Copper(II)-Mediated Synthesis of Indolequinones from Bromoquinones and Enamines

Martyn Inman and Christopher J. Moody

Reaction of enamines and bromoquinones in the presence of copper(II) acetate and potassium carbonate results in a regiospecific synthesis of indolequinones. The reaction is broad in scope, scalable and provides a route to the core structure of several biologically interesting natural and synthetic compounds.

Introduction

The indolequinone motif forms the core structure in a number of natural product classes, including the murrayaquinones, zyzzyanones, exiguamines, calothrixins and terreusinone (Figure 1).[1] The most important of the indolequinone natural products, mitomycin C **1**, is used clinically in the treatment of several solid tumors,[2] and a synthetic analogue of mitomycin C, EO9 **2**, is currently in clinical trials for bladder cancer.[3] Other indolequinone structures ES936 **3**[4] and **5**[5] have found use as potent and selective inhibitors of the human quinone reductases NQO1 and NQO2 respectively, whilst related indolequinones such as **4**[6] show great promise against pancreatic cancer. Furthermore, the indolequinone core has been used as in the design of bioreductive prodrugs of various active agents such as 5-fluorodeoxyuridine, camptothecin and naloxone.[7] Hence, there is significant interest in the development of improved methods for the synthesis of indolequinones.
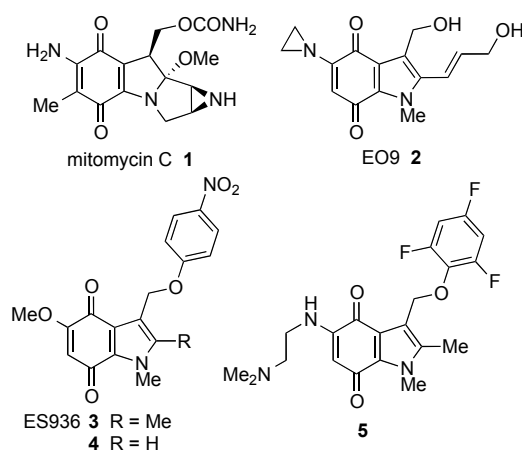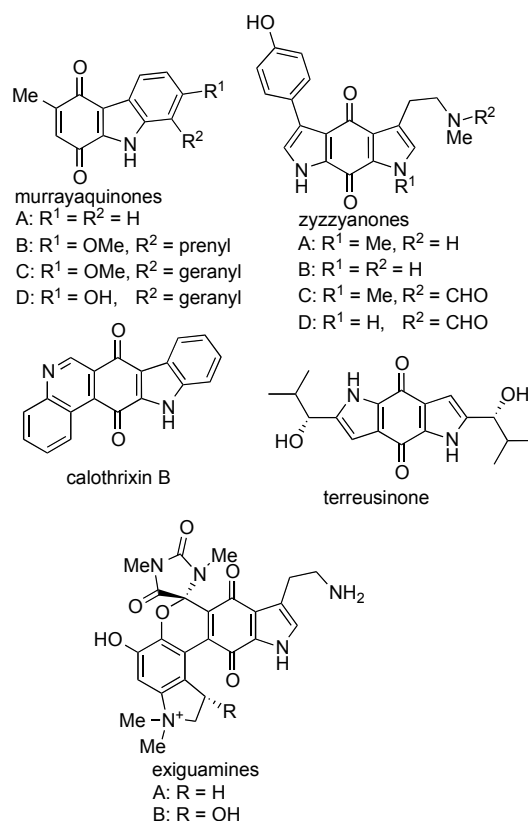

**Figure 2**. Bioactive indolequinones.

Figure 1. Naturally occurring indolequinones.

Our continuing studies of the chemistry and biology of indolequinones required a synthetic route which would provide rapid access to a range of structures, with sufficiently broad substrate scope to allow us to study the effect of each substituent in turn. We now report in full detail our development of such a route via an oxidative Cu(II)-mediated reaction of bromoquinones and enamines.

