hexahydroacridine **25 c** in 75% yield. Electron-neutral and electron-poor anilines proved generally more amenable to cyclisation. Indeed, anilines bearing a halogen substituent (R = F, Cl) proved good substrates, giving **25 d**,**e** in 71–79% yield. More electron-rich anilines (R = Me) required a stoichiometric amount of copper to give a modest yield of **25 f**, while incorporation of a *para*-methoxy group retarded the reaction completely, leading to complete decomposition of the starting material. Assuming a similar mechanism to that proposed for the synthesis of oxindoles is in operation, these results are somewhat incongruous given that homolytic aromatic substitution should actually be preferred between an electron-rich aromatic ring and the electron-deficient radical derived from a malonate. To ensure that a radical mechanism was indeed in operation, control reactions were carried out by performing the cyclisation of **24 e** and **24 j** in the presence of DIPEA but without cop-

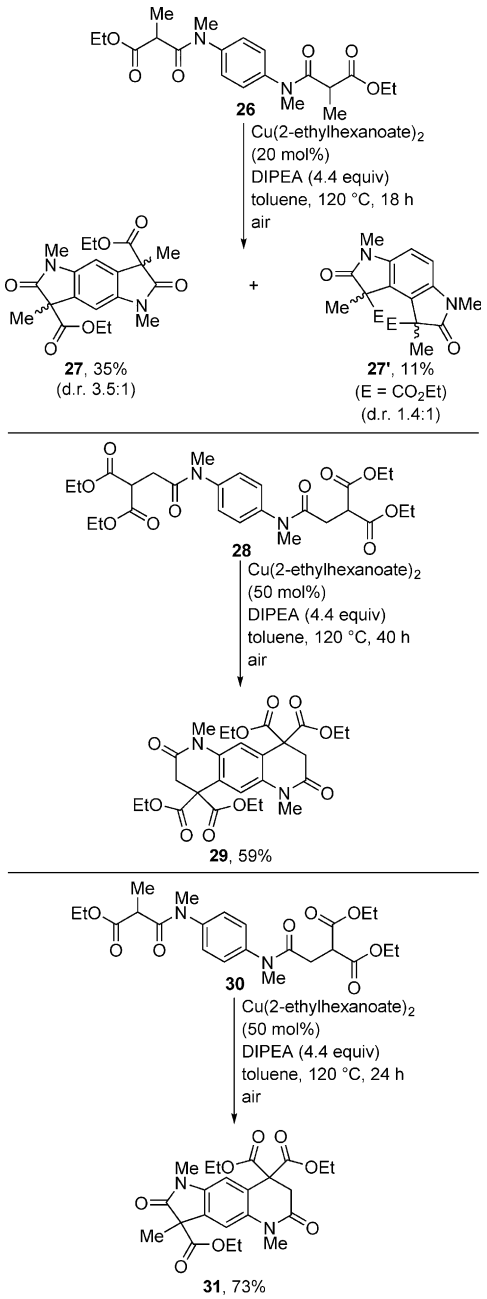


Scheme 8. Synthesis of tetrahydroquinolines **25a–j**. Reactions were performed using 0.30–1.00 mmol of **24** with 10 mol% catalyst and 2.2 equiv DIPEA at a concentration of 0.1 M unless otherwise stated. [a] In the absence of DIPEA, 69% conversion was observed based on the ratio of aniline to product in the ^{1}H NMR spectrum of the crude reaction mixture. [b] 100 mol% catalyst used. [c] 20 mol% catalyst used.

per(II) 2-ethylhexanoate. In both cases only starting material was recovered, ruling out nucleophilic aromatic substitution as a competing mechanism. Further support for a radical mechanism was obtained by observing the regioselectivity in the cyclisation of *meta*-substituted substrates **24h** and **24j**. In the event, *meta*-methoxy substrate **24h** gave a separable 2:1 mixture of *ortho*- and *para*-cyclisation products (**25h**/**25h**′), while the *meta*-nitro aniline **24j** gave solely *para*-cyclised product **25j**. Both these results may be rationalised by homolytic aromatic substitution to give preferentially the most stable radical, as previously observed in the synthesis of oxindoles.[17b]

Double cyclisations to access fused tricyclic systems

Dihydropyrroloindolediones have recently been accessed by a double Pummerer rearrangement,[33] and have been used to prepare copolymers that have shown promise in organic electronics applications.[34] However, the substrates for the Pummerer rearrangement required multi-step synthesis. We envisaged an expeditious route to this class of heterocycle by using our copper(II)-catalysed transformation. As such, the double cyclisation of 1,4-diaminobenzene derivatives was examined (Scheme 9).



Scheme 9. Double copper(II)-catalysed cyclisation of linear 1,4-bis-anilides.

Firstly, cyclisation of linear bis-anilide **26** gave a separable mixture of bis-oxindoles **27**/**27**′ in 35% and 11% yield, respectively, the structures of which were assigned based on HMBC correlations.[35] Both **27** and **27**′ were obtained as an inseparable mixture of diastereomers, in a ratio of 3.5:1 and 1.4:1, respectively. Furthermore, cyclisation of anilide **28** gave bis-3,4-dihydro-1*H*-quinolin-2-one **29** as a single product in 59% yield. Finally, a mixed linear precursor **30** corresponding to both the oxindole and 3,4-dihydro-1*H*-quinolin-2-one ring systems was prepared, giving tricyclic product **31** in good yield.

Conclusion

In summary, we report a simple copper(II) catalyst for the synthesis of oxindoles, thio-oxindoles, 3,4-dihydro-1*H*-quinolin-2-ones, and 1,2,3,4-tetrahydroquinolines from linear precursors by direct C–H, Ar–H coupling. The cyclisations are simple to perform, are run open to the air, are moisture insensitive, and use an inexpensive catalyst. Furthermore, our catalyst system has been shown to be superior to existing methods, including $Cu(OAc)_2{\cdot}H_2O$ and $Mn(OAc)_3$. Applications involving double cyclisations hold promise for future studies. Application of this copper(II)-catalysed methodology in the total synthesis of natural products is also under investigation.

