ELSEVIER

Journal of Organometallic Chemistry 576 (1999) 65–87

Journal of Organometallic Chemistry

Review

Palladium catalysed cascade cyclisation-anion capture, relay switches and molecular queues☆

Ronald Grigg *, Visuvanathar Sridharan

Molecular Innovation, Diversity and Automated Synthesis (MIDAS) Centre, School of Chemistry, Leeds University, Leeds LS2 9JT, UK

Received 1 August 1998

Abstract

Cyclic carbopalladation can be achieved by a group of related reactions that provide versatile and powerful methodology for the construction of carbocyclic and heterocyclic rings. These ring forming processes are marked by their tolerance of a wide range of functionality together with their ability to process a variety of starter species and to effect cyclisation onto all types of C–C unsaturated bonds. Substantial additional pre- and post-cyclisation functionality can be incorporated via cyclisation-anion capture and/or polycomponent cascades that switch between inter- and intra-molecular processes. The polycomponent cascades can be regarded as proceeding via molecular queuing processes and when gaseous reactants are employed the queuing processes are sensitive to pressure. These wide ranging processes occur with excellent chemo-, regio- and stereo-selectivity and allow incorporation of precisely located complex functionality whilst generating bridged, fused and spirocyclic systems and multiple C–C/C-heteroatom bonds.

Keywords: Palladium; Catalysis; Cyclic carbopalladation; Anion-capture; Carbonylation; Allenes; Heterocyclic synthesis; Polycyclisation

1. Introduction

Organic synthesis is concerned with developing viable processes to useful materials by methods that minimise waste, maximise molecular complexity and are highly selective (regio-, stereo, chiro- and chemo-specific). Cascade processes [1] aspire to meet these criteria. Cascade reactions may be defined as multireaction 'one-pot' sequences in which the first reaction creates the functionality to trigger the second reaction and so on. Cascade reactions are also termed tandem or domino processes by some authors. The concept is not new as Robinson's elegant synthesis of tropinone, albeit in low yield, from succindialdehyde, methylamine and acetone demonstrated in 1917 [2]. However, the last decade has witnessed an increasingly sharper focus on cascade reaction design and implementation, driven by a combination of environmental legislation, economics and the substantial range of highly selective organic reactions now available. Cascade reaction design based on transition metal catalysts in combination with concerted cycloaddition reactions offers the ultimate in clean technology especially if the complex molecules required by the agrochemical and pharmaceutical industries, and increasingly by the fine chemicals industry, can largely be prepared from a series of small 'off-the-shelf' building blocks. Essentially what will be needed to advance this area is a good understanding of the relative rates of potentially competing processes and the development of

☆ This review is dedicated to Professor R.F. Heck who planted the acorn.

* Corresponding author. Fax: +44-113-233-6501.

E-mail address: r.grigg@chem.leeds.ac.uk (R. Grigg)

0022-328X/99/$ - see front matter
PII: S0022-328X(98)01052-3

protocols for selectively promoting/suppressing some of these. This will provide the tools necessary to develop controlled cascades involving combinations of 2, 3, 4…*n* different substrate molecules which switch between intra- and inter- molecular cascade processes. It is clear such processes will offer immense power and startling increases in molecular complexity far outstripping conventional organic synthesis, whilst forcing a critical re-evaluation of protecting group strategies that frequently dominate and complicate sequential organic synthesis.

In our current studies we have particularly selected palladium catalysed processes and their combination with cycloaddition reactions, as areas in which to develop new cascades to interface with each other. Additionally, other core organic reactions may be incorporated leading to extended cascades. Palladium salts and complexes [3] are exceptionally versatile catalysts for the construction of carbon–carbon and carbon-heteroatom bonds and their versatility has been significantly enhanced by a range of recently introduced highly reactive catalysts [4]. Much attention has focused on the Heck reaction [5] due to developments which have considerably extended the scope of this palladium-catalysed vinylation of aryl, heteroaryl, vinyl and benzyl halides. Thus, the Heck reaction has been extended to the synthesis of bridged rings, spirocycles, and tetrasubstituted carbon centres [6–8]. These latter developments and the ongoing high level of activity have been further fostered by the advent of a range of additives which variously enhance the rate of Heck reactions, control the regioselectivity of the β-hydride elimination step, and suppress double bond isomerisation in the product. Thus addition of tetraalkylammonium salts often allow Heck reactions to be carried out at, or near, room temperature in good yield [9], whilst addition of Ag(I) salts [10] or Tl(I) [11] salts can control the direction of β-hydride elimination, suppress double bond isomerisation and influence the reaction rate. Although the Heck reaction has considerable versatility it processes only a small subset of the wide range of chemically distinctive substrates that undergo palladium catalysed processes. Additionally, it suffers from the drawback that, as usually practised, only one C–C bond is made.

2. Palladium catalysed cascade cyclisation-anion capture

The continuing advances in palladium catalysed processes referred to above offer opportunities and challenges to employ palladium catalysts in more cost effective ways. In particular we were interested in devising ring forming processes with concomitant introduction of functionality by replacing the β-hydride elimination step of a Heck reaction with a group or atom transfer. This led to the versatile and wide ranging cascade cyclisation-anion capture methodology summarised in Table 1 [12].

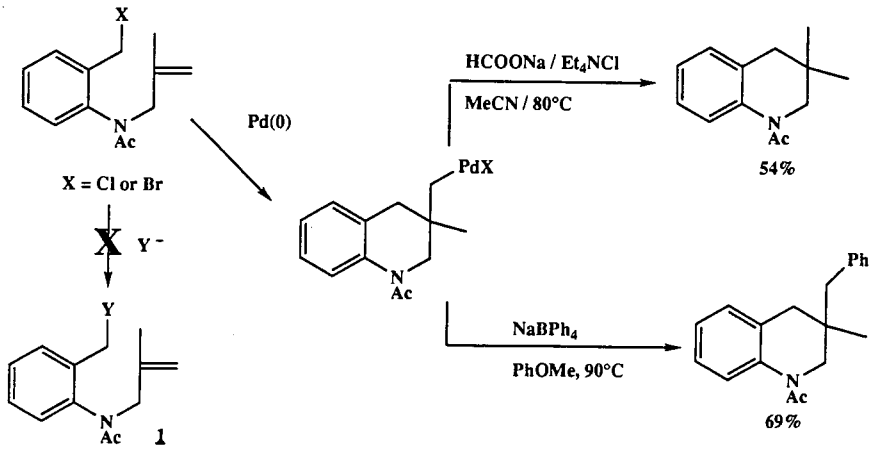
The use of the word 'anion' in this context embraces both ionic and covalent sources of Y (Table 1) and is felt to be more appropriate than cross-coupling. Each species referred to in Table 1 is accessed sequentially in a controlled cascade.

The starter species is usually employed as the appropriate halide (Cl, Br, I), or triflate 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 [13a–d] or chloropalladation [13e,f] of an alkyne to generate a vinylpalladium(II) species. In monocyclisations the organopalladium(II) species cyclises onto the terminating species. Exchange of halide or triflate with the anion capture agent followed by reductive elimination generates the regiospecifically functionalised monocyclised product and regenerates Pd(0). An illustrative example is shown in Scheme 1 [14].

In Scheme 1 the starter species is an alkyl halide, the terminating species is an alkene and the anion capture agent Y is hydride or phenyl. The efficient creation of a wide range of tetrasubstituted carbon centres is a particularly attractive feature of the cyclisation-anion capture methodology. A further distinctive feature is that cyclisations, in the absence of adverse steric constraints, invariably proceed via the *exo*-mode rather than the alternative *endo*-mode. Thus Scheme 1 involves 6-*exo*-trig, rather than 7-*endo*-trig, cyclisation and polycyclisation-anion capture processes are also readily achieved. In these latter processes the initial product of oxidative addition cyclises onto a proximate relay moi-

Table 1
Potential combinations for (poly)cyclisation 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	Neutral (amines, MeOH/CO, acrylates, allenes)
Vinyl	1,2-Diene	1,2-Diene	Organometallics RM[M = Sn(IV), B(III), Zn(II)]
Allyl	1,3-Diene	1,3-Diene	
Allenyl			



Scheme 1.

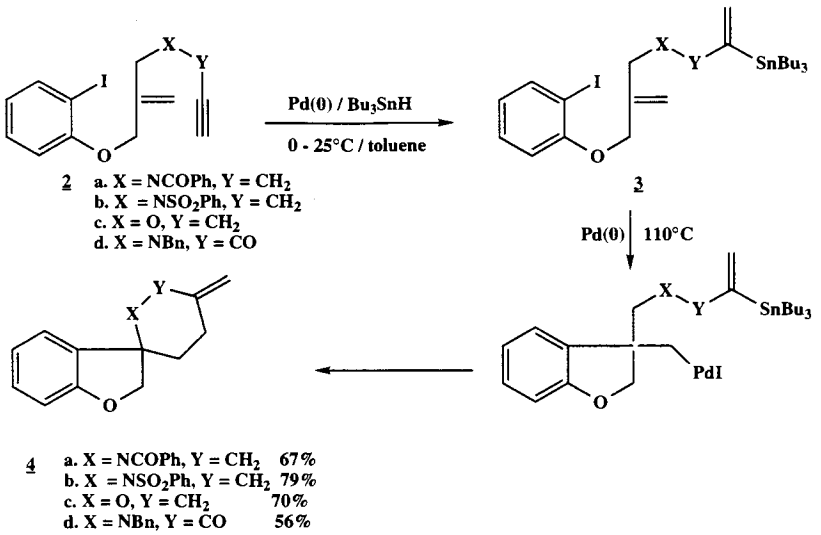
ety. Cyclisation can proceed in the relay phase for two, three or more cycles accessing a combination of relay species before engaging the terminating species and, subsequently, Y. Additional general features of the methodology are as follows:

1. The methodology is dependent on cyclisation rates being significantly faster than anion capture. Our experience thus far indicates that 3–7 membered rings can be constructed according to Table 1 with little or no competition from the direct capture, or 'shunt' pathway, e.g. in Scheme 1 the 'shunt' pathway, which is not observed, would generate **1** (Y = H or Ph).
2. When an alkene is used as relay, or as a terminating species, it may be necessary to incorporate a blocking substituent to prevent β-hydride elimination superseding further cyclisation/anion capture. An alternative strategy is to utilise bridgehead strain effects (Bredt's rule) [15] and several examples of this will be described. Such strategies are unnecessary for the other relay/terminating species. Moreover, in certain instances, e.g. 3-*exo*-trig cyclisation (see Scheme 14), or certain carbonylations (see **75** → **76** and **81** → **82**) blocking groups etc. are unnecessary for alkenes due to rapid cyclisation rates. In certain instances it is advantageous to allow β-hydride elimination occur as a final step if this generates desirable functionality (see Schemes 28 and 29).
3. Carbocyclisation rates normally follow the expected order with respect to the size of the ring formed: 3 > 5 > 6 > 7.
4. Any starter moiety can be conceptionally combined with any relay or terminating species or anion capture agent.
5. The anion capture agents Y, listed in Table 1, are illustrative rather than exhaustive and much further development remains to be done in this area.
6. When the terminating species is a 1,2- or 1,3-diene the resulting π-allylpalladium(II) species can undergo the anion capture step in two mechanistically distinct ways depending on the nature of Y. Thus Y can attack as an external nucleophile [Y = $CH(CO_2R)_2$ CN, OAc, amines] in which case the nucleophile attacks *trans* to the Pd(II), or Y can be transferred to the π-allyl moiety via the Pd(II) centre, i.e. *cis* with respect to Pd(II) (Y = H, alkyl, aryl, CO). Moreover, the π-allyl species will, in many cases, be unsymmetrical. The regio- and stereochemical outcome is thus dependent on the nature of Y and the reaction conditions (e.g. Scheme 4).

The current state of development of Table 1 will be discussed first, followed by later and ongoing developments which incorporate expansion of the relay phase by intermolecular processes. These latter processes involve 'relay switch' components and extended molecular queuing processes.

2.1. One component processes

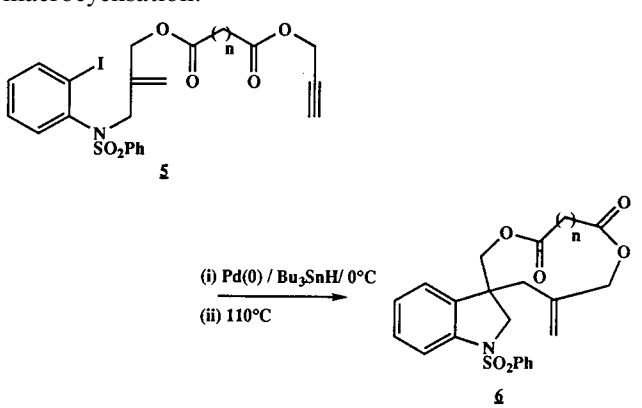
The potential cascades summarised in Table 1 are largely two component processes comprising the starter/relay/terminating component and the anion capture agent Y. However it is sometimes synthetically advantageous to engineer one component processes. A typical example [16] is provided by bis-cyclisation processes involving α, ω-enynes. In these substrates the ready hydrostannylation of alkynes offers the possibility of an intramolecular anion capture. Good to excellent regioselective hydrostannylation of terminal alkynes can be achieved by incorporation of a proximate (β- or γ-) heteroatom [17]. Moreover, this strategy offers the opportunity to explore sp^2–sp^3 Stille coupling as part of a polycyclisation strategy incorporating macrocyclisation. Macrocycle formation via sp^2–sp^3 Stille coupling had not hitherto been reported despite



Scheme 2.

the growing number of imaginative applications of intramolecular Stille reactions for the construction of macrocycles employing sp^2–sp^2 [18] or sp–sp^2 [19] coupling.

In these intramolecular cyclisation-anion capture processes the vinylstannes (e.g. **3**) are generated by Pd(0) catalysed hydrostannylation at 0–25°C over 1 h followed by raising the reaction temperature to 110°C which triggers the cyclisation-anion capture cascade. Scheme 2 **2**→**4** illustrates the process for small ring formation whilst the conversion of **5** to **6** and Table 2 [16] provide impressive examples of spiro-macrocyclisation.



The hydrostannylation of **2a, b, d** gave only the desired α-vinylstannanes whilst **2c** gave a 3:1 mixture of the α- and β-vinylstannanes. The preferred catalyst system for these cascades comprised 10 mol% $Pd(OAc)_2$ and 20 mol% PPh_3. Cyclisation to the 5/6-spiro heterocycles occurred smoothly at 110°C furnishing **4a–d**.

The preferred catalyst system for conversion of **5** to **6** comprised 5 mol% Pd_2 $(dba)_3$ and 20 mol% tri-(2-furyl)phosphine. Hydrostannylation of **5** at 0°C was less selective than that of **2a–d** and afforded 2:1 mixtures of the α- and β-vinylstannes. Bis-cyclisation of the α-vinylstannes proceeded smoothly at 100°C (5×10^{-3} molar solutions) over 12 h to afford the spiro-macrocycles 6 (Table 2). A series of macrocyclic bridged rings has been similarly prepared [16].

