ELSEVIER

Journal of Organometallic Chemistry 576 (1999) 111–124

Journal of Organometallic Chemistry

Review

Palladium-catalyzed annulation☆

Richard C. Larock *

Department of Chemistry, Iowa State University, Ames, IA 50011, USA

Received 1 August 1998

Abstract

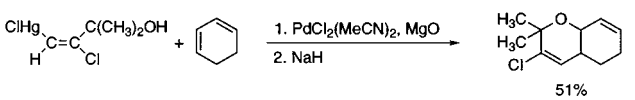
The palladium-catalyzed annulation of cyclic and bicyclic alkenes, unsaturated cyclopropanes and cyclobutanes, allenes, 1,3- and 1,4-dienes, as well as internal alkynes, by appropriately-substituted aryl or vinylic halides and triflates provides a very efficient, yet versatile route to a wide variety of heterocycles and carbocycles. © 1999 Elsevier Science S.A. All rights reserved.

Keywords: Alkenes; Alkynes; Annulation; Carbocycles; Dienes; Heterocycles; Palladium catalysis

1. Introduction

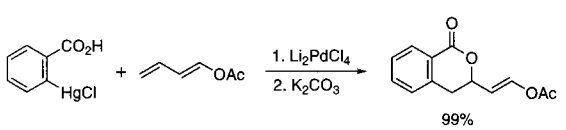
Palladium has proven extraordinarily useful for the synthesis of a wide variety of heterocycles and carbocycles [1]. Prior to 1990, there were a number of reports of the palladium-catalyzed synthesis of heterocycles by appending a heteroatom-containing unit onto existing functionality (heteroannulation) [2], but few of those processes were very general in scope. 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 carbon–carbon unsaturation that have proven very versatile. We wish at this time to review that chemistry and illustrate some of the more recent applications of that chemistry by our group and others.

In the 1980's, we reported some useful new chemistry involving the synthesis of a variety of heterocycles by a two step process involving the palladium-promoted reaction of functionalized aryl or vinylic mercurials with 1,3- and 1,4-dienes, as well as vinylic cyclopropanes, followed by base promoted cyclization of the initially formed π-allylpalladium intermediates [3] (see Eq. (1)).



(1)

A variety of five- and six-membered ring lactones, 2,3-dihydrobenzofurans, benzopyrans and 2,3-dihydroindoles were prepared in this manner. This chemistry was subsequently extended to acetoxy-substituted 1,3-dienes [4] (see Eq. (2)). The major drawback to this approach was the use of stoichiometric amounts of palladium salts and toxic organomercurials.



(2)

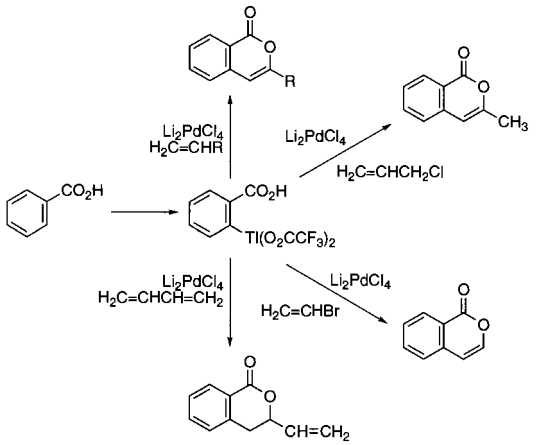
It was subsequently observed that arylthallium compounds prepared by the direct electrophilic thallation of benzoic acids react with a range of olefins to afford a variety of isocoumarins in good yields using only catalytic amounts of palladium [5] (Scheme 1). The thallium(III) salts present after transmetallation with palladium apparently reoxidize palladium quite effi-

☆ Dedicated to Professor Richard F. Heck and to Professor Jiro Tsuji.

* Fax: +1-515-2940105.

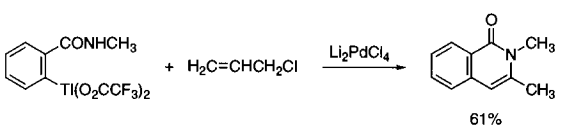
E-mail address: larock@iastate.edu (R.C. Larock)

0022-328X/99/$ - see front matter
PII: S0022-328X(98)01053-5



Scheme 1.

ciently, so that the metal can often be employed in more than one reaction step and usually in only catalytic amounts. A number of lactones, lactams, isoquinolines and indoles were subsequently prepared in this manner [6] (see Eq. (3)).

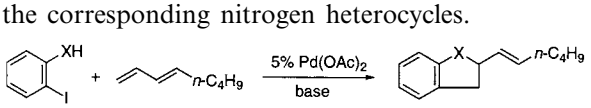


61% (3)

The solution to working with stoichiometric amounts of palladium salts and toxic organometallics turned out to be the use of aryl halides, which only require catalytic amounts of palladium. By employing appropriately functionalized aryl and vinylic halides or triflates, one can readily annulate a wide variety of dienes, alkenes and even alkynes.

2. 1,3-Dienes

Following the lead of Dieck and co-workers [7], we have been highly successful in effecting the heteroannulation of a wide range of cyclic and acyclic 1,3-dienes using appropriately functionalized aryl iodides and 5% of a suitable palladium catalyst [8] (see Eq. (4)). *o*-Iodophenols afford 2,3-dihydrobenzofurans, *o*-iodobenzylic alcohols produce benzopyrans, and *o*-iodoaniline and *o*-benzylic amine derivatives generate the corresponding nitrogen heterocycles.



X	% yield
O	75
CH_2O	56
NAc	63
NTs	84
CH_2NTs	81

(4)

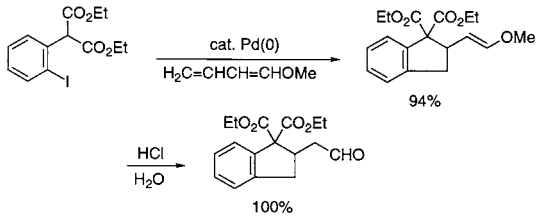
The reaction conditions employed in this and subsequent annulation processes to be discussed later are critical to the success or failure of the reaction. Surprisingly, the nature of the Pd catalyst seems not to have a major effect on the annulation. Both $Pd(OAc)_2$ and $Pd(DBA)_2$ (DBA = dibenzylideneacetone) have been employed, usually with comparable results, although the former reagent is generally more readily available and therefore preferable. Similar results can sometimes be achieved using $Pd(PPh_3)_4$ as the catalyst. Polar solvents are required. In general, the use of *N*,*N*-dimethylformamide as solvent seems to afford the best results. Temperatures of 80–120°C are generally required to effect the process. The rate determining step appears to be oxidative addition of the aryl halides to palladium(0) (see the later mechanistic discussion). The lower temperatures are successful if the aryl or vinylic substrate bears an electron-withdrawing group and the higher temperatures are necessary when electron-rich aryl substrates are employed, such as phenols and anilines.

Other factors critical to the success of the process are the nature and stoichiometry of the base employed and the presence or absence of triphenylphosphine and a chloride source. Of these, the nature of the base is often the most important. Very mild acetate, carbonate and bicarbonate bases have proven the most successful. The base is not simply there to neutralize the one equivalent of acid generated during the annulation, since the nature of the base and the corresponding cation is often critical to the rate of the reaction and the yield of product. Sodium and potassium bases have proven the most generally useful.

The presence of a phosphine, usually just one equivalent of triphenylphosphine per palladium, can sometimes improve the yield, but at present there seems to be no way to predict when this might be true.

The addition of LiCl or n-Bu_4NCl to the reaction often has a profound effect on the yield and rate of reaction. Usually one equivalent of the chloride reagent per aryl or vinylic halide or triflate is employed, although only catalytic amounts are sometimes effective. The addition of more chloride reagent usually slows the reaction down substantially and usually affords little improvement in yields. The effect of n-Bu_4NCl seems to have little to do with solubility or phase transfer effects, since LiCl is generally equally effective and often more reproducible. The chloride appears to coordinate strongly to the Pd(0) catalyst making it more nucleophilic and thus enhancing its ability to undergo oxidative addition.

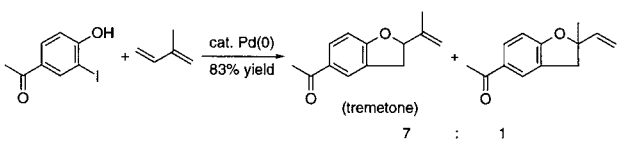
The reaction has proven general for a range of 1,3-dienes. Usually the diene has been used in excess (from two to five equivalents), because the dienes commonly employed are quite volatile and can be lost at the elevated temperatures at which the reaction is usually run, but decent yields of annulation product can usually be obtained by using less diene.



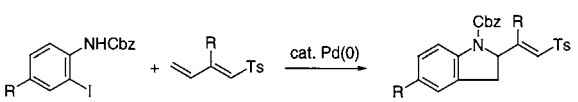
Scheme 2.

In general, the regioselectivity of the annulation of 1,3-dienes is very high. When simple dienes like 1,3-octadiene are employed, only the product of annulation across the less hindered terminal double bond is observed, with the aryl group adding to the terminal carbon. However, annulations of phenolic substrates onto isoprene and derivatives have been observed to give 8–12% of the product from annulation of the more highly substituted double bond [8].

