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Radical 1,4-aryl transfer in arylcarboxamides leading to phthalimides, biaryls and enantiomerically enriched β-arylethylamines

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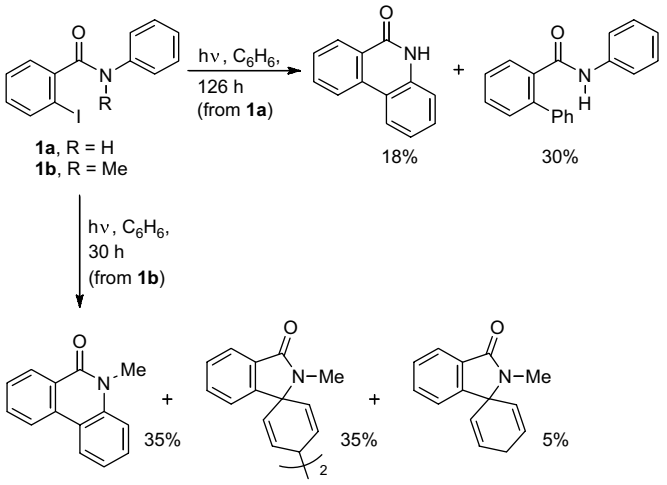
ABSTRACT

5-*exo* Cyclisation of vinyl-, aryl- and alkyl-radicals onto the aryl group of arylcarboxamides is followed by β-scission of the resulting spirocyclohexadienyl radicals with ejection of a carbamoyl radical. The fate of this radical depends on the substrate but, in the cases studied, either 5-*endo* cyclisation or direct reduction follows to give phthalimides, biaryls or β-arylethylamines.

1. Introduction

Authenticated radical cyclisations of amides, in which the radical acceptor is an aryl group, have been known for over 40 years.[1] In these processes, irrespective of the location of the aryl group on the carboxyl carbon or the amide nitrogen, the presence or absence of a second *N*-alkyl substituent exerts a strong influence on the outcome. For example, photolysis of substrate **1a** (Scheme 1), in which the amide nitrogen bears a proton, was only 50% complete after 126 h, the yield of cyclisation products being only 18% with the major product arising from addition to the solvent. In contrast, photolysis of the corresponding *N*-methyl precursor **1b**, under otherwise identical conditions, proceeded to 80% conversion after only 30 h, resulting in an overall 75% yield of cyclisation products with no evidence of reaction with the solvent.[2] The authors of this study attributed the differences to rotameric preferences, the secondary amides heavily favouring an *s-Z* conformation with a high barrier to interconversion with the *s-E* conformation;[3] conversely, in the corresponding tertiary amides, either the relative populations of the two rotamers are more in favour of the *s-E* conformation or, less likely,[4] the barrier to interconversion is sufficiently low that interconversion is fast relative to the lifetime of the aryl radical.

In the intervening period since this early work there have been numerous reports of similar cyclisations and there has arisen a certain amount of confusion in, and reinterpretation of, the literature as small variations in the experimental parameters led to apparently conflicting results. A snapshot of this situation can be found in a publication by Jones, which discusses the importance of



Scheme 1. The positive effect of N-methylation on the efficiency of radical cyclisations in amide substrates.

conformational preferences around the aryl–N bond in influencing the reactions of certain *ortho*-haloanilide substrates.[5] More recently, there has been a focus on achieving clean formation of spirocyclic lactams in such cyclisations; for example, by minimising rearomatisation through stabilisation of the cyclised radical by the reagent[6] or by careful choice of substrate,[7] or by trapping the radical before it has time to fragment or ring-expand.[8] This has led to a greater understanding of the relative rates of the two modes of cyclisation, onto the *ortho*- (typically 6-*endo*$_{Ar}$)[9] or *ipso*- (typically 5-*exo*$_{Ar}$) position. Nevertheless, yields in many of these reactions remain low, which we attribute to the operation of reaction pathways that have been overlooked or whose significance has not been fully appreciated. This report discusses one such pathway.

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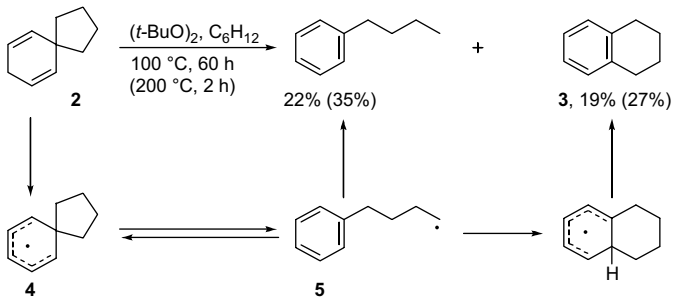
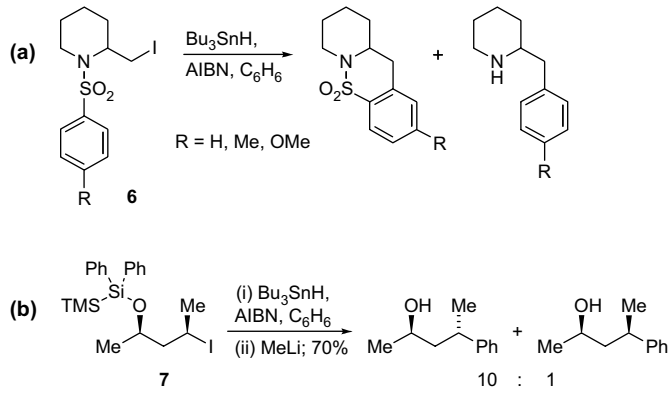
Julia showed that the radical (**4**) derived by H-abstraction from spiro[4.5]deca-6,9-diene (**2**) fragments to give 4-phenylbutyl radical (**5**).[10] This experiment provided insight into the formation of tetralins (e.g., **3**) from straight-chain precursors to 4-phenylbutyl radicals, and supported the view that both 5-*exo*$_{Ar}$ and 6-*endo*$_{Ar}$ cyclisation modes operate in competition (Scheme 2); in a naphthyl system the data indicated a 70:30 5-*exo*$_{Ar}$/6-*endo*$_{Ar}$ ratio.



Scheme 2. Reversibility of 5-*exo* cyclisations onto aromatic rings.

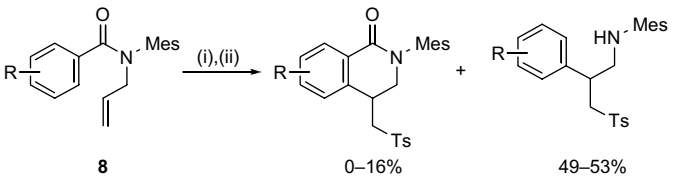
The fragmentation (β-scission) of spirocyclohexadienyl radical intermediates such as **4** should proceed more rapidly when substituents are present that can stabilise the fragmented radical (cf. **5**) and, as expected, this fragmentation occurs as an undesired side-reaction in amide 'tethered' radical cyclisations onto aromatic rings, see below.[11] However, fragmentations of this general type have been employed for planned aryl transfer from one end of a chain to the other where the linking chain incorporates a cleavable tether.[12] Notable examples include sulfonamide tethers for formation of biphenyls[13] and 2-benzyl piperidine derivatives[14] (**6**→, Scheme 3), and silyl tethers for stereocontrolled arylation at sp^3 centres[15] (**7**→, Scheme 3).



Scheme 3. Sulfonamide (a) and silyl ether (b) tethers for controlled aryl transfer.

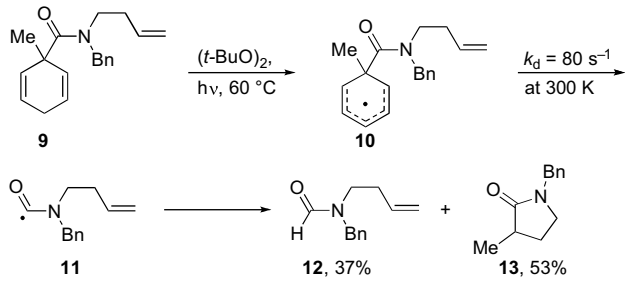
The sulfonamide tethered aryl transfer in Scheme 3a was discovered by accident and, presumably in view of the large body of apparently uncomplicated radical cyclisations of amide substrates, amides have not found application in similar reactions. An important exception to this generalisation is found in a single publication by Chuang et al. that describes five examples of amide tethered aryl transfer in a process initiated by toluenesulfinyl radical addition to various *N*-allyl-*N*-mesitylenesulfonyl carboxamides (**8**, Scheme 4).[16]

The observation of aryl transfer in the examples in Scheme 4 is accommodated by the picture established by Walton's studies of the fragmentation of cyclohexadienyl carboxamide radicals (**10**, Scheme 5) to form carbamoyl radicals (**11**).[17] These studies showed that the cyclohexadienyl radical is relatively long-lived below 30 °C but fragmentation completes quickly at around 60 °C; the rate constant



Scheme 4. 1,4-Aryl transfer involving Ar–CO cleavage in an amide substrate. Reagents: (i) NaTs, Cu(OAc)$_2$; (ii) MesCl, Et$_3$N [Mes=mesitylenesulfonyl].

for dissociation was later shown to be in the range 50–90 s^{-1} at 27 °C.[17b] The carbamoyl radicals could be trapped by simple reduction (**11**→**12**) or, in appropriate cases, cyclisation in 4-*exo* and 5-*exo* modes onto alkene and oxime acceptors (e.g., **11**→**13**).



Scheme 5. Formation and cyclisation of carbamoyl radicals from the radical fragmentation of cyclohexadienyl carboxamides.

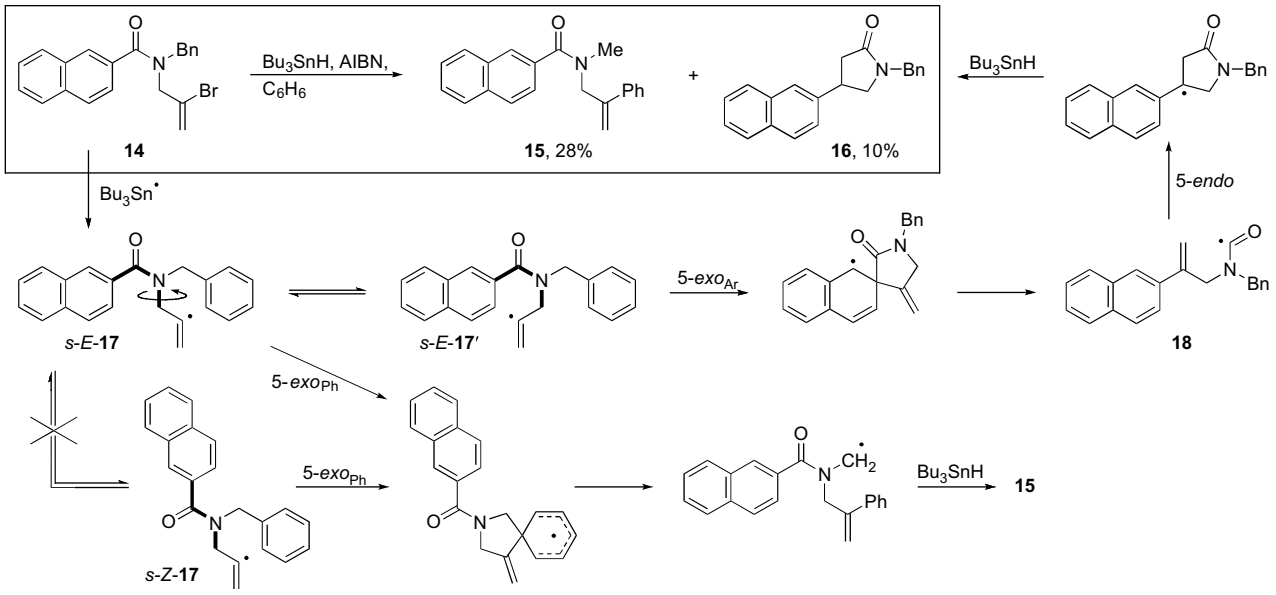
Our own entry into this field derives from an attempted radical spirocyclisation of substrate **14** (Scheme 6) in which two products, **15** and **16**, were obtained in low yield, both retaining an intact naphthalene ring. Both products arise by 1,4-aryl migrations, compound **15** following cyclisation onto the phenyl ring, compound **16** following cyclisation onto the naphthalene core to generate carbamoyl radical **18**, which then cyclises in an overall 5-*endo* sense to give the observed pyrrolidinone.[18]

In substrates in which the *N*-benzyl substituent is replaced by *N*-methyl, moderate yields of pyrrolidinones could be obtained but these were always formed in roughly 1:1 ratio with the products of direct reduction. Altering the concentration of the tin hydride or the temperature of the reaction had little impact on the ratio of pyrrolidinone/reduction product, which we attributed to slow amide rotamer interconversion when compared to the likely life times of the radicals; only the *s*-*E* conformer (*s*-*E*-**17′**, Scheme 6) can cyclise onto the aryl ring, which is a pre-requisite for pyrrolidinone formation, the *s*-*Z* conformer (*s*-*Z*-**17**), in the *N*-methyl series, being able only to reduce.

2. Imide substrates

The free energy barrier towards rotameric interconversion in imides is approximately half that in analogous amides (e.g., 8.2 kJ mol^{-1} for *N*-methyldiacetamide vs 17.3 kJ mol^{-1} for *N*,*N*-dimethylacetamide)[19] and for simple cases the *E*,*Z*-conformer is the major form in solution (Fig. 1).

