Heterocycle Synthesis by Palladium Catalysed Cyclisation-Anion Capture Processes. A Powerful New Strategy

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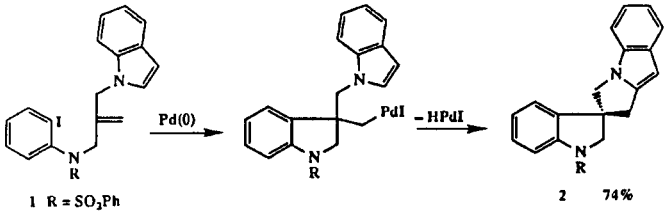
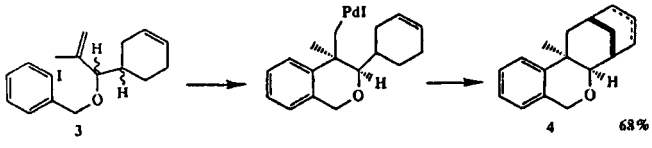
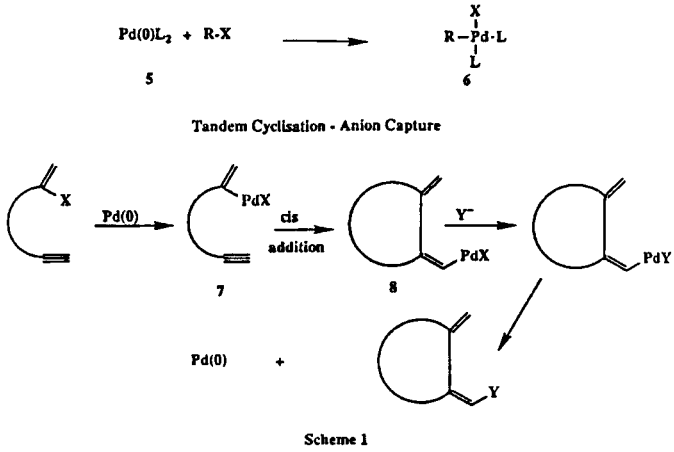
Palladium salts and complexes are exceptionally versatile catalysts for the construction of carbon-carbon and carbon-heteroatom bonds [1]. Much recent attention has focused on the Heck reaction [2] due to its technical simplicity and tolerance of a wide variety of functional groups. The scope of this palladium catalysed vinylation of aryl, heteroaryl, vinyl and benzyl halides has been substantially extended over the past decade. Our own early researches [3] demonstrated the considerable versatility of the intramolecular Heck reaction [4] for the construction of bridged-rings [5], spirocycles and tetrasubstituted carbon centers [7]. Typical examples are provided by **1** → **2** [6] and **3** → **4** [5].





The intramolecular Heck reaction is invariably regiospecific [8] with a clear kinetic preference for a 5-exo-trig cyclisation mode, *e.g.* **1** → **2**, as compared to a 6-endo-trig cyclisation and for a 6-exo-trig cyclisation over a 7-endo-trig cyclisation, *e.g.* **3** → **4**.

We normally generate the active Pd(0) catalyst *in situ* from palladium acetate and triphenylphosphine and it is rarely necessary to resort to preformed Pd(0) catalysts such as $Pd(PPh_3)_4$ or $Pd_2(dba)_3L$ (dba = dibenzylidine acetone, L = $CHCl_3$) or to phosphines other than triphenylphosphines. However, substitution of triphenylphosphine by tri(2-furyl)phosphine [9] or triphenylarsine [10] has proved advantageous in a few cases. The catalytically active Pd(0) species requires two vacant coordination sites for the initial oxidative addition **5** → **6** to occur. Thus when generating Pd(0) *in situ* it is usually advantageous to use a 1:2 molar ratio of Pd(II) to phosphine. [$Pd(0)L_4$ is coordinatively saturated and catalytically inactive].

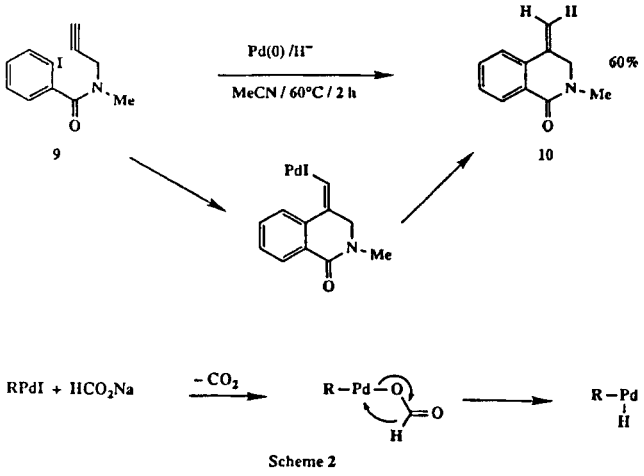


Scheme 1

The Heck reaction terminates each catalytic cycle by a β-hydride elimination. Hence it is not possible to incorporate alkynes into these processes. A considerable increase in synthetic complexity would open up if (a) alkynes could be incorporated and (b) the β-hydride elimination step could be replaced by a group or atom transfer. These considerations led us to devise the tandem cyclisation anion capture methodology illustrated for alkynes in Scheme 1. The use of the word "anion" in this context embraces both ionic and covalent sources of Y and is felt to be more appropriate than the term cross-coupling. The initial oxidative addition generates a vinyl (or aryl/heteroaryl) Pd(II) species **7** which will undergo *cis*-addition to a proximate alkyne to give **8**. Absence of a β-hydride elimination pathway precludes further development of a Heck-type catalytic cycle. However if the anion X in **8** (X = Br, I, OTf *etc*) could be exchanged for Y such that Y facilitates reductive elimination with formation of C-Y bond and regeneration of Pd(0), then a catalytic cycle would be established that enables an atom or group Y to be precisely and stereospecifically placed on the carbon framework.