2.2. Two component processes

2.2.1. Monocyclisation-anion capture

All the starter, terminating species and anion-capture agents have been exemplified in monocyclisation processes apart from the allenyl starter species. However, all the possible combinations inherent in Table 1 have not been demonstrated as yet. Thus Table 1 offers many, as yet unexplored, synthetic opportunities. The allenyl starter moiety is most effectively used in polycyclisation processes and these will be discussed later (Sections 2.3.2 and 2.4).

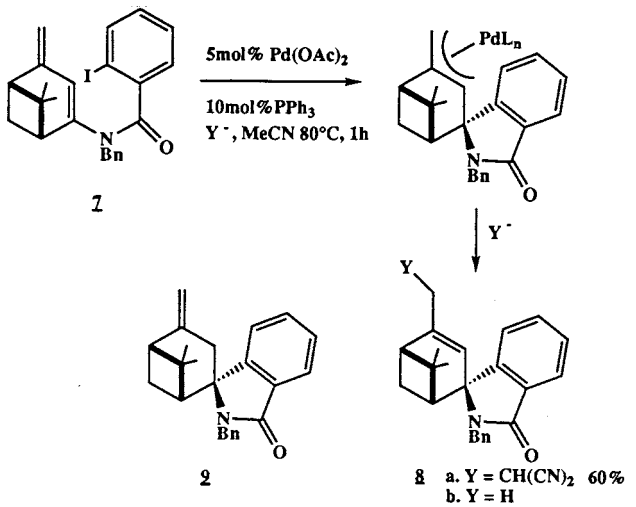
2.2.2. Alkyl halide starter species

Examples of these have already been discussed (Scheme 1) [14].

Table 2
Biscyclisation-intramolecular anion capture of (**5**) to (**6**)

n	Macrocyclic ring	Yield (%)[a]
3	12	53(71)
4	13	52(70)
5	14	52(70)
6	15	53(71)
7	16	50(67)
8	17	53(71)

[a] Yields in brackets are corrected for the α-/β-stannane ratio.



Scheme 3.

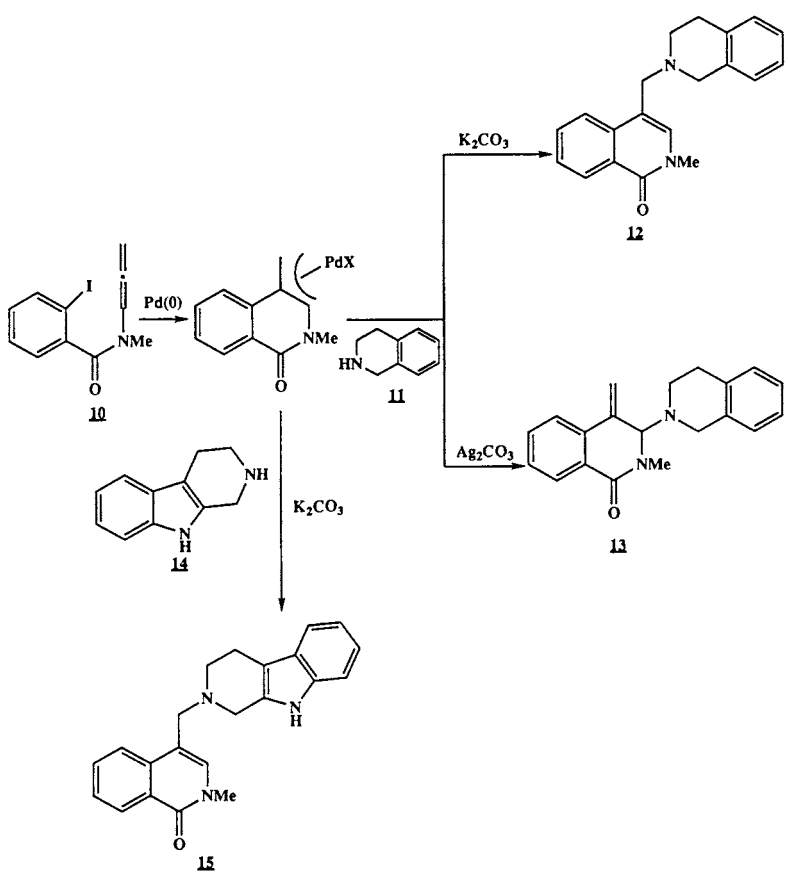
2.2.3. Aryl halide starter species

Cyclisation onto proximate 1,2- or 1,3-dienes occurs regioselectively at the centre carbon of the 1,2-diene moiety and the proximal carbon of the 1,3-diene in the absence of any compelling stereoelectronic constraints. In both cases π-allylpalladium(II) species are generated, thus opening up the rich catalytic chemistry of these species. For example, the dienamide **7** undergoes regio- and stereo-specific 5-*exo*-trig cyclisation generating the intermediate π-allyl species which can be intercepted with a range of nucleophiles including sodiomalononitrile which gives **8** in 60% yield [20] (Scheme 3).

The regioselectivity of π-allyl capture was reversed when the anion capture agent was hydride (HCO_2Na). The reaction (DMF, 80°C, 24 h) afforded a 4:1 mixture (80%) of **9** and **8b** [21] (Scheme 3).

The palladium catalysed cyclisation of aryl iodides onto proximal allenes occurs at the centre carbon of the allene forming 5–7 membered rings and generating a π-allyl intermediate. The regiochemistry of attack of secondary amines on the π-allyl species is sensitive to added inorganic base, steric effects and the nature of the adjacent heteroatom [22]. Thus allene **10** (Scheme 4) undergoes cyclisation (MeCN, 80°C) using a catalyst system comprising 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3 and K_2CO_3 (1 mol eq) in the presence of amine **11** to afford **12** (91%) [22].

Replacing K_2CO_3 with Ag_2CO_3 (1 mol eq) cleanly generates the regioisomer **13** (77%). Monitoring (^{1}H-NMR) of the reaction employing K_2CO_3 as base showed that mixtures of **12** and **13** were present initially [time (**12**:**13**): 2 h (2.5:1), 4 h (4:1), 24 h (8:1), 28 h ($>$10:1); an additional 10 mol% $Pd(OAc)_2$ was added



Scheme 4.

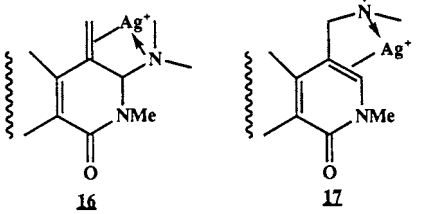
Table 3
Influence of temperature on the diastereoselectivity for the conversion of **18** to **19** and **20**

T (°C)	t (h)	19:20[a,b]	Yield (%)[c]
80	2	3:1	78
25	2	8:1	87
0	4	11:1	–

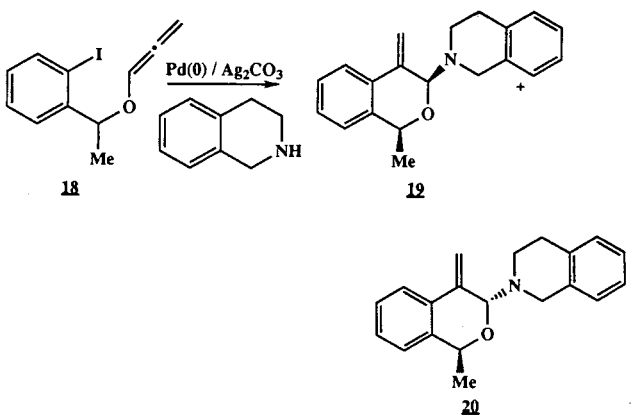
[a] Diastereoisomer ratios determined from the ^{1}H-NMR spectra of the reaction mixtures.
[b] Note that workup by chromatography on silica affords a 1:1 mixture of diastereoisomers.
[c] Isolated yield.

after 24 h]. As expected, **10** reacts with amine **14** using the same catalyst system with K_2CO_3 as base to give only **15** (60%) (Scheme 4).

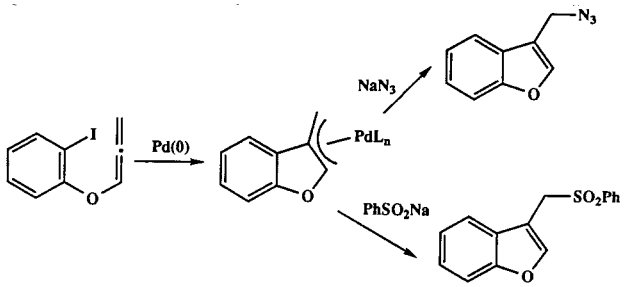
These observations demonstrate that only moderate initial regioselectivity is achieved with K_2CO_3 as the base and that 12 is the thermodynamically most stable product. The reason for the increased regioselectivity with Ag_2CO_3 as the base is ascribed to a cationic Pd(II) intermediate potentiating attack at the most electron deficient allylic terminus. The cause of the lack of equilibration of **13** with **12** in the presence Ag_2CO_3 is at present unclear. However, it might reflect the greater stability of **16** versus **17**.



When the allene starter contains a stereocentre the resultant diastereoselectivity is sensitive to temperature, as illustrated for conversion of **18** to **19** and **20** (Table 3) [22].



The π-allyl species generated by cyclisation of aryl halides onto proximal allenes can be intercepted by a wide range of nucleophiles. Further examples are shown in Scheme 5 [23], with azide capture occurring in 71% yield and benzene sulphinate capture in 64% yield. Interception of π-allyl intermediates by azide ion provides access to extended cascades via 1,3-dipolar cycloaddition of the azide moiety to appropriate alkenes and alkynes [23].



Scheme 5.

The versatility of the allenyl moiety is further emphasised by employing a sequential 'one-pot' hydrostannylation-cyclisation strategy which permits cyclisation at the proximal carbon of the allene [24]. Regioselective hydrostannylation of heteroatom substituted allenes is readily achieved but the E/Z-stereoselectivity of the hydrostannylation (Pd(0), THF, 0°C) is dependent on the heteroatom (Scheme 6). Moreover, the *Z*-stannane cyclises faster than the *E*-isomer [24].

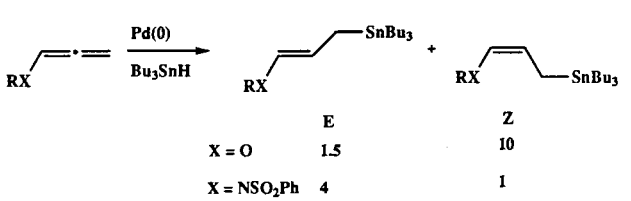
Both small (5–7) rings and macrocycles (11–17) can be assembled in this way. For example **21** gives **22** (85%) and **23** gives **24** (46%).

The overall process produces α-vinyl heterocycles and the final step involves chemoselective elimination of BuSnPdX in preference to β-hydride elimination (Scheme 7). Others have reported related preferential elimination of HOPdX [25a] and ROPdX [25b].

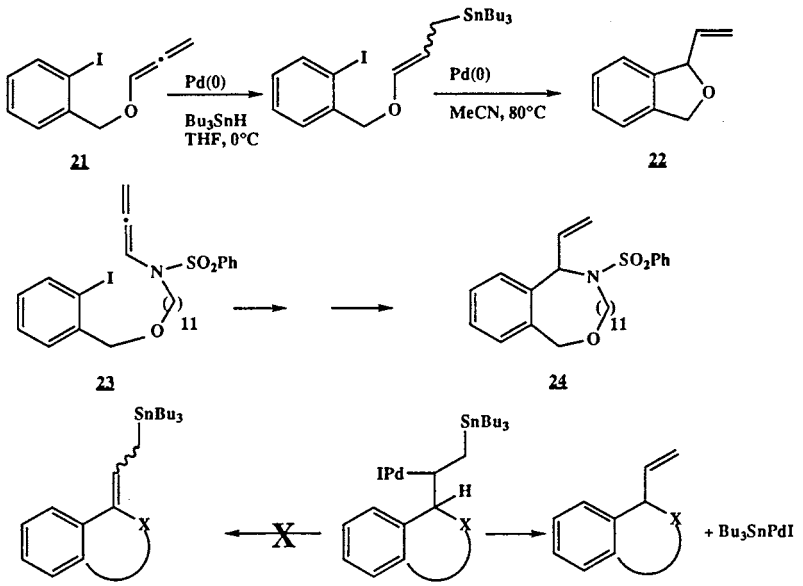
Cyclisation onto proximate alkenes with capture by hydride from HCO_2Na [21] or a range of boron [26] or Sn(IV) [27] anion capture agents occur in good yield. Some representative examples of the latter two are shown in Tables 4 and 5.

Our original studies of cyclisation with organotin(IV) anion capture agents were carried out in acetonitrile. Subsequent studies employed toluene as solvent which resulted in a significant increase in yield.

The large variety of organotin(IV) [29] and boron reagents that are available in conjunction with their



Scheme 6.

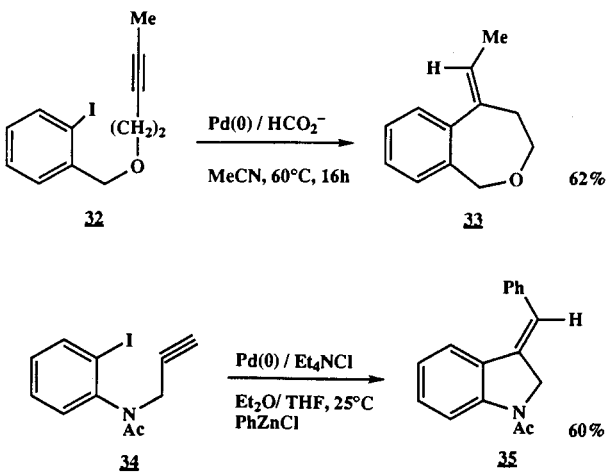


Scheme 7.

stability, ease of handling and synthetic accessibility make these classes of reagents particularly valuable components of the cyclisation-anion capture methodology.

Cyclisation with cyanide capture can also be achieved in boiling toluene using in situ generated Pd(0) in combination with KCN (1.2 mol eq) and 10 mol% 18-crown-6 [28]. Representative examples are shown in Scheme 8.