On this basis, and assuming unrestricted N–C(alkyl) rotation, radical cyclisations of symmetrical diarylcarboxamide variants of substrate **14** were expected to proceed readily and, at relatively high dilution, with much less competing direct reduction. Suitable substrates were readily prepared by diacylation of 2-bromoallylamine[20] followed by an extended alkaline work-up to hydrolyse the excess acid chloride, which was otherwise difficult to separate from the products. After some experimentation, with the radical reaction of the simplest substrate (**19a**, Scheme 7), consistent results were obtained when tributyltin hydride was added over 2 h to a 20 mM



Scheme 6. Aryl transfer products in the radical reaction of an *N*-2-bromoallyl arylcarboxamide.

benzene solution of the substrate with a further 2 h heating period; under these conditions, two major components could be observed along with varying amounts of starting material and up to six further products. The most significant component was found to be the phthalimide derivative **20a**[21] formed by a cascade 5-*exo*$_{Ph}$/β-scission/5-*endo*$_{Ph}$/oxidation process. The formation of the second component (**21a**) could be explained either by ring expansion of intermediate **28a** or by direct 6-*endo*$_{Ph}$ cyclisation and oxidation. The minor components included the product of direct reduction (**22a**), pyrrolidinone **23a**[22] formed as before, *N*-formyl product **24a** arising from trapping of the intermediate carbamoyl radical **30a**, and secondary products (**25a**–**27a**) arising from the formal 6-*endo*$_{Ph}$ pathway. This mechanistic manifold is summarised in Scheme 7. From this scheme it is apparent that the formation of both phthalimide **20a** and phenanthridinone **21a** requires an oxidative step[23] and we found that use of much less than a stoichiometric amount of AIBN resulted in poor turnover and recovery of a significant quantity of starting material.

Similar results, summarised in Table 1, were obtained for *p*-tolyl (**19b**), *p*-anisyl (**19c**) and *p*-(trifluoromethyl)-phenyl (**19d**) substrates. In all these reactions, isolated yields cannot be quoted because many of the components required repeated chromatography to be isolated in a pure form. Some could not be isolated in sufficient purity for full characterisation and their formation was inferred by comparison of NMR data with those of isolated compounds in the other series. In particular, the *p*-methoxy substrate **19c** afforded the cleanest reactions and all products were isolated, fully characterised and used as standards to aid product identification in the reactions of substrates **19a**,**b** and **d**.

Replacing the *N*-methyl substituent with a second carboxyl had achieved significant improvement in the overall conversion of substrate to cyclised products and, under the syringe pump conditions, in the worst case (entry 2 B) the directly reduced material was present only to the extent of ca. 13%. However, this modification had led to diversion of the reaction away from the formation of pyrrolidinones (**23a**–**d**) in favour of phthalimides (**20a**–**d**), a 5-*endo*$_{Ar}$ cyclisation out-competing the 5-*endo-trig* process. This study had also led to a more thorough analysis of the minor components that made up the mass balance in moderate-yielding reactions and, because some of these (**26**, **27**) originated through stannyl radical additions to the *exo*-methylene group, attention was turned towards aryl radical precursors. In addition, to avoid phthalimide formation, but retain the conformational advantages of an imide-like nitrogen, the second carboxamide substituent was replaced with Boc.[24]

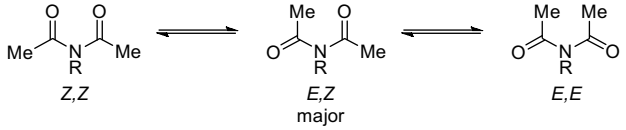


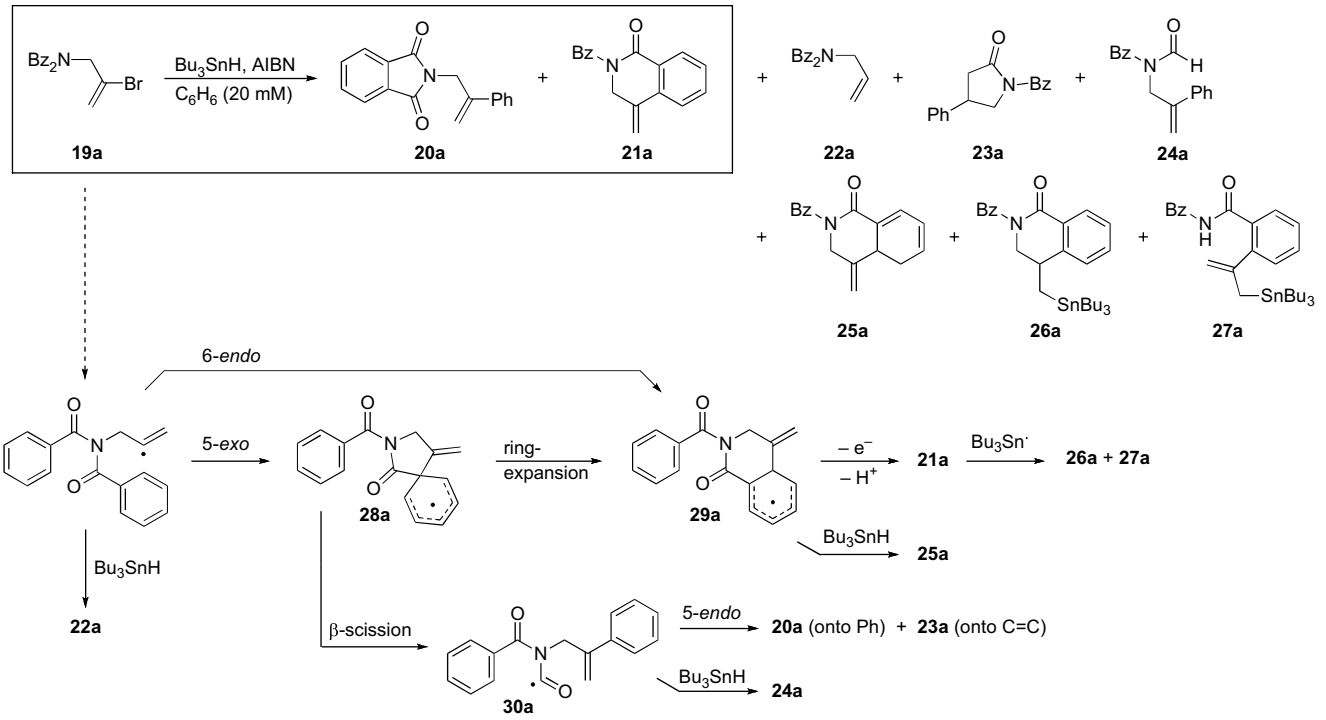
Figure 1. Solution conformations of diacetamide (R=H) and *N*-methyldiacetamide (R=Me).

3. *N*-Boc substrates

The new substrates, **31a**–**e**, Scheme 8, were prepared by Boc-protection of known amides[25] and then subjected to the standard conditions for radical reaction. In these cases the reactions were comparatively clean, resulting in two major products, biaryls **32a**–**e** and phenanthridinones **33a**–**e**, with the biaryls predominating.

Whilst the biaryls (**32**) must arise via initial 5-*exo*$_{Ar}$ cyclisation and β-scission, the phenanthridinones (**33**) could arise by either 5-*exo*$_{Ar}$ cyclisation and ring expansion (cf. **28a**→**29a**), or via direct 6-*endo*$_{Ar}$ cyclisation, or via 6-*endo*$_{Ar}$ cyclisation of the fragmented carbamoyl radical. The last pathway can be discounted by, for example, the reactions of *p*-methoxy substrate **31b** and *m*-methoxy substrate **31c** because such a process would result in a change in the relationship between the methoxy and carbonyl groups in the phenanthridinones **33b** and **33c**, respectively. In the ^{1}H NMR data for **33b**, a 1H singlet at δ 7.56 ppm was observed corresponding to the isolated H-10; in **33c** a 1H doublet (J 2.8 Hz) at δ 7.92 ppm was observed corresponding to the isolated H-7 shifted by the adjacent carbonyl. These indicated that the Ar–CO bond had remained intact during the formation of the phenanthridinones **33**.

As illustrated in Scheme 9 for substrate **31c**, the ring-expansion route could result in the co-production of phenanthridinone **35**; however, this compound could also be formed by 6-*endo*$_{Ar}$ cyclisation *ortho*- to the methoxy substituent. Therefore, the apparent

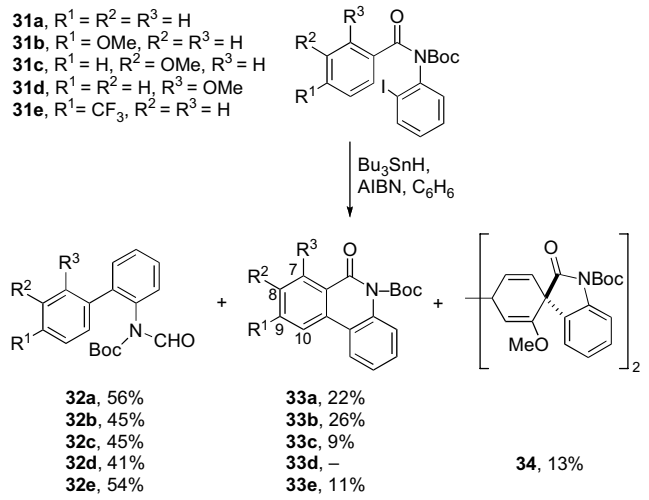


Scheme 7. Diverse products from the radical reaction of dibenzamide **19a** via cyclised intermediates **28a** and **29a**.

Table 1
Product distributions in the radical reactions of imides **19a–d**, $(ArCO)_2NCH_2C(Br)=CH_2$

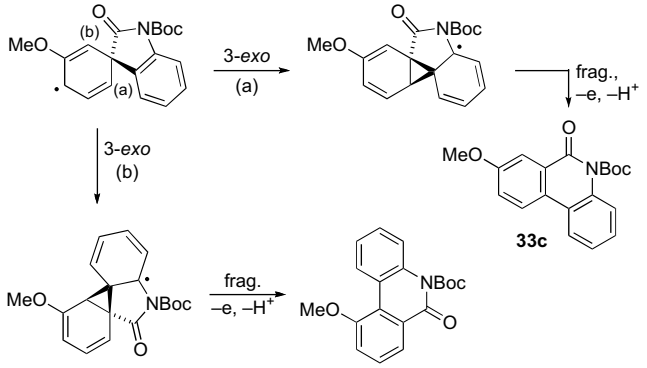
Entry[b]	Ar	Products %[a]								
		19a–d	**20a–d**	**21a–d**	**22a–d**	**23a–d**	**24a–d**	**25a–d**	**26a–d**	**27a–d**
1 A	Ph– (**19a**)	—	56	21	9	7	3	Trace	4	Trace
1 B	Ph– (**19a**)	16	54	14	—	3	—	13	—	—
2 A	*p*-MeC_6H_4– (**19b**)	—	46	16	12	4	5	—	17	Trace
2 B	*p*-MeC_6H_4– (**19b**)	—	51	10	13	5	4	—	14	3
3 A	*p*-$MeOC_6H_4$– (**19c**)	—	42	12	26	3	Trace	—	12	5
3 B	*p*-$MeOC_6H_4$– (**19c**)	—	63	25	Trace	3	Trace	—	9	Trace
4 A	*p*-$F_3CC_6H_4$– (**19d**)	12	50	5	—	17	7	9	—	—
4 B	*p*-$F_3CC_6H_4$– (**19d**)	10	63	8	—	9	6	4	—	—

[a] These values were calculated from relative integrations in the ^1H NMR spectra of crude products and are rounded to the nearest percent.
[b] Conditions: A: Bu_3SnH (1.4 equiv), AIBN (2×0.4 equiv), C_6H_6 (→20 mM solution), reflux, 5 h; B: Bu_3SnH (1.2–1.4 equiv) and AIBN (0.4–1.0 equiv) added via syringe pump over 2 h, C_6H_6 (→20 mM solution), reflux, 2 h.



Scheme 8. 1,4-Aryl transfer in *N*-Boc carboxamide substrates leading to biaryl derivatives.

absence of phenanthridinone regioisomers (such as **35**) in these reactions does not allow a distinction to be made concerning the relative importance of the 5-*exo*$_{Ar}$/ring-expansion or direct 6-*endo*$_{Ar}$ pathways; a more detailed kinetic analysis is required to address this point.



Scheme 9. A ring-expansion pathway to the phenanthridinones could result in two products in the reaction of substrate **31c**.

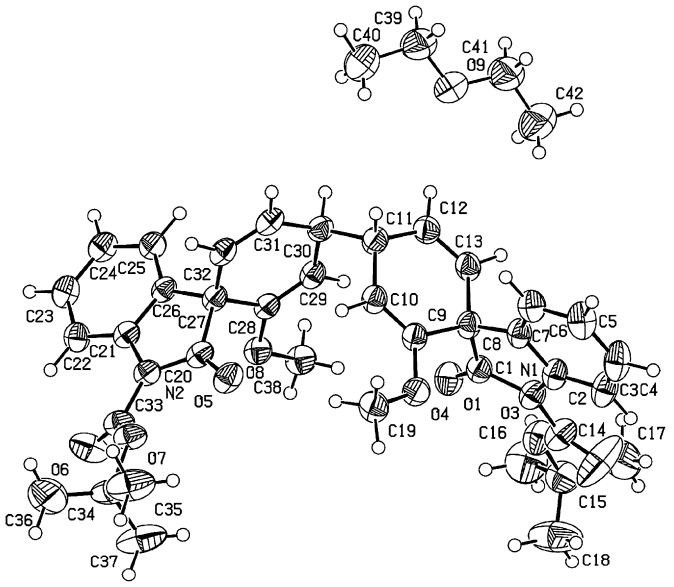


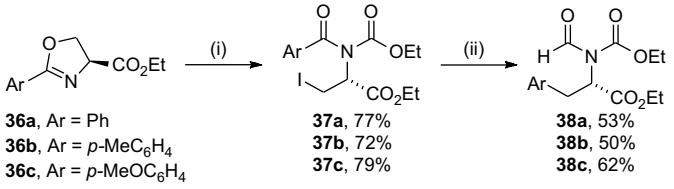
Figure 2. Ortep representation of dimer **34**·Et_2O.[26]

In the reaction of *ortho*-methoxy substrate **31d**, none of the phenanthridinone **33d** was observed but, instead, the dimerised product **34** was isolated whose structure was confirmed by X-ray analysis (Fig. 2) of the C_2-symmetric diastereomer that crystallised upon slow evaporation of an ethereal solution.

