

Palladium-catalyzed annulation*

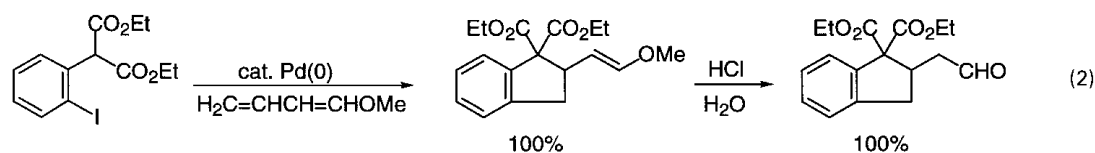
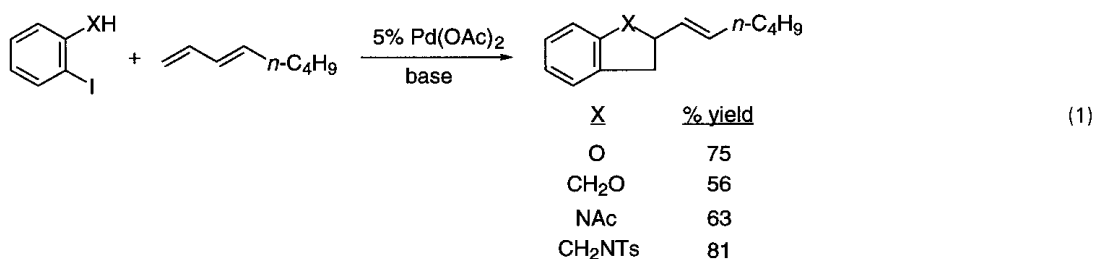
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Abstract: The palladium-catalyzed annulation of cyclic and bicyclic alkenes; unsaturated cyclopropanes and cyclobutanes; 1,2-, 1,3- and 1,4-dienes; as well as internal alkynes, by functionally substituted aryl or vinylic halides and triflates provides a very versatile route to a wide variety of heterocycles and carbocycles.

In recent years, we have developed a number of novel new routes to heterocycles and carbocycles that involve the heteroannulation or carboannulation of appropriately functionalized aryl or vinylic halides or triflates onto a wide variety of dienes, alkenes and alkynes.

1,3-Dienes readily undergo heteroannulation using appropriately functionalized aryl iodides and a suitable Pd catalyst (Eqn 1) [1]. Oxygen-substituted 1,3-dienes afford carboannulation and heteroannulation products easily hydrolyzed to carbonyl compounds (Eqn 2) [2].



The annulation of 1,3-dienes no doubt proceeds by (i) reduction of the palladium(II) salt to Pd(0), the actual catalyst, (ii) oxidative addition of the aryl halide to Pd(0), (iii) arylpalladation of the carbon-carbon double bond to initially produce a σ -allylpalladium intermediate, which rapidly rearranges to the more stable π -allylpalladium intermediate, and (iv) nucleophilic displacement of Pd by the internal nucleophile.

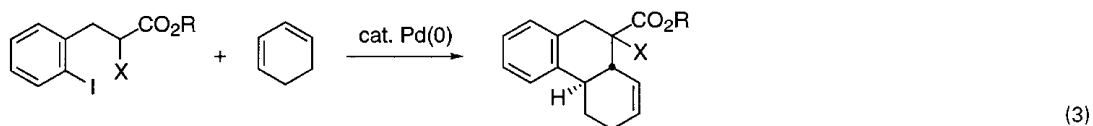
As seen above, one can effect the carboannulation of 1,3-dienes by employing stabilized carbanions in the aromatic side chain (Eqn 3) [3]. Most importantly, one is not limited to highly stabilized carbanions. One can employ a single ester, ketone or nitro group as the electron-withdrawing substituent (Eqn 4).

Since organopalladium compounds add to 1,2-dienes to produce π -allylpalladium compounds, 1,2-dienes readily undergo annulation by a wide variety of functionalized aryl halides (Eqns 5 and 6) [4]. The regiochemistry of this process is highly dependent on the nature of the nucleophile, the structure of the allene, the size of the ring being formed and the reaction conditions.