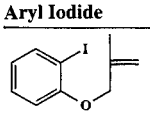
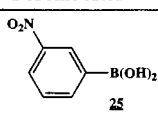
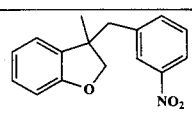
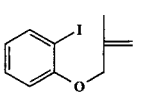
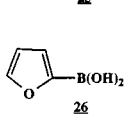
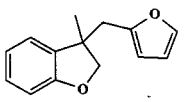
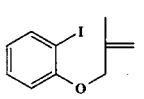
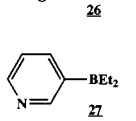
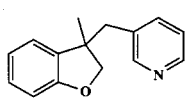
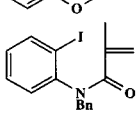
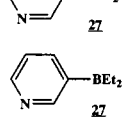
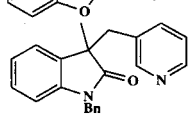
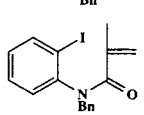
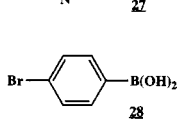
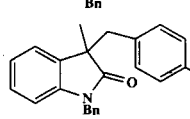
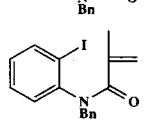
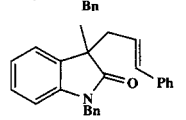
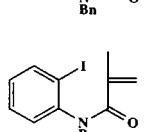
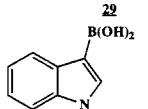
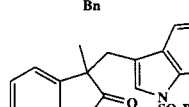
Cyclisation onto proximate alkynes with anion capture is illustrated by the 7-*exo*-dig cyclisation hydride capture (HCO_2Na) process **32** → **33** [30] and the 5-*exo*-dig process with anion transfer from PhZnCl **34** → **35** [31].



2.2.4. Vinyl triflate/halide starter species

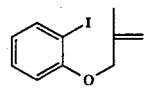
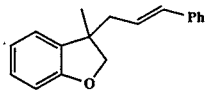
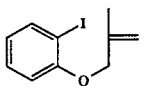
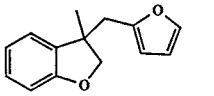
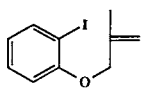
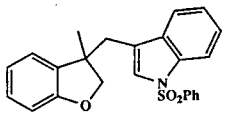
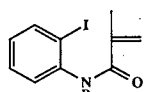
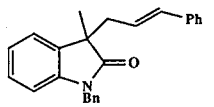
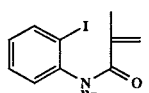
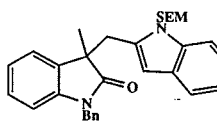
The ready accessibility of vinyl triflates from aldehydes and ketones provides a large potential substrate base for our cyclisation-anion capture methodology. That enol triflates are excellent substrates for cyclisation with anion capture from boron derivatives is illustrated by the application of such processes to **36**. Enol

Table 4
Cyclisation of aryl iodides with boron anion capture agents[a]

Aryl Iodide	Boronic Acid	Product	Yield(%)
	 25		93
	 26		85
	 27		72
	 27		76
	 28		96
	E-PhCH=CHB(OH)2 29		72
	 30		96

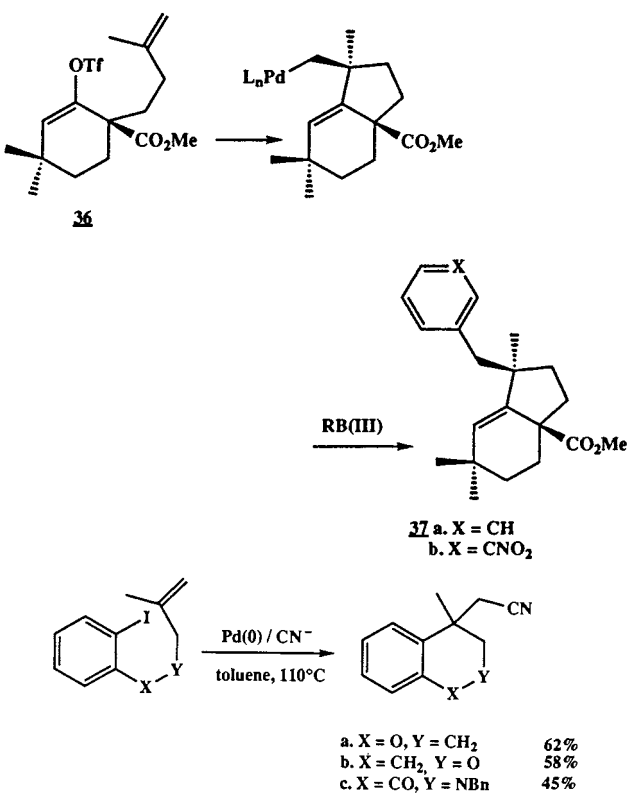
[a] Reactions were carried out in boiling toluene at 90–100°C with Na_2CO_3 (2 mol eq) as base.

Table 5
Cyclisation of aryl iodines with Sn(IV) anion capture agents ([27]b)[a,b]

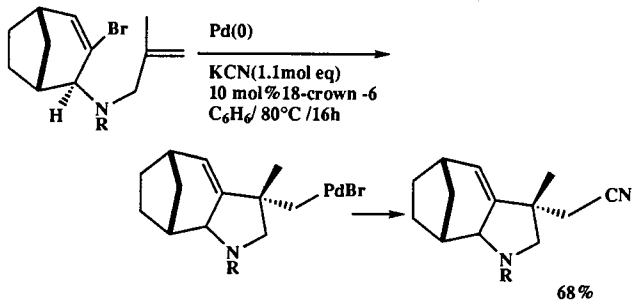
Aryl Iodide	Bu_3SnR	Product	Yield(%)
	R = 		90
	R = 		85
	R = 		86
	R = 		89
	R = 		82

[a] All reactions carried out in toluene at 90°C for 8 h.
[b] Catalyst system comprised 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3 and Et_4NCl (1 mol eq).

triflate **36** was prepared in 72% yield from the corresponding ketone using *N*-(5-chloro-2-pyridyl)triflimide as the triflating agent.



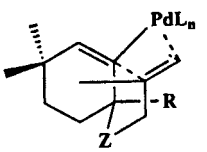
Scheme 8.



Scheme 9.

Vinyl triflate **36** undergoes cyclisation-anion capture (DMF, 100°C, 8 h) from $NaBPh_4$ (1 mol eq) by a 5-*exo*-trig process to afford **37a** (90%) as a single diastereomer. Analogous reactions (toluene, 110°C, 8 h) with *m*-nitrophenyl boronic acid (1.5 mol eq) or diethyl-3-pyridyl borane (1.5 mol eq) afford **37b** (94%), and **37c** (92%), respectively. All reactions employed 10 mol% Pd $(OAc)_2$ and 20 mol% PPh_3 with the addition of Na_2CO_3 (2 mol eq) and Et_4NCl (1 mol eq) in the two latter cases. The stereochemistry of **37b** was established by X-ray crystallography and that of **37a** is assigned by analogy [26].

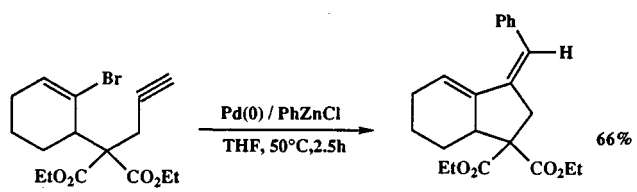
The excellent diastereoselectivity is a feature of the cyclisation-anion capture methodology and is especially significant and valuable in polycyclisation-anion capture processes (vide infra). Diastereoselectivity arises from stereoelectronic effects in the relevant cyclisation transition states e.g. **38** for **36** → **37**.



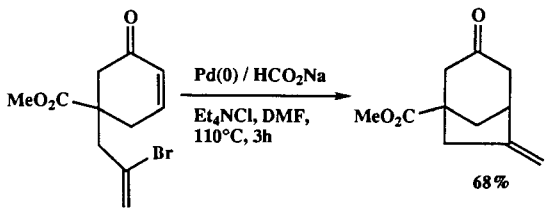
38

Related vinyl bromide examples are shown in Scheme 9 [28], 10 [31] and 11 [32], involving cyanide, phenyl, and hydride capture, respectively (Schemes 10 and 11).

Competition between direct capture and cyclisation-anion capture in the 6-*exo*-dig cyclisation of certain vinyl iodides is reported to favour direct capture when organo- zinc and -copper anion capture agents are involved [33].



Scheme 10.



Scheme 11.

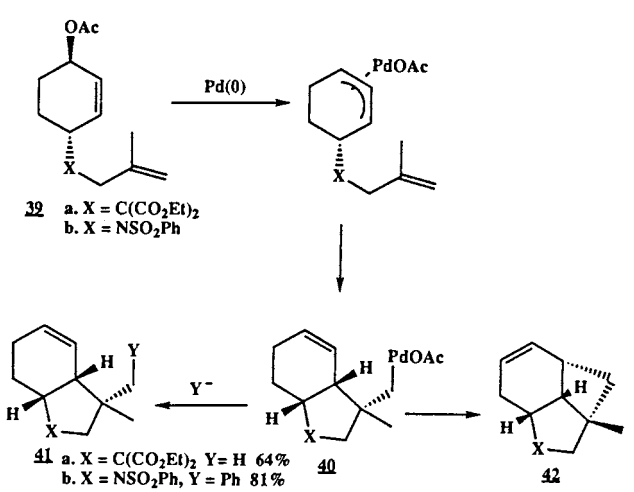
2.2.5. Allylic acetate starter species

Stereodefined 4-substituted cyclic allylic acetates are readily available from chemistry developed by Bäckvall et al. [34], and they provide ideal substrates for cyclisation-anion capture processes. Thus **39a** cyclises (MeCN, 80°C, 19 h) to **41a** (Scheme 12) with a catalyst system comprising 10 mol% Pd $(OAc)_2$ and 20 mol% PPh_3 and piperidium formate as the hydride source [21].

In an analogous manner **39b** cyclises (anisole, 60°C, 3 h) to **41b** with phenyl capture from sodium tetraphenylborate. In the absence of anion capture agents the alkylpalladium(II) intermediates **40** undergo 4-*exo*-trig cyclisation to the cyclobutyl products 42 [35]. Whilst 4-membered ring forming processes are readily achievable they are also readily intercepted by anion capture agents as Scheme 12 shows. However, the anion capture versus cyclisation competition for 3-*exo*-trig processes favours 3-membered ring formation but is open to manipulation by variation of reaction conditions in certain cases (vide infra).

2.3. Bicyclisation-anion capture

We and others have developed biscyclisation processes which generate fused-, spirocyclic and bridged-ring products via a β-hydride elimination termination step [36]. However, biscyclisation-anion capture offers the significant advantage of incorporation of an additional, precisely located, functional group at the cyclisation terminus. Even though polycyclisation-anion capture processes are much less well developed than monocyclisation processes those substrates studied thus far display encouraging diastereoselectivity.

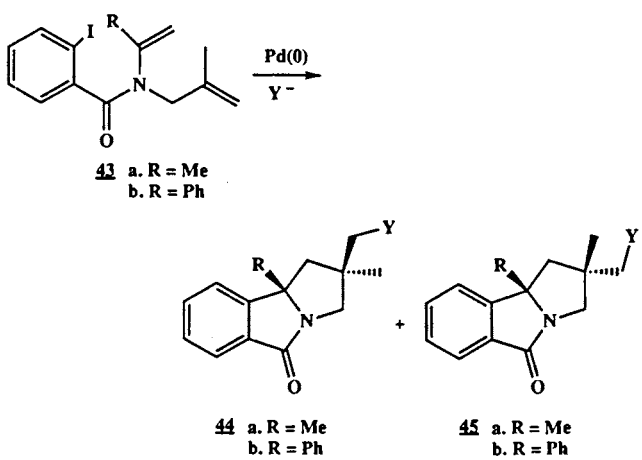


Scheme 12.

2.3.1. Aryl halide starter species

This class of starter species is the most widely studied to date. In some instances products arising from monocyclisation-anion capture are also formed but these can generally be eliminated or minimised by adjustment of the reaction conditions. Tl(I) salts are often useful in this respect.

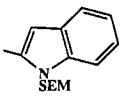
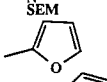
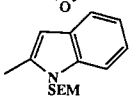
Enamides **43a,b** were prepared by acylation of the corresponding ketone imines with 2-iodobenzoyl chloride. These substrates have alkene relay and terminating species and both undergo the expected regiospecific bis-5-*exo*-trig cyclisation (DMF, 80°C) followed by hydride capture to afford **44a,b** (Y = H) in 60–70% yield [21] or phenyl capture from $NaBPh_4$ to afford **44a** (R = Ph) in 30% yield [26].



Reduced stereoselectivity was observed for Sn(IV) anion capture agents. Thus **43a** afforded 5:1 mixtures of **44a** and **45a** (Y = *N*-sem-2-indolyl or 2-furyl) whilst **43b** gave 3:1 mixtures of **44b** and **45b** (Y = *N*-sem-2-indolyl or 2-furyl) (Table 6) [37a] suggesting a steric influence on the diastereoselectivity as illustrated in Scheme 13. Note that this accords with the observation that the chair form of cycloheptane is more stable than the boat [37b].

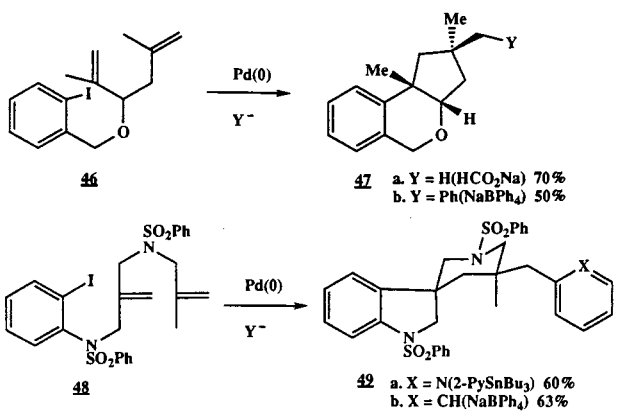
The second cyclisation requires an eclipsed alignment of the Pd–C and olefin C–C bonds. This arrangement creates a pseudo seven membered ring which can adopt a chair or boat-like conformation (Scheme 13). The developing Me/R steric interaction in the boat-like transition state is destabilising with respect to the *trans* Me/R arrangement in the chair-like transition state.

Table 6
Biscyclisation-anion capture of **43a,b**[a]

Substrate	Anion Capture Agent	Product(ratio)	Y	Yield(%)
43a	HCO_2Na	44a	H	70
43b	HCO_2Na	44b	H	60
43a	$NaBPh_4$	44a	Ph	30
43a	(N - sem- 2-indolyl) $SnBu_3$	44a(5):45a(1)		74
43a	2-furyl$SnBu_3$	44a(5):45a(1)		66
43b	(N - sem - 2 - indolyl)$SnBu_3$	44b(3):45b(1)		70
43b	2 - furyl$SnBu_3$	44b(30:45b(1)		64

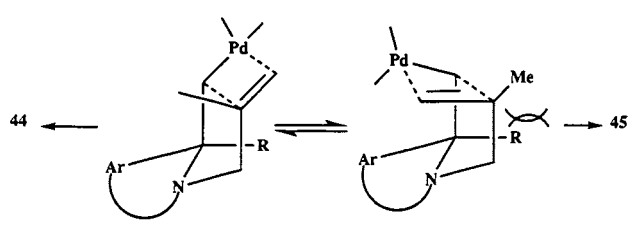
[a] All reactions employed 10 mol% $Pd(OAc)_2$ and 20 mol% PPh_3.