4. β-Arylethylamines

More recently we recognised that amide tethered 1,4-aryl transfer reactions applied to sp^3-centred radicals could provide convenient access to a wide range of β-phenylethylamines, the key pharmacophoric substructure of a wide variety of important pharmaceutical agents as well as notorious drugs of abuse.[27] In addition, our aryl transfer process provides *N*-formylamines directly and such compounds have been reported to be anorectic agents that lack undesirable CNS-stimulating effects.[28] Building on the lessons learned from the chemistry described in the previous sections, we targeted *N*-carbamoyl arylcarboxamides bearing a simple ethyl radical precursor, the most direct approach to which appeared to be the ring-opening of 2-aryloxazolines following Jugé's procedure.[29]

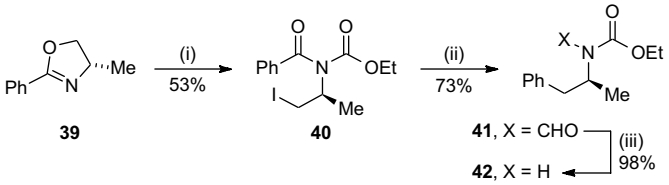
In the first reaction L-serine was converted into radical precursor **37a** (Scheme 10); we found the ring-opening process to be somewhat capricious with varying amounts of chloride being formed. However, use of a large excess of sodium iodide, with benzene as the solvent, gave the most reproducible results. It was gratifying to find that this substrate then behaved exactly as predicted under the standard conditions that had resulted in aryl transfer previously and L-phenylalanine derivative **38a** was isolated in 53% yield, lower than expected based on the ^1H NMR spectrum of the crude product and the TLC, both of which were, for a radical reaction, remarkably clean. We speculate that material was lost simply through



Scheme 10. Production of L-phenylalanine derivatives by aryl transfer. Reagents: (i) EtOCOCl, NaI, C_6H_6; (ii) Bu_3SnH, VAZO-88,[31] C_6H_6.

processing small quantities through two chromatographic operations, one (on KF-impregnated silica)[30] to remove the bulk of the tin residues, the second to effect final purification. Regardless, the principle was established and two further substrates were prepared and converted into the 4-methyl L-phenylalanine (**38b**) and *O*-methyl L-tyrosine (**38c**) derivatives in similar yields.

L-Alaninol was processed similarly via oxazoline **39**,[32] Scheme 11. Again, the derived radical precursor (**40**) was found to behave well in the aryl transfer reaction, affording formamide **41** in 73% yield. Selective removal of the formyl group afforded known (*S*)-amphetamine carbamate **42**. The specific rotation for this compound, $[\alpha]_D^{23}$ −4.2 (*c* 1.25, CH_2Cl_2), was of opposite sign to that obtained by Buckley and Rapoport[33] at a higher concentration, $[\alpha]_D^{23}$ +2.9 (*c* 5, CH_2Cl_2), but in qualitative agreement with the negative value obtained by Diener et al. who also commented on the discrepancy.[34]

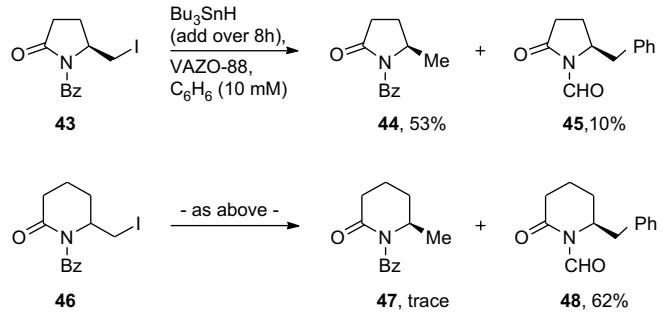


Scheme 11. Formation of *N*-ethoxycarbonyl (*S*)-amphetamine (**42**). Reagents: (i) EtOCO·Cl, NaI, C_6H_6; (ii) Bu_3SnH, VAZO-88, C_6H_6; (iii) aq LiOH, THF.

Next, we sought to extend the substrate range to encompass lactam precursors since their reactions were expected to provide insight into the electronic and conformational factors delineating the scope of the reaction, and the so-formed products form the substructures of a variety of interesting, biologically active compounds such as clausenamide.[35] It is notable that in the Speckamp sulfonamide tethered aryl transfer reactions,[14] no pyrrolidine examples were reported, therefore our first targeted precursor was that (**43**, Scheme 12) derived in three straightforward steps from (*S*)-pyroglutamic acid.[36] Piperidine analogue **46** was also prepared, in six steps from L-lysine.[37]

The radical reactions of these two substrates proved instructive. With slow addition of tributyltin hydride, pyrrolidinone precursor **43** afforded a 5.3:1 ratio of the directly reduced (**44**)[38] and phenyl transfer (**45**) products. In contrast, under the same conditions, the piperidine precursor **46** gave the phenyl transfer product **48** almost exclusively, just a trace of the directly reduced compound (**47**)[39] being present in the crude product.

It is not clear why these two substrates behave so differently. Resonances in the ^1H NMR spectra are sharp for both substrates, showing no evidence of restricted rotation about the *N*-acyl bonds. The calculated[40] low-energy conformations of the first-formed radicals are broadly similar, adopting a skewed *Z*,*E*-conformation (**49** and **50**, Fig. 3). However, the 1-azabicyclo[3.3.0]octane (pyrrolizidine) structure is significantly more rigid and strained than the 1-azabicyclo[4.3.0]nonane (indolizidine) system, and in the



Scheme 12. Aryl transfer in lactam substrates.

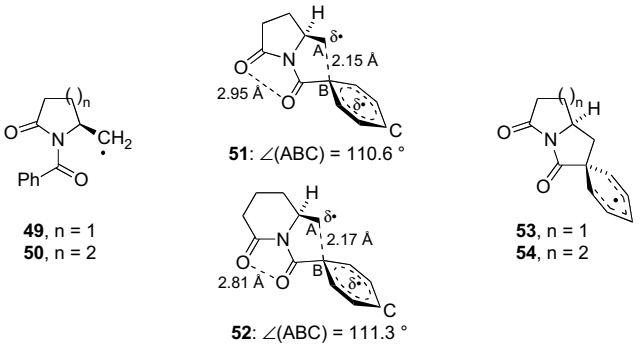


Figure 3. Radical species en route to aryl transfer products **45** and **48**.

parent rings and the computed spirocyclohexadienyl radical intermediates (**53** and **54**) the nitrogen is somewhat pyramidalised in the pyrrolizidine structures and essentially planar in the indolizidine structures. In an attempt to quantify this effect, we located transition state structures (**51** and **52**) for the 5-*exo*$_{Ar}$ cyclisation in both substrates using the B3LYP/6-31G(d) basis set. The key features of these structures are almost identical: from **43** the forming $RCH_2\cdots Ph$ bond is 2.15 Å and the *ipso*-carbon shows a slight pyramidalisation (0.24 Å out of plane); from **46** the corresponding values are 2.17 Å and 0.22 Å.[41]

On the basis of these preliminary computational results and inspection of models, we can only conclude that partial loss of amide conjugation during the cyclisation probably contributes to reducing the efficiency of aryl transfer in the pyrrolidinone case.

Finally, it is noteworthy that in the radical reactions in Schemes 10–12, in which the radical initiating 5-*exo*$_{Ar}$ cyclisation is formally sp^3-centred, there was no evidence of 3,4-dihydroisoquinolin-1(2*H*)-one derivatives in the crude products. This is intriguing in view of both the phenanthridinone products obtained earlier and the reported formation of tetralin from 4-phenylbutyl radical, discussed above. It is probable that conformational constraints in all these arylcarboxamide substrates markedly reduce access to conformations in which the 6-*endo*$_{Ar}$ pathway can compete effectively and that the earlier '6-*endo*' products arise by ring-expansion of spirocyclic intermediates. Further work is needed to support this assertion.

5. Conclusions

This study unites the large area of radical cyclisations onto aryl groups in amide substrates with the work of Walton who showed that carbamoyl radicals could be generated by fragmentation of cyclohexadienyl carboxamides. Walton's results, in turn, mirror the process that Julia had originally applied to the all-carbon system during an investigation into the production of tetralin from 4-phenylbutyl radical cyclisation. Our results show that β-scission following 5-*exo*$_{Ar}$ cyclisation is a reliable process with particular application in the formation of β-arylethylamines, providing an alternative to cross-coupling processes that achieve the same overall transformation.[42] We suspect that this mode of reaction will have operated in previous studies but that this has been largely overlooked.

6. Experimental section

6.1. General procedure for imide formation

To a stirred solution of 2-bromoprop-2-enamine[20] (0.5 g, 3.7 mmol) in dry pyridine (2.27 mL) at 0 °C was added the appropriate acid chloride (26.0 mmol) dropwise. The resulting suspension was allowed to warm to rt and then heated at 60 °C for 18 h. The mixture was cooled to rt then dichloromethane (10 mL), water (20 mL) and NaOH (1.2 g, 30 mmol) were added, and vigorous stirring continued for 2 days. The separated aqueous phase was extracted with dichloromethane (3×20 mL), and the combined extracts were washed successively with saturated aqueous $NaHCO_3$ solution (2×50 mL) and water (2×50 mL). The solution was dried ($MgSO_4$), concentrated in vacuo and the residue purified by flash column chromatography to afford the imide.

6.1.1. *N*-Benzoyl-*N*-(2-bromoprop-2-enyl)benzamide (**19a**)

White crystalline solid (0.92 g, 73%); R_f 0.25 (petrol/ethyl acetate, 5:1); mp 71–73 °C; ν_{max} (thin film)/cm^{-1} 1699 m, 1660 s, 1599 w, 1490 w, 1335 s, 1235 s, 1177 w, 1111 m, 970 m, 722 m, 695 m; δ_H (400 MHz, $CDCl_3$) 4.94 (2H, s, NCH_2), 5.70 (1H, d, *J* 2.0) and 6.02 (1H, d, *J* 2.0, $=CH_2$), 7.15–7.20 (4H, m), 7.25–7.30 (2H, m) and 7.48–7.53 (4H, m, 2×Ph); δ_C (100 MHz, $CDCl_3$) 53.8, 120.0, 127.7, 128.3, 129.0, 132.0, 136.0, 173.4; *m*/*z* (GC–MS, CI$^+$) 363 ($M^{81}BrNH_4^+$, 50%), 361 ($M^{79}BrNH_4^+$, 55), 347 (40), 346 ($M^{81}BrH^+$, 100), 345 (45), 344 ($M^{79}BrH^+$, 100), 265 (15), 264 (80), 105 (70); HRMS (GC–MS, CI$^+$) found 344.0280, $C_{17}H_{15}{}^{79}BrNO_2$ (MH^+) requires 344.0286.

6.1.2. *N*-(2-Bromoprop-2-enyl)-*N*-(4-methylbenzoyl)-4-methylbenzamide (**19b**)

White crystalline solid (1.15 g, 82%); R_f 0.45 (petrol/ethyl acetate, 5:1); mp 77–79 °C; ν_{max} (thin film)/cm^{-1} 1695 m, 1657 s, 1609 m, 1417 w, 1332 s, 1237 s, 1180 m, 1111 w, 966 m, 833 w, 784 m; δ_H (400 MHz, $CDCl_3$) 2.26 (6H, s, 2×Me), 4.89 (2H, s, NCH_2), 5.66 (1H, d, *J* 2.1) and 6.02 (1H, d, *J* 2.1, $=CH_2$), 7.00 (4H, d, *J* 8.2) and 7.44 (4H, d, *J* 8.2, 2×Ar); δ_C (100 MHz, $CDCl_3$) 21.5, 53.9, 119.5, 127.9, 128.9, 129.2, 133.0, 142.8, 173.4; *m*/*z* (GC–MS, CI$^+$) 375 (15%), 374 ($M^{81}BrH^+$, 80), 373 (25), 372 ($M^{79}BrH^+$, 85), 293 (50), 292 (90), 238 (50), 236 (50), 175 (10), 174 (40), 120 (20), 119 (100), 91 (55); HRMS (GC–MS, CI$^+$) found 372.0591, $C_{19}H_{19}{}^{79}BrNO_2$ (MH^+) requires 372.0599.

6.1.3. *N*-(2-Bromoprop-2-enyl)-*N*-(4-methoxybenzoyl)-4-methoxybenzamide (**19c**)

White crystalline solid (1.41 g, 93%); R_f 0.11 (petrol/ethyl acetate, 5:1); mp 70–72 °C; ν_{max} (thin film)/cm^{-1} 1689 m, 1653 s, 1604 s, 1511 m, 1420 m, 1332 s, 1260 s, 1168 m, 1112 w, 1029 m, 966 w, 912 w, 844 m, 760 w; δ_H (400 MHz, $CDCl_3$) 3.75 (6H, s, 2×OMe), 4.87 (2H, s, NCH_2), 5.65 (1H, d, *J* 2.1) and 5.97 (1H, d, *J* 2.1, $=CH_2$), 6.69 (4H, d, *J* 8.8) and 7.53 (4H, d, *J* 8.8, 2×Ar); δ_C (100 MHz, $CDCl_3$) 54.1, 55.4, 113.6, 119.4, 128.2 (×2), 131.3, 162.6, 172.8; *m*/*z* (ESI$^+$) 428 ($M^{81}BrNa^+$, 100%), 426 ($M^{79}BrNa^+$, 100); HRMS (ESI$^+$) found 426.0313, $C_{19}H_{18}{}^{79}BrNNaO_4$ (MNa^+) requires 426.0311.