Traditionally, indolequinones have been synthesized by oxidation of indole derivatives, usually bearing at least one hydroxy, methoxy and/or amino group in the 4- and 7-positions.[8] While such methods are usually effective, they require access to highly substituted indole precursors, usually requiring a laborious synthetic route overall;[9] the subsequent oxidation can also be subject to problems with regiochemistry and functional group tolerance. Alternative approaches have been developed, including intramolecular cycloadditions of alkynes with azomethine ylides (Scheme 1A),[10] reaction of Fischer carbenes with alkynes (Scheme 1B),[11] addition of lithiated pyrroles to cyclobutenediones (Scheme 1C)[12] and cerium(IV)- or manganese(III)-mediated oxidative cyclizations of aminoquinones with 1,3-dicarbonyl compounds (Scheme 1D).[13] Palladium-catalysed Hegedus,[14] Castro[15] and Mori-Ban[16] indole syntheses have also been performed on aminoquinone derivatives, to give indolequinones in moderate yield.
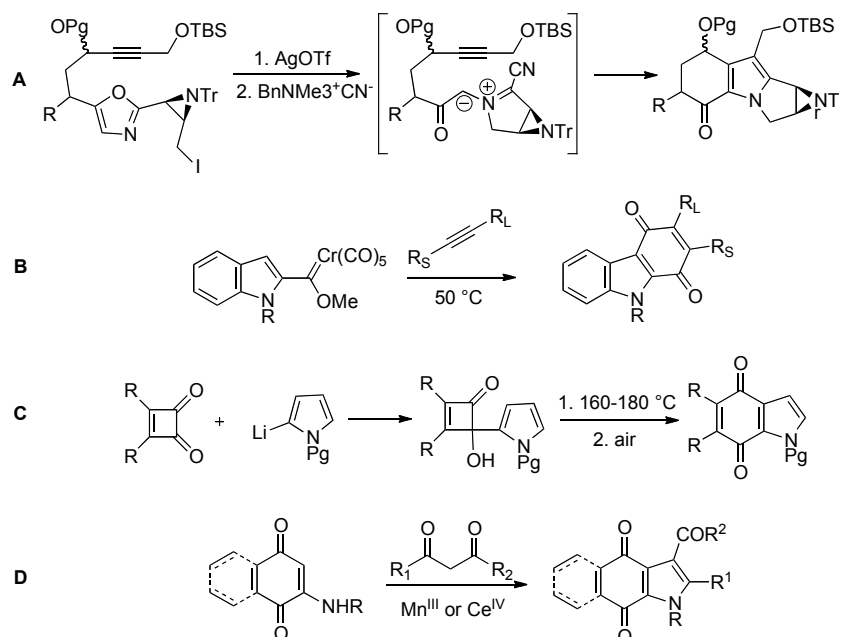
Scheme 1. Approaches to the synthesis of indolequinones (Pg = protecting group).
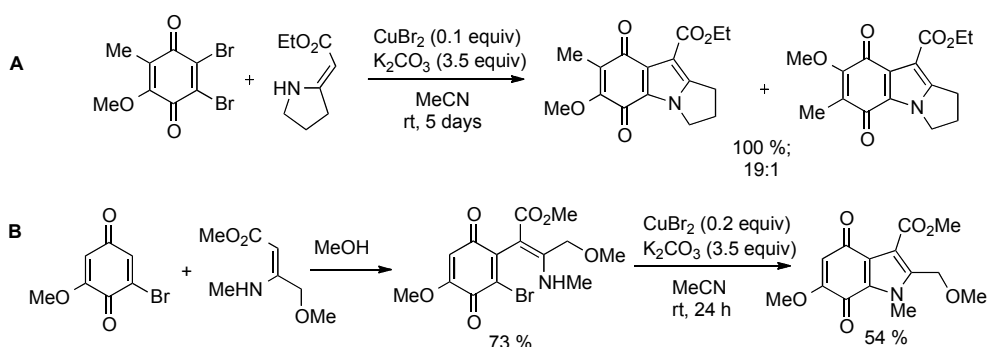
Scheme 2. Reactions of bromoquinones with enamines.[19]

Results and Discussion

As part of their approach to the synthesis of mitosenes, Luly and Rapoport reported the reaction of 2,3-dibromobenzoquinones with vinylogous carbamates in the presence of copper(II) bromide to give indolequinones bearing esters at the 3-position (Scheme 2A).[17] Although proceeding in excellent yield, the reaction took five days to reach completion, and gave a mixture of regioisomers which could only be separated by preparative MPLC. The issue of regioselectivity was resolved by Murphy's development of a similar reaction using mono-bromoquinones as the starting materials and air as a terminal oxidant; the bromine substituent was found to indicate the position at which nitrogen became attached (Scheme 2B).[18] This reaction was applied to the total syntheses of EO9 and murrayaquinone A;[19] however, the improved regioselectivity came at the expense of generally low yields, and a poor substrate scope, as evidenced by the wide range of conditions employed. In our search for methods to synthesize indolequinones, we were attracted by the convergent nature of this reaction and ready availability of the requisite starting materials, and sought to develop a set of reaction conditions which would give reliably good yields for a wide range of substrates.[20,21]

3

With this aim in mind, a series of optimization experiments was performed using the reaction of 2-bromo-6-methoxy-1,4-benzoquinone **6a** with methyl *N*-methylaminocrotonate **7a** (Table 1). A breakthrough was the discovery that relatively forcing conditions – 3 equiv of Cu(OAc)$_2$·H$_2$O at 140 °C in DMF – gave a satisfactory result (Table 1, Entry 7). Further optimization revealed that 1.5 equiv of Cu(OAc)$_2$·H$_2$O and 3 equiv of K$_2$CO$_3$ in acetonitrile at reflux under air gave a yield of 89 %. The reaction could be repeated on large scale (25 mmol) without significant reduction in yield, and the product could be isolated by recrystallization, although in a diminished yield of 65 %.
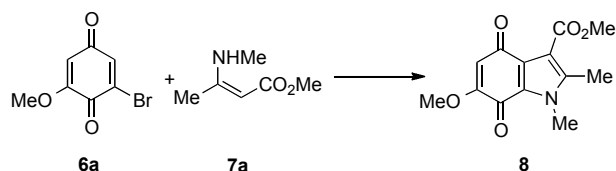

Table 1. Optimization of the synthesis of indolequinone **8**.