Biscyclisation-anion capture forming single diastereomers of fused 6/5-and spiro 5/6-rings have been achieved. Thus **46** gives **47a,b** [21,26] and **48** gives **49a,b** [26,38].



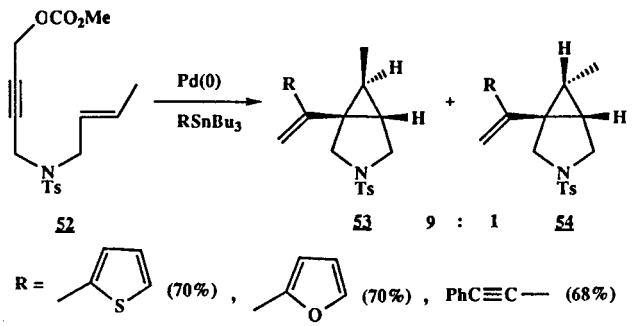
2.3.2. Allenyl starter species

Allenylpalladium(II) species are readily accessed by Tsuji's simple and efficient method of reacting Pd(0) with propargylic carbonates [39]. They are versatile species as they can serve a double function of both starter and terminating species as illustrated by Scheme 14 [40].



Scheme 13.

Using a catalyst system comprising 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3 and LiCl (2 mol eq) the substrate **50** generates (THF, reflux) an allenylpalladium(II) species which cyclises to **51**. This alkylpalladium(II) intermediate could undergo a β-hydride elimination when R = H and hence interrupt the catalytic cycle. That this deleterious process is not observed is ascribed to a combination of complexation of the palladium by the adjacent allenyl moiety and a rapid 3-*exo*-trig cyclisation. Subsequent to the publication of our results similar observations were published by Oppolzer et al. [41]. Further illustration of the dominance of 3-*exo*-trig cyclisation in this potentially competitive situation is provided by studies with **52**. It was found that **52** undergoes biscyclisation-anion capture in excellent yield and 9:1 diastereoselectivity for **53** over **54** despite possessing a further avenue for β-hydride elimination [42].

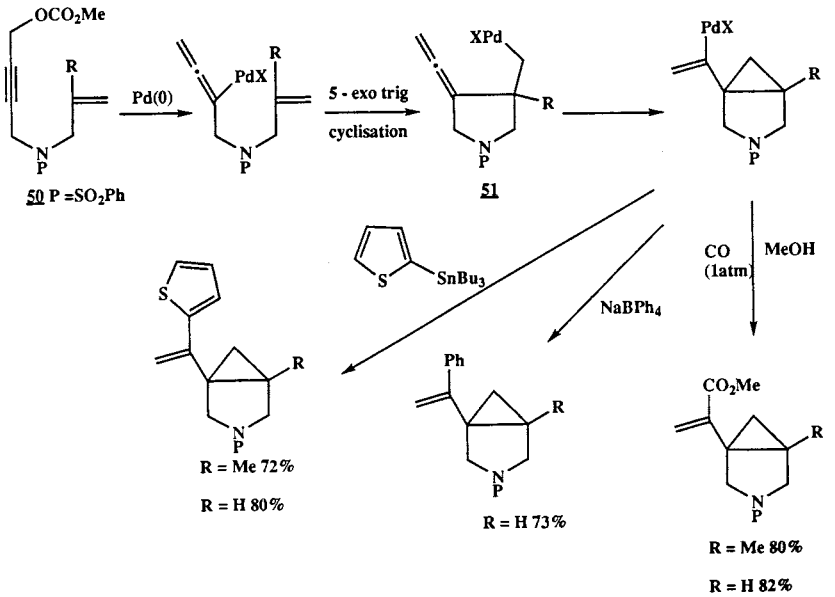


The observed diastereoselectivity again reflects developing steric interactions in the 3-*exo*-trig cyclisation transition state.

Additional examples of steric control of diastereoselectivity in cyclopropane forming palladium cascades are provided by the two component intermolecular cyclopropanation processes shown in Scheme 15 [43]. Additionally, these cascade reactions feature 3-*exo*-trig cyclopropanation in competition with 5-membered ring formation via a formal Friedel–Crafts process. It was found, as shown, that the favoured processes was dependent upon the alkynyl relay species.

2.4. Triscyclisation-anion capture

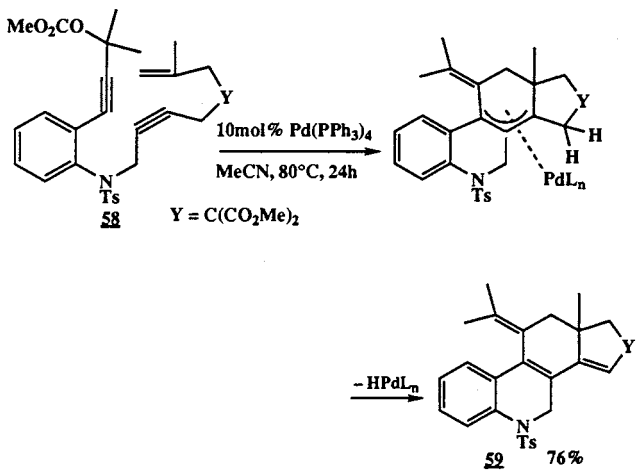
Only one substrate for two component cyclisation-anion capture processes has been studied to date. This substrate **55** employs an allenylpalladium(II) species generated in an analogous manner to that discussed above. Thus **55** undergoes triscyclisation (THF, reflux, 2–4 h) with anion capture from organotin(IV) reagents using a catalyst system comprising 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3 and LiCl (2 mol eq) (Scheme 16) [44]. An alternative mechanism for Scheme 16 is that involv-

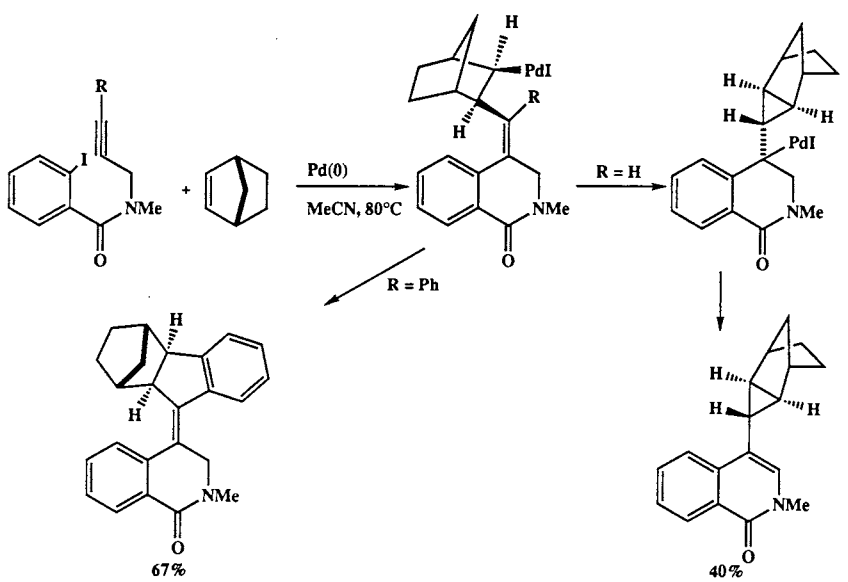


Scheme 14.

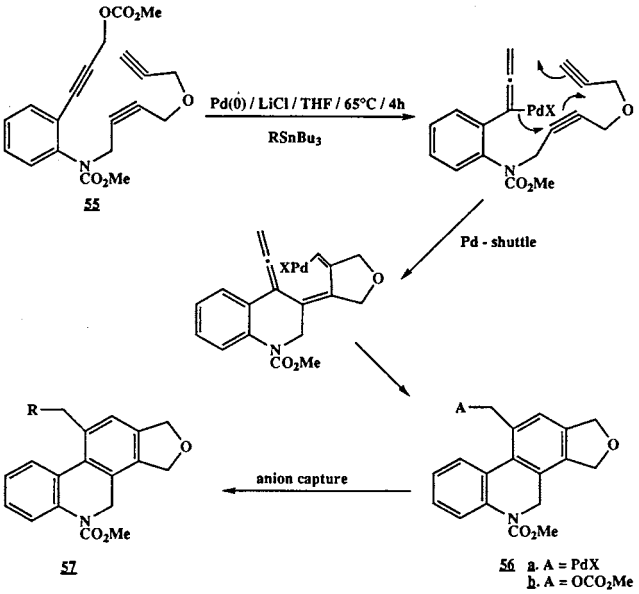
ing a palladium catalysed [2 + 2 + 2]-cycloaddition to give **56b** followed by oxidative addition of Pd(0) to give **56a** an intermediate common to both cascades. Apparently both mechanisms can operate since mixtures of **56b** and **57** are obtained under certain conditions. For example, **55** reacts (THF, reflux, 16 h) with 2-thienyl tributyltin(IV) using a catalyst system comprising 10 mol% Pd_2 dba_3 and 40 mol% $AsPh_3$ to afford a mixture of **56b** (27%) and **57** (R = 2-thienyl) (45%). Significantly under the conditions of Scheme 16 **56b** is not converted into **57**.

The related substrate **58** undergoes triscyclisation followed by β-hydride elimination, in the absence of anion capture agents, to afford **59** [42].





Scheme 15.



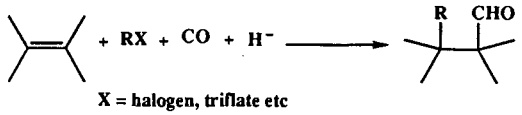
R		Ph	S	O	PhC≡C
Yield (%)	82	80	77	74	62

Scheme 16.

3. Polycomponent processes and relay switches

Table 1 and the foregoing discussion emphasises the versatility of the general cyclisation-anion capture concepts although much detail still remains to be explored. However, as initially conceived, our cyclisation-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 intra-molecular segments. In this context, for example, the formation of the ester in Scheme 14 would be representative of a 3-component process. Thus the potential exists to intersperse the relay species summarised in Table 1 with additional components which would offer the potential to switch the cascade between inter- and intra-molecular processes whilst incorporating valuable additional functionality. Such components might intercept the cyclisation-anion capture cascade only at the relay phase, only at the terminating 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 switch the cascade between intra- and intermolecular processes. Such components impart a major increase in the scope of the original cyclisation-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 followed by incorporation into the cascade. The following discussion illustrates applications of carbon monoxide and allenes in queuing cascades.



Scheme 17.

3.1. Termolecular queuing cascades

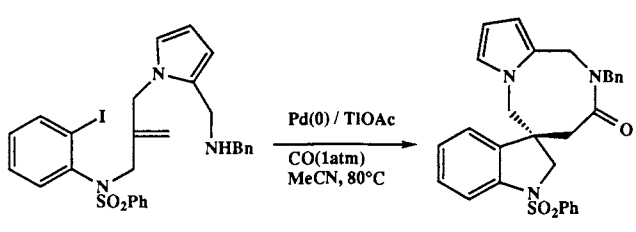
3.1.1. Carbon monoxide as relay switch

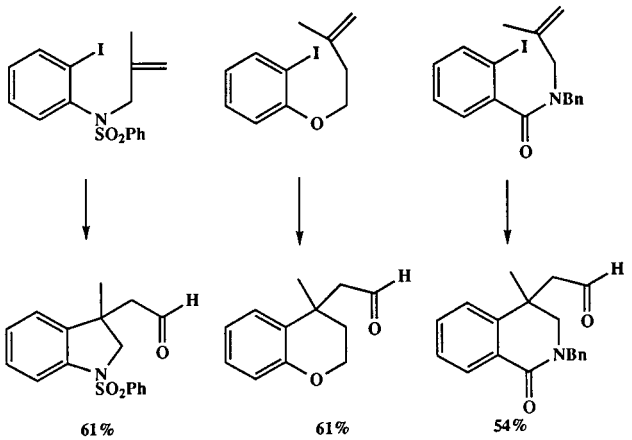
Our studies have focused on employing carbon monoxide at atmospheric pressure. When the starter species in an aryl halide this frequently requires the addition of Tl(I) salts to promote the process [45]. Aryl/vinyl triflates do not require addition of Tl(I) salts thus implicating cationic Pd(II) species in the observed rate enhancement.

The catalytic hydroformylation of alkenes is a major industrial process which has attracted substantial application in fine chemical synthesis [46]. It is, nevertheless, a process in which control of regioselectivity is a perennial problem. A related process of potentially far greater scope would be the hitherto unknown catalytic carboformylation (Scheme 17).

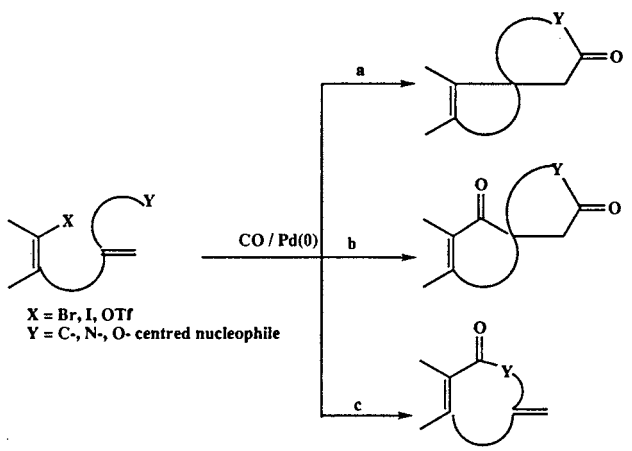
For the operation of a termolecular cyclisation-carboformylation queuing cascade, the ring forming version of Scheme 17, the relative rate of hydride capture is required to be slower than both cyclisation and carbonylation. Diphenylmethylsilane (2 mol eq) as the hydride source was found to provide a satisfactory rate differential. Typical examples of 5- and 6-membered cyclo-carboformylation, which occur in 54–61% yield, are illustrated in Scheme 18. These processes utilise a catalyst system comprising 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3 and Et_4NCl(1 mol eq) [47].

There are many examples of intramolecular capture of an acylpalladium(II) species generated by cyclisation-carbonylation employing 1 atm of CO. An interesting example is the cascade **60** → **61** which generates an 8-membered ring [48].





Scheme 18.



Scheme 19.

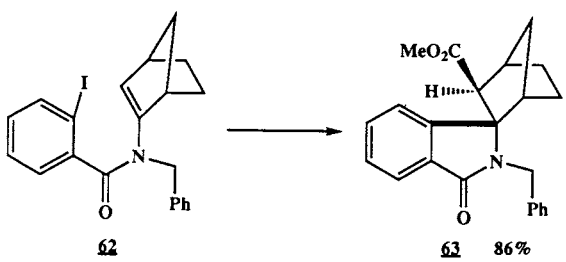
In general there are three types of reaction path open to acylpalladium(II) species generated by a monocyclisation-carbonylation sequence and these are illustrated for spirocyclisation substrates in Scheme 19 [48]. Analogous paths can be envisaged for fused- and bridged-ring forming cascades.