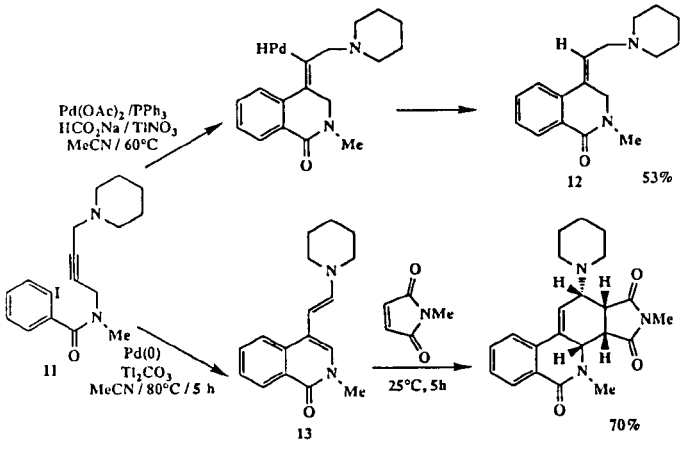
Our initial evaluation of Scheme 1 centered on using hydride as the anion exchange agent. Thus the alkyne substrate **9** furnished **10**.

A range of potential hydride ion sources was surveyed: formic acid-piperidine, alkali metal formates, $NaBH_4$, $LiAlH_4$, Ph_2SiH_2, Bu_3SnH and *i*-PrOH. Formic acid-piperidine was used in our early work but sodium formate is now the preferred reagent and palladium hydride generation from formate is outlined in Scheme 2.



Scheme 2

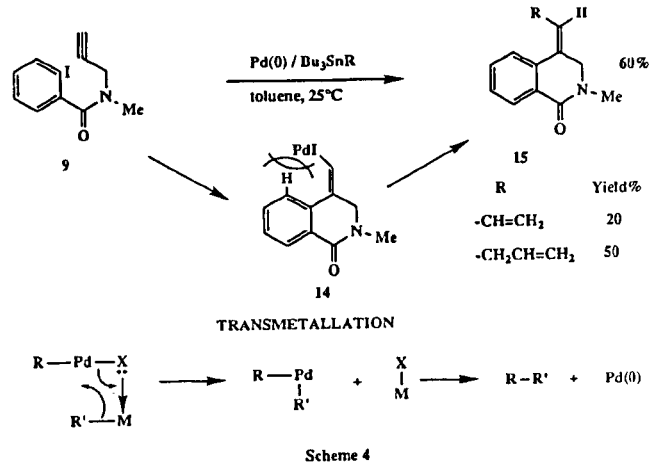
In studying the extension of the cyclisation-hydride capture process to disubstituted alkynes a further interesting process was uncovered. The alkyne **11** initially underwent the cyclisation-anion capture process to **12** in < 30% yield but the addition of thallium (I) nitrate (1 mole) significantly increased the yield (Scheme 3). In evaluating other Tl(I) salts we discovered that Tl_2CO_3 diverted the reaction into a new channel and furnished the diene **13** which could be trapped as its maleimide Diels-Alder cycloadduct in good yield (Scheme 3). The stereochemistry of **12**, the Diels-Alder cycloadducts, and other cyclisation-anion capture products described in this paper has been established by nOe studies. Several mechanisms can be formulated for **11** → **13** *e.g.* alkyne → allene interconversion followed by cyclisation or dehydrogenation of **12** to an iminium species followed by isomerisation. Good evidence for the former process is provided by prior formation of the allene from **11** and its cyclisation to **13** in good yield (unpublished results).



Scheme 3

The role of the Tl(I) salts is to effect a double decomposition with the organopalladium iodide generating an organopalladium species with a nitrate or carbonate counterion leading to a more ionic, more reactive palladium species. We have shown that Tl(I) salts are effective in promoting a range of palladium catalysed processes [11].

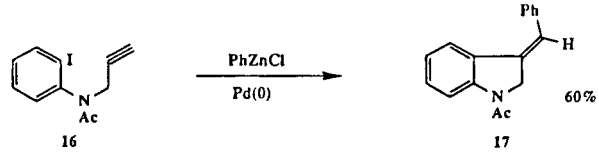
The cyclisation-anion capture process can also be achieved with organotin species. Thus **9** reacts with Pd(0) and Bu_3SnR to give **15** albeit in disappointing yield.



