Tetrahedron 66 (2010) 6399–6410

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

An oxidative coupling for the synthesis of arylated quaternary stereocentres and its application in the total synthesis of powelline and buphanidrine

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ARTICLE INFO

Article history:
Received 26 February 2010
Received in revised form 21 April 2010
Accepted 29 April 2010
Available online 13 May 2010

Keywords:
Arylation
Quinone
Organocatalytic
Powelline
Buphanidrine

ABSTRACT

Catechol derivatives directly bonded to all-carbon quaternary stereocentres are prevalent in nature. An oxidative coupling strategy for the synthesis of this motif is described. Pivoting on the base-catalysed Michael addition of carbon-centred pro-nucleophiles to in situ generated *ortho*-benzoquinones, the method is broad in scope, high yielding and provides remarkably simple access to this challenging motif. The application of this methodology in the total synthesis of the crinane-type amaryllidaceae alkaloids (±)-powelline and (±)-buphanidrine is demonstrated and our efforts towards an enantioselective synthesis described.

1. Introduction

All-carbon quaternary stereocentres covalently bonded to catechol (1,2-dihydroxylated aromatic rings) derivatives are prevalent in natural and pharmaceutical products (Fig. 1). Examples include the calcium channel antagonist Verapamil,[1] the paraherquamide family of antiparasitic alkaloids,[2] the mastigophorenes[3] and several families of the structurally diverse Amaryllidaceae alkaloids, of which nearly 500 have been isolated and shown to exhibit cytotoxic, antibacterial, antifungal, antiviral, antiparasitic and *anti*-inflammatory properties.[4] The Amaryllidaceae alkaloid Galanthamine inhibits acetylcholinesterase and has been approved for the treatment of Alzheimer's disease.[5]

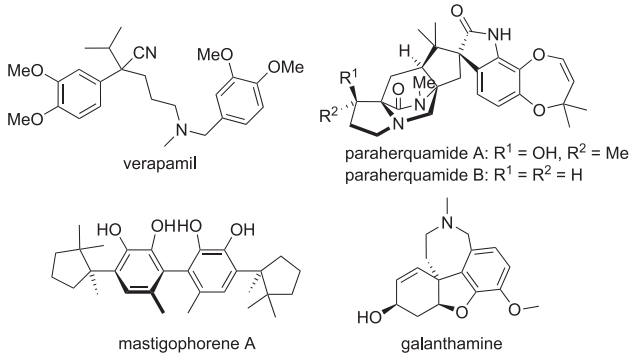

Figure 1. Pharmaceutical and natural products containing catechol derivatives bonded to all-carbon quaternary stereocentres.

The direct synthesis of all-carbon quaternary arylated stereocentres remains a significant synthetic challenge.[6] Attractive synthetic solutions include Friedel–Crafts alkylations,[7] intramolecular Heck-couplings,[8] S_NAr reactions of 1,3-dicarbonyl compounds with *para*-fluoro nitrobenzenes[9] and transition metal catalysed couplings of carbon-centred nucleophiles to aryl halides. The latter approach is arguably the most powerful to date with palladium,[10] copper[11] and nickel[12] catalysts being employed in often highly enantioselective arylation reactions. More recently, and during the course of our research documented here, an organocatalytic, enantioselective arylation reaction with commercially available 1,4-quinones as electrophiles was reported.[13,14]

Alert to the number of biologically active natural products containing catechol derivatives bonded to all-carbon quaternary stereocentres, we became interested in developing a novel organocatalytic methodology for their stereocontrolled synthesis. To this end we recently published an oxidative coupling methodology[15] for the direct construction of this motif, and the application of this reaction in the total synthesis of the crinane-type Amaryllidaceae alkaloids (±)-powelline and (±)-buphanidrine.[16] Herein we disclose our full efforts in this field.

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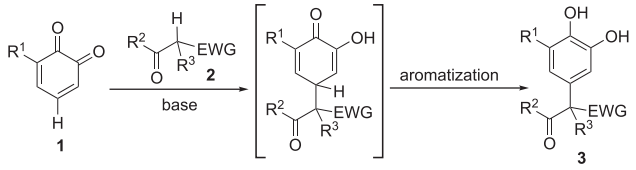
0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.04.132

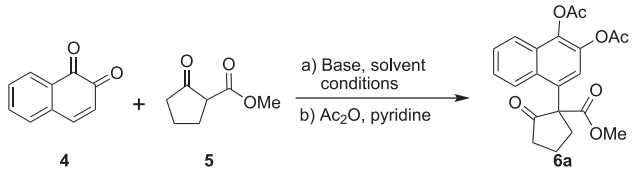
2. Results and discussion

We believed an attractive strategy for the direct construction of catechol derived arylated quaternary stereocentres would be the Michael addition of a carbon based pro-nucleophile (**2**) to *o*-benzoquinone reagents (**1**) (Scheme 1). *o*-Quinones are powerful electrophilic reagents, reactive towards a range of carbon and heteroatom based nucleophiles,[17] however in contrast to *p*-quinones, reports on the use of *o*-quinones as Michael acceptors are rare due to their rapid decomposition under attempted reaction conditions.[18] Allyl stannanes, silyl enol ethers and pre-formed sodium enolates of β-dicarbonyl reagents have been used with limited success in reactions with relatively stable *o*-quinones, and one organocatalytic example with 1,2-naphthoquinone with poor yield and enantiocontrol have been reported.[19]



Scheme 1. Concept for the synthesis of arylated quaternary stereocentres with *o*-quinone electrophiles.

Initial proof of principle studies for the base-catalysed Michael addition to *o*-quinone reagents were conducted with commercially available 1,2-naphthoquinone **4** and methyl cyclopentanone-2-carboxylate **5** as a representative pro-nucleophile using a range of base catalysts (Scheme 2, Table 1). 2-*tert*-Butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (BEMP) was quickly identified as the most efficient catalytic base and *tert*-butyl methyl ether (TBME) as the most effective solvent. The optimal reaction conditions are illustrated in Table 1, entry 8; 2 equiv of pro-nucleophile in the presence of 10 mol % BEMP were required to minimise side reactions of the quinone. Crude ^{1}H NMR spectra indicated excellent conversion to the catechol intermediate,[20] however the only product isolable following silica gel chromatography was at the quinone oxidation level and was obtained in low yield. The catechol adduct was found to be liable to oxidation in air and so to aid handling, the catechol functionality was capped as the di-acetate. This procedure allowed the desired product to be isolated following chromatography in a pleasing 83% over two steps.

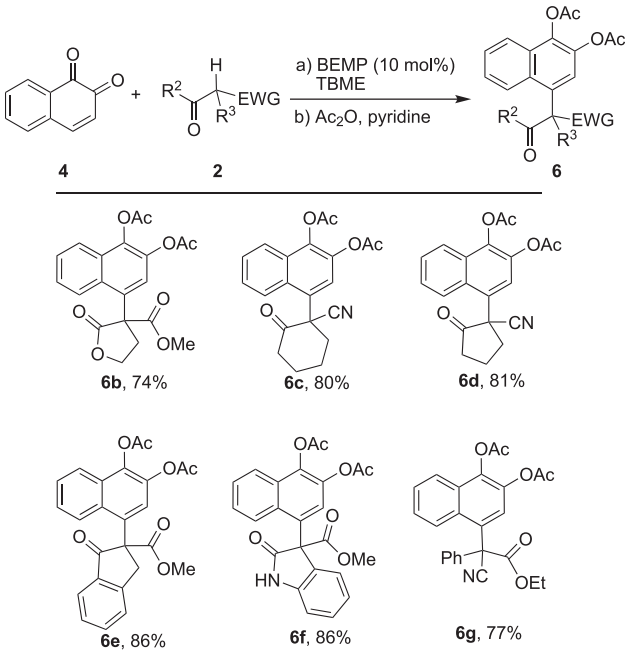


Scheme 2. Proof of principle studies and optimization studies with 1,2-naphthoquinone.

Table 1
Optimization of the base-catalysed Michael addition to 1,2-naphthoquinone

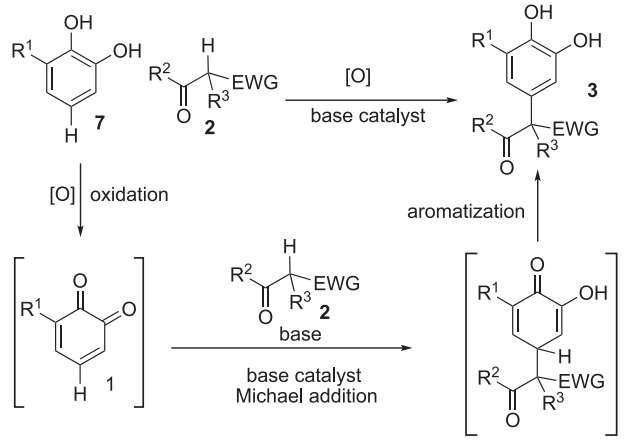
Entry	Base, %	Solvent	**5** (mol equiv)	Temp, °C	Time (h)	Yield %
1	NEt_3, 10%	TBME	2	−20 °C–RT	1	66
2	DABCO, 10%	TBME	2	−20 °C–RT	1	57
3	TMG, 10%	TBME	2	−20 °C–RT	1	56
4	BEMP, 1%	TBME	2	RT	24	46
5	BEMP 5%	TBME	2	RT	3	59
6	BEMP, 10%	TBME	2	RT	1	77
7	BEMP, 10%	TBME	1	−20 °C–RT	1	42
8	BEMP, 10%	TBME	2	−20 °C–RT	1	83
9	BEMP, 10%	TBME	3	−20 °C–RT	1	84
10	BEMP, 10%	TBME	2	−20 °C	5	73

The scope of the pro-nucleophile was then investigated; five-membered cyclic lactone-, indanone- and oxindole-derived pro-nucleophiles were well-tolerated as five and six-membered cyclic α-cyanoketones and acyclic α-cyano acetates,[21] illustrated in Scheme 3.



Scheme 3. Range of naphthoquinone adducts formed.

We then looked to expand the scope of the methodology to a range of *o*-benzoquinone electrophiles and attempted to synthesize a range of 3-substituted *o*-benzoquinones through oxidation of the parent catechol.[22] 3-*tert*-Butyl, 3-methoxy and 3-phenyl catechols were oxidized with sodium periodate or polymer-supported periodate[23] (PS-IO_4^-) and in all cases a complex mixture was obtained. Rapidly it became clear that in situ generation of the reactive *o*-benzoquinone would be required. Accordingly we developed a strategy based on a formal oxidative-coupling of 5-unsubstituted catechols **7** (Scheme 4). In situ oxidation of a catechol would generate the electrophilic *o*-benzoquinone intermediate **1** primed for attack by the conjugate base of the carbon-centred pro-nucleophile **2**. Following Michael addition, aromatization would generate the catechol product **3**, substituted at the 5-position as desired. As 3-substituted catechols are either commercially



Scheme 4. Oxidative coupling concept for the construction of arylated quaternary stereocentres.

available or readily prepared,[24] this strategy would provide a powerful and general route to compounds containing arylated quaternary stereogenic centres.

Initially ^{1}H NMR studies were conducted to demonstrate the requirement for in situ generation of the *o*-benzoquinone. 3-Methoxy and 3-*tert*-butyl catechols were oxidized with PS-IO_4^- in $CDCl_3$ and the decomposition of the quinone monitored over time. Figure 2 demonstrates that whilst 1,2-naphthoquinone is stable indefinitely, *o*-benzoquinone reagents rapidly degrade even when bulky or electron donating groups are present.[25]

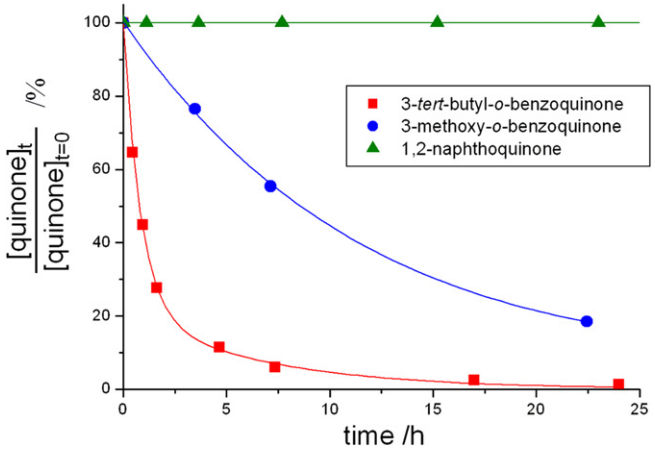
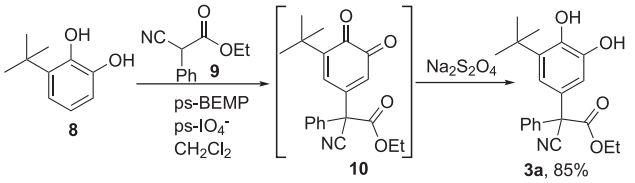


Figure 2. Decomposition of *o*-benzoquinones in $CDCl_3$ compared with stable 1,2-naphthoquinone, measured against an internal standard.[15]