The cyclisation selectivity between paths a–c will depend on the nature of the substrate, carbon monoxide pressure and reaction temperature all of which will influence the relative rates of cyclisation and carbonylation. Examples of path b will be considered under tetramolecular queuing processes (Section 3.2).

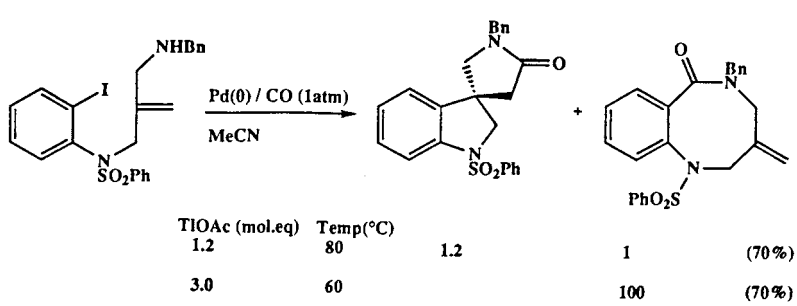
An example displaying competition between paths a and c, employing 10 mol% $Pd(OAc)_2$/20 mol% PPh_3, is shown in Scheme 20 [48].

In this cascade the lower temperature increases the solubility of CO and the increased amount of TlOAc potentiates the concentration of cationic palladium species.

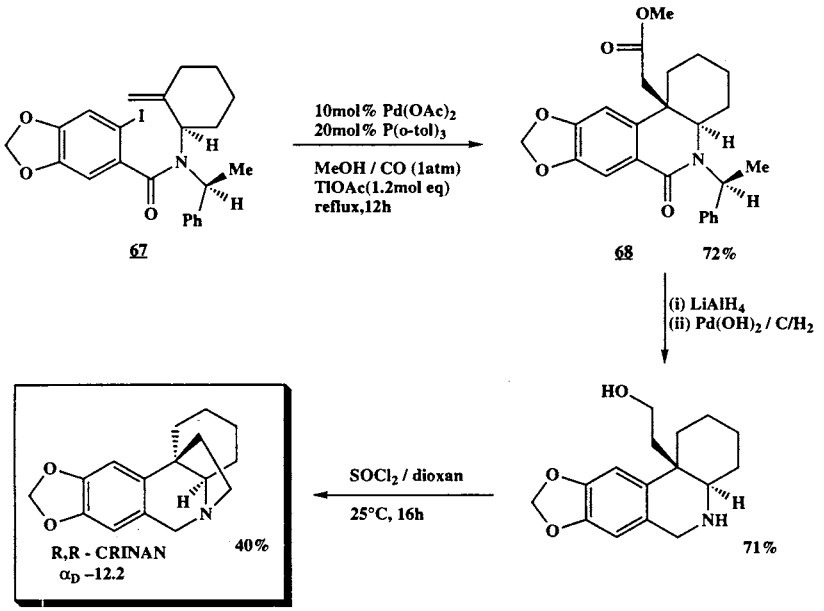
The expected diastereoselectivity of these processes is illustrated and confirmed by conversion [MeOH, 1 atm CO, 5 mol% $PdCl_2(PPh_3)_2$, 65°C] of **62** to **63** [44]. For a recent detailed review of such termolecular carbonylation reactions with the emphasis on CO pressures > 1 atm see Negishi et al. [8g].



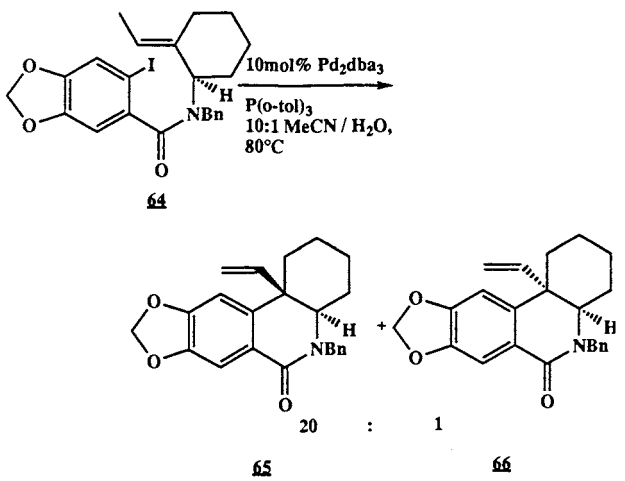
Termolecular queuing cascades employing carbon monoxide and capture of the acylpalladium(II) intermediate by alcohols or amines provide versatile strategies for key steps in natural product synthesis. Following an earlier synthesis of [*R*,*R*]-Crinan [49] in which the key step was an intramolecular Heck reaction of enantiopure **64** furnishing a 20:1 mixture (68%) of **65** and **66**, we applied a termolecular queuing process to enantiopure **67** (Scheme 21) [50]. Cyclisation-anion capture proceeded with high diastereoselectivity to afford enantiopure **68** (72%). Conversion of **68** to *R*,*R*-Crinan was then achieved in a conventional manner, but avoided a low yielding hydroboration step in our previous synthesis.



Scheme 20.



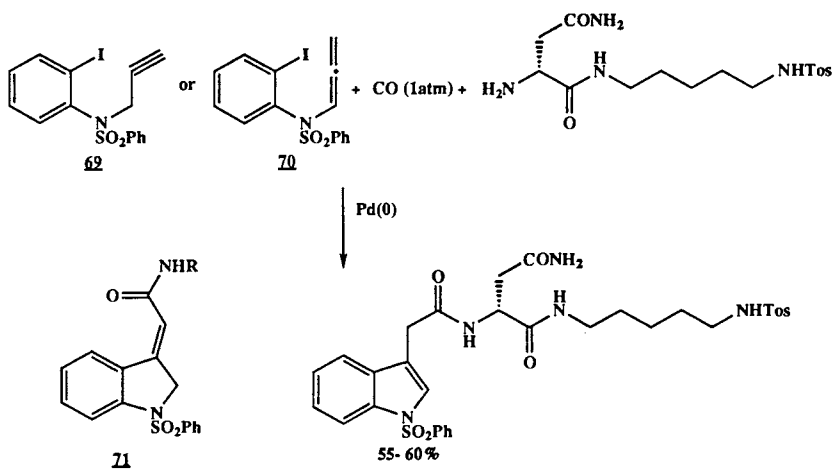
Scheme 21.



Several termolecular queuing approaches to indolic polyamine spider toxins [51] have been developed [52]. An example of the most direct approach employing **69** or **70** is shown in Scheme 22.

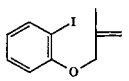
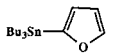
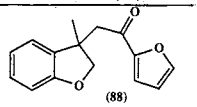
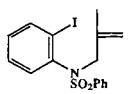
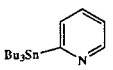
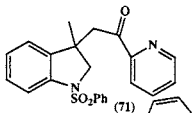
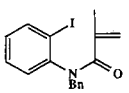
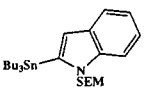
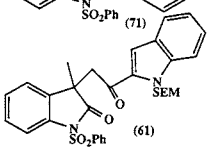
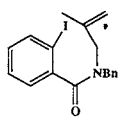
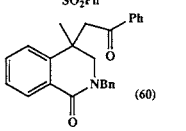
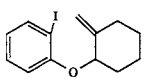
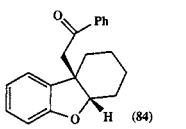
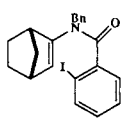
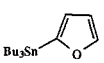
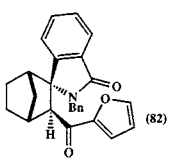
The product is a protected form of pseudoargiopinine III, a toxin from *Argiope lobata* [53]. The direct route from **69** utilised proton sponge as the base to ensure isomerisation of intermediate **71** and is somewhat capricious. Omission of proton sponge leads to clean formation of **71** which can be isomerised to the desired product in a subsequent step. Alternatively, the allene **70** affords the product directly but this route is most efficient if 2 atm of CO are employed.

Termolecular queuing processes employing transfer from organo-boron or -tin(IV) species occur in excellent



Scheme 22.

Table 7
Termolecular queuing cascade with CO (1 atm) and anion transfer from B[a] and Sn(IV)[b]

Substrate	Anion transfer agent	Solvent(temp.°C)	Product (%)
		toluene (110)	 (88)
		toluene (110)	 (71)
		toluene (110)	 (61)
	$NaBPh_4$	anisole (120)	 (60)
	$NaBPh_4$	anisole (120)	 (84)
		toluene (110)	 (82)

[a] Catalyst system comprised 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3 and Et_4NCl (1 mol eq).
[b] Catalyst system comprised 10 mol% $Pd(OAc)_2$ and 20 mol% tri(2-furyl) phosphine.

yield. Some typical examples are shown in Table 7 [54] which illustrates the flexibility of the cascade with respect to ring size and type, together with the ability to generate fused- and spiro-cyclic products with excellent diastereoselectivity.

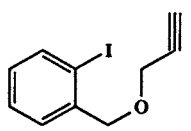
3.1.2. Allenes as relay switches

The versatility of allenes as substrates in palladium catalysed processes is attested to by the recent surge in publications covering both intermolecular and cyclisation/cycloaddition processes [23,55–57].

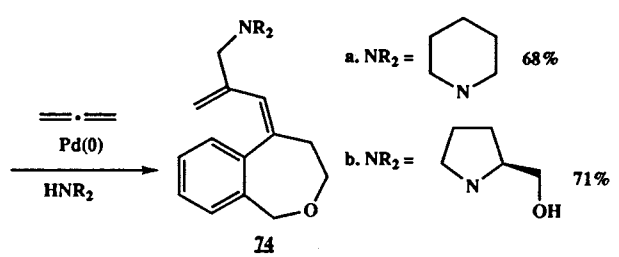
Our initial studies of cyclisation-anion capture with allene as relay switch generated allylic amines in excellent yield (Scheme 23) [58]. Reactions were conducted (toluene, 90–110°C, 20 h) in Schlenk tubes and employed 0.5–1 atm of allene and various amines (2.5 mol eq).

Attack of the alkylpalladium(II) intermediate **72** at the centre carbon of the allene affords a π-allyl species which is efficiently trapped by secondary amines (Table 8). A similar sequence leads to 6-membered rings [58] (Table 8).

Analogous termolecular queuing processes occur with alkyne substrates to afford 1,3-dienes [59]. 5–8 Membered heterocycles can be assembled in this manner as illustrated by conversion (toluene, 70°C, 20 h) of **73** to **74a,b** with allene (1 atm) and the appropriate amine (2 mol eq).



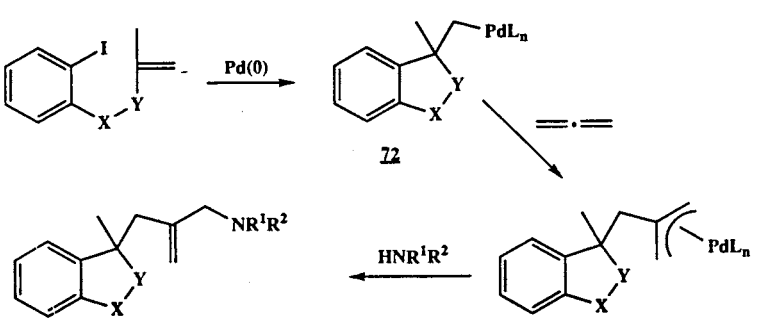
73



74

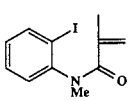
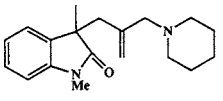
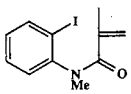
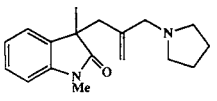
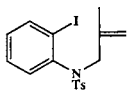
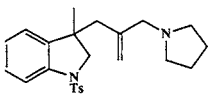
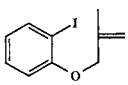
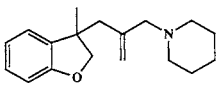
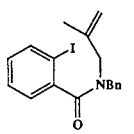
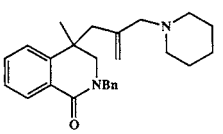
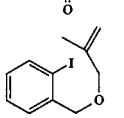
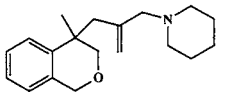
These termolecular queuing cascades can be achieved in excellent yield even with an extended relay phase as illustrated by triscyclisation-allene insertion-anion capture cascades (Schemes 24 and 25) [44].

Scheme 24 employs a vinyl starter species, two alkynyl relay species and an alkynyl terminating species with the final vinylpalladium(II) intermediate adding to the allene. When piperidine was employed as nucleophile the product proved to be very unstable and could only be isolated in 40% yield.



Scheme 23.

Table 8
Termolecular queuing cascades with allene and secondary amines[a]

Substrate	Amine	Product	Yield(%)
	piperidine		82
	pyrrolidine		76
	pyrrolidine		72
	piperidine		60
	piperidine		50
	pyrrolidine		50[b]

[a] Catalyst system comprised 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, Et_4NCl (1 mol eq) and K_2CO_3 (2 mol eq).
[b] Reaction carried out in xylene at 140°C.

Scheme 25 also employs a vinyl starter species and engages alkyne and alkene relay species sequentially followed by an alkene terminating species. The products are obtained as single diastereomers with the *trans* relationship of the two methyl groups assigned on the basis of n.O.e. data. Both cascades (Schemes 24 and 25) result in the formation of three rings and five C–C/C-heteroatom bonds.

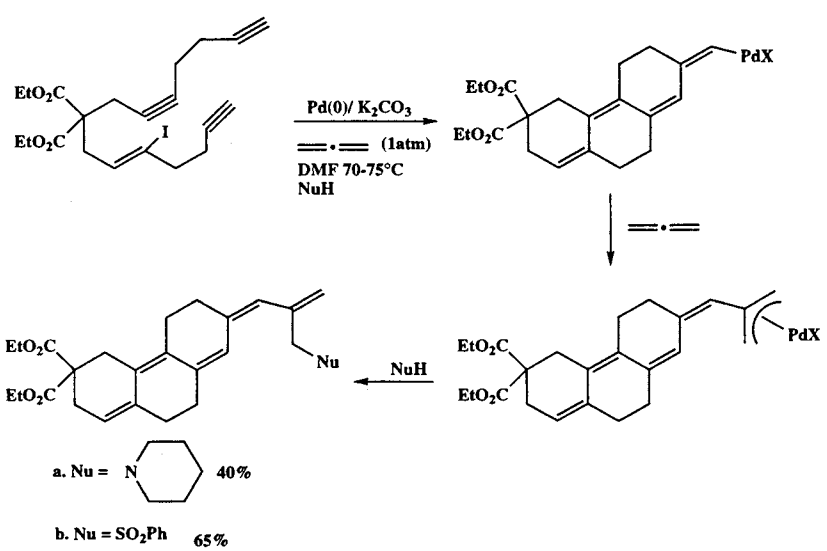
3.2. Tetramolecular queuing cascades

Tactically these polycomponent molecular queuing cascades can be engineered such that the relay switch component is incorporated pre- or post-cyclisation, or the relay switch components can be used both pre- and post-cyclisation. In the latter case the relay switch components can be the same or different.