| Entry	Oxidant (equiv)	Solvent	Base (equiv)	t / h	T / °C	Yield / %
1	CuBr$_2$ (0.2)	MeOH	K$_2$CO$_3$ (3.5)	2	rt	39
2	CuBr$_2$ (1)	MeOH	K$_2$CO$_3$ (3.5)	2	rt	22
3	CuBr$_2$ (0.2)	MeOH	NEt$_3$ (3.5)	2	rt	0
4	-	MeCN	-	20	rt	32
5	CuBr$_2$ (0.2)	MeCN	K$_2$CO$_3$ (3.5)	24	rt	41
6	CuBr$_2$ (1.5)	MeCN	K$_2$CO$_3$ (3.5)	2.5	80	46
7	Cu(OAc)$_2$·H$_2$O (3)	DMF	K$_2$CO$_3$ (3)	0.17	140	62
8	Cu(OAc)$_2$·H$_2$O (3)	DMF	K$_2$CO$_3$ (3)	0.25	100	63
9	Cu(OAc)$_2$·H$_2$O (3)	MeCN	K$_2$CO$_3$ (3)	2.5	80	78
10	Cu(OAc)$_2$·H$_2$O (0.2)	MeCN	K$_2$CO$_3$ (3)	3.5	80	60
11	Cu(OAc)$_2$·H$_2$O (1.5)	MeCN	K$_2$CO$_3$ (3)	3.5	80	62[a]
12	Cu(OAc)$_2$·H$_2$O (1.5)	MeCN	K$_2$CO$_3$ (3)	3.5	80	89
13	-	MeCN	K$_2$CO$_3$ (3)	4.5	80	46

[a] reaction was carried out under argon.

The regiochemistry of the reaction was confirmed by reduction of the product using sodium dithionite followed by lithium aluminium hydride, and reoxidation to the known quinone **9** using iron(III) chloride (Scheme 3). Comparison of the ^{13}C NMR spectrum of **9** to the known 5-methoxy and 6-methoxy indolequinones[22] provided clear evidence that the regioselectivity matched that reported by Murphy.
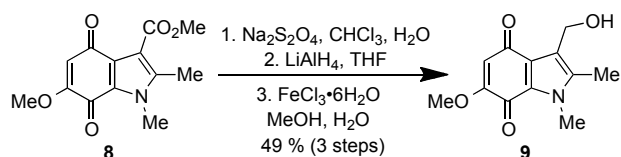
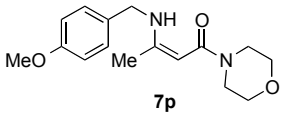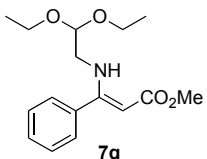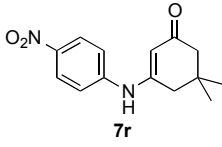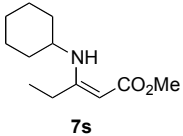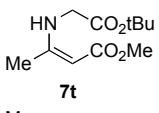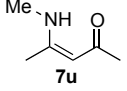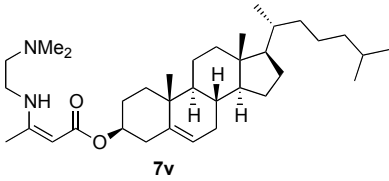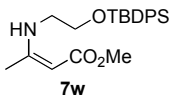**Scheme 3**. Conversion of indolequinone **8** into known compound **9**.

With an optimized set of conditions in hand, a range of bromoquinones and enamines was synthesized in order to examine the substrate scope. The enamines **7a-w** were readily available in excellent yield either by condensation of primary amines with β-ketoesters or symmetrical 1,3-diketones, or by 1,4-addition of primary amines to electron-deficient alkynes (Scheme 4 and Table 2).

A

B
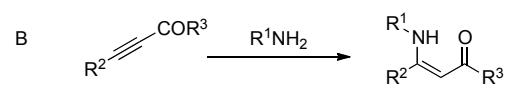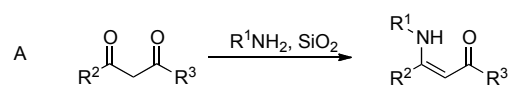
Scheme 4. Synthesis of enamines.

Table 2. Synthesis of enamines.

Entry	Enamine	Yield / % (Method)
1	NHMe, Me, CO_2Me **7a**	94 (A)
2	NHMe, CO_2Me **7b**	25 (B)
3	NHMe, CO_2Et, allyl-O **7c**	96 (A)
4	NHMe, Me, $CO_2{}^tBu$ **7d**	97 (A)
5	HN–CH2–C6H4–OMe, Me, CO_2Me **7e**	100 (A)
6	HN–C6H4–OMe, Me, $CO_2{}^tBu$ **7f**	58 (A)
7	HN–CH2CH2–N(morpholine), Me, $CO_2{}^tBu$ **7g**	99 (A)
8	HN–CH2–C6H4–OMe, MeO_2C, CO_2Me **7h**	66 (B)
9	HN–CH2CH2–OTBS, Me, CO_2Me **7i**	92 (A)
10	HN–CH2CH2–NHBoc, Me, CO_2Me **7j**	100 (A)
11	NHMe, PMBO, CO_2Et **7k**	95 (A)
12	MeHN–cyclohexenone **7l**	100 (A) [a]
13	indole–CH2CH2–NH, Me, $CO_2{}^tBu$ **7m**	97 (A)
14	CO_2Me, NH, Me, $CO_2{}^tBu$ **7n**	93 (A)
15	indole–CH2CH2–NH, Me, menthyl ester **7o**	98 (A)

6

Entry	Structure	Yield
16	7p (MeO, NH, Me, O, N, morpholine)	100 (A)
17	7q (OEt, OEt, NH, Ph, CO$_2$Me)	93 (A)
18	7r (O$_2$N, NH, dimethyl cyclohexenone)	70 (A)[a]
19	7s (cyclohexyl, NH, CO$_2$Me)	97 (A)
20	7t (HN, CO$_2$tBu, Me, CO$_2$Me)	95 (A)
21	7u (Me-NH, O)	94 (A)
22	7v (NMe$_2$, NH, O, cholesteryl ester)	84 (A)
23	7w (HN, OTBDPS, CO$_2$Me)	94 (A)

[a] Condensation was carried out under Dean-Stark conditions. TBS = *tert*-butyldimethylsilyl; Boc = *tert*-butoxycarbonyl; PMB = *para*-methoxybenzyl; TBDPS = *tert*-butyldiphenylsilyl.