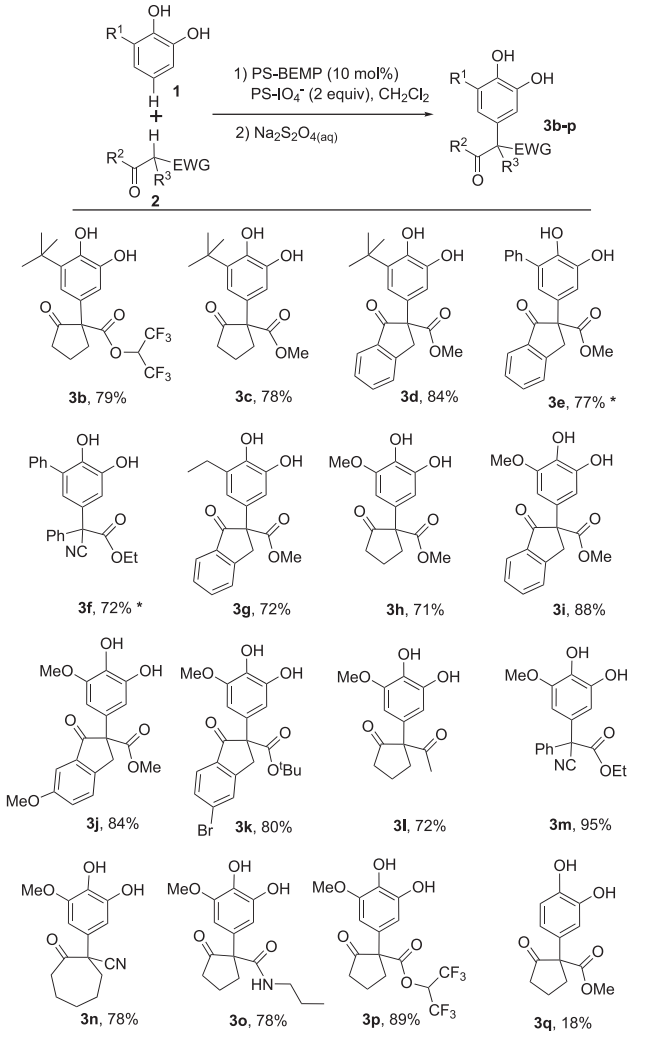
Proof of principle studies for the oxidative coupling strategy was conducted with 3-*tert*-butyl catechol **7** and ethyl phenylcyanoacetate **8**, as representative quinone precursor and pro-nucleophile in conjunction with PS-IO_4^- (Scheme 5). Feasibility was readily established and optimization showed that 2 equiv of PS-IO_4^- were required for complete consumption of the starting materials, and that only 1 equiv of pro-nucleophile was required with 10 mol % of polymer-supported BEMP (PS-BEMP) in CH_2Cl_2 at −20 °C. Under these conditions, following reductive work-up with $Na_2S_2O_{4(aq)}$, the desired arylated product **3a** was isolated in a gratifying 85% overall yield.



Scheme 5. Proof-of-principle studies: Oxidative coupling of 3-*tert*-butylcatachol and ethyl phenylcyanoacetate.

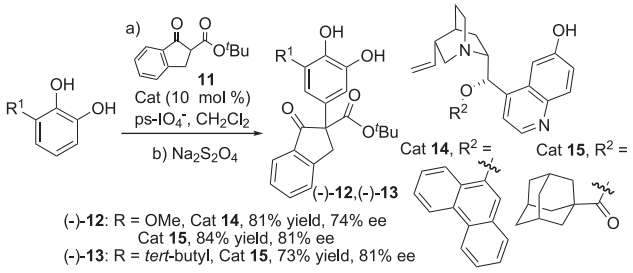
The scope of the reaction with respect to the 3-substituted catechol and pro-nucleophile was then investigated. *tert*-Butyl, ethyl, phenyl and methoxy-substituted catechols were all found to be effective substrates and the scope of the reaction with respect to the pro-nucleophile was also found to be broad; β-ketoesters, β-diketones, β-ketoamides, α-cyanoketones and α-cyanoacetates were all found to be effective. In most cases equimolar amounts of pro-nucleophile and catechol were employed and in all cases the addition was rapid, completely regioselective and high yielding (Scheme 6).

The significance of the catechol 3-substituent on the reaction yield is demonstrated by example **3q**. When catechol was reacted with 2 equiv of methyl cyclopentanone-2-carboxylate under the standard oxidative coupling conditions the 3-unsubstituted arylated adduct **3q** was obtained in only 18% yield. Despite this low yield no other arylated products could be isolated from the reaction mixture.



Scheme 6. Scope of the organocatalytic oxidative coupling, *2 equiv of **2** was required.

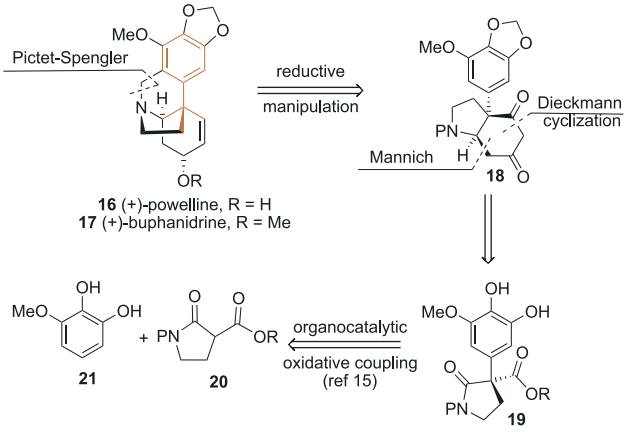
This organocatalytic methodology was readily adapted to allow an efficient asymmetric organocatalytic variant. The ability of triethylamine to catalyse the Michael addition to 1,2-naphthoquinone (Table 1, entry 1) lead us to investigate the ability of cinchona alkaloid derived organocatalysts to catalyse the arylation reaction. Replacing PS-BEMP with known catalyst **14** in the reaction of 3-methoxycatechol with *tert*-butyl 1-oxoindane-2-carboxylate **11** afforded the arylated adduct (−)-**12** in 81% yield and 74% ee.[26] This was improved through the synthesis of organocatalyst **15**,[15] affording adduct (−)-**12** in 84% yield and 81% ee (Scheme 7). Pleasingly this level of enantioselectivity was also achieved with 3-*tert*-butyl catechol, affording adduct (−)-**13** in 73% yield and 81% ee.



Scheme 7. Asymmetric organocatalytic oxidative coupling.

Having developed a broadly applicable protocol for the synthesis of catechol derivatives bonded to all-carbon quaternary stereocentres, and demonstrated the methodology to be amenable to asymmetric induction, we turned our attention to the application of our methodology in total synthesis.

The crinane-type Amaryllidaceae alkaloids powelline **16** and buphanidrine **17**, characterized by the 5,10b-ethanophenanthridine crinane skeleton, both contain 3 stereogenic centres one of which is quaternary, and differ in the substituent on the allylic alcohol. They have been isolated from several Amaryllidaceae species,[27] and both have shown affinity for the serotonin transporter in [H3]-citalopram binding assays.[28] Several syntheses of crinane-type alkaloids have been reported and recently a synthesis of powelline utilizing similar chemistries was disclosed.[29] Construction of the sterically congested arylated quaternary stereocentre is pivotal to the synthesis of this class of alkaloid and we believed that these two alkaloids would be ideal targets to showcase our methodology for the synthesis of this motif. Our retrosynthetic analysis is illustrated in Scheme 8.

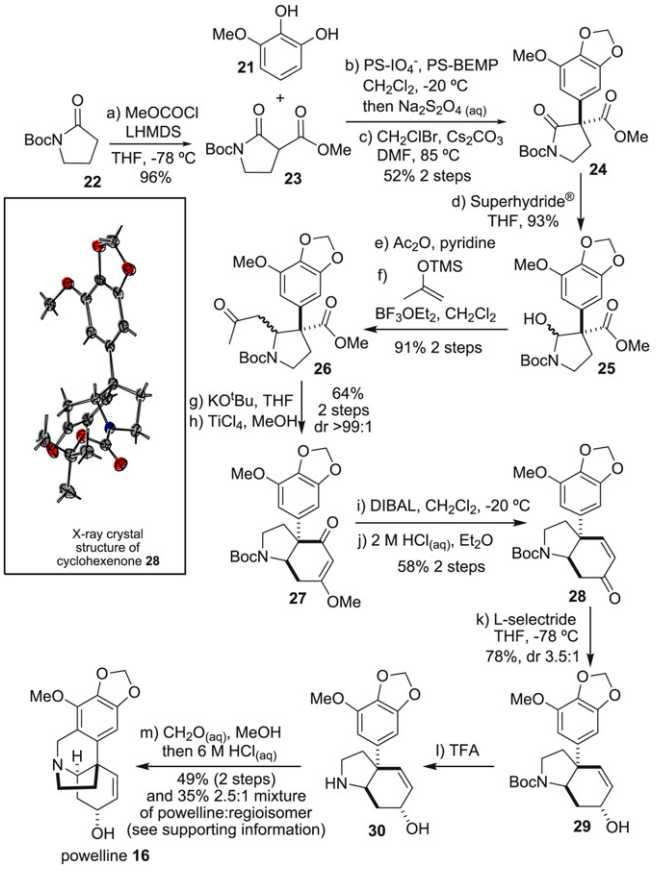


Scheme 8. Retrosynthetic analysis.

The synthetic plan was based on the direct catalysed construction of the quaternary carbon-to-aryl bond via the oxidative coupling of readily prepared pro-nucleophile of type **20** and commercially available 3-methoxycatechol **21**. We envisaged that transformation of **19** to the key cyclohexandione late-stage intermediate **18**, common to both targets, would be possible via formal reductive homologation followed by Dieckmann-type cyclization. Reductive manipulation of cyclohexandione **18**, followed by deprotection and Pictet/Spengler cyclization should provide rapid access to the target alkaloids.

Initially we concentrated on the synthesis of the target alkaloids in racemic form. *N*-Boc was chosen as the protecting group for the pro-nucleophile **23**, in order to heighten acidity and allow selective removal at a late stage in the synthesis. Methyl ester pro-nucleophile **23** was readily synthesized from 1-(*tert*-butoxycarbonyl)-2-pyrollidinone and reacted with 3-methoxycatechol **21** according to the oxidative coupling protocol. The crude catechol intermediate was not purified but reacted directly with bromochloromethane under standard conditions to give the desired methylenedioxy product **24** in 52% yield over the two steps (Scheme 9).[30]

Continuing with the planned synthesis of the key cyclohexandione intermediate of type **18**, a three carbon homologation of the lactam was required to give the keto-ester **26** substrate ready for the Dieckmann-type cyclization. Chemoselective reduction of the ketonic gamma-lactam carbonyl was achieved



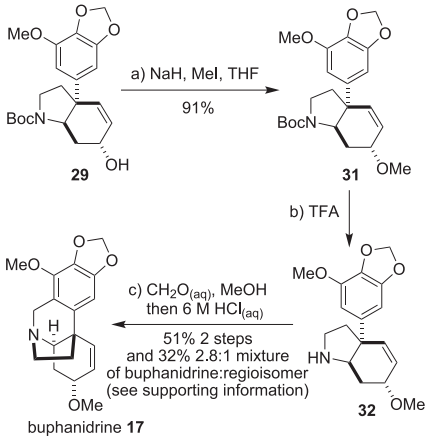
Scheme 9. Total synthesis of (±)-powelline.

with superhydride® and gave aminol **25** in 93% yield. Subsequent acetylation followed by $BF_3{\cdot}OEt_2$ mediated *N*-acyliminium ion homologation using (isopropenyloxy)trimethylsilane as a nucleophilic trap afforded keto-ester **26**. The diastereoselectivity in the formation of **26** was dependent upon the reaction solvent and ranged from 3:1 in dichloromethane to 7:1 in acetone. The Dieckmann-type cyclization, mediated by 2.1 equiv of potassium *tert*-butoxide, proceeded smoothly to give the diketone as a single diastereoisomer, the yield and diastereoselectivity of the cyclization step were found to be independent of the diastereomeric ratio of the keto-ester starting material **26**. This is consistent with a rapid and reversible base-catalysed epimerization process, presumably via retro Michael/Michael addition, occurring faster than the Dieckmann-type cyclization step to give the *cis*-fused 5,6-bicyclic diketone. The diketone product (of type **18**) was transformed without purification into methyl enol ether **27** through treatment with $TiCl_4$ in methanol.[31] The DIBAL reduction/acid hydrolysis of alkyl enol ether systems to their enone products is known in the literature,[32] however, in THF and toluene the predominant product was that resulting from a competing reaction sequence of 1,4-reduction, elimination of methanol and a further 1,4-reduction to give a saturated ketone.[16] The amount of 1,4-reduction product was reduced by switching the reaction solvent to dichloromethane and gave the desired cyclohexenone **28** in 58% yield over two steps. The *cis*-stereochemistry of **28** was unambiguously proven by single crystal X-ray diffraction (inset Scheme 9).