This chemistry has provided one of the most direct routes to naturally-occurring 2,3-dihydrobenzofurans like tremetone [8] (see Eq. (5)) and it has recently been developed as a convenient approach to sulfone-substituted indolines [9] (see Eq. (6)).



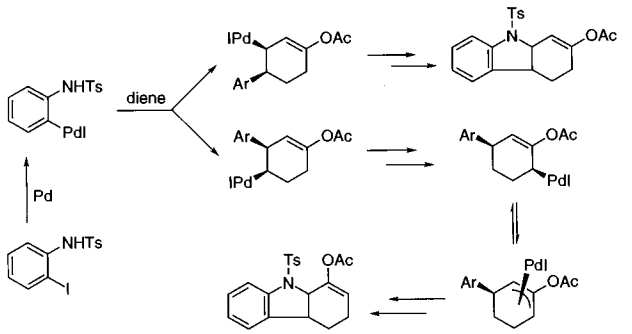
(5)



(6)

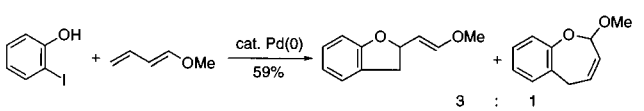
By employing methoxy- or acetoxy-substituted 1,3-dienes as substrates, one obtains carboannulation and heteroannulation products easily hydrolyzed to carbonyl compounds [10] (Schemes 2 and 3).

This chemistry provides a novel route to carbonyl compounds annulated in the 3 and 4 positions and demonstrates the powerful effect of the oxygen substituents. The annulation of 1-acetoxy-1,3-cyclohexadiene by *N*-(2-iodophenyl)tosylamide was observed to afford a 75% yield of the anticipated annulation product **1**, plus 16% of enol acetate **2** (Scheme 3). The latter product could be obtained cleanly by the analogous annulation of 2-acetoxy-1,3-cyclohexadiene. The unexpected product mixture from 1-acetoxy-1,3-cyclohexadiene can best be explained by addition of the initial arylpalladium intermediate to the less substituted carbon–carbon double bond of the diene from two different directions (Scheme 4). Subsequent palladium migration in the minor product by a series of palladium hydride eliminations and readditions eventually leads to a π-allylpalladium intermediate, which undergoes cyclization to the observed minor product. While the hydrolysis of enol acetate **1** generated the anticipated ketone in 88% yield, the hydrolysis of compound **2** produced the unexpected indole **3** in 81% yield (Scheme 3).



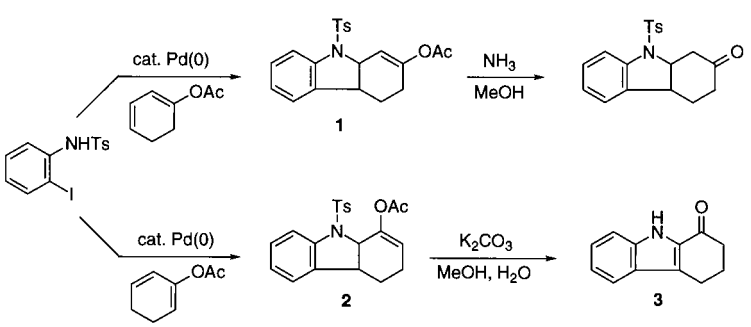
Scheme 4.

This chemistry also afforded as minor products the first examples of 1,4-annulation of a 1,3-diene (see Eq. (7)). Apparently, the directing effect of the oxygen substituent is powerful enough to produce a product of a less favorable larger ring size.



(7)

The annulation of 1,3-dienes no doubt proceeds by (1) reduction of the palladium(II) salt to Pd(0), the actual catalyst, (2) oxidative addition of the aryl halide

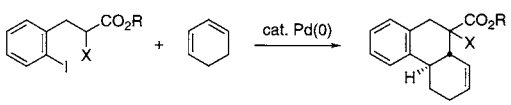


Scheme 3.

to Pd(0), (3) 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 (4) nucleophilic displacement of palladium by the internal nucleophile (Scheme 5).

The displacement step may involve either backside attack of the nucleophile on the π-allylpalladium carbon or frontal attack at the metal, followed by reductive elimination of Pd(0). Both mechanisms for π-allylpalladium substitution are well known [11], and the actual pathway no doubt depends on the geometry of the intermediate and the nature of the nucleophile effecting the substitution. Consistent with the intermediacy of a π-allylpalladium species is the fact that no matter what the stereochemistry of the carbon–carbon double bond not undergoing annulation, that double bond ends up in the more thermodynamically stable configuration after annulation. For example, either a *cis* or a *trans* double bond will end up *trans* in the product. This is a direct result of the formation of the more thermodynamically stable *syn* π-allylpalladium intermediate.

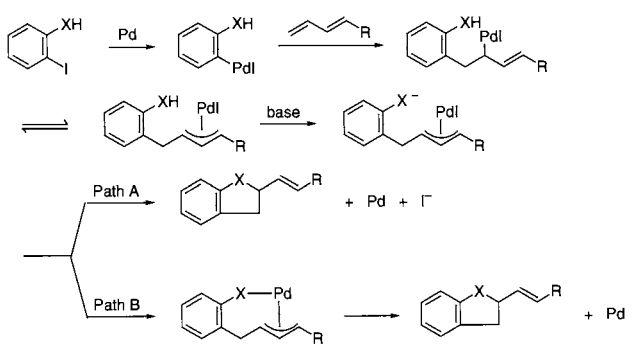
As seen in Scheme 2 above, one can effect the carboannulation of 1,3-dienes by employing stabilized carbanions in the aromatic side chain [12] (see Eq. (8)). Once again a range of cyclic and acyclic 1,3-dienes has proven successful.



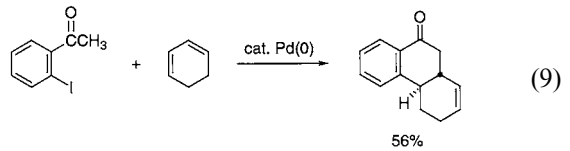
X	%
CO_2R	85
CN	73
SPh	96

(8)

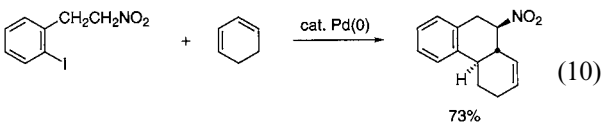
Most importantly, one is not limited to highly stabilized carbanions like malonates. In fact, one can employ a single ester, ketone or nitro group as the electron-withdrawing substitutent and still get excellent results (Eqs. 9, 10). The nitro group is significant, since it can be readily oxidized directly to a carbonyl group or reduced to the corresponding alkane.



Scheme 5.



(9)

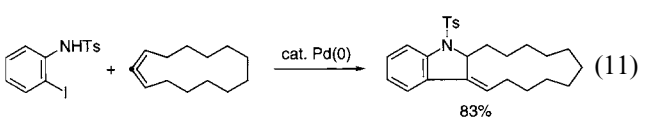


(10)

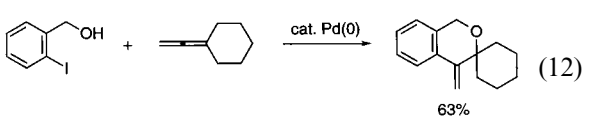
All five-membered ring products formed in this carboannulation process have contained exclusive *cis* ring fusion, suggesting that displacement of the palladium by the carbanion nucleophile is occurring by frontal displacement, an unusual mode of substitution for carbanions. All six-membered ring products contain a *trans* ring fusion indicating that the more normal backside displacement process is apparently in effect here.

3. 1,2-Dienes

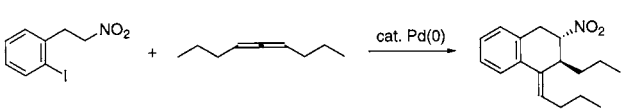
Since it is well known that organopalladium compounds will add to 1,2-dienes to produce π-allylpalladium compounds [5,13], it was anticipated that these hetero- and carboannulation processes should be readily extended to allenes. Indeed, this has turned out to be true. In fact, 1,2-dienes have generally proven to be more easily annulated by a wider variety of nucleophiles than 1,3-dienes. Thus, a range of acyclic and cyclic 1,2-dienes have been successfully annulated by a wide variety of functionalized aryl halides [14] (see Eqs. 11–15). Phenols, alcohols, tosylamides and carbanions have all afforded the anticipated products in good yields.



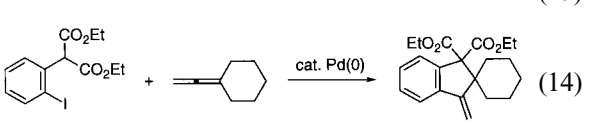
(11)



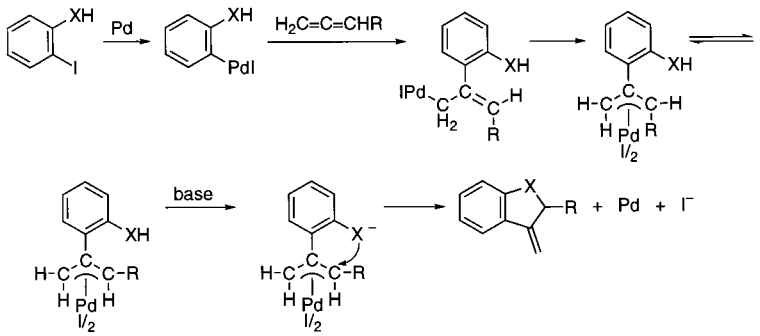
(12)



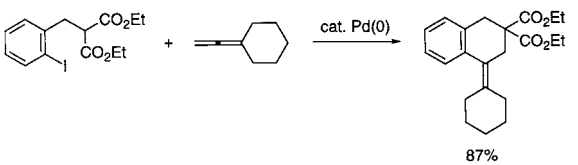
(13)



(14)



Scheme 6.