Where commercially unavailable, the bromoquinone substrates **6b-h** were typically synthesized in good yield from phenolic precursors *via* bromination and oxidation (Scheme 5B-F), while 2-methoxy-6-bromobenzoquinone **6a** was made *via* Dakin oxidation of 5-bromovanillin with sodium percarbonate, followed by oxidation with iron(III) chloride (Scheme 5A).
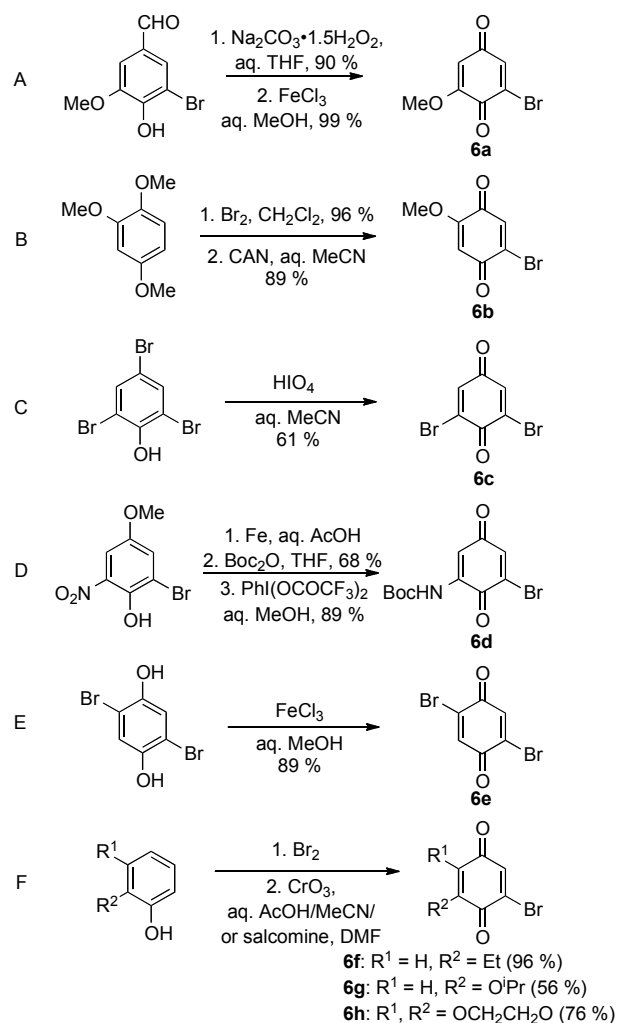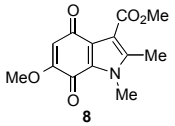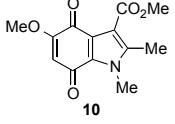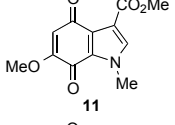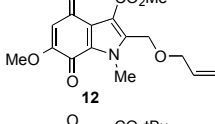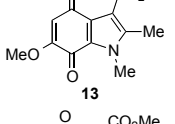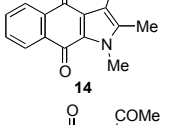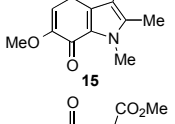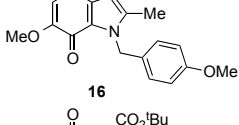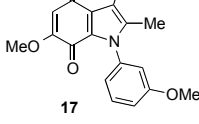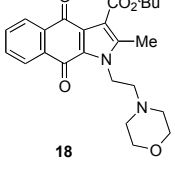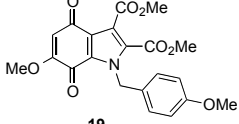
Scheme 5. Synthesis of bromoquinones. CAN = cerium(IV) ammonium nitrate; Boc = *tert*-butoxycarbonyl.
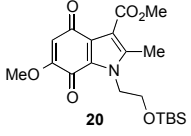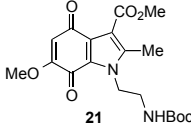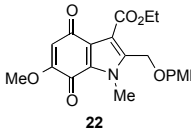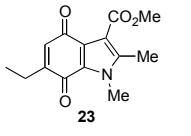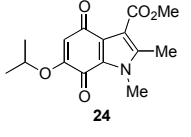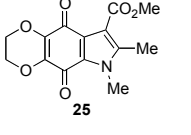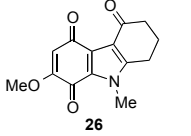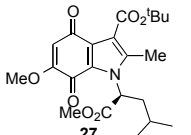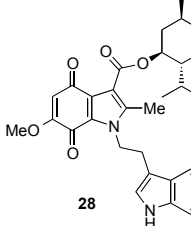
A wide variety of functionalities and protecting groups was tolerated in the annulation reaction, including methyl, ethyl, *tert*-butyl, menthyl and cholesteryl esters; cyclic and acyclic ketones; amides; TBS, TBDPS, allyl and PMB ethers; basic tertiary amines; Boc and PMB-protected amines; nitro groups and acetals (Table 3). The *N*-substituent could be alkyl or aryl, but all attempts to synthesise *N*-unsubstituted indolequinones using methyl aminocrotonate were unsuccessful, as were attempts to deprotect the corresponding PMB-protected indolequinones. Attempts to synthesize *N*-acyl indolequinones from enamides were also unsuccessful.
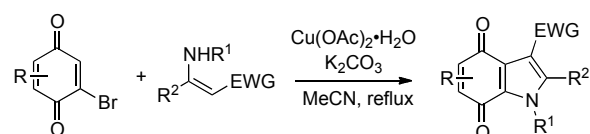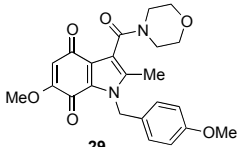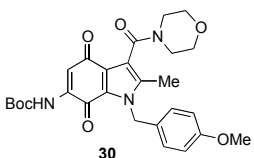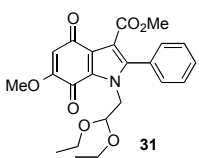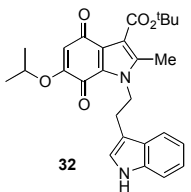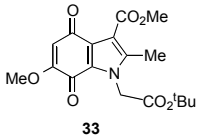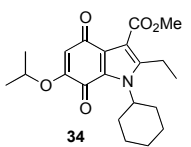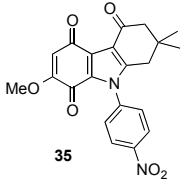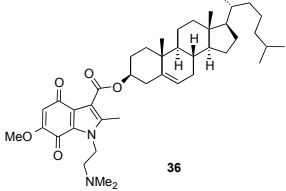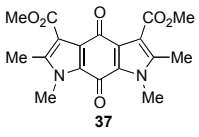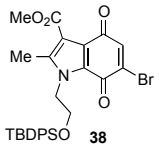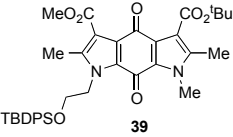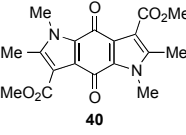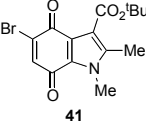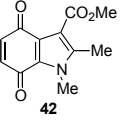
Scheme 6. Synthesis of indolequinones. EWG = electron-withdrawing group.

