Pergamon

Tetrahedron 57 (2001) 1347–1359

TETRAHEDRON

Palladium catalysed queuing processes. Part 1: Termolecular cyclization–anion capture employing carbon monoxide as a relay switch and hydride, organotin(IV) or boron reagents

Stephen Brown,[a] Stephen Clarkson,[b] Ronald Grigg,[b,*] W. Anthony Thomas,[b] Visuvanathar Sridharan[b] and D. M. Wilson[b]

[a]*AstraZeneca, PO Box A38, Huddersfield HD2 1FF, UK*

[b]*Molecular Innovation, Diversity and Automated Synthesis (MIDAS) Centre, Leeds University, Leeds LS2 9JT, UK*

Received 29 August 2000; revised 10 November 2000; accepted 16 November 2000

Abstract—The concept of relay switch reactants, which substantially enhance the scope of our cyclization–anion capture methodology, is introduced and exemplified by a wide variety of catalytic cyclization–carbonylation–anion capture processes employing hydride, organostannanes and $NaBPh_4$ as anion capture agents. Mono- and bis-cyclization processes forming 5- and 6-membered rings are described, all of which employ CO at atmospheric pressure. Cyclocarboformylation processes provide interesting analogues of hydroformylation.

1. Background

In current studies we have been developing palladium catalysed cyclization–anion capture cascades that result in the formation of one or more rings with concomitant introduction of a wide range of functionality by replacing the β-hydride elimination step of a Heck reaction with a group or atom transfer.[1] This versatile and wide ranging methodology is summarized in Table 1 and illustrated for a bis-cyclization sequence with an aryl starter species in Scheme 1.[2]

The starter species is usually employed as the appropriate halide (Cl, Br, I), triflate or carbonate (allenyl starter) and the cascade begins with an oxidative addition reaction between the starter species and Pd(0) to generate an organopalladium(II) species. An alternative initiation sequence involves hydropalladation or chloropalladation of an alkyne to generate a vinyl palladium(II) species. In monocyclizations the organopalladium(II) species cyclizes onto the terminating species. Exchange of halide or triflate with the anion capture agent followed by reductive elimination generates the functionalized monocyclized product regiospecifically and regenerates Pd(0).

In Scheme 1 the starter species is an aryl halide, the relay and terminating species are alkenes and the anion capture agent Y is the organostannane. The efficient creation of a wide range of tetrasubstituted carbon centres is a particularly attractive feature of the cyclization–anion capture methodology. A further distinctive feature is that cyclizations, in the absence of adverse steric constraints, invariably proceed via the *exo*-mode. Thus Scheme 1 involves 5-*exo*-trig, rather than 6-*endo*-trig, cyclizations. Table 1

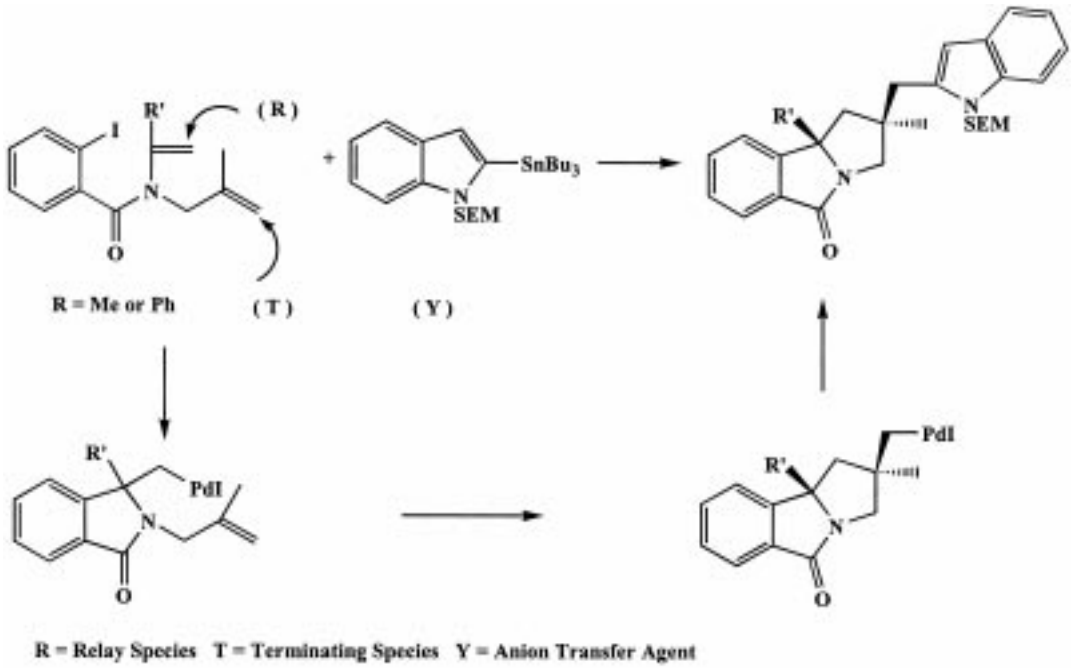
Table 1. Potential combinations for polycyclization anion capture processes

Starter species	Relay species (R)	Terminating species (T)	Y
Alkyl	Alkene	Alkene	Anionic [H, OAc, CN, N_3, TsNR, SO_2Ph $CH(CO_2R)_2$]
Aryl	Alkyne	Alkyne	
Vinyl	1,2-Diene	1,2-Diene	Neutral (amines, MeOH/CO, acrylates, allenes)
Allyl	1,3-Diene	1,3-Diene	
Carbamyl			Organometallics RM [M=Sn(IV), B(III), Zn(II)]
Oxycarbonyl			

Keywords: cascade reactions; palladium catalysis; cyclization; carboformylation; Stille coupling.

* Corresponding author. Tel.: +44-113-233-6501; fax: +44-113-233-6501; e-mail: r.grigg@chem.leeds.ac.uk

0040–4020/01/$ - see front matter
PII: S0040-4020(00)01103-0



Scheme 1.

and the foregoing discussion emphasize the versatility of the general cyclization–anion capture concepts although many details still remain to be explored. However, as initially conceived, our cyclization–anion capture methodology suffers from the constraint that most cascades are two component processes, i.e. the ring 'zipper' precursor and Y. This constraint would be circumvented if polycomponent processes could be achieved by extension of the relay phase with incorporation of both inter- and intramolecular segments. Thus the potential exists to intersperse the relay species summarized in Table 1 with additional components which would offer the potential to switch the cascade between inter- and intramolecular processes whilst incorporating valuable additional functionality. Such components might intercept the cyclization–anion capture cascade only at the relay phase, only at the termination phase or participate in both relay and terminating phases. We have called such components relay switches because of their ability to extend the relay phase and their potential to switch the cascade between intra- and intermolecular processes. Such components impart a major increase in the scope of the original cyclization–anion capture scheme whilst offering tremendous increases in the diversity and complexity of the products.

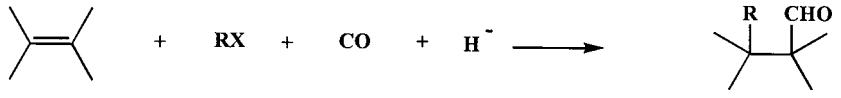
At present the most fully developed relay switches are carbon monoxide and allenes. The successful implementation of these components is predicated a fortiori on the relative rates of all the possible reactions conspiring to facilitate the desired cascade. In this context the substrates can be regarded as queuing for access to the palladium, a process followed by their incorporation into the cascade. An important additional feature of relay switch components is that they may be combined to provide access to polycomponent queuing processes which, in combination with Table 1 processes and core reactions such as 1,3-cycloaddition,[3] Diels–Alder,[4] [2+2]-Staudinger synthesis of β-lactams,[5] etc., provide cascades of exceptional range and diversity.

At present we have developed a range of ter-, tetra-, penta-, hexa- and octamolecular queuing processes.[1] This paper describes the use of carbon monoxide (1 atm) in conjunction with either diphenylmethylsilane (as hydride source)[6] or preformed organostannanes or $NaBPh_4$.[7] The accompanying paper[8] describes analogous processes employing *in situ generated vinylstannanes*.

2. Results and discussion

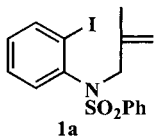
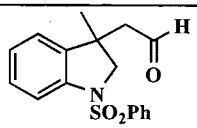
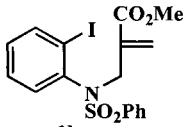
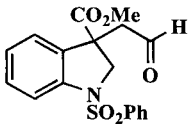
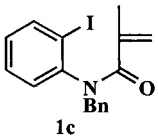
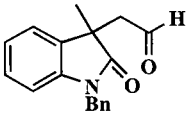
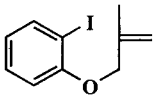
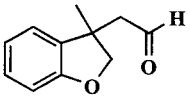
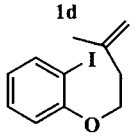
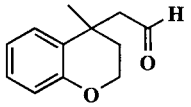
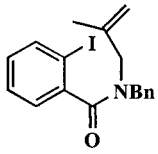
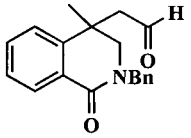
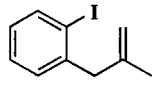
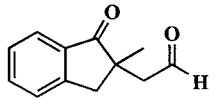
2.1. Cyclocarboformylation

The catalytic hydroformylation of alkenes is a major industrial process[9] which has attracted a substantial number of applications in fine chemical synthesis.[10] A related process of similar wide potential would be catalytic carboformylation (Scheme 2). Cyclocarboformylation, in which RX and the alkene are contained within a single molecule, can potentially be accessed by a termolecular queuing process of which Scheme 3 is a typical example.



