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Palladium Catalysed Cascade Carbonylation-Cyclisation-Carbometallation-Anion Capture. Tetramolecular Queuing Processes.

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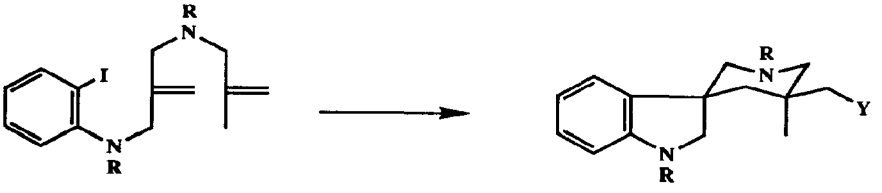
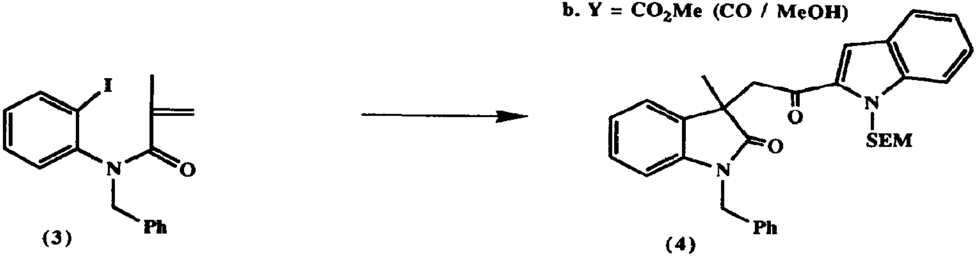
Abstract. *Palladium catalysed processes involving sequential carbonylation-cyclisation-carbometallation-anion capture from Sn(IV) and B(III) are described. These molecular queuing processes occur in good yield under 1 atm. of carbon monoxide. Reactivity/selectivity guidelines are delineated for carbopalladation, acylpalladation and anion capture.*

We have developed a synthetically powerful palladium catalysed cyclisation-anion capture process involving formation of one or more 3 - 7 membered rings followed by interception of the organopalladium (II) species by the "anion" capture reagent.[1] The latter can be anionic [$^{-}$H, $^{-}$OAc, $^{-}$CN, $^{-}CH(CO_2Et)_2$ etc], neutral (secondary amines, CO/MeOH, acrylate esters] or an organometallic species RML_n [M = Zn(II), B(III), Sn(IV), Zr(IV)]. The success of these reactions is predicated on the relative rates of cyclisation and "anion" capture. Thus we have shown that cyclisations forming 3 - 7 membered rings are invariably faster than anion capture allowing the rational design of bimolecular cascade processes such as (1) → (2a)[1] and termolecular cascade processes such as (1) → (2b)[2] and (3) → (4)[3]. Our recent observation that carbonylation was competitive with a 3-exo-trig cyclisation of an alkyl-palladium(II) species (Scheme 1)[4] suggested that selective tetramolecular



(1) R = SO_2Ph

(2) a. Y = Ph ($NaBPh_4$)
b. Y = CO_2Me (CO / MeOH)

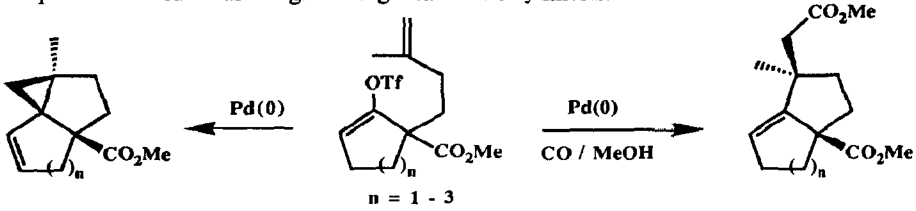


(3)

