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Palladium Catalysed Termolecular Queuing Cascades. Facile Cyclisation-Anion Capture Routes to Heterocyclic Dienes via Allene Insertion Processes.

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Abstract: Pd(0) catalysed termolecular queuing processes involving oxidative addition to aryl or vinyl halides followed by cyclisation onto a proximate alkyne, allene (1atm) insertion, and capture of the resulting π-allylpalladium(II) species by secondary amines affords 5-8 membered benzoannelated heterocyclic dienes or electrocyclisation products respectively in good yield.
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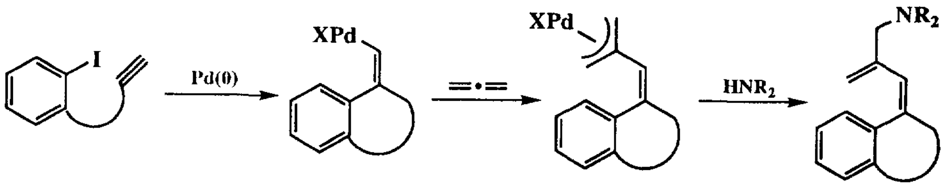
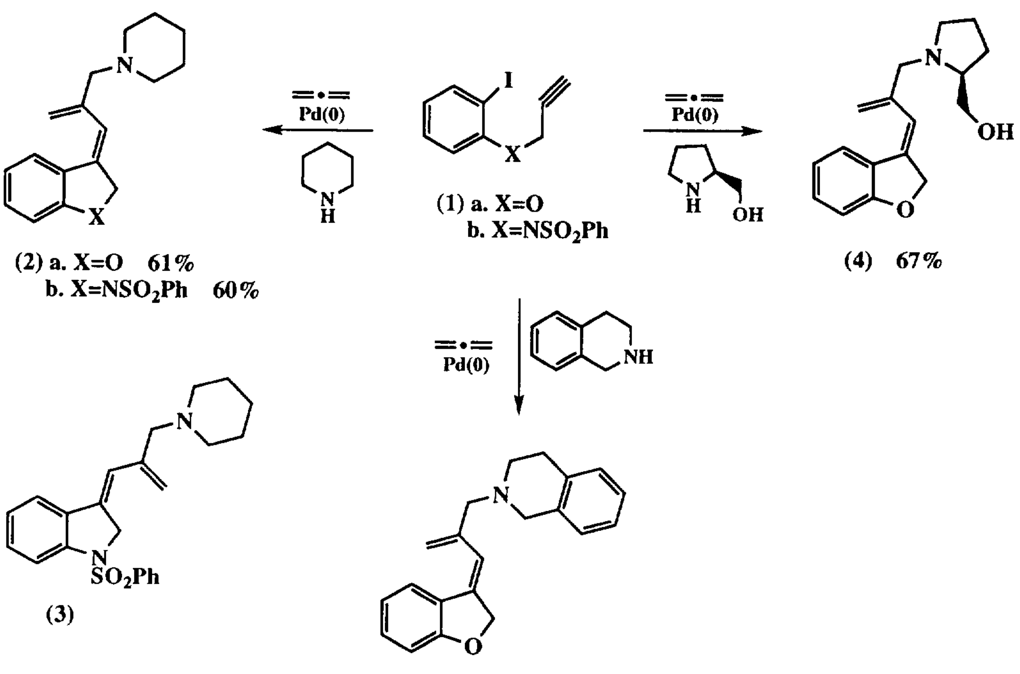
There is a growing awareness that allenes constitute underutilised and versatile substrates for palladium catalysed processes. Tsuji has shown that allenylpalladium(II) species can be generated *in situ* from propargyl carbonates in a facile and irreversible manner and these intermediates are being actively developed.[1] We have recently implemented propargylic carbonates as precursors of allenylpalladium(II) species in bis-cyclisation-anion capture processes[2] and we[3] and others[4] have begun exploring the chemistry of allenes in both cyclisation and cycloaddition processes.

In this communication we describe termolecular queuing cascades involving palladium catalysed cyclisation onto proximate alkynes followed by allene insertion and capture of the resulting π-allylpalladium|(II) species by secondary amines as depicted in Scheme 1.