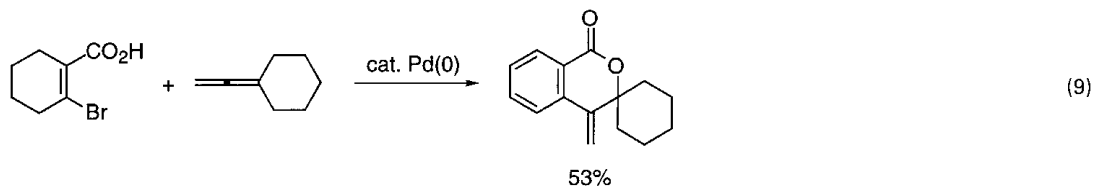
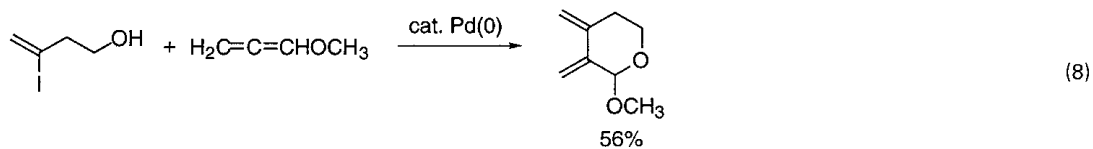
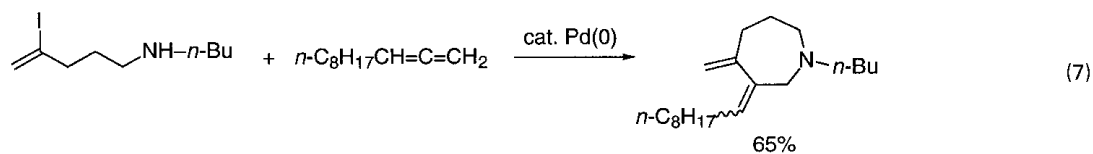
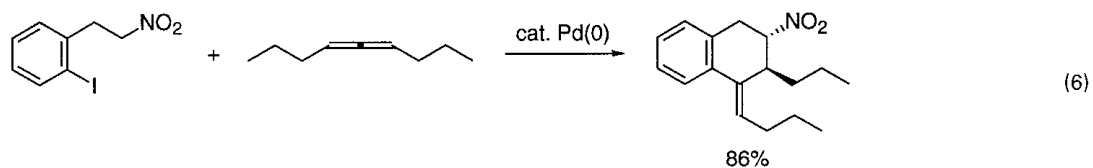
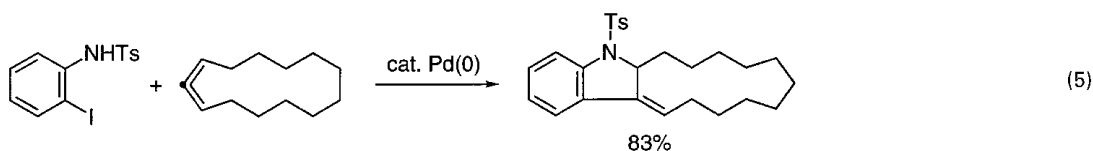
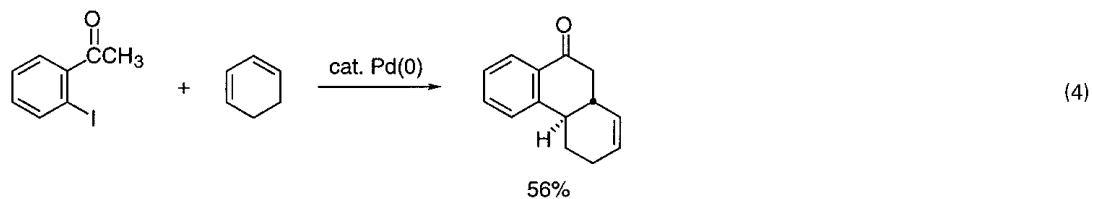
This 1,2-diene chemistry can be extended to the formation of 7-, 8- and even 9-membered ring nitrogen heterocycles (Eqn 7) [5]. Both amines and tosylamides, as well as aryl and vinylic halides, may