Scheme 2.

Table 2. Termolecular queuing cascades with CO (1 atm) and hydride transfer from $Ph_2Si(Me)H$[a]

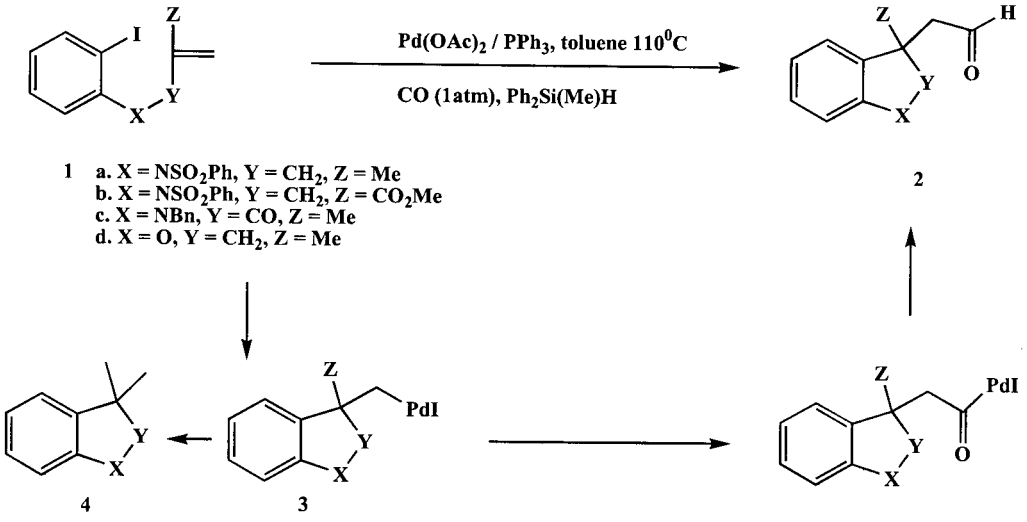
Substrate	Product (%)b
 **1a**	 2a (61)[c]
 **1b**	 2b (40)
 **1c**	 2c (40)[d]
 **1d**	 2d (51)[e]
 **6a**	 7a (61)
 **6b**	 7b (54)
 **8**	 9 (45)[f]

[a] Reactions carried out in toluene (90°C, 7 h) using 10 mol% $Pd(Oac)_2$/20 mol% PPh_3, Et_4NCl (1 equiv), $Ph_2Si(Me)H$ (2 equiv) and CO (1 atm).
[b] Isolated yield.
[c] Approximate 10% of corresponding carboxylic acid 5a also obtained.
[d] Product separated from the corresponding carboxylic acid 5c by oxime formation.
[e] Approximately 4% of carboxylic acid 5d also formed.
[f] Reaction carried out at 110°C for 7 h.

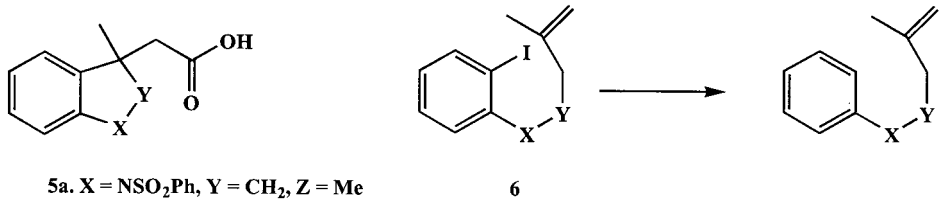
Molecular queuing processes employing gaseous components such as CO and allene are clearly going to be sensitive to the concentration (solubility) of the reactant gases in the solvent. This in turn will be sensitive to the nature of the solvent, the reaction temperature and the gas pressure. To enhance the general applicability of our queuing processes we elected to use CO at 1 atm pressure.[11] For the operation of the desired termolecular queuing process (Scheme 3) the relative rate of hydride capture is required to be slower than both cyclization and carbonylation.

Reaction (toluene/110°C/18 h) of **1a** with CO (1 atm) and sodium formate (1 equiv.) in the presence of 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3 and Et_4NCl (1 equiv.) did not lead to the desired product **2a**. Instead the alkylpalladium(II) intermediate **3** was captured by hydride transfer to afford **4** (70%) as the sole product. However, when diphenylmethylsilane (2 mol equiv.) was used as the hydride source at a lower temperature (90°C, 7 h) the desired queuing process occurred to give a 6:1 mixture of **2a** and the corresponding carboxylic acid **5a**. These were separated by flash chromatography (1:1 v/v petroleum ether–ethyl acetate) to give **2a** (61%).

The modified conditions proved effective for a variety of substrates (Table 2). The formation of small amounts of the corresponding carboxylic acids was observed in several cases (Table 2, footnotes). These by-products



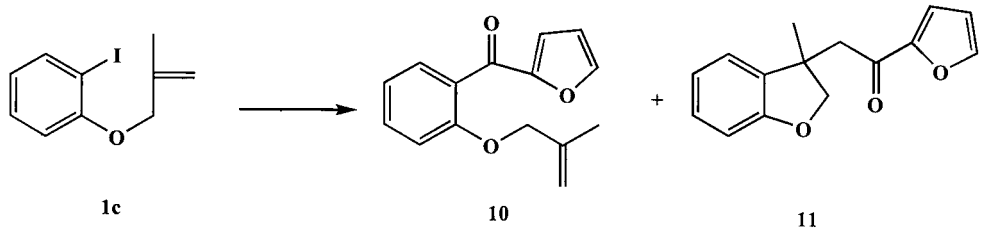
Scheme 3.



Scheme 4.

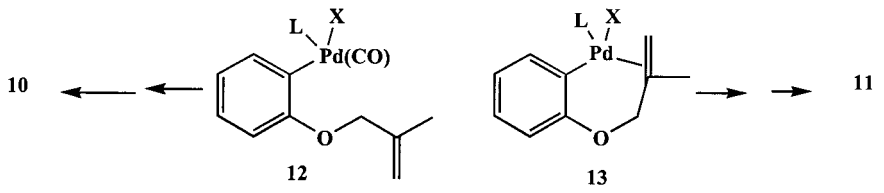
could arise via oxidation of the corresponding aldehyde or by interception of the acylpalladium(II) species by adventitious water. Attempted chromatographic separation of the 7:1 aldehyde–carboxylic acid mixture arising from **1c** led to further oxidation of aldehyde **2c** to carboxylic acid **5c**. The 7:1 mixture was therefore treated with hydroxylamine and the oxime of **2c** was separated chromatographically.

The expected slower rate of 6- versus 5-*exo*-trig cyclization



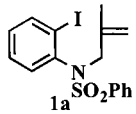
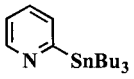
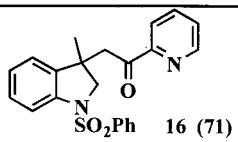
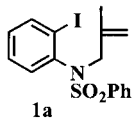
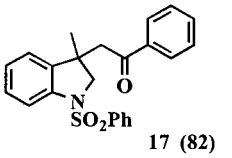
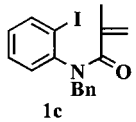
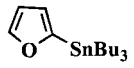
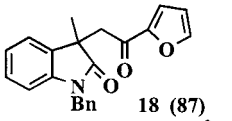
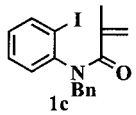
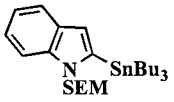
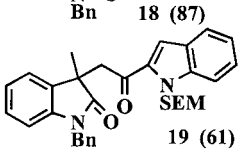
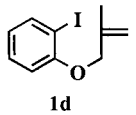
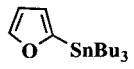
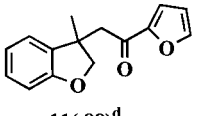
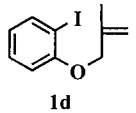
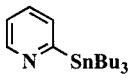
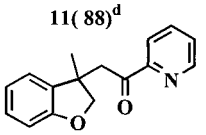
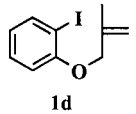
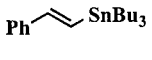
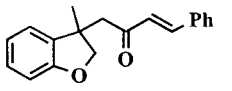
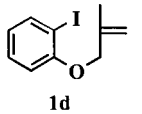
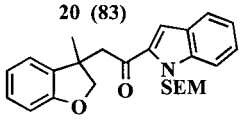
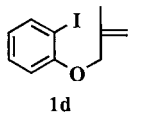
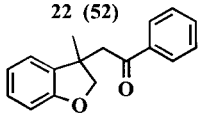
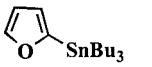
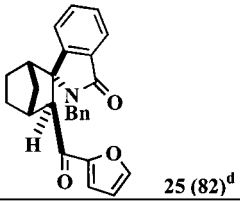
Solvent	Temp (°C)	Ratio 10 : 11
toluene	90	2 : 1
toluene	90	2 : 1
xylene	110	0 : 100

Scheme 5.



Scheme 6.