Table 3. Synthesis of indolequinones.

Entry	Starting materials[a]		Indolequinone	Time (h)	Yield %
1	**6a**	**7a**	8	3.5	89
2	**6b**	**7a**	10	7	49
3	**6a**	**7b**	11	20	64
4	**6a**	**7c**	12	16	64
5	**6a**	**7d**	13	6	72
6	**6i**	**7a**	14	4.5	71 (55)[b]
7	**6a**	**7u**	15	3	91
8	**6a**	**7e**	16	4.5	89
9	**6a**	**7f**	17	4	73
10	**6i**	**7g**	18	4	71
11	**6a**	**7h**	19	4	52

9

12	6a	7i	20	2.5	78
13	6a	7j	21	4	90
14	6a	7k	22	14	75
15	6f	7a	23	3.5	32
16	6g	7a	24	4	79
17	6h	7a	25	4	26
18	6a	7l	26	5	59
19	6a	7n	27	6	63
20	6a	7o	28	14	53

21	**6a**	**7p**	**29**	6	63
22	**6d**	**7p**	**30**	5	41
23	**6a**	**7q**	**31**	16	93
24	**6g**	**7m**	**32**	17	47
25	**6a**	**7t**	**33**	16	78
26	**6g**	**7s**	**34**	16	79
27	**6a**	**7r**	**35**	5	74
28	**6a**	**7v**	**36**	5	56
29	**6c**	**7a**	**37**	14	51
30	**6c**	**7w**	**38**	3.5	45

11

Entry			Structure		
31	**38**	**7d**	**39** (MeO$_2$C, CO$_2^t$Bu, Me, Me, N–Me, N–CH$_2$CH$_2$OTBDPS)	14	89
32	**6e**	**7a**	**40** (Me, CO$_2$Me, Me, Me, MeO$_2$C, Me)	15	20
33	**6e**	**7d**	**41** (Br, CO$_2^t$Bu, Me, N–Me)	3.5	31
34	**6j**	**7a**	**42** (CO$_2$Me, Me, N–Me)	5	0

[a] One equivalent enamine used except for Entry 2 (4 equiv), Entries 29, 31, 32 (2 equiv), and Entry 30 (0.5 equiv); [b] Chloroquinone used in place of bromoquinones; **6i** is 2-bromo-1,4-naphthoquinone. TBS = *tert*-butyldimethylsilyl; Boc = *tert*-butoxycarbonyl; PMB = *para*-methoxybenzyl; TBDPS = *tert*-butyldiphenylsilyl.

With respect to the substituents on the 5- and 6-positions of the quinone, the substrate scope was slightly more limited. 2-Bromo-1,4-benzoquinone **6j** failed to give the expected 5,6-unsubstituted product, resulting instead in decomposition (Table 3, Entry 34). Strong electron donating 5- or 6-substituents such as alkoxy groups gave the best results, with alkyl and carbamate substituents performing somewhat less well. Presumably, an electron donor is required to suppress undesired nucleophilic attack at these positions. Optimum results were obtained with an electron donating substituent at the 6-position rather than the 5-position; this is consistent with the proposed mechanism (Scheme 8).