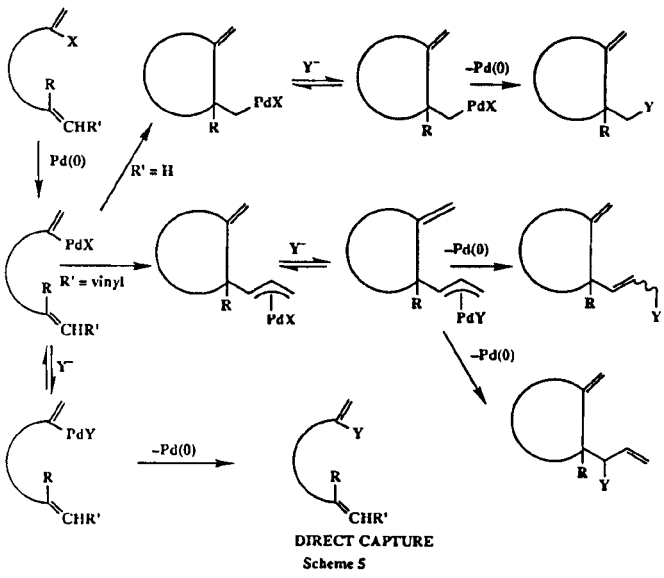
Scheme 4

A possible reason for the poor yields in these processes is the steric hindrance between the peri-hydrogen atom and the bulky PdI moiety both in intermediate **14** and in the transmetallation transition state (Scheme 4). The transmetallation is generally expected to be the rate determining step although little mechanistic detail is known for such processes. In transmetallations involving metals or metalloids capable of ate complex formation (*e.g.* Sn,B *etc*) an association complex such as that shown in Scheme 4 may be important.

Analogous cyclisation anion capture processes occur with organozinc reagents *e.g.* **16** → **17**.



The successful demonstration of the cyclisation-anion capture concept strongly suggested such processes should also occur by cyclisation of organopalladium(II) intermediates onto alkenes, 1,2-dienes and 1,3-dienes, provided a β-hydride elimination step is unavailable. Moreover the initiation step could conceptually involve oxidative addition of Pd(0) to an alkyl, aryl, vinyl or allylic halide (triflate *etc.*). Scheme 5 illustrates the process for a vinyl/aryl halide (triflate)cyclising onto a proximate alkene or 1,3-diene.

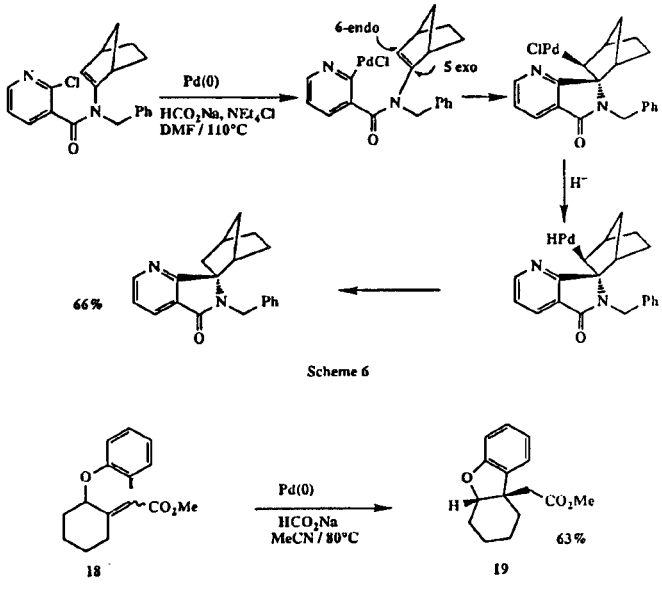


Scheme 5

Insertion of Pd(0) into a suitable C-X bond (X = Br, I, OTf *etc*) generates the organopalladium(II) species which can cyclise onto a proximate alkene or 1,3-diene moiety to generate alkyl- and π-allyl-palladium(II) species respectively. Exchange of X for a new "anion" Y can then occur. If the new "anion" Y facilitates a reductive elimination the catalytic cycle becomes established resulting in a new ring forming process which is accompanied by the introduction of functionality Y in a regio- and stereo-defined way. Incorporation of the blocking substituent R on the proximate alkene is necessary to prevent β-hydride elimination although incorporation of R into the dienyl substrates is unlikely to be necessary since β-hydride elimination from palladium π-allyl species is known to be slow [13]. An alternative strategy to a blocking group R (Scheme 5) is to utilise bridgehead strain effects (Bredt's rule) [14] and several examples of this will be described below. The efficiency of Scheme 5 will depend on a fast cyclisation step compared to anion exchange and reductive elimination. In the absence of this rate advantage direct coupling of Y without cyclisation will be a competitive process (Scheme 5) and in unfavourable cases may occur to the exclusion of the desired cyclisation-anion capture process. Our experience to date indicates that when the cyclisation step involves formation of 3-6 membered rings the direct capture process does not effectively compete with cyclisation-anion capture.

Preliminary evaluation of Scheme 5 utilising the hydride capture sequence revealed its potential as illutrated by Scheme 6 and **18** → **19** (unpublished).

The palladium catalysed cyclisation-anion capture concept thus appears to offer great promise and the potential scope of the process is emphasised by Table 1 [15] which incorporates the, as yet little explored, polycyclisation-anion capture strategy.