6.1.4. *N*-(2-Bromoprop-2-enyl)-*N*-[4-(trifluoromethyl)-benzoyl]-4-(trifluoromethyl)benzamide (**19d**)

White crystalline solid (1.23 g, 69%); R_f 0.34 (petrol/ethyl acetate, 5:1); mp 89 °C; ν_{max} (thin film)/cm^{-1} 1708 w, 1664 s, 1411 w, 1324 s, 1223 m, 1169 m, 1129 s, 1067 m, 857 w, 766 w, 715 m; δ_H (500 MHz, $CDCl_3$) 4.93 (2H, s, NCH_2), 5.74 (1H, s) and 6.03 (1H, s, $=CH_2$), 7.48 (4H, d, *J* 8.2) and 7.61 (4H, d, *J* 8.2, 2×Ar); δ_C (125 MHz, $CDCl_3$) 53.7, 121.1, 123.1 (q, *J* 272.8), 125.3 (q, *J* 3.6), 126.9, 129.2, 133.7 (q, *J* 32.9), 138.8, 172.8; δ_F (377 MHz, $CDCl_3$) −63.5; *m*/*z* (ESI$^+$) 502 (MNa^+, 100%); HRMS (ESI$^+$) found 501.9844, $C_{19}H_{12}{}^{79}BrF_6NNaO_2$ (MNa^+) requires 501.9848.

6.2. General procedure A for imide radical reactions

A 100 mL round-bottomed flask containing the imide (1.0 mmol) and AIBN (67 mg, 0.40 mmol) was fitted with a condenser, all joints were sealed, and the apparatus was purged with argon several times. Degassed benzene (50 mL) was added via cannula then tributyltin hydride (0.38 mL, 1.40 mmol) was added and the reaction mixture was heated at reflux for 2 h. A second portion of AIBN (67 mg, 0.40 mmol) was added in degassed

benzene (5 mL) and heating continued for a further 3 h. The solution was cooled and concentrated in vacuo; the residue was eluted with ethyl acetate through a stationary phase of KF (10%) impregnated silica to remove the tin residues. Subsequent purification by flash column chromatography afforded the products (see Table 1). The following compounds were either not observed or were only observed as trace components in crude product mixtures: **22d**; **24b**,**c**; **25b**,**c**; **26d**; **27a**,**d**. The following compounds were not isolated in a pure form and spectroscopic data are not provided: **20d**; **21b**,**d**; **22b**; **23d**; **24a**,**b**; **25d**; **27b**.

6.3. General procedure B for imide radical reactions

A 100 mL round-bottomed flask containing the imide (1.0 mmol) and AIBN (17 mg, 0.10 mmol) was fitted with a condenser, all joints were sealed, and the apparatus was purged with argon several times. Degassed benzene (50 mL) was then added via cannula and the resulting solution was brought to reflux. A solution of tributyltin hydride (0.38 mL, 1.40 mmol) and AIBN (147 mg, 0.90 mmol) in degassed benzene (5 mL) was added to the heated mixture over a 2 h period. Heating was continued for a further 2 h then the solution was cooled and concentrated in vacuo. Selected products were isolated from the residue as in procedure A (see Table 1).

6.3.1. 2-(2-Phenylprop-2-enyl)isoindoline-1,3-dione (**20a**)[21]

White crystalline solid; R_f 0.50 (petrol/ethyl acetate, 3:1); ν_{max} (thin film)/cm^{-1} 1705 s, 1426 w, 1428 w, 1394 w, 1109 m, 954 m, 709 m; δ_H (500 MHz, $CDCl_3$) 4.72 (2H, s, NCH_2), 5.16 (1H, s) and 5.44 (1H, s, $=CH_2$), 7.26–7.38 (3H, m) and 7.49–7.53 (2H, Ph), 7.71 (2H, app. dd, *J* 5.5, 3.0) and 7.85 (2H, app. dd, *J* 5.5, 3.0, phthal.); δ_C (125 MHz, $CDCl_3$) 41.4, 113.7, 123.4, 126.4, 128.0, 128.4, 132.0, 134.0, 138.5, 142.4, 168.0; *m*/*z* (GC–MS, CI$^+$) 264 (MH$^+$, 90%), 172 (65), 160 (100), 130 (100), 115 (60); HRMS (GC–MS, CI$^+$) found 264.1026, $C_{17}H_{14}NO_2$ (MH$^+$) requires 264.1025.

6.3.2. N-Benzoyl-N-(prop-2-enyl)benzamide (**22a**)

Colourless oil; R_f 0.59 (petrol/ethyl acetate, 3:1); ν_{max} (thin film)/cm^{-1} 3386 br, 2927 w, 1656 s, 1600 w, 1449 w, 1326 s, 1236 m, 1169 m, 1126 m, 1668 w, 1017 w, 842 w; δ_H (200 MHz, $CDCl_3$) 4.62 (2H, d, *J* 6.1, NCH_2), 5.25 (1H, dd, *J* 10.2, 1.0) and 5.36 (1H, dd, *J* 17.0, 1.0, $=CH_2$), 5.97–6.18 (1H, m, $CH{=}CH_2$), 7.17–7.30 (6H, m) and 7.42–7.50 (4H, m, 2×Ph); δ_C (100 MHz, $CDCl_3$) 49.3, 118.5, 128.2, 128.7, 131.9, 132.6, 136.3, 174.0; *m*/*z* 288 (MNa$^+$, 100%); HRMS (ESI$^+$) found 288.0994, $C_{17}H_{15}NNaO_2$ (MNa$^+$) requires 288.0995.

6.3.3. 1-Benzoyl-4-phenylpyrrolidin-2-one (**23a**)[22]

Colourless oil; R_f 0.26 (petrol/ethyl acetate, 3:1); ν_{max} (thin film)/cm^{-1} 1799 w, 1716 m, 1664 s, 1419 m, 699 w; δ_H (500 MHz, $CDCl_3$) 2.82 (1H, dd, *J* 17.7, 9.3) and 3.02 (1H, dd, *J* 17.7, 8.3, $COCH_2$), 3.66–3.76 (1H, m, C*H*Ph), 3.97 (1H, dd, *J* 11.4, 8.3) and 4.36 (1H, dd, *J* 11.4, 7.7, NCH_2), 7.30–7.35 (2H, m), 7.38–7.46 (4H, m), 7.52–7.57 (1H, m) and 7.65 (2H, d, *J* 7.3, 2×Ph); δ_C (125 MHz, $CDCl_3$) 36.5, 40.5, 52.9, 126.7, 127.5, 127.8, 129.0, 129.1, 132.1, 134.2, 140.3, 170.4, 173.3; *m*/*z* (ESI$^+$) 288 (MNa$^+$, 100%); HRMS (ESI$^+$) found 288.0990, $C_{17}H_{15}NNaO_2$ (MNa$^+$) requires 288.0995.

6.3.4. 2-Benzoyl-4-methylene-3,4,4a,5-tetrahydroisoquinoline-1(2H)-one (**25a**)

Colourless oil; R_f 0.41 (petrol/ethyl acetate, 3:1); ν_{max} (thin film)/cm^{-1} 3352 br, 2963 w, 1674 s, 1632 m, 1601 w, 1460 m, 1375 m, 1262 s, 1231 s, 1122 w, 1063 w, 1027 w, 800 w; δ_H (500 MHz, $CDCl_3$) 2.94 (2H, app. dd, *J* 8.8, 3.2, $CHCH_2$), 3.84 (1H, app. t, *J* 8.8, $CHCH_2$), 4.48 (2H, s, NCH_2), 5.02 (1H, s) and 5.22 (1H, s, $=CH_2$), 5.93 (2H, app. s) and 6.94 (1H, br s, CH=CHCH=), 7.40 (2H, t, *J* 7.4), 7.48 (1H, t, *J* 7.4) and 7.54 (2H, d, *J* 7.4, Ph); δ_C (125 MHz, $CDCl_3$) 27.3, 37.7, 50.6, 110.9, 123.2, 124.9, 127.8, 128.1, 129.4, 131.4, 135.8, 136.0, 141.0, 167.1, 173.8; *m*/*z* (ESI$^+$) 324 ($MNH_4{\cdot}CH_3CN^+$, 20%), 291 (100); HRMS (ESI$^+$) found 288.0993, $C_{17}H_{15}NNaO_2$ (MNa$^+$) requires 288.0995.

6.3.5. 2-Benzoyl-4-[(tributylstannyl)methyl]-3,4-dihydroisoquinoline-1(2H)-one (**26a**)

Colourless oil; R_f 0.82 (petrol/ethyl acetate, 3:1); ν_{max} (thin film)/cm^{-1} 2957 m, 2926 s, 1681 s, 1603 m, 1573 m, 1452 m, 1376 m, 1286 m, 1232 w, 1071 w, 1025 w, 767 m; δ_H (500 MHz, $CDCl_3$) 0.81–0.86 (15H, m), 1.21–1.31 (8H, m) and 1.39–1.47 (6H, m, CH_2SnBu_3), 3.30–3.42 (1H, m, C*H*Ar), 4.06 (2H, d, *J* 4.1, NCH_2), 7.31 (1H, d, *J* 7.6), 7.35 (1H, t, *J* 7.6), 7.40–7.45 (2H, m), 7.49–7.58 (2H, m), 7.66 (2H, d, *J* 7.4) and 8.07 (1H, d, *J* 7.6, Ph and Ar); δ_C (125 MHz, $CDCl_3$) 9.5, 13.6, 14.7, 27.3, 29.2, 36.6, 51.0, 126.6, 126.8, 127.1, 128.2, 128.2, 129.8, 131.6, 133.8, 136.4, 147.2, 165.5, 174.4; *m*/*z* (ESI$^+$) 614 ($M^{120}SnNH_4{\cdot}CH_3CN$, 100%); HRMS (ESI$^+$) found 556.2227, $C_{29}H_{42}NO_2^{120}Sn$ (MH$^+$) requires 556.2238.

6.3.6. 5-Methyl-2-[2-(4-methylphenyl)prop-2-enyl]isoindoline-1,3-dione (**20b**)

White crystalline solid; R_f 0.50 (petrol/ethyl acetate, 3:1); ν_{max} (thin film)/cm^{-1} 1771 w, 1703 s, 1610 m, 1433 w, 1388 s, 1332 m, 1277 m, 1235 s, 1180 w, 1143 m, 1109 m, 960 w, 823 w; δ_H (400 MHz, $CDCl_3$) 2.32 (3H, s, Me), 2.48 (3H, s, Me), 4.67 (2H, s, NCH_2), 5.09 (1H, s) and 5.40 (1H, s, $=CH_2$), 7.02 (1H, d, *J* 8.0, H-6), 7.14 (2H, d, *J* 8.0) and 7.39 (2H, d, *J* 8.0, *p*-Tol), 7.63 (1H, s, H-4), 7.70 (1H, d, *J* 8.0, H-7); δ_C (100 MHz, $CDCl_3$) 21.1, 22.0, 41.4, 112.9, 123.3, 123.9, 126.2, 129.0, 129.1, 134.5, 135.6, 137.8, 142.3, 142.6, 145.3, 168.1, 168.2; *m*/*z* (GC–MS, CI$^+$) 292 (MH$^+$, 100%), 291 (90), 273 (50), 174 (40), 119 (20), 117 (35), 115 (45), 91 (45); HRMS (GC–MS, CI$^+$) found 292.1339, $C_{19}H_{18}NO_2$ (MH$^+$) requires 292.1338.

6.3.7. 1-(4-Methylbenzoyl)-4-(4-methylphenyl)pyrrolidin-2-one (**23b**)

Colourless oil; R_f 0.22 (petrol/ethyl acetate, 5:1); ν_{max} (thin film)/cm^{-1} 2922 m, 1746 s, 1669 s, 1610 w, 1305 m, 1182 w, 817 w, 755 w; δ_H (400 MHz, $CDCl_3$) 2.37 (3H, s, Me), 2.42 (3H, s, Me), 2.78 (1H, dd, *J* 17.6, 9.3) and 2.99 (1H, dd, *J* 17.6, 8.3, $COCH_2$), 3.62–3.68 (1H, m, C*H*Ar), 3.93 (1H, dd, *J* 11.2, 8.3) and 4.32 (1H, dd, *J* 11.2, 7.7, NCH_2), 7.20 (4H, app. s, 4-(*p*-Tol)), 7.23 (2H, d, *J* 8.0) and 7.57 (2H, d, *J* 8.0, *p*-TolCO); δ_C (100 MHz, $CDCl_3$) 21.0, 21.7, 36.2, 40.7, 53.1, 126.6, 128.6, 129.3, 129.7, 131.2, 137.2, 137.3, 142.9, 170.4, 173.4; *m*/*z* (GC–MS, CI$^+$) 294 (MH$^+$, 100%); HRMS (GC–MS, CI$^+$) found 294.1495, $C_{19}H_{20}NO_2$ (MH$^+$) requires 294.1494.

6.3.8. 6-Methyl-2-(4-methylbenzoyl)-4-[(tributylstannyl)-methyl]-3,4-dihydroisoquinoline-1(2H)-one (**26b**)

Colourless oil; R_f 0.66 (petrol/ethyl acetate, 5:1); ν_{max} (thin film)/cm^{-1} 2965 m, 2925 s, 1682 s, 1611 m, 1465 w, 1377 w, 1288 m, 1234 m, 1141 w, 1094 w, 751 w; δ_H (400 MHz, $CDCl_3$) 0.72–0.87 (15H, m), 1.21–1.33 (8H, m) and 1.37–1.46 (6H, m, CH_2SnBu_3), 2.40 (3H, s, Me), 2.44 (3H, s, Me), 3.26–3.36 (1H, m, C*H*Ar), 3.97–4.08 (2H, m, NCH_2), 7.10 (1H, app. s, H-6), 7.16 (1H, d, *J* 8.0, H-7), 7.21 (2H, d, *J* 8.0) and 7.57 (2H, d, *J* 8.0, *p*-Tol), 7.97 (1H, d, *J* 8.0, H-8); δ_C (100 MHz, $CDCl_3$) 9.5, 13.6, 14.7, 21.6, 21.8, 27.3, 29.1, 36.6, 51.3, 124.3, 127.1, 128.1, 128.4, 128.8, 130.0, 133.6, 142.2, 144.7, 147.1, 165.6, 174.5; *m*/*z* (ESI$^+$) 584 ($M^{120}SnH^+$, 100%); HRMS (ESI$^+$) found 584.2540, $C_{31}H_{46}NO_2^{120}Sn$ (MH$^+$) requires 584.2551.