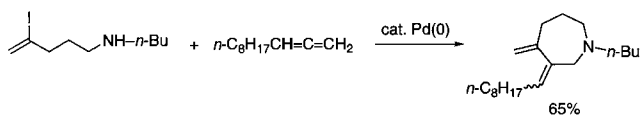
(15)

Most of the time this process is highly stereo- and regioselective, as shown in the above examples, all of which produced the single product shown. The stereoselectivity presumably arises from formation of the more thermodynamically stable π-allylpalladium intermediate. When neither the *syn* or *anti* π-allylpalladium intermediate is strongly favored due to steric factors, mixtures of stereoisomers are observed.

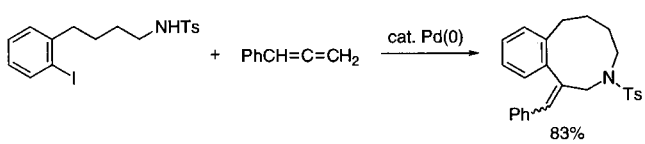
The regioselectivity of the annulation of 1,2-dienes is quite interesting. The formation of five-membered rings involves exclusive annulation across the more substituted carbon–carbon double bond. Even carbanions, which generally undergo intermolecular π-allylpalladium displacement processes at the less substituted termini, afford exclusively the products of attack at the more substituted end of the 1,2-diene when five-membered rings are being formed (see Eq. (14)). On the other hand, six-membered rings are generally formed by annulation primarily across the less substituted carbon–carbon double bond, although exceptions have been observed (see Eq. (12)). The regiochemistry is apparently highly dependent on the nature of the nucleophile and the size of the ring being formed as indicated by comparing Eqs. 12, 14, 15. This process provides an exciting new way to generate quaternary carbon centers, even adjacent quaternary centers (see Eq. (14)).

This process probably proceeds by a process analogous to that shown in Scheme 5, except that the aryl moiety now adds to the central carbon of the 1,2-diene (Scheme 6). One crucial difference is the fact that substitution of palladium at either end of the π-allyl unit is now geometrically readily accessible, so that either regioisomer is in fact possible by simple intramolecular displacement.

While we have not devoted much effort to the formation of rings larger than five or six members, we have recently observed that this 1,2-diene chemistry can be extended to the formation of seven-, eight- and even nine-membered ring nitrogen heterocycles [15] (Eqs.16, 17). Both amines and tosylamides, as well as aryl and vinylic halides, may be employed as starting materials. Mixtures of stereoisomers are commonly observed in the products.

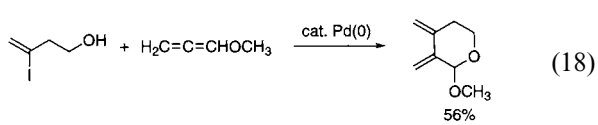


(16)

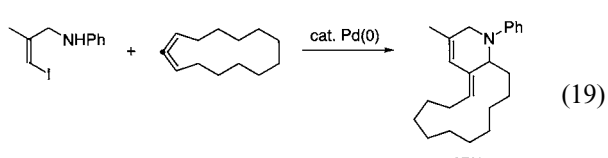


(17)

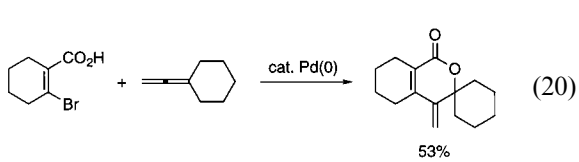
As illustrated in Eq. (16), functionalized vinylic halides and triflates have turned out to be excellent substrates for the annulation of allenes [16] (Eqs. 18–22).



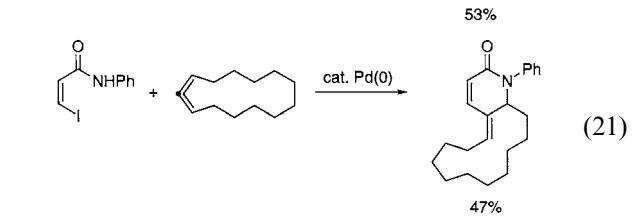
(18)



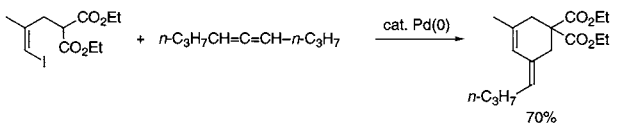
(19)



(20)



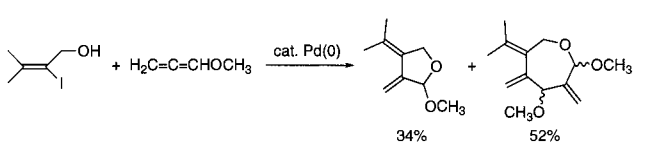
(21)



(22)

Vinylic halides expand the scope of this annulation process, since the products may now contain exocyclic or endocyclic carbon–carbon double bonds arising from the vinylic halide. Note that a wide variety of cyclic and acyclic, mono- and disubstituted, aliphatic and functionalized allenes may be utilized in this process and the range of successful nucleophiles has been expanded to include not only alcohols, amines, sulfonamides and carbanion-stabilizing groups, but also carboxylic acids and amides. When the latter functional groups are present, one can run some reactions at room temperature or employ vinylic bromides as starting materials, since the electron-withdrawing carbonyl group activates the neighboring vinylic halide towards oxidative addition.

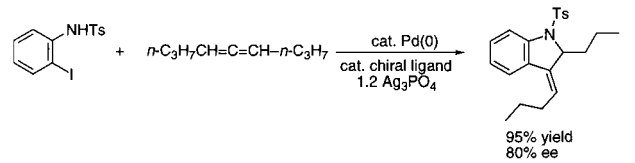
Six-membered ring compounds have generally been formed in higher yields than five-membered rings. In fact, we have been unsuccessful in forming five-membered ring products by carboannulation. The reluctance to form five-membered rings is illustrated by our observation of the preferential formation of a seven-membered ring double insertion product (see Eq. (23)).



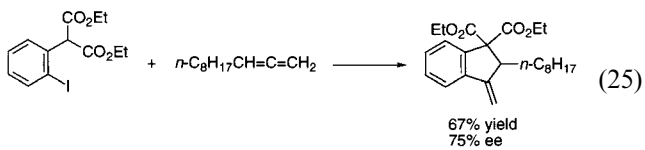
(23)

The regioselectivity of this annulation is highly dependent on the structure of the allene, the size of the ring being formed, the reaction conditions and the nature of the functional group producing the nucleophile. The stereoselectivity of the reaction can be excellent, but is very dependent on the structure of the π-allylpalladium intermediate, and often affords mixtures of stereoisomers.

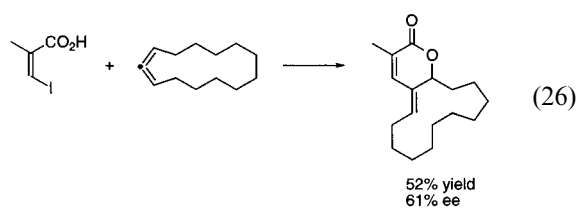
Enantioselective, palladium-catalyzed allylic substitution has recently been shown to be a useful means of forming new chiral carbon–carbon and carbon nitrogen bonds [17], but there have been only a couple of examples of asymmetric induction in intramolecular π-allylpalladium displacement processes [18]. By appropriately modifying our usual allene reaction conditions to include silver salts and only catalytic amounts of a chiral bis(oxazoline) ligand, we can very effectively generate chiral products with high enantioselectivities in the hetero- and carboannulation of 1,2-dienes by aryl and vinylic halides [19] (Eqs. 24–27). The regioselectivity of this enantioselective process is often higher than that observed under our previously reported conditions using PPh_3 as the ligand.