A diastereoselective reduction of the cyclohexenone carbonyl was required to transform **28** to the required allylic alcohol system. Standard Luche reduction conditions gave the desired diastereomer **29** as the minor component of a separable 5.5:1

mixture. Inversion of the allylic alcohol through mesylation, displacement with CsOAc and hydrolysis has been shown to be an effective but lengthy strategy for synthesis of the desired allylic alcohol in related alkaloids.[33] However when this approach was adopted on our system loss of the stereochemical integrity of the allylic alcohol was observed. A screen of reducing agents for **28** showed that N, K and L-Selectride all afforded the desired diastereomer as the major component, with L-Selectride being the optimal reagent, efficiently generated the desired diastereomer **29** with 3.5:1 dr. NOE studies on both allylic alcohol diastereomers allowed assignment of relative stereochemical configurations. The *N*-Boc protecting group was readily removed in neat TFA, and the free base of amine **30** was used directly in the final Pictet/Spengler cyclization without purification. Treatment of **30** with formaldehyde in 6 M HCl at room temperature achieved, after 10 min, formation of the final ring, completing the 13 step total synthesis of (±)-powelline. Gratifyingly the two possible regioisomers in the Pictet/Spengler reaction were formed with ~7:1 ratio in favour of the desired product and were separable by silica gel chromatography.[34] The spectroscopic data (^{1}H NMR, ^{13}C NMR) and high resolution mass spectrometric data of synthetic powelline were consistent with the published data.[35]

The total synthesis of (±)-buphanidrine was accomplished through *O*-methylation of allylic alcohol **29** under standard conditions followed by the same deprotection/Pictet/Spengler sequence (Scheme 10). Again, the Pictet/Spengler step was found to be regioselective, forming the desired isomer in a ~10:1 ratio. (±)-Buphanidrine was synthesized in 14 linear steps and a 6% overall yield. The spectroscopic data (^{1}H NMR, ^{13}C NMR) and high resolution mass spectrometric data of synthetic buphanidrine were in excellent agreement with the published data.[28b,36]

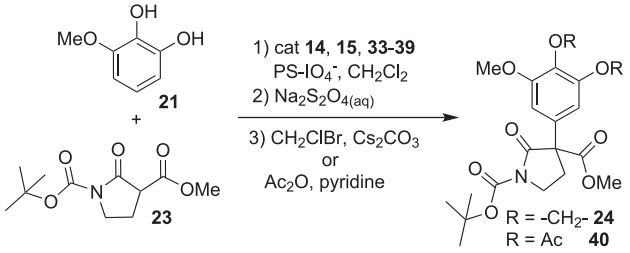


Scheme 10. Total synthesis of (±)-buphanidrine.

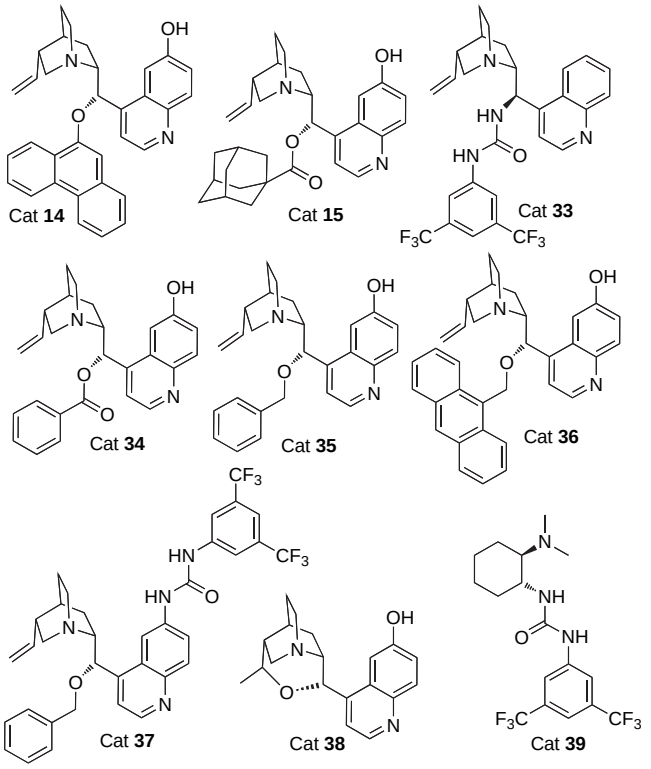
Having established a synthesis of the target alkaloids in racemic form, we turned our attention to an asymmetric synthesis, which we aimed to accomplish through the use of a cinchona-derived organocatalyst in the oxidative coupling step. A screen of organocatalysts (Table 2)[37] was undertaken on 0.1 mmol scale and the enantioselectivities determined by chiral HPLC. No attempts were made to optimize the reaction yields. To expedite the measurement of enantiomeric excess during catalyst screening, in some cases the catechol product was protected as the di-acetate.

Whilst all the enantiomeric excesses were moderate in the initial catalyst screen, the quinidine-derived benzyl catalysts **35** and **36** emerged as the most promising scaffolds. The wide variation of enantiomeric excess observed with, previously optimal,

Table 2
Initial screen of organocatalysts and conditions for the synthesis of **24** and **40**



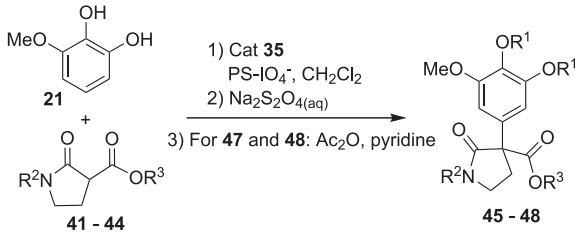
Entry	Catalyst (loading)	Conc. (M)	Product	ee %	Yield %
1	Cat **14** (10 mol %)	0.1	(+)-**24**	49	20
2	Cat **15** (10 mol %)	0.1	(+)-**24**	11	28
3	Cat **33** (10 mol %)	0.1	(−)-**24**	34	15
4	Cat **34** (10 mol %)	0.1	(+)-**40**	6	35
5	Cat **35** (10 mol %)	0.1	(+)-**24**	50	35
6	Cat **36** (10 mol %)	0.1	(+)-**24**	55	25
7	Cat **37** (10 mol %)	0.1	(±)-**40**	0	25
8	Cat **38** (10 mol %)	0.1	(+)-**40**	15	30
9	Cat **39** (10 mol %)	0.1	(−)-**24**	35	18
10	Cat **35** (30 mol %)	0.01	(+)-**40**	60	38



catalyst **15** demonstrates the need to match the catalyst and pro-nucleophile. The initial enantiomeric excess achieved with catalyst **35** was increased by 10% by increasing the dilution and the catalyst loading (entry 10). CH_2Cl_2 remained the optimal solvent.

A range of alternative pro-nucleophiles of type **20** were synthesized and screened with catalyst **35** to identify any opportunity to increase the levels of enantioselectivity obtained previously with pro-nucleophile **23** (Table 3). The steric bulk of the protecting group and ester was varied, however, no improvements in enantioselectivity were obtained.

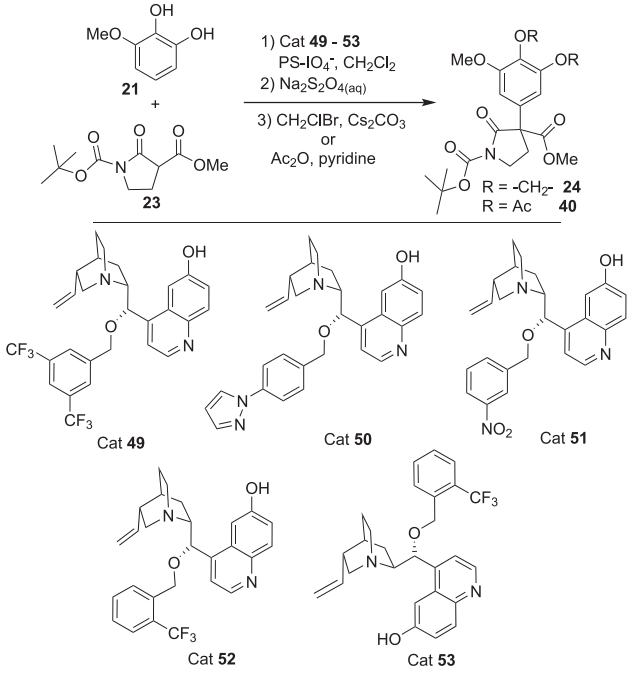
Table 3
Screen of pro-nucleophiles



Pro-nucleophile	R^1	R^2	R^3	Product	ee %	Yield %
41	H	COO^{t}Bu	Ph	(+)-**45**	40	29
42	H	COOMe	Ph	(+)-**46**	9	34
43	Ac	CBz	Me	(+)-**47**	30	30
44	Ac	Ts	Me	(+)-**48**	1	24

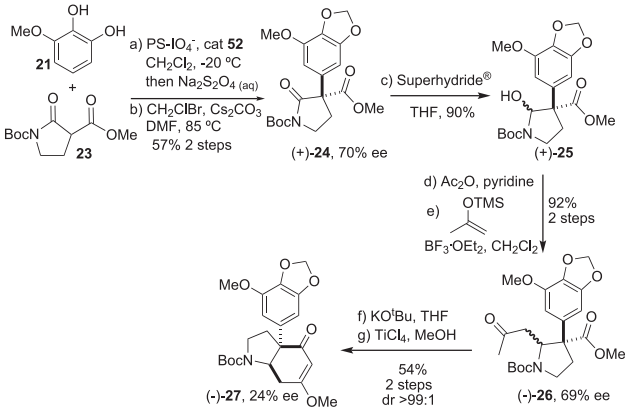
A range of novel quinidine-derived organocatalysts with varying benzyl substitutents (Table 4) were then synthesized from quinidine and screened in the oxidative coupling step.

Table 4
Screen of novel substituted-benzyl catalysts



Entry	Catalyst (loading)	Product	Conc./M	ee %	Yield %
1	Cat **49** (10 mol %)	(+)-**40**	0.1	43	41
2	Cat **50** (10 mol %)	(+)-**40**	0.1	50	25
3	Cat **51** (10 mol %)	(+)-**40**	0.1	43	38
4	Cat **52** (10 mol %)	(+)-**40**	0.1	64	56
5	Cat **52** (20 mol %)	(+)-**24**	0.025	70	57
6	Cat **53** (20 mol %)	(−)-**24**	0.025	70	55

Catalysts **49**–**51** were not found to offer improvements over the simple benzyl system **35**, however *ortho*-CF_3 derivative **52** increased the enantiomeric excess to 64%. This was further increased to 70% by increasing the catalyst loading to 20 mol % at a concentration of 0.025 M. The absolute stereochemistry of the major enantiomer is not known, however the opposite enantiomer (−)-**24** was obtained in 70% ee with the pseudo-enantiomeric catalyst **53**. Since the racemic enone **28** was known to be highly crystalline the enantioselective synthesis was begun with the intention of increasing the enantiopurity through recrystallisation. Accordingly enantioenriched arylated adduct (+)-**24** was prepared in 57% yield and 70% ee on a 10 mmol scale and treated with superhydride® affording aminol (+)-**25** in 90% yield (Scheme 11).



Scheme 11. Attempted enantioselective total synthesis.

Acylation and $BF_3{\cdot}OEt_2$ mediated *N*-acyliminium ion homologation gave keto-ester (−)-**26** in 3:1 dr and with no loss of stereochemical integrity. Subsequent Dieckmann-type cyclization and methyl enol ether formation yielded (−)-**27**, however HPLC analysis showed a decrease in enantiomeric excess to 24%. This is attributed to a fast epimerization process, which is presumably also responsible for the formation of only one diastereomer of (±)-**27** (see Scheme 9 and accompanying text). Due to the loss of stereochemical integrity the enantioselective synthesis was halted, with an alternative strategy being required to avoid the epimerization problems.

In summary we have exemplified the ability of *o*-quinones to act as Michael acceptors towards carbon-centred nucleophiles and developed a broadly applicable oxidative coupling process for in situ generation of the highly reactive and unstable *o*-benzoquinone intermediate. The methodology pivots on the base catalysed addition of a carbon-centred pro-nucleophile and is general, high yielding, atom economical and provides remarkably efficient access to this challenging structural motif. We have subsequently exemplified the utility of our methodology in the total synthesis of two members of the crinane-type Amaryllidaceae alkaloids powelline and buphanidrine.

3. Experimental

3.1. General

All ^{1}H and ^{13}C NMR spectra were recorded using a Bruker AVII 500 MHz, Bruker DPX 500, Bruker DPX 400 and 500 MHz, and Varian 300 MHz spectrometers. Chemical shifts (δ) are given in parts per million, and coupling constants (J) are given in hertz (Hz). The ^{1}H NMR spectra are reported as follows: δ/ppm (number of protons, multiplicity, coupling constants J/Hz, assignment). DEPT135, two-dimensional (COSY, HSQC, HMBC) and NOE/NOESY NMR spectroscopy were used where appropriate to assist the assignment of signals in the ^{1}H and ^{13}C NMR spectra. Low resolution mass spectrometry (electrospray) was recorded on a Micromass Platform II spectrometer, Micromass Trio 2000 quadrupole and a Micromass LCT premier. High resolution mass spectra (accurate mass) were recorded on a Thermo Finnigan Mat95XP mass spectrometer and a Bruker MicroTof spectrometer. Infrared spectra were recorded on a Perkin Elmer Spectrum RX1 FTIR and a Bruker Tensor FT-IR spectrometer (thin film deposited onto a sodium chloride plate), only selected absorbances (λ_{max}) are reported. Melting points were recorded using a Gallenkamp and a Leica Galen II melting point apparatus and are uncorrected. Optical rotations

were recorded using an Optical Activity AA-1000 polarimeter and a Perkin–Elmer 241 polarimeter; $[\alpha]_D$ values are reported in 10^{-1} degcm^2 g^{-1}; concentration (c) is given in g/100 ml at 589 nm. (+) and (−) compound number prefixes indicate the sign of the optical rotation. Bulk solutions were evaporated under reduced pressure using a Büchi rotary evaporator. Reagents and solvents used were obtained from commercial suppliers and used without further purification unless stated otherwise. Petroleum ether refers to distilled light petroleum of fraction (40–60 °C). 1,2-Naphthoquinone was purchased from fluka and used as received. 3-Substituted catechols were synthesized from the appropriate 2-substituted phenol through a one-pot *ortho*-formylation and Dakin oxidation procedure as described by Hansen and Skattebøl[24a] Polymer-supported periodate was prepared from amberlite® IRA-900 chloride form resin (Aldrich) as described by Hodge and Harrison.[23] For determination of the PS-IO_4^- loading, ^{1}H NMR quinone stability studies, and synthesis and characterization of adducts **3a**–**p** see Ref. 15. For the preparation of pro-nucleophiles see Ref. 21. For the synthesis of catalysts **14**, **33**–**39** see Ref. 37 and for **15** see Ref. 15. For the synthesis of compounds **23**–**32**, (±)-powelline and (±)-buphanidrine and X-ray data for **28** see Ref. 16.

