Tetrahedron Letters, Vol. 34, No. 1, pp. 157-160, 1993
Printed in Great Britain

0040-4039/93 $5.00 + .00
Pergamon Press Ltd

Palladium Catalysed [2+2+2]-Cycloaddition Reactions via Carbopalladation of 1,6-Enynes.

Stephen Brown,[a] Steven Clarkson,[b] Ronald Grigg[b]* and Visuvanathar Sridharan.[b]

a. I.C.I. F.C.M.O., Leeds Road, Huddersfield HD2 1FF.
b. School of Chemistry, Leeds University, Leeds LS2 9JT.

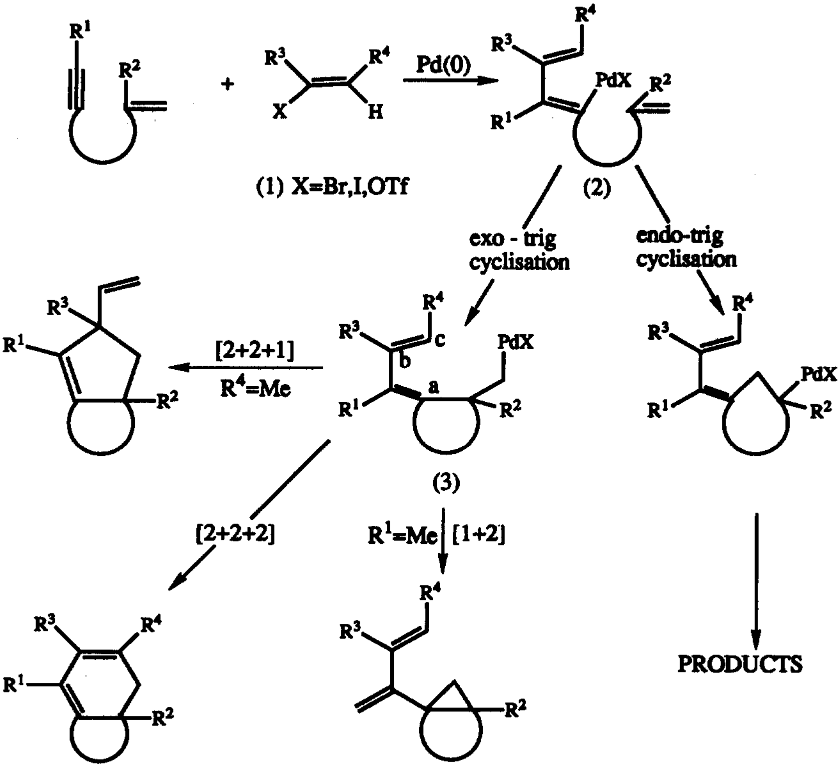
Abstact: 1,6-Enynes react with aryl and heteroaryl halides via a [2+2+2]- process to furnish bicyclic products in moderate to good yields. In some cases the alkylpalladium(II) intermediate can be diverted to a [1+2]-process furnishing cyclopropanes or to a cyclohexene derivative. The cascade process is initiated by regiospecific carbopalladation of the enyne by the aryl- or heteroaryl-palladium (II) halide.

In the preceding paper[1] we outlined a general strategy for palladium catalysed cycloaddition reactions involving initial oxidative addition of alkyl-, aryl-, allyl-[2] or vinyl halide starter molecules to Pd(0) followed by intermolecular carbopalladation and a subsequent series of intramolecular carbopalladations leading to ring formation. Several years ago we reported the rhodium(I) catalysed [2+2+2]- cyclotrimerisation of alkynes via either a partially or a totally intramolecular process.[3] Recently Negishi[4] has reported palladium catalysed versions of this latter process. We now report an alternative [2+2+2]-process that can be diverted to 5-membered [2+2+1] or 3-membered [1+2] ring forming processes (Scheme). Related, but conceptually different, approaches have been reported by de Meijere[5,6].

Oxidative addition of Pd(0) and (1) is followed by regio- and chemo-specific carbopalladation of the enyne to give (2) (Scheme). Trost has recently observed chemoselectivity in carbopalladation of an alkyne versus an olefin[7]. Cyclisation of (2) can occur by exo- or endo-trig processes but our extensive previous studies have shown that exo-specific cyclisation is invariably observed[8]. Thus the key intermediate in our scheme is likely to be (3) and this can conceptually cyclise to a 3-, 5- or 6-membered ring provided the substituents R^1 and R^4 permit a β-hydride elimination and hence recycling of the catalyst with base. In the examples described herein the starter molecule is an aryl or heteroaryl iodide and R^1=Me. Hence the cyclisation of (3) via sites a or c, but not b, can occur.