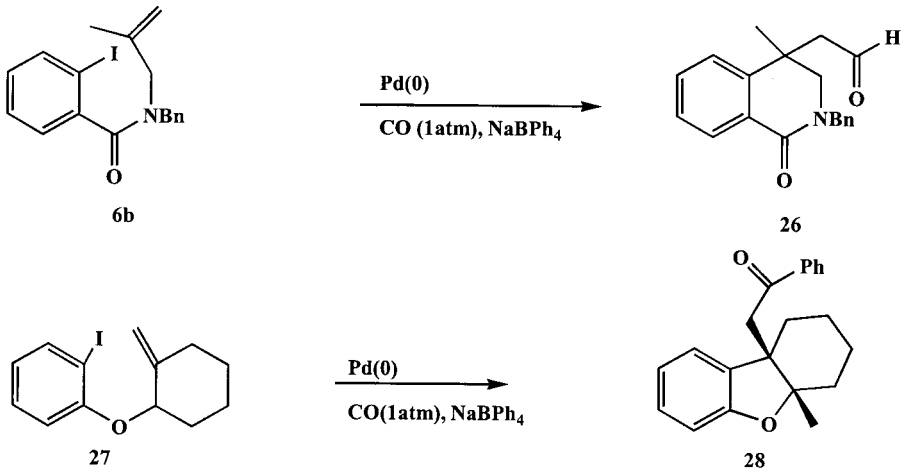
Table 3. Termolecular queuing cascades with CO (1 atm) and anion transfer from Sn(IV) and B

Substrate	Anion transfer agent	Product (%)
 1a		 16 (71)
 1a	$NaBPh_4$	 17 (82)
 1c		 18 (87)
 1c		 19 (61)
 1d		 11(88)[d]
 1d		 20 (83)
 1d		 20 (83)
 1d		 22 (52)
 1d	$NaBPh_4$	 23 (80)
 24		 25 (82)[d]

[a] Reactions carried out in toluene at 110°C, for 15 h, unless otherwise noted, using a catalyst system comprising 10 mol% $Pd(Oac)_2$, 20 mol% PPh_3, Et_4NCl (1 equiv).
[b] Reactions carried out in anisole at 110°C for 15 h employing a catalyst system comprising 10 mol% $Pd(Oac)_2$, 20 mol% tri(2-furyl) phosphine.
[c] Isolated yields.
[d] Xylene as solvent (see Scheme 5).

posed a threat of competition between cyclization and direct hydride capture (Scheme 4). However, this did not materialize and **7a** and **7b** were obtained in 61 and 54% yield, respectively (Table 2).

One example of the tetramolecular cyclocarboformylation has been studied thus far which illustrates the relay switch principle. Thus **8** reacts (toluene, 110°C, 7 h) with the standard catalyst system to give **9** (45%). In this double



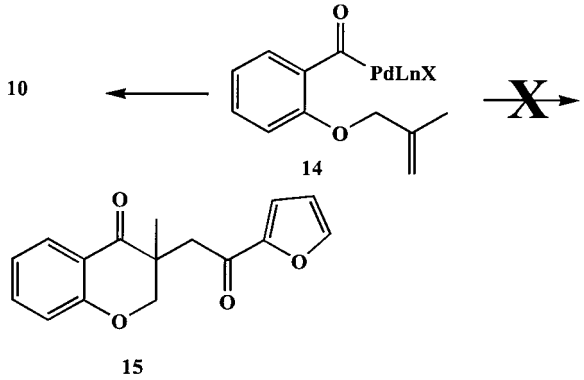
Scheme 7.

carbonylation process the incorporation of the first carbon monoxide (intermolecular) is followed by a 5-*exo*-trig cyclization (intramolecular) and then two further intermolecular steps. The first carbonylation step uprates a kinetically unfavourable 4-*exo*-trig process to a favourable 5-*exo*-trig process.

2.2. Cascades terminating with Sn(IV) and B reagents

2.2.1. 5-*exo*-Trig processes. A second series of termolecular queuing processes has been evaluated in which CO is combined with preformed organostannanes or $NaBPh_4$. Previous studies (above) had established that CO (1 atm) insertion occurs at a faster rate than hydride capture with $Ph_2Si(Me)H$. This order need not necessarily be maintained in competition with organostannanes and $NaBPh_4$. For example, the outcome of the reaction of **1c** with CO (1 atm) and 2-furyltributylstannane (1.1 mol equiv.) using the same catalyst system described above was found to be solvent and temperature dependent (Scheme 5).

Thus there is competition between the desired molecular queuing process giving **11** and the corresponding direct capture sequence furnishing **10**. Increasing the temperature to 110°C with xylene as the solvent, organized the molecular queue allowing the reaction to proceed exclusively to the desired product **11** in 88% yield. It is interesting to note that no products lacking incorporation of carbon monoxide were detected. The intriguing variation of selectivity for **10** versus **11** is clearly mechanism based.



The key steps in the formation of **10** and **11** are migratory insertions from intermediates such as **12** and **13** (Scheme 6). These migratory insertions are expected to be solvent or ligand driven. Toluene cannot function in such a role. This role is therefore assumed by either PPh_3, CO or Cl^- (from Et_4NCl)[12] together with, in the case of organostannanes, the possible influence of, the in situ generated Lewis acid Bu_3SnX.

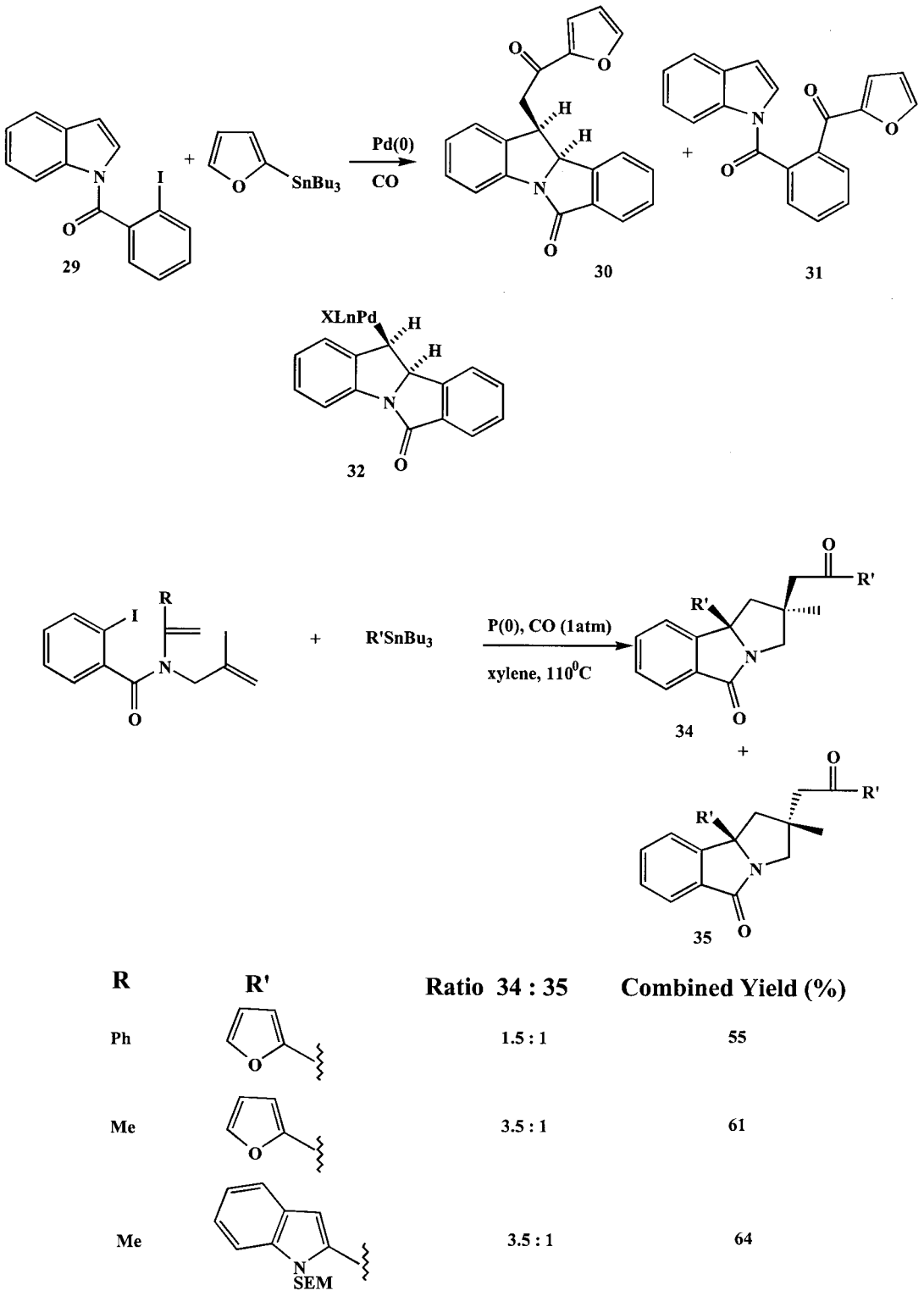
Solvent and temperature, as discussed above, will control the concentration of CO in solution and influence the concentration of **12**, **13** and related species. In this context it is instructive that the corresponding tetramolecular queuing product **15** was not observed in the solvent/temperature study summarized in Scheme 5. Thus the rate of 6-*exo*-trig acylpalladation is slower than anion capture for intermediate **14** in toluene at 90°C with 1 atm of CO.

Following these studies we extended the termolecular queuing processes to a variety of starter species, organostannanes and $NaBPh_4$ (Table 3).