The use of 2,6-dibromobenzoquinone **6c** allowed the synthesis of symmetrical (Table 3, Entry 29) and unsymmetrical (Table 3, Entry 31) pyrroloindolequinones in moderate yield, in one or two steps respectively. The corresponding reactions of 2,5-dibromobenzoquinone **6e** proved much less satisfactory, presumably for similar reasons to the poorer performance of 2-bromo-5-methoxybenzoquinone **6b**. Unsymmetrical pyrrolo-indolequinones could not be synthesised from 2,5-dibromo-1,4-benzoquinone in detectable quantities, and the symmetrical dimethyl ester **40** was obtained in only 20 % yield, compared with 51 % for the corresponding compound **37** derived from the 2,6-dibromoquinone.
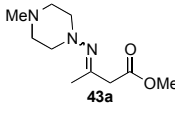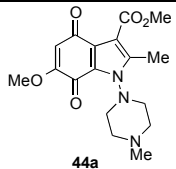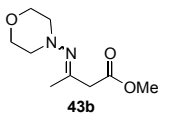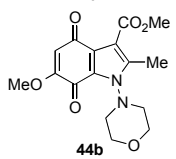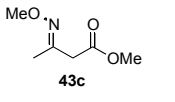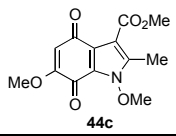
The scope of the reaction was next extended to include the synthesis of indolequinones bearing heteroatom substituents at the 1-position. The reaction of β-ketoesters with 1,1-dialkylhydrazines gave inseparable mixtures of *E* and *Z* hydrazones with *E* and *Z* enehydrazines **43a-b**. Reaction of these mixtures with bromoquinones under the optimised conditions gave the corresponding 1-aminoindolequinones **44a-b** in moderate yield (Scheme 7 and Table 4). Similarly, the oxime ether **43c**, derived from reaction of methoxylamine hydrochloride with methyl

acetoacetate, gave the corresponding 1-methoxyindolequinone **44c**, albeit in only 16 % yield, when sodium *tert*-butoxide was used in place of potassium carbonate; variation of the copper salt, base and solvent failed to improve this yield.
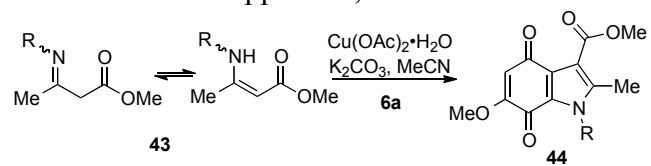
Scheme 7. Synthesis of 1-amino- and 1-alkoxyindolequinones.

Table 4. Synthesis of 1-amino- and 1-alkoxyindolequinones.

Entry	Starting material	Product	Time, h	Yield %
1	**43a**	**44a**	6	59
2	**43b**	**44b**	7	59
3	**43c**	**44c**	6.5	16[a]

[a] sodium *tert*-butoxide was used in place of potassium carbonate.

The relatively low cost of $Cu(OAc)_2 \cdot H_2O$ compensates for the need to use stoichiometric quantities – indeed, the HPLC-grade acetonitrile used as solvent represents the most expensive reagent. The reaction proceeded with catalytic amounts of $Cu(OAc)_2$ under air, or with 1.5 equiv of $Cu(OAc)_2$ under argon, albeit in lower yield in both cases, indicating that either air or Cu(II) can act as terminal oxidant, but the optimum conditions utilize both. Surprisingly, the reaction also proceeds under air in the absence of added copper salts, although with a diminished yield. Termination of the reaction prior to completion allowed the isolation of intermediate enamine **7**, indicating a reaction mechanism beginning with nucleophilic attack by the enamine through carbon at the more electrophilic 3-position on the quinone, bearing no bromine atom.[23] Oxidation of the resulting hydroquinone to **45** is followed by a C-N bond formation with loss of HBr to deliver the product. The precise mechanism by which this occurs is unclear; it has been attributed to activation of the C-Br bond through the Lewis acidity of the copper salt,[19] and although an Ullmann-Goldberg type reaction cannot be entirely discounted, it seems unlikely given the success of the reaction without the addition of $Cu(OAc)_2$. Using a chloroquinone in place of a bromoquinone gives the same reaction, but with a significant decrease in the rate of the C-N bond formation, and consequently lower yield. This finding could be consistent with either the Lewis acid activation hypothesis or an Ullmann-Goldberg reaction.

5-Alkoxy substituents on the quinone generally resulted in lower yield, most likely due to their deactivating influence on the 3-position; in these cases, the formation of side-product **46** indicated competitive nucleophilic addition at the 2-position, followed by loss of bromide to give the 2-aminovinyl quinone, which is unable to cyclize to the indolequinone under the reaction conditions.
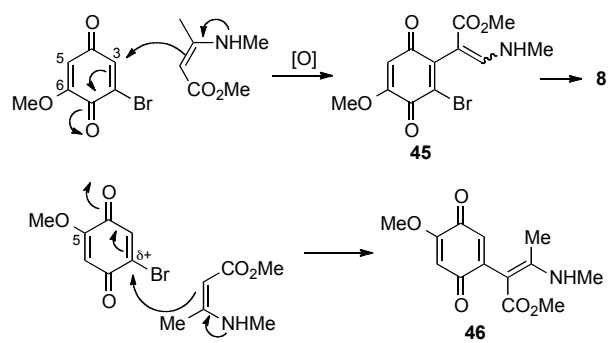
Scheme 8. Mechanistic considerations.