2-Iodonitrobenzene (4a) and the 1,6-enyne (5) undergo a formal [2+2+2]-cycloaddition when heated with 10mol% palladium acetate and 20mol% triphenyphosphine in DMF (120-130°C, 18h) containing thallium acetate (1.2mol)[9] to give the tricyclic system (7a) (60%). The carbopalladation of (5) thus occurs regiospecifically and the alkylpalladium(II) intermediate (6) undergoes a 6-endo-trig cyclisation onto the aryl ring followed by β-hydride elimination to give (7a). In a similar manner the reaction of (1b) and (1c) with (5) gives (7b) and (7c) in 54-68% yield.

1-Iodonaphthalene (8a) and 4-bromoisoquinoline (8b) were also evaluated as starter molecules since they could conceptually function as 2- or 3- C components.

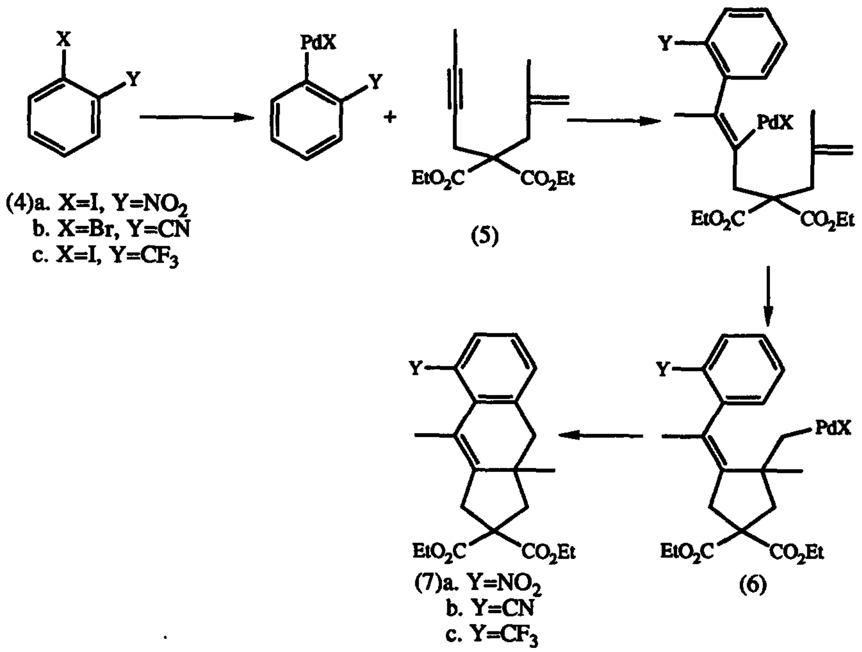


SCHEME

When (8a) and (8b) were reacted with the enyne (5), using the same catalyst system and conditions as before, they reacted regiospecifically as 2C-components furnishing (9a) and (9b) respectively in 53-63% yield via the [2+2+2]-process. No [3+2+2]-products (10a,b) were observed.

N.O.e. data and decoupling experiments established the structures of the products as (9a,b). In a typical n.O.e. experiment irradiation of the vinylic methyl group (δ2.3) of (9b) effected enhancement of the aromatic proton H_A which appears as a doublet (J 8Hz) at δ 8.1. The corresponding proton in (10b) would not exhibit the large ortho-coupling observed for (9b).

Evidence that the intermediate (3) can furnish cyclopropyl derivatives was provided by studies of the reaction of (5) with iodobenzene and with 4-nitro-iodobenzene. In these two cases using the same catalyst system and solvent as above the product comprised a 2.5-2.0:1 mixture of cyclopropane derivative (11a,b) and (12a,b). The cyclopropyl methylene protons occur as doublets at δ 0.55 and 0.7 for (11a) whilst the olefinic protons of (11a) give rise to two singlets at δ 5.1 and 5.5. The vinylic proton signal for (12a) occurs as a singlet at δ 6.4. Interestingly when the thallium acetate is replaced by potassium carbonate (2 mol) the major product is (12) with only trace amounts (11) being formed. The cyclohexene derivatives arise as a result of 6-endo-trig cyclisation of the intermediate (2) (Scheme).