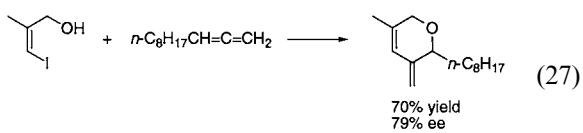
(24)



(25)



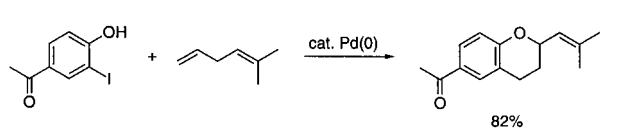
(26)



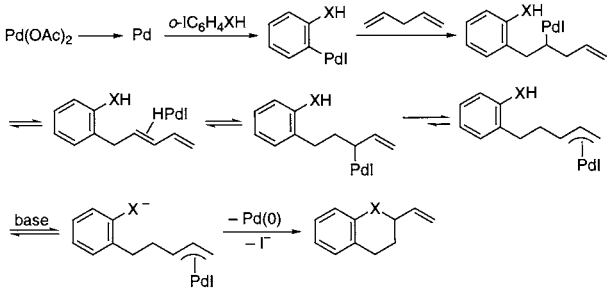
(27)

4. 1,4-Dienes

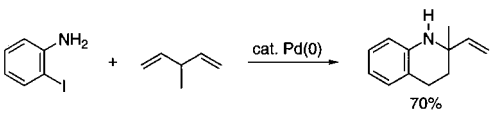
We and others have reported a number of useful synthetic processes based on the ability of palladium to migrate along a carbon chain by a series of palladium hydride elimination and subsequent readdition reactions to afford π-allylpalladium intermediates, which subsequently undergo nucleophilic displacement to produce the desired organic products [20]. It, therefore, appeared feasible to effect the annulation of 1,4-dienes under our usual reaction conditions and this has indeed proven to be true as illustrated by the following examples [21] (Eqs. 28–30). Once again this process has been



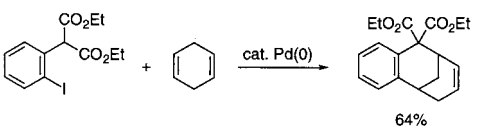
(28)



Scheme 7.



(29)



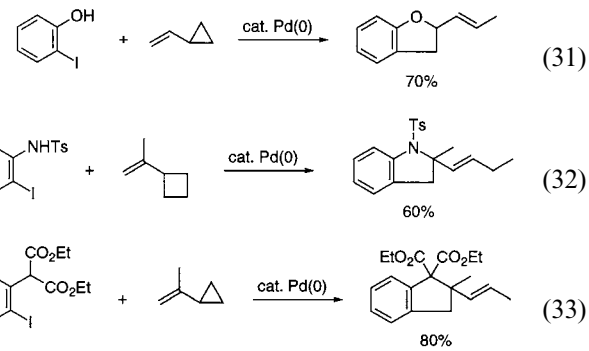
(30)

successful on a variety of functionalized aryl halides and substituted acyclic and even cyclic 1,4-dienes. The regioselectivity of this reaction is excellent.

Mechanistically, this process appears to proceed as shown in Scheme 7.

5. Unsaturated cyclopropanes and cyclobutanes

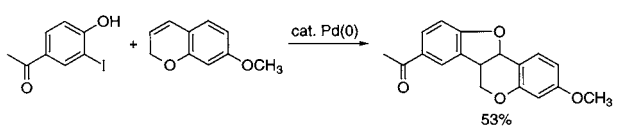
In earlier work, we established that organopalladium compounds would add to unsaturated cyclopropanes and cyclobutanes to produce intermediates which readily undergo ring opening to π-allylpalladium compounds [22]. This suggested that the annulation of these same olefinic substrates might produce π-allylpalladium intermediates, which would ultimately lead to interesting annulation products. Indeed, we have been successful in achieving the annulation of unsaturated cyclopropanes and cyclobutanes by a variety of functionalized aryl halides [23] (Eqs. 31–33).



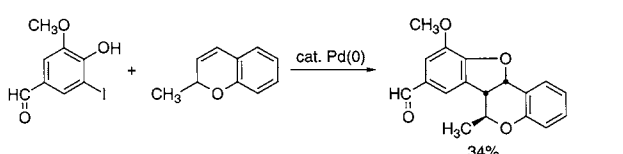
This novel annulation process presumably proceeds by the mechanism shown in Scheme 8.

6. Cyclic and bicyclic alkenes

All of the annulation processes discussed so far have proceeded via π-allylpalladium intermediates. Previous reports of the formation of the biologically interesting pterocarpan ring system by the cross-coupling of benzopyrans, functionalized arylmercurials and stoichiometric amounts of palladium salts [24] suggested that we might be able to effect a similar palladium-catalyzed annulation process by using appropriately functionalized aryl halides and benzopyrans. Indeed, this process has been successful, although the yields are only modest [25] (Eqs. 34, 35).

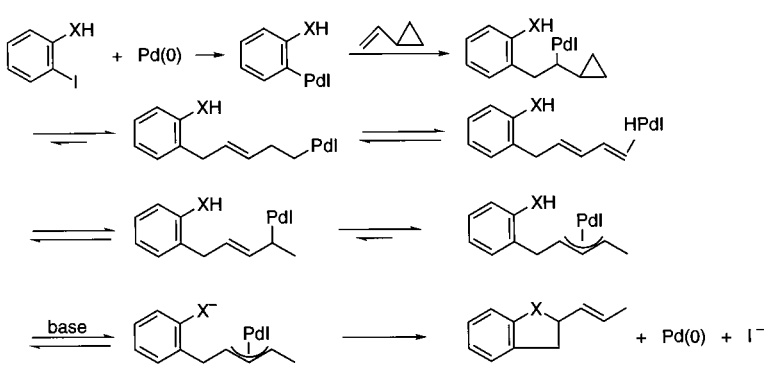


(34)

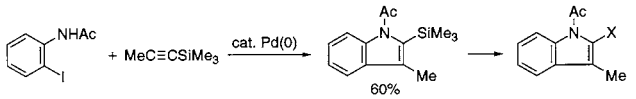


(35)

This process apparently proceeds by oxidative addition of the aryl halide to Pd(0), followed by olefin



Scheme 8.

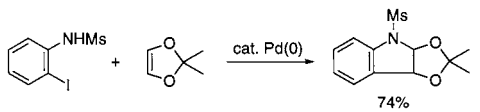


X = H (1. $AlCl_3$, 2. H_2O; 87%); Br (NBS, 70%); *E*- CH=CHCOCH$_3$ (H_2C=CHCOCH$_3$, $Pd(OAc)_2$; 50%); *E*- CH=CHCO$_2$Et (H_2C=CHCO$_2$Et, $Pd(OAc)_2$; 75%)

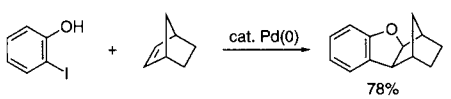
Scheme 9.

insertion. Although the mechanism of the subsequent palladium displacement step is not known, it is possible that a π-benzylic palladium intermediate is involved, much like the π-allylpalladium reactions discussed thus far. This process raises the very interesting question as to whether to effect annulation it is sufficient simply to block palladium hydride beta elimination in the intermediate formed by olefin insertion or whether one needs specific types of organopalladium intermediates, such as π-allyl- or π-benzylpalladium intermediates, in order to be able to effect cyclization.

Our recent work with simple cyclic and bicyclic alkenes suggests that this annulation process is very general and a wide variety of palladium intermediates will undergo the process [26] (Eqs. 36, 37). The key seems



(36)



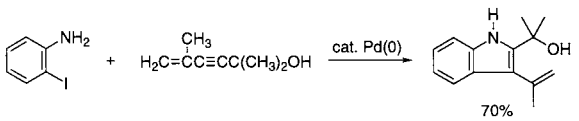
(37)

to be that one simply needs to block beta hydride elimination in the organopalladium intermediate formed by olefin insertion.

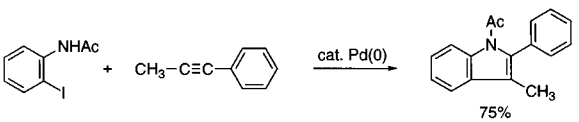
7. Alkynes

The fact that this annulation methodology seems to be very broad in scope encouraged us to examine the possible annulation of alkynes. While there has been considerable recent interest in the reactions of alkynes and organopalladium intermediates [27], these reactions have often proven difficult to control and only recently have useful synthetic processes been developed based on this methodology. A number of examples of the annulation of alkynes by stoichiometric amounts of *o*-palladated arenes have been reported, but these are of little synthetic interest, because they involve stoichiometric amounts of palladium and require two steps to effect overall annulation. We have been interested in the catalytic annulation of internal alkynes and have found that this chemistry can provide a very general route to a wide variety of heterocycles and carbocycles.

We first examined the palladium-catalyzed coupling of 2-iodoaniline and the corresponding *N*-methyl, -acetyl and -tosyl derivatives with a wide variety of internal alkynes and found that this provides a very valuable new route to the corresponding 2,3-disubstituted indoles in good to excellent yields [28] (Eqs. 38, 39).

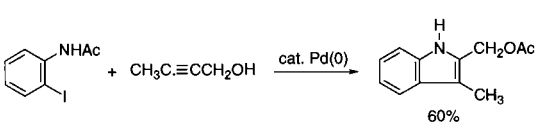


(38)



(39)

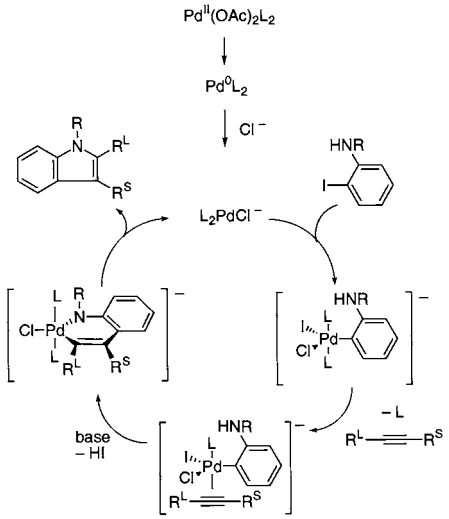
The best results have been obtained by employing an excess of the alkyne and a sodium or potassium acetate or carbonate base, plus one equivalent of either LiCl or *n*-Bu_4NCl and occasionally adding 5 mol% PPh_3. The yields with LiCl appear to be higher and more reproducible than those obtained with *n*-Bu_4NCl. 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. On the alkyne, primary, secondary and tertiary alkyl groups and aryl groups with or without functionality afford indoles in good yields. The presence of alcohol groups in the alkyne seems to have a particularly strong directing effect, perhaps due to coordination with palladium, and products of acetyl migration from nitrogen to oxygen have been observed (see Eq. (40)). In general, this process is very regioselective, placing the aryl group of the aniline on the less sterically hindered end of the triple bond and the nitrogen moiety on the more sterically hindered end.