3.2. Experimental procedures and characterization

*3.2.1. Methyl 1-(3,4-diacetoxy-1-naphthyl)-2-oxo-cyclopentanecarboxylate **6a**.* To a stirred solution of 2-oxocyclopentanecarboxylate **5** (501 mg, 3.42 mmol) and 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (BEMP) (50 μL, 0.17 mmol) in *tert*-butyl methyl ether (8 mL) at −20 °C was added, portion-wise over 10 min, 1,2-naphthoquinone **4** (300 mg, 1.71 mmol). The resulting brown suspension was stirred at this temperature for 1 h, then allowed to warm to room temperature and stirred for a further 1 h. The solvent was removed by rotary evaporator and the residue dissolved in pyridine (5 mL) and acetic anhydride (0.53 mL, 5.64 mmol) was added. The mixture was stirred at room temperature overnight then diluted with Et_2O (15 mL) and washed with saturated aqueous $CuSO_4$ (3×10 mL). The aqueous washings were re-extracted with Et_2O (2×5 mL) and the combined organic portions dried over sodium sulfate, filtered and concentrated by rotary evaporator. The crude residue was purified by chromatography on silica gel to give **6a** (546 mg, 83%) as an off-white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.89 (1H, d, *J*=8.0 Hz, Ar*H*), 7.70 (1H, d, *J*=8.0 Hz, Ar*H*), 7.55–7.48 (2H, m, Ar*H*), 7.02 (1H, s, Ar*H*), 3.65 (3H, s, C(O)OC*H*$_3$), 3.23 (1H, ddd, *J*=13.0, 9.5, 7.0 Hz, C(O)CH$_2$CH$_2$C*H*$_2$), 2.61–2.52 (3H, m, C(O)CH$_2$CH$_2$C*H*$_2$ and C(O)C*H*$_2$CH$_2$CH$_2$), 2.46 (3H, s, OC(O)C*H*$_3$), 2.31 (3H, s, OC(O)C*H*$_3$), 2.16–2.09 (1H, m, C(O)CH$_2$C*H*$_2$CH$_2$), 1.89–1.79 (1H, m, C(O)CH$_2$C*H*$_2$CH$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 213.6 (*C*(O)), 171.6 (*C*(O)OCH$_3$), 168.2 (O*C*(O)CH$_3$), 167.9 (O*C*(O)CH$_3$), 137.9 (4° Ar*C*), 136.7 (4° Ar*C*), 133.7 (4° Ar*C*), 129.9 (4° Ar*C*), 128.9 (4° Ar*C*), 126.7 (Ar*C*H), 126.5 (Ar*C*H), 124.5 (Ar*C*H), 122.4 (Ar*C*H), 121.3 (Ar*C*H), 65.6, (4° *C*) 53.3 (C(O)*C*H$_3$), 38.9 (C(O)CH$_2$CH$_2$CH$_2$), 36.4 (C(O)CH$_2$CH$_2$CH$_2$), 20.7 (OC(O)*C*H$_3$), 20.5 (OC(O)*C*H$_3$), 19.5 (C(O)CH$_2$*C*H$_2$CH$_2$); IR ν_{max}/cm^{-1} 1765, 1754, 1716, 1371, 1240, 1212, 1199, 770; mp 151–153 °C decomp.; MS (CI$^+$) *m*/*z* (relative intensity %) 402 (M+NH$_4^+$, 100%); HRMS (ES$^+$): calcd for $C_{21}H_{24}O_7N$ (M+NH$_4^+$) 402.1547, found 402.1548.

*3.2.2. Methyl 3-(3,4-diacetoxy-1-naphthyl)-2-oxo-tetrahydrofuran-3-carboxylate **6b**.* According to the above procedure for the preparation of **6a**, 1,2-naphthoquinone **4** (300 mg, 1.71 mmol) was reacted with methyl 2-oxotetrahydrofuran-3-carboxylate (493 mg, 3.42 mmol) to give compound **6b** (488 mg, 74%) as an off-white solid after chromatography on silica gel, eluting with petroleum ether containing 30% ethyl acetate; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.93 (1H, dd, *J*=8.0, 1.5 Hz, Ar*H*), 7.61–7.51 (3H, m, 3 of Ar*H*), 7.31 (1H, s, Ar*H*), 4.54 (1H, dt, *J*=9.0, 3.0 Hz, OC*H*$_2$CH$_2$), 4.19 (1H, dt, *J*=9.0, 6.5 Hz, OC*H*$_2$CH$_2$), 3.73–3.66 (4H, m, OCH$_2$C*H*$_2$ and C(O)OC*H*$_3$), 2.67 (1H, ddd, *J*=13.0, 6.5, 3.0 Hz, OCH$_2$C*H*$_2$), 2.47 (3H, s, OC(O)C*H*$_3$), 2.33 (3H, s, O(CO)C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 173.3 (*C*(O)O), 170.1 (*C*(O)O), 168.1 (O*C*(O)CH$_3$), 167.9 (O*C*(O)CH$_3$), 138.1 (4° Ar*C*), 137.5 (4° Ar*C*), 131.1 (4° Ar*C*), 129.3 (4° Ar*C*), 129.0 (4° Ar*C*), 127.1 (Ar*C*H), 126.9 (Ar*C*H), 123.5 (Ar*C*H), 122.8 (Ar*C*H), 122.0 (Ar*C*H), 66.4 (OCH$_2$), 60.1 (4°*C*), 54.0 (C(O)OCH$_3$), 35.1 (OCH$_2$CH$_2$), 20.7 (OC(O)*C*H$_3$), 20.5 (OC(O)*C*H$_3$); IR ν_{max}/cm^{-1} 1768, 1763, 1758, 1737, 1609, 1369, 1204, 1168, 1156, 772; mp 141–143 °C; MS (CI$^+$) *m*/*z* (relative intensity %) 404 (M+NH$_4^+$, 100%); HRMS (ES$^+$) calcd for $C_{20}H_{22}O_8N$ (M+NH$_4^+$) 404.1340, found 404.1331.

*3.2.3. [2-Acetoxy-4-(1-cyano-2-oxo-cyclohexyl)-1-naphthyl] acetate **6c**.* According to the above procedure for the preparation of **6a**, 1,2-naphthoquinone **4** (90 mg, 0.57 mmol) was reacted with 2-oxocyclohexanecarbonitrile (140 mg, 1.14 mmol) to give compound **6c** (167 mg, 80%) as a white solid after chromatography on silica gel, eluting with petroleum ether containing 30% ethyl acetate; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.96–7.93 (1H, m, Ar*H*), 7.85–7.82 (1H, m, Ar*H*), 7.59–7.54 (2H, m, Ar*H*), 7.49 (1H, s, Ar*H*), 2.97–2.91 (1H, ddd, *J*=13.0, 10.0, 5.0 Hz, C*H*$_2$), 2.84–2.73 (2H, m, C*H*$_2$), 2.53–2.48 (4H, m, C*H*$_2$ and OC(O)C*H*$_3$), 2.36 (3H, s, 1 of OC(O)C*H*$_3$), 2.29–2.18 (3H, m, C*H*$_2$), 2.04–1.96 (1H, m, C*H*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 202.6 (*C*(O)), 168.2 (O*C*(O)CH$_3$), 167.7 (O*C*(O)CH$_3$), 138.2 (4° Ar*C*), 137.9 (4° Ar*C*), 129.7 (4° Ar*C*), 128.7 (4° Ar*C*), 128.4 (4° Ar*C*), 127.1 (Ar*C*H), 127.0 (Ar*C*H), 124.9 (Ar*C*H), 122.4 (Ar*C*H), 121.8 (Ar*C*H), 119.1 (*C*N), 54.8 (4°*C*), 39.1 (*C*H$_2$), 38.5 (*C*H$_2$), 28.7 (*C*H$_2$), 21.9 (*C*H$_2$), 20.8 (OC(O)*C*H$_3$), 20.5 (OC(O)*C*H$_3$); IR ν_{max}/cm^{-1} 1769, 1764, 1754, 1749, 1608, 1369, 1195, 1164, 1095, 1015, 765; mp 142–144 °C; MS (ES$^+$) *m*/*z* (relative intensity %) 383 (M+NH$_4^+$, 15%), 388 (M+Na$^+$, 100%); HRMS (ES$^+$) calcd for $C_{21}H_{19}O_5NNa$ (M+Na$^+$) 388.1155, found 388.1155.

*3.2.4. [2-Acetoxy-4-(1-cyano-2-oxo-cyclopentyl)-1-naphthyl] acetate **6d**.* According to the above procedure for the preparation of **6a**, 1,2-naphthoquinone **4** (158 mg, 1.00 mmol) was reacted with 2-oxocyclopentanecarbonitrile (218 mg, 2.00 mmol) to give compound **6d** (283 mg, 81%) as a cream coloured solid after chromatography on silica gel, eluting with petroleum ether containing 50–70% diethyl ether; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.21 (1H, d, *J*=7.5 Hz, Ar*H*), 7.94 (1H, d, *J*=7.5 Hz, Ar*H*), 7.65–6.57 (2H, m, Ar*H*), 7.25 (1H, s, Ar*H*), 2.90–2.80 (2H, m, C(O)C*H*$_2$CH$_2$CH$_2$), 2.66 (2H, app. t, *J*=8.0 Hz, C(O)CH$_2$CH$_2$C*H*$_2$), 2.45 (3H, s, OC(O)C*H*$_3$), 2.32 (3H, s, OC(O)C*H*$_3$), 2.26–2.18 (1H, m, C(O)CH$_2$C*H*$_2$CH$_2$), 2.08–1.99 (1H, m, C(O)CH$_2$C*H*$_2$CH$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 207.7 (*C*(O)), 168.1 (O*C*(O)CH$_3$), 167.7 (O*C*(O)CH$_3$), 137.9 (4° Ar*C*), 137.8 (4° Ar*C*), 129.0 (4° Ar*C*), 128.7 (4° Ar*C*), 127.9 (4° Ar*C*), 127.2 (Ar*C*H), 127.0 (Ar*C*H), 124.7 (Ar*C*H), 122.5 (Ar*C*H), 122.0 (Ar*C*H), 118.5 (*C*N), 52.7 (4°*C*), 37.4 (*C*H$_2$), 36.7 (*C*H$_2$), 20.6 (OC(O)*C*H$_3$), 20.3 (OC(O)*C*H$_3$), 19.3 (*C*H$_2$); IR ν_{max}/cm^{-1} 1769, 1766, 1758, 1608, 1369, 1200, 1164, 1015, 768; mp 70–71 °C (decomp.); MS (ES$^+$) *m*/*z* (relative intensity %) 406 (M+Na$^+$+MeOH, 100%), 374 (M+Na$^+$, 85%); HRMS (ES$^+$): calcd for $C_{20}H_{18}O_5N$ (M+H$^+$) 352.1179, found 352.1178.

*3.2.5. Methyl 2-(3,4-diacetoxy-1-naphthyl)-1-oxo-indane-2-carboxylate **6e**.* According to the above procedure for the preparation of **6a**, 1,2-naphthoquinone **4** (300 mg, 1.71 mmol) was reacted with methyl 1-oxoindane-2-carboxylate (650 mg, 3.42 mmol) to give compound **6e** (639 mg, 86%) as a yellow solid after chromatography on silica gel, eluting with petroleum ether containing 30% ethyl acetate; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.92–7.89 (2H, m, Ar*H*), 7.76–7.74 (1H, m, Ar*H*), 7.65 (1H, t, *J*=7.5, Ar*H*), 7.58–7.53 (2H, m, Ar*H*), 7.45–7.42 (2H, m, Ar*H*), 7.27 (1H, s. Ar*H*), 4.69 (1H, d, *J*=17.0 Hz, C*H*$_2$), 3.67 (3H, s, C(O)OC*H*$_3$), 3.49 (1H, d, *J*=17.0 Hz, C*H*$_2$), 2.44 (3H, s, OC(O)C*H*$_3$), 2.28 (3H, s, OC(O)C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 200.4 (*C*(O)), 171.2 (*C*(O)OCH$_3$), 168.1 (O*C*(O)CH$_3$), 168.0 (O*C*(O)CH$_3$), 153.1 (4° Ar*C*), 138.1 (4°

ArC), 136.8 (4° ArC), 136.3 (ArCH), 135.2 (4° ArC), 134.4 (4° ArC), 130.6 (4° ArC), 128.8 (4° ArC), 128.1 (ArCH), 126.8 (ArCH), 126.7 (ArCH), 126.5 (ArCH), 125.3 (ArCH), 124.1 (ArCH), 122.6 (ArCH), 121.4 (ArCH), 65.3 (4°C), 53.7 (C(O)OCH_3), 41.6 (CH_2), 20.7 (OC(O)CH_3), 20.5 (OC(O)CH_3); IR ν_{max}/cm^{-1} 1765, 1760, 1748, 1733, 1610, 1426, 1368, 1199, 1170, 763; mp 187–189 °C; MS (CI^+) *m*/*z* (relative intensity %) 450 ($M+NH_4^+$, 100%); HRMS (ES^+) calcd for $C_{25}H_{24}O_7N$ ($M+NH_4^+$) 450.1547, found 450.1537.

