Pergamon

Tetrahedron Letters, Vol. 38, No. 10, pp. 1825-1828, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00161-5

Palladium Catalysed Triscyclisation-Anion Capture Queuing Cascades.

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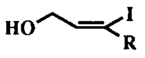
Abstract: Palladium catalysed regio- and, where appropriate, stereo-specific triscyclisation-anion capture processes are described involving vinyl- and allenyl-starter species, alkene/alkyne relay and terminating species and anion capture by allene/nucleophile ($PhSO_2Na$ or s-amine) or 2-thienyl tributylstannane. © 1997 Elsevier Science Ltd. All rights reserved.

Palladium catalysts have proved extraordinarily versatile for the construction of multiple ring systems from acyclic precursors.[1] Our cyclisation-anion capture methodology greatly extends the molecular complexity achievable in such processes[2] particularly when allied to our polymolecular queuing cascades.[3] We now report the first examples of stereospecific triscyclisation-anion capture queuing cascades employing vinyl- and allenyl-Pd(II) starter species.[2]

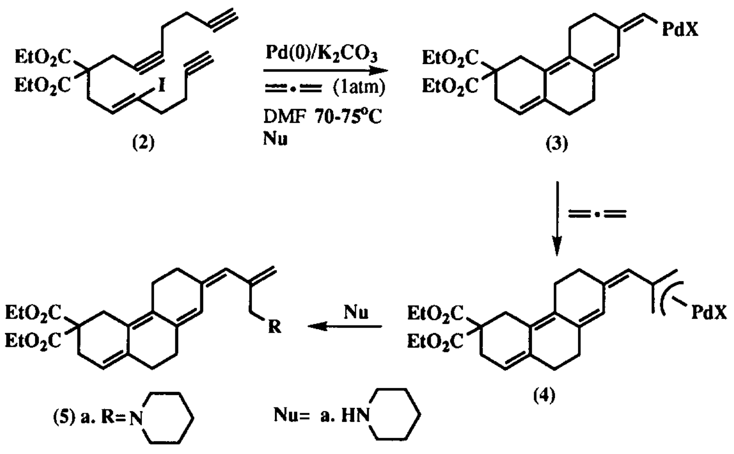
The known vinyl iodide (1a)[4] was converted into ene triyne (2)[5] by conventional methodology involving sequential alkylation of diethyl malonate.

When (2) was treated with allene (1atm) and a nucleophile in DMF (70-75°C oil bath temperature, 15h) in the presence of 10mol% [$Pd(PPh_3)_4$] and K_2CO_3 (2mol eq) a termolecular queuing process ensued proceeding via the vinylpalladium(II) species (3). The latter intermediate reacts with allene at the centre carbon atom to afford a π-allyl species (4) which is then captured by a suitable nucleophile. When piperidine was employed as the nucleophile the product (5a) proved to be very unstable and could only be isolated in 40% yield. However, when sodium phenylsulphinate was employed as nucleophile the product (5b) could be isolated in 65% yield. In the case of (5a)/(5b) the vinyl starter species engages two alkyne moieties in the relay phase followed by an alkyne terminating species[2a]

The yne triene (6) was prepared from (1b) and cyclised under similar conditions (MeCN, 70-75°C, 15h) using the same catalyst system and allene (1atm). When 1,2,3,4- tetrahydroisoquinoline was used as the nucleophile the product (7a) was isolated in 76% yield (57% conversion) as a single diastereomer. When sodium phenysulphinate was employed as the nucleophile, and DMF as solvent, the product (7b) (66% isolated yield) was again a single diastereomer. The *trans*-relationship of the two methyl groups in (7a)/(7b) is assigned on the basis of n.O.e. data. In these cascade cyclisation-anion capture processes the vinyl starter