(40)

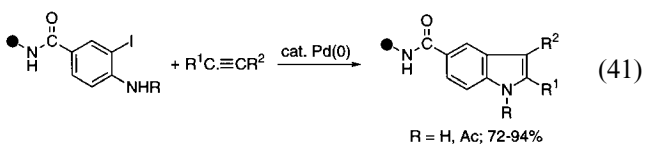
This methodology readily affords 2-silylindoles, which can be easily protodesilylated, halogenated or reacted with alkenes and $Pd(OAc)_2$ to produce 3-substituted indoles, 2-haloindoles or 2-(1-alkenyl)indoles respectively (Scheme 9). This chemistry has recently been employed in the synthesis of 3-substituted indoles of great current interest as potent 5-HT_{1D} receptor agonists for the treatment of migraine headaches [29].

This catalytic annulation process apparently involves arylpalladium formation, regioselective addition to the carbon–carbon triple bond of the alkyne, and subsequent intramolecular palladium displacement (Scheme 10). The mechanism of the actual palladium displacement process is not clear.

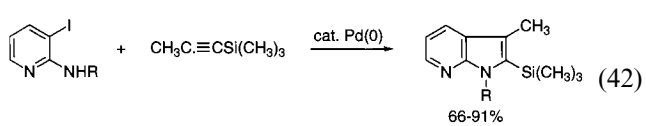


Scheme 10.

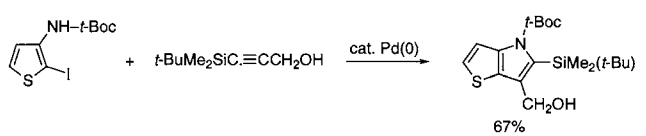
The great current interest in the pharmaceutically important indole ring system has encouraged the development of solid phase resin-bound versions of this chemistry [30] (see Eq. (41)) and the synthesis of tryptophan derivatives [31]. More recently our indole synthesis has been employed by others to prepare various heteroatom-substituted analogs, including 5-, 6- and 7-azaindoles [32], thienopyrroles [33], pyrrolopyrimidines [33] and pyrrolopyridines [33] (Eqs. 42, 43).



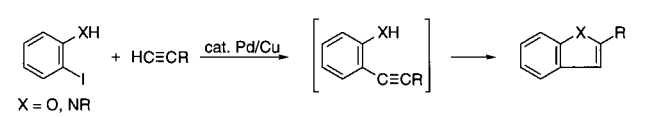
R = H, Ac; 72-94% (41)



66-91% (42)



67% (43)

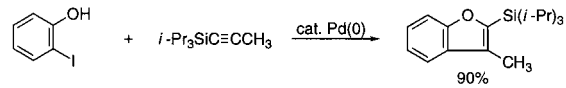


X = O, NR

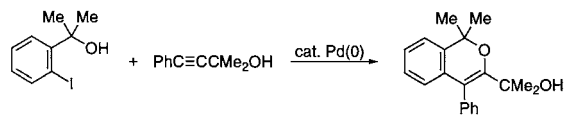
Scheme 11.

There has also been considerable interest of late in a related approach to 5-azaindoles [34], indoles [35], and benzofurans [36] involving the coupling of terminal alkynes with analogous aryl iodides using palladium and copper reagents and subsequent cyclization (Scheme 11). This methodology has also been employed on solid supports [35,36].

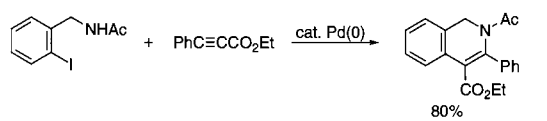
We have been able to extend the scope of our alkyne annulation chemistry to the synthesis of a wide variety of other heterocycles, including benzofurans, benzopyrans and 1,2-dihydroisoquinolines [37] (Eqs. 44–46).



90% (44)

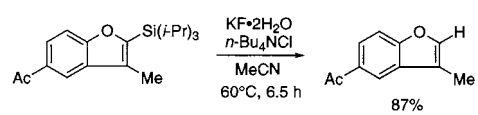


57% (45)



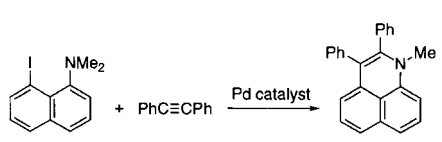
80% (46)

The range of alkynes which work well in these reactions is, however, more limited than those which have proven successful in our 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 (see Eq. (47)).



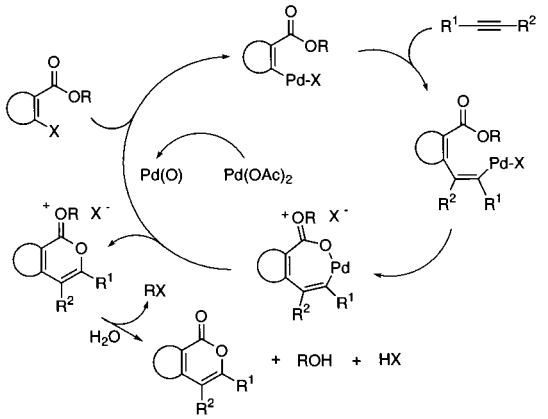
87% (47)

Others have reported the synthesis of *N*-methylbenzo[*d*,*e*]quinolines by the palladium-catalyzed annulation of internal alkynes using 1-iodo-8-(dimethylamino)naphthalene [38] (see Eq. (48)). This is an interesting example of demethylation during annulation.



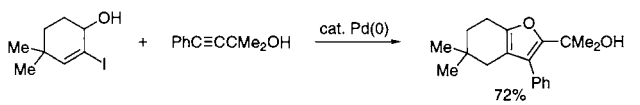
98% (48)

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 [39] (Eqs. 49–51). Note that if high temperatures are employed and the reaction is run long enough, the initial heterocycle can isomerize to a

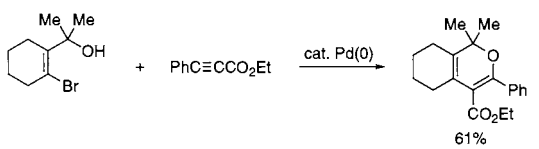


Scheme 12.

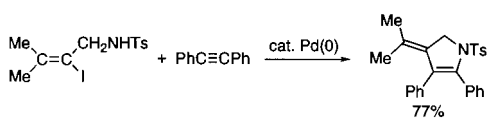
more stable aromatic heterocycle (see Eq. (49)). This chemistry provides a novel new approach to highly substituted furans.



(49)

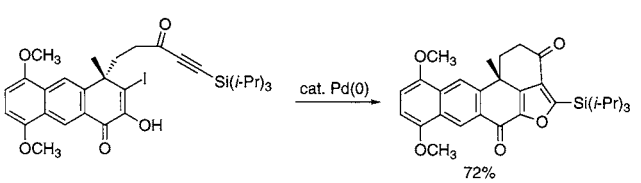


(50)



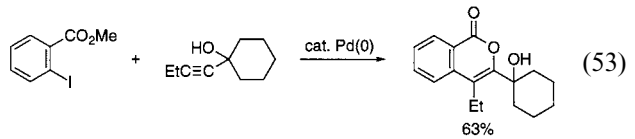
(51)

Shibasaki and co-workers have employed an intramolecular variation of this chemistry to prepare halenaquinone and helenaquinol [40] (see Eq. (52)).

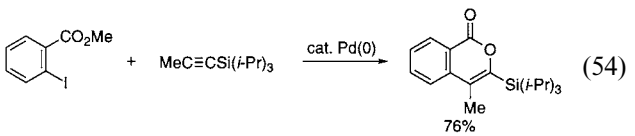


(52)

The annulation of internal alkynes by *o*-iodobenzoic acid affords only low yields of a mixture of products. However, Heck and co-workers previously reported that the use of the corresponding methyl ester gives a good yield of 3,4-diphenylisocoumarin when diphenylacetylene is employed as the alkyne [41]. Unfortunately, 3-hexyne afforded very poor results for Heck. We have explored the scope of this isocoumarin synthesis and found it to be reasonably general [37] (Eqs. 53, 54).