6.3.9. 5-Methoxy-2-[2-(4-methoxyphenyl)prop-2-enyl]isoindoline-1,3-dione (**20c**)

White crystalline solid; R_f 0.44 (petrol/ethyl acetate, 1:1); mp 140–142 °C; ν_{max} (thin film)/cm^{-1} 1699 s, 1621 m, 1489 m, 1437 w, 1397 m, 1287 w, 1240 m, 1110 m, 834 m; δ_H (500 MHz, $CDCl_3$) 3.80 (3H, s, OMe), 3.92 (3H, s, OMe), 4.65 (2H, s, NCH_2), 5.07 (1H, s) and 5.36 (1H, s, $=CH_2$), 6.87 (2H, d, *J* 8.7, two of *p*-Anis), 7.15 (1H, dd, *J*

8.3, 2.2, H-6), 7.32 (1H, d, *J* 2.2, H-4), 7.44 (2H, d, *J* 8.7, two of *p*-Anis), 7.74 (1H, d, *J* 8.3, H-7); δ_C (125 MHz, $CDCl_3$) 41.5, 55.2, 56.1, 108.1, 112.3, 113.7, 119.7, 123.9, 125.0, 127.5, 131.0, 134.6, 141.5, 159.5, 164.5, 167.8, 167.9; *m*/*z* (ESI^+) 346 (MNa^+, 100%); HRMS (ESI^+) found 346.1050, $C_{19}H_{17}NNaO_4$ (MNa^+) requires 346.1050.

6.3.10. 6-Methoxy-2-(4-methoxybenzoyl)-4-methylene-3,4-dihydroisoquinoline-1(2H)-one (**21c**)

Pale yellow oil; R_f 0.39 (petrol/ethyl acetate, 1:1); ν_{max} (thin film)/cm^{-1} 2963 w, 2841 w, 1674 s, 1604 s, 1511 m, 1461 w, 1241 m, 1168 m, 1030 w, 912 w, 844 w, 731 w; δ_H (500 MHz, $CDCl_3$) 3.84 (3H, s, OMe), 3.92 (3H, s, OMe), 4.62 (2H, s, NCH_2), 5.45 (1H, s) and 5.73 (1H, s, $=CH_2$), 6.88 (2H, d, *J* 8.8, two of *p*-Anis), 6.97 (1H, dd, *J* 8.7, 2.5, H-7), 7.09 (1H, d, *J* 2.5, H-5), 7.62 (2H, d, *J* 8.8, two of *p*-Anis), 8.09 (1H, d, *J* 8.7, H-8); δ_C (125 MHz, $CDCl_3$) 50.8, 55.3, 55.6, 107.8, 113.4, 113.5, 115.4, 120.0, 128.1, 130.9, 132.1, 136.8, 139.3, 162.6, 163.9, 165.1, 173.4; *m*/*z* (ESI^+) 382 ($MNH_4{\cdot}CH_3CN^+$, 100%); HRMS (ESI^+) found 346.1049, $C_{19}H_{17}NNaO_4$ (MNa^+) requires 346.1050.

6.3.11. N-(4-Methoxybenzoyl)-N-(prop-2-enyl)-4-methoxybenzamide (**22c**)

Pale yellow oil; R_f 0.40 (petrol/ethyl acetate, 1:1); ν_{max} (thin film)/cm^{-1} 2937 w, 2840 w, 1685 m, 1648 m, 1604 s, 1511 m, 1461 w, 1420 w, 1334 m, 1241 s, 1168 m, 1029 w, 844 w, 761 w; δ_H (500 MHz, $CDCl_3$) 3.75 (6H, s, 2×OMe), 4.58 (2H, d, *J* 5.8, NCH_2), 5.21 (1H, d, *J* 10.3) and 5.32 (1H, d, *J* 17.2, $=CH_2$), 6.05 (1H, ddt, *J* 17.2, 10.3, 5.8, C*H*$=CH_2$), 6.70 (4H, d, *J* 8.8) and 7.50 (4H, d, *J* 8.8, 2×*p*-Anis); δ_C (125 MHz, $CDCl_3$) 49.6, 55.3, 113.6, 118.1, 128.6, 131.0, 133.0, 162.5, 173.3; *m*/*z* (ESI^+) 384 ($MNH_4{\cdot}CH_3CN^+$, 50%), 382 (100); HRMS (ESI^+) found 348.1208, $C_{19}H_{19}NNaO_4$ (MNa^+) requires 348.1206.

6.3.12. 1-(4-Methoxybenzoyl)-4-(4-methoxyphenyl) pyrrolidin-2-one (**23c**)[43]

Colourless oil; R_f 0.19 (petrol/ethyl acetate, 1:1); ν_{max} (thin film)/cm^{-1} 1672 s, 1605 s, 1514 m, 1255 s; δ_H (500 MHz, $CDCl_3$) 2.77 (1H, dd, *J* 17.4, 9.3) and 2.99 (1H, dd, *J* 17.4, 8.3, $COCH_2$), 3.62–3.68 (1H, m, C*H*Ar), 3.83 (3H, s, OMe), 3.87 (3H, s, OMe) overlaying 3.87–3.95 (1H, m) and 4.28 (1H, dd, *J* 11.4, 7.6, NCH_2), 6.93 (4H, d, *J* 8.6), 7.25 (2H, d, *J* 8.6) and 7.69 (2H, d, *J* 8.6, 2×*p*-Anis); δ_C (125 MHz, $CDCl_3$) 35.9, 40.9, 54.4, 55.3, 55.4, 113.2, 114.4, 126.1, 127.7, 131.8, 132.3, 158.9, 163.0, 169.8, 173.5; *m*/*z* (GC–MS, CI^+) 326 (MH^+, 10%), 192 (100), 152 (40), 148 (60), 135 (20); HRMS (GC–MS, CI^+) found 326.1403, $C_{19}H_{20}NO_4$ (MH^+) requires 326.1392.

6.3.13. 6-Methoxy-2-(4-methoxybenzoyl)-4-[(tributylstannyl) methyl]-3,4-dihydroisoquinoline-1(2H)-one (**26c**)

Colourless oil; R_f 0.67 (petrol/ethyl acetate, 1:1); ν_{max} (thin film)/cm^{-1} 2957 m, 2962 m, 1679 s, 1605 s, 1512 w, 1493 w, 1377 w, 1238 s, 1167 m, 1032 m, 841 w, 802 w; δ_H (500 MHz, $CDCl_3$) 0.81–0.88 (15H, m), 1.21–1.32 (8H, m) and 1.37–1.46 (6H, m, CH_2SnBu_3), 3.25–3.32 (1H, m, C*H*Ar), 3.85 (3H, s, OMe), 3.90 (3H, s, OMe), 3.95 (1H, dd, *J* 12.7, 4.5) and 4.03 (1H, dd, *J* 12.7, 3.3, NCH_2), 6.77 (1H, d, *J* 2.3, H-5), 6.86 (1H, dd, *J* 8.7, 2.3, H-7), 6.91 (2H, d, *J* 8.8) and 7.68 (2H, d, *J* 8.8, *p*-Anis), 8.05 (1H, d, *J* 8.7, H-8); δ_C (125 MHz, $CDCl_3$) 9.5, 13.6, 14.6, 27.3, 29.1, 37.0, 51.4, 55.4, 55.5, 111.5, 112.6, 113.4, 119.7, 128.5, 130.8, 132.3, 149.5, 162.5, 163.9, 165.3, 173.9; *m*/*z* (ESI^+) 673 ($M^{120}SnNH_4{\cdot}CH_3CN$, 100%); HRMS ($ESI^+$) found 616.2437, $C_{31}H_{46}NO_4{}^{120}Sn$ (MH^+) requires 616.2450.

6.3.14. N-(4-Methoxybenzoyl)-N-4-methoxy-2-[3-(tributylstannyl)prop-1-en-2-yl]benzamide (**27c**)

Colourless oil; R_f 0.24 (petrol/ethyl acetate, 1:1); ν_{max} (thin film)/cm^{-1} 2957 m, 2926 m, 1731 m, 1677 w, 1604 s, 1474 m, 1228 s, 1174 w, 1030 w; δ_H (500 MHz, $CDCl_3$) 0.69–0.74 (6H, m), 0.80–0.85 (9H, m), 1.15–1.32 (12H, m, $SnBu_3$), 2.10 (2H, s, CH_2SnBu_3), 3.87 (3H, s, OMe), 3.88 (3H, s, OMe), 5.04 (1H, s) and 5.10 (1H, s, $=CH_2$), 6.72 (1H, d, *J* 2.5, $H_{(Ar)}$-3), 6.92 (1H, dd, *J* 8.6, 2.5, $H_{(Ar)}$-5), 6.97 (2H, d, *J* 8.8) and 7.86 (2H, d, *J* 8.8, *p*-Anis), 7.94 (1H, d, *J* 8.6, $H_{(Ar)}$-6), 9.71 (1H, s, NH); δ_C (125 MHz, $CDCl_3$) 9.6, 13.6, 22.4, 27.3, 28.7, 55.5 (×2), 110.3, 112.7, 114.0, 115.2, 124.9, 125.8, 129.7, 133.3, 144.6, 152.8, 162.2, 163.3, 164.3, 165.7; *m*/*z* (ESI^+) 673 ($M^{120}SnNH_4{\cdot}CH_3CN$, 100%), 384 (20); HRMS (ESI^+) found 616.2447, $C_{31}H_{46}NO_4{}^{120}Sn$ (MH^+) requires 616.2450.

6.3.15. N-Formyl-N-{2-[4-(trifluoromethyl)phenyl]prop-2-enyl}-4-(trifluoromethyl)benzamide (**24d**)

Pale yellow oil; R_f 0.26 (petrol/ethyl acetate, 3:1); ν_{max} (thin film)/cm^{-1} 2919 w, 1729 w, 1674 s, 1514 w, 1410 s, 1169 w, 1128 m, 1067 m, 850 w; δ_H (500 MHz, $CDCl_3$) 4.93 (2H, s, NCH_2), 5.35 (1H, s) and 5.49 (1H, s, $=CH_2$), 7.42 (2H, d, *J* 8.1), 7.55 (2H, d, *J* 8.3), 7.62 (2H, d, *J* 8.3) and 7.72 (2H, d, *J* 8.1, 2×Ar), 8.85 (1H, s, CHO); δ_C (125 MHz, $CDCl_3$) [some overlapping, weak ^{19}F-coupled peaks in the region 120–130 ppm could not be deconvoluted] 43.6, 116.5, 125.5, 126.1, 127.1, 128.9, 134.0, 136.5, 141.9, 142.3, 162.9, 170.6; δ_F (377 MHz, $CDCl_3$) −63.2, −62.6; *m*/*z* (ESI^+) 424 (MNa^+, 100%); HRMS (ESI^+) found 424.0739, $C_{19}H_{13}F_6NNaO_2$ (MNa^+) requires 424.0743.

6.4. General procedure for radical reaction of 30a–e

To a stirred solution of the benzamide derivative (0.9 mmol) and AIBN (12 mg, 73 μmol) in degassed benzene (20 mL) at reflux was added a solution of tributyltin hydride (290 μL, 1.08 mmol) and AIBN (36 mg, 0.22 mmol) in benzene (10 mL) over 1 h. The reaction mixture was heated at reflux for a further 2 h, then cooled, concentrated in vacuo and the residue eluted with ethyl acetate through a stationary phase of KF (10%) impregnated silica (10 g) to remove tin residues. The products were then isolated by flash chromatography (petrol/ethyl acetate, 10:1).

6.4.1. tert-Butyl biphenyl-2-yl-N-formylcarbamate **32a**

Starting with benzamide **31a** (400 mg, 0.94 mmol), formamide **32a** was obtained as a colourless oil (156 mg, 56%); ν_{max} (thin film)/cm^{-1} 1738 s, 1713 s, 1504 m, 1370 s, 1290 s, 1153 m, 772 w; δ_H (400 MHz, $CDCl_3$) 1.27 (9H, s, $C(CH_3)_3$), 7.19 (1H, d *J* 7.5) and 7.22–7.48 (8H, m, 2×Ar), 9.28 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$) 27.5, 84.1, 127.6, 128.3, 128.4, 129.0, 129.1 129.2, 130.6, 132.2, 138.6, 140.7, 151.8, 163.5; HRMS (ESI^+) found 198.0919, $C_{13}H_{12}NO$ [(M−Boc)H^+] requires 198.0919. Also obtained was 5-*tert*-butyloxycarbonylphenanthridin-6(5*H*)-one (**33a**) (61 mg, 22%) as a white solid; mp 139–140 °C; ν_{max} (KBr)/cm^{-1} 1767 s, 1668 s, 1609 m, 1456 m, 1371 s, 1247 m, 1150 m; δ_H (400 MHz, $CDCl_3$) 1.75 (9H, s, $C(CH_3)_3$), 7.13 (1H, d, *J* 7.5), 7.31 (1H, dd, *J* 7.5, 7.0), 7.49 (1H, dd, *J* 7.5, 7.0), 7.59 (1H, dd, *J* 7.5, 7.0), 7.79 (1H, t, *J* 7.0), 8.20–8.25 (2H, m) and 8.49 (1H, d, *J* 7.5, Ar); δ_C (100 MHz, $CDCl_3$) 27.6, 86.5, 114.5, 118.4, 122.0, 123.4, 125.1, 127.6, 128.3, 129.1, 130.6, 132.3, 134.5, 151.2, 159.9, 163.5; HRMS (ESI^+) found 196.0763, $C_{13}H_{10}NO$ [M(−Boc)H^+] requires 196.0762.