(1) a. R= $(CH_2)_2C{\equiv}CTMS$
b. R= $CH_2C(Me)=CH_2$



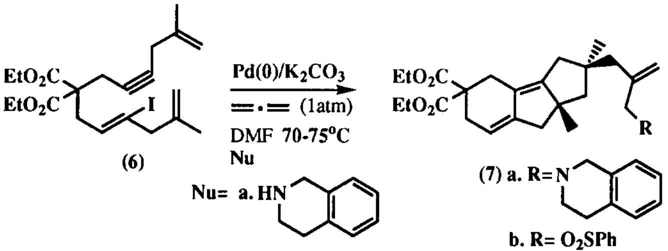
(2)

(3)

(4)

(5) a. R= N-piperidinyl
b. R= SO_2Ph

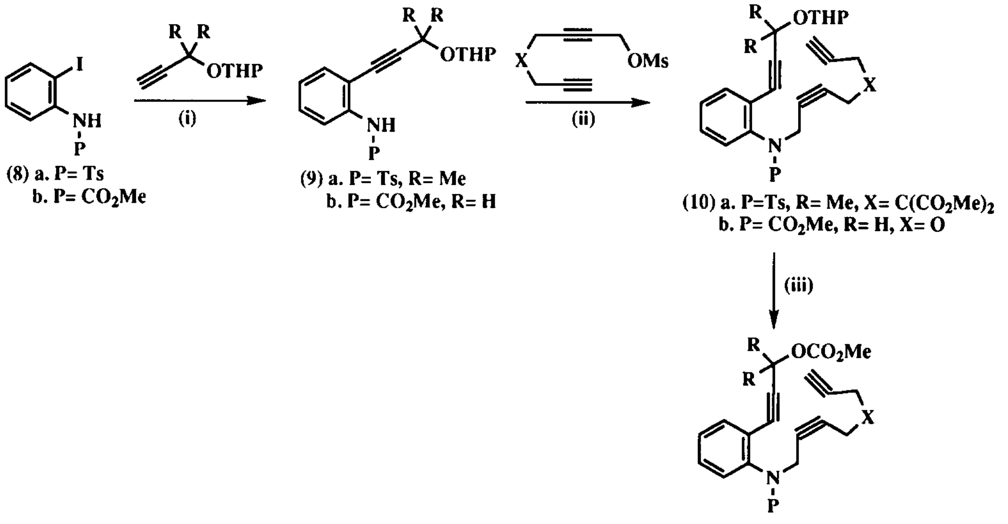
Nu= a. HN-piperidine
b. NaO_2SPh



(6)

Nu= a. HN-tetrahydroisoquinoline
b. NaO_2SPh

(7) a. R= N-tetrahydroisoquinolinyl
b. R= O_2SPh



(8) a. P= Ts
b. P= CO_2Me

(9) a. P= Ts, R= Me
b. P= CO_2Me, R= H

(10) a. P=Ts, R= Me, X= $C(CO_2Me)_2$
b. P= CO_2Me, R= H, X= O

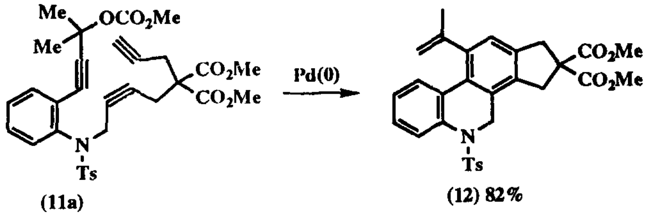
(11) a. P=Ts, R= Me, X= $C(CO_2Me)_2$
b. P= CO_2Me, R= H, X= O

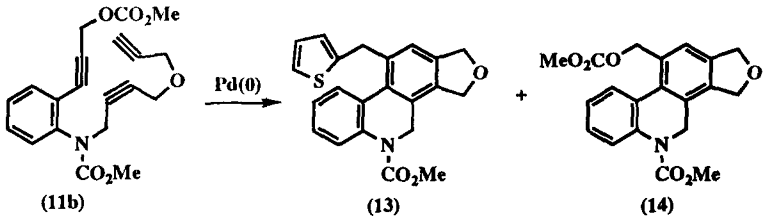
species engages alkyne and alkene species sequentially in the relay phase followed by an alkene terminating species.