Experimental Section

General procedure for the copper(II)-catalysed synthesis of oxindoles 16a–e (Scheme 3)

A solution of the anilide **15** (0.285 mmol) and copper(II) 2-ethylhexanoate (10.0 mg, 10 mol%) in toluene (5 mL) was stirred at 120 °C for 19 h under a reflux condenser open to the air. After cooling to rt, the toluene was removed under reduced pressure and EtOAc (10 mL) was added. The organic phase was washed with saturated NH_4Cl (10 mL), and the aqueous layer back extracted with EtOAc (10 mL). The combined organic layers were washed with 10% NH_4OH (10 mL) and saturated brine (2×10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with EtOAc/petroleum ether (1:4), to afford the title compound.

Ethyl 1,3-dimethyl-2-oxoindoline-3-carboxylate 16a: yellow oil; $R_f = 0.21$ (EtOAc/petroleum ether 1:4); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.30$ (td, $J = 7.6$, 1.2 Hz, 1H), 7.23 (dd, $J = 7.6$, 1.2 Hz, 1H), 7.04 (td, $J = 7.6$, 1.2 Hz, 1H), 6.85 (d, $J = 7.6$ Hz, 1H), 4.12 (dq, $J = 11.0$, 7.1 Hz, 1H), 4.07 (dq, $J = 11.0$, 7.1 Hz, 1H), 3.23 (s, 3H), 1.64 (s, 3H), 1.13 ppm (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 175.1$ (C), 169.6 (C), 143.5 (C), 130.1 (C), 128.9 (CH), 122.8 (CH), 122.7 (CH), 108.3 (CH), 61.8 (CH_2), 54.9 (C), 26.4 (Me), 20.0 (Me), 13.8 ppm (Me); IR (ATR): $\tilde{\nu} = 1729$ (C=O), 1689 cm^{-1} (C=O); HRMS (ESI): *m/z* calcd for $C_{13}H_{15}NO_3 + H^+$: 234.1125 [$M + H^+$]; found: 234.1126. Physical and spectral data were found to be consistent with those reported.[16a]

***tert*-Butyl 1,3-dimethyl-2-oxoindoline-3-carboxylate 16b**: colourless oil; $R_f = 0.50$ (EtOAc/petroleum ether, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.29$ (td, $J = 7.6$, 1.0 Hz, 1H), 7.22 (dd, $J = 7.6$, 1.0 Hz,1H), 7.03 (td, $J = 7.6$, 1.0 Hz,1H), 6.83 (d, $J = 7.6$ Hz,1H), 3.21 (s,3H), 1.59 (s, 3H), 1.32 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 175.6$ (C), 168.7 (C), 143.8 (C), 130.7 (C), 128.8 (CH), 122.8 (CH),122.8 (CH), 108.3 (CH), 82.3 (C), 56.1 (C), 27.7(Me), 26.5 (Me), 19.8 ppm (Me). Physical and spectral data were found to be consistent with those reported.[16a]

1,3-Dimethyl-2-oxoindoline-3-carbonitrile 16c: reaction was conducted in mesitylene at 170 °C for 3 h; pale yellow oil; $R_f = 0.60$ (EtOAc/petroleum ether, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.41$ (d, $J = 7.6$ Hz, 1H), 7.39 (td, $J = 7.6$, 1.0 Hz, 1H), 7.16 (td, $J = 7.6$, 1.0 Hz, 1H), 6.90 (d, $J = 7.9$ Hz, 1H), 3.25 (s, 3H), 1.80 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.1$ (C), 142.6 (C), 130.4 (CH), 126.9 (C), 124.0 (CH), 123.8 (CH), 117.8 (C), 109.3 (CH), 42.2 (C), 27.1 (Me), 23.5 ppm (Me). Physical and spectral data were found to be consistent with those reported.[16a]

Diethyl 1,3-dimethyl-2-oxoindolin-3-ylphosphonate 16d: reaction was conducted in mesitylene at 170 °C for 3 h; colourless oil; $R_f = 0.20$ (EtOAc/petroleum ether 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.43$ (d, $J = 7.9$ Hz, 1H), 7.26 (tt, $J = 7.9$, 1.5 Hz, 1H), 7.04 (t, $J = 7.9$ Hz, 1H), 6.80 (d, $J = 7.9$ Hz, 1H), 4.14 (dq, $J = 8.6$(H,P), 7.1 Hz, 2H), 3.92 (ddq, $J = 10.2$, 8.6(H,P), 7.1 Hz, 1H), 3.81 (ddq, $J = 10.2$, 8.6(H,P), 7.1 Hz, 1H), 3.19 (s, 3H), 1.66 (d, J(H,P) = 17.3 Hz, 3H), 1.31 (t, $J = 7.1$ Hz, 3H), 1.02 ppm (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 174.7$ (d, J(C,P) = 2.5 Hz, C), 143.7 (d, J(C,P) = 7.5 Hz, C), 128.8 (d, J(C,P) = 2.8 Hz, CH), 127.9 (d, J(C,P) = 6.0 Hz, C), 125.2 (d, J(C,P) = 3.7 Hz, CH), 122.7 (d, J(C,P) = 3.0 Hz, CH), 108.1 (d, J(C,P) = 1.3 Hz, CH), 64.0 (d, J(C,P) = 6.9 Hz, CH_2), 63.2 (d, J(C,P) = 7.5 Hz, CH_2), 50.0 (d, J(C,P) = 136.9 Hz, C), 26.7 (Me), 18.6 (d, J(C,P) = 6.2 Hz, Me), 16.5 (d, J(C,P) = 5.7 Hz, Me), 16.2 ppm (d, J(C,P) = 5.6 Hz, Me); IR (ATR): $\tilde{\nu} = 1711$ cm^{-1} (C=O); HRMS (ESI): *m/z* calcd for $C_{14}H_{20}NO_4P + Na^+$: 320.1022 [$M + Na^+$]; found: 320.1022. Physical and spectral data were found to be consistent with those reported.[16a]

