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Palladium Catalysed Ter- and Tetra-molecular Queuing Processes. One-pot Routes to 3-Spiro-2-Oxindoles and 3-Spiro-2(3H)-Benzofuranones.

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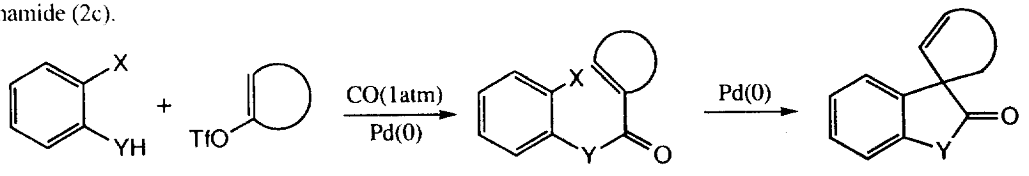
Abstract. The palladium catalysed reactions of 2-halophenols and -anilines with vinyl halides or triflates and CO(1atm) generates 3-spiro-2-oxindoles and 3-spiro-2(3H)-benzofuranones. Analogous tetramolecular reactions employing norbornenyl triflate and organo-tin(IV) or -boron(III) reagents allow additional functionality to be incorporated regio- and stereo-specifically.

The versatility of the intramolecular Heck reaction in accessing all ring motifs (bridged, fused, spiro) and tetrasubstituted carbon centres has been amply confirmed by many groups following our original observations.[1-3] The scope of the intramolecular Heck reaction has been considerably further enhanced by the advent of a range of additives in particular tetraalkylammonium salts,[4] Ag(I) salts,[5] Tl(I) salts,[6] which variously substantially enhance the rate, allow phosphine ligands to be omitted and suppress double bond isomerisation.

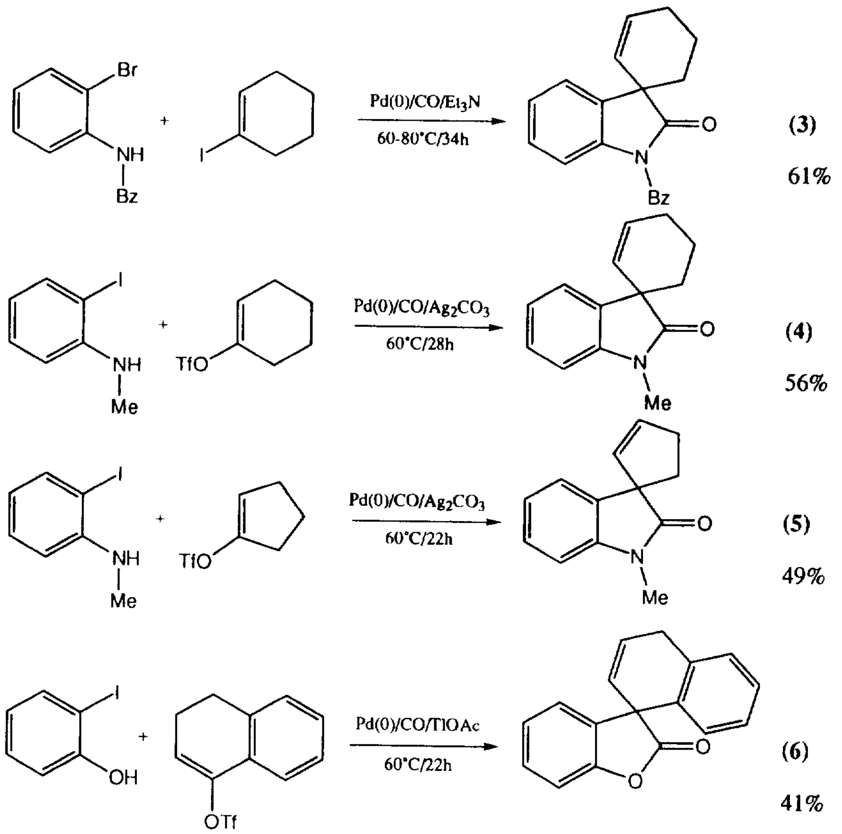
The occurrence of the 3-spiro-2-oxindole[7] and 3-spiro-2(3H)-benzofuranone[8] moieties in natural products and xenobiotic bioactive compounds has focused attention on their generation by the intramolecular Heck reaction. Several groups have taken advantage of the selective insertion of Pd(0) into vinyl triflates in preference to aryl bromides or iodides[9,10] to develop two step sequences to these ring systems (Scheme 1).[5a,10,11] One step protocols were reported not to be achievable and it was considered that a primary amino function was required for the carbonylation step involving (1b). Thus (1c) gave <10% of the corresponding enamide (2c).