All the processes in Table 3 form well-ordered queues and, apart from **24→25**, involve the formation of three new bonds, one tetrasubstituted carbon centre and one ring. The conversion of **24** to **25** proceeds via cyclization of the arylpalladium(II) species onto the least hindered face of the norbornene and results in the creation of an additional stereocentre. Whilst the sp^3–sp^2 Stille type coupling reactions proceed most efficiently in toluene or xylene, the reactions involving $NaBPh_4$ proceeded most effectively in anisole.[2,13]

It is instructive to note that whilst formation of **25** from **24** occurs in excellent yield the corresponding two component [**24**+tributyl(2-furyl)stannane] non-carbonylative cascade occurs in poor yield (32%).[2] Thus, CO insertion is less sterically demanding than transmetallation, and by interposing CO the transmetallation is moved further away from the steric congestion posed by the bicyclo[2.2.1] heptane skeleton and its spirocyclic substituent.

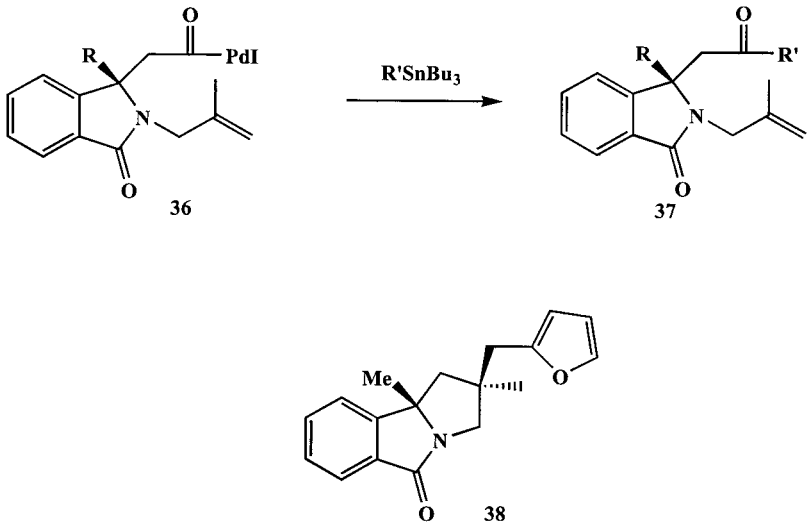
2.2.2. 6-*exo*-Trig processes. Two examples of the termolecular queuing cascade involving an initial 6-*exo*-trig



Scheme 8.

cyclization have been explored; both involve $NaBPh_4$ as the anion transfer agent. Thus **6b** reacts (anisole, 120°C, 15 h) with $NaBPh_4$ using the usual catalyst system (Table 3, footnote b) to give **26** (60%) and **27** reacts under analogous conditions to give **28** (84%) (Scheme 7). The *cis*-ring junction stereochemistry in the latter case was assigned from n.O.e. data (see Experimental).

2.2.3. Bis-cyclization processes. *N*-(2-Iodobenzoyl)indole **29** was prepared by acylation of indole (NaH, DMF) in 76% yield. Reaction of **29** (xylene, 110°C) with CO (1 atm) and 2-furyltributylstannane using the usual catalyst system (Table 3, footnote a) afforded the desired product **30** in 32% yield together with direct capture product **31** (NMR).



Scheme 9.

The desired process would appear to suffer from two inherent problems. Firstly, the 5-*exo*-trig cyclization onto the aromatic indole system is understandably slow. Secondly the reactivity of the resulting secondary alkylpalladium(II) intermediate **32** is sterically compromised by its bowl shape and the peri-H (H_A). Product **31** is unusual in that it is the only product involving cyclization onto a double bond in an aromatic system observed to date.

Enamides **34a,b** proved more effective substrates for the bis-cyclization termolecular queuing cascades (Scheme 8) using the catalyst system described above.

The molecular queue in the enamide systems **33a,b** could undergo carbonylation and $R'SnBn_3$ capture at the monocyclization stage **36→37**. Such products are present in some cases but always in <20% yield. The major diastereoisomer **34** is always the one with a *cis*-relationship between the ring junction R group and the R^1COCH_2 moiety. However, the diastereoselectivity of these processes is lower than that observed for the analogous cyclization–anion capture process proceeding without carbonylation. Thus for **33a** a diastereomer ratio of 3:1 was observed, whilst **33b** gave a 5:1 diastereomer ratio for formation of **39**.[2] The lower diastereoselectivity observed in Scheme 8 may be occasioned by the higher temperatures (110°C) for Scheme 8 versus that (90°C) for **38** (Scheme 9).[2] The possible transition states for the second cyclization in the formation of **38** have been discussed previously.[14]

In summary, the relay switch concept provides significant enhancement of the original cyclization–anion capture concept. Cyclocarboformylation can be achieved regioselectively and provides novel access to cyclic acetaldehyde derivatives. Analogous cyclization–carbonylation–anion capture processes occur with organostannanes and $NaBPh_4$ and signpost many further developments of Table 1.

3. Experimental

Melting points were determined on a Koffler hot-stage apparatus and are uncorrected. Infrared spectra were recorded on Perkin-Elmer Model 598 and 983G instruments and refer to films unless otherwise noted. Mass spectral data were obtained from a VG AutoSpec operating at 70 eV. Nuclear magnetic resonance spectra were recorded on Bruker QE 300 and AM 400 machines operating at 300 and 400 MHz, respectively. Unless otherwise specified, deuterochloroform was used as solvent with tetramethylsilane as internal standard. Microanalyses were obtained using a Carlo Erba MOD 11016 instrument. Thin layer chromatography was carried out on Whatman PESIL G/UV polyester plates coated with a 0.2 mm layer of silica-gel and column chromatography was performed with silica-gel 60 (Merck 9385). Anhydrous DMF was commercially available (Aldrich), THF was sodium dried under a nitrogen atmosphere and *n*-hexane was distilled prior to use. Non-commercially available organotin(IV) compounds were synthesized according to known methods.[15] Precursors **1a–d**, **6a,b**, **25** and **34b** were prepared as previously described (see Ref. 2 and earlier papers).

3.1. Cyclization precursors

3.1.1. 2-Methallyliodobenzene 8. Prepared by adaptation of a literature method.[16] Anhydrous benzene (15 ml) was added to a freshly prepared solution of 2-propenylmagnesium bromide (20 mmol) in THF (100 ml). A mixture of 2-iodobenzyl chloride (5.04 g, 20 mmol), CuI (0.38 g, 2 mmol) and 2,2-bipyridyl (0.31 g, 2 mmol) in benzene (10 ml) was prepared under N_2 in a 250 ml flask with stirring at 0°C. The propenylmagnesium bromide solution was transferred by cannula as rapidly as possible into the stirred 2-iodobenzyl chloride mixture causing a gentle reflux. The reaction was allowed to reach room temperature and stirred for 4 h before solid NH_4Cl was added followed by ether (100 ml) and water (100 ml). The mixture was transferred to a beaker, conc. NH_3 (1.5 ml) added, the mixture stirred for 1.5 h, the layers separated and the aqueous phase extracted with ether (3×50 ml). The combined ether extracts were washed successively with 2 M HCl (40 ml) and sat. $NaHCO_3$ solution (50 ml), dried ($MgSO_4$) and the solvent

removed in vacuo. The residue was then purified by column chromatography eluting with petroleum ether to afford the product (2.43 g, 47%) as a colourless oil. (Found: C, 46.35; H, 4.15. $C_{10}H_{11}I$ requires: C, 46.55; H, 4.25%); δ 7.85 (d, 1H, J=7 Hz, ArH), 7.35–7.20 (m, 2H, ArH), 6.91 (dt, 1H, J=5.0 and 2.0 Hz, ArH), 4.90 and 4.57 (2×s, 2×1H, C=CH_2), 3.25 (s, 2H, $ArCH_2$) and 1.79 (s, 3H, Me); *m/z* (%) 258 (M^+, 86), 131 (100), 116 (43) and 91 (44).

3.1.2. 2-(2′-Iodophenyloxy)cyclohexanone 28 (with Dr V. Santhakumar). Sodium methoxide (68 mg, 1.25 mmol) was added to a solution of iodophenol (0.275 g, 1.25 mmol) in methanol (10 ml) and the mixture stirred at room temperature for 10 min. The solvent was then removed and the residue dissolved in ether (25 ml) and chlorocyclohexanone (0.165 g, 1.25 mmol) in dry ether (5 ml) added dropwise over 5 min with stirring. Stirring was then continued at room temperature for 2 h, then ether (50 ml) was added and the mixture washed with water (15 ml), dried ($MgSO_4$) and solvent removed. The residue was purified by flash chromatography eluting with 1:4 v/v ether–petroleum ether to afford the product (0.21 g, 53%) as colourless needles from ether–petroleum ether, mp 92–93°C. (Found: C, 45.6; H, 4.2. $C_{12}H_{13}IO_2$ requires: C, 45.6; H, 4.15%); δ 7.76 and 7.23 (2×m, 2×1H, ArH), 6.71 (m, 2H, ArH), 4.62 (t, 1H, OCH), and 2.37–1.68 (m, 8H, 4×CH_2); *m/z* (%) 316 (M^+, 43), 220 (99), 189 (100) and 121 (38); ν_{max} (nujol) 1735, 1585, 1480, 1395, 1295 and 1265 cm^{-1}.