1,3-Dimethyl-3-(phenylsulfonyl)indolin-2-one 16e: reaction was conducted with 2 equiv of catalyst and with 5 equiv of DIPEA in mesitylene at 170 °C for 19 h; colourless solid; $R_f = 0.30$ (EtOAc/petroleum 1:1); m.p. 109–111 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.64$ (dd, $J = 7.6$, 1.0 Hz, 1H), 7.56–7.50 (m, 3H), 7.37–7.29 (m, 3H), 7.15 (td, $J = 7.6$, 1.0 Hz, 1H), 6.59 (d, $J = 7.6$ Hz, 1H), 2.91 (s, 3H), 1.90 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.9$ (C), 143.9 (C), 134.6 (C), 134.2 (CH), 130.6 (CH), 130.2 (CH), 128.3 (CH), 126.4 (CH), 124.1 (C), 123.3 (CH), 108.2 (CH), 70.9 (C), 26.4 (Me), 15.8 ppm (Me); IR (ATR): $\tilde{\nu} = 1718$ cm^{-1} (C=O); HRMS (ESI): *m/z* calcd for $C_{16}H_{15}NO_3S + Na^+$: 324.0665 [$M + Na^+$]; found: 324.0659.

Ethyl 1,3-dimethyl-2-thioxoindoline-3-carboxylate 16f: A solution of ethyl 2-methyl-3-(methyl(phenyl)amino)-3-thioxopropanoate **15f** (3.50 g, 13.9 mmol), copper(II) 2-ethylhexanoate (0.486 g, 10 mol%), and DIPEA (5.81 mL, 33.4 mmol) in toluene (360 mL) was stirred at 120 °C for 24 h under a reflux condenser open to the air. Further catalyst (0.486 g, 10 mol%) was added and stirring continued at 120 °C for a further 24 h. After cooling to rt, the toluene was removed under reduced pressure and EtOAc (100 mL) was added. The organic phase was washed with 10% HCl (60 mL), 10% NH_4OH (60 mL), and saturated brine (60 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with EtOAc/petroleum ether (3:17), to afford the title compound as an off-white powder (2.69 g, 78%). $R_f = 0.23$ (EtOAc/petroleum 2:5); m.p. 66–67 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.38$ (td, $J = 7.6$, 1.2 Hz, 1H), 7.28 (dd, $J = 7.6$, 1.2 Hz, 1H), 7.18 (td, $J = 7.6$, 1.2 Hz, 1H), 7.04 (d, $J = 7.6$ Hz, 1H), 4.14 (dq, $J = 10.8$, 7.1 Hz, 1H), 4.03 (dq, $J = 10.8$, 7.1 Hz, 1H), 3.66 (s, 3H), 1.74 (s, 3H), 1.10 ppm (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 203.9$ (C), 169.2 (C), 145.1 (C), 134.7 (C), 128.9 (CH), 124.5 (CH), 122.9 (CH), 109.7 (CH), 65.2 (C), 61.9 (CH_2), 31.5 (Me), 23.9 (Me), 13.8 ppm (Me); IR (ATR): $\tilde{\nu} = 1736$ (C=O), 1101 cm^{-1} (C=S); HRMS (ESI): *m/z* calcd for $C_{13}H_{15}NO_2S + Na^+$: 272.0896 [$M + Na^+$]; found: 272.0905.

Ethyl 1-benzyl-3-methyl-2-thioxoindoline-3-carboxylate 16g: A solution of ethyl 3-(benzyl(phenyl)amino)-2-methyl-3-thioxopropanoate **15g** (0.107 g, 0.326 mmol), copper(II) 2-ethylhexanoate (11.4 mg, 10 mol%), and DIPEA (0.136 mL, 0.782 mmol) in toluene (8 mL) was stirred at 120 °C for 15 h under a reflux condenser open

to the air. After cooling to rt, the toluene was removed under reduced pressure and EtOAc (15 mL) was added. The organic phase was washed with 10% HCl (2×15 mL), 10% NH_4OH (2×15 mL), and saturated brine (15 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with EtOAc/petroleum ether (1:9), to afford the title compound as a colourless powder. $R_f = 0.21$ (EtOAc/petroleum ether 1:9); m.p. 76–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.35$–7.22 (m, 7H), 7.14 (t, $J = 7.5$ Hz, 1H), 6.87 (d, $J = 7.5$ Hz, 1H), 5.79 (d, $J = 15.5$ Hz, 1H), 5.17 (d, $J = 15.5$ Hz, 1H), 4.24–4.16 (m, 1H), 4.06–3.98 (m, 1H), 1.81 (s, 3H), 1.13 ppm (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 204.7$ (C), 169.2 (C), 144.3 (C), 134.6 (C), 134.3 (C), 128.9 (CH), 128.7 (CH), 127.7 (CH), 126.9 (CH), 124.4 (CH), 122.9 (CH), 110.6 (CH), 65.3 (C), 62.0 (CH_2), 47.8 (CH_2), 23.8 (Me), 13.7 ppm (Me); IR (ATR): $\tilde{\nu} = 1738$ (C=O), 1108 cm^{-1} (C=S); HRMS (ESI): *m/z* calcd for $C_{19}H_{19}NO_2S + H^+$: 326.1209 [$M + H^+$]; found: 326.1216.

General procedure for the copper(II)-catalysed synthesis of 3,4-dihydro-1*H*-quinolin-2-ones 21 a–g (Scheme 5)

To a solution of the anilide **20** (0.165 mmol) and copper(II) 2-ethylhexanoate (5.8 mg, 10 mol%) in toluene (4 mL) was added DIPEA (69.0 μL, 0.432 mmol). The reaction mixture was stirred at 120 °C for 15 h under a reflux condenser open to the air. After cooling to rt, the toluene was removed under reduced pressure and EtOAc (10 mL) was added. The organic phase was washed with 10% HCl (10 mL), 10% NH_4OH (10 mL), and saturated brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with EtOAc/petroleum ether (1:3 to 2:3), to afford the title compound.