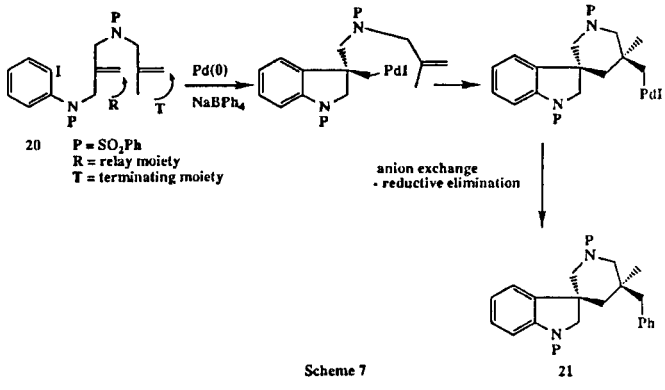


Scheme 6

Table 1

Potential Combinations for (Poly)cyclisation Anion-Capture Processes

Starter Species	Relay Species (R)	Terminating Species (T)	Y
alkyl	alkene	alkene	anionic (H, OAcCN, SO_2Ph, $CH(CO_2R)_2$]
aryl	alkyne	alkyne	neutral (amines, MeOH/CO, acrylates)
vinyl	1,2-diene	1,2-diene	organometallics RM [M = Sn (IV),
allyl	1,3-diene	1,3-diene	B(III), Zn(II)]



Scheme 7

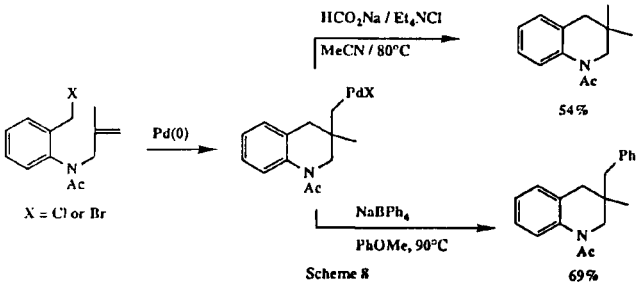
Any starter moiety can conceptually be combined with any relay moiety, any terminating moiety, and any anion

transfer reagent. Moreover, the relay phase can, in principle, incorporate several successive cyclisations before engaging the terminating moiety. The "anion" transfer reagents listed in the Table are illustrative rather than exhaustive and much further development remains to be done in this area. It should be noted that when the terminating species is a 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) ion *i.e. cis* with respect to Pd(II) (Y = H, alkyl, aryl, CO). The regio- and stereochemical outcome is thus dependant on the nature of Y [13,16]. A typical example of processes encompassed by Table 1 is shown (Scheme 7) by the cyclisation of (20) to a single diastereomer of (21) [7]. Here we have an aryl starter species combined with a single alkene relay (R) and alkene terminator (T) (20, R and T) followed by anion (Ph⁻) transfer from sodium tetraphenylborate. The process occurs in anisole at 100° in 63% yield.

We have achieved examples of monocyclisation processes which employ all the starter, terminating and anion capture species listed in Table 1 [15,18-21] but by no means all the possible combinations of these have been investigated. Additionally we have begun to explore biscyclisation-anion capture and our initial studies indicate these are remarkably stereoselective [22]. Illustrative examples of various monocyclisation-anion capture processes will be discussed first followed biscyclisation-anion capture processes and palladium catalysed cycloaddition reactions.

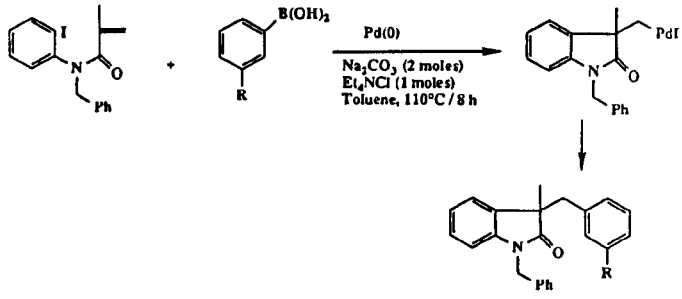
Monocyclisation-Anion Capture.

A typical example of an alkyl halide starter is provided in Scheme 8 [20]. The flexible creation of various gem-substituted centres is a particularly attractive feature of the cyclisation-anion capture methodology, which in this case proceeds *via* a 6-exo-trig cyclisation.



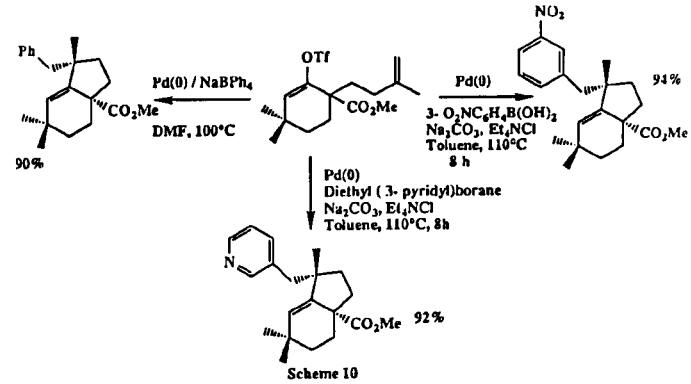
Scheme 8

Aryl halides and triflates provide readily accessible substrates for the new methodology and have been widely utilised in our studies. Thus monocyclisations using boronic acids as "anion" transfer reagents occur in good yield (Scheme 9, unpublished).