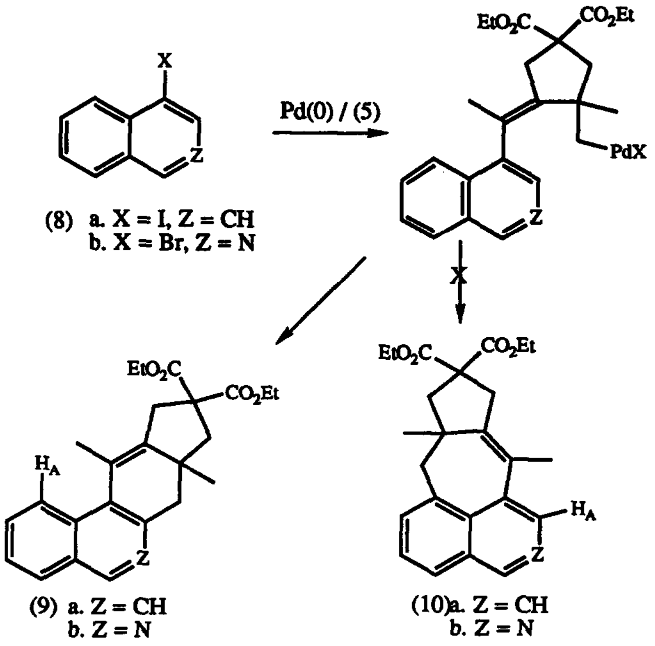


(4)a. X=I, Y=NO_2
b. X=Br, Y=CN
c. X=I, Y=CF_3

(5)

(6)

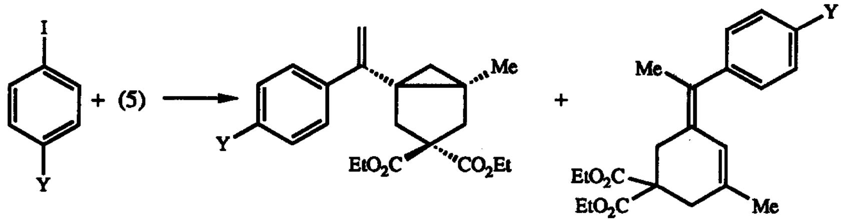
(7)a. Y=NO_2
b. Y=CN
c. Y=CF_3



(8) a. X = I, Z = CH
b. X = Br, Z = N

(9) a. Z = CH
b. Z = N

(10)a. Z = CH
b. Z = N



(11) a. Y=H
b. Y=NO_2

(12) a. Y=H
b. Y=NO_2

Further studies of these and related cycloaddition processes are underway.

We thank SERC, Leeds University and I.C.I. (Huddersfield) for support.

REFERENCES

1 Grigg, R; Kennewell, P., Teasdale, A. and Sridharan, V.,*Tetrahedron Lett.*, preceding paper.

2 Allylic halide or acetate starters have yet to be studied.

3 Grigg, R.; Scott, R., and Stevenson, P., *J. Chem. Soc., Perkin Trans. 1,* 1988,1357-1364.

4 Negishi, E-I.; Hawing, S.L., Owczarczyk, Z., Mohamud, M.M., and Ay, M., *Tetrahedron Lett.*, 1992, 33, 3253-3256.

5 Meyer, F.E.; de Meijere, A., *Synlett.*, 1991, 777-778.

6 Meyer, F.E., Brandenburg, J., Parsons, P.J., and de Meijere, A., *J. Chem. Soc., Chem.Commun.*, 1992, 390-392.

7 Trost, B.M.; Pfrengle, N.and Dumas, J., *J. Org. Chem.*, 1992, 114, 1923-1924.

8 Grigg, R.; Santhakumar, S., Sridharan, V., Stevenson, P., Teasdale, A., Thornton-Pett, M., and Worakun, T., *Tetrahedron*, 1991, 47, 9703-9720 and references therein.

9 This catalyst system was used throughout the work described in this paper. The efficacy of Tl(I) salts in promoting cascade processes and suppressing double bond isomerisation has been previously demonstrated by us. See Grigg, R.; Loganathan, V., Santhakumar, V., Sridharan, V., and Teasdale, A., *Tetrahedron Lett.*, 1991, 32, 687-690.; Grigg, R.; Loganathan, V., Sukirthalingam, S., and Sridharan, V., *ibid*, 1990, 31, 6573-6576.; Grigg, R.; Kennewell, P., and Teasdale, A.J., *ibid*, in press.

(Received in UK 16 October 1992)