Scheme 1

Reaction (toluene, 70°C, 20h) of (1a) and (1b) with allene (1atm) and piperidine (2eq) in the presence of a catalyst system comprising 10mol% $Pd(OAc)_2$, 20mol% PPh_3 and K_2CO_3 (1mol eq) proceeded according to Scheme 1 to afford (2a)(61%) and (2b)(60%). In the latter case the product consisted of a 1:1 mixture of (2b) and its double bond isomer (3). Reaction of (1a) with (S)-(+)-2-pyrrolidine methanol under analogous conditions afforded (4)(67%) whilst (1a) and tetrahydroisoquinoline gave (5)(61%).



(1) a. X=O
b. X=NSO$_2$Ph

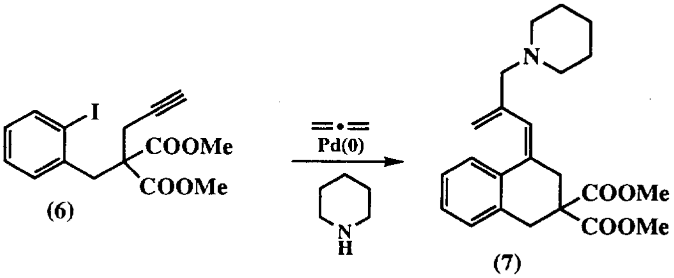
(2) a. X=O 61%
b. X=NSO$_2$Ph 60%

(3)

(4) 67%

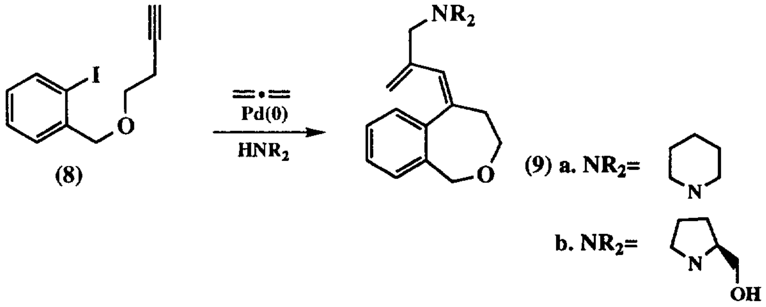
(5) 61%

Carbocycles can be efficiently assembled in an analogous manner as demonstrated by the conversion of (6) into (7)(73%) under the conditions employed for (1). The (2-iodobenzyl) propargyl ether (8) undergoes a similar termolecular cascade process under the same conditions. Trapping the π-allylpalladium(II) intermediate with piperidine affords the tetrahydro-2-benzoxepin (9a)(68%), whilst trapping with (S)-(+)-2-pyrrolidinemethanol affords (9b)(71%).



(6)

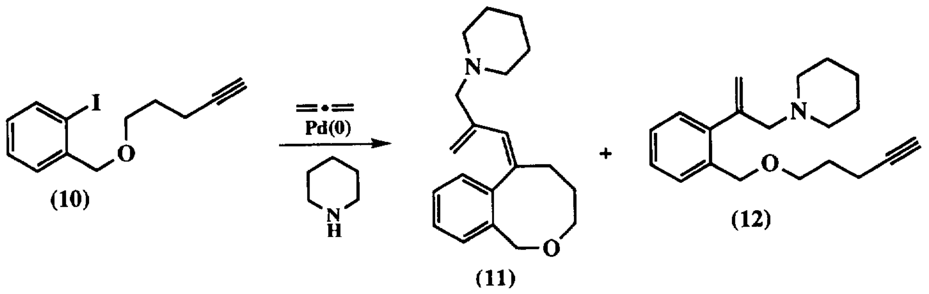
(7)