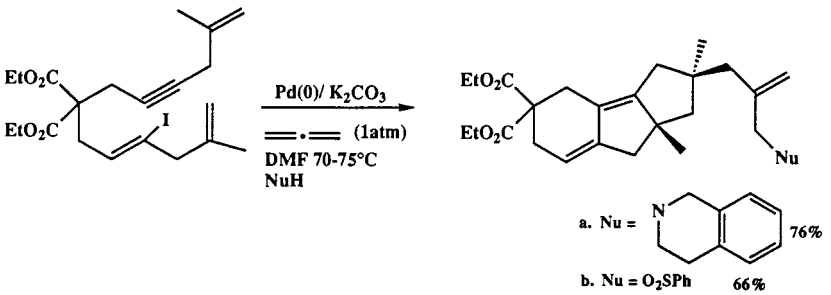
3.2.1. Double carbon monoxide insertions

Previous experience with cyclisation-anion capture processes indicated that carbonylation could be competitive with a 3-*exo*-trig cyclisation of an alkylpalladium(II) species [60] whilst cyclisation forming a 4-membered ring [35] was likely to be slower than carbonylation. A series of substrates was designed which would take advantage of this latter rate differential and permit incorporation of two carbon monoxide molecules into the cascade (Scheme 26). These processes are related to Scheme 19, path c.

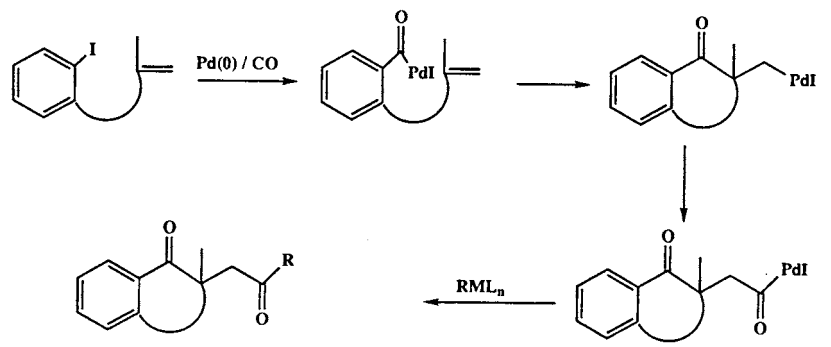
Some typical examples are collected in Table 9 [61], the final entry of which illustrates the potential for synthesis design in which a 6-*exo*-trig cyclisation precedes the first CO insertion and permits construction of spirocycles. In the latter case the product is obtained as a ca. 1:1 mixture of diastereomers. In all the cases illustrated (Table 9) the first CO insertion uprates a slow 4-*exo*-trig carbopalladation to a significantly faster 5-*exo*-trig acylpalladation. In the first four entries the initial relay sequence is an intermolecular CO insertion followed by an intramolecular cyclisation, i.e. a relay switch.



Scheme 24.

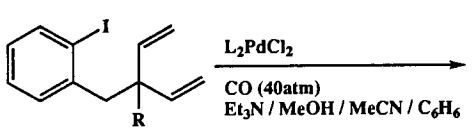


Scheme 25.

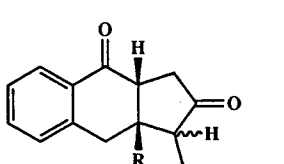


Scheme 26.

These tetramolecular processes involve substrate queuing for access to the metal centre of the organopalladium(II) species. It is now possible to summarise a number of general features important in palladium catalysed cyclisation-carbonylation-anion capture queuing processes. Firstly, the obvious one, that the relative rates of CO insertion and intramolecular carbopalladation will be dependent on CO pressure [8g] (CO insertion is a reversible process) and ring size of the incipient ring in the cyclisation-carbopalladation. The effect of pressure is beautifully illustrated by studies of Negishi et al. [62]. For example, at a CO pressure of 40 atm, carbonylation is faster than 5-*exo*-trig cyclisation and β-hydride elimination as illustrated by the triple carbonylation **75** → **76**. This constitutes a pentamolecular queuing process and produces mixtures of diastereomers ranging from ca. 2:1 to 5:1 [62a].

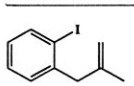
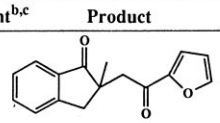
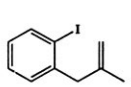
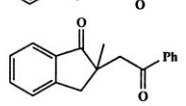
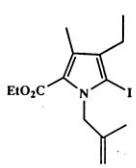
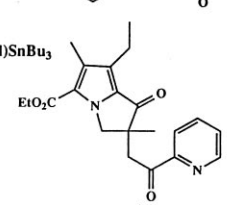
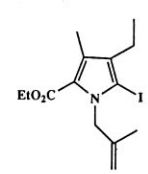
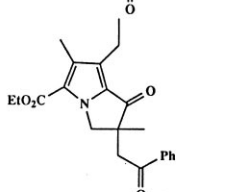
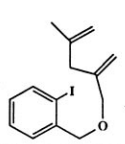
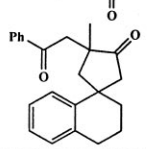


75

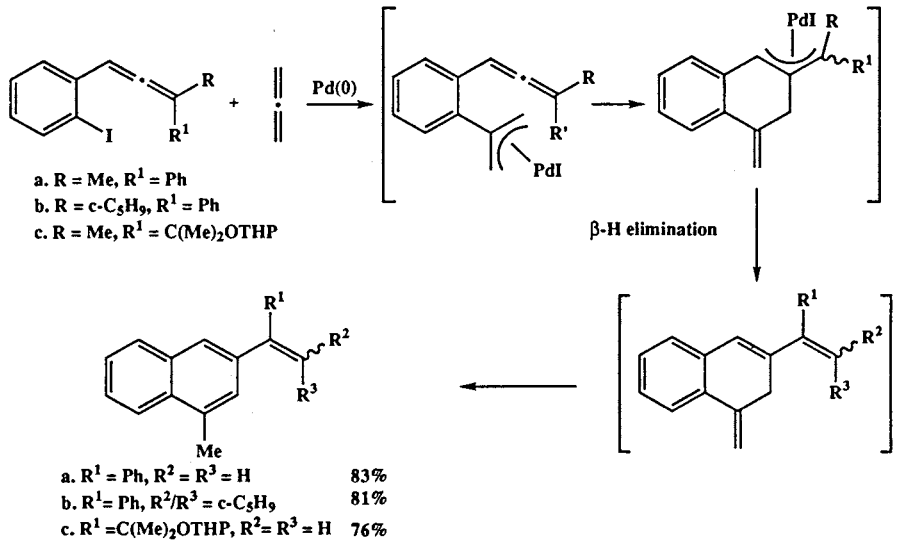


76 40 - 70%

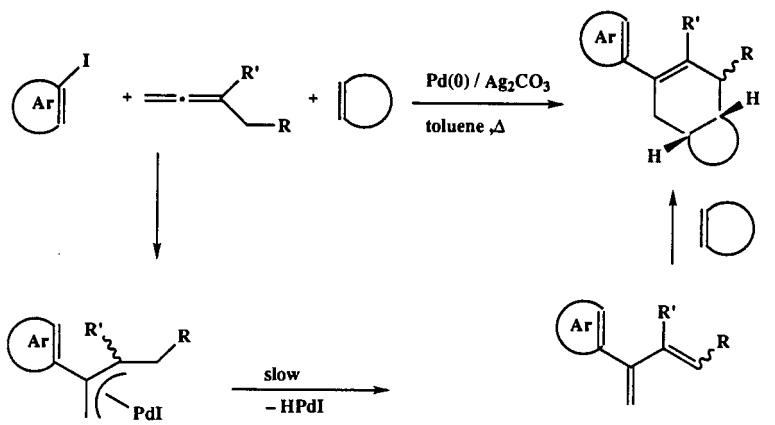
Table 9
Tetramolecular queuing cascades with double CO insertion[a]

Substrate	Anion Capture Agent[b,c]	Product	Yield(%)
	(2- furyl) $SnBu_3$		76
	$NaBPh_4$		86
	(2 - pyridyl)$SnBu_3$		70
	$NaBPh_4$		62
	$NaBPh_4$		70

[a] The catalyst system comprised 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3 and Et_4NCl(1 mol eq).
[b] Reactions employing, Sn(IV) anion capture agents were conducted in toluene at 110°C.
[c] Reactions employing $NaBPh_4$ were conducted in anisole at 120°C.



Scheme 27.



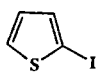
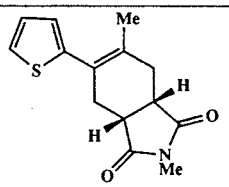
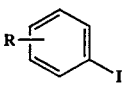
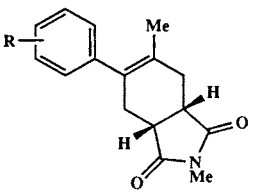
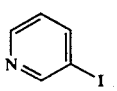
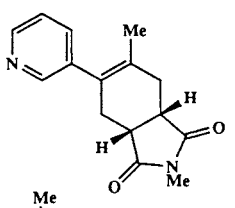
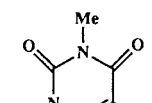
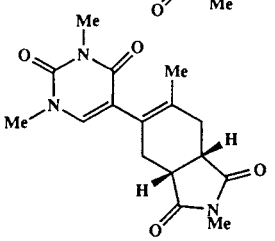
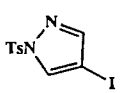
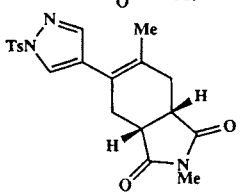
Scheme 28.

For reactions conducted under 1 atm of carbon monoxide the following reactivity profile obtains for aryl- and vinyl-palladium(II) species.

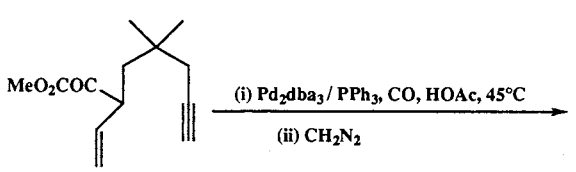
1. The relative rate of sequential carbon monoxide insertion-5-*exo*-trig acylpalladation > 4-*exo*-trig cyclopalladation.
2. The relative rates of 5-*exo*- and 6-*exo*-trig cyclopalladation > sequential carbon monoxide insertion 6-*exo*- and 7-*exo*-trig acylpalladation [48].
3. Anion capture by intramolecular neutral (such as alcohols, secondary amines) [48], or anionic intra (malonate) [48], or inter (hydride) [47]-molecular nucleophiles is slower than 5-*exo*- and 6-*exo*-trig cyclopalladation-carbonylation and 5-*exo*-acylpalladation.
4. Anion capture by sodium tetraphenylborate or $RSnBu_3$ is slower than 5-*exo*- and 6-*exo*-trig cyclopalladation-carbonylation and 5-*exo*-acylpalladation-carbonylation.
5. Preliminary results indicate that *exo*-dig cyclisation of aryl- or vinyl-palladium(II) species exhibit similar selectivities. Thus the rate of 5- and 6-*exo*-dig cyclopalladation > sequential carbon monoxide insertion-6- and -7-*exo*-dig acylpalladation [45,63].
6. For related reactions proceeding via alkylpalladium(II) species the relative rates of 3-*exo*-trig cyclopalladation and carbon monoxide insertion-methanol capture are similar. Appropriate modification of reaction conditions can produce high selectivity for either process [60].

The extensive work of Oppolzer et al. [36b] on the metallo-ene reaction substantially increased the scope and understanding of alkene/allylpalladium(II) and alkyne/allylpalladium(II) insertion reactions. These processes were extended to incorporate two carbon monoxide molecules in a series of tetramolecular processes based on allyl starter species and applied imaginatively in natural product synthesis. A typical example is **77** → **78** [64] a key step in the synthesis of (±)-pentalenolactone. Others have applied this approach to an efficient synthesis of [5.5.5.5] fenestene **79** → **80** [65] and an intriguing polycyclisation-carbonylation **81** → **82** [66] which generates four rings and six C–C bonds.

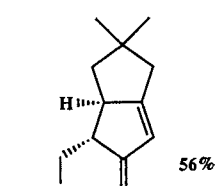
Table 10
Products of intramolecular Heck–Diels–Alder cascades of 1,1-dimethylallene[a]

Aryl Iodide	Product	Yield(%)[b]
		84
		R H 76 p-Me 71 p-SMe 56 m-OMe 71 o-OMe 40
		78
		65
		50

[a] All reactions carried out in toluene [120°C(bath temp.) 48 h] in a Schlenk tube, with 1,1-dimethylallene (5 mol eq) and *N*-methylmaleimide (1.1 mol eq). The catalyst system comprised 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3 and Ag_2CO_3 (2 mol eq).
[b] Isolated yields.

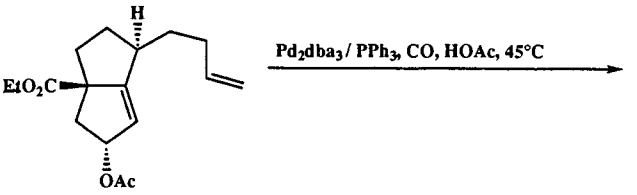


77

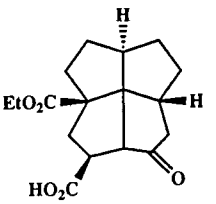


56%

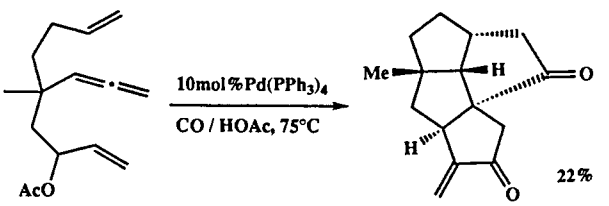
78



79



80 60%



81 82 22%

The foregoing section amply demonstrates the extraordinary versatility of cascade carbonylation reactions and their potential for further development.