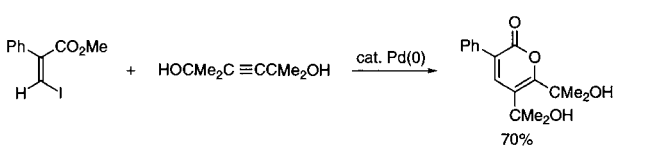
(53)



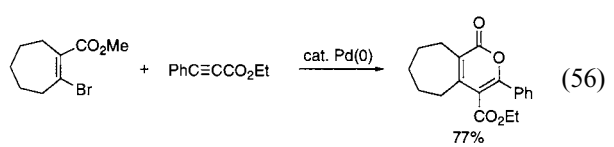
(54)

A variety of alkynes can be utilized in this isocoumarin synthesis and the nature of the *R* group in the ester makes little difference. Virtually identical yields of isocoumarin have been obtained using methyl, ethyl, isopropyl, *t*-butyl, neopentyl or phenyl esters, suggesting that the ring closure involves attack of the carbonyl oxygen on the palladium to form an oxonium intermediate, which subsequently undergoes reductive elimination to the isocoumarin (Scheme 12).

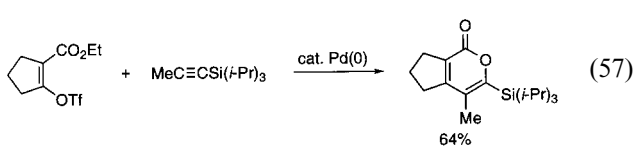
This annulation chemistry has recently been extended to the synthesis of α-pyrones [42] (Eqs. 55–57). Note that one can employ acyclic and cyclic vinylic iodides, bromides and triflates and a reasonable variety of substitutents can be accommodated on the alkyne.



(55)



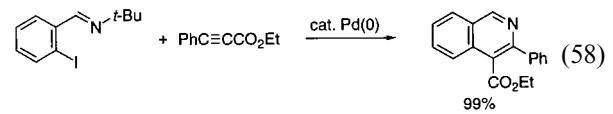
(56)



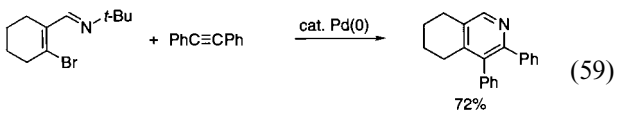
(57)

Substituted isoquinolines have previously been synthesized by employing palladium annulation methodology. For instance, Pfeffer reported the formation of a disubstituted isoquinoline derivative from a cyclopalladated *N*,*N*-dimethylbenzylamine complex [43], and Heck observed the formation of 3,4-diphenylisoquinoline in 22% yield by the reaction of cyclopalladated *N*-*t*-butylbenzaldimine tetrafluoroborate with diphenylacetylene [44]. Widdowson has also reported an isoquinoline synthesis based on cyclopalladated *N*-*t*-butylarylaldimines [45]. This methodology suffers from the fact that it is stoichiometric with respect to palladium, and in the latter synthesis, a final pyrolysis step is necessary.

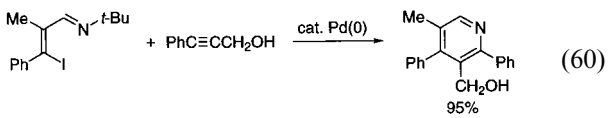
We have discovered that the palladium-catalyzed iminoannulation of internal alkynes by the *t*-butylimines of *o*-iodobenzaldehydes readily affords isoquinolines [46] (see Eq. (58)). One can also prepare tetrahydroisoquinolines, pyrindines, and pyridines using this methodology (Eqs. 59, 60).



(58)

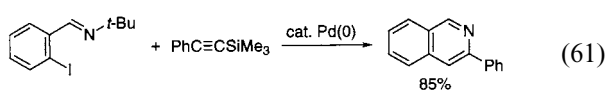


(59)

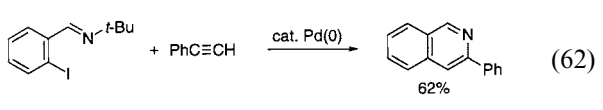


(60)

We have also observed that silylalkynes and terminal alkynes afford simple 3-substituted isoquinolines by a process apparently involving initial cross-coupling of the terminal alkyne (obtained by desilylation of the silylalkyne) with the aryl halide to form an aryl alkyne and subsequent cyclization and loss of the *t*-butyl group [47] (Eqs. 61, 62).

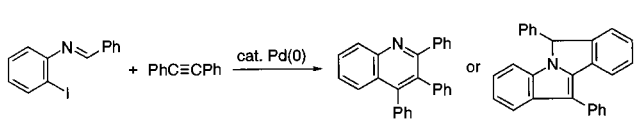


(61)

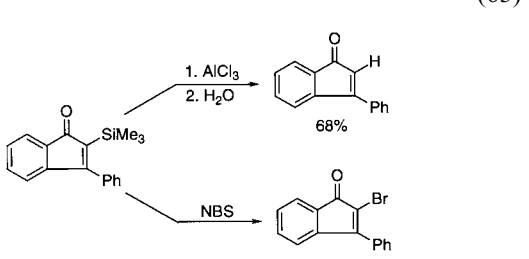


(62)

When imines derived from *o*-iodoaniline and benzaldehyde are reacted with internal aryl alkynes under the appropriate conditions, we can obtain either isoquinolines or tetracyclic indole products depending on the reaction conditions used [47] (see Eq. (63)).

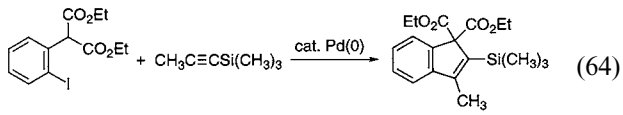


(63)

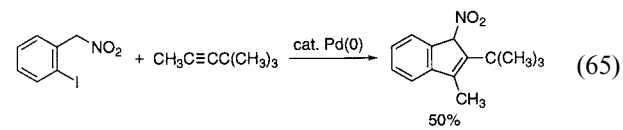


Scheme 13.

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 indenes using this methodology [48] (Eqs. 64, 65). So far, this chemistry has not worked well for the synthesis of six-membered carbocyclic rings.

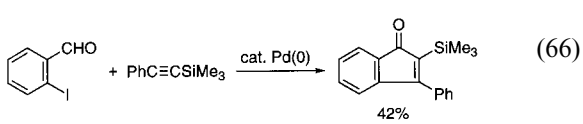


(64)

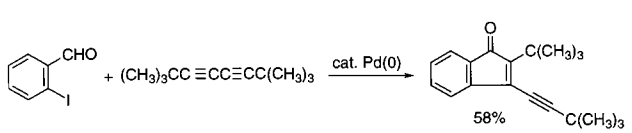


(65)

In 1989, Heck reported that the reaction of *o*-iodobenzaldehyde and diphenylacetylene in the presence of a palladium catalyst produces 2,3-diphenylindenone [41]. We subsequently optimized reaction conditions, explored the scope of this process, and reported that it is an effective way to prepare a number of interesting indenones, which would be very difficult to prepare by any previous methodology [49] (Eqs. 66, 67).



(66)

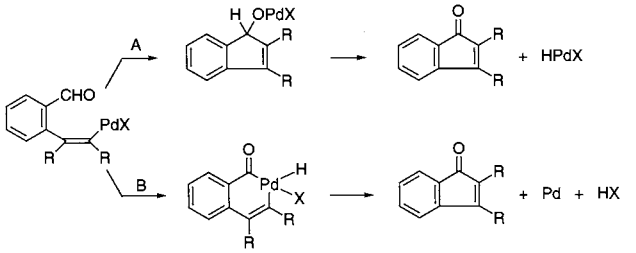


(67)

Once again silylalkynes provide the anticipated silylindenones, which are readily desilylated or halogenated (Scheme 13).

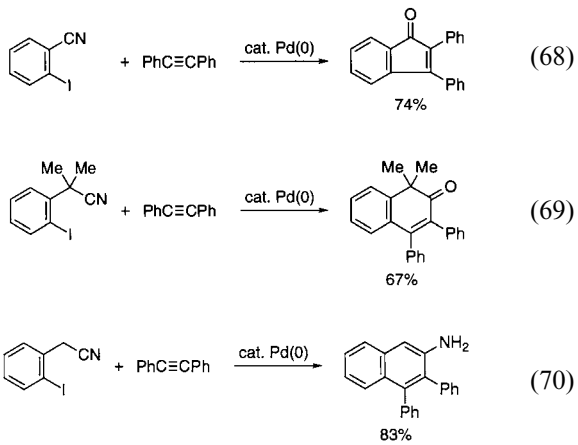
The mechanism of this indenone synthesis presumably follows closely those previously discussed, although the mode of actual ring closure of the vinylpalladium intermediate to the indenone is unclear. Either the vinylpalladium intermediate can add to the carbonyl group and subsequently undergo β-hydride elimination (path A) or the aldehydic C–H bond may oxidatively add to the palladium to produce an organopalladium(IV) intermediate (path B), which subsequently undergoes a rapid reductive elimination of indenone and palladium (Scheme 14).

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



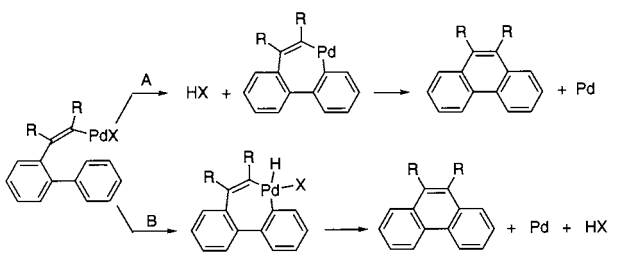
Scheme 14.

preceding indenone synthesis where an aldehyde is so involved. For example, while acetonitrile is often used as a solvent and palladium salts with nitrile ligands are common reagents in organopalladium reactions, the annulation of alkynes by nitrile-bearing aryl halides affords novel annulation products [50] (Eqs. 68–70).