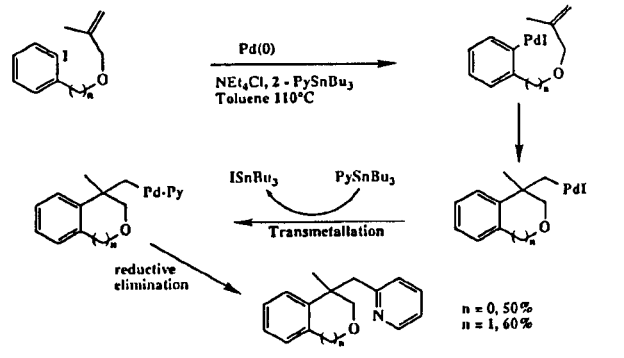
Scheme 9 Quantitative R = H, Br, NO_2

Vinyl triflates are also excellent substrates, and cyclisation with capture of groups from a wide variety of boron reagents occurs stereospecifically in good yield as illustrated by Scheme 10 (unpublished). The stereochemistry of these products was established by a combination of nOe studies and X-ray crystallography.

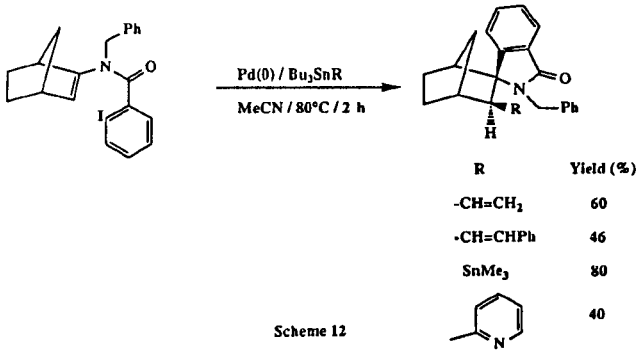


Scheme 10

The availability and stability of a wide range of both boronic acids and organotin(IV) compounds make these two classes of "anion" transfer reagents particularly attractive and versatile. Monocyclisation of aryl iodide substrates with transfer of groups from tin(IV) is illustrated by Schemes 11 (unpublished) and 12 [18].



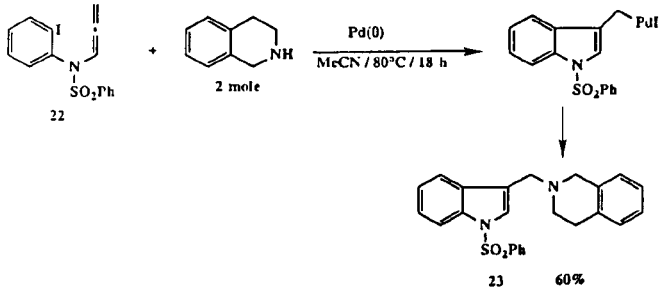
Scheme 11



Scheme 12

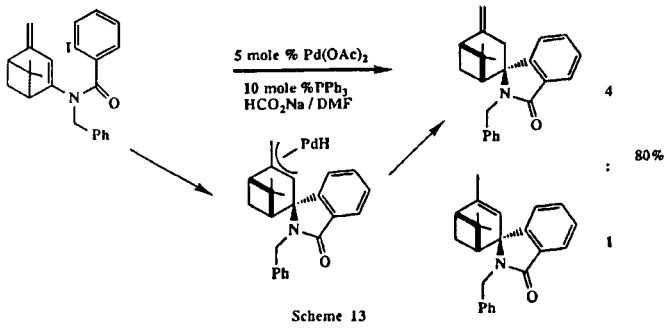
The stereochemistry of the products in Scheme 12 follows from the expected *cis*-addition of the intermediate arylpalladium iodide to the least hindered face of the norbornene and was confirmed by nOe studies. The $SnMe_3$ group transfer occurred from hexamethylditin as the tin(IV) reagent.

An example of a monocyclisation involving a 1,2-diene as the terminator is provided by the cyclisation of **22** to **23** (unpublished).

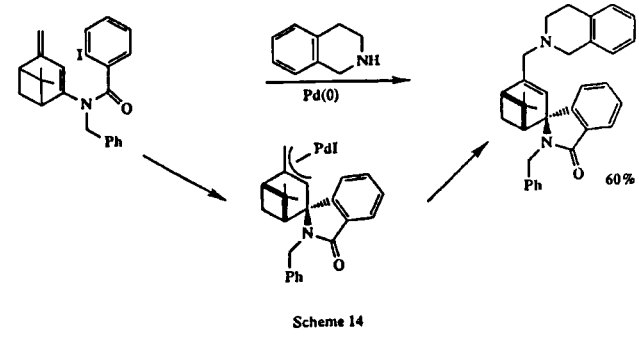


In this case a 5-exo-dig cyclisation furnishes an indole. Two moles of the secondary amine are added with one mole acting as a base.

Cyclisation onto a 1,3-diene generates a π-allyl intermediate which can progress to products by transfer of a group or atom *via* palladium (Scheme 13) [15] or by external attack of a nucleophile on the π-allyl species (Scheme 14) [19].