6.4.2. tert-Butyl N-formyl-(4′-methoxybiphenyl-2-yl) carbamate **32b**

Starting with benzamide **31b** (500 mg, 1.10 mmol), formamide **32b** (162 mg, 45%) was obtained as a pale yellow oil; ν_{max} (thin film)/cm^{-1} 1736 s, 1714 s, 1479 m, 1293 s, 1154 m, 1029 m; δ_H (400 MHz, $CDCl_3$) 1.28 (9H, s, $C(CH_3)_3$), 3.80 (3H, s, CH_3O), 6.90 (2H, d, *J* 7.0), 7.13 (1H, d, *J* 6.5), 7.18 (2H, d, *J* 7.0) and 7.35–7.45 (3H, m, 2×Ar), 9.27 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$) 27.6, 55.3, 84.1, 113.8, 128.0, 129.0, 129.1, 129.6, 130.7, 131.0, 132.3, 140.4, 151.9, 159.2, 163.5; HRMS (ESI^+) found 228.1023, $C_{14}H_{14}NO_2$ [(M−Boc)H^+] requires 228.1025. Also obtained was 5-*tert*-butyloxycarbonyl-9-methoxyphenanthridin-6(5*H*)-one (**33b**) (93 mg, 25%) as a white solid; mp 132–135 °C; ν_{max} (KBr)/cm^{-1} 1774 s, 1695 s, 1570 m, 1465 m, 1273 m, 1040 m; δ_H (400 MHz, $CDCl_3$) 1.72 (9H, s, $C(CH_3)_3$), 3.98 (3H, s, CH_3O), 7.11 (2H, d, *J* 8.8), 7.27 (1H, t, *J* 7.5), 7.43 (1H, dd, *J* 8.0,

7.5), 7.56 (1H, s), 8.10 (1H, d, *J* 8.0) and 8.38 (1H, d, *J* 8.8, Ar); δ_C (100 MHz, $CDCl_3$) 27.6, 55.6, 86.3, 105.1, 114.6, 115.9, 118.3, 118.6, 123.2, 123.4, 129.8, 130.7, 134.9, 136.0, 151.4, 159.7, 163.6; HRMS (ESI^+) found 226.0867, $C_{14}H_{12}NO_2$ [(M−Boc)H^+] requires 226.0868.

6.4.3. *tert*-Butyl N-formyl-(3′-methoxybiphenyl-2-yl) carbamate (**32c**)

Starting with benzamide **31c** (200 mg, 0.44 mmol), formamide **32c** (65 mg, 45%) was obtained as a yellow oil. R_f 0.36 (petrol/ethyl acetate, 10:1); ν_{max} (thin film)/cm^{-1} 3436 br, 2981 m, 1738 s, 1711 s, 1478 s, 1425 m, 1395 w, 1371 s, 1351 s, 1292 s, 1154 s, 1071 m, 1050 m, 913 m, 849 m, 760 s, 733 s, 702 m, 615 m; δ_H (400 MHz, $CDCl_3$) 1.29 (9H, s, $C(CH_3)_3$), 3.80 (3H, s, OCH_3), 6.80–6.91 (3H, m), 7.16–7.19 (1H, m), 7.26–731 (1H, m) and 7.41–7.48 (3H, m, 2×Ar), 9.29 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$) 27.6, 55.3, 84.2, 113.4, 114.0, 120.9, 128.4, 129.0, 129.1, 129.3, 130.6, 132.3, 140.0, 140.6, 151.9, 159.4, 163.5; *m*/*z* (ESI^+) 350 (MNa^+, 100%); HRMS (ESI^+) found 350.1361, $C_{19}H_{21}NNaO_4$ (MNa^+) requires 350.1368. Also obtained was 5-*tert*-butyloxycarbonyl-8-methoxyphenanthridin-6(5*H*)-one (**33c**) (13 mg, 9%) as a pale yellow crystalline solid. R_f 0.41 (petrol/ethyl acetate, 18:1); mp 136–138 °C; ν_{max} (thin film)/cm^{-1} 3432 br, 3073 m, 2975 m, 1765 s, 1660 s, 1613 s, 1514 s, 1489 s, 1466 s, 1436 s, 1355 s, 1245 s, 1151 s, 1097 m, 1043 s, 914 m, 842 s, 829 m, 756 s, 735 s; δ_H (400 MHz, $CDCl_3$) 1.74 (9H, s, $C(CH_3)_3$), 3.94 (3H, s, OCH_3), 7.15 (1H, d, *J* 8.0), 7.26–7.48 (3H, m), 7.92 (1H, d, *J* 2.8) and 8.15–8.20 (2H, m, Ar); δ_C (l00 MHz, $CDCl_3$) 27.6, 55.7, 86.5, 108.8, 114.5, 118.6, 122.8, 123.2, 123.4, 123.8, 126.4, 127.6, 128.6, 133.5, 151.3, 159.6, 159.7; *m*/*z* (ESI^+) 348 (MNa^+, 100%); HRMS (ESI^+) found 348.1217, $C_{19}H_{19}NaNO_4$ requires 348.1212.

6.4.4. *tert*-Butyl N-formyl-(2′-methoxybiphenyl-2-yl) carbamate (**32d**)

Starting with benzamide **31d** (500 mg, 1.10 mmol), formamide **32d** (148 mg, 41%) was obtained as a pale yellow oil; ν_{max} (thin film)/cm^{-1} 1752s, 1711 s, 1535 s, 1369 s, 1145 s, 1069 m; δ_H (400 MHz, $CDCl_3$) 1.38 (9H, s, $C(CH_3)_3$), 3.70 (3H, s, CH_3O), 6.91 (1H, d, *J* 8.0), 6.99 (1H, dd, *J* 8.0, 7.0), 7.11 (1H, d, *J* 3.5), 7.20 (1H, d, *J* 3.5), 7.33 (1H, dd, *J* 7.5, 7.0) and 7.39–7.47 (3H, m, 2×Ar), 9.23 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$) 27.6, 56.3, 83.8, 110.9, 120.5, 128.0, 128.5, 128.7, 128.9, 129.3, 131.8, 133.0, 135.5, 137.3, 152.5, 156.4, 163.1; HRMS (ESI^+) found 228.1026, $C_{14}H_{14}NO_2$ [(M−Boc)H^+] requires 228.1025. Also obtained was the spirocyclic dimer (**34**), bis{2-methoxy-1′-(*tert*-butyloxycarbonyl)spiro[cyclohexa[2,5]diene-1,3′-indolin]-2′-one-4-yl} (47 mg, 13%) as a solid from which the C_2-symmetric diastereomer crystallised as colourless plates, suitable for X-ray structural analysis;[26] ν_{max} (thin film)/cm^{-1} 1698 s, 1675 s, 1515 m, 1437 m, 1251 m, 1086 m; δ_H (400 MHz, $CDCl_3$) 1.65 (18H, s, 2×$C(CH_3)_3$), 3.40 (2H, s, 2×H-4), 3.57 (6H, s, 2×CH_3O), 5.09 (2H, s, 2×H-3), 5.49 (2H, d, *J* 10.0, 2×H-6), 6.07 (2H, d, *J* 10.0, 2×H-5), 7.08–7.15 (4H, m), 7.30 (2H, dd, *J* 8.0, 7.0) and 7.82 (2H, d, *J* 8.0, Ar); δ_C (100 MHz, $CDCl_3$) 28.1, 41.4, 55.1, 55.3, 84.2, 96.5, 115.0, 123.9, 124.6, 125.3, 128.5, 130.3, 131.6, 139.8, 152.7, 174.7; *m*/*z* (ESI^+) 228 [($^1/_2$ M−Boc)H^+, 100%].

6.4.5. *tert*-Butyl N-formyl[4′-(trifluoromethyl)biphenyl-2-yl]carbamate **32e**

Starting with benzamide **31e** (200 mg, 0.41 mmol), formamide **32e** (79 mg, 54%) was obtained as a yellow oil. R_f 0.32 (petrol/ethyl acetate, 12:1); ν_{max} (thin fiIm)/cm^{-1} 2982 m, 2935 m, 1742 s, 1703 s, 1620 m, 1488 m, 1451 m, 1407 m, 1371 s, 1326 s, 1128 s, 1072 s, 1031 s, 911 s, 848 s, 799 m, 735 s, 708 w, 610 m, 586 m; δ_H (400 MHz, $CDCl_3$) 1.30 (9H, s, $C(CH_3)_3$), 7.20–7.24 (1H, m, Ar), 7.39 (2H, d, *J* 8.0, *p*-$CF_3C_6H_4$), 7.41–7.43 (1H, m) and 7.47–7.52 (2H, m, Ar), 7.65 (2H, d, *J* 8.0, *p*-$CF_3C_6H_4$), 9.24 (1H, s, CHO); δ_F (377 MHz, $CDCl_3$) −62.9; *m*/*z* (ESI^+) 365 (MH^+, 100%); HRMS (ESI^+) found 365.1249, $C_{19}H_{18}F_3NO_3$ (MH^+) requires 365.1239. Also obtained was 5-*tert*-butyloxycarbonyl-8-(trifluoromethyl)phenanthridin-6(5*H*)-one (**33e**) (17 mg, 11%) as an off-white crystalline solid. R_f 0.39 (petrol/ethyl acetate, 12:1); mp 183–185 °C; ν_{max} (thin film)/cm^{-1} 1769 s, 1669 s, 1427 m, 1373 m, 1317 m, 1287 m, 1249 m, 1148 s, 1076 m, 1023 m, 908 s, 850 m, 732 s, 650 m; δ_H (400 MHz, $CDCl_3$) 1.74 (9H, s, $C(CH_3)_3$), 7.20 (1H, d, *J* 8.5), 7.41 (1H, t, *J* 8.5), 7.57 (1H, t, *J* 8.5), 7.83 (1H, d, *J* 8.5), 8.30 (1H, d, *J* 8.5), 8.53 (1H, s) and 8.63 (1H, d, *J* 8.5, Ar); δ_F (377 MHz, $CDCl_3$) −63.0; *m*/*z* (ESI^+) 363 (MH^+, 100%); HRMS (ESI^+) found 264.0628, $C_{14}H_9F_3NO$ [M(−Boc)H^+] requires 264.0636.

6.5. General procedure for the synthesis of oxazolines 36a–c

To a stirred solution of the benzimidate hydrochloride (1.0 mmol) in chloroform (8.3 mL) were added L-serine ethyl ester hydrochloride (170 mg, 1.0 mmol) and triethylamine (140 μL, 1.0 mmol). The mixture was heated at reflux for 24 h, the solvent removed in vacuo and the residue purified by flash column chromatography (petrol/ethyl acetate, 1:1) to afford the oxazoline.

6.5.1. (*S*)-Ethyl 2-phenyl-4,5-dihydrooxazole-4-carboxylate (**36a**)[29]

Reaction of ethyl benzimidate hydrochloride (1.0 g, 5.39 mmol) under the general procedure afforded the title compound (**36a**) as a white, crystalline solid (0.981 g, 83%). R_f 0.48 (petrol/ethyl acetate, 1:1); mp 44 °C (lit.[29] <40 °C); $[\alpha]_D^{20}$ +111 (*c* 1.0, EtOH) [lit.[29] +90.9 (*c* 0.2, $CHCl_3$)]; ν_{max} (KBr disc)/cm^{-1} 2982 m, 1738 s, 1643 s, 1197 m, 1089 s, 780 w, 697 s; δ_H (200 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.0, CH_3), 4.28 (2H, q, *J* 7.0, CH_2CH_3), 4.60 (1H, dd, *J* 10.8, 8.7) and 4.70 (1H, dd, *J* 8.7, 7.7, OCH_2), 4.95 (1H, dd, *J* 10.8, 7.7, CHN), 7.37–7.56 (3H, m) and 7.94–8.06 (2H, m, Ph); δ_C (100 MHz, $CDCl_3$) 14.2, 61.8, 68.7, 69.6, 127.0, 128.3, 128.6, 131.8, 166.2, 171.2; *m*/*z* (ESI^+) 242 (MNa^+, 100%).

6.5.2. (*S*)-Ethyl 2-(4-methylphenyl)-4,5-dihydrooxazole-4-carboxylate (**36b**)

Reaction of ethyl 4-methylbenzimidate hydrochloride (3.0 g, 15.0 mmol) under the general procedure afforded the title compound (**36b**) as a white, crystalline solid (2.58 g, 74%). R_f 0.49 (petrol/ethyl acetate, 1:1); mp 84 °C; $[\alpha]_D^{20}$ +77.5 (*c* 1.0, $CHCl_3$); ν_{max} (KBr disc)/cm^{-1} 1726 s, 1633 s, 1358 m, 1297 m, 1207 m, 1089 s, 1046 m, 956 s; δ_H (200 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.2, CH_2CH_3), 2.40 (3H, s, CH_3Ar), 4.28 (2H, q, *J* 7.2, CH_2CH_3), 4.58 (1H, dd, *J* 10.8, 8.7) and 4.67 (1H, dd, *J* 8.7, 7.8, OCH_2), 4.92 (1H, dd, *J* 10.8, 7.8, CHN), 7.22 (2H, d, *J* 8.1) and 7.88 (2H, d, *J* 8.1, *p*-Tol); δ_C (100 MHz, $CDCl_3$) 14.2, 21.6, 61.7, 68.7, 69.5, 124.1, 128.6, 129.1, 142.3, 166.3, 171.3; *m*/*z* (ESI^+) 489 (M_2Na^+, 100%), 467 (M_2H^+, 70), 234 (MH^+, 90); HRMS (ESI^+) found 256.0943, $C_{13}H_{15}NNaO_3^+$ (MNa^+) requires 256.0944.