3.1.3. *N*-(2-Iodobenzoyl)-indole 29. Indole (10 g, 0.085 mol) in DMF (50 ml) was added dropwise over 0.25 h to a suspension of NaH (4.11 g, 0.087 mol, 50% weight in oil) at 0°C in anhydrous DMF (200 ml). 2-Iodobenzoyl chloride (22.65 g, 0.085 mol) in DMF (50 ml) was then added dropwise over 0.5 h and the resulting mixture stirred for 2 h at room temperature, the solvent removed under vacuo, the residue dissolved in ether (300 ml) and washed successively with water (150 ml), brine (150 ml) and dried ($MgSO_4$). The ether was then removed in vacuo and the residue crystallized from ether–petroleum ether to yield the product (22.41 g, 76%) as colourless prisms, mp 94–95°C. (Found: C, 52.05; H, 2.9; N, 3.85. $C_{15}H_{10}INO$ requires: C, 51.9; H, 2.9; N, 4.05%); δ 8.4–7.0 (m, 8H, ArH), 6.8 (d, 1H, indole-2-H) and 6.5 (d, 1H, indole-3-H); *m/z* (%) 347 (M^+, 48), 231 (100), 219 (23), 203 (29) and 76 (40).

3.2. General procedure for cyclocarboformylation

Carbon monoxide was bubbled through a mixture of the substrate (0.25 g), diphenylmethylsilane (2 equiv.), tetraethylammonium chloride (1 equiv.) and a catalyst system comprising $Pd(OAc)_2$ (10 mol%) and PPh_3 (20 mol%) in dry toluene (15 ml) for 10 min. The reaction mixture was then heated at 90°C with stirring over 7 h under an atmosphere of carbon monoxide (balloon). After this time the mixture was filtered and the solvent removed under reduced pressure. The residue was taken up in diethyl ether, washed with water (2×10 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography to afford the product.

3.2.1. 1-Benzenesulphonyl-3,3-dimethyl-2,3-dihydro-1*H*-indole 4a.[17] Prepared by the general procedure for **1a** (0.25 g, 0.6 mmol) but using sodium formate (1 equiv.) as the hydride source. The reaction was carried out at 110°C for 18 h. Purification by flash chromatography eluting with 1:2 v/v petroleum ether–diethyl ether afforded the product (0.12 g, 70%) as a colourless oil. δ 7.80–7.03 (m, 9H, ArH), 3.65 (s, 2H, NCH_2) and 1.10 (s, 6H, 2×CH_3).

3.2.2. (1-Benzenesulphonyl-3-methyl-2,3-dihydro-1*H*-indole-3-yl)-acetaldehyde 2a and (1-benzensulphonyl-3-methyl-2,3-dihydro-1*H*-indole-3-yl)-acetic acid 5a. Prepared from **1a** (0.25 g, 0.6 mmol) by the general procedure. Purification of the residue by flash chromatography eluting with 1:1 v/v petroleum ether–diethyl ether and subsequent crystallization from petroleum ether–diethyl ether afforded the product **2a** (0.115 g, 61%) as pale brown plates, mp 89–89.5°C. (Found: C, 64.65; H, 5.2; N, 4.6; S, 10.25. $C_{17}H_{17}NO_3S$ requires: C, 64.75; H, 5.45; N, 4.6; S, 10.15%); δ 9.55 (s, 1H, CHO), 7.83 (d, J=7.6 Hz, 2H, ArH), 7.69 (d, J=8.2 Hz, 1H, ArH), 7.56 (d, J=7.7 Hz, 1H, ArH), 7.46 (m, 2H, ArH), 7.25 (m, 1H, ArH), 7.03 (m, 2H, ArH), 3.91 and 3.75 (2×d, J=11.0 Hz, 2×1H, NCH_2), 2.66 and 2.39 (2×d, J=17.0 Hz, 2×1H, CH_2CO) and 1.22 (s, 3H, CH_3); *m/z* (%) 315 (M^+, 25), 272 (53), 146 (43), 130 (100), 103 (14), 77 (90) and 51 (25); ν_{max} (nujol) 3040 (m), 3000 (m), 2900 (m), 1730 (w), 1230 (s), 1150 (s) and 750 (s).

3.2.3. Carboxylic acid 5a. Not isolated. Characterized from the PMR spectrum of the mixture. δ 7.80–7.10 (m, 9H, ArH), 4.15 and 3.77 (2×d, J=11.7 Hz, 2×1H, NCH_2), 2.54 and 2.29 (2×d, J=17.5 Hz, 2×1H, CH_2CO_2) and 1.20 (s, 3H, Me).

3.2.4. (1-Benzenesulphonyl-3-methoxycarbonyl-2,3-dihydro-1*H*-indole-3-yl)-acetaldehyde 2b. Prepared from **1b**. Purification of the residue by flash chromatography eluting with 1:1 v/v petroleum ether–diethyl ether afforded the product (40%) as colourless prisms, mp 103–104.5°C. (Found: C, 60.1; H, 4.7; N, 3.9; S, 8.85. $C_{18}H_{17}NO_5S$ requires: C, 60.15; H, 4.75; N, 3.9; S, 8.9%); δ 9.61 (s, 1H, CHO), 7.85 (d, J=7.9 Hz, 2H, ArH), 7.69 (d, J=8.2 Hz, 1H, ArH), 7.59 (m, 1H, ArH), 7.48 (m, 2H, ArH), 7.30–7.01 (m, 3H, ArH), 4.73 and 3.79 (2×d, J=11.8 Hz, 2×1H, NCH_2), 3.52 (s, 3H, CH_3), 3.39 and 2.51 (2×d, J=18.9 Hz, CH_2CHO); *m/z* (%) 359 (M^+, 28), 315 (16), 300 (23), 258 (21), 190 (19), 159 (30), 130 (100), 116 (9), 103 (18), 77 (84) and 51 (17); ν_{max} 2950 (m), 1670 (brs), 1300 (m), 1210 (s) and 1110 (s).

3.2.5. (*N*-Benzyl-3-methyloxindol-3-yl)-acetaldoxime 2c (oxime). Prepared from **1c** but worked up without chromatography. The residue was stirred for 15 h in 5:1 v/v methanol–water with sodium acetate (1.4 mol equiv.) and hydroxylamine hydrochloride (1.4 mol equiv.). Methanol was then removed and the aqueous mixture extracted with DCM (2×20 ml). The organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure to afford the product (40% overall) as a pale yellow oil which comprised a 1:1 mixture of *syn*- and *anti*-oximes. Found (H.R.M.S.): 294.2853. $C_{18}H_{18}N_2O_2$ requires: 294.2814; *m/z* (%) (mixed isomers) 294 (M^+, 43), 276

(14), 236 (75), 206 (7), 130 (12), 91 (100) and 65 (18); δ (*syn*-oxime) 7.35–7.17 (m, 8H, ArH and N=CH), 7.06 and 6.73 (2×d, J=7.9 Hz, 2×1H, ArH), 5.01 and 4.85 (2×d, J=15.7 Hz, 2×1H, $PhCH_2N$), 2.77 and 2.71 (2×dd, J=15.9 and 8.1 Hz, 2×1H, N=CCH_2), 1.47 (s, 3H, Me); δ (*anti*-oxime) 8.4 (brs, 1H, OH), 7.35–7.17 (m, 7H, ArH), 7.01 (t, J=8.4 Hz, 1H, ArH), 6.79 (d, J=8.5 Hz, 1H, ArH), 6.51 (t, J=5.3 Hz, 1H, N=CH), 4.88 and 4.95 (2×d, J=13.5 Hz, 2×1H, $PhCH_2N$), 3.02 and 2.90 (2×dd, J=15.7 and 4.3 Hz, 2×1H, N=CCH_2), 1.49 (s, 3H, Me).

3.2.6. (3-Methyl-2,3-dihydrobenzofuran-3-yl)-acetaldehyde 2d. Prepared (51%) from **1d** by the general method. The product was obtained as a pale yellow oil. Found (H.R.M.S.): 176.0841. $C_{11}H_{12}O_2$ requires: 176.0837. δ 9.69 (s, 1H, CHO), 7.16–6.80 (m, 4H, ArH), 4.42 and 4.33 (2×d, J=11.8 Hz, 2×1H, OCH_2), 2.86 and 2.69 (2×d, J=16.9 Hz, 2×1H, CH_2CHO) and 1.42 (s, 3H, Me); *m/z* (%) 176 (M^+, 38), 161 (17), 133 (100), 119 (15), 105 (80), 91 (15), 77 (22) and 63 (8); ν_{max} (film) 3000 (m), 1720 (s), 1610 (s), 1465 (m), 990 (m) and 750 (m) cm^{-1}.

3.2.7. 2,4-Dinitrophenylhydrazone of 2d. Crystallized as orange prisms from EtOH, mp 176–178°C. (Found: C, 57.0; H, 4.3; N, 15.85. $C_{17}H_{16}N_4O_5$ requires: C, 57.3; H, 4.55; N, 15.7%); δ 9.11 (s, 1H, ArH), 8.30 (d, J=9.5 Hz, 1H, ArH), 7.85 (d, J=9.6 Hz, 1H, ArH), 7.18–6.82 (m, 4H, ArH), 4.49 and 4.23 (2×d, J=8.5 Hz, 2×1H, CH_2O), 2.74 and 2.7 (2×s, 2×1H, CH_2C=N) and 1.50 (s, 3H, Me); *m/z* (%) 356 (M^+, 1), 322 (2), 281 (2), 224 (2), 190 (2) 176 (3), 133 (100), 105 (84) and 77 (30); ν_{max} (nujol) 3140 (m), 2390 (w), 1540 (m), 1520 (m), 1280 (s), 1210 (s) and 840 (m) cm^{-1}.