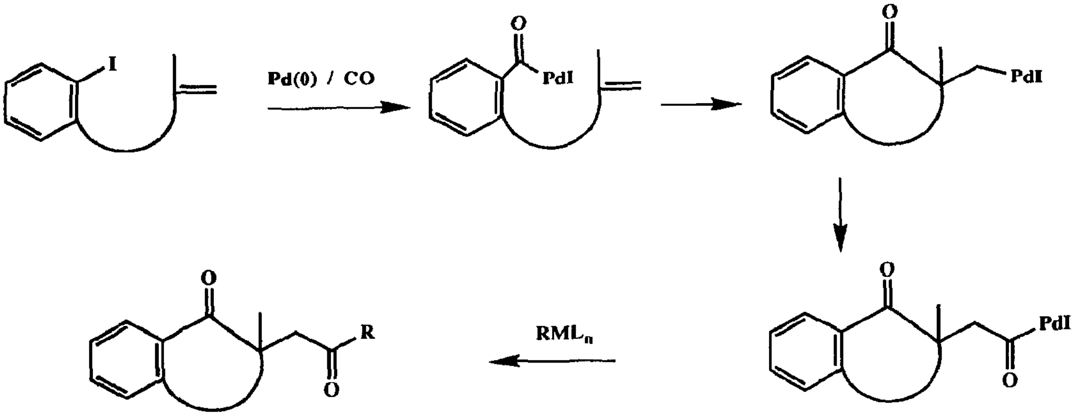
(4)

queuing processes should be possible (Scheme 2) when the relative rates of cyclisation and carbonylation were favourable. We now report the first examples of such processes involving organo-boron and - tin (IV) reagents.

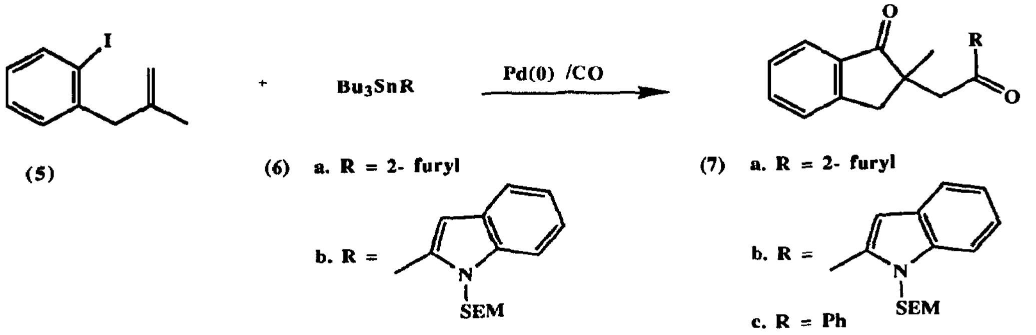
Previous experience with cyclisation-anion capture processes suggested that cyclisation forming a 4-membered ring[5] was likely to be slower than carbonylation and led us to explore (5) as a substrate. Reaction (toluene, 110 °C, 18h) of (5) with organotin(IV) reagents (6a,b), carbon monoxide (1 atm) and a catalyst system[6] comprising 10mol% $Pd(OAc)_2$, 20mol% PPh_3 and Et_4NCl (1mol)[7] afforded the desired products (7a,b) in 76 and 53% yield respectively. An analogous reaction of (5) with sodium tetraphenylborate and carbon monoxide in anisole at 120 °C for 6h gave (7c)(86%). There are a variety of pathways open to the initially formed arylpalladium(II) species and the specificity for the tetramolecular queuing cascade is both notable and of great import for the rational design of target molecule synthesis.



Scheme 1



Scheme 2



(5)