3.2.6. Methyl 3-(3,4-diacetoxy-1-naphthyl)-2-oxo-3a,7a-dihydro-1H-indole-3-carboxylate ***6f***. According to the above procedure for the preparation of **6a**, 1,2-naphthoquinone **4** (47 mg, 0.30 mmol) was reacted with methyl 2-oxoindoline-3-carboxylate (114 mg, 0.60 mmol) to give compound **6f** (112 mg, 86%) as an off-white solid after chromatography on silica gel eluting with diethyl ether; ^1H NMR (500 MHz, DMSO-d_6) δ_H 11.0 (1H, s, N*H*), 8.17–8.15 (1H, m, Ar*H*), 8.01–7.98 (1H, m, Ar*H*), 7.68–7.64 (2H, m, Ar*H*), 7.43 (1H, dt, *J*=7.5, 1.0 Hz, Ar*H*), 7.29 (1H, d, *J*=7.5 Hz, Ar*H*), 7.17 (1H, t, *J*=7.5 Hz, Ar*H*), 7.04 (1H, d, *J*=7.5 Hz, Ar*H*), 6.85 (1H, s, Ar*H*), 3.69 (3H, s, C(O)OCH_3), 2.48 (3H, s, OC(O)CH_3), 2.25 (3H, s, OC(O)CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 172.4 (*C*(O)), 169.8 (*C*(O)), 168.3 (OC(O)CH_3), 168.2 (OC(O)CH_3), 142.5 (ArC), 137.8 (ArC), 137.1 (ArC), 131.9 (ArC), 130.4 (ArC), 130.0 (ArC), 128.2 (ArC), 127.1 (ArC), 126.9 (ArC), 126.7 (ArC), 126.2 (ArC), 125.6 (ArC), 122.7 (ArC), 121.8 (ArC), 121.7 (ArC), 110.5 (ArC), 63.5 (4°C), 53.5 (C(O)OCH_3), 20.3 (OC(O)CH_3), 20.2 (OC(O)CH_3); IR ν_{max}/cm^{-1} 3361, 1769, 1755, 1738, 1729, 1474, 1370, 1212, 1193, 1165, 767, 750; mp 242–246 °C decomp.; MS (CI^+) *m*/*z* (relative intensity %) 451 ($M+NH_4^+$, 100%); HRMS (ES^+) calcd for $C_{24}H_{23}O_7N_2$ ($M+NH_4^+$) 451.1500, found 451.1495.

3.2.7. Ethyl 2-cyano-2-(3,4-diacetoxy-1-naphthyl)-2-phenyl-acetate ***6g***. According to the above procedure for the preparation of **6a**, 1,2-naphthoquinone **4** (300 mg, 1.71 mmol) was reacted with ethyl phenylcyanoacetate (647 mg, 3.42 mmol) to give compound **6g** (565 mg, 77%) as a yellow solid after chromatography on silica gel, eluting with petroleum ether containing 30% ethyl acetate; ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.98 (1H, d, *J*=8.0 Hz, Ar*H*), 7.94 (1H, d, *J*=8.0 Hz, Ar*H*), 7.64–7.63 (2H, m, Ar*H*), 7.59–7.53 (2H, m, Ar*H*), 7.51–7.47 (3H, m, Ar*H*), 6.91 (1H, s, Ar*H*), 4.43–4.31 (2H, m, OC$H_2$$CH_3$), 2.46 (3H, s, 1 of OC(O)CH_3), 2.26 (3H, s, 1 of OC(O)CH_3), 1.29 (3H, t, *J*=7.0 Hz, OCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_c 167.8 (*C*(O)), 167.6 (*C*(O)), 167.0 (*C*(O)), 138.2 (4° ArC), 137.9 (4° ArC), 133.3 (4° ArC), 130.8 (4° ArC), 129.4 (ArCH), 129.4 (ArCH), 129.3 (4° ArC), 128.6 (4° ArC), 128.2 (ArCH), 127.1 (ArCH), 127.1 (ArCH), 124.4 (ArCH), 124.1 (ArCH), 122.4 (ArCH), 118.0 (*C*N), 64.0 (OCH_2), 57.6 (4°*C*), 20.6 (OC(O)CH_3), 20.4 (OC(O)CH_3), 13.7 (OCH_2CH_3); IR ν_{max}/cm^{-1} 1787, 1761, 1750, 1608, 1373, 1216, 1192, 1175, 1166, 1156, 895, 744, 734; mp 126–128 °C; MS (CI^+) *m*/*z* (relative intensity %) 449 ($M+NH_4^+$, 100%); HRMS (ES^+) calcd for $C_{25}H_{25}O_6N_2$ ($M+NH_4^+$) 449.1707, found 449.1698.

3.3. General oxidative coupling procedure

To a stirred solution of catechol (1 equiv), pro-nucleophile (1 equiv) and PS-BEMP (10 mol%) in dichloromethane (10 mL/mmol) at −20 °C, in a flask wrapped in aluminium foil, was added PS-IO_4^- (2 equiv). The resulting suspension was stirred at this temperature until TLC analysis showed complete consumption of starting materials. The reaction mixture was filtered to remove the polymer supported reagents, and the resin washed on the sinter with CH_2Cl_2 (10 mL/mmol). The typically deep red filtrate was stirred vigorously with saturated aqueous $Na_2S_2O_4$ (20 mL/mmol) for 10 min (the colour typically fades to pale yellow). The organic layer was separated and the aqueous extracted with CH_2Cl_2 (2×5 mL/mmol). The combined organic portions were dried over sodium sulfate, filtered and concentrated by rotary evaporator. The residue was purified by chromatography on silica gel to give the desired arylated products.[15]

3.3.1. Methyl 1-(3,4-dihydroxyphenyl)-2-oxo-cyclopentanecarboxylate ***3q***. According to the general oxidative coupling procedure, except that PS-IO_4^- was added portion-wise, catechol (55 mg, 0.50 mmol) was reacted with 2-oxocyclopentanecarboxylate (142 mg, 1.00 mmol) to give, after 2 h reaction time, **3q** (23 mg, 18%) as a yellow oil following chromatography on silica gel, eluting with petroleum ether containing 50–70% diethyl ether; ^1H NMR (500 MHz, $CDCl_3$) δ_H 6.95 (1H, d, *J*=2.0 Hz, Ar*H*), 6.80–6.74 (2H, m, Ar*H*), 6.30 (1H, br s, O*H*), 5.94 (1H, br s, O*H*), 3.71 (3H, s, OCH_3), 2.79 (1H, td, *J*=13.5, 7.0 Hz, CH_2), 2.55–2.43 (2H, m, CH_2), 2.40–2.34 (1H, m, CH_2), 2.02–1.86 (2H, m, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 212.9 (*C*=O), 171.6 (*C*(O)O), 143.6 (4° ArC), 143.5 (4° ArC), 128.0 (4° ArC), 119.8 (ArCH), 115.3 (ArCH), 114.9 (ArCH), 64.3 (4° *C*), 53.1 (OCH_3), 37.7 (CH_2), 34.8 (CH_2), 19.2 (CH_2); IR ν_{max}/cm^{-1} 3430, 1745, 1718, 1638, 1523, 1436, 1261; MS (ES^+) *m*/*z* (relative intensity %) 273 ($M+Na^+$, 100%), 523 (dimer+Na^+, 45%); HRMS (ES^+): calcd for $C_{13}H_{14}O_5Na$ ($M+Na^+$) 273.0733, found 273.0731.

3.3.2. tert-Butyl 2-(3-tert-butyl-4,5-dihydroxy-phenyl)-1-oxo-indane-2-carboxylate (−)- ***13***. According to the general oxidative coupling procedure, replacing PS-BEMP with catalyst **15**, 3-*tert*-butyl catechol **8** (16 mg, 0.10 mmol) was reacted with **11** (23 mg, 0.10 mmol) to give, after 2 h reaction time, compound (−)-**13** (29 mg, 73%) as a yellow solid after chromatography on silica gel, eluting with petroleum ether containing 50–70% diethyl ether, in 81% ee, determined by HPLC analysis [Chiralpak AD, hexane/*iso*-propanol 95:5, 1.0 mL min^{-1}, λ=230 nm, *t* (minor)=37.62 min, *t* (major)=40.96 min] by comparison to a racemic sample prepared according to the general oxidative coupling procedure; $[\alpha]_D^{24}$ −5.3 (*c* 3.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.78 (1H, d, *J*=7.5 Hz, Ar*H*), 7.63 (1H, t, *J*=7.5 Hz, Ar*H*), 7.48 (1H, d, *J*=7.5 Hz, Ar*H*), 7.39 (1H, t, *J*=7.5 Hz, Ar*H*), 6.91 (1H, d, *J*=2.0 Hz Ar*H*), 6.83 (1H, d, *J*=2.0 Hz, Ar*H*), 6.24 (1H, br s, O*H*), 5.71 (1H, s, O*H*), 4.09 (1H, d, *J*=17.0 Hz, CH_2), 3.54 (1H, d, *J*=17.0 Hz, CH_2), 1.37 (18H, s, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 202.7 (*C*=O), 170.0 (*C*(O)O), 152.7 (4° ArC), 143.2 (4° ArC), 143.0 (4° ArC), 135.7 (4° ArC), 135.6 (ArCH), 135.1 (4° ArC), 128.6 (4° ArC),127.8 (ArCH), 126.1 (ArCH), 125.0 (ArCH), 117.6 (ArCH), 112.1 (ArCH), 82.7 (C(O)OC(CH_3)$_3$), 66.1 (4° *C*), 40.8 (CH_2), 34.8 (*C*(CH_3)$_3$), 29.4 (C(*C*H_3)$_3$), 27.7 (C(*C*H_3)$_3$); mp: 124–126 °C (142–144 °C for racemate); IR ν_{max}/cm^{-1} 3388, 2953, 1708, 1693, 1601, 1426, 1368, 1250, 1150; MS (ES^+) *m*/*z* (relative intensity %) 419 ($M+Na^+$, 100%); HRMS (EI^+): calcd for $C_{24}H_{32}O_5N$ ($M+NH_4^+$) 414.2275, found 414.2276.

3.3.3. 1-tert-Butyl 3-phenyl 2-oxopyrrolidine-1,3-dicarboxylate ***41***. A solution of *tert*-butyl-2-oxopyrrolidine-1-carboxylate (500 mg, 2.70 mmol) in THF (2 mL) was added to a solution of LHMDS (5.7 mL of a 1 M solution in THF, 5.70 mmol) at −78 °C. The reaction mixture was stirred at this temperature for 5 min, then phenyl chloroformate (0.34 mL, 2.70 mmol) was added. The reaction mixture was stirred for 15 min then quenched with 1 M HCl (20 mL) and warmed to room temperature. The biphasic mixture was extracted with EtOAc (3×10 mL) and the combined organic extracts dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel, eluting with cyclohexane containing 0–40% EtOAc to give **41** (450 mg, 55%) as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.31 (2H, t, *J*=7.5 Hz, Ar*H*), 7.17 (1H, t, *J*=7.5 Hz, Ar*H*), 7.13 (2H, d, *J*=7.5 Hz, Ar*H*), 3.87 (1H, ddd, *J*=10.5, 9.0, 4.5 Hz, CH_2N), 3.72 (1H, t, *J*=9.0 Hz *CH*), 3.68 (1H, dt, *J*=10.5, 7.5 Hz, CH_2N), 2.48–2.40 (1H, m, CH_2CH_2N), 2.31–2.24 (1H, m, CH_2CH_2N), 1.47 (9H, s, C(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 168.2 (*C*(O)), 167.4 (*C*(O)), 150.3 (OC(O)N), 149.7 (4° ArC), 129.4 (ArCH), 126.1 (ArCH), 121.3 (ArCH), 83.5 (*C*(CH_3)$_3$), 50.2 (*CH*), 44.7 (CH_2), 27.9 (C(CH_3)$_3$), 21.4 (CH_2); mp: 72–74 °C; IR ν_{max}/cm^{-1} 2980,

2934, 1788, 1756, 1721, 1492, 1370, 1295, 1255, 1192, 1143, 1020, 936; MS (ES^+) *m*/*z* (relative intensity %) 328 ($M+Na^+$, 100%), 360 ($M+Na^+$+MeOH, 10%); HRMS (ES^+): calcd for $C_{16}H_{19}O_5NNa$ ($M+Na^+$) 328.1155, found 328.1151.