3.2.8. (4-Methylchroman-4-yl)-acetaldehyde 7a. Prepared (61%) from **6a** as a colourless oil. (Found: C, 75.85; H, 7.25. $C_{12}H_{14}O_2$ requires: C, 75.75; H, 7.4%); δ 9.62 (t, J=2.8 Hz, 1H, CHO), 7.11 (m, 2H, ArH), 6.87 (m, 2H, ArH), 4.24 (m, 2H, CH_2O), 2.78 and 2.69 (2×dd, J=15.4 and 2.5 Hz, 2×1H, CH_2=O), 2.11 (ddd, J=17.4, 6.2 and 3.2 Hz, 1H, CH_2CH_2O), and 1.46 (s, 3H, Me); *m/z* (%) 190 (M^+, 55), 147 (100), 131 (21), 119 (13), 115 (19), 91 (72), 77 (20) and 65 (11); ν_{max} (film) 2650 (m), 1670 (s), 1560 (m), 1535 (m), 1440 (s), 1400 (s) and 710 (s) cm^{-1}.

3.2.9. (*N*-Benzyl-4-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-acetaldehyde 7b. Column chromatography eluting with 4:1 v/v ether–petroleum ether afforded the product (54%) as a pale yellow oil. Found (H.R.M.S.) (electrospray): 316.1323. $C_{19}H_{19}NO_2$+Na requires: 316.1313. δ 9.32 (t, 1H, J=2.4 Hz, CHO), 8.2–7.2 (m, 9H, ArH), 4.84 and 4.66 (2×d, 2×1H, J=13.35 Hz, NCH_2Ph), 3.42 and 3.6 (2×d, 2×1H, J=12.8 Hz, NCH_2), 2.5 (m, 2H, CH_2CO) and 1.4 (s, 3H, Me); *m/z* (%) 293 (M^+, 17), 265 (38), 145 (60), 120 (24), 91 (100) and 77 (10).

3.2.10. (2-Methyl-1-oxo-indan-2-yl)-acetaldehyde 9. Work up by flash chromatography eluting with 3:1 v/v petroleum ether–ether to afford the product (45%) as a colourless oil. (Found: C, 76.35; H, 6.2. $C_{12}H_{12}O_2$ requires: C, 76.6; H, 6.45%); δ 9.71 (s, 1H, CHO), 7.79 (d, J=7.6 Hz, 1H, ArH), 7.62 (t, J=7.2 Hz, 1H, ArH), 7.59–737 (m, 2H, ArH), 3.18 and 2.99 (2×d, J=17.1 Hz, 2×1H, CH_2), 2.92 and 2.83 (2×d, J=18.3 Hz, 2×1H, CH_2CHO) and 1.25 (s, 3H, Me); *m/z* (%) 188 (M^+, 4), 159 (14), 145 (100), 131 (34), 91 (42), 77 (13), 63 (17) and 51 (14).

3.3. General procedure for cyclization–carbonylation–anion capture cascades with aryl iodides and organostannanes

A mixture of $Pd(OAc)_2$ (0.011 g, 0.05 mmol), PPh_3 (0.026 g, 0.1 mmol), aryl iodide (0.5 mmol), organostannane (0.55 mmol), Et_4NCl (0.083 g, 0.5 mmol) and xylene (5 ml) was saturated with carbon monoxide (CO bubbled into the solution for 5 min). A balloon filled with CO was then attached to the condenser and the mixture stirred and heated at 110°C for 8 h. The mixture was then cooled, the solvent removed in vacuo, the residue dissolved in ether (20 ml), washed with water (10 ml), dried ($MgSO_4$) and the solvent removed. The residue was purified by column chromatography to afford the product.

3.4. General procedure for tetramolecular cascades with sodium tetraphenylborate

A mixture of $Pd(OAc)_2$ (0.011 g, 0.05 mmol), PPh_3 (0.026 g, 0.1 mmol), aryl iodide (0.5 mmol), sodium tetraphenylborate (0.188 g, 0.55 mmol) and anisole (5 ml) was saturated with carbon monoxide (CO bubbled into the solution for 5 min). A balloon filled with CO was then attached to the condenser and the mixture stirred and heated at 110°C for 15 h. The mixture was then cooled, the solvent removed in vacuo, the residue dissolved in ether (20 ml), washed with water (10 ml) and dried ($MgSO_4$). The solvent was then removed and the residue purified by column chromatography.

3.4.1. 2-(1-Benzenesulphonyl-3-methyl-2,3-dihydro-1*H*-indole-3-yl)-1-(pyridin-2′-yl)-ethanone 16. Column chromatography eluting with 3:7 v/v ether–petroleum ether afforded the product (71%) as colourless prisms, mp 65–67°C from ether–petroleum ether. (Found: C, 63.6; H, 4.4; N, 6.75. $C_{22}H_{20}N_2O_3S{\cdot}H_2O$ requires: C, 63.9; H, 4.8; N, 6.8%); δ 8.6 (brs, 1H, py-H), 8.0–7.0 (m, 12H, ArH, py-H), 4.13 and 3.9 (2×d, 2H, J=11 Hz, NCH_2), 3.8 and 3.0 (2×d, 2×1H, J=17.7 Hz, CH_2CO) and 1.2 (s, 3H, Me); *m/z* (%) 392 (M^+, 5), 271 (63), 144 (32), 130 (97), 121 (100), 78 (50) and 51 (19).

3.4.2. 2-(1-Benzenesulphonyl-3-methyl-2,3-dihydro-1*H*-indol-3-yl)-1-phenyl-ethanone 17. Column chromatography eluting with 1:9 v/v ether–petroleum ether afforded the product (82%) as colourless prisms, mp 98–100°C. (Found: C, 70.3; H, 5.55; N, 3.4. $C_{23}H_{21}NO_3S$ requires: C, 70.58; H, 5.35; N, 3.6%); δ 8.0–7.0 (m, 14H, ArH), 4.1 and 3.9 (2×d, 2H, J=10.8 Hz, NCH_2), 3.3 and 2.8 (2×d, 2H, J=17.5 Hz, CH_2CO) and 1.25 (s, 3H, Me); *m/z* (%) 391 (M^+, 3), 271 (100), 130 (93), 105 (47) and 73 (64).

3.4.3. *N*-Benzyl-3-(2-furan-2-yl-2-oxo-ethyl)-3-methyl-1,3-dihydroindol-2-one 18. Column chromatography eluting with 2:3 v/v ether–petroleum ether afforded the product (87%) as colourless prisms, mp 104–105°C. (Found: C, 76.5; H, 5.65; N, 4.1. $C_{22}H_{19}NO_3$ requires: C, 76.5; H, 5.5; N, 4.05%); δ 7.6–7.11 (m, 9H, ArH+1×furyl-H), 6.93 (d, 1H, J=6 Hz, ArH), 6.71 and 6.49 (2×d, 2×1H,

J=3 and 2 Hz, furyl-H), 5.08 and 4.96 (2×d, AB, 2×1H, J=9 Hz, NCH_2Ph), 3.63 and 3.55 (2×d, AB, 2×1H, J=11 Hz, CH_2CO) and 1.57 (s, 3H, Me); m/z (%) 345 (M^+, 71), 235 (99), 95 (53) and 91 (100); ν_{max} (nujol) 3010, 2905, 1700, 1645 and 1350 cm^{-1}.

3.4.4. 1-Benzyl-3-methyl-3-[2-oxo-2-(1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-indol-2-yl)-ethyl]-indolin-2-one 19. Column chromatography eluting with 3:7 v/v ether–petroleum ether afforded the product (61%) as a colourless oil. (Found: C, 73.35; H, 7.1; N, 5.35. $C_{32}H_{36}N_2O_3Si$ requires: C, 73.3; H, 6.85; N, 5.35%); δ 7.7 (d, 1H, J=8 Hz, ArH), 7.51–7.11 (m, 10H, ArH+indole 3-H), 7.08 (t, 1H, J=7 Hz, ArH), 6.93 (t, 1H, 8 Hz, ArH), 6.69 (d, 1H, J=8 Hz, ArH), 5.87 and 5.79 (2×d, AB, 2×1H, J=11 Hz, NCH_2O), 5.07 and 4.95 (2×d, AB, 21×1H, J=15 Hz, NCH_2Ph), 3.80 and 3.70 (2×d, AB, 2×1H, J=17 Hz, CH_2CO), 3.24 (t, 2H, J=8 Hz, OCH_2), 1.50 (s, 3H, Me), 0.69 (t, 2H J=8 Hz, CH_2Si) and −0.19 (s, 9H, $SiMe_3$); m/z (%) 524 (M^+, 24), 423 (62), 309 (41), 260 (57), 236 (97), 91 (100) and 73 (83); ν_{max} (film) 3040, 2925, 1695, 1650, 1595 and 1345 cm^{-1}.

