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Palladium Catalysed Cascade Cycloaddition Reactions. General Concepts and Illustrative Examples.

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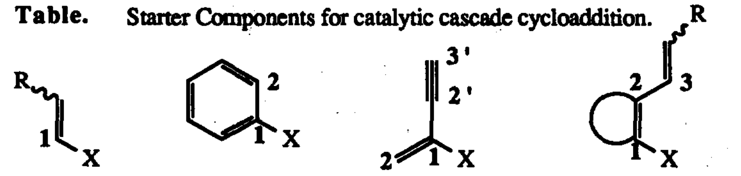
Abstract: A general palladium catalysed cycloaddition strategy is proposed involving inital oxidative - addition of alkyl -, aryl - and vinyl - halides to Pd(0) followed intermolecular carbopalladation and subsequent intramolecular carbopalladation leading to ring formation. Examples of 5 - and 6 - ring formation are given.

The recent literature illustrates that palladium catalysts are capable of a wide range of cyclisation processes[1] This prompts us to propose a new general scheme for palladium catalysed cascade cycloaddition reactions that is both flexible and wide ranging in concept, potential ring sizes, and applications. These processes can be represented as the combination of "starter" molecule, which comprises a vinyl -, aryl -, allylic - or benzylic - halides,[2]with one or more acceptor molecules (alkene, alkyne, diene).

Some potential starter molecules are shown in the Table (note that regiochemical diversity is often possible though in practise this is unlikely to be a problem)

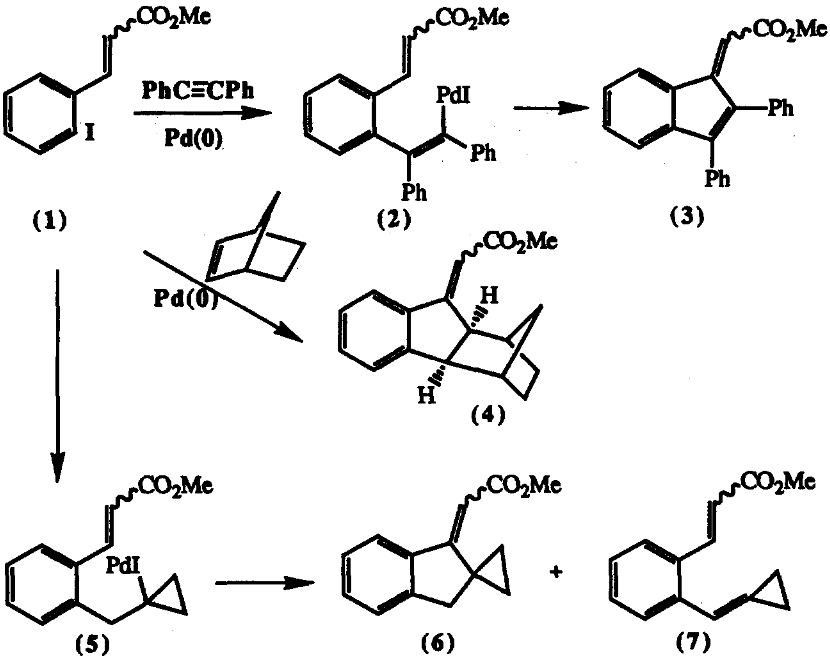
Table. Starter Components for catalytic cascade cycloaddition.



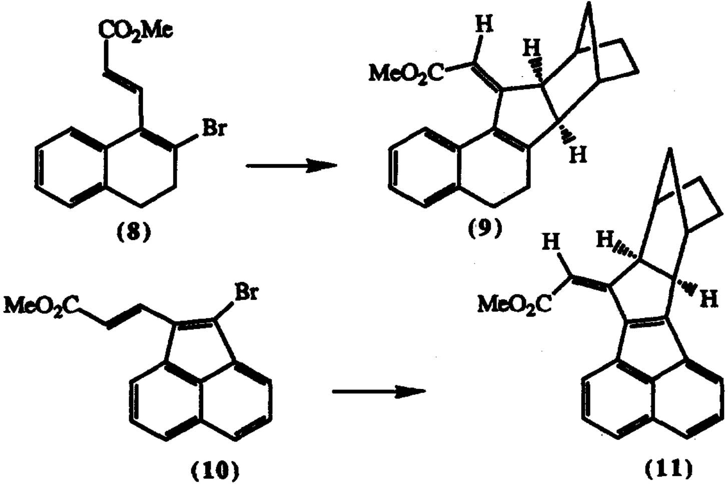
1- or 2 - C component **2 - C component** **2 - C or 3-C component** **3 - or 4 - C component**

(X = Br, I, OTf, N_2^+etc)

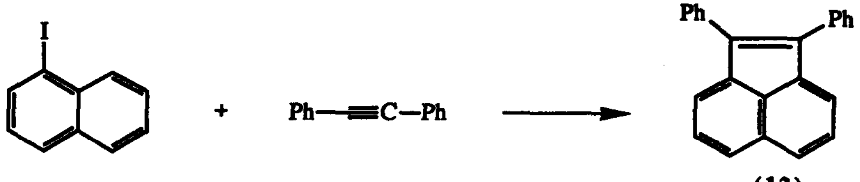
[3+2] - Processes. The aryl starter molecule (1) (5:1 E/Z isomer mixture) reacts (anisole, 120°C, 18h) with diphenyl acetylene using catalyst system A[3] to give the fulvene (3) (80%) as a 5:1 Z/E isomer mixture via the vinylpalladium(II) intermediate (2).