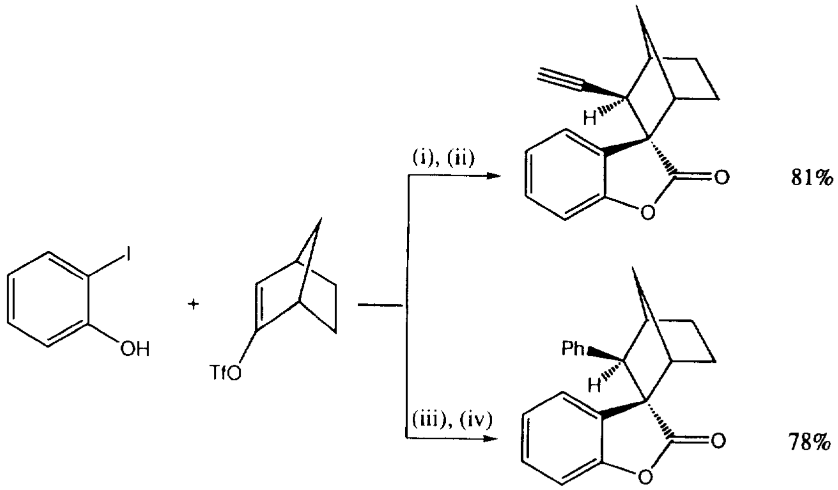
(1) a. X= I, Y= O
b. X= Br, Y= NH
c. X= Br, Y= NR

(2)

Scheme 1



Scheme 2



Scheme 3. (i) CO(1atm)/10mol% Pd(OAc)$_2$/20mol% P(o-Tol)$_3$/3 equiv. K$_2$CO$_3$/MeCN/50°C/12h. (ii) 1.4 equiv. Bu$_3$SnCCH/80°C/18h. (iii) CO(1atm)/10mol% (PPh$_3$)$_2$PdCl$_2$/ 3 equiv. K$_2$CO$_3$/anisole/ 50°C/12h. (iv) 1.2 equiv. NaBPh$_4$/110°C/24h.

We have recently begun developing a range of palladium catalysed ter- and tetra-molecular queuing processes[12] as an extension of our palladium catalysed cyclisation-anion capture methodology.[13] The success of the studies encouraged us to reinvestigate conditions for achieving Scheme 1 as a termolecular one-pot queuing process. This has been successfully achieved for a range of substrates as shown in Scheme 2.

All reactions were carried out in MeCN and employed a 1:1.1mol ratio of haloarene to vinyl iodide/triflate together with 1atm. of CO. In all cases, except formation of (3), the Pd(0) catalyst was generated in situ from 10mol% $Pd(OAc)_2$ and 20mol% PPh_3. In the case of (3) the first phase of the reaction (MeCN, 60°C, 16h) corresponding to (1) → (2) (Scheme 1) was carried out with 10mol% $Pd(OAc)_2$ and triethylamine (1.5mol) but no Ph_3P.[14] At the end of this time 20mol% PPh_3 was added and the reaction allowed to proceed for a further 18h at 80°C. Silver carbonate (3mol) proved the base of choice for formation of (4) and (5) whilst TlOAc(3mol) gave the best results for formation of (6). A high pressure (300 - 1200 psi) tetramolecular carbonylation process involving an alkyne and forming 3-arylidene-2-furanones has been reported.[15]

Several examples of tetramolecular queuing cascades have been achieved. These processes (Scheme 3) intersect with our cyclisation-anion capture methodology.

In these processes (Scheme 3) a slight excess (1.1 equiv.) of the enol triflate is employed and the atmosphere of carbon monoxide is removed after the initial carbonylation phase, corresponding to (1) → (2) (Scheme 1), has been allowed to proceed for 12h. Cyclisation-anion capture then occurs following addition of the appropriate Sn(IV) and B(III) reagents. These latter processes occur regio- and stereo-specifically as established in our previous work.[13]

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