6.5.3. (*S*)-Ethyl 2-(4-methoxyphenyl)-4,5-dihydrooxazole-4-carboxylate (**36c**)

Reaction of ethyl 4-methoxybenzimidate hydrochloride (3.0 g, 13.9 mmol) under the general procedure afforded the title compound (**36c**) as a white, crystalline solid (2.22 g, 64%). R_f 0.38 (petrol/ethyl acetate, 1:1); mp 89 °C; $[\alpha]_D^{20}$ +61.7 (*c* 1.0, $CHCl_3$); ν_{max} (KBr disc)/cm^{-1} 1727 s, 1635 s, 1468 m, 1358 m, 1260 s, 1207 m, 1089 m, 1031 m; δ_H (200 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.2, CH_2CH_3), 3.85 (3H, s, CH_3OAr), 4.28 (2H, q, *J* 7.2, CH_2CH_3), 4.57 (1H, dd, *J* 10.6, 8.5) and 4.66 (1H, dd, *J* 8.5, 7.5, OCH_2), 4.91 (1H, dd, *J* 10.6, 7.5, CHN), 6.91 (2H, d, *J* 9.1) and 7.94 (2H, d, *J* 9.1, *p*-Anis); δ_C (100 MHz, $CDCl_3$) 14.2, 55.4, 61.7, 68.6, 69.5, 113.7, 119.4, 130.5, 162.5, 166.1, 171.4; *m*/*z* (ESI^+) 521 (M_2Na^+, 100%), 499 (M_2H^+, 70), 250 (MH^+, 90); HRMS (ESI^+) found 272.0888, $C_{13}H_{15}NNaO_4$ (MNa^+) requires 272.0893.

6.6. General procedure for ring-opening of oxazolines 36a–c

To a stirred solution of the oxazoline (1.0 mmol) in benzene (10.8 mL) was added ethyl chloroformate (311 μL, 4.0 mmol) and NaI (see below for quantities). The mixture was heated at reflux for

24 h in the dark, then allowed to cool and the solvent removed in vacuo. The residue was purified by flash column chromatography to afford the product.

*6.6.1. (R)-Ethyl 2-[N-(ethoxycarbonyl)benzamido]-3-iodopropanoate (**37a**)[29]*

Reaction of oxazoline **36a** (101 mg, 0.461 mmol) and NaI (690 mg, 4.6 mmol) under the general procedure afforded the title compound (**37a**) as a yellow oil (149 mg, 77%). R_f 0.43 (petrol/ethyl acetate, 5:1); $[\alpha]_D^{20}$ −25.2 (*c* 0.4, $CHCl_3$) [lit.[29] −20.6 (*c* 1.2, $CHCl_3$)]; ν_{max} (thin film)/cm^{-1} 2983 br, 1709 s, 1682 s, 1375 s, 1338 s, 1020 m, 771 m; δ_H (500 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.2, $NCO_2CH_2CH_3$), 1.27 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 3.88–3.97 (2H, m, CH_2I), 4.02 (2H, q, *J* 7.2, $NCO_2CH_2CH_3$), 4.24 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 5.35 (1H, dd, *J* 9.5, 6.0, CHN), 7.39–7.45 (2H, m), 7.48–7.55 (1H, m) and 7.68–7.74 (2H, m, Ph); δ_C (125 MHz, $CDCl_3$) 2.0, 13.4, 14.1, 59.7, 62.6, 63.4, 127.8, 128.8, 131.7, 136.3, 154.3, 167.3, 172.3; *m*/*z* (ESI^+) 861 (M_2Na^+, 84%), 420 (MH^+, 69%).

*6.6.2. (R)-Ethyl 2-[N-(ethoxycarbonyl)-4-methylbenzamido]-3-iodopropanoate (**37b**)*

Reaction of oxazoline **36b** (200 mg, 0.857 mmol) and NaI (2.31 g, 15.4 mmol) under the general procedure afforded the title compound (**37b**) as a yellow oil (267 mg, 72%). R_f 0.28 (petrol/ethyl acetate, 5:1); $[\alpha]_D^{20}$ −20.8 (*c* 1.0, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 1740 s, 1682 m, 1610 m, 1375 s, 1337 s, 1259 m, 1201 m, 1179 m, 1057 m; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, t, *J* 7.0, $NCO_2CH_2CH_3$), 1.28 (3H, t, *J* 7.2, $CO_2CH_2CH_3$), 2.41 (3H, s, CH_3Ar), 3.90–3.98 (2H, m, CH_2I), 4.06 (2H, q, *J* 7.0, $NCO_2CH_2CH_2$), 4.24 (2H, q, *J* 7.2, $CO_2CH_2CH_3$), 5.33 (1H, dd, *J* 10.0, 5.8, CHN), 7.20–7.25 (2H, m) and 7.61–7.67 (2H, m, *p*-Tol); δ_C (100 MHz, $CDCl_3$) 2.2, 13.5, 14.1, 21.6, 59.8, 62.3, 63.4, 128.4, 128.8, 136.3, 142.5, 154.3, 167.5, 172.4; *m*/*z* (ESI^+) 889 (M_2Na^+, 100%), 434 (MH^+, 84); HRMS (ESI^+) found 456.0280, $C_{16}H_{20}INNaO_5^+$ (MNa^+) requires 456.0278.

*6.6.3. (R)-Ethyl 2-[N-(ethoxycarbonyl)-4-methoxybenzamido]-3-iodopropanoate (**37c**)*

Reaction of oxazoline **36c** (200 mg, 0.802 mmol) and NaI (2.16 g, 14.4 mmol) under the general procedure afforded the title compound (**37c**) as a yellow oil (285 mg, 79%). R_f 0.16 (petrol/ethyl acetate, 5:1); $[\alpha]_D^{20}$ −22.7 (*c* 1.0, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 1738 br, 1678 br, 1606 s, 1375 s, 1337 s, 1257 m, 1171 s, 1025 m; δ_H (400 MHz, $CDCl_3$) 1.00 (3H, t, *J* 7.2, $NCO_2CH_2CH_3$), 1.28 (3H, t, *J* 7.2, $CO_2CH_2CH_3$), 3.87 (3H, s, OCH_3), 3.88–3.97 (2H, m, CH_2I), 4.15–4.20 (2H, m, $NCO_2CH_2CH_3$), 4.21–4.30 (2H, m, $CO_2CH_2CH_3$), 5.30 (1H, dd, *J* 10.3, 5.6, CHN), 6.89–6.96 (2H, m) and 7.70–7.77 (2H, m, *p*-Anis); δ_C (100 MHz, $CDCl_3$) 2.3, 13.7, 14.1, 55.5, 60.0, 62.2, 63.3, 113.4, 128.2, 130.8, 154.5, 162.7, 167.5, 171.6; *m*/*z* (ESI^+) 921 (M_2Na^+, 75%), 450 (MH^+, 100); HRMS (EI) found 472.0223, $C_{16}H_{20}INNaO_6^+$ (MNa^+) requires 472.0228.

6.7. General procedure for radical reactions of 37a–c, 40, 43 and 46

A round-bottomed flask containing the iodide (1.0 mmol) and AIBN (16 mg, 0.1 mmol) was fitted with a condenser, all joints sealed, and the flask was evacuated and purged with argon several times. Degassed benzene (106 mL) was then added via cannula and the resulting solution was brought to reflux. A solution of tributyltin hydride (296 μL, 1.1 mmol) and AIBN (148 mg, 0.9 mmol) in degassed benzene (18 mL) was then added to this mixture over a 4–8 h period and heating continued for a further 2 h. The resulting mixture was concentrated in vacuo and eluted with ethyl acetate through a stationary phase of KF (10%) impregnated silica, to remove the majority of the tin residues. The product was then further purified by flash column chromatography.

*6.7.1. (S)-Ethyl 2-[N-(ethoxycarbonyl)formamido]-3-phenylpropanoate (**38a**)*

Reaction of iodide **37a** (138 mg, 0.328 mmol) under the general procedure afforded the title compound (**38a**) as a colourless oil (51 mg, 53%). R_f 0.25 (petrol/ethyl acetate, 5:1); $[\alpha]_D^{20}$ +44.2 (*c* 0.5, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2985 br, 1743 s, 1697 s, 1497 w, 1375 m, 1335 m, 1252 m, 1095 m, 1024 m, 869 w, 775 m, 701 m; δ_H (500 MHz, $CDCl_3$) 1.28 (6H, 2×t, *J* 7.2, 2×CH_3), 3.24 (1H, dd, *J* 14.2, 10.6) and 3.51 (1H, dd, *J* 14.2, 5.5, CH_2Ph), 4.16–4.32 (4H, m, 2×CH_2CH_3), 5.29 (1H, dd, *J* 10.6, 5.5, CHN), 7.12–7.28 (5H, m, Ph), 9.05 (1H, s, CHO); δ_C (125 MHz, $CDCl_3$) 14.1 (×2), 34.8, 54.5, 61.7, 63.6, 126.8, 128.5, 129.2, 136.8, 153.1, 162.1, 169.1; *m*/*z* (ESI^+) 316 (MNa^+, 100%); HRMS (ESI^+) found 316.1156, $C_{15}H_{19}NNaO_5$ (MNa^+) requires 316.1161.

*6.7.2. (S)-Ethyl 2-[N-(ethoxycarbonyl)formamido]-3-(4-methylphenyl)propanoate (**38b**)*

Reaction of iodide **37b** (99 mg, 0.229 mmol) under the general procedure afforded the title compound (**38b**) as a pale yellow oil (35 mg, 50%). R_f 0.50 (petrol/ethyl acetate, 2:1); $[\alpha]_D^{18}$ −98.1 (*c* 0.4, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2894 br, 1744 s, 1698 s, 1517 m, 1447 m, 1406 s, 1375 s, 1334 s, 1252 s, 1062 m; δ_H (400 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.1, $NCO_2CH_2CH_3$), 1.28 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 2.29 (3H, s, CH_3Ar), 3.19 (1H, dd, *J* 14.2, 10.6) and 3.46 (1H, dd, *J* 14.2, 5.3, CH_2Ar), 4.17–4.31 (4H, m, 2×$CO_2CH_2CH_3$), 5.27 (1H, dd, *J* 10.6, 5.3, CHN), 7.00–7.09 (4H, m, *p*-Tol), 9.05 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$) 14.1, 14.2, 21.0, 34.4, 54.5, 61.7, 63.6, 128.8, 129.0, 133.6, 136.3, 153.1, 162.1, 169.1; *m*/*z* (ESI^+) 637 (M_2Na^+, 70%), 330 (MNa^+, 50), 308 (MH^+, 100); HRMS (ESI^+) found 330.1308, $C_{16}H_{21}NO_5$ (MNa^+) requires 330.1312.

*6.7.3. (S)-Ethyl 2-[N-(ethoxycarbonyl)formamido]-3-(4-methoxyphenyl)propanoate (**38c**)*

Reaction of iodide **37c** (130 mg, 0.289 mmol) under the general procedure afforded the title compound (**38c**) as a yellow oil (58 mg, 62%). R_f 0.34 (petrol/ethyl acetate, 2:1); $[\alpha]_D^{18}$ −85.0 (*c* 0.8, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2892 br, 1742 s, 1696 s, 1613 w, 1514 s, 1466 w, 1375 m, 1334 m, 1248 s, 1028 m; δ_H (400 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.1, $NCO_2CH_2CH_3$), 1.29 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 3.18 (1H, dd, *J* 14.4, 10.7) and 3.44 (1H, dd, *J* 14.4, 5.4, CH_2Ar), 3.77 (3H, s, OCH_3), 4.18–4.31 (4H, m, 2×$CO_2CH_2CH_3$), 5.25 (1H, dd, *J* 10.7, 5.4, CHN), 6.78–6.82 (2H, m) and 7.04–7.07 (2H, m, *p*-Anis), 9.06 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$) 14.1 (×2), 34.0, 54.5, 55.2, 61.7, 63.6, 113.9, 128.7, 130.1, 153.3, 158.4, 162.1, 169.1; *m*/*z* (ESI^+) 346 (MNa^+, 25%), 324 (MH^+, 60); HRMS (ESI^+) found 346.1260, $C_{16}H_{21}NNaO_6$ (MNa^+) requires 346.1261.

*6.7.4. (S)-4-Methyl-2-phenyl-4,5-dihydrooxazole (**39**)[32]*

Method 1. $ZnCl_2$ (24 mg, 0.178 mmol) was melted in a 25 mL round-bottomed flask three times under high vacuum using a heat gun and then cooled under nitrogen. A solution of benzonitrile (182 μL, 1.78 mmol) and L-alaninol (200 mg, 2.66 mmol) in chlorobenzene (2.0 mL) was added and the resulting mixture was heated at reflux under nitrogen for 48 h, then cooled and concentrated in vacuo. The residue was dissolved in dichloromethane (10 mL), and water (5.0 mL) was added. The separated aqueous solution was extracted with dichloromethane (3×5.0 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash column chromatography (petrol/ethyl acetate, 3:1) to afford the title compound (**39**) as a colourless oil (148 mg, 52%).