3.3.4. 1-Methyl 3-phenyl 2-oxopyrrolidine-1,3-dicarboxylate ***42***. According to the above procedure for the preparation of **41**, methyl 2-oxopyrrolidine-1-carboxylate[38] (429 mg, 3.00 mmol) was reacted with phenyl chloroformate (0.38 mL, 3.00 mmol) to give **42** (320 mg, 41%) as a white solid after chromatography on silica gel, eluting with cyclohexane containing 20–60% EtOAc. ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.39–7.34 (2H, m, Ar*H*), 7.25–7.21 (1H, m, Ar*H*), 7.14–7.10 (2H, m, Ar*H*), 3.97 (1H, ddd, *J*=11.0, 8.5, 5.0 Hz, CH_2N), 3.86 (3H, s, OCH_3), 3.82–3.75 (2H, m, C*H* and CH_2N), 2.52 (1H, dtd, *J*=13.0, 8.5, 7.5 Hz, CHCH_2CH$_2$N), 2.37 (1H, m, CHCH_2CH$_2$N); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 168.2 (*C*(O)), 167.2 (*C*(O)), 151.7 (OC(O)N), 150.3 (4° Ar*C*), 129.4 (Ar*C*H), 126.2 (Ar*C*H), 121.2 (Ar*C*H), 53.7 (OCH_3), 49.9 (*C*H), 44.7 (NCH_2), 21.5 (NCH$_2$CH_2); mp: 88–90 °C; IR ν_{max}/cm^{-1} 1794, 1755, 1731, 1439, 1375, 1293, 1194, 1162, 1142; MS (ES^+) *m*/*z* (relative intensity %) 286 ($M+Na^+$, 100%); HRMS (ES^+): calcd for $C_{13}H_{13}O_5NNa$ ($M+Na^+$) 286.0686, found 286.0684.

3.3.5. 1-Benzyl 3-methyl 2-oxopyrrolidine-1,3-dicarboxylate ***43***. According to the above procedure for the preparation of **41**, benzyl 2-oxopyrrolidine-1-carboxylate[38] (440 mg, 2.00 mmol) was reacted with methyl chloroformate (0.15 mL, 2.00 mmol) to give **43** (400 mg, 72%) as a colourless solid following chromatography on silica gel, eluting with petroleum ether containing 70% diethyl ether. ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.42–7.41 (2H, m, Ar*H*), 7.37–7.30 (3H, m, Ar*H*), 5.29 (1H, d, *J*=12.5 Hz, OCH_2Ph), 5.26 (1H, d, *J*=12.5 Hz, OCH_2Ph), 3.93 (1H, ddd, *J*=10.5, 8.5, 5.5 Hz, CH_2N), 3.78–3.73 (1H, m, CH_2N), 3.77 (3H, s, OCH_3), 3.56 (1H, dd, *J*=9.0, 7.5 Hz, C*H*), 2.44–2.37 (1H, m, CH_2CH$_2$N), 2.29–2.22 (1H, m, CH_2CH$_2$N); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 168.8 (*C*(O)), 168.5 (*C*(O)), 151.1 (NC(O)O), 134.9 (4° Ar*C*), 128.5 (Ar*C*H), 128.4 (Ar*C*H), 128.1 (Ar*C*H), 68.3 (OCH$_2$Ph), 52.8 (OCH_3), 49.8 (*C*H), 44.8 (*C*H$_2$N), 21.5 (*C*H$_2$CH$_2$N); IR ν_{max}/cm^{-1} 2956, 1792, 1730, 1638, 1375, 1289, 1164; mp 39–41 °C; MS (ES^-) *m*/*z* (relative intensity %) 276 ($M-H^+$, 100%); HRMS (ES^+): calcd for $C_{14}H_{15}O_5NNa$ ($M+Na^+$) 300.0842, found 300.0838.

3.3.6. 1-[(4-Methylphenyl)sulfonyl]-2-oxopyrrolidine-3-carboxylate ***44***. According to the above procedure for the preparation of **41**, 1-[(4-methylphenyl)sulfonyl]pyrrolidin-2-one (239 mg, 1.00 mmol) was reacted with methyl chloroformate (77 μL, 1.00 mmol) to give **44** (173 mg, 59%) as a colourless solid following chromatography on silica gel, eluting with petroleum ether containing 50–70% diethyl ether. ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.90 (2H, d, *J*=8.0 Hz, Ar*H*), 7.33 (2H, d, *J*=8.0 Hz, Ar*H*), 3.99 (1H, ddd, *J*=9.5, 8.5, 5.5 Hz, NCH_2), 3.84 (1H, ddd, *J*=9.5, 8.0, 7.0 Hz, NCH_2), 3.67 (3H, s, OCH_3), 3.45 (1H, dd, *J*=9.0, 7.5 Hz, C*H*), 2.46–2.39 (1H, m, CH_2CH$_2$N), 2.43 (3H, s, CH_3), 2.33–2.26 (1H, m, CH_2CH$_2$N); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 168.2 (*C*(O)), 168.1 (*C*(O)), 145.5 (4° Ar*C*), 134.5 (4° Ar*C*), 129.7 (Ar*C*H), 128.1 (Ar*C*H), 52.8 (OCH_3), 49.2 (*C*H), 45.6 (NCH_2), 22.2 (NCH$_2$CH_2), 21.6 (*C*H$_3$); IR ν_{max}/cm^{-1} 2956, 1750, 130, 1596, 1437, 1361, 1170, 1123; mp 70–71 °C; MS (ES^+) *m*/*z* (relative intensity %) 320 ($M+Na^+$, 100%); HRMS (ES^+): calcd for $C_{13}H_{15}O_5NSNa$ ($M+Na^+$) 320.0563, found 320.0559.

*3.3.7. O1-tert-Butyl O3-phenyl 3-(3,4-dihydroxy-5-methoxy-phenyl)-2-oxo-pyrrolidine-1,3-dicarboxylate (+)-****45***. According to the general oxidative coupling procedure, replacing PS-BEMP with catalyst **35**, 3-methoxycatechol **21** (28 mg, 0.20 mmol) was reacted with **41** (73 mg, 0.20 mol) to give (+)-**45** (26 mg, 29%) as a peach coloured solid in 40% ee determined by HPLC analysis [Chiralpak AD, heptane/ethanol 55:45, 1.0 mL min^{-1}, λ=215 nm, *t* (minor)=10.78 min, *t* (major)=14.85 min] by comparison to a racemic sample prepared according to the general oxidative coupling procedure. $[\alpha]_D^{24}$ +34.2 (*c* 0.7, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.36–7.32 (2H, m, Ar*H*), 7.21 (1H, t, *J*=7.5 Hz, Ar*H*), 7.06–7.04 (2H, m, Ar*H*), 6.84 (1H, d, *J*=2.0 Hz, Ar*H*), 6.74 (1H, d, *J*=2.0 Hz, Ar*H*), 5.47 (2H, br s, O*H*), 3.88–3.82 (1H, m, CH_2N), 3.87 (3H, s, OCH_3), 3.69 (1H, dt, *J*=10.5, 7.0 Hz, CH_2N), 3.04 (1H, td, *J*=13.0, 7.0 Hz, CH_2CH$_2$N), 2.57 (1H, ddd, *J*=13.0, 7.0, 5.5 Hz, CH_2CH$_2$N), 1.54 (9H, s, C(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 169.4 (*C*(O)), 168.6 (*C*(O)), 150.6 (OC(O)N), 150.0 (4° Ar*C*), 147.0 (4° Ar*C*), 143.8 (4° Ar*C*), 132.5 (4° Ar*C*), 129.4 (Ar*C*H), 126.8 (4° Ar*C*), 126.1 (Ar*C*H), 121.2 (Ar*C*H), 107.6 (Ar*C*H), 103.0 (Ar*C*H), 83.7 (*C*(CH$_3$)$_3$), 61.3 (4° *C*), 56.3 (OCH$_3$), 43.3 (CH$_2$), 29.9 (*C*H$_2$), 28.0 (C(*C*H$_3$)$_3$); mp 137–139 °C (140–141 °C for racemate); IR ν_{max}/cm^{-1} 3400, 2980, 2934, 1778, 1745, 1723, 1521, 1370, 1308, 1188, 1150; MS (ES^+) *m*/*z* (relative intensity %) 466 ($M+Na^+$, 100%); HRMS (ES^+) calcd for $C_{23}H_{25}O_8NNa$ ($M+Na^+$) 466.1472, found 466.1473.

*3.3.8. O1-Methyl O3-phenyl 3-(3,4-dihydroxy-5-methoxy-phenyl)-2-oxo-pyrrolidine-1,3-dicarboxylate (+)-****46***. According to the general oxidative coupling procedure, replacing PS-BEMP with catalyst **35**, 3-methoxycatechol **21** (28 mg, 0.20 mmol) was reacted with pronucleophile **42** (53 mg, 0.20 mmol) to give, (+)-**46** (27 mg, 34%) as a cream coloured solid in 9% ee, determined by HPLC analysis [Chiralpak AD, heptane/ethanol 70:30, 1.0 mL min^{-1}, λ=215 nm, *t* (minor)=6.74 min, *t* (major)=12.37 min] by comparison to a racemic sample prepared according to the general oxidative coupling procedure (racemate mp 74–75 °C); $[\alpha]_D^{24}$ +12.3 (*c* 0.65, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.36–7.32 (2H, m, Ar*H*), 7.23–7.19 (1H, m, Ar*H*), 7.05–7.02 (2H, m, Ar*H*), 6.84 (1H, d, *J*=2 Hz, Ar*H*), 6.74 (1H, d, *J*=2 Hz, Ar*H*), 3.94–3.90 (1H, m, CH_2N), 3.90 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.75 (1H, td, *J*=10.5, 7.0 Hz, CH_2N), 3.08 (1H, ddd, *J*=13.0, 7.5, 7.0 Hz, CH_2CH$_2$N), 2.61 (1H, ddd, *J*=13.0, 7.0, 5.5 Hz, CH_2CH$_2$N); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 169.3 (*C*(O)), 168.3 (*C*(O)), 152.1 (OC(O)N), 150.6 (4° Ar*C*), 147.1 (4° Ar*C*), 143.9 (4° Ar*C*), 132.6 (4° Ar*C*), 130.1 (4° Ar*C*), 129.4 (Ar*C*H), 126.2 (Ar*C*H), 121.1 (Ar*C*H), 107.7 (Ar*C*H), 102.9 (Ar*C*H), 61.2 (4° *C*), 56.3 (OCH$_3$), 53.9 (OCH$_3$), 43.3 (CH$_2$), 30.1 (CH$_2$); mp 74–75 °C; IR ν_{max}/cm^{-1} 3417, 1783, 1738, 1615, 1439, 1372, 1305, 1223, 1188, 1091; MS (ES^+) *m*/*z* (relative intensity %) 424 ($M+Na^+$, 100%); HRMS (ES^+): calcd for $C_{20}H_{19}O_8NNa$ ($M+Na^+$) 424.1003, found 424.1001.

*3.3.9. O1-Benzyl O3-methyl 3-(3,4-diacetoxy-5-methoxy-phenyl)-2-oxo-pyrrolidine-1,3-dicarboxylate (+)-****47***. According to the general oxidative coupling procedure, replacing PS-BEMP with catalyst **35**, 3-methoxycatechol **21** (28 mg, 0.20 mmol) was reacted with **43** (55 mg, 0.20 mmol) and the crude reaction mixture was treated with Ac_2O (0.75 mL) in pyridine (1.5 mL) (see preparation of **40**) to give (+)-**47** (30 mg, 30%) as a pale yellow oil, in 30% ee, determined by HPLC analysis [Chiralpak AS, hexane/*iso*-propanol 70:30, 1.0 mL min^{-1}, λ=220 nm, *t* (minor)=15.14 min, *t* (major)=18.71 min] by comparison to a racemic sample prepared according to the general oxidative coupling procedure; $[\alpha]_D^{25}$ +7.1 (*c* 2.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.43–7.42 (2H, m, Ar*H*), 7.38–7.32 (3H, m, Ar*H*), 7.17 (1H, d, *J*=2.0 Hz, Ar*H*), 6.87 (1H, d, *J*=2.0 Hz, Ar*H*), 5.32–5.27 (2H, m, OCH_2Ph), 3.83 (3H, s, OCH_3), 3.81–3.77 (2H, m, CH_2N), 3.75 (3H, s, OCH_3), 3.01–2.96 (1H, m, CH_2CH$_2$N), 2.45 (1H, td, *J*=13.0, 7.5 Hz, CH_2CH$_2$N), 2.28 (3H, s, OC(O)CH_3), 2.26 (3H, s, OC(O)CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 169.1 (*C*(O)), 168.8 (*C*(O)), 168.0 (*C*(O)), 167.5 (*C*(O)), 152.3 (4° Ar*C*), 151.2 (NC(O)O), 143.1 (4° Ar*C*), 134.9 (4° Ar*C*), 133.9 (4° Ar*C*), 131.9 (4° Ar*C*), 128.6 (Ar*C*H), 128.5 (Ar*C*H), 128.2 (Ar*C*H), 113.8 (Ar*C*H), 109.3 (Ar*C*H), 68.4 (OCH$_2$Ph), 60.6 (4° *C*), 56.4 (OCH$_3$), 53.7 (OCH$_3$), 43.2 (CH$_2$N), 30.2 (*C*H$_2$CH$_2$N), 20.5 (OC(O)*C*H$_3$), 20.3 (OC(O)*C*H$_3$); IR ν_{max}/cm^{-1} 1781, 1774, 1731, 1371, 1296, 1207, 1098; MS (ES^+) *m*/*z* (relative

intensity %) 522 (M+Na, 100%); HRMS (ES^+): calcd for $C_{25}H_{25}O_{10}NNa$ ($M+Na^+$) 522.1371, found 522.1366.