Diethyl 1-methyl-2-oxo-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 21 a: colourless powder; $R_f = 0.23$ (EtOAc/petroleum ether 3:10); m.p. 80–81 °C (lit. 86–87 °C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.35$ (ddd, $J = 8.0$, 7.2, 1.6 Hz, 1H), 7.28 (dd, $J = 8.0$, 1.6 Hz, 1H), 7.09 (td, $J = 7.6$, 1.2 Hz, 1H), 7.01 (dd, $J = 8.0$, 1.2 Hz, 1H), 4.28–4.21 (m, 4H), 3.32 (s, 3H), 3.22 (s, 2H), 1.25 ppm (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 169.1$ (C), 166.8 (C), 140.0 (C), 129.5 (CH), 127.9 (CH), 123.3 (CH), 122.7 (C), 115.4 (CH), 62.5 (CH_2), 57.0 (C), 38.1 (CH_2), 29.7 (Me), 14.0 ppm (Me); IR (ATR): $\tilde{\nu} = 1729$ (C=O), 1658 cm^{-1} (C=O); HRMS (ESI): *m/z* calcd for $C_{16}H_{19}NO_5 + H^+$: 306.1336 [$M + H^+$]; found: 306.1336. Physical and spectral data were found to be consistent with those reported.[24d]

Di(*tert*-butyl) 1-methyl-2-oxo-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 21 b: reaction was conducted in mesitylene at 165 °C for 2 h; colourless solid; $R_f = 0.58$ (EtOAc/petroleum 1:1); m.p. 69–71 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.39$ (dd, $J = 7.7$, 1.5 Hz, 1H), 7.34 (ddd, $J = 8.1$, 7.5, 1.5 Hz, 1H), 7.10 (td, $J = 7.6$, 1.2 Hz, 1H), 7.01 (dd, $J = 8.2$, 1.0 Hz, 1H), 3.33 (s, 3H), 3.10 (s, 2H), 1.47 ppm (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 168.1$(C), 167.2 (C), 139.9 (C), 129.0 (CH), 127.5 (CH), 123.6 (C), 123.0 (CH), 115.2 (CH), 82.9 (C), 57.8 (C), 38.4 (CH_2), 29.6 (Me), 27.7 ppm (Me); IR (ATR): $\tilde{\nu} = 1728$ (C=O), 1686 cm^{-1} (C=O); HRMS (ESI): *m/z* calcd for $C_{20}H_{27}NO_5 + Na$: 384.1718 [$M + Na$]; found: 384.1788.

Diethyl 1-benzyl-2-oxo-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 21 c: colourless crystals; $R_f = 0.50$ (EtOAc/petroleum ether 1:1); m.p. 80–81 °C (lit. 96–97 °C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.34$–7.14 (m, 7H), 7.05 (td, $J = 7.6$, 1.2 Hz, 1H), 6.92 (dd, $J = 8.2$, 1.0 Hz, 1H), 5.17 (s, 2H), 4.32–4.21 (m, 4H), 3.36 (s, 2H), 1.27 ppm (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 169.0$ (C), 166.8 (C), 138.9 (C), 136.4 (C), 129.3 (CH), 128.7 (CH), 128.1 (CH), 127.1 (CH), 126.4 (CH), 123.3 (CH), 122.7 (C), 116.2 (CH), 62.5 (CH_2), 57.0 (C), 45.9 (CH_2), 38.1 (CH_2), 13.9 ppm (Me); IR (ATR): $\tilde{\nu} = 1757$ (C=O), 1724 (C=O), 1678 cm^{-1} (C=O); HRMS (ESI): *m/z* calcd for $C_{22}H_{23}NO_5 + Na^+$: 404.1468 [$M + Na^+$]; found: 404.1465. Physical and spectral data were found to be consistent with those reported.[24d]

Diethyl 6-methoxy-1-methyl-2-oxo-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 21 d: yellow oil; $R_f = 0.38$ (EtOAc/petroleum ether 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.95$–6.91 (m, 1H), 6.89–6.84 (m, 2H), 4.31–4.19 (m, 4H), 3.77 (s, 3H), 3.28 (s, 3H), 3.18 (s, 2H), 2.25 ppm (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 168.8$ (C), 166.3 (C), 155.3 (C), 133.4 (C), 123.8 (C), 116.2 (CH), 114.1 (CH), 113.7 (CH), 62.4 (CH_2), 56.9 (C), 55.5 (Me), 38.0 (CH_2), 29.7 (Me), 13.9 ppm (Me); IR (ATR): $\tilde{\nu} = 1730$ (C=O), 1675 cm^{-1}(C=O); HRMS (ESI): *m/z* calcd for $C_{17}H_{21}NO_6 + Na^+$: 358.1261 [$M + Na^+$]; found: 358.1258. Physical and spectral data were found to be consistent with those reported.[24d]

Diethyl 1-methyl-6-nitro-2-oxo-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 21 e: yellow solid; $R_f = 0.23$ (EtOAc/petroleum ether 2:3); m.p. 82–84 °C (lit. 89 °C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.30$–8.23 (m, 2H), 7.13 (d, $J = 8.9$ Hz, 1H), 4.32–4.22 (m, 4H), 3.39 (s, 3H), 3.27 (s, 2H), 1.31–1.27 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 167.9$ (C), 166.3 (C), 145.2 (C), 142.8 (C), 125.2 (CH), 124.0 (CH), 123.0 (C), 115.4 (CH), 63.0 (CH_2), 56.3 (C), 37.3 (CH_2), 30.0 (Me), 13.9 ppm (Me); IR (ATR): $\tilde{\nu} = 1731$ (C=O), 1696 cm^{-1}(C=O); HRMS (ESI): *m/z* calcd for $C_{16}H_{18}N_2O_7 + Na^+$: 373.1006 [$M + Na^+$]; found: 373.1000. Physical and spectral data were found to be consistent with those reported.[24d]