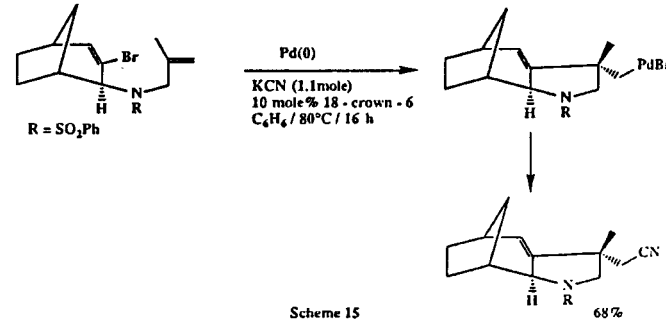


Scheme 13



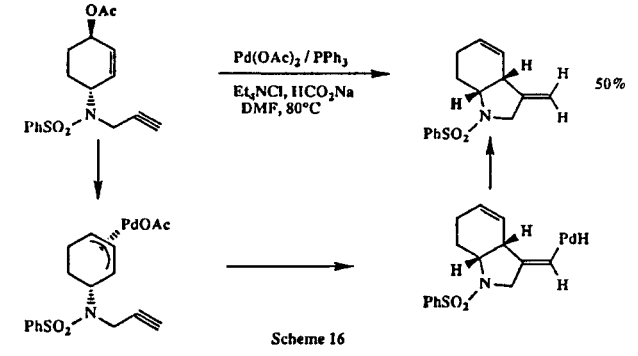
Scheme 14

Monocyclisation with cyanide ion capture has recently been achieved for a range of substrates [21] and is illustrated by the stereospecific vinyl halide cyclisation shown in Scheme 15.

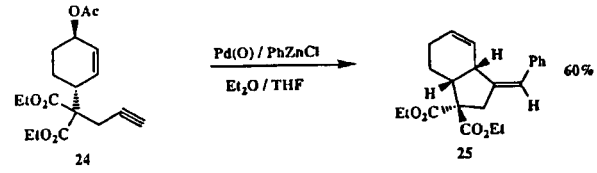


Scheme 15

Allylic acetates also function well as starter species for cyclisation-anion capture [20]. Typical examples of hydride capture and transfer from zinc(II) are provided by Scheme 16 and the cyclisation of **24** → **25** respectively. In the formation of the initial π-allylpalladium species the palladium coordinates to the face of the ring *trans* to the leaving group resulting in stereospecific π-allyl formation [13]. Cyclisation-anion capture then occurs regio- and stereo-specifically and no double bond isomerisation is observed in the product.



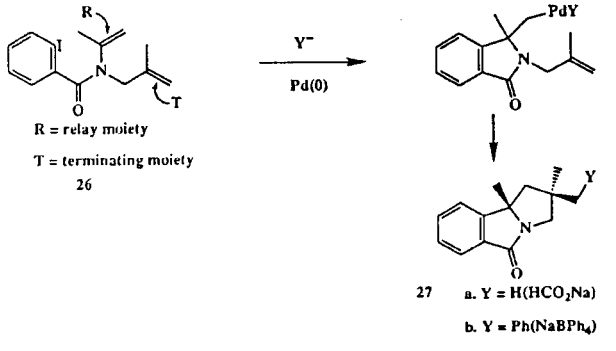
Scheme 16



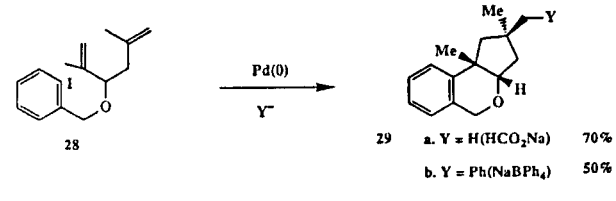
24 25

Biscyclisation-Anion Capture.

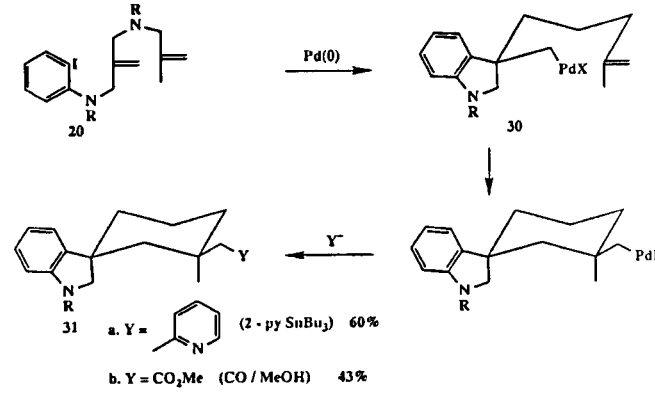
A series of biscyclisation-anion capture processes has been studied [17]. In some instances products arising from monocyclisation-anion capture were also formed but these can generally be eliminated or minimised by adjustment of the reaction conditions. Tl(I) salts are often useful in this respect.



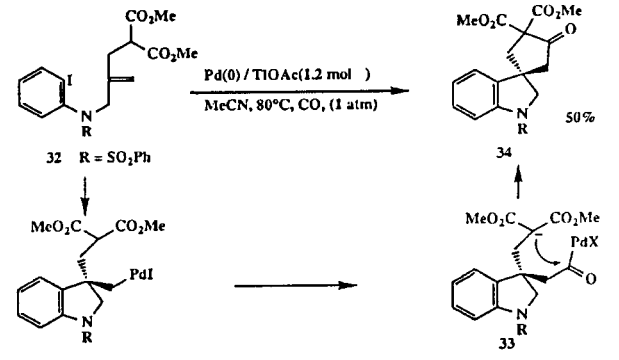
The palladium catalysed cyclisation of **26** in the presence of a hydride ion source or sodium tetraphenylborate furnishes the tricyclic products **27a** and **27b**. Although the yield of **27b** is low it is significant that only a single stereoisomer is produced. This stereospecificity has been observed in all biscyclisation-anion capture processes studied to date. Thus the ether **28** is converted into **29a** and **29b** by the same reagents.