Conclusions

In summary, we report a versatile and practical synthesis of indolequinones by reaction of bromoquinones with enamines in the presence of copper(II) acetate and potassium carbonate. The method is effective on gram scale, and can be extended to the synthesis of pyrroloindolequinones, *N*-amino quinones and *N*-alkoxyquinones, while tolerating a wide range of functional groups.

Experimental Section
General experimental details

Commercially available reagents were used throughout without purification, except tetrahydrofuran and dichloromethane, which were freshly distilled from sodium/benzophenone and calcium hydride respectively. Light petroleum refers to the fraction with bp 40-60 °C and ether refers to diethyl ether. Thin layer chromatography was carried out on aluminum foil backed plates, visualized under UV light (at 254 and/or 360 nm) or by vanillin or permanganate stains. Chromatography was carried out using silica gel, with the eluent specified. Fully characterized compounds are chromatographically homogeneous. Infrared spectra were recorded on an FTIR spectrometer, in the range 4000-600 cm^{-1} using chloroform as solvent, or as solids in attenuated total reflectance (ATR) mode. NMR spectra were recorded at 300, 400 and 500 MHz (^{1}H frequencies, corresponding ^{13}C frequencies 75, 100 and 125 MHz). Chemical shifts are quoted in ppm and are referenced to residual H in the deuterated solvent as the internal standard. *J* values are recorded in Hz. In the ^{13}C spectra, signals corresponding to CH, CH$_2$, or Me groups, as assigned from DEPT, are noted; all others are quaternary C. High and low resolution mass spectra were recorded on a time-of-flight mass spectrometer.

General procedure for the synthesis of enamines 7

A mixture of primary amine (1.0 equiv), β-ketoester (1.0 equiv) and silica gel (0.01-0.1 g/mmol) was stirred at room temperature overnight, diluted with dichloromethane, filtered and concentrated to give the enamine, which was used without further purification.

General Procedure for the Synthesis of Indolequinones

A solution of enamine **7** (1.0-4.0 equiv) in acetonitrile (5-10 mL/mmol) was added to a mixture of bromoquinones **6** (1.0 equiv), copper(II) acetate monohydrate (1.5-2.0 equiv) and potassium carbonate (3.0 equiv). The resulting mixture was stirred at reflux for the indicated time, cooled to room temperature and diluted with dichloromethane (20 mL/mmol), filtered through Celite and concentrated *in vacuo*. Column chromatography of the residue gave the indolequinone.

Methyl 6-methoxy-1,2-dimethyl-4,7-dioxo-4,7-dihydro-1*H*-indole-3-carboxylate (8): Prepared by the general procedure from 2-bromo-6-methoxy-1,4-benzoquinone **6a** (0.109 g, 0.5 mmol), methyl 3-(methylamino)but-2-enoate **7a** (0.065 g, 0.5 mmol), copper(II) acetate monohydrate (0.150 g, 0.75 mmol) and potassium carbonate (0.207 g, 1.5 mmol) stirred at reflux in acetonitrile (5 mL) for 3.5 h. Column chromatography eluting with ethyl acetate and light petroleum (1:1) gave **8** (0.117 g, 89 %) as a yellow solid; mp 209-211 °C. ν$_{max}$ (CHCl$_3$)/cm^{-1} 3620, 3007, 2976, 1447, 1248, 1046. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.71 (s, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.82 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (75 MHz; CDCl$_3$): δ = 181.3, 172.3, 164.7, 158.7, 142.6, 127.8,

124.5, 112.9, 107.5 (CH), 56.6 (Me), 52.0 (Me), 32.8 (Me), 10.9 (Me). HRMS (ESI) calcd. for $C_{13}H_{13}NO_5Na$ $[M+Na]^+$ 286.0686; found 286.0676.

Supporting Information: Full experimental details and copies of the ^{1}H NMR and ^{13}C NMR spectra.