3.2.2. Sequential carbon monoxide and allene insertions

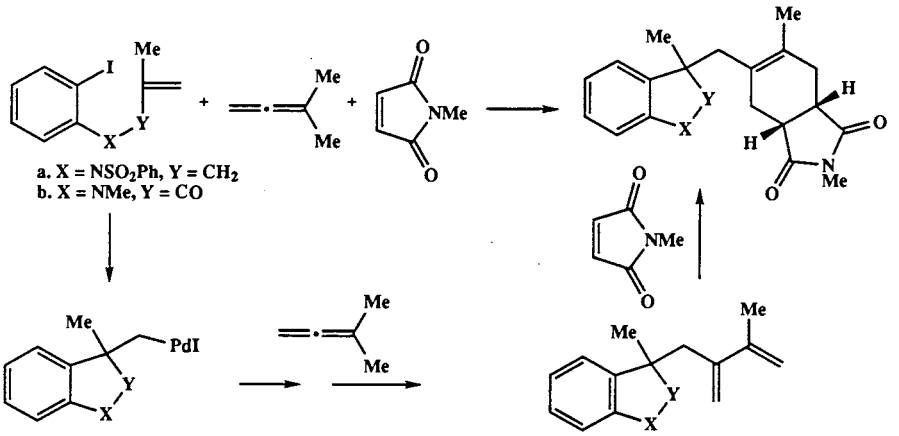
Whilst allene has not been fully developed as a relay switch component on its own its potential is foreshadowed by sequences such as those in Scheme 27 which terminate with a β-hydride elimination [67].

The reactions in Scheme 27 employed a catalyst system comprising 10 mol% Pd $(OAc)_2$, 20 mol% PPh_3, K_2CO_3 (3–5 mol eq) and Et_4NCl(1 mol eq) and proceed via sequential formation of two π-allyl intermediates both generated via attack at the centre carbon of the respective allene groups.

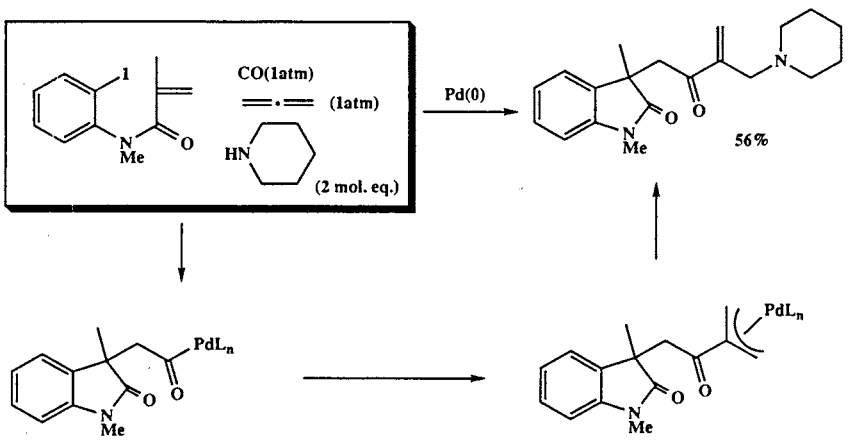
We have applied the β-hydride elimination in π-allyl species as the key step in a 3-component cascade terminating in a Diels–Alder reaction [68] (Scheme 28). Typical examples in which *N*-methylmaleimide was used as dienophile are collected in Table 10.

This cascade can be further extended by interfacing with the cyclisation-anion capture methodology as illustrated in Scheme 29 [68]. These cascades generate four new C–C bonds and two rings and give rise to diastereomer mixtures (ca. 1.6:1) in 69–72% yield.

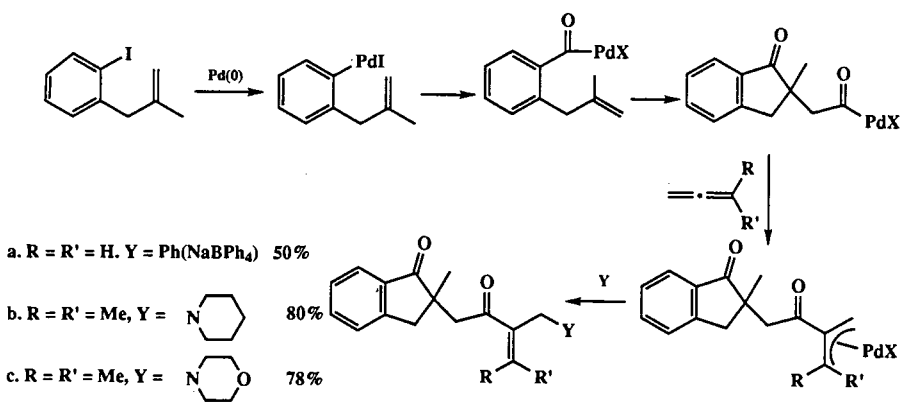
A typical tetramolecular queuing cascade (toluene, 110°C) employing our cyclisation-anion capture methodology and a catalyst system comprising 10 mol% Pd $(OAc)_2$, 20 mol% PPh_3 and Et_4NCl (1 mol eq) is shown in Scheme 30 [69].



Scheme 29.



Scheme 30.



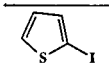
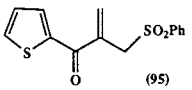
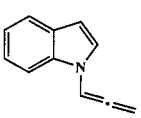
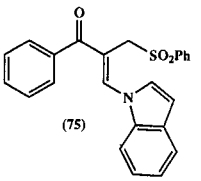
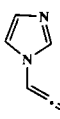
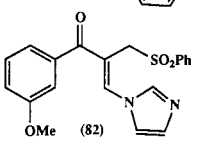
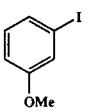
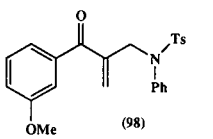
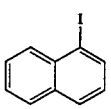
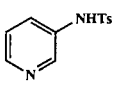
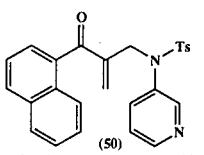
Scheme 31.

Acyclic versions of Scheme 30 have been achieved with allene and substituted allenes [70]. Representative examples employing $PhSO_2Na$ and ArNHTs as nucleophiles are collected in Table 11. In the cascades involving allene and CO there is an orderly molecular queue with incorporation of CO occurring prior to incorporation of allene(s) which are highly stereoselective for the for the *Z*-isomers (Table 11, entries 2 and 3).

3.3. Pentamolecular queuing cascades

A series of pentamolecular queuing cascades employing aryl (triflate, iodide) (Scheme 31) and vinyl (bromide, triflate) (Scheme 32) starter species and several allenes have been achieved [71]. The strategy employed in these cascades is analogous to that in Scheme 26 in that the initial oxidative product undergoes CO insertion in preference to a 4-*exo*-trig cyclisation.

Table 11
Tetramolecular queuing cascades employing CO and allenes[a]

Aryl Iodide	Allene[b]	Nucleophile[c,d]	Product(%Yield)
		$PhSO_2Na$	 (95)
		$PhSO_2Na$	 (75)
		$PhSO_2Na$	 (82)
		PhNHTs	 (98)
			 (50)

[a] All reactions carried out at 50°C in a Schlenk tube and employed CO (1 atm) and allene (1 atm). [b] A total of 3 mol eq of substituted allenes were employed. [c] $PhSO_2Na$ and allene: catalyst comprised 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3 [or 5 mol% $Pd(PPh_3)_4$] and Et_4NCl (1 mol eq) in DMF. $PhSO_2Na$ and substituted allenes: PPh_3 replaced by tris (2-furyl) phosphine ArNHTs: K_2CO_3 (2 mol eq) used as base with $Pd(OAc)_2/PPh_3$. [d] A total of 2 mol eq used in all reactions.

The reactions in Scheme 31 were carried out in toluene at 110°C with either $Pd(PPh_3)_4$ or $Pd(OAc)_2/PPh_3$ and used 2 mol eq of $NaBPh_4$ and 5–10 mol eq of dimethylallene [71a]. When employing vinyl triflates (Scheme 32) as starter species the reactions required careful optimisation to achieve high diastereoselectivity. Thus the optimised cascade of the 6-membered vinyl triflate [71b] (conditions shown in Scheme) afforded the pentamolecular product as a single diastereomer whilst the unoptimised 7-membered vinyl triflate cascade [71a] affords a 3:1 diastereomer mixture.

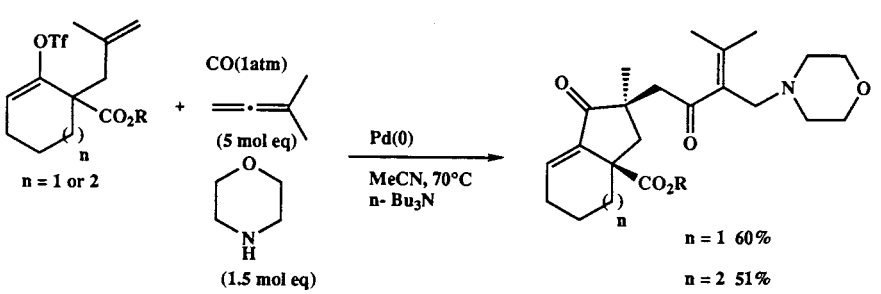
3.4. Hexa- and octa-molecular queuing cascades

Preliminary results have been obtained for processes involving hexa- and octa-molecular queuing processes. Thus 2-thienyl iodide reacts (toluene, 50°C) with CO (1 atm) and dimethylallene (5 mol eq) in the presence of *N*-tosylaniline (2 mol eq) and 10 mol% Pd_2dba_3 to give a mixture of hexa- and octa-molecular products (Scheme 33) which varies according to the reaction time [72].

The alternating insertions of carbon monoxide and allenes are related to the co-polymerisation of carbon monoxide and alkenes to form polyketone polymers. The latter processes have been extensively studied both mechanistically [73] and preparatively [74]. Mechanistic studies of the allene/CO systems have also been reported [75]. Allene concentration dependent and allene concentration independent pathways were detected. Migratory insertion of precoordinated allene appears to be rate determining.

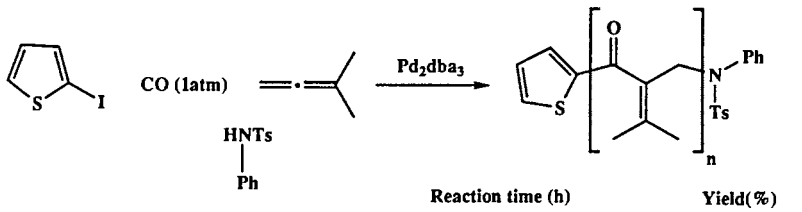
4. Conclusions

Cyclisation-carbopalladation has developed into a formidable reaction at a rapid pace following the demonstration in 1986 that the intramolecular Heck reaction provides access to both fused-, bridged- and spiro-cyclic systems and a reliable and flexible method for generating tetrasubstituted carbon centres. The ongoing development of novel palladium catalysts and additives to promote desirable features or suppress certain undesirable features of the reactions will continue to enhance the precision and scope of the basic cyclisation-carbopalladation and the wide range of processes developing from this. The advent of polycomponent queuing processes offers a new, productive avenue for organic synthesis.



catalyst: 10mol% $Pd(OAc)_2$ / 20mol% PR_3

Scheme 32.



Reaction time (h)	Yield(%)	
	n = 2	n = 3
24	60	10
48	59	40

Scheme 33.

Acknowledgements

The authors are deeply indebted to our co-workers whose names appear on the papers cited herein. The work reviewed has been supported by the EPSRC, the EU, Leeds University, GlaxoWellcome, Merck Sharp and Dohme, Organon, Pfizer, Rhone-Poulenc Rorer, Roussel, SKB and Zeneca. We also thank Johnson-Matthey for a loan of palladium salts.

References

[1] For reviews see: (a) L.F. Tietze, Chem. Rev. 96 (1996) 115. (b) Cascade Reactions, R Grigg (Ed.), Tetrahedron Symp.-in-Print. 52 (1996) 11385. (c) Tandem Organic Reactions, T.-L. Ho, Wiley (1992).

[2] R. Robinson, J. Chem. Soc. (1917) 762.

[3] J. Tsuji, Palladium Reagents and Catalysts, Wiley, New York, 1995.

[4] (a) B.L. Shaw, S.D. Perera, E.A. Staley, Chem. Commun. (1998) 1361. (b) W.A. Herrmann, C. Brossmer, C.-P. Reisinger, T.H. Riermeier, K. Ofele, M. Beller, Chem. Eur. J. 3 (1997) 1357. (c) M. Beller, T.H. Riermeier, Eur. J. Inorg. Chem. 1 (1998) 29. (d) M.T. Reetz, G. Lohmer, R. Schwickordi, Angew. Chem. Int. Ed. 37 (1998) 481. (e) M. Oliff, A. Oliff, M.E. van der Boon, D. Milstein, J. Am. Chem. Soc. 119 (1997) 11687. (f) M.T. Reetz, R. Breinbauer, K. Wanninger, Tetrahedron Lett. 37 (1996) 4499.

[5] For reviews see: (a) B.C. Soderberg., Comprehensive Organometallic Chemistry II, in: E.W. Abel, F.G.A. Stone, G. Wilkinson (Eds.), Pergamon Press, vol. 12, (1995); L.S. Hegedus, (Ed.), pp. 260–287, Elsevier Science (1995). (b) A. de Meijere, F.E. Meyer, Angew. Chem. Int. Ed. Engl. 33 (1994) 2379. (c) S.E. Gibson, R.J. Middleton, Contemporary Organic Synthesis (1996) 447. (d) M. Shibasaki, C.D.J. Boden, A. Kojima, Tetrahedron 53 (1997) 7371.

[6] (a) R. Grigg, V. Sridharan, P. Stevenson, T. Worakun, J. Chem. Soc. Chem. Commun. (1986) 1697. (b) R. Grigg, V. Sridharan, P. Stevenson, S. Sukirthalingam, Tetrahedron 45 (1989) 3557. (c) R Grigg, V. Sridharan, P. Stevenson, S. Sukirthalingam, T. Worakun Tetrahedron 46 (1990) 4003. (d) R. Grigg, S. Santhakumar, V. Sridharan, P. Stevenson, A. Teasdale, M. Thornton-Pett, T. Worakun, Tetrahedron 47 (1991) 9703.

[7] (a) M.M. Abelman, T. Oh, L.E. Overman, J. Org. Chem. 53 (1987) 4130. (b) M.M. Abelman, L.E. Overman, V.D. Tran, J. Am. Chem. Soc. 112 (1990) 6959. (c) L.E. Overman, Pure App. Chem. 66 (1994) 1423.

[8] (a) E.I. Negishi, Y. Zhang, B. O'Connor, Tetrahedron Lett. 29 (1988) 2915. (b) E.I. Negishi, T. Nguyen, B. O'Conner, Heterocycles 28 (1989) 55. (c) R.C. Larock, H. Song, B.E. Baker, W.H. Gong, Tetrahedron Lett. 29 (1988) 2919. (d) W.S. Young, J.J. Masters, S. Danishefsky, J. Am. Chem. Soc. 117 (1995) 5228. (e) L.F. Tietze, H. Schirok, Angew. Chem. Int. Ed. Engl. 36 (1997) 1124. (f) J.H. Rigby, R.C. Hughes, M.J. Hee, J. Am. Chem. Soc. 117 (1995) 7834. (g) E.I. Negishi, C. Coperet, S. Ma, S.Y. Liou, F. Liu, Chem. Rev. 96 (1996) 365.

[9] T. Jeffery, Tetrahedron 52 (1996) 10113.