*3.3.10. Methyl 3-(3,4-diacetoxy-5-methoxy-phenyl)-2-oxo-1-(p-tolylsulfonyl)pyrrolidine-3-carboxylate (+)-**48**.* According to the general oxidative coupling procedure, replacing PS-BEMP with catalyst **35**, 3-methoxycatechol **21** (28 mg, 0.20 mmol) was reacted with **44** (59 mg, 0.20 mmol) and the crude reaction mixture treated with Ac_2O (0.75 mL) in pyridine (1.5 mL) (see preparation of **40**) to give (+)-**48** (25 mg, 24%) as a pale yellow oil, in 1% ee, determined by HPLC analysis [Chiralpak AD, hexane/*iso*-propanol 85:15, 1.0 mL min^{-1}, λ=215 nm, *t* (major)=22.39 min, *t* (minor)=28.95 min] by comparison to a racemic sample prepared according to the general oxidative coupling procedure; $[\alpha]_D^{25}$ +5.1 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.89 (2H, d, *J*=8.0 Hz, Ar*H*), 7.33 (2H, d, *J*=8.0 Hz, Ar*H*), 6.95 (1H, d, *J*=2.0 Hz, Ar*H*), 6.72 (1H, d, *J*=2.0 Hz, Ar*H*), 3.87–3.84 (2H, m, CH_2N), 3.72 (3H, s, OCH_3), 3.58 (3H, s, OCH_3), 3.01–2.96 (1H, m, CH_2CH$_2$N), 2.50–2.43 (1H, m, CH_2CH$_2$N), 2.43 (3H, s, CH_3), 2.27 (OC(O)CH_3), 2.25(3H, s, OC(O)CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 168.6 (*C*(O)), 168.6 (*C*(O)), 167.9 (*C*(O)), 167.5 (*C*(O)), 152.2 (4° Ar*C*), 145.5 (4° Ar*C*), 143.2 (4° Ar*C*), 134.3 (4° Ar*C*), 133.2 (4° Ar*C*), 131.9 (4° Ar*C*), 129.7 (Ar*C*H), 128.2 (Ar*C*H), 113.7 (Ar*C*H), 109.0 (Ar*C*H), 60.1 (4° *C*), 56.2 (O*C*H$_3$), 53.6 (O*C*H$_3$), 44.0 (*C*H$_2$N), 30.9 (*C*H$_2$CH$_2$N), 21.6 (*C*H$_3$), 20.5 (OC(O)*C*H$_3$), 20.3 (OC(O)*C*H$_3$); IR ν_{max}/cm^{-1} 1774, 1751, 1734, 1422, 1207, 1173, 1093; MS (ES^+) *m*/*z* (relative intensity %) 542 ($M+Na^+$, 100%); HRMS (ES^+): calcd for $C_{24}H_{25}O_{10}NSNa$ ($M+Na^+$) 542.1091, found 542.1091.

*3.3.11. 1. O1-tert-Butyl O3-methyl 3-(3,4-diacetoxy-5-methoxy-phenyl)-2-oxo-pyrrolidine-1,3-dicarboxylate (+)-**40**.* According to the general oxidative coupling procedure, replacing PS-BEMP with catalyst **52**, 3-methoxycatechol **21** (14 mg, 0.10 mmol) was reacted with **23** (24 mg, 0.10 mmol) and the crude reaction products was dissolved in pyridine (0.5 mL) and Ac_2O (0.25 mL) and stirred at room temperature overnight. The reaction mixture was diluted with EtOAc (5 mL) and washed with saturated aqueous $CuSO_4$ (3×5 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel, eluting with 70:30 diethyl ether/petroleum ether, to give the arylated product **40** (26 mg, 56%) as a colourless oil in 64% ee, determined by HPLC analysis [Chiralpak AD, hexane/*iso*-propanol 85:15, 1.0 mL min^{-1}, λ=215 nm, *t* (major)=11.382 min, *t* (minor)=22.29 min] by comparison to a racemic sample prepared in according to the general oxidative coupling procedure. $[\alpha]_D^{24}$ +34.4 (*c* 0.90, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.17 (1H, d, *J*=2.0 Hz, Ar*H*), 6.87 (1H, d, *J*=2.0 Hz, Ar*H*), 3.83 (3H, s, ArOCH_3), 3.75–3.67 (2H, m, CH_2N), 3.74 (3H, s, OCH_3), 2.95 (1H, ddd, *J*=12.5, 7.0, 5.0 Hz, CH_2CH$_2$N), 2.42 (1H, dt, *J*=13.0, 7.5 Hz, CH_2CH$_2$N), 2.28 (3H, s, OC(O)CH_3), 2.26 (3H, s, OC(O)CH_3), 1.52 (9H, s, C(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 169.4 (N*C*(O)), 168.9 (O*C*(O)OCH$_3$), 168.0 (O*C*(O)CH$_3$), 167.6 (O*C*(O)CH$_3$), 152.2 (4° Ar*C*), 149.8 (N*C*(O)O), 143.1 (4° Ar*C*), 134.1 (4° Ar*C*), 131.8 (4° Ar*C*), 113.8 (Ar*C*H), 109.4 (Ar*C*H), 83.6 (*C*(CH$_3$)$_3$), 60.8 (4° *C*), 56.3 (ArO*C*H$_3$), 53.6 (O*C*H$_3$), 43.2 (NCH$_2$), 30.0 (NCH$_2$*C*H$_2$), 27.9 (C(*C*H$_3$)$_3$), 20.5 (OC(O)*C*H$_3$), 20.3 (OC(O)*C*H$_3$); IR ν_{max}/cm^{-1} 2981, 1777, 1730, 1611, 1370, 1306, 1206, 1096; MS (ES^+) *m*/*z* (relative intensity %) 524 ($M+MeCN+NH_4^+$, 100%); HRMS (ES^+): calcd for $C_{22}H_{27}O_{10}NNa$ ($M+Na^+$) 488.1527, found 488.1536.

*3.3.12. O1-tert-Butyl O3-methyl 3-(7-methoxy-1,3-benzodioxol-5-yl)-2-oxo-pyrrolidine-1,3-dicarboxylate (+)-**24**.* To a stirred solution of 3-methoxycatechol **21** (1.40 g, 10.0 mmol) and **23** (2.43 g, 10.0 mmol) in CH_2Cl_2 (400 mL) at −20 °C was added cat. **52** (936 mg, 2.00 mmol) followed by PS-IO_4 (3.22 g 20.0 mmol). The reaction mixture was stirred at this temperature for 7 h then filtered and the resin on the filter washed with CH_2Cl_2 (3×100 mL). The filtrate was stirred with saturated aqueous $Na_2S_2O_4$ (200 mL), the organic phase separated and the aqueous extracted with CH_2Cl_2 (2×50 mL). The combined organic portions were dried over Na_2SO_4, filtered and concentrated. The residue was dissolved in DMF and divided equally between five sealable vials. To each vial was added CH_2ClBr (0.19 mL, 3 mmol) and Cs_2CO_3 (977 mg, 3 mmol). The vials were sealed and heated at 85 °C for 1 h then cooled to room temperature. The resulting purple-brown solution was concentrated and purified by column chromatography on silica gel, eluting with petroleum ether containing 30–60% diethyl ether to give the arylated product (+)-**24** (2.24 g, 57% yield) as a pale yellow oil in 70% ee, determined by HPLC analysis [Chiralpak AD, hexane/*iso*-propanol 85:15, 1.0 mL min^{-1}, λ=215 nm, *t* (minor)=11.95 min, *t* (major)=18.30 min] by comparison to a racemic sample prepared in according to the general oxidative coupling procedure. $[\alpha]_D^{24}$ +38.1 (*c* 0.52, $CHCl_3$). Other data identical to racemic compound.[16]

*3.3.13. O1-tert-Butyl O3-methyl 2-hydroxy-3-(7-methoxy-1,3-benzodioxol-5-yl)pyrrolidine-1,3-dicarboxylate (+)-**25**.* According to the procedure for racemate synthesis,[16] (+)-**24** (2.06 g, 5.25 mmol) was reacted with superhydride® (6.3 mL of a 1 M solution in THF, 6.30 mmol) to give (+)-**25** (1.87 g, 90%) as a colourless solid, the four stereoisomers could not be completely separated by chiral HPLC analysis, $[\alpha]_D^{24}$ +22.6 (*c* 0.95, $CHCl_3$); mp 40–44 °C. Other data identical to racemic compound.[16]

*3.3.14. O1-tert-Butyl O3-methyl 2-acetonyl-3-(7-methoxy-1,3-benzodioxol-5-yl)pyrrolidine-1,3-dicarboxylate (−)-**26**.* According to the procedure for racemate synthesis,[16] (+)-**25** (1.87 g, 4.73 mmol) was treated with acetic anhydride (2 mL) in pyridine (10 mL) and the crude acetylated product reacted with (isopropenyloxy)trimethylsilane (7.9 mL, 47.3 mmol) to give (−)-**26** (1.89 g, 92%) as a colourless oil in 3:1 dr and 69% ee determined by HPLC analysis [Chiralpak AD, hexane/*iso*-propanol 95:5, 1.0 mL min^{-1}, λ=215 nm, minor diastereomer: *t* (major)=16.12 min, *t* (minor)=19.90 min], major diastereomer: *t* (minor)=24.41 min, *t* (major)=32.41 min] by comparison to a racemic sample. $[\alpha]_D^{24}$ −15.4 (*c* 0.46, $CHCl_3$). Other data identical to racemic compound.[16]

*3.3.15. tert-Butyl 6-methoxy-3a-(7-methoxy-1,3-benzodioxol-5-yl)-4-oxo-2,3,7,7a-tetrahydroindole-1-carboxylate (−)-**27**.* According to the procedure for racemate synthesis[16] (−)-**26b**(1.83 g, 4.20 mmol) was treated with KO^{t}Bu (8.83 mL of a 1 M solution in THF, 8.83 mmol) and the crude di-ketone treated with $TiCl_4$ (0.19 mL, 0.19 mmol) in MeOH (20 mL) to give (−)-**27** (950 mg, 54%) as a colourless solid in 24% ee determined by HPLC analysis [Chiralpak AD, hexane/*iso*-propanol 95:5, 1.0 mL min^{-1}, λ=215 nm, *t* (major)=27.73 min, *t* (minor)=31.62 min], by comparison to a racemic sample. $[\alpha]_D^{24}$ −18.9 (*c* 1.82, $CHCl_3$); mp 48–52 °C. Other data identical to racemic compound.[16]

*3.3.16. 4-[(1R)-5-[(Ethyl(methyl)amino)methyl]-4-methyl-1-[(4-pyrazol-1-ylphenyl)methoxy]hept-6-enyl]quinolin-6-ol **50**.* Catalyst **50** was prepared according to the procedures reported by Deng and coworkers,[26e,f] $[\alpha]_D^{25}$ +88.7 (*c* 1.10, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ_H 6.64 (1H, d, *J*=4.5 Hz, Ar*H*), 8.22 (1H, d, *J*=2.5 Hz, Ar*H*), 7.94 (1H, d, *J*=9.0 Hz, Ar*H*), 7.74–7.72 (3H, m, Ar*H*), 7.58 (1H, br s, Ar*H*), 7.48 (2H, br d, *J*=8.0 Hz, Ar*H*), 7.36 (1H, dd, *J*=9.0, 2.5 Hz, Ar*H*), 7.33 (1H, br s, Ar*H*), 6.53 (1H, t, *J*=2.0 Hz, ArH), 5.99 (1H, ddd, *J*=17.5, 10.0, 7.5 Hz, C*H*=CH$_2$), 5.32 (1H, br s, C*H*OCH$_2$Ar), 5.03–4.97 (2H, m, CH=C*H*$_2$), 4.53 (1H, d, *J*=11.5 Hz, OC*H*$_2$Ar), 4.44 (1H, d, *J*=11.5 Hz, OC*H*$_2$Ar), 4.31 (1H, br s, aliphatic C*H*), 3.09 (1H, br s, aliphatic C*H*), 2.92–2.85 (2H, br m, aliphatic C*H*), 2.79–2.73 (1H, br m, aliphatic CH), 2.29 (1H, dd, *J*=17.0, 8.0 Hz, aliphatic C*H*), 2.18 (1H, br m, aliphatic C*H*), 1.73 (1H, br s, aliphatic C*H*), 1.60–1.50 (2H, br m, aliphatic C*H*), 1.24 (1H, br s, aliphatic C*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 158.0 (4° Ar*C*), 147.5 (Ar*C*H), 145.8 (4° Ar*C*), 144.4 (4° Ar*C*), 142.3 (Ar*C*H), 141.5 (*C*H=CH$_2$), 141.1 (4° Ar*C*), 137.6 (4° Ar*C*), 131.7 (Ar*C*H), 130.7 (Ar*C*H), 129.2 (4° Ar*C*), 129.0 (Ar*C*H),

123.5 (ArCH), 120.5 (ArCH), 120.3 (ArCH), 115.3 (CH=CH_2), 108.8 (ArCH), 105.2 (ArCH), 81.0 ($COCH_2Ar$), 72.0 (OCH_2Ar), 60.7 (NCH), 50.9 (NCH_2), 50.4 (NCH_2), 41.1 (CH), 29.5 (CH), 27.1 (CH_2), 22.2 (CH_2); IR ν_{max}/cm^{-1} 3070, 2940, 1614, 1526, 1467, 1394, 1030, 830; mp 139–144 °C; MS (ES^+) *m/z* (relative intensity %) 467 ($M+H^+$, 100%); HRMS (ES^+): calcd for $C_{29}H_{31}O_2N_4$ ($M+X^+$) 467.2442, found 467.2439.