---

[1] a) Murrayaquinones: T. S. Wu, T. Ohta, H. Furukawa, *Heterocycles*, **1983**, *20***,** 1267-1269; b) Calothrixins: R. W. Rickards, J. M. Rothschild, A. C. Willis, N. M. deChazal, J. Kirk, K. Kirk, K. J. Saliba, G. D. Smith, *Tetrahedron*, **1999**, *55*, 13513-13520; c) Exiguamines: H. C. Brastianos, E. Vottero, B. O. Patrick, R. Van Soest, T. Matainaho, A. G. Mauk, R. J. Andersen, *J. Am. Chem. Soc*, **2006**, *128*, 16046-16047; d) Terreusinone: S. M. Lee, X. F. Li, H. Jiang, J. G. Cheng, S. Seong, H. D. Choi, B. W. Son, *Tetrahedron Lett.*, **2003**, *44*, 7707-7710; e) Zyzzyanones: N. K. Utkina, A. E. Makarchenko, V. A. Denisenko, P. S. Dmitrenok, *Tetrahedron Lett.*, **2004**, *45*, 7491-7494.
[2] S. K. Carter, S. T. Crooke, *Mitomycin C: Current Status and New Developments*; Academic Press, New York, **1979**.
[3] A. Jain, R. M. Phillips, A. J. Scally, G. Lenaz, M. Beer, R. Puri, *Urology*, **2009,** *73*, 1083-1086.
[4] a) M. A. Colucci, G. D. Couch, C. J. Moody, *Org. Biomol. Chem.*, **2008**, *6*, 637-656; b) S. L. Winski, M. Faig, M. A. Bianchet, D. Siegel, E. Swann, K. Fung, M. W. Duncan, C. J. Moody, M. Amzel, D. Ross, Biochemistry, **2001**, *40*, 15135-15142.
[5] a) C. Yan, M. Dufour, D. Seigel, P. Reigan, J. Gomez, B. Shieh, C. J. Moody, D. Ross, *Biochemistry*, **2011**, *50*, 6678-6688; b) M. Dufour, C. Yan, D. Siegel, M. A. Colucci, M. Jenner, N. J. Oldham, J. Gomez, P. Reigan, Y. Li, C. I. De Matteis, D. Ross, C. J. Moody, *ChemBioChem,* **2011**, *12*, 1203-1208.
[6] C. Yan, D. Seigel, J. Newsome, A. Chilloux, C. J. Moody, D. Ross, *Mol. Pharm.*, **2012**, *81*, 401-410.
[7] a) K. Tanabe, Y. Makimura, Y. Tachi, A. Imagawa-Sato, S. Nishimoto, *Bioorg. Med. Chem. Lett.*, **2005**, *15*, 2321-2324; b) Z. Zhang, K. Tanabe, H. Hatta, S. Nishimoto, *Org. Biomol. Chem.*, **2005**, *3*, 1905-1910; c) B. Huang, A. Desai, S. Tang, T. P. Thomas, J. R. Baker, *Org. Lett.*, **2010**, *12*, 1384-1387; d) B. Huang, S. Tang, A. Desai, X. Cheng, A. Kotlyar, A. Van Der Spek, T. P. Thomas, J. R. Baker, *Bioorg. Med. Chem. Lett.*, **2009**, *19*, 5016-5020.
[8] For direct oxidation of 4,7-unsubstituted indoles to indolequinones, see: K. C. Nicolaou, K. Sugita, P. S. Baran, Y.-L. Zhong, *J. Am. Chem. Soc.*, **2002**, *124*, 2221-2232.
[9] M. Inman, C. J. Moody, *Chem. Sci.*, **2013**, *4*, 29-41.
[10] a) E. Vedejs,, B. N. Naidu, A. Klapars, D. L. Warner, V.-S. Li, Y. Na, H. Kohn, *J. Am. Chem. Soc.*, **2003**, *125*, 15796-15806; D. R. Bobeck, D. L. Warner, E. Vedejs, *J. Org. Chem.*, **2007**, *72*, 8506-8518.
[11] W. E. Bauta, W. D. Wulff, S. F. Pavkovic, E. J. Zuluzec, *J. Org. Chem.*, **1989**, *54*, 3249-3252.
[12] a) L. S. Liebeskind, S. Iyer, C. F. Newell, *J. Org. Chem.*, **1986**, *51***,** 3065-3067; b) H. W. Moore, S. T. Perri, *J. Org. Chem.*, **1988**, *53***,** 996-1003.

[13] a) Y.-L. Wu, C.-P. Chuang, P.-Y. Lin, *Tetrahedron*, **2001**, *57*, 5543-5549; b) C.-P. Chuang, A.-I. Tsai, *Tetrahedron*, **2007**, *63*, 11911-11919.

[14] P. R. Weider, L. S. Hegedus, H. Asada, V. D'Andreq, *J. Org. Chem.*, **1985**, *50*, 4276-4281.

[15] M. S. Shvartsberg, E. A. Kolodina, N. I. Lebedeva, L. G. Fedenok, *Tetrahedron Lett.*, **2009**, *50*, 6769-6771.

[16] a) M. Yamashita, K. Ueda, K. Sakaguchi, A. Iida, *Tetrahedron Lett.*, **2011**, *52*, 4665-4670; b) L. S. Hegedus, T. A. Mulhern, A. Mori, *J. Org. Chem.*, **1985**, *50*, 4282-4288.

[17] J. R. Luly, H. Rapoport, *J. Am. Chem. Soc.*, **1983**, *105*, 2859-2866.

[18] W. S. Murphy, P. J. O'Sullivan, *Tetrahedron Lett.*, **1992**, *33*, 531-534.

[19] a) E. Comer, W. S. Murphy, *ARKIVOC*, **2003**, 286-296; b) W. S. Murphy, M. Bertrand, *J. Chem. Soc., Perkin Trans. 1*, **1998**, 4115-4119

[20] For reviews of related copper catalyzed processes, see: a) T. Liu, H. Fu, *Synthesis*, **2012**, *44*, 2805-2824; b) F. Monnier, M. Taillefer, *Angew. Chem. Int. Ed.*, **2009**, *48*, 6954-6971; c) C. Zhang, C. Tang, N. Jiao, *Chem. Soc. Rev.*, **2012**, *41*, 3464-3484; d) A. E. Wendlandt, A. M. Suess, S. S. Stahl, *Angew. Chem. Int. Ed.*, **2011**, *50*, 11062-11087; e) K. Hirano, M. Miura, *Chem. Commun.*, **2012**, *48*, 10704-10714; f) S. V. Ley, A. W. Thomas, *Angew. Chem. Int. Ed.*, **2003**, *42*, 5400-5449; g) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.*, **2008**, *108*, 3054-3131.

[21] Preliminary communication, M. Inman, C. J. Moody, *J. Org. Chem.*, **2010**, *75*, 6023-6026.

[22] M. A. Colucci, P. Reigan, D. Siegel, A. Chilloux, D. Ross, C. J. Moody, *J. Med. Chem.*, **2007**, *50*, 5780-5789.

[23] L. Boisvert, P. Brassard, *J. Org. Chem.*, **1988**, *53*, 4052-4059.