Diethyl 1,3-dimethyl-2-oxo-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 21 f: colourless solid; $R_f = 0.45$ (EtOAc/petroleum ether 1:1); m.p. 59–61 °C (lit. 60–61 °C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.53$ (dd, $J = 7.6$, 1.2 Hz, 1H), 7.36–7.31 (m, 1H), 7.10 (td, $J = 7.6$, 1.2 Hz, 1H), 6.98 (dd, $J = 7.6$, 1.2 Hz, 1H), 4.30–4.07 (m, 4H), 3.33 (s, 3H), 3.30 (q, $J = 7.2$ Hz, 1H), 1.23 (t, $J = 7.1$ Hz, 3H), 1.21 (t, $J = 7.2$ Hz, 3H), 1.21 ppm (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 169.9$ (C), 169.1 (C), 167.7 (C), 139.6 (C), 129.5 (CH), 129.2 (CH), 123.0 (CH), 121.5 (C), 114.9 (CH), 62.1 (CH_2), 61.7 (CH_2), 60.6 (C), 41.3 (CH), 29.8 (Me), 13.9 (Me), 13.8 (Me), 12.5 ppm (Me); IR (ATR): $\tilde{\nu} = 1706$ (C=O), 1659 cm^{-1} (C=O); HRMS (ESI): *m/z* calcd for $C_{17}H_{21}NO_5 + Na^+$: 342.1312 [$M + Na^+$]; found: 342.1309. Physical and spectral data were found to be consistent with those reported.[24d]

4,4-Diethyl 1-methyl-2,7,12-trioxo-1,2,3,4,7,12-hexahydro-1-azatetraphene-4,4-dicarboxylate 21 g: reaction was conducted with 1 equiv of catalyst and with 2.2 equiv of DIPEA in mesitylene at 165 °C for 21 h; yellow solid; $R_f = 0.50$ (EtOAc/CH_2Cl_2 1:9); m.p. 160.5–162.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.26$–8.24 (m, 1H), 8.21–8.18 (m, 1H), 8.16 (d, $J = 8.0$ Hz, 1H), 7.83–7.76 (m, 2H), 7.71 (d, $J = 8.0$ Hz, 1H), 4.36–4.24 (m, 4H), 3.30 (s, 2H), 3.11 (s, 3H), 1.29 ppm (t, $J = 7.1$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 182.6$ (C), 182.4 (C), 168.0 (C), 167.4 (C), 142.5 (C), 135.3 (C), 135.0 (C), 134.5 (CH), 133.9 (CH), 133.7 (C), 132.3 (C), 131.9 (CH), 127.2 (CH), 126.9 (CH), 124.3 (C), 123.3 (CH), 63.0 (CH_2), 57.1 (C), 38.1 (CH_2), 37.9 (Me), 14.0 ppm (Me); IR (ATR): $\tilde{\nu} = 1732$ (C=O), 1695 (C=O), 1669 cm^{-1} (C=O); HRMS (ESI): *m/z* calcd for $C_{24}H_{21}NO_7 + Na^+$: 458.1210 [$M + Na^+$]; found: 458.1229.

One-pot synthesis of diethyl 1-methyl-2-oxo-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 21a from 2-bromo-*N*-methyl-*N*-phenylacetamide 19a (Scheme 6): To a stirred solution of diethylmalonate (66.0 μL, 0.432 mmol) in toluene (4 mL) was added KO*t*Bu (54.0 mg, 0.482 mmol) and the reaction mixture stirred at rt for 10 min. 2-Bromo-*N*-methyl-*N*-phenylacetamide **19a** (0.100 g, 0.438 mmol) in toluene (2 mL) was then added by cannula and stirring maintained at 60 °C for 6 h under an atmosphere of air. Copper(II) 2-ethylhexanoate (15.0 mg, 10 mol%) and DIPEA (0.182 mL, 1.05 mmol) were added and the solution stirred at 120 °C for 18 h. The reaction mixture was worked up and purified as outlined in the general procedure to afford the title compound (77.0 mg, 58%) as a colourless powder. Data as above.

General procedure for the copper(II)-catalysed synthesis of 1,2,3,4-tetrahydroquinolines 25a–j (Scheme 8)

To a solution of the diethyl 2-(2-(methyl(aryl)amino)ethyl)malonate **24** (1.00 mmol) and copper(II) 2-ethylhexanoate (35.0 mg, 10 mol%) in toluene (10 mL) was added DIPEA (0.383 mL, 2.20 mmol). The reaction mixture was heated at 120 °C for 19 h under a reflux condenser open to the air. After cooling to rt, saturated NH_4Cl (20 mL) was added and the aqueous phase extracted with EtOAc (3×20 mL). The combined organics were washed with 10% NH_4OH (20 mL) and saturated brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with EtOAc/petroleum ether (1:49 to 1:19), to afford the title compound.

Diethyl 1-methyl-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 25a: colourless solid; R_f = 0.28 (EtOAc/petroleum ether 1:9); m.p. 44.5–45.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (dd, J = 7.7, 1.6 Hz, 1H), 7.19 (ddd, J = 8.3, 7.3, 1.6 Hz, 1H), 6.69 (dd, J = 7.3, 1.2 Hz, 1H), 6.67 (td, J = 8.3, 1.2 Hz, 1H), 4.30–4.17 (m, 4H), 3.24–3.21 (m, 2H), 2.90 (s, 3H), 2.55–2.52 (m, 2H), 1.27 ppm (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4 (C), 145.9 (C), 130.4 (CH), 129.0 (CH), 117.6 (C), 116.1 (CH), 111.7 (CH), 61.7 (CH_2), 56.9 (CH_2), 47.6 (C), 39.2 (Me), 29.6 (CH_2), 13.9 ppm (Me); IR (ATR): $\tilde{\nu}$ = 1717 cm^{-1} (C=O); HRMS (ESI): *m/z* calcd for $C_{16}H_{21}NO_4+H^+$:292.1543 [$M+H^+$]; found: 292.1539.