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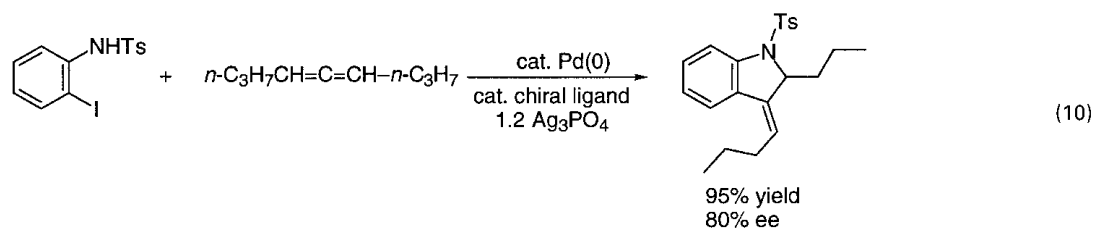


X	%
CO ₂ R	85
CN	73
SPh	96

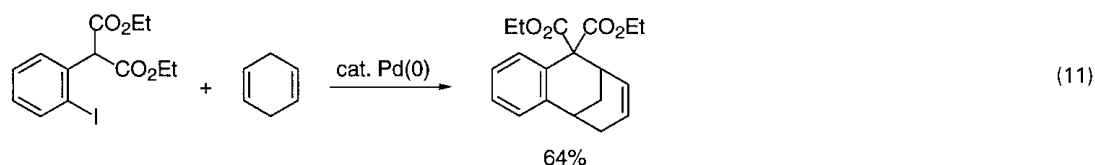


be employed as starting materials. In fact, functionalized vinylic halides and triflates have turned out to be excellent substrates for the annulation of allenes (Eqns 8 and 9) [6].

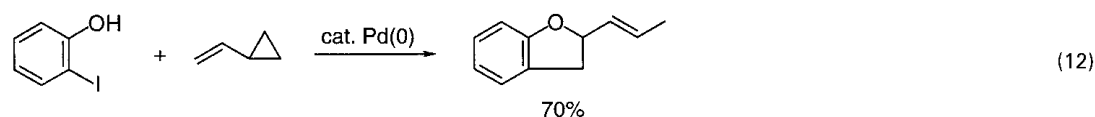
By appropriately modifying our usual allene reaction conditions to include silver salts and only catalytic amounts of a chiral bis(oxazoline) ligand, one can readily effect the hetero- and carboannulation of 1,2-dienes enantioselectively (Eqn 10) [7].



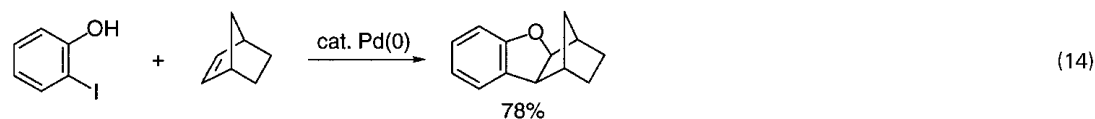
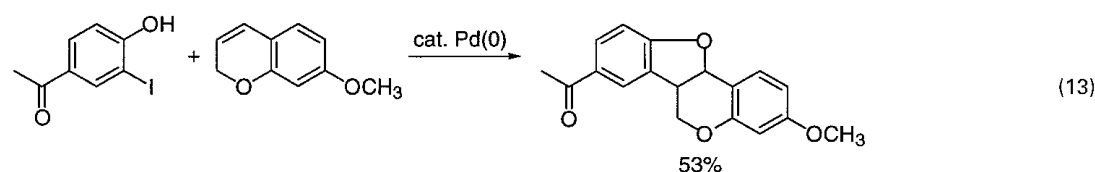
Since Pd possesses the unique ability to migrate down carbon chains by a process involving palladium hydride elimination and subsequent readdition reactions to afford π -allylpalladium intermediates, it is possible to effect the carbo- and heteroannulation of 1,4-dienes as well (Eqn 11) [8].



Since organopalladium compounds add to unsaturated cyclopropanes and cyclobutanes to produce intermediates which readily undergo ring opening to π -allylpalladium compounds, these substrates also readily undergo annulation by a variety of functionalized aryl halides (Eqn 12) [9].

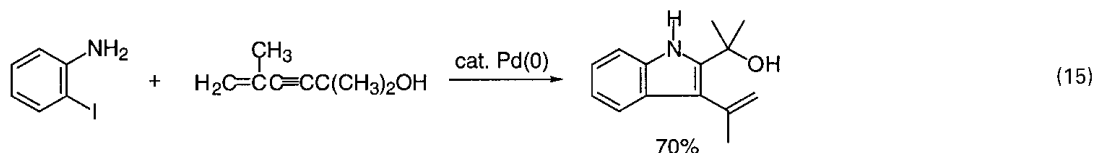


All of the annulation processes discussed so far no doubt proceed via π -allylpalladium intermediates. We have recently observed that even simple cyclic and bicyclic alkenes will undergo annulation if the intermediate organopalladium adduct is prevented from undergoing facile beta hydride elimination (Eqns 13 and 14) [10,11].