Method 2. The reaction of L-alaninol (0.947 g, 12.7 mmol) and ethyl benzimidate hydrochloride following the general procedure for oxazoline formation above afforded the title compound (**39**, 1.74 g, 85%) as an oil. R_f 0.32 (petrol/ethyl acetate, 3:1); $[\alpha]_D^{18}$ −74.5 (*c* 1.0, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2969 m, 1650 s, 1450 m, 1357 m,

1259 w, 1057 s, 1026 m, 971 m; δ_H (200 MHz, $CDCl_3$) 1.37 (3H, d, *J* 6.5, CH_3), 3.97 (1H, app. t, *J* 7.7, C*H*H′), 4.30–4.48 (1H, m, CHN), 4.54 (1H, dd, *J* 9.4, 7.7, CH*H*′), 7.36–7.53 (3H, m) and 7.92–7.99 (2H, m, Ph); δ_C (100 MHz, $CDCl_3$) 21.5, 62.0, 74.0, 127.8, 128.2, 128.4, 131.2, 163.4; *m*/*z* (ESI^+) 162 (MH^+, 74%).

6.7.5. (S)-Ethyl N-benzoyl(1-iodopropan-2-yl)carbamate (**40**)

The reaction of oxazoline **39** (300 mg, 1.86 mmol) and NaI (5.02 g, 33.5 mmol) at 95 °C for 48 h following the general procedure for oxazoline ring-opening afforded the title compound (**40**) as a yellow oil (356 mg, 53%). R_f 0.20 (petrol/ethyl acetate, 10:1); $[\alpha]_D^{18}$ −38.8 (*c* 0.4, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3347 br, 2981 w, 1721 s, 1532 m, 1452 m, 1277 s, 1114 m, 1071 m; δ_H (400 MHz, $CDCl_3$) 0.81 (3H, t, *J* 7.2, CH_2CH_3), 1.56 (3H, d, *J* 6.8, CH_3), 3.49 (1H, dd, *J* 10.1, 5.8, C*H*H′), 3.88–4.03 (3H, m, CH*H*′ and CH_2CH_3), 4.74–4.92 (1H, m, CHN) 7.36–7.55 (3H, m) and 7.66–7.72 (2H, m, Ph); δ_C (100 MHz, $CDCl_3$) 8.6, 13.3, 18.0, 54.9, 62.8, 127.8, 128.2, 131.6, 137.3, 154.6, 172.9; *m*/*z* (ESI^+) 362 (MH^+, 62%); HRMS (ESI^+) found 384.0065, $C_{13}H_{16}INNaO_3$ (MNa^+) requires 384.0067.

6.7.6. (S)-Ethyl N-formyl(1-phenylpropan-2-yl)carbamate (**41**)

The reaction of iodide **40** (238 mg, 0.659 mmol) under the general procedure for radical aryl transfer reaction yielded the title compound (**41**) as a yellow oil (113 mg, 73%). R_f 0.59 (petrol/ethyl acetate, 2:1); $[\alpha]_D^{18}$ +48.9 (*c* 0.8, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2980 br, 1737 m, 1693 s, 1455 w, 1373 m, 1321 s, 1186 m, 1115 m, 1030 m; δ_H (400 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.2, CH_2CH_3), 1.41 (3H, d, *J* 6.8, CH_3), 2.98 (1H, dd, *J* 13.6, 7.0) and 3.17 (1H, dd, *J* 13.6, 9.1, CH_2Ph), 4.28 (2H, q, *J* 7.2, CH_2CH_3), 4.73–4.92 (1H, m, CHN), 7.13–7.32 (5H, m, Ph), 9.08 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$) 14.2, 18.0, 39.8, 50.0, 63.1, 126.5, 128.4, 129.0, 138.5, 153.9, 163.3; *m*/*z* (ESI^+) 493 (M_2Na^+, 19%), 258 (MNa^+, 20), 236 (MH^+, 41); HRMS (ESI^+) found 258.1099, $C_{13}H_{17}NNaO_3$ (MNa^+) requires 258.1101.

6.7.7. (S)-Ethyl 1-phenylpropan-2-ylcarbamate (**42**)[33,34]

To a stirred solution of *N*-formyl derivative **41** (54 mg, 0.230 mmol) in THF (7.0 mL) was added LiOH solution (3.0 mL, 0.1 M, aqueous). The mixture was heated to reflux for 1 h then cooled to rt and acidified with hydrochloric acid (5.0 mL, 2.0 M). The organic phase was separated and the aqueous phase was extracted with ether (3×10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil that was purified by flash column chromatography (petrol/ethyl acetate, 5:1) to afford the title compound (**42**) as a colourless oil (47 mg, 98%). R_f 0.20 (petrol/ethyl acetate, 5:1); $[\alpha]_D^{23}$ −4.2 (*c* 1.25, CH_2Cl_2) [lit.[33] +2.9 (*c* 5.0, CH_2Cl_2); lit.[34] 'laevorotatory']; ν_{max} (thin film)/cm^{-1} 3329 br, 2977 br, 1694 s, 1532 m, 1454 m, 1253 m, 1068 m; δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* 6.5, CH_3), 1.23 (3H, t, *J* 7.2, CH_2CH_3), 2.68 (1H, dd, *J* 13.5, 7.2) and 2.86 (1H, dd, *J* 13.5, 5.6, CH_2Ph), 3.88–4.03 (1H, m, CHN), 4.09 (2H, q, *J* 7.2, CH_2CH_3), 4.52 (1H, br s, NH), 7.14–7.35 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 14.6, 20.2, 43.5, 47.8, 60.6, 126.4, 128.4, 129.5, 138.0 (CO_2Et resonance not observed); *m*/*z* (ESI^+) 437 (M_2Na^+, 90%), 230 (MNa^+, 95), 208 (MH^+, 100%).

6.7.8. (S)-1-Benzoyl-5-(iodomethyl)pyrrolidin-2-one (**43**)

To a suspension of NaH (71 mg, 60% dispersion in mineral oil, 1.78 mmol) in THF (1.0 mL) cooled to −15 °C was added dropwise a solution of (*S*)-5-(iodomethyl)pyrrolidin-2-one[36] (200 mg, 0.889 mmol) in THF (1.0 mL). After gas evolution had ceased, benzoyl chloride (310 mL, 2.67 mmol) was added and the reaction mixture allowed to warm to rt and stirred for a further 1 h. The mixture was then diluted with ethyl acetate (15 mL), poured into water (5 mL) and the organic phase separated. The aqueous phase was extracted with ethyl acetate (2×15 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 3:1) to afford the title compound (**41**) as a yellow oil (177 mg, 60%). R_f 0.16 (petrol/ethyl acetate, 3:1); $[\alpha]_D^{18}$ −119 (*c* 0.7, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2958 br, 1748 s, 1673 s, 1600 m, 1449 m, 1418 m, 1287 s, 1231 s, 1156 m; δ_H (400 MHz, $CDCl_3$) 1.96–2.06 (1H, m) and 2.25–2.35 (1H, m, 4-CH_2), 2.49–2.59 (1H, m) and 2.76–2.86 (1H, m, 3-CH_2), 3.52 (1H, dd, *J* 10.6, 1.8) and 3.82 (1H, dd, *J* 10.6, 5.3, CH_2I), 4.33–4.40 (1H, m, CHN), 7.40–7.47 (2H, m), 7.52–7.57 (1H, m) and 7.70–7.74 (2H, m, Ph); δ_C (100 MHz, $CDCl_3$) 11.7, 23.7, 31.6, 56.1, 127.9, 129.4, 132.4, 134.3, 170.8, 174.4; *m*/*z* (ESI^+) 681 (M_2Na^+, 100%), 352 (MNa^+, 75), 330 (MH^+, 100); HRMS (ESI^+) found 351.9803, $C_{12}H_{12}INNaO_2$ (MNa^+) requires 351.9805.

6.7.9. (R)-1-Benzoyl-5-methylpyrrolidin-2-one (**44**)[38]

The reaction of iodide **43** (352 mg, 1.07 mmol) under the general procedure for radical aryl transfer reaction (8 h addition time), with VAZO-88 as the radical initiator in place of AIBN, afforded the title compound (**44**) as a white solid (115 mg, 53%). R_f 0.27 (petrol/ethyl acetate, 2:1); mp 64–66 °C (lit.[38] 74–76 °C); $[\alpha]_D^{22}$ −166 (*c* 1.0, $CHCl_3$) [lit.[38] −177.1 (*c* 1.01, EtOH)]; ν_{max} (KBr disc)/cm^{-1} 2975 br, 1741 s, 1661 s, 1446 w, 1356 m, 1312 s, 1230 s, 1198 s, 1158 m; δ_H (400 MHz, $CDCl_3$) 1.45 (3H, d, *J* 6.3, CH_3), 1.75–1.84 (1H, m) and 2.28–2.38 (1H, m, 4-CH_2), 2.47–2.57 (1H, m) and 2.63–2.73 (1H, m, 3-CH_2), 4.51–4.59 (1H, m, CHN), 7.39–7.45 (2H, m), 7.50–7.55 (1H, m) and 7.59–7.64 (2H, m, Ph); δ_C (100 MHz, $CDCl_3$) 20.0, 25.9, 31.8, 53.9, 127.9, 128.9, 132.0, 135.0, 170.9, 174.9; *m*/*z* (ESI^+) 429 (M_2Na^+, 100%), 226 (MNa^+, 75), 204 (MH^+, 75). Also obtained was (*S*)-2-benzyl-1-formylpyrrolidin-2-one (**45**) as a colourless oil (21 mg, 10%). R_f 0.33 (petrol/ethyl acetate, 2:1); $[\alpha]_D^{22}$ −144 (*c* 0.4, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2932 m, 1749 s, 1695 s, 1495 m, 1455 m, 1346 s, 1291 s, 1232 s; δ_H (400 MHz, $CDCl_3$) 1.92–2.00 (1H, m) and 2.01–2.10 (1H, m, 4-CH_2), 2.15–2.25 (1H, m) and 2.31–2.40 (1H, m, 3-CH_2), 2.83 (1H, dd, *J* 13.5, 8.3) and 3.16 (1H, dd, *J* 13.5, 3.4, CH_2Ph), 4.48–4.54 (1H, m, CHN), 7.18–7.22 (2H, m), 7.25–7.36 (3H, m, Ph), 9.18 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$) 22.2, 30.5, 38.4, 55.2, 127.1, 128.8, 129.5, 136.4, 160.4, 177.1; *m*/*z* (ESI^+) 429 (M_2Na^+, 80%), 226 (MNa^+, 70), 204 (MH^+, 90); HRMS (ESI^+) found 226.0838, $C_{12}H_{13}NNaO_2$ (MNa^+) requires 226.0838.

6.7.10. (S)-1-Benzoyl-6-(iodomethyl)piperidin-2-one (**46**)

To a suspension of NaH (67 mg, 60% dispersion in mineral oil, 1.68 mmol) in THF (2.0 mL) at −15 °C was added dropwise a solution of 6-(iodomethyl)piperidin-2-one[37] (200 mg, 0.836 mmol) in THF (10 mL). After gas evolution had ceased, benzoyl chloride (0.291 mL, 2.51 mmol) was added and the reaction mixture was allowed to warm to rt. The mixture was stirred for 4 h and then diluted with ethyl acetate (15 mL), poured into water (5.0 mL) and the organic phase separated. The aqueous phase was extracted with ethyl acetate (2×15 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 3:1) to afford the title compound (**46**) as a yellow oil (157 mg, 55%). R_f 0.22 (petrol/ethyl acetate, 3:1); $[\alpha]_D^{19}$ +3.2 (*c* 1.25, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2956 m, 1682 s, 1449 w, 1376 m, 1281 s, 1161 m, 1099 w; δ_H (400 MHz, $CDCl_3$) 1.88–2.15 (3H, m, H-5 and 4-CH_2), 2.35–2.43 (1H, m, H-5), 2.56–2.61 (2H, m, 3-CH_2), 3.38 (1H, t, *J* 9.5) and 3.64 (1H, dd, *J* 9.5, 2.4, CH_2I), 4.40–4.47 (1H, m, CHN), 7.38–7.43 (2H, m), 7.47–7.52 (1H, m) and 7.59–7.64 (2H, m, Ph); δ_C (100 MHz, $CDCl_3$) 7.6, 17.6, 26.7, 34.2, 55.8, 128.2, 130.2, 131.9, 135.6, 173.6, 174.4; *m*/*z* (ESI^+) 709 (M_2Na^+, 80%), 366 (MNa^+, 45), 344 (MH^+, 100); HRMS (ESI^+) found 365.9961, $C_{13}H_{14}INNaO_2$ (MNa^+) requires 365.9961.

6.7.11. (S)-2-Benzyl-6-oxopiperidine-1-carbaldehyde (**48**)

The reaction of iodide **46** (149 mg, 0.434 mmol) under the general procedure for radical aryl transfer reaction, with VAZO-88 as the radical initiator and an addition time of 8 h, followed by

stirring for a further 2 h, afforded the title compound (**48**) as a colourless oil (58 mg, 62%). R_f 0.31 (petrol/ethyl acetate, 3:1); $[\alpha]_D^{19}$ −8.5 (*c* 0.4, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2951 m, 1715 s, 1689s, 1454 m, 1397 m, 1236 s, 1168 m, 1095 m; δ_H (400 MHz, $CDCl_3$) 1.57–1.67 (1H, m, H-5), 1.76–1.85 (2H, m, H-5 and H-4), 1.98–2.12 (1H, m, H-4), 2.49–2.70 (3H, m, C*H*H′Ph and 3-CH_2), 3.06 (1H, dd, *J* 13.1, 3.8, CH*H*′Ph), 4.49–4.56 (1H, m, CHN), 7.23–7.36 (5H, m, Ph), 9.52 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$) 15.7, 23.3, 33.0, 38.5, 52.6, 126.8, 128.7, 129.3, 137.6, 162.8, 173.4; *m*/*z* (ESI$^+$) 457 (M_2Na^+, 75%), 240 (MNa^+, 85), 218 (MH^+, 100); HRMS (ESI$^+$) found 272.1250, $C_{14}H_{19}NNaO_3$ ($M\cdot MeOH\cdot Na^+$) requires 272.1257.

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