1-Methyl-2,3-dihydroquinoline-4,4(1*H*)-dicarbonitrile 25b: reaction was conducted with 1 equiv of catalyst; colourless solid; R_f = 0.13 (EtOAc/petroleum ether 1:9); m.p. 70–72 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (dd, J = 7.9, 1.5 Hz, 1H), 7.29 (ddd, J = 8.4, 7.3, 1.5 Hz, 1H), 6.79 (td, J = 7.6, 1.1 Hz, 1H), 6.68 (dd, J = 8.4, 0.8 Hz, 1H), 3.51–3.48 (m, 2H), 2.96 (s, 3H), 2.66–2.64 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.5 (C), 131.7 (CH), 128.7 (CH), 117.5 (CH), 115.6 (C), 112.6 (CH), 111.1 (C), 46.1 (CH_2), 38.8 (Me), 33.9 (C), 31.9 ppm (CH_2); IR (ATR): $\tilde{\nu}$ = 2241 cm^{-1} (C≡N); HRMS (ESI): *m/z* calcd for $C_{12}H_{11}N_3+H^+$: 198.1026 [$M+H^+$]; found: 198.1021.

Diethyl 10-methyl-1,3,4,4a,9a,10-hexahydroacridine-9,9(2*H*)-dicarboxylate 25c: colourless solid; R_f = 0.44 (EtOAc/petroleum ether 1:9); m.p. 57–59 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (ddd, J = 8.2, 7.3, 1.6 Hz, 1H), 6.89 (dd, J = 7.9, 1.6 Hz, 1H), 6.62–6.58 (m, 2H), 4.39–4.25 (m, 2H), 4.20–4.08 (m, 2H), 3.06 (td, J = 11.0, 3.5 Hz, 1H), 2.92 (s, 3H), 2.38–2.32 (m, 1H), 2.15 (td, J = 11.0, 3.8 Hz, 1H), 1.90–1.75 (m, 4H), 1.42–1.08 (m, 3H), 1.32 (t, J = 7.0 Hz, 3H), 1.18 ppm (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1 (C), 169.8 (C), 145.5 (C), 128.7 (CH), 127.4 (CH), 122.1 (C), 115.5 (CH), 112.8 (CH), 61.4 (CH_2), 61.3 (CH_2), 61.0 (C), 58.8 (CH), 46.2 (CH), 36.3 (Me), 33.3 (CH_2), 27.8 (CH_2), 26.2 (CH_2), 24.7 (CH_2), 14.1 (Me), 14.0 ppm (Me); IR (ATR): $\tilde{\nu}$ = 1735 (C=O), 1716 cm^{-1} (C=O); HRMS (ESI): *m/z* calcd for $C_{20}H_{27}NO_4+H^+$: 346.2013 [$M+H^+$]; found: 346.2009.

Diethyl 6-fluoro-1-methyl-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 25d: colourless solid; R_f = 0.31 (EtOAc/petroleum ether 1:9); m.p. 44–45.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03 (dd, J = 9.9, 3.0 Hz, 1H), 6.91 (ddd, J = 9.0, 7.8, 3.0 Hz, 1H), 6.57 (dd, J = 9.0, 4.7 Hz, 1H), 4.29–4.18 (m, 4H), 3.18–3.16 (m, 2H), 2.86 (s, 3H), 2.53–2.50 (m, 2H), 1.27 ppm (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0 (C), 154.7 (d, J(C,F) = 237 Hz, C), 143.0 (d, J(C,F) = 1.5 Hz, C), 118.7 (d, J(C,F) = 7.1 Hz, C), 117.0 (d, J(C,F) = 23.4 Hz, CH), 115.8 (d, J(C,F) = 21.8 Hz, CH), 112.7 (d, J(C,F) = 7.4 Hz, CH), 62.1 (CH_2), 57.1 (d, J(C,F) = 1.1 Hz, C), 47.9 (CH_2), 39.8 (Me), 29.8 (CH_2), 14.1 ppm (Me); IR (ATR): $\tilde{\nu}$ = 1725 cm^{-1} (C=O); HRMS (ESI): *m/z* calcd for $C_{16}H_{20}FNO_4+H^+$: 310.1449 [$M+H^+$]; found: 310.1459.

Diethyl 6-chloro-1-methyl-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 25e: colourless solid; R_f = 0.25 (EtOAc/petroleum ether 1:9); m.p. 71–73 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, J = 2.5 Hz, 1H), 7.11 (dd, J = 8.9, 2.5 Hz, 1H), 6.55 (d, J = 8.9 Hz, 1H), 4.30–4.18 (m, 4H), 3.22–3.19 (m, 2H), 2.88 (s, 3H), 2.51–2.48 (m, 2H), 1.27 ppm (t, J = 7.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8 (C), 144.6 (C), 130.0 (CH), 128.8 (CH), 120.8 (C), 118.8 (C), 112.8 (CH), 61.9 (CH_2), 56.8 (C), 47.4 (CH_2), 39.3 (Me), 29.3 (CH_2), 13.9 ppm (Me); IR (ATR): $\tilde{\nu}$ = 1727 cm^{-1} (C=O); HRMS (ESI): *m/z* calcd for $C_{16}H_{20}ClNO_4+H^+$: 326.1154 [$M+H^+$]; found: 326.1150.