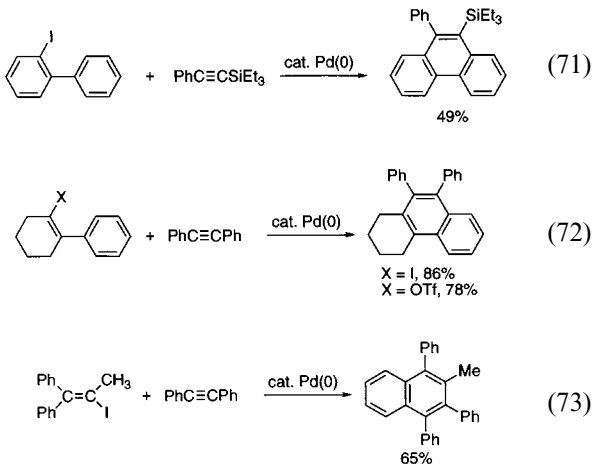


Thus, indenones, naphthalenones and even β-naphthylamines have been prepared in high yields by carboannulation using nitriles. These reactions are apparently proceeding by addition of the vinylic palladium intermediate across the nitrile triple bond. The ketone products are presumably formed by hydrolysis of the resulting imines, while the naphthylamine is produced by tautomerization of the imine.

Another type of carboannulation process recently developed in our laboratories involves the insertion of alkynes into aryl or vinylic palladium intermediates and subsequent cyclization onto an aromatic ring already present in the starting material [51] (Eqs. 71–73).



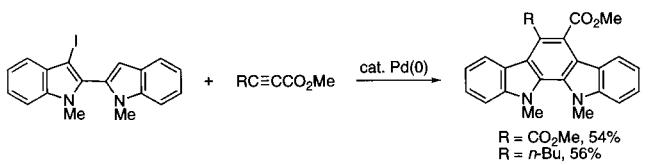
Scheme 15.



While Heck reported the first example of this type of process, his yield was very low [44a]. After optimization, we have been able to get excellent yields using a wide variety of aryl halides and vinylic halides or triflates. Unfortunately, the regiochemistry of the alkyne insertion is surprisingly low. Only with relatively hindered vinylic halides or triflates do we see the high regioselectivity usually observed in our other annulation chemistry. Both cyclic and acyclic vinylic substrates can be used in this process.

The ring closure step in these annulations may proceed by either of two mechanisms (Scheme 15). The vinylic palladium intermediate may either undergo direct electrophilic attack on the neighboring arene to produce a diorganopalladium(II) intermediate, which subsequently undergoes reductive elimination (path A), or the neighboring arene may oxidatively add a C–H bond to the vinylic palladium(II) intermediate to generate an organopalladium(IV) intermediate, which affords the observed products after reductive elimination (path B).

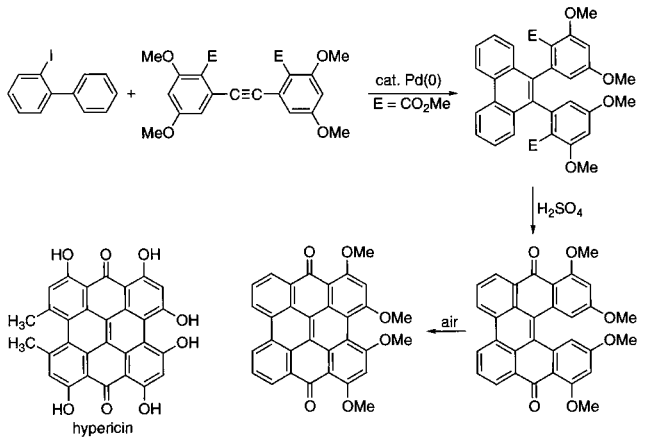
This annulation process has been used by Merlic to produce the biologically potent indolocarbazole class of compounds [52] (see Eq. (74)) and we have employed



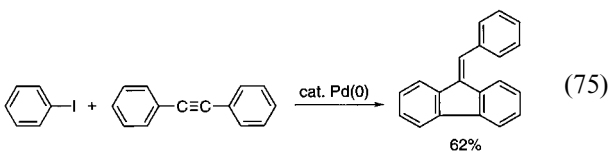
(74)

this process for the preparation of analogs of the very interesting, antiviral agent hypericin [53] (Scheme 16).

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 [54] (see Eq. (75)).



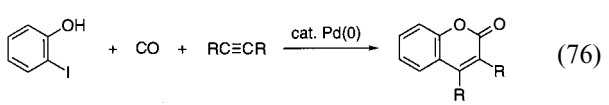
Scheme 16.



(75)

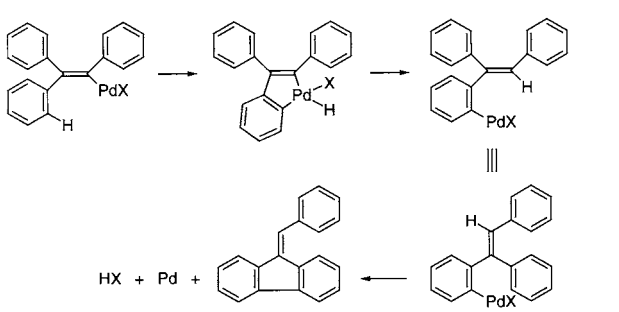
This reaction apparently involves oxidative addition of a neighboring aryl C–H bond to the palladium moiety in the initially produced vinylic palladium intermediate, followed by subsequent reductive elimination, to produce an arylpalladium intermediate that eventually cyclizes onto the adjacent arene (Scheme 17).

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 [55] (see Eq. (76)).



(76)

Note that the alkyne, apparently inserts more rapidly into the arylpalladium bond than the carbon monoxide as judged by the formation of coumarins, rather than the corresponding cyclic ketones. This carbonylative annulation of alkynes appears promising as a new route to carbonyl compounds by palladium-catalyzed annulation.



Scheme 17.

8. Conclusions

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. Other workers have reported a number of related reactions, which are too numerous to report here. One can anticipate that many more applications of this useful annulation methodology will be reported in the future.

References

[1] (a) R.F. Heck, Palladium Reagents in Organic Syntheses, Academic Press, London, 1985. (b) J. Tsuji, Palladium Reagents and Catalysts, Wiley, Chichester, 1995.
[2] (a) J. van der Louw, G.J.J. Out, J.L. van der Baan, F.J.J. de Kanter, F. Bickelhaupt, G.W. Klumpp, Tetrahedron Lett. 30 (1989) 4863. (b) K. Ohno, T. Mitsuyasu, J. Tsuji, Tetrahedron 28 (1972) 3705. (c) P. Braunstein, D. Matt, D. Nobel, J. Am. Chem. Soc. 110 (1988) 3207. (d) B.M. Trost, P.J. Bonk, J. Am. Chem. Soc. 107 (1985) 8277. (e) B.M. Trost, S.A. King, T. Schmidt, J. Am. Chem. Soc. 111 (1989) 5902. (f) B.M. Trost, P.J. Bonk, J. Am. Chem. Soc. 107 (1985) 1778. (g) B.M. Trost, S.A. King, T.N. Nanninga, Chem. Lett. (1987) 15. (h) B.M. Trost, S.A. King, Tetrahedron Lett. 27 (1986) 5971. (i) K. Ohno, J. Tsuji, J. Chem. Soc. Chem. Commun. (1971) 247. (j) R.C. Larock, D.J. Leuck, L.W. Harrison, Tetrahedron Lett. 29 (1988) 6399. (k) H. Horino, N. Inoue, J. Chem. Soc. Chem. Commun. (1976) 500. (l) H. Horino, N. Inoue, Heterocycles 11 (1978) 281.
[3] R.C. Larock, L.W. Harrison, M.H. Hsu, J. Org. Chem. 49 (1984) 3662.
[4] R.C. Larock, H. Song, Syn. Commun. 19 (1989) 1463.
[5] R.C. Larock, S. Varaprath, H.H. Lau, C.A. Fellows, J. Am. Chem. Soc. 106 (1984) 5274.
[6] R.C. Larock, C.-L. Liu, H.H. Lau, S. Varaprath, Tetrahedron Lett. 25 (1984) 4459.
[7] J.M. O'Connor, B.J. Stallman, W.G. Clark, A.Y.L. Shu, R.E. Spada, T.M. Stevenson, H.A. Dieck, J. Org. Chem. 48 (1983) 807.
[8] R.C. Larock, N. Berrios-Peña, K. Narayanan, J. Org. Chem. 55 (1990) 3447.
[9] T.G. Back, R.J. Bethell, Tetrahedron Lett. 39 (1998) 5463.
[10] R.C. Larock, L. Guo, Synlett (1995) 465.
[11] (a) B.M. Trost, Tetrahedron 33 (1977) 2615. (b) B.M. Trost, T.R. Verhoeven, in: G. Wilkinson (Ed.), Comprehensive Organometallic Chemistry, vol. 8, Pergamon Press, New York, 1982, p. 799. (c) J. Tsuji, in: F.R. Hartley, S. Patai (Eds.), The Chemistry of the Metal–Carbon Bond, Wiley, vol. 3, New York, 1985, p. 163. (d) S.A. Godleski, in: B.M. Trost, I. Fleming, M.F. Semmelhack (Eds.), Comprehensive Organic Synthesis, vol. 4,

Pergamon Press, New York, 1991, p. 585. (e) L.S. Hegedus, in: F.R. Hartley, S. Patai (Eds.), The Chemistry of the Metal–Carbon Bond, Wiley, vol. 2, New York, 1985, p. 401. (f) A.J. Pearson, in: F.R. Hartley, S. Patai (Eds.), The Chemistry of the Metal–Carbon Bond, Wiley, vol. 4, New York, 1985, p. 889. (g) B.M. Trost, Angew. Chem. Int. Ed. Engl. 28 (1989) 1173. (h) C.G. Frost, J. Howarth, J.M.J. Williams, Tetrahedron Asymmetry 3 (1992) 1089.