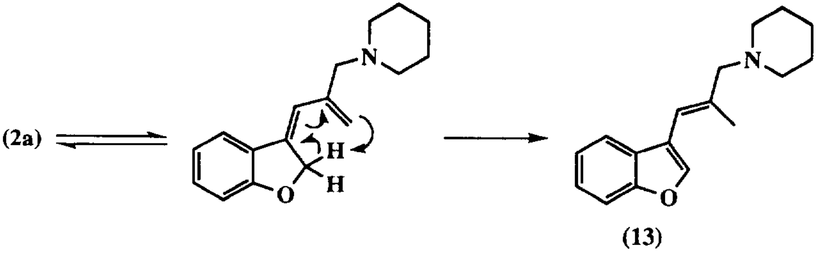
(8)

(9) a. NR$_2$=
b. NR$_2$=

Formation of the tetrahydro-2-benzoxocin ring under the same conditions as above is much less efficient. Thus (10) reacts (toluene, 70°C, 20h) with allene (1atm) and piperidine (2eq) to give a 1:1.4 mixture of (11) and (12) in 43% combined yield.

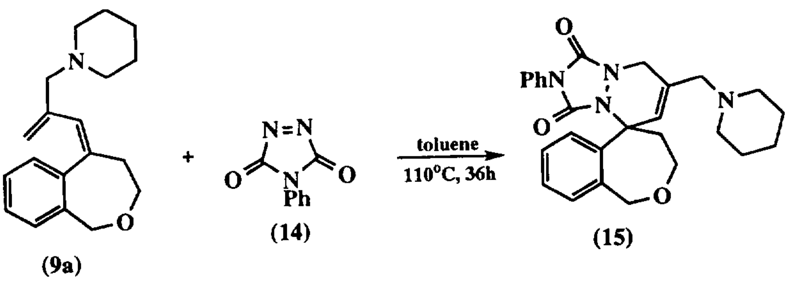


The potential of the heterocyclic dienes to participate in Diels-Alder reactions has been briefly explored in thermal uncatalysed reactions. The dienes are not very reactive and this allows competitive processes to predominate in many cases. Thus (2a) and N-methylmaleimide on heating in boiling toluene for 18h afford the benzofuran (13) in 84% yield. A plausible mechanism involving diene isomerisation and a 1,5-H shift is shown in Scheme 2.

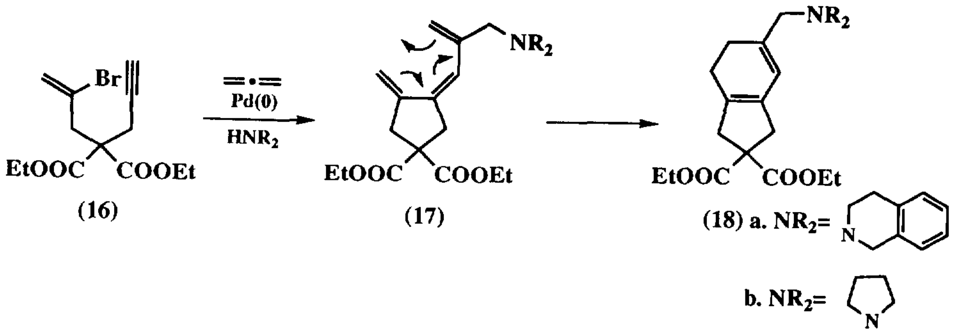


Scheme 2

Diels-Alder reactions, albeit in moderate yield, can be achieved with the triazoline dione (14) as dipolarophile. Thus (9a) and (14) react over 36h in boiling toluene to afford cycloadduct (15) in 44% yield.



Vinyl halides offer additional synthetic opportunities as illustrated by cascades involving (16) and secondary amines. In this case the cascade proceeded [MeCN, K_2CO_3(1mol.eq.), 75°C, 15h] more efficiently when 10mol % $Pd(PPh_3)_4$ was employed as catalyst. The initial products (17) were not detected under these conditions but were further transformed into (18a) (77%) and (18b) (60%) respectively by a 6π-electrocyclisation.[5]



The results report herein demonstrate that under 1atm of allene the relative rates of exo-dig cyclisations forming 5-7 membered rings are substantially faster than aryl-or vinyl-Pd(II) insertion of allene whilst the 8-membered ring forming cyclisation rate and rate of aryl-Pd(II) insertion of allene are comparable.

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