3.3.17. 4-[(1R)-5-[(Ethyl(methyl)amino)methyl]-4-methyl-1-[(4-nitrophenyl)methoxy]hept-6-enyl]quinolin-6-ol ***51***. Catalyst **51** was prepared according to the procedures reported by Deng and co-workers,[26e,f] $[\alpha]_D^{25}$ +75.4 (*c* 0.76, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ_H 8.63 (1H, d, *J*=4.5 Hz, ArH), 8.30 (1H, s, ArH), 8.17 (1H, dd, *J*=8.0, 1.0 Hz, ArH), 7.93 (1H, d, *J*=9.0 Hz, ArH), 7.73 (1H, d, *J*=8.0 Hz, ArH), 7.59 (1H, t, *J*=8.0 Hz, ArH), 7.56 (1H, br d, *J*=4.5 Hz, ArH), 7.36 (1H, dd, *J*=9.0, 2.5 Hz, ArH), 7.33 (1H, br s, ArH), 6.04 (1H, ddd, *J*=17.5, 10.0, 7.5 Hz, CH=CH_2), 5.36 (1H, br s, CHOCH_2Ar), 5.05–5.00 (2H, m, CH=CH_2), 4.61 (1H, d, *J*=12.0 Hz, OCH_2Ar), 4.58 (1H, d, *J*=12.0 Hz, OCH_2Ar), 3.37 (1H, br s, aliphatic CH), 3.14 (1H, br s, aliphatic CH), 2.95–2.86 (2H, m, aliphatic CH), 2.82–2.76 (1H, m, aliphatic CH), 2.32 (1H, q, *J*=8.5 Hz, aliphatic CH), 2.21 (1H, br t, *J*=10.0 Hz, aliphatic CH), 1.77 (1H, br s, aliphatic CH), 1.63–1.53 (2H, m, aliphatic CH), 1.29 (1H, br s, aliphatic CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 158.0 (4° ArC), 149.8 (4° ArC), 147.6 (ArCH), 145.4 (4° ArC), 144.4 (4° ArC), 141.6 (4° ArC), 141.4 (CH=CH_2), 135.1 (ArCH), 131.7 (ArCH), 130.8 (ArCH), 129.1 (4° ArC), 123.7 (ArCH), 123.6 (ArCH), 123.5 (ArCH), 120.4 (ArCH), 115.3 (CH=CH_2), 105.2 (ArCH), 81.8 ($COCH_2Ar$), 71.4 (OCH_2Ar), 60.7 (NCH), 50.9 (NCH_2), 50.5 (NCH_2), 40.9 (CH), 29.4 (CH), 27.0 (CH_2), 22.4 (CH_2); IR ν_{max}/cm^{-1} 3386, 2941, 1617, 1529, 1350, 1270, 809; mp 118–122 °C; MS (ES^+) *m/z* (relative intensity %) 446 (M+H, 100%); HRMS (ES^+): calcd for $C_{26}H_{28}O_4N_3$ ($M+H^+$) 446.2074, found 446.2071.

3.3.18. 4-[(1R)-1-[[3,5-Bis(trifluoromethyl)phenyl]methoxy]-5-[(ethyl(methyl)amino)methyl]-4-methyl-hept-6-enyl]quinolin-6-ol ***49***. To a stirred solution of quinidine (324 mg, 1.00 mmol) in DMF (5 mL) was added NaH (80 mg of a 60% dispersion in mineral oil, 2.00 mmol) and the reaction mixture was stirred at room temperature for 30 min before adding 1-(bromomethyl)-3,5-bis(trifluoromethyl)benzene (0.18 mL, 1.00 mmol). The reaction mixture was stirred for 4 h then quenched with saturated $NaHCO_{3(aq)}$ (10 mL), diluted with EtOAc (20 mL) and washed with water (3×10 mL) and brine (10 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was dissolved in DMF (10 mL). To the DMF solution was added 1-dodecanethiol (1.2 mL, 5 mmol) followed by portion-wise addition of NaH (200 mg of a 60% dispersion in mineral oil, 5 mmol). CAUTION: significant foaming of the reaction mixture occurred upon addition of NaH. The reaction mixture was heated to 110 °C overnight, cooled to room temperature and quenched with saturated NH_4Cl (30 mL). The mixture was diluted with EtOAc (50 mL) and washed with water (3×20 mL) and brine (20 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel to give **49** (300 mg, 56%) as an off-white solid. $[\alpha]_D^{25}$ +76.3 (*c* 0.82, $CHCl_3$); ^1H NMR (500 MHz, CD_3OD) δ_H 8.62 (1H, d, *J*=4.5 Hz, ArH), 7.98 (2H, br s, ArH), 7.93 (1H, d, *J*=9.0 Hz, ArH), 7.89 (1H, br s, ArH), 7.55 (1H, br d, *J*=4.0 Hz, ArH), 7.37–7.35 (2H, br m, ArH), 6.01 (1H, ddd, *J*=17.5, 10.5, 7.5 Hz, CH=CH_2), 5.46 (1H, br s. CHOCH_2Ar), 5.05–5.01 (2H, m, CH=CH_2), 4.69–4.64 (2H, br m, OCH_2Ar), 3.41 (1H, br s, aliphatic CH), 3.21 (1H, br s, aliphatic CH), 3.02–2.96 (2H, m, aliphatic CH), 2.88–2.82 (1H, m, aliphatic CH), 2.37 (1H, q, *J*=8.0 Hz, aliphatic CH), 2.24 (1H, br t, *J*=10.0 Hz, aliphatic CH), 1.80 (1H, br s, aliphatic CH), 1.65–1.55 (2H, m, aliphatic CH), 1.29 (1H, br s, aliphatic CH); ^{13}C NMR (125 MHz, CD_3OD) δ_C 158.1 (4° ArC), 147.6 (ArCH), 144.7 (4° ArC), 144.4 (4° ArC), 142.5 (4° ArC), 140.8 (CH=CH_2), 132.82 (q, *J*=33.5 Hz, CF_3) 131.8 (ArCH), 129.2 (ArCH), 129.0 (4° ArC), 123.7 (ArCH), 123.5 (ArCH), 122.5 (m, $ArCCF_3$), 120.1 (ArCH), 115.6 (CH=CH_2), 105.1 (ArCH), 81.6 ($COCH_2Ar$), 71.2 (OCH_2Ar), 60.7 (NCH), 50.9 (NCH_2), 50.5 (NCH_2), 40.5 (CH), 29.2 (CH), 26.6 (CH_2), 22.1 (CH_2); IR ν_{max}/cm^{-1} 3077, 2941, 2877, 1620, 1469, 1280, 1177, 1134; mp 97–101 °C; MS (ES^+) *m/z* (relative intensity %); 537 ($M+H^+$, 100%); HRMS (ES^+): calcd for $C_{28}H_{27}F_6O_2N_2$ ($M+H^+$) 537.1971, found 537.1957.

3.3.19. 4-[(1R)-5-[(Ethyl(methyl)amino)methyl]-4-methyl-1-[[2-(trifluoromethyl)phenyl]methoxy]hept-6-enyl]quinolin-6-ol ***52***. According to the above procedure for the preparation of catalyst **49**, quinidine (3.24 g, 10.0 mmol) was benzylated with 1-(bromomethyl)-2-(trifluoromethyl)benzene (1.52 mL, 10.0 mmol) and demethylated with 1-dodecanethiol (12.0 mL, 50.0 mmol) to give cat. **52** (3.81 g, 82%) as a pale yellow solid. $[\alpha]_D^{25}$ +104.4 (*c* 1.78, $CHCl_3$); ^1H NMR (500 MHz, CD_3OD) δ_H 8.63 (1H, d, *J*=4.5 Hz, ArH) 7.95 (1H, d, *J*=9.5 Hz, ArH), 7.81 (1H, br d, *J*=7.5 Hz, ArH), 7.68–7.63 (2H, m, ArH), 7.56 (1H, br d, *J*=4.0 Hz, ArH), 7.48 (1H, t, *J*=7.5 Hz, ArH), 7.38–7.36 (2H, m, ArH), 5.95 (1H, ddd, *J*=17.5, 10.0, 7.5 Hz, CH=CH_2), 5.43 (1H, br s, CHOCH_2Ar), 4.99–4.96 (2H, m, CH=CH_2), 4.64 (1H, d, *J*=12.0 Hz, OCH_2Ar), 4.60 (1H, d, *J*=12.0 Hz, OCH_2Ar), 3.39 (1H, br s, aliphatic CH), 3.14 (1H, br s. aliphatic CH), 2.95–2.90 (2H, m, aliphatic CH), 2.82–2.76 (1H, m, aliphatic CH), 2.31 (1H, q, *J*=8.0 Hz, aliphatic CH), 2.19 (1H, br m, aliphatic CH), 1.74 (1H, br s, aliphatic CH), 1.61–1.50 (2H, m, aliphatic CH), 1.25 (1H, br s, aliphatic CH); ^{13}C NMR (125 MHz, CD_3OD) δ_C 158.0 (4° ArC), 147.5 (ArCH), 145.0 (4° ArC), 144.4 (4° ArC), 141.0 (CH=CH_2), 137.3 (4° ArC), 133.5 (ArCH), 131.8 (ArCH), 131.78 (ArCH), 129.4 (4° ArC), 129.0 (ArCH), 128.9 (q, *J*=30.5 Hz, CF_3), 126.9 (q, *J*=5.5 Hz, $ArCCF_3$) 126.9 (ArCH), 123.6 (ArCH), 120.1 (ArCH), 115.4 (CH=CH_2), 105.1 (ArCH), 81.7 (CHOCH_2Ar), 68.8 (CHOCH_2Ar), 60.8 (NCH), 50.8 (NCH_2), 50.3 (NCH_2), 40.7 (CH), 29.3 (CH), 26.8 (CH_2), 22.1 (CH_2); IR ν_{max}/cm^{-1} 3074, 2941, 2877, 1670, 1619, 1469, 1316, 1167, 1119; mp 98–101 °C; MS (ES^+) *m/z* (relative intensity %); 469 ($M+H^+$, 100%); HRMS (ES^+): calcd for $C_{27}H_{28}F_3O_2N_2$ ($M+H^+$) 469.2097, found 469.2088.

3.3.20. 4-[(1S)-5-[(Ethyl(methyl)amino)methyl]-4-methyl-1-[[2-(trifluoromethyl)phenyl]methoxy]hept-6-enyl]quinolin-6-ol ***53***. According to the above procedure for the synthesis of catalyst **49**, quinine (1.62 g, 5.00 mmol) was benzylated with 1-(bromomethyl)-2-(trifluoromethyl)benzene (0.76 mL, 5.00 mmol) and demethylated with 1-dodecanethiol (6.0 mL, 25.0 mmol) to give cat. **53** (1.61 g, 69%) $[\alpha]_D^{25}$ −18.5 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, CD_3OD) δ_H 8.61 (1H, d, *J*=4.5 Hz, ArH), 7.95 (1H, d, *J*=9.0 Hz, ArH), 7.78 (1H, br s, ArH), 7.67–7.63 (2H, m, ArH), 7.56 (1H, d, *J*=4.0 Hz, ArH), 7.48–7.36 (1H, br s, ArH), 7.47 (1H, t, *J*=7.5 Hz, ArH), 7.37 (1H, d, *J*=9.0 Hz, ArH), 5.74 (1H, br m, CH=CH_2), 5.35 (1H, br s, CHOCH_2Ar), 4.97–4.88 (2H, m, CH=CH_2), 4.65 (1H, d, *J*=12.0 Hz, OCH_2Ar), 4.58 (1H, d, *J*=12.0 Hz, OCH_2Ar), 3.45 (1H, br s, aliphatic CH), 3.17 (1H, br s, aliphatic CH), 3.07 (1H, br t, *J*=10.0 Hz, aliphatic CH), 2.71–2.60 (2H, br m, aliphatic CH), 2.33 (1H, br s, aliphatic CH), 1.90 (1H, br s, aliphatic CH), 1.79–1.75 (2H, br m, aliphatic CH), 1.64 (1H, br s, aliphatic CH), 1.59–1.54 (1H, br m, aliphatic CH); ^{13}C NMR (75 MHz, CD_3OD) δ_C 158.0 (4° ArC), 147.5 (ArCH), 145.3 (4° ArC), 144.5 (4° ArC), 142.5 (CH=CH_2), 137.5 (4° ArC), 133.5 (ArCH), 131.8 (ArCH), 131.3 (ArCH), 129.3 (4° ArC), 129.0 (ArCH), 128.7 (q, *J*=30.5 Hz, CF_3), 126.9 (q, *J*=5.5 Hz, $ArCCF_3$), 126.9 (ArCH), 123.5 (ArCH), 120.0 (ArCH), 115.2 (CH=CH_2), 105.0 (ArCH), 81.0 (CHOCH_2Ar), 68.7 (OCH_2Ar), 61.1 (NCH), 57.5 (NCH_2), 44.1 (NCH_2), 40.8 (CH), 29.1 (CH), 28.2 (CH_2), 22.4 (CH_2); IR ν_{max}/cm^{-1} 3424, 2943, 1637, 1620, 1315, 1167, 1118; mp 207–212 °C; MS (ES^+) *m/z* (relative intensity %) 469 ($M+H^+$, 100%); HRMS (ES^+): calcd for $C_{27}H_{28}F_3O_2N_2$ ($M+H^+$) 469.2097, found 469.2094.

Acknowledgements

We gratefully thank The University of Manchester and GlaxoSmithKline (for a studentship to KMB), the EPSRC for a Leadership

Fellowship to DJD, and the Oxford Chemical Crystallography Service for the use of the instrumentation.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.04.132. These data include MOL files and InChIKeys of the most important compounds described in this article.

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