As mentioned above the biscyclisation substrate **20** cyclised with anion capture from sodium tetraphenylborate to yield **21** as a single diastereomer. Similarly cyclisation of **20** with anion transfer from tin(IV) affords **31a** and capture of carbon monoxide/methanol affords the ester **31b** both as single diastereomers. The origin of the diasteroselectivity lies, we believe, in the conformational preferences in the monocyclisation intermediate **30** for the bulky substituents to adopt a pseudo-equatorial conformation in the transition state for the second cyclisation and for the second cyclisation to transfer the bulky PdI group to an equatorial site.



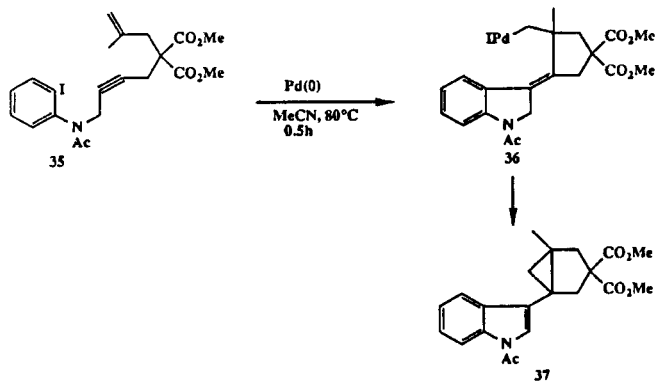
The transfer of the ester group (CO/MeOH) in the formation of **31b** required $(PPh_3)_2PdCl_2$ as catalyst and the addition of TlOAc (3 moles). Using this combination carbonylation could be achieved at atmospheric pressure. The promoting effect of Tl(I) salts on carbonylation reactions [23] has proved a general phenomena as illustrated by the conversion of **32** to **34**. In this case the carbonylated palladium intermediate **33** is intercepted by the proximate carbanion.



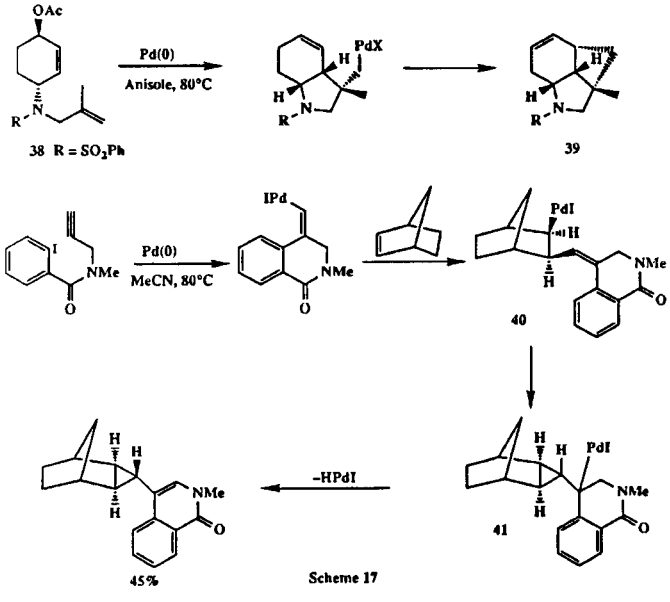
Cyclopropanation Cascades.

In exploring alkynes as relay moieties in biscyclisation processes we studied the cyclisation of **35**. The initial 5-exo-dig cyclisation was followed by a 5-exo-trig cyclisation generating **36**. Attempts to intercept **36** with sodium formate (H) or sodium tetraphenylborate (Ph) were unsuccessful. The product was the indole derivative **37** (>70%) arising from 3-exo-trig cyclisation of **36** followed by β-hydride elimination.

The formation of the highly strained 5/3-annulated system encouraged us to explore the generality of strained ring forming cascade cyclisations [24]. Thus we found the allylic acetate **38** furnishes the 4/5/6-tricyclic system **39**



in 82% yield by an analogous cascade even in the presence of sodium formate as a hydride ion source.



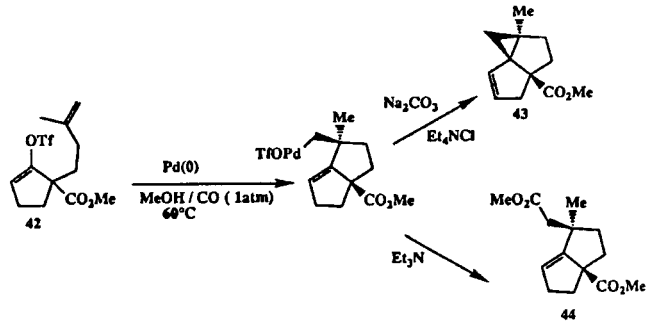
Scheme 17

The strained ring forming cascade processes can be carried out in an intermolecular fashion as illustrated by Scheme 17 [25]. The stereochemistry of the product is dictated by steric effects arising in the cyclopropanation transition state **40** → **41** [25].

Additives can be used in some cases to promote selectivcity between cyclisation-anion capture and cyclisation-cyclopropanation. A typical case is provided by the cyclisation of the vinyl triflate **42**.

When the cascade process is carried out with sodium carbonate as the base and in the presence of tetraethylammonium chloride (1 mole) the product is the cyclopropane **43** (65%). However, using triethylamine as base in the absence of tetraethylammonium chloride affords the bicyclic ester **44** (70%). Both processes are stereospecific [25a].