3.4.5. 1-Furan-2-yl-2-(3-methyl-2,3-dihydrobenzofuran-3-yl)-ethanone 11. Column chromatography eluting with 1:4 v/v ether–petroleum ether afforded the product (0.107 g, 88%) as a colourless oil. (Found: C, 74.25; H, 5.65. $C_{15}H_{14}O_3$ requires: C, 74.4; H, 5.8); δ 7.55 (s, 1H, furyl-H), 7.17–6.80 (m, 5H, ArH+1×furyl-H), 6.51 (dd, 1H, J=2 Hz, furyl-H), 4.6 and 4.43 (2×d, AB, 2×1H, J=9 Hz, OCH_2), 3.39 and 3.05 (2×d, AB, 2×1H, J=16 Hz, CH_2CO) and 1.47 (s, 3H, Me); m/z (%) 242 (M^+, 13), 227 (15), 132 (100), 110 (71), 105 (62) and 95 (46); ν_{max} (film) 2940, 2855, 1645, 1480 cm^{-1}.

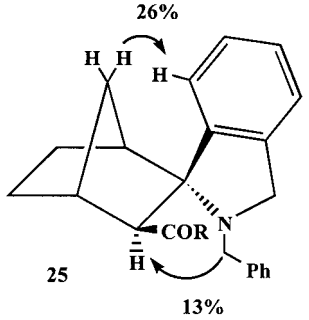
3.4.6. 2-(3-Methyl-2,3-dihydrobenzofuran-3-yl)-1-pyridin-2-yl-ethanone 20. Column chromatography eluting with 3:7 v/v ether–petroleum ether afforded the product (83%) as a pale yellow oil. (Found: C, 73.0; H, 5.5; N, 5.65. $C_{16}H_{15}NO_2{\cdot}0.5H_2O$ requires: C, 73.3; H, 5.35; N, 5.7%); δ 8.59 (br s, 1H, py-H), 7.9–6.7 (m, 7H, ArH), 4.51 (br s, 2H, OCH_2), 3.97 and 3.37 (2×d, 2×1H, J=17.4 Hz, CH_2CO) and 1.28 (s, 3H, Me); m/z (%) 253 (M^+, 11), 133 (25), 121 (100), 93 (35) and 78 (51).

3.4.7. (*E*)-1-(3-Methyl-2,3-dihydrobenzofuran-3-yl)-4-phenyl-but-3-en-2-one 21. Column chromatography eluting with 3:7 v/v ether–petroleum ether afforded the product (61%) as a colourless oil. (Found: C, 81.75; H, 6.35. $C_{19}H_{18}O_2$ requires: C, 82.0; H, 6.5%); δ 7.35–6.8 (m, 10H, ArH+=CHPh), 6.58 (d, 1H, J=15 Hz, COCH=), 4.74 and 4.58 (2×d, AB, 2×1H, J=8 Hz, OCH_2), 3.51 and 3.28 (2×d, AB, 2×1H, J=15 Hz, CH_2CO) and 1.61 (s, 3H, Me); m/z (%) 278 (M^+, 5), 263 (7), 146 (56), 132 (100) and 105 (72); ν_{max} (film) 2995, 2900, 1630, 1480 and 1450 cm^{-1}.

3.4.8. 2-(3-Methyl-2,3-dihydrobenzofuran-3-yl)-1-[1-(2-trimethylsilanylethoxymethyl)-1*H*-indol-2-yl]-ethanone 22. Column chromatography eluting with 1:4 v/v ether–petroleum ether afforded the product (52%) as a colourless oil. (Found: C, 71.05; H, 7.55; N, 3.35. $C_{25}H_{31}NO_3Si$ requires: C, 71.25; H, 7.35, N, 3.35%); δ 7.75 (d, 1H, J=7 Hz, ArH), 7.63 (d, 1H, J=9 Hz, ArH), 7.48 (t, 1H, J=7 Hz, ArH), 7.39–6.89 (m, 6H, ArH+indole-3-H), 6.07 (s, 2H, NCH_2O), 4.75 and 4.55 (2×d, AB, 2×1H, J=9 Hz, $ArOCH_2$), 3.61 (m, 2H, OCH_2), 3.5 and 3.3 (2×d, AB, 2×1H, J=16 Hz, CH_2CO), 1.58 (s, 3H, Me), 0.95 (m, 2H, CH_2Si), and 0.0 (s, 9H, $SiMe_3$); m/z (%) 421 (M^+, 7), 406 (6), 171 (68), 133 (100), 105 (77) and 73 (91); ν_{max} (film) 2940, 2874, 1650 and 1480 cm^{-1}.

3.4.9. 2-(3-Methyl-2,3-dihydrobenzofuran-3-yl)-1-phenyl-ethanone 23. Column chromatography eluting with 3:7 v/v ether–petroleum ether afforded the product (80%) as colourless needles from ether–petroleum ether, mp 78–80°C. (Found: C, 81.0; H, 6.55. $C_{17}H_{16}O_2$ requires: C, 80.95; H, 6.35%); δ 7.9–6.8 (m, 9H, ArH), 4.56 (s, 2H, OCH_2), 3.6 and 3.2 (2×d, 2×1H, J=17.5 Hz, OCH_2) and 1.4 (s, 3H, Me); m/z (%) 252 (M^+, 2), 237 (5), 132 (43), 105 (93), 77 (100) and 51 (41).

3.4.10. 3-(2-Furanylcarbonyl)-2′-phenylmethyl-spiro[bicyclo[2.2.1]heptane-2,1′-[1*H*]isoindole]-3′(2′*H*)-one 25. Chromatography eluting with 2:3 v/v ether–petroleum ether afforded the product (82%) as colourless prisms, mp 202–204°C. (Found: C, 78.7; H, 6.05; N, 3.4. $C_{26}H_{23}NO_3$ requires: C, 78.6; H, 5.8; N, 3.55%); δ 7.57 (d, 1H, J=7 Hz, ArH), 7.46 (d, 1H, J=8 Hz, ArH), 7.39–7.21 (m, 8H, ArH, 1×furyl-H), 6.53 (d, 1H, J=3 Hz, furyl-H), 6.13 (m, 1H, furyl-H), 5.29 and 4.69 (2×d, AB, 2×1H, J=16 Hz, NCH_2Ph), 3.62 (d, 1H, J=3 Hz, CHCO furyl), 2.97 (d, 1H, J=5.0 Hz, CHCHCO furyl), 2.4 (d, 1H, J=3 Hz, CHCNBn), 2.70 and 1.61 (m, 2×1H, CH_2) and 1.9–1.43 (m, 4H, CH_2CH_2); n.O.e data.



3.4.11. *N*-Benzyl-4-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl-1-phenyl-ethanone 26. Column chromatography eluting with 3:7 v/v ether–petroleum ether followed by crystallization from ether–petroleum ether afforded the product (60%) as colourless prisms, mp 68–70°C. (Found: C, 81.05; H, 6.3; N, 3.5. $C_{25}H_{23}NO_2$ requires: C, 81.3; H, 6.25; N, 3.8%); δ 8.1–7.06 (m, 14 H, ArH), 4.74 and 4.71 (2×d, 2H, J=14.5 Hz, NCH_2Ph), 3.75 and 3.71 (2×d, 2×1H, J=12.7 Hz, NCH_2), 3.17 and 2.97 (2×d, 2×1H, J=16.5 Hz, CH_2CO) and 1.49 (s, 3H, Me); m/z (%) 369 (M^+, 12), 286 (15), 249 (100) 105 (74), 91 (95) and 84 (55).

3.4.12. 1-Phenyl-2-(6,7,8,9-tetrahydro-5a*H*-dibenzofuran-9a-yl)-ethanone 28. Column chromatography eluting with 1:1 v/v ether–petroleum ether afforded the product (84%) as a pale yellow oil. Found (H.R.M.S.) (electrospray): 315.1370. $C_{20}H_{20}O_2$+Na requires: 315.1361. δ 7.84–6.8 (m, 9H, ArH), 4.85 (t, 1H, J=5.5 Hz, CHO), 3.35 and

3.25 (2×d, 2H, J=16.3 Hz, CH_2COPh) and 2.0–1.2 (m, 8H, $(CH_2)_4$); m/z (%) 292 (M^+, 5), 249 (16), 172 (100), 144 (28), 105 (25), 91 (16) and 77 (18).

3.4.13. 11-(2-Furan-2-yl-2-oxo-ethyl)-10b, 11-dihydro-isoindolo[2,1-a]-indol-6-one 30. Column chromatography eluting with 2:3 v/v ether–petroleum ether afforded the product (32%) as colourless needles, mp 142–144°C. Found (H.R.M.S.): 315.0900. $C_{20}H_{13}NO_3$ requires: 315.0895. δ 7.86–7.22 (m, 7H, ArH), 7.52 (d, 1H, J=1.0 Hz, furyl-H), 7.09 (t, 1H, J=7.0 Hz, ArH), 6.87 (d, 1H, J=3.0 Hz, furyl-H), 6.43 (dd, 1H, J=1.0, 3.0 Hz, furyl-H), 5.84 (d, 1H, J=8.0 Hz, NCH) and 5.17 (d, 1H, J=8.0 Hz, CHCO); m/z (%) 315 (M^+, 31), 220 (100), 165 (33) and 95 (15); ν_{max} (nujol) 3010, 1690, 1650 and 1430 cm^{-1}.

3.4.14. Compound 34a/35a. Column chromatography eluting with 1:1 v/v ether–petroleum ether afforded the product (55%) as a colourless viscous oil which comprised a 1.5:1 mixture of diastereomers. Found (H.R.M.S.): 371.1526. $C_{24}H_{21}NO_3$ requires: 371.1521; m/z (%) 272 (M^++1, 46), 261 (100), 220 (46) and 165 (24); ν_{max} (film) 2915, 2845, 1670, 1650, 1450 and 1360 cm^{-1}.

