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REGIOSPECIFIC PALLADIUM CATALYSED TANDEM CYCLISATION-ANION CAPTURE PROCESSES. CARBON-, NITROGEN- AND OXYGEN-CENTRED NUCLEOPHILES

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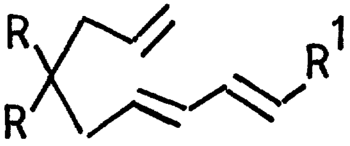
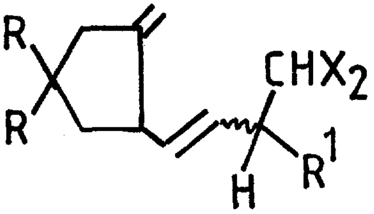
Abstract. *π-Allyl- and alkyl-palladium species arising from* regiospecific palladium catalysed 5-exo-trig cyclisations onto a proximate diene or alkene can be intercepted regiospecifically by stabilised carbanions, secondary amines or acetate ion giving carbo- and hetero-cyclic compounds good to excellent yields.

Our early studies on the regioselectivity of intramolecular Heck-type reactions showed such processes to be regiospecific or highly regioselective with 5-exo-processes favoured over 6-endo-reactions, and 6-exo-processes favoured over 7-endo-reactions. These cyclisations provide facile routes to spirocyclic compounds and bridged ring products, and allow the creation of tetrasubstituted carbon centres[1-3], and are currently being further developed by others.[4] Subsequently we utilised our earlier observations to develop a novel palladium catalysed tandem cyclisation-anion capture process in which the palladium species resulting from the regiospecific cyclisation is intercepted stereo-specifically by a suitable anion transfer reagent. Suitable anion transfer reagents include hydride ion sources[5], organotin reagents[6], and organozinc and organoboron reagents.[7] We now describe similar processes in which the organopalladium species are intercepted by carbon-, nitrogen- and oxygen-centred nucleophiles.

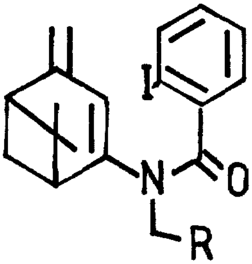
Palladium π-allyl species have a rich, and largely well understood, catalytic chemistry[8] that makes them especially useful for anion capture. Trost, in particular, has provided many elegant applications to natural product synthesis[9]. Attack of stabilised carbanions such as malonate, malononitrile, or β-diketone derived species on π-allylpalladium derivatives is well known[10] and we directed our first approaches to tandem processes to this area.

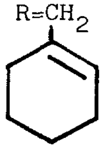


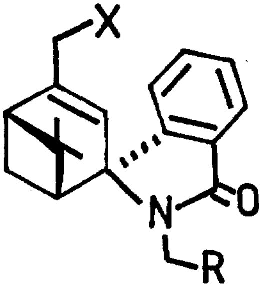
(1) a. R=CO$_2$Et, R^1=H
b. R=CO$_2$Et, R^1=Me
c. R=SO$_2$Ph, R^1=Me

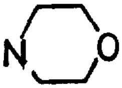
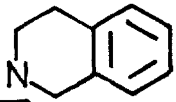
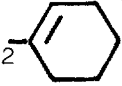


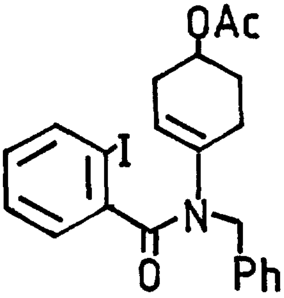
(2) a. R=CO$_2$Et, R^1=H, X=CN
b. R=CO$_2$Et, R^1=Me, X=CN
c. R=SO$_2$Ph, R^1=Me, X=CN
d. R=CO$_2$Et, R^1=Me, X=CO$_2$Et