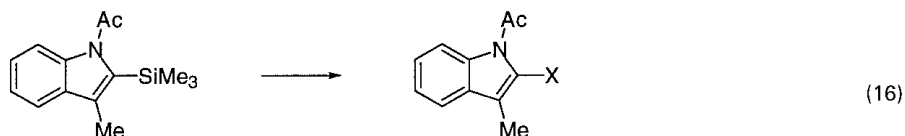


The fact that this annulation methodology seems to be very broad in scope encouraged us to examine the possible annulation of alkynes. The Pd-catalyzed coupling of 2-iodoaniline and derivatives with a wide variety of internal alkynes provides a very valuable new route to the corresponding 2,3-disubstituted indoles (Eqn 15) [12]. The process is quite general as far as the types of substituents which can be accommodated on the nitrogen of the aniline and the two ends of the alkyne triple bond. In general, this process is very regioselective, placing the aryl group of the aniline on the less sterically hindered end of the triple bond. This catalytic annulation process apparently involves arylpalladium formation, regioselective addition to the C–C triple bond of the alkyne, and subsequent intramolecular palladium displacement.

This methodology readily affords 2-silylindoles, which can be easily protodesilylated, halogenated or

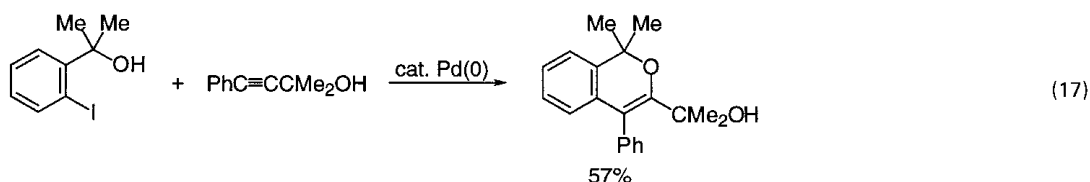


reacted with alkenes and Pd(OAc)₂ to produce 3-substituted indoles, 2-haloindoles or 2-(1-alkenyl)indoles, respectively (Eqn 16).

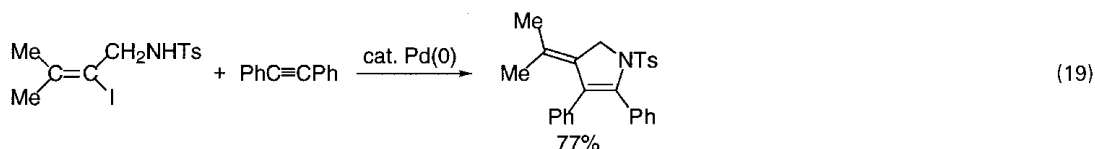


X = H (1. AlCl₃, 2. H₂O; 87%); Br (NBS, 70%); *E*-CH=CHCOCH₃ (H₂C=CHCOCH₃, Pd(OAc)₂; 50%);
E-CH=CHCO₂Et (H₂C=CHCO₂Et, Pd(OAc)₂; 75%)

We have been able to extend the scope of our alkyne annulation chemistry to the synthesis of a wide variety of other heterocycles, including benzofurans, benzopyrans and 1,2-dihydroisoquinolines (Eqn 17) [13]. The range of alkynes which work well in these reactions is, however, more limited than those which have proven successful in the indole chemistry. Generally, only alkynes substituted with aryl, silyl, carbonyl or hindered alkyl groups work well. However, the use of silylalkynes and subsequent electrophilic substitution or desilylation greatly expands the scope of this synthesis.