The ^{1}H NMR spectra of the major and minor isomers were obtained from the mixture.

3.4.15. Major isomer 34a. δ 7.78 (d, 1H, J=7.0 Hz, ArH), 7.54–7.20 (m, 9H, ArH+1×furyl-H), 6.99 (d, 1H, J=3.0 Hz, furyl-H), 6.47 (dd, 1H, J=1.0 and 2.0 Hz, furyl-H), 4.1 and 3.28 (2×d, AB, 2×1H, J=12.0 Hz, NCH_2), 3.07 and 2.04 (2×d, AB, 2×1H, J=13.0 Hz, CH_2C(Me)), 2.81 and 2.70 (2×d, AB, 2×1H, J=16.0 Hz, CH_2CO) and 1.16 (s, 3H, Me).

3.4.16. Minor isomer 35a. δ 7.77 (d, 1H, J=7.0 Hz, ArH), 7.56–7.25 (m, 9H, ArH+1×furyl-H), 7.07 (d, 1H, J=3.0 Hz, furyl-H), 6.47 (dd, 1H, J=1.0 and 2.0 Hz, furyl-H), 4.17 and 3.18 (2×d, AB, 2×1H, J=12.0 Hz, NCH_2), 2.99 and 2.89 (2×d, AB, 2×1H, J=16.0 Hz, CH_2CO) 2.85 and 2.1 (2×d, AB, 2×1H, J=13.0 Hz, CH_2C(Me)) and 1.01 (s, 3H, Me).

3.4.17. Compound 34b/35b. Column chromatography eluting with 3:2 v/v ether–petroleum ether afforded the product (61%) as a colourless viscous oil which comprised a 3.5:1 mixture of diastereomers. (Found (mixed isomers): C, 73.65; H, 5.85; N, 4.3. $C_{19}H_{19}NO_3$ requires: C, 73.8; H, 6.15; N, 4.55%); m/z (%) (FAB, mixed isomers) 310 (M^++1, 100), 200 (22), 146 (12) and 95 (13); ν_{max} (film) 2950, 1660, 1465 and 1370 cm^{-1}.

The ^{1}H NMR spectra of the major and minor isomers were assigned from the mixture.

3.4.18. Major isomer 34b. δ 7.75–7.32 (m, 4H, Ar-H), 7.56 (m, 1H, furyl-H), 7.18 (d, 1H, J=3.0 Hz, furyl-H), 6.52 (dd, 1H, J=1.0 and 3.0 Hz, furyl-H), 4.01 and 3.31 (2×d, AB, 2×1H, J=12.0 Hz, NCH_2), 3.05 and 3.00 (2×d, AB, 2×1H, J=15.0 Hz, CH_2CO), 2.15 and 1.88 (2×d, AB, 2×1H, J=13.0 Hz, CH_2C(Me)) and 1.52 and 0.85 (2×s, 2×3H, Me).

3.4.19. Minor isomer 35b. δ 7.75–7.32 (m, 5H, Ar-H and 1×furyl-H), 6.89 (dd, 1H, J=0.5, 3.0 Hz, furyl-H), 6.52 (t, 1H, J=2.0 Hz, furyl-H), 4.12 and 3.15 (2×d, AB, 2×1H, J=13.0 Hz, NCH_2), 2.71–2.62 (2×d, AB, 2×1H, J=16.0 Hz, CH_2CO), 2.02 and 1.94 (2×d, AB, 2×1H, J=14.0 Hz, CH_2C(Me)) and 1.54 and 1.39 (2×s, 2×3H, Me).

3.4.20. Compound 34c/35c. Column chromatography eluting with 2:3 v/v ether–petroleum ether afforded the product (64%) as a colourless viscous oil which comprised a 3.5:1 mixture of diastereomers. Found (H.R.M.S., mixed isomers): 488.2512. $C_{29}H_{36}N_2O_3Si$ requires: 488.2495. m/z (%) (mixed isomers) 488 (M^+, 10), 415 (9), 370 (100), 212 (32), 200 (79), 184 (65), 171 (96), 159 (55) and 73 (63); ν_{max} (film) 2955, 1680, 1650, 1365 cm^{-1}.

The ^{1}H NMR spectra of the major and minor isomers were assigned from the mixture.

3.4.21. Major isomer 34c. δ 7.79 and 7.70 (2×d, 2×1H, J=7.0 Hz, ArH), 7.58–7.14 (m, 7H, ArH and indole 3-H), 6.03 (s, 2H, OCH_2N), 4.1 and 3.39 (2×d, AB, 2×1H, J=12.0 Hz, NCH_2), 3.53 (t, 2H, J=8.0 Hz, OCH_2), 3.21 and 3.19 (2×d, AB, 2×1H, J=15.0 Hz, CH_2CO), 2.25 and 1.97 (2×d, AB, 2×1H, J=14.0 Hz, CH_2C(Me)), 1.57 and 0.91 (2×s, 2×3H, Me), 0.88 (m, 2H, CH_2Si), and −0.89 (s, 9H, $SiMe_3$).

3.4.22. Minor isomer 35c. δ 7.83 (d, 1H, J=7.0 Hz, ArH), 7.54–7.14 (m, 7H, ArH), 6.78 (s, 1H, indole 3-H), 5.94 and 5.92 (2×d, AB, 2×1H, J=9.0 Hz, NCH_2O), 4.19 and 3.2 (2×d, AB, 2×1H, J=13.0 Hz, NCH_2), 3.4 (t, 2H, J=9.0 Hz, OCH_2), 2.83 (s, 2H, CH_2CO), 2.15 and 1.94 (2×d, AB, 2×1H, J=14.0 Hz, CH_2C(Me)), 1.59 and 1.44 (2×s, 2×3H, Me), 0.82 (t, 2H, J=8.0 Hz, CH_2Si) and −0.13 (s, 9H, $SiMe_3$).

Acknowledgements

We thank Leeds University, AstraZeneca, Organon and the EPSRC for support.

References

1. For a review see: Grigg, R.; Sridharan, V. *J. Organomet. Chem.* **1999**, *576*, 65–87.
2. Fretwell, P.; Grigg, R.; Sansano, J. M.; Sridharan, V.; Sukirthalingam, S.; Wilson, D.; Redpath, J. *Tetrahedron* **2000**, *56*, 7525–7539.
3. (a) Grigg, R.; Liu, A.; Shaw, D.; Suganthan, S.; Washington, M.; Woodall, D.; Yoganathan, G. *Tetrahedron Lett.*, **2000**, *41*, 7129–7133. (b) Grigg, R.; Sridharan, V. In *Transition Metal Catalysed Reactions*, Davies, S. G., Murahashi, S.-I., Eds.; Blackwell Science: Oxford, 1999; pp 81–97. (c) Gardiner, M.; Grigg, R.; Sridharan, V.; Vickers, N. *Tetrahedron Lett.* **1998**, *39*, 435–438. (d) Grigg, R.; Sridharan, V.; Suganthan, S.; Bridge, A. W. *Tetrahedron* **1995**, *51*, 295–306.
4. Grigg, R.; Brown, S.; Sridharan, V.; Uttley, M. D. *Tetrahedron Lett.* **1998**, *39*, 3247–3250.
5. Burwood, M.; Davies, B.; Diaz, I.; Grigg, R.; Molina, P.;

Sridharan, V.; Hughes, M. *Tetrahedron Lett.* **1995**, *36*, 9053–9056.
6. Brown, S.; Clarkson, S.; Grigg, R.; Sridharan, V. *J. Chem. Soc., Chem. Commun.* **1995**, 1135–1136.
7. Grigg, R.; Redpath, J.; Sridharan, V.; Wilson, D. *Tetrahedron Lett.* **1994**, *35*, 4429–4432.
8. Anwar, U.; Casaschi, A.; Grigg, R.; Sansano, J. M. *Tetrahedron*, **2001**, *57*, 1361–1367.
9. Trzeciak, A. M.; Ziolkowski, J. J. *Coord. Chem. Rev.* **1999**, *192*, 883–900.
10. (a) Reetz, M. T.; Waldvogel, S. R.; Goddard, R. *Heterocycles* **2000**, *52*, 935–938. (b) Roggenbuck, R.; Eidbracht, P. *Tetrahedron Lett.* **1999**, *40*, 7455–7456. (c) Hoffmann, R. W.; Bruckner, D.; Gerusz, V. J. *Heterocycles* **2000**, *52*, 121–124.
11. (a) El Ali, B.; Alper, H. *Synlett* **2000**, 161–171 For a recent review see:. (b) Yamamoto, A.; Kayaki, Y.; Nagayama, K.; Shimizu, I. *Synlett* **2000**, 925–937.
12. Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314–321 For a discussion of the role of R_4NCl and polychloro anionic palladium species see:.
13. (a) Casaschi, A.; Grigg, R.; Sansano, J. M.; Wilson, D.; Redpath, J. *Tetrahedron* **2000**, *56*, 7541–7551. (b) Casaschi, A.; Grigg, R.; Sansano, J. M. *Tetrahedron* **2000**, *56*, 7553–7560.
14. See Ref. 2 for a discussion of the possible transition states for the second cyclization.
15. Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1–669.
16. Parsons, P. J.; Knight, J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 979–984.
17. Burns, B.; Grigg, R.; Santhakumar, V.; Sridharan, V.; Stevenson, P.; Worakun, T. *Tetrahedron* **1992**, *48*, 7297–7320.