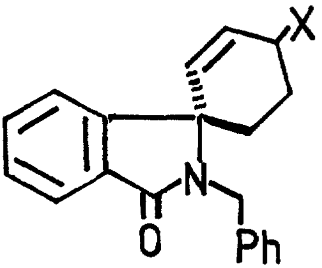
(3) a. R=Ph
b. R=CH$_2$ 



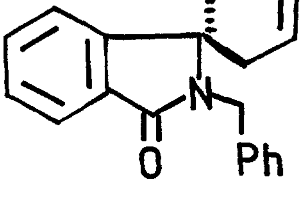
4) a. R=Ph, X=CH(CN)$_2$
b. R=Ph, X= 
c. R=Ph, X= 
d. R=Ph, X= 
e. R=CH$_2$-  , X=OAc



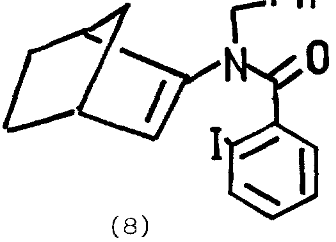
(5)



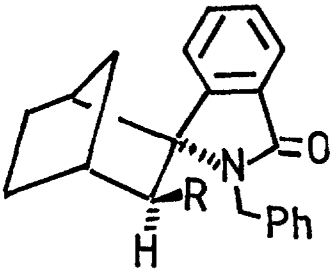
(6) a. X=OAc
b. X=CH(CO$_2$Me)$_2$



(7)



(8)



(9) R= C≡CPh

Reaction [5 mol % $Pd(OAc)_2$, 10 mol % PPh_3, MeCN, 80°C, 1h] of (1a) with sodiomalononitrile (1 mol) afforded (2a)(91%) as an 8:1 mixture of cis- and trans-isomers. The regiospecificity of the reaction is maintained even in the case of (1b) and (1c), both of which react under analogous conditions to give respectively, (2b)(56%) as a 3:1 mixture of cis- and trans-isomers, and (2c)(83%) as a 1:1 mixture of cis- and trans- isomers. In contrast, (1b) reacts with diethyl sodiomalonate to give solely trans-(2d)(83%). Attack of resonance stabilised carbanions usually occurs predominantly at the less substituted position of η^3-allylpalladium species, but is known to be sensitive to reaction conditions[11] and remote functionality.[12]

Similar processes can be achieved with the dienamide (3a) which reacts with sodiomalononitrile (2 mol) under analogous conditions to (1a-c) to give (4a)(60%). The enamide (5) was designed as a potential precursor of a π-allylpalladium species. Initial palladium catalysed cyclisation of (5) would be expected[1] to give (6a) which might then give rise to the corresponding π-allylpalladium complex. In the event reaction [10 mol % $Pd(OAc)_2$, 20 mol % PPh_3, DMF, 100°C, 18h][13] of (5) with dimethyl sodiomalonate (1.5 mol) gives a 4:1 mixture (50%) of (6b) and (7) in which (6b) could have arisen via the projected π-allylpalladium species.

An example of carbanion capture by an intermediate alkyl-palladium species is provided by the palladium catalysed[13] cyclisation of (8) (benzene, 80°C, 8h) in the presence of phenylacetylene (1 mol) and potassium acetate (1 mol) to give (9)(30%).

Secondary amines are among the most efficient nucleophiles in reactions with η^3-allylpalladium species[14] and they are also tolerated in our tandem cyclisation-anion capture process. Thus (3a) undergoes the palladium catalysed tandem process (MeCN, 80°C, 3h) in the presence of 2 mol of morpholine, piperidine or 1,2,3,4-tetrahydroisoquinoline to give (4b-d) in 40-60% yield. The palladium catalysed reaction of (5) and 1,2,3,4-tetrahydroisoquinoline (toluene, 110°C, 18h) gives (7)(60%).

One example of an oxygen centred nucleophile has been demonstrated so far. Thus the palladium catalysed cyclisation of (4b) (DMF, 80°C,4h) in the presence of lithium acetate (1 mol), tetraethylammonium chloride (1 mol) and anhydrous potassium carbonate (2 mol) gives (5e)(50%). A related example of acetate capture by a π-allyl species has recently been reported by Trost.[15]

The palladium catalysed tandem cyclisation-anion capture is both synthetically powerful and flexible, and permits the rapid assembly of complex molecular frameworks regio- and stereo-specifically. Further extensions and applications of these processes are under investigation.

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