(6) a. R = 2- furyl

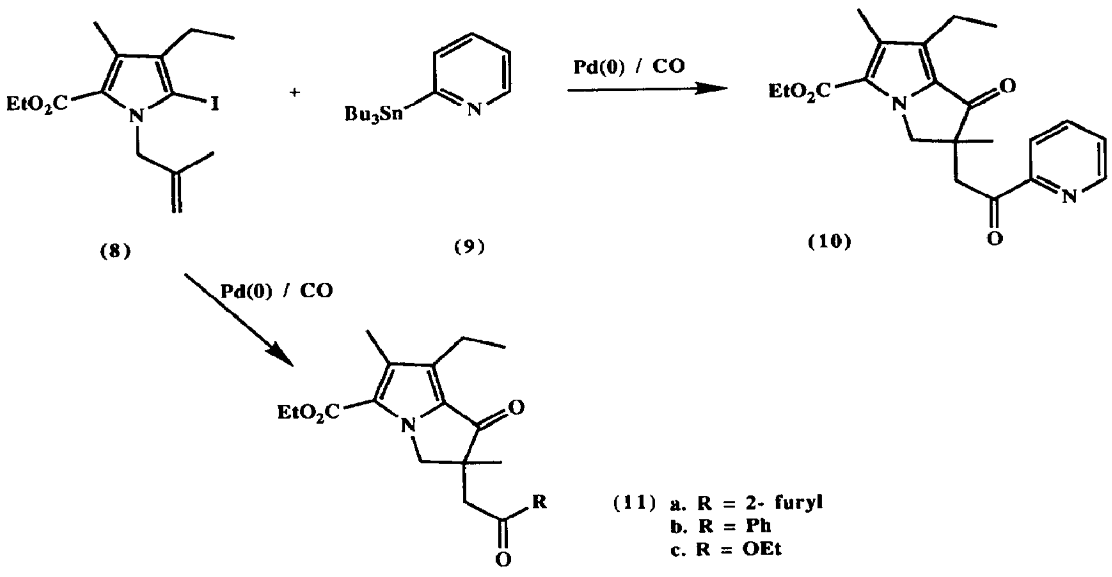
b. R =

(7) a. R = 2- furyl

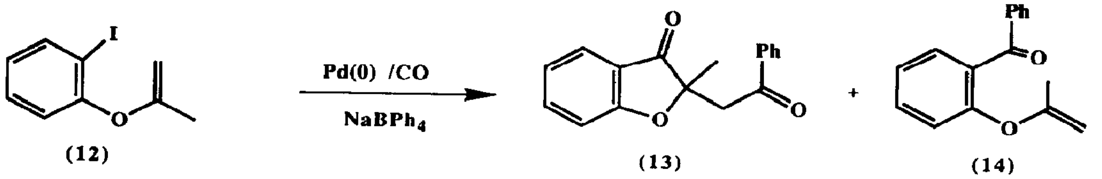
b. R =

c. R = Ph

A similar series of reactions was carried out with the iodopyrrole (8). Reaction (toluene, 110 °C, 18h) of (8) with (9) and carbon monoxide using the same catalyst system as above afforded (10)(70%) whilst replacing (9) with (6a) led to formation of (11a)(68%) under the same conditions. The iodopyrrole (8) also reacted (anisole, 120 °C, 24h) with sodium tetraphenylborate to afford (11b)(62%). In previous Pd catalysed carbonylation studies[8] we have shown that (8) is converted to (11c) (50%) when the carbonylation is carried out in ethanol. A related carboalkoxylation sequence has been reported by Oppolzer[9].



In all the above reactions no direct capture products were detected. However, studies with (12) showed that for certain substrates this can be a competitive process. Thus reaction (anisole, 110 °C, 18h) of (12) with sodium tetraphenylborate using the same catalyst system as above afforded a 2.5:1 mixture of the desired product (13) and the direct capture product (14). The former could be isolated in 50% yield from the mixture. Appropriate modification of the reaction conditions to promote greater selectivity for (13) is under study.



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 control 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[10] (CO insertion is a reversible process) and ring size of the incipient ring in the cyclic carbopalladation. For reactions conducted **under 1 atm of carbon monoxide** the following reactivity profile obtains for aryl- and vinylpalladium(II) species.

(i) the relative rate of sequential carbon monoxide insertion-5-exo-trig acylpalladation > 4-exo-trig cyclopalladation.

(ii) the relative rates of 5-exo- and 6-exo-trig cyclopalladation > sequential carbon monoxide insertion -6-exo- and 7-exo-trig acylpalladation[8].

(iii) anion capture by intramolecular neutral (such as alcohols, secondary amines)[8] - or anionic intra (malonate)[8] - or inter (hydride)[11] - molecular nucleophiles is slower than 5-exo- and 6-exo-trig cyclopalladation-carbonylation and 5-exo-acylpalladation.

(iv) anion capture by sodium tetraphenylborate or $RSnBu_3$ is slower than 5-exo- and 6-exo-trig cyclopalladation-carbonylation and 5-exo-acylpalladation-carbonylation.

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 acypalladation.[2,12]

For related reactions proceding 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[4].

These effects and other aspects of cascade processes are under further study.

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