[10] (a) K. Karabelas, C. Westerlund, A. Hallberg, J. Org. Chem. 50 (1985) 3896. (b) K. Karabelas, A. Hallberg, J. Org. Chem. 51 (1986) 5286. (c) K. Karabelas, A. Hallberg, J. Org. Chem. 54 (1989) 1773. (d) M.M. Abelman, L.E. Overman, J. Am. Chem. Soc. 110 (1988) 2328. (e) R C. Larock, W.H. Gong, J. Org. Chem. 54 (1989) 2047. (f) K. Nilsson, A. Hallberg, J. Org. Chem. 55 (1990) 2464. (g) T. Jeffrey, Tetrahedron Lett. 33 (1992) 1989. (h) A. Ashimori, L.E. Overman, J. Org. Chem. 57 (1992) 4571. (i) Y. Sato, S. Watanabe, M. Shibasaki, Tetrahedron Lett. 35 (1992) 2589.

[11] (a) R. Grigg, V. Loganathan, S. Sukirthalingam, V. Sridharan, Tetrahedron Lett. 31 (1990) 6573. (b) R. Grigg, V. Loganathan, V. Santhakumar, V. Sridharan, A. Teasdale, Tetrahedron Lett. 32 (1991) 687. (c) C. Carfagna, A. Musco, G. Sallese, R. Santi, G. Fiorani, J. Org. Chem. 56 (1991) 261 (d) W. Cabri, I. Candiani, A. Bedeschi, R. Senti, Tetrahedron Lett. 32 (1991) 1753. (e) T. Jeffrey, Tetrahedron Lett. 33 (1192) 1989. (f) L. Ripa, A. Hallberg, J. Org. Chem. 61 (1996) 7147. (g) N. Chida, N. Ohtsuki, S. Ogawa, Tetrahedron Lett. 32 (1991) 4525. (h) M.C. McIntosh, S.M. Weinreb, J. Org. Chem. 58 (1993) 4823. (i) T. Hudlicky, H.F. Olivo, J. Am. Chem. Soc. 114 (1992) 9694.

[12] For a previous review see: R Grigg, J. Heterocyclic Chem. 31 (1994) 631.

[13] (a) C.H. Oh, C.Y. Rhim, J.H. Kang, A. Khim, B.S. Park, Y. Seo, Tetrahedron Lett. 37 (1996) 8875. (b) C.H. Oh, C.Y. Rhim, K.Y. Hwang, Chem. Lett. (1997) 777. (c) C.H. Oh, J.H. Kang, C.Y. Rhim, J.H. Kim, Chem. Lett. (1998) 375. (d) R. Grigg, M. Monteith, V. Sridharan, C. Terrier, Tetrahedron 54 (1998) 3885. (e) H. Jiang, S. Ma, G. Zu, X. Lu, Tetrahedron 52 (1996) 10945. (f) G. Zu, X. Lu, J. Organomet. Chem. 508 (1996) 83.

[14] R. Grigg, S. Sukirthalingam, V. Sridharan, Tetrahedron Lett. 32 (1991) 2545.

[15] J. March, Advanced Organic Chemistry Reaction Mechanisms and Structure, 3rd, Wiley-Interscience, New York, 1985, p. 138.

[16] A. Casaschi, R. Grigg, J.M. Sansano, D. Wilson, J. Redpath, Tetrahedron Lett. 37 (1996) 4413.

[17] (a) F. Guibe, G. Balavoine, H.X. Zhang, J. Org. Chem. 55 (1990) 1857. (b) Y. Ito, M. Inouye, H. Yokata, M. Murakami, J. Org. Chem. 55 (1990) 2567.

[18] (a) J.K. Stille, M.J. Tanaka, J. Am. Chem. Soc. 109 (1987) 3785. (b) A. Kalivetenos, J.K. Stille, L.S. Hegedus, J. Org. Chem. 56

(1991) 2883. (c) J.E. Baldwin, R.M. Aldington, S.H. Ramcharitar, Tetrahedron 48 (1992) 2957. (d) G. Pattenden, S.M. Thom, Synlett. (1993) 215. (e) K.C. Nicolaou, T.K. Chakrabarty, A.D. Piscopio, N. Minowa, P. Bertino, J. Am. Chem. Soc. 115 (1993) 4419. A.G.M. Barrett, M.L. Boys, T.L. Boehm, J. Chem. Soc. Chem. Commun. (1994) 1881.

[19] (a) M. Hirama, K. Fujiwara, K. Shigematu, Y. Fukazawa, J. Am. Chem. Soc. 111 (1989) 4120. (b) M.D. Shair, T. Yoou, S.J. Daniskefsky, J. Org. Chem. 59 (1994) 3755.

[20] R. Grigg, V. Sridharan, S. Sukirthalingam, T. Worakun, Tetrahedron Lett. 30 (1989) 1139.

[21] B. Burns, R. Grigg, V. Santhakumar, V. Sridharan, P. Stevenson, T. Workun, Tetrahedron 48 (1992) 7297.

[22] R. Grigg, V. Sridharan, L.-H. Xu, J. Chem. Soc. Chem. Commun. (1995) 1903.

[23] M. Gardiner, R. Grigg, V. Sridharan, N. Vickers, Tetrahedron Lett. 39 (1998) 435.

[24] R. Grigg, J.M. Sansano, Tetrahedron 52 (1996) 13441.

[25] (a) J. Mann, S. Barbey, Tetrahedron 51 (1995) 12763. (b) J.-F. Nguefack, V. Bolitt, D. Sinou, J. Chem. Soc. Chem. Commun. (1995) 1893 and references therein.

[26] R. Grigg, J.M. Sansano, V. Santhakumar, V. Sridharan, R. Thangavelanthum, M. Thornton-Pett, D. Wilson, Tetrahedron 53 (1997) 11803.

[27] (a) B. Burns, R. Grigg, P. Ratananokul, V. Sridharan, P. Stevenson, S. Sukirthalingham, T. Worakun, Tetrahedron Lett. 43 (1988) 5565. (b) R. Grigg, D. Wilson (unpublished results).

[28] R. Grigg, V. Santhakumar, V. Sridharan, Tetrahedron Lett. 34 (1993) 3163.

[29] (a) V. Farina, V. Krishnamurthy, W.J. Scott, The Stille Reaction, Organic Reactions, Wiley (1997) vol. 50. (b) M. Pereyre, J.-P. Quintard, A. Rohm, Tin in Organic Synthesis, Butterworths (1987).

[30] (a) R. Grigg, V. Loganathan, V. Sridharan, P. Stevenson, S. Sukirthalingam, T. Worakun, Tetrahedron 52 (1996) 11479. (b) H. Finch, N.A. Pegg, B. Evans, Tetrahedron Lett. 34 (1993) 8353.

[31] B. Burns, R. Grigg, V. Sridharan, P. Stevenson, S. Sukirthalingam, T. Worakun, Tetrahedron Lett. 30 (1989) 1135.

[32] A. Brown, R. Grigg, R Thangavelanthum, unpublished results.

[33] E.-I. Negishi, Y. Noda, F. Lamaty, E.J. Vawter, Tetrahedron Lett. 31 (1991) 4393.

[34] J.E. Bäckvall, R.E. Nordberg, J.E. Nystron, R.G. Nordberg, J. Am. Chem. Soc. 107 (1985) 3676.

[35] R. Grigg, V. Sridharan, S. Sukirthalingam, Tetrahedron Lett. 31 (1991) 3855.

[36] For reviews see: (a) R. Grigg, V. Sridharan, Comprehensive Organometallic Chemistry II, E.W. Abel, F.G.A. Stone, G. Wilkinson (Eds.), Pergamon Press (1995), vol. 12, L.S. Hegedus (Ed.), p. 299. (b) W. Oppolzer, Comprehensive Organometallic Chemistry II, E.W. Abel, F.G.A. Stone, G. Wilkinson (Eds.), Pergamon Press (1995), vol. 12, L.S. Hegedus (Ed.), p. 905.

[37] (a) R. Grigg, D. Wilson, unpublished results. (b) E.L. Eliel, S.H. Wilen, Stereochemistry of Organic Compounds, Wiley, 2nd ed. (1994), p. 764.

[38] R. Grigg, V. Santhakumar, unpublished results.

[39] J. Tsuji, T. Mandai, Angew. Chem. Int. Ed. Engl. 34 (1995) 2589.

[40] R. Grigg, R. Rasul, D. Wilson, Tetrahedron Lett. 37 (1996) 4609.

[41] W. Oppolzer, A. Pimm, B. Stammen, W. Hulme, Helv. Chim. Acta. 80 (1997) 623.

[42] R. Grigg, R. Rasul, unpublished observations.

[43] D. Brown, R. Grigg, V. Sridharan, V. Tambyrajah, M. Thornton-Pett, Tetrahedron 54 (1998) 2595.

[44] R. Grigg, R. Rasul, V. Savic, Tetrahedron Lett. 38 (1997) 1825.

[45] R. Grigg, P. Kennewell, A.J. Teasdale, Tetrahedron Lett. 33 (1992) 7789.

[46] For reviews see: (a) J.K. Stille, Comprehensive Organic Synthesis, B.M. Trost, I. Fleming, M.E. Semmelhack (Eds.), Pergamon Press (1991) vol. 4, M.F. Semmelhack (Ed.), p. 913. (b) I. Ojima,, M. Eguchi, M. Tzamcrioudaki, Comprehensive Organometallic Chemistry II, E.W. Abel, F.G.A. Stone, G. WiLkinson (Eds.), Pergamon Press, (1995) vol. 12, L.S. Hegedus (Ed.) p. 27.

[47] S. Brown, S. Clarkson, R. Grigg, V. Sridharan, J. Chem. Soc. Chem. Commun., (1995) 1135.

[48] R. Grigg, V. Sridharan, Tetrahedron Lett. 34 (1993) 7471.

[49] R. Grigg, V. Santhakumar, V. Sridharan, M. Thornton-Pett, A.W. Bridge, Tetrahedron 49 (1993) 5177.

[50] R. Grigg, S. Suganthan, unpublished observations.

[51] A.L. Mueller, R. Roeloffs, H. Jackson, in: G.A. Cordell (Ed.), The Alkaloids, vol. 46, Academic Press, New York, 1995, p. 63.

[52] R. Grigg, B. Putnikovic, D. Sykes, V. Savic, unpublished observations.

[53] E.V. Grishin, T.M. Volkova, A.S. Arsenier, Bioorg. Khim. 14 (1998) 883.

[54] R. Grigg, J. Redpath, V. Sridharan, D. Wilson, Tetrahedron Lett. 35 (1994) 4429.

[55] (a) B. Caze, Pure Appl. Chem. 62 (1990) 1867. (b) L. Besson, J. Goré, B. Caze, Tetrahedron Lett. 36 (1995) 3857. (c) M. Al-Masum, M. Meguro, Y. Yarnamoto, Tetrahedron Lett. 38 (1997) 6071. (d) M. Lautens, T. Rovis, N.D. Smith, D. Ostrovsky, Pure Appl. Chem. 70 (1998) 1059.

[56] Cyclisation: (a) I.W. Davies, D.I.C. Scopes, T. Gallagher, Synlett. (1993) 85. (b) R.D. Walkup, L. Guan, Y.S. Kim, S.W. Kim, Tetrahedron Lett 36 (1995) 3805. (c) S. Ma, E.-I. Negishi, J. Am. Chem. Soc. 117 (1995) 6345.

[57] Cycloaddition: (a) R.C. Larock, N.G. Berrios-Pena, C.A. Fried, J. Org. Chem. 56 (1991) 2615. (b) R.C. Larock, J.M. Zenner, J. Org. Chem. 60 (1995) 482. (c) T. Jescke, D. Wenshe, U. Annaby, S. Gronowitz, L.A. Cohen, Tetrahedron Lett. 34 (1993) 2823 and 6471.

[58] R. Grigg, V. Sridharan, C. Terrier, Tetrahedron Lett. 37 (1996) 4221.

[59] R. Grigg, V. Savic, Tetrahedron Lett. 37 (1996) 6565.

[60] A. Brown, R. Grigg, T. Ravishanker, M. Thornton-Pett, Tetrahedron Lett. 35 (1994) 2753.

[61] R. Grigg, J. Redpath, V. Sridharan, D. Wilson, Tetrahedron Lett. 35 (1994) 7661.

[62] (a) C. Coperet, S. Ma, E.-I. Negishi, Angew. Chem. Int. Ed. Engl. 35 (1996) 2125. (b) E.-I. Negishi, S. Ma, J. Emanfu, C. Coperet, J.A. Miller, J.M. Tour, J. Am. Chem. Soc. 118 (1996) 5919. (c) E.-I. Negishi, C. Coperet, S. Ma, T. Mita, T. Sugihara, J.M. Tour, J. Am. Chem. Soc. 118 (1996) 5904.

[63] R. Grigg, P. Levett, unpublished observations.

[64] W. Oppolzer, J.-Z. Xu, C. Stone, Helv. Chim. Acta 74 (1991) 465.

[65] R. Keese, R. Guidetti-Grept, B. Herzog, Tetrahedron Lett. 33 (1992) 1207.

[66] (a) T. Doi, A. Yanagisawa, K. Yamamoto, T. Takahashi, Chem. Lett. (1996) 1085. (b) T. Doi, A. Yanagisawa, S. Nakanishi, K. Yamamoto, T. Takahashi, J. Org. Chem. 61 (1996) 2602.

[67] R. Grigg, L.-H. Xu, Tetrahedron Lett. 37 (1996) 4251.

[68] R. Grigg, S. Brown, V. Sridharan, M.D. Uttley, Tetrahedron Lett. 39 (1998) 3247.

[69] R. Grigg, C. Terrier, unpublished results.

[70] (a) R. Grigg, S. Brown, V. Sridharan, M.D. Uttley, Tetrahedron Lett. 38 (1997) 5031. (b) R. Grigg, S. Brown, V. Sridharan, M.D. Uttley, unpublished observations.

[71] (a) R. Grigg, R. Pratt, Tetrahedron Lett. 38 (1997) 4489. (b) R. Grigg, P. Quadrelli, unpublished observations.

[72] R. Grigg, M.D. Uttley, unpublished observations.

[73] (a) F.C. Rix, M. Brookhart, J. Am. Chem. Soc. 117 (1995) 1137. (b) F.C. Rix, M. Brookhart, P.S. White, J. Am. Chem. Soc. 118 (1996) 4746. (c) R. van Asselt, E.E.C.G. Gielens, R.E. Rülke, K. Vrieze, C.J. Elsevier, J. Am. Chem. Soc. 116 (1994) 977.

[74] E. Drent, P.H.M. Budzelaar, Chem. Rev. 96 (1996) 663.

[75] (a) J.H. Groen, C.J. Elsevier, K. Vrieze, W.J.J. Sweets, A.L. Spek, Organometallics 15 (1996) 3445. (b) H.A. Ankersmit, N. Veldman, A.L. Spek, K. Eriksen, K. Goubitz, K. Vrieze, G. van Koten, Inorg. Chim. Acta. 252 (1996) 203.