Diethyl 1,6-dimethyl-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 25f: reaction was conducted with 1 equiv of catalyst; colourless oil; R_f = 0.31 (EtOAc/petroleum ether 1:9); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06 (d, J = 1.9 Hz, 1H), 7.00 (ddd, J = 8.4, 1.9, 0.6 Hz, 1H), 6.59 (d, J = 8.4 Hz, 1H), 4.29–4.17 (m, 4H), 3.18–3.15 (m, 2H), 2.86 (s, 3H), 2.54–2.51 (m, 2H), 2.24 (s, 3H), 1.27 ppm (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5 (C), 144.0 (C), 130.8 (CH), 129.7 (CH), 125.3 (C), 117.7 (C), 112.0 (CH), 61.7 (CH_2), 57.0 (C), 47.8 (CH_2), 39.4 (Me), 29.8 (CH_2), 20.4 (Me), 14.0 ppm (Me); IR (ATR): $\tilde{\nu}$ = 1725 cm^{-1} (C=O); HRMS (ESI): *m/z* calcd for$C_{17}H_{23}NO_4+H^+$: 306.1700 [$M+H^+$]; found: 306.1687.

Diethyl 5-methoxy-1-methyl-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 25h: colourless oil; R_f = 0.14 (EtOAc/petroleum ether 1:9); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (dd, J = 8.4, 8.2 Hz, 1H), 6.32 (dd, J = 8.4, 0.8 Hz, 1H), 6.29 (dd, J = 8.2, 0.8 Hz, 1H), 4.27–4.11 (m, 4H), 3.72 (s, 3H), 3.16–3.13 (m, 2H), 2.89 (s, 3H), 2.51–2.48 (m, 2H), 1.23 ppm (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7 (C), 158.3 (C), 146.3 (C), 129.1 (CH), 108.1 (C), 105.0 (CH), 100.2 (CH), 61.1 (CH_2), 55.6 (Me), 54.6 (C), 47.5 (CH_2), 39.4 (Me), 30.2 (CH_2), 13.9 ppm (Me); IR (ATR): $\tilde{\nu}$ = 1723 cm^{-1} (C=O); HRMS (ESI): *m/z* calcd for $C_{17}H_{23}NO_5+H^+$: 322.1649 [$M+H^+$]; found: 322.1649.

Diethyl 7-methoxy-1-methyl-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 25h′: colourless oil; R_f = 0.19 (EtOAc/petroleum ether 1:9); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (d, J = 8.6 Hz, 1H), 6.26 (dd, J = 8.6, 2.5 Hz, 1H), 6.17 (d, J = 2.5 Hz, 1H), 4.28–4.15 (m, 4H), 3.78 (s, 3H), 3.22–3.19 (m, 2H), 2.88 (s, 3H), 2.50–2.47 (m, 2H), 1.26 ppm (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6 (C), 160.3 (C), 147.2 (C), 131.5 (CH), 110.4 (C), 101.4 (CH), 97.7 (CH), 61.7 (CH_2), 56.3 (C), 55.0 (Me), 47.6 (CH_2), 39.3 (Me), 29.7 (CH_2), 14.0 ppm (Me); IR (ATR): $\tilde{\nu}$ = 1725 cm^{-1} (C=O); HRMS (ESI): *m/z* calcd for $C_{17}H_{23}NO_5+H^+$: 322.1649 [$M+H^+$]; found: 322.1645.

Diethyl 1-methyl-6-nitro-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 25i: reaction was conducted with 20 mol% catalyst; yellow solid; $R_f = 0.06$ (EtOAc/petroleum ether 1:9); m.p. 82.5–84.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.16$ (d, $J = 2.7$ Hz, 1H), 8.00 (dd, $J = 9.4$, 2.7 Hz, 1H), 6.52 (d, $J = 9.4$ Hz, 1H), 4.24 (q, $J = 7.2$ Hz, 4H), 3.39–3.36 (m, 2H), 3.01 (s, 3H), 2.49–2.46 (m, 2H), 1.26 ppm (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.0$ (C), 150.0 (C), 136.4 (C), 126.7 (CH), 125.6 (CH), 116.3 (C), 110.0 (CH), 62.2 (CH_2), 56.3 (C), 47.2 (CH_2), 39.1 (Me), 28.1 (CH_2), 13.8 ppm (Me); IR (ATR): $\tilde{\nu} = 1726$ cm^{-1} (C=O); HRMS (ESI): *m/z* calcd for $C_{16}H_{20}N_2O_6 + H^+$: 337.1394 [$M + H^+$]; found: 337.1392.

Diethyl 1-methyl-7-nitro-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 25j: yellow solid; $R_f = 0.14$ (EtOAc/petroleum ether 1:9); m.p. 83.5–85.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.46$ (dd, $J = 8.5$, 2.3 Hz, 1H), 7.42 (d, $J = 2.3$ Hz, 1H), 7.34 (d, $J = 8.5$ Hz, 1H), 4.31–4.18 (m, 4H), 3.32–3.29 (m, 2H), 2.99 (s, 3H), 2.53–2.50 (m, 2H), 1.27 ppm (t, $J = 7.1$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.3$ (C), 148.7 (C), 146.3 (C), 131.0 (CH), 123.6 (C), 110.1 (CH), 105.7 (CH), 62.2 (CH_2), 56.9 (C), 47.1 (CH_2), 39.1 (Me), 28.7 (CH_2), 13.9 ppm (Me); IR (ATR): $\tilde{\nu} = 1741$ (C=O), 1720 (C=O), 1348 cm^{-1} (N–O); HRMS (ESI): *m/z* calcd for $C_{16}H_{20}N_2O_6 + H^+$: 337.1394 [$M + H^+$]; found: 337.1384.

General procedure for the copper(II)-catalysed double cyclisation of linear anilides 26, 28, and 30 (Scheme 9)

To a solution of the anilide (0.605 mmol) and copper(II) 2-ethylhexanoate (42.0 mg, 20 mol% or 0.106 g, 50 mol%) in toluene (6 mL) was added DIPEA (0.464 mL, 2.66 mmol). The reaction mixture was heated at 120 °C for 18–40 h under a reflux condenser open to the air. After cooling to rt, saturated NH_4Cl (20 mL) was added and the aqueous phase extracted with EtOAc (3×20 mL). The combined organics were washed with 10% NH_4OH (20 mL) and saturated brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with EtOAc/petroleum ether (1:3 to 1:1), to afford the title compound.