The foregoing summary illustrates the power of the cyclisation-anion capture strategy even at this early stage



of its development. The ability to achieve cascade cyclisations forming 1,2,3,- or more rings and to terminate the cascade by placing a wide range of functionality regio- and stereo-specifically at the cyclisation terminus results in a major increase in molecular complexity and synthetic efficiency.

Cascade Cycloadditions.

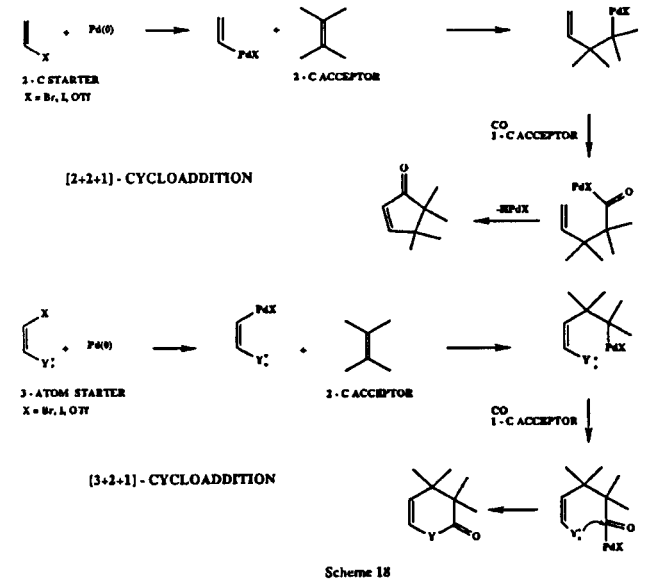
We have recently proposed a general palladium catalysed cascade cycloaddition process capable of producing a range ring sizes and which employ aryl or vinyl halides (or triflates) as "starter" molecules [26]. Examples of such processes are also under development in other laboratories [27]. The promoting effect of Tl(I) additives in allowing carbonylation processes to be carried out at atmospheric pressure suggested that carbon monoxide could be employed as a 1-C component in such cycloaddition cascades. This application is outlined in Scheme 18 for two representative 3-component cycloaddition processes. A wide range of such combinations can be envisaged.

A typical example of the [2+2+1]-cycloaddition is provided by the reaction of 2-iodothiophen **45** with norbornene and carbon monoxide. Facially specific addition of the thienylpalladium iodide to norbornene followed by CO insertion and cyclisation leads to **46** in excellent yield [27a]. A related [3+2+1]-cycloaddition with heteroatom participation ensues when the 2-iodoaniline derivative **47** is reacted with norbornene and carbon monoxide. The lactam **48** is obtained in 70% yield [27a].

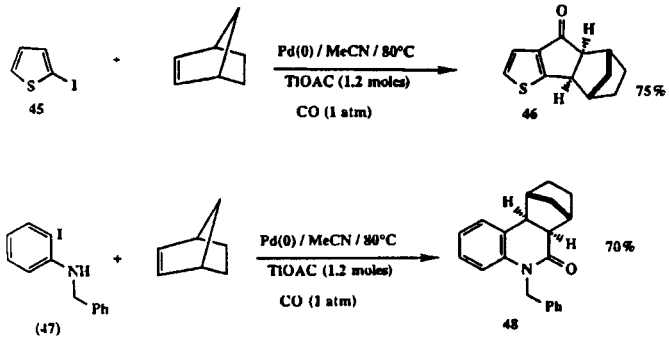
These cascade cycloadditions are capable of substantial further development and are under active study in our laboratories.

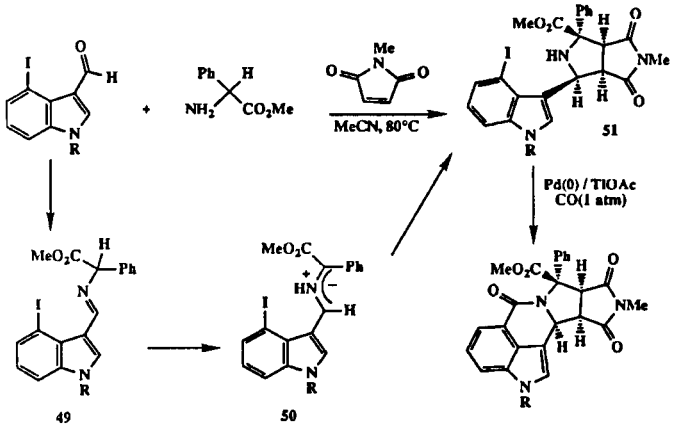
Finally, the mild carbonylation process can be combined with our novel 1,3-dipolar cycloaddition chemistry [28,29]. A typical example is shown in Scheme 19 (unpublished).

The α-amino ester and the aldehyde generate the imine *in situ*. The imine **49** undergoes thermal 1,2-prototropy generating the azomethine ylide **50** stereospecifically and this, in turn reacts stereospecifically with *N*-methylmaleimide furnishing the endo-cycloadduct **51**. Palladium catalysed carbonylation with heteroatom capture then furnishes the pentacyclic lactam in 60% overall yield.



Scheme 18





Scheme 19

Finally I wish to record my thanks to my collaborators whose enthusiasm and dedication are responsible for the chemistry described above, and whose names are recorded in the references. Financial support from the SERC, Roussel, Rhone-Poulenc Rorer and Queens and Leeds Universities is gratefully acknowledged.

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