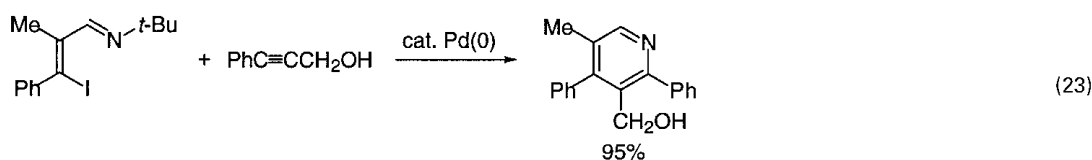
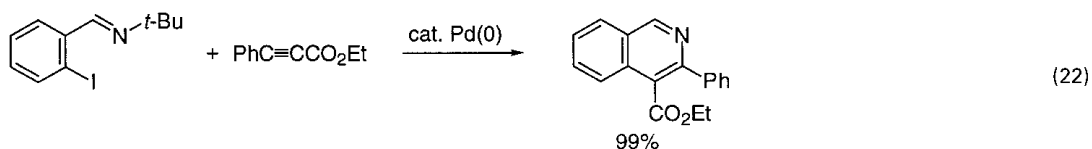
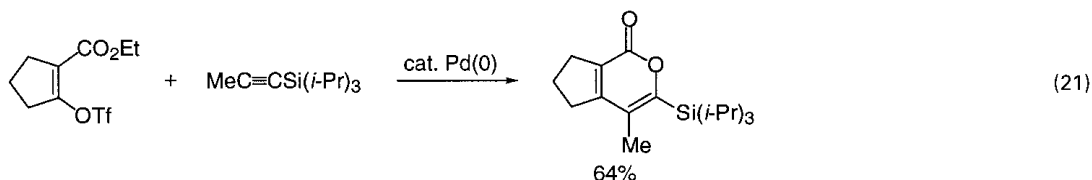
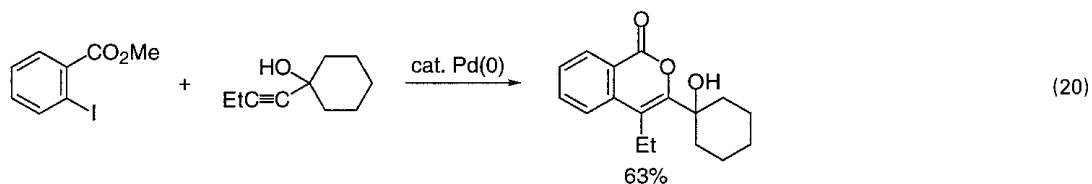
We have recently reported that this alkyne heteroannulation chemistry can be readily extended to vinylic halides to produce a variety of interesting oxygen and nitrogen heterocycles (Eqns 18 and 19) [14]. Note that if high temperatures are employed and the reaction is run long enough, the initial heterocycle can isomerize to a more stable aromatic heterocycle.



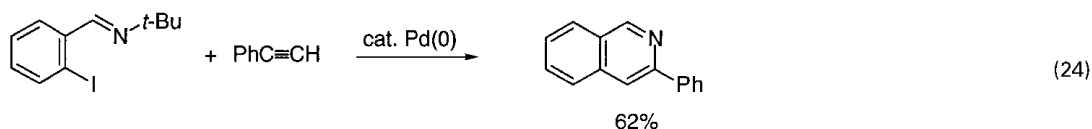
The annulation of internal alkynes by unsaturated esters affords isocoumarins and α -pyrones (Eqns 20 and 21) [13,15,16]. A variety of alkynes can be utilized in this isocoumarin synthesis and the nature of the R group in the ester makes little difference.

We have discovered that the palladium-catalyzed iminoannulation of internal alkynes by the *t*-butylimines of *o*-iodobenzaldehydes readily affords isoquinolines (Eqn 22) [17]. One can also prepare tetrahydroisoquinolines, pyridines, and pyridines using this methodology (Eqn 23).

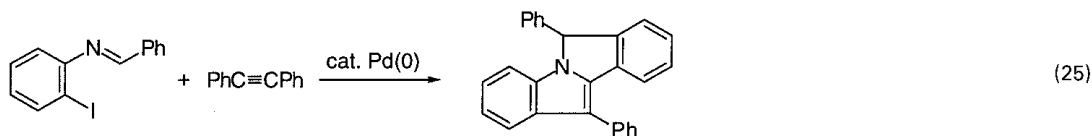
Terminal alkynes afford simple 3-substituted isoquinolines by a process apparently involving initial



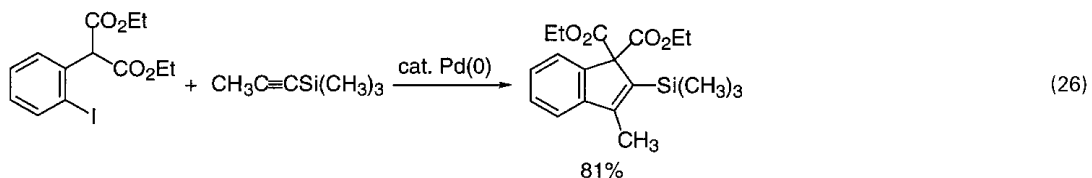
cross-coupling of the terminal alkyne with the aryl halide to form an aryl alkyne and subsequent cyclization and loss of the *t*-butyl group (Eqn 24) [18].