3,7-Diethyl 1,3,5,7-tetramethyl-2,6-dioxo-1*H*,2*H*,3*H*,5*H*,6*H*,7*H*-pyrrolo[2,3-*f*]indole-3,7-dicarboxylate 27: 3.5:1 mixture of diastereomers; colourless solid; $R_f = 0.25$ (EtOAc/petroleum ether 1:1); m.p. 223.5–225.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.78$ (s, 1.6H, major), 6.77 (s, 0.4H, minor), 4.20–4.03 (m, 4H, both), 3.21 (s, 6H, both), 1.64 (s, 1.3H, minor), 1.63 (s, 4.7H, major), 1.152 (t, $J = 7.1$ Hz, 4.7H, major), 1.150 ppm (t, $J = 7.1$ Hz, 1.3H, minor); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 174.4$ (C, both), 169.5 (C, minor), 169.4 (C, major), 139.2 (C, both), 130.39 (C, major), 130.36 (C, minor), 104.4 (CH, major), 104.3 (CH, minor), 62.1 (CH_2, both), 55.3 (C, both), 26.7 (Me, both), 20.4 (Me, major), 20.2 (Me, minor), 13.83 (Me, minor), 13.81 ppm (Me, major); IR (ATR): $\tilde{\nu} = 1738$ (C=O), 1698 cm^{-1} (C=O); HRMS (ESI): *m/z* calcd for $C_{20}H_{24}N_2O_6 + Na^+$: 411.1527 [$M + Na^+$]; found: 411.1532.

1,8-Diethyl 1,3,6,8-tetramethyl-2,7-dioxo-1*H*,2*H*,3*H*,6*H*,7*H*,8*H*-pyrrolo[3,2-*e*]indole-1,8-dicarboxylate 27′: 1.4:1 mixture of diastereomers; colourless solid; $R_f = 0.18$ (EtOAc/petroleum ether 1:1); m.p. 155–157 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.82$ (s, 0.8H, minor), 6.81 (s, 1.2H, major), 4.26–3.95 (m, 4H, both), 3.24 (s, 2.5H, minor), 3.23 (s, 3.5H, major), 1.77 (s, 3.5H, major), 1.54 (s, 2.5H, minor), 1.21 (t, $J = 7.2$ Hz, 3.5H, major), 1.15 ppm (t, $J = 7.1$ Hz, 2.5H, minor); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 174.1$ (C, major), 173.8 (C, minor), 169.0 (C, minor), 168.2 (C, major), 140.23 (C, minor), 140.18 (C, major), 127.5 (C, major), 127.1 (C, minor), 108.0 (CH, major), 107.9 (CH, minor), 62.3 (CH_2, minor), 62.2 (CH_2, major), 55.7 (C, major), 55.4 (C, minor), 27.0 (Me, minor), 26.9 (Me, major), 20.8 (Me, major), 17.7 (Me, minor), 13.85 (Me, minor), 13.77 ppm (Me, major); IR (ATR): $\tilde{\nu} = 1733$ (C=O), 1710 cm^{-1} (C=O); HRMS (ESI): *m/z* calcd for $C_{20}H_{24}N_2O_6 + Na^+$: 411.1527 [$M + Na^+$]; found: 411.1530.

Tetraethyl 1,6-dimethyl-2,7-dioxo-1,2,3,6,7,8-hexahydropyrido-[2,3-*g*]quinoline-4,4,9,9-tetracarboxylate 29: colourless solid; $R_f = 0.26$ (EtOAc/petroleum ether 1:1); m.p. 177–179 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.04$ (s, 2H), 4.33–4.23 (m, 8H), 3.30 (s, 6H), 3.21 (s, 4H), 1.28 ppm (t, $J = 7.0$ Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 168.5$ (C), 166.0 (C), 135.6 (C), 123.2 (C), 115.3 (CH), 62.7 (CH_2), 56.5 (C), 37.8 (CH_2), 29.7 (Me), 14.0 ppm (Me); IR (ATR): $\tilde{\nu} = 1748$ (C=O), 1727 (C=O), 1672 cm^{-1} (C=O); HRMS (ESI): *m/z* calcd for $C_{26}H_{32}N_2O_{10} + H^+$: 533.2130 [$M + H^+$]; found:533.2139.

Triethyl 1,3,5-trimethyl-2,6-dioxo-1,2,3,5,6,7-hexahydro-8*H*-pyrrolo[2,3-*g*]quinoline-3,8,8-tricarboxylate 31: colourless solid; $R_f = 0.29$ (EtOAc/petroleum ether 1:1); m.p. 153.5–155 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.94$ (s, 1H), 6.79 (s, 1H), 4.31–4.24 (m, 4H), 4.22–4.14 (m, 1H), 4.11–4.03 (m, 1H), 3.30 (s, 3H), 3.21 (s, 3H), 3.18 (s, 2H), 1.65 (s, 3H), 1.28 (t, $J = 7.1$ Hz, 3H), 1.27 (t, $J = 7.1$ Hz, 3H), 1.17 ppm (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 174.5$ (C), 169.2 (C), 168.71 (C), 168.69 (C), 166.1 (C), 139.1 (C), 135.9 (C), 131.0 (C), 123.2 (C), 111.0 (CH), 107.7 (CH), 62.6 (CH_2), 62.2 (CH_2), 56.9 (C), 55.1 (C), 37.8 (CH_2), 30.0 (Me), 26.6 (Me), 20.3 (Me), 13.9 (Me), 13.8 ppm (Me); IR (ATR): $\tilde{\nu} = 1745$ (C=O), 1726 (C=O), 1711 (C=O), 1674 cm^{-1} (C=O); HRMS (ESI): *m/z* calcd for $C_{23}H_{28}N_2O_8 + H^+$: 461.1918 [$M + H^+$]; found:461.1904.

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