Aryl iodide (1) and norbornene react (MeCN, 80°C) using catalyst system B^{3}to give (4) (5:1 Z/E) (82%). The stereochemistry of (4) was established by n.O.e. studies combined with decoupling experiments. When (1) was reacted with methylene cyclopropane as the 2π- component using catalyst system B^3 the product comprised a mixture of (6) (5:1 Z/E) (32%) and (7) (5:1 E/Z) (30%). Thus although the [3+2]- process is regiospecific β - hydride elimination in intermediate (5) competes with cyclisation to (6) even though unfavourable ring strain accumulates in (7).



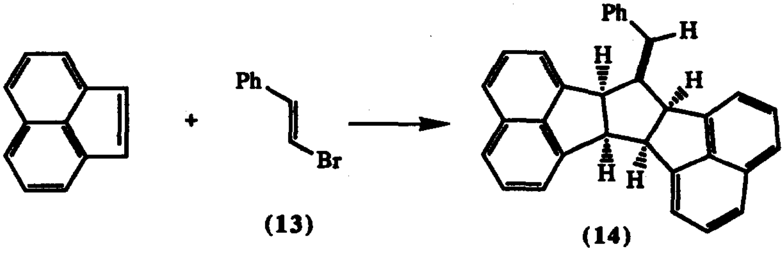
The vinyl bromides (8) and (10), function as 3 - C components. Thus (8) gives (9) (46%) and (10) gives (11) (62%) as single stereoisomers when reacted with norbornene in boiling acetonitrile using catalyst system C. The stereochemistry of (9) and (11) were established by n.O.e. studies in conjunction with decoupling experiments. 1-Iodonaphthalene also functions as a 3-C component and undergoes palladium catalysed cycloaddition (DMF,120°C, 36h) to diphenylacetylene using catalyst system C^3 to give(12) (45%)



(12)

Related studies on fulvene formation have recently been reported^5 and Chiusoli has reported an example of a norbornene annulation^6.

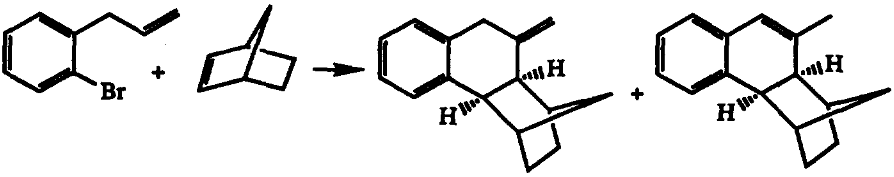
[2+2+1] - Process. Two moles of acenaphthylene react (anisole, 120°C) with β - bromostyrene(13) (1 - C component) using catalyst system A^3 to give the methylene cyclopentane (14) (50%). The stereochemistry of (14) was established by n.O.e. studies. A related example employing norbornene as the 2π - component has been reported^6.



(13)

(14)

[4+2] - Process. 2 - Allyl bromobenzene (15) functions as a 4 - C component and reacts (C_6H_6, 80°C, 16h) with norbornene using catalyst system A^{3}to give a 1.2:4 mixture (51%) of (16) and (17).



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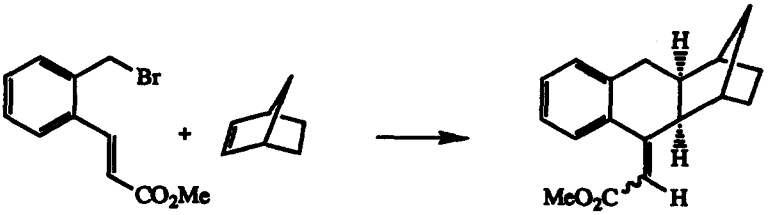
(17)



(18)

(19)

The benzylic bromide (18) reacts (C_6H_6, 80°C, 18h) with norbornene using catalyst system B to give a 2:1 - Z/E mixture (64%) of (19) . The process was repeated in the prescence of TlOAc (2 mol) afforded Z-(19) (50%) as a single stereoisomer. Further examples of these and related process are under study.

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2. Halide may be replaced by triflate or other species known to undergo facile oxidative - addition to Pd(0). Alternatively alkynes can function as starter molecules via addition of HPdX e.g. Trost. B.M., Rise.F.E., *J.Am.Chem.Soc.*, 1987, 104, 3161-3163.
3. All the catalysts used 10 mol% $Pd(OAc)_2$ and 20 mol% PPh_3 but there was a variation in base and in some cases other additives were present. Catalyst A used KOAc (2 mol) as base. Catalyst system B used K_2CO_3(2 mol) as a base together with Et_4NCl(1 mol)^4. Catalyst system C used TlOAc(2 mol) as base.
4. The use of R_4NCl to speed up palladium catalysed intermolecular reactions was introduced by Jeffery. See Jeffery, T.; *Tetrahedron Lett.*, 1991, 32, 2121-2124. and earlier papers.
5. Lee, C.M.; Tobias, B., and Holmes, J.M., *J.Am.Soc.*, 1990 , 9330-9336; Heck, R.F.; Silverberg, L.J., *J.Organomet.Chem.*, 1991, 404, 411-420.
6. Catellani, M.; Chiusoli, G.P., and Sagarabotto, P., *J.Organomet.Chem.*, 1982, 240, 311-319.
7. See: Brown, S.; Clarkson,S., Grigg, R., and Sridharan, V., accompanying paper.

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