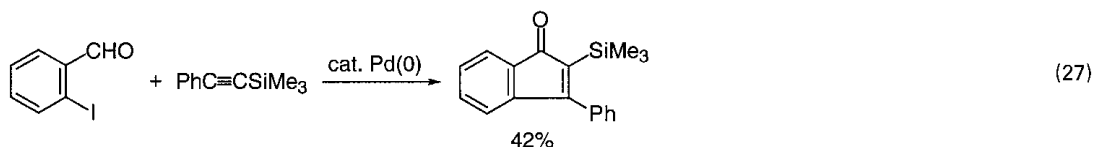
When imines derived from *o*-iodoaniline and benzaldehyde are reacted with internal aryl alkynes, tetracyclic indole products are produced (Eqn 25) [19].



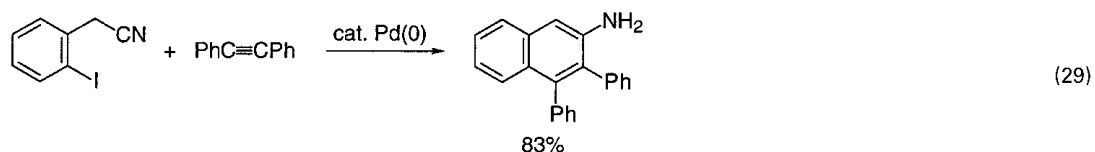
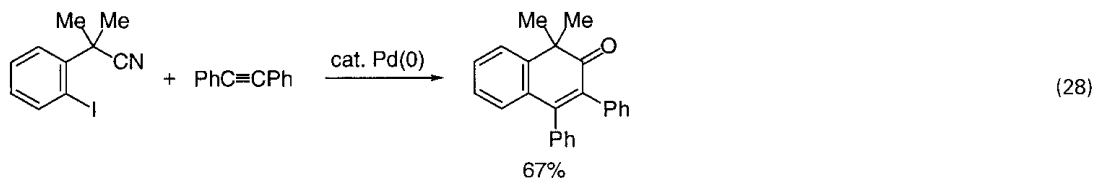
There are a variety of ways that one can effect the carboannulation of alkynes as well. For example, one can employ carbanion-stabilizing groups in the carbon side chain of an aryl halide and generate a variety of indenenes using this methodology (Eqn 26) [20].



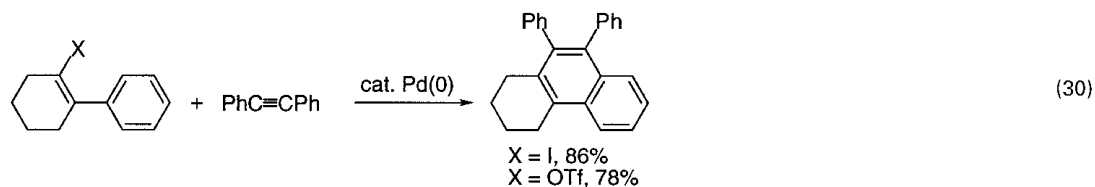
The reaction of *o*-iodobenzaldehyde and internal acetylenes affords indenones, which would be very difficult to prepare by any previous methodology (Eqn 27) [15,21].



Organopalladium intermediates appear to be able to undergo a number of intramolecular reactions with functional groups that they would not normally undergo if the reaction were intermolecular, as seen in the preceding indenone synthesis. For example, the annulation of alkynes by nitrile-bearing aryl halides affords novel annulation products (Eqns 28 and 29) [22].