A second series of triscyclisations has been developed based on allenyl starter species. The triyne precursors (11a) and (11b) were prepared as outlined in Scheme 1.

Propargylic carbonates are excellent precursors of allenylpalladium(II) species as elegantly demonstrated by Tsuji and Mandai[6] and we had previously shown that this chemistry was compatible with our cyclisation-anion capture methodology.[2b]

Accordingly when (11a) was treated with 10mol% [Pd(PPh$_3$)$_4$] in boiling acetonitrile over 2h it afforded (12) (82%), whilst (11b) on treatment with 2-thienyl tributylstannane in the presence 10mol% [Pd$_2$ (dba$_3$)] and 40mol% AsPh$_3$ (boiling THF, 24h) afforded a mixture of (13) (40%) and (14)(27%). When the latter reaction was repeated using a catalyst system comprising 10mol% Pd(OAc)$_2$, 20mol% PPh$_3$ and LiCl (1mol. eq), the sole product was (13) (60%).

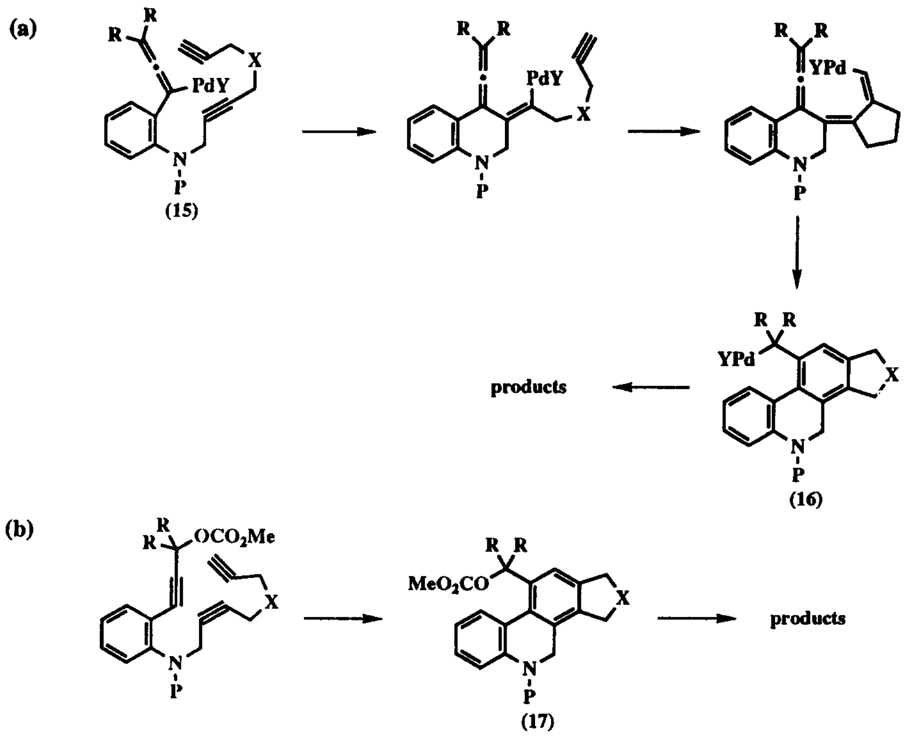




At present we do not have unequivocal evidence that the cascades involving (11a) and (11b) proceed via the allenyl starter species (15) (Scheme 2) followed by sequential engagement of two alkyne moieties in the relay phase and subsequently terminating with the allenyl moiety (Scheme 2a).

An alternative mechanism (Scheme 2b) involves a palladium catalysed [2+2+2]- cycloaddition to give (17) followed by oxidative addition to (16), an intermediate common to both Scheme 2a and Scheme 2b. Work is in hand to resolve this uncertainty. However, it is clear that the ability of an allenyl group to function as both starter and terminating species makes it particularly versatile and attractive.

We thanks the EPSR, Zeneca and Leeds University for support.



Scheme 2

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(*Received in UK* 18 *December* 1996; *revised* 23 *January* 1997; *accepted* 24 *January* 1997)