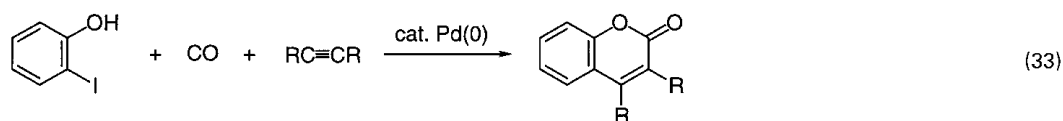
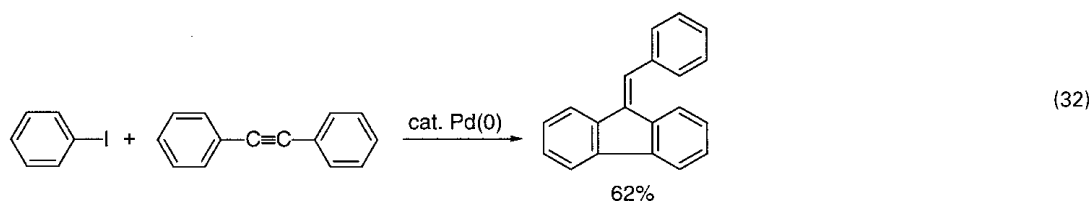
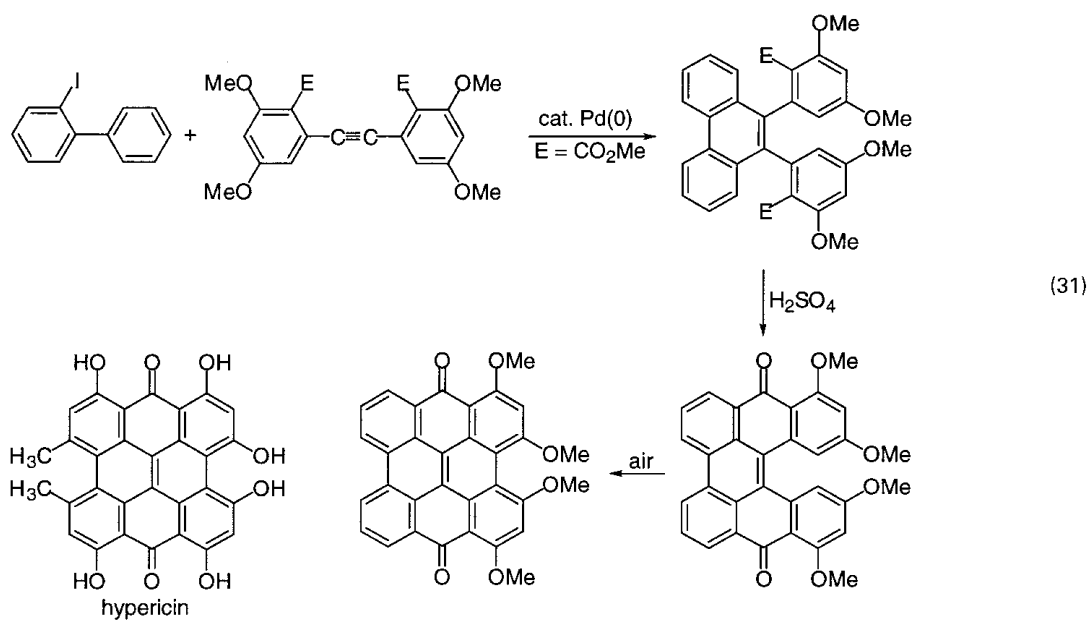
Another type of carboannulation process recently developed in our group involves the insertion of alkynes into aryl or vinylic palladium intermediates and subsequent cyclization onto an aromatic ring already present in the starting material (Eqn 30) [23]. We have employed this process for the preparation of analogs of the very interesting, anti-viral agent hypericin (Eqn 31) [24].



During our examination of this alkyne annulation chemistry, we have observed an unusual rearrangement which leads to the production of good yields of 9-alkylidene fluorenes (Eqn 32) [25].

Finally, we have recently observed that one can simultaneously insert both alkynes and carbon monoxide under the right reaction conditions to produce coumarins in reasonable yields (Eqn 33) [26].

In the last 10 years, we have discovered a number of very useful new ways to effect the hetero- and carboannulation of alkenes, dienes and alkynes to produce a wide range of heterocycles and carbocycles. This chemistry employs only catalytic amounts of palladium and relatively simple starting materials to effect a myriad of valuable synthetic transformations. The reactions take advantage of the ease with which one can generate organopalladium compounds from simple aryl or vinylic halides or triflates by oxidative addition, the facility with which these intermediates add to carbon-carbon unsaturation, and the mild conditions under which the palladium is readily substituted by a variety of heteroatom- or carbon-containing groups.



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