[12] R.C. Larock, C.A. Fried, J. Am. Chem. Soc. 112 (1990) 5882.

[13] (a) R.P. Hughes, J. Powell, J. Organomet. Chem. 60 (1973) 409. (b) R.R. Stevens, G.D. Shier, J. Organomet. Chem. 21 (1970) 495. (c) E. Ban, R. Hughes, J. Powell, J. Organomet. Chem. 69 (1974) 455. (d) R.P. Hughes, J. Powell, J. Organomet. Chem. 34 (1972) C51. (e) R.P. Hughes, J. Powell, J. Chem. Soc. Chem. Commun. (1971) 275. (f) D. Medema, R. van Helden, C.F. Kohll, Inorg. Chim. Acta 3 (1969) 255. (g) R. van Helden, C.F. Kohll, D. Medema, G. Verberg, T. Jonkhoff, Recl. Trav. Chim. Pays-Bas 87 (1968) 961. (h) D. Medema, R. van Helden, Recl. Trav. Chim. Pays-Bas 90 (1971) 304. (i) Y. Yamamoto, M. Al-Masum, N. Asao, J. Am. Chem. Soc. 116 (1994) 6019. (J) B.M. Trost, G. Kottirsch, J. Am. Chem. Soc. 112 (1990) 2816. (k) A. Ogawa, J. Kawakami, N. Sonoda, T. Hirao, J. Org. Chem. 61 (1996) 4161. (l) I. Shimizu, J. Tsuji, Chem. Lett. (1984) 233. (m) M. Ahmar, B. Cazes, J. Gore, Tetrahedron Lett. 25 (1984) 4505. (n) M. Ahmar, J.-J. Barieux, B. Cazes, J. Gore, Tetrahedron 43 (1987) 513. (o) B. Cazes, V. Colovray, J. Gore, Tetrahedron Lett. 29 (1988) 627. (p) B. Friess, B. Cazes, J. Gore, Tetrahedron Lett. 29 (1988) 4089. (q) N. Kopola, B. Friess, B. Cazes, J. Gore, Tetrahedron Lett. 30 (1989) 3963. (r) M. Ahmar, B. Cazes, J. Gore, Tetrahedron Lett. 26 (1985) 3795. (s) M. Ahmar, B. Cazes, J. Gore, Tetrahedron 43 (1987) 3453. (t) I. Shimizu, T. Sugiura, J. Tsuji, J. Org. Chem. 50 (1985) 537.

[14] R.C. Larock, N.G. Bemos-Peña, C.A. Fried, J. Org. Chem. 56 (1991) 2615.

[15] R.C. Larock, C. Tu, P. Pace, J. Org. Chem. 63 (1998) 6859.

[16] R.C. Larock, Y. He, W.W. Leong, X. Han, M.D. Refvik, J.M. Zenner, J. Org. Chem. 63 (1998) 2154.

[17] (a) B.M. Trost, P.E. Strege, J. Am. Chem. Soc. 99 (1977) 1649. (b) J.C. Fiaud, J.Y. Legros, J. Org. Chem. 55 (1990) 4840. (c) M. Yamaguchi, T. Shima, T. Yamagishi, M. Hida, Tetrahedron Asymmetry 2 (1991) 663. (d) P. von Matt, O. Loiseleur, G. Koch, A. Pfaltz, C. Lefeber, T. Feucht, G. Helmchen, Tetrahedron Asymmetry 5 (1994) 573. (e) B.M. Trost, R.C. Bunt, J. Am. Chem. Soc. 116 (1994) 4089.

[18] (a) K. Yamamoto, J. Tsuji, Tetrahedron Lett. 23 (1982) 3089. (b) J.P. Genet, S. Grisoni, Tetrahedron Lett. 29 (1988) 4543.

[19] R.C. Larock, J.M. Zenner, J. Org. Chem. 60 (1995) 482.

[20] (a) R.C. Larock, Y. Lu, A.C. Bain, C.E. Russell, J. Org. Chem. 56 (1991) 4589. (b) R.C. Larock, Y. Wang, Y. Lu, C.E. Russell, J. Org. Chem. 59 (1994) 8107. (c) R.C. Larock, W.-Y. Leung, J. Org. Chem 55 (1990) 6244. (d) B.C. Söderberg, B. Åkermark, Y.-H. Chen, S.S. Hall, J. Org. Chem. 55 (1990) 1344. (e) G.D. Harris, Jr., R.J. Herr, S.M. Weinreb, J. Org. Chem. 57 (1992) 2528.

[21] R.C. Larock, N.G. Berrios-Peña, C.A. Fried, E.K. Yum, C. Tu, W. Leong, J. Org. Chem. 58 (1993) 4509.

[22] (a) R.C. Larock, S. Varaprath, J. Org. Chem. 49 (1984) 3432. (b) R.C. Larock, H. Song, Bull. Korean Chem. Soc. 17 (1996) 877.

[23] (a) R.C. Larock, E.K. Yum, Synlett (1990) 529. (b) R.C. Larock, E.K. Yum, Tetrahedron 52 (1996) 2743.

[24] (a) H. Horino, N. Inoue, J. Chem. Soc. Chem. Commun. (1976) 500. (b) D.D. Narkhede, P.R. Iyer, C.S.R. Iyer, Tetrahedron 46 (1990) 2031.

[25] R.C. Larock, L. Wei, in preparation.

[26] D.E. Emrich, C. Jia, R.C. Larock, unpublished results.

[27] (a) P.M. Maitlis, J. Organomet. Chem. 200 (1980) 161. (b) M. Pfeffer, Recl. Trav. Chim. Pays-Bas 109 (1990) 567.

[28] (a) R.C. Larock, E.K. Yum, J. Am. Chem. Soc. 113 (1991) 6689. (b) R.C. Larock, E.K. Yum, M.D. Refvik, J. Org. Chem. 63 (1998) 7652.

[29] (a) C. Chen, D.R. Lieberman, R.D. Larsen, R.A. Reamer, T.R. Verhoeven, P.J. Reider, Tetrahedron. Lett. 35 (1994) 6981. (b) C.-Y. Chen, D.R. Lieberman, L.J. Street, A.R. Guiblin, R.D. Larsen, T.R. Verhoeven, Synth. Commun. 26 (1996) 1977.

[30] H.-C. Zhang, K.K. Brumfield, B.E. Maryanoff, Tetrahedron Lett. 38 (1997) 2439.

[31] T. Jeschke, D. Wensbo, U. Annby, S. Gronowitz, L.A. Cohen, Tetrahedron Lett. 34 (1993) 6471.

[32] (a) S.S. Park, J.-K. Choi, E.K. Yum, D.-C. Ha, Tetrahedron Lett. 39 (1998) 627. (b) F. Ujjainwalla, D. Warner, Tetrahedron Lett. 39 (1998) 5355.

[33] D. Wensbo, A. Eriksson, T. Jeschke, U. Annby, S. Gronowitz, L.A. Cohen, Tetrahedron Lett. 34 (1993) 2823.

[34] X. Lianhong, I.R. Lewis, S.K. Davidsen, J.B. Summers, Tetrahedron Lett. 39 (1998) 5159.

[35] (a) M.C. Fagnola, I. Candiani, G. Visentin, W. Cabri, F. Zarini, N. Mongelli, A. Bedeschi, Tetrahedron Lett. 38 (1997) 2307. (b) H.-C. Zhang, K.K. Brumfield, L. Jaroskova, B.E. Maryanoff, Tetrahedron Lett. 39 (1998) 4449.

[36] D. Fancelli, M.C. Fagnola, D. Severino, A. Bedeschi, Tetrahedron Lett. 38 (1997) 2311.

[37] R.C. Larock, E.K. Yum, M.J. Doty, K.K.C. Sham, J. Org. Chem. 60 (1995) 3270.

[38] N. Beydoun, M. Pfeffer, Synthesis (1990) 729.

[39] R.C. Larock, M.J. Doty, X. Han, Tetrahedron Lett. 39 (1998) 5143.

[40] A. Kojima, T. Takemoto, M. Sodeoka, M. Shibasaki, J. Org. Chem. 61 (1996) 4876.

[41] W. Tao, L.J. Silverberg, A.L. Rheingold, R.F. Heck, Organometallics 8 (1989) 2550.

[42] R.C. Larock, X. Han, M.J. Doty, Tetrahedron Lett. 39 (1998) 5713.

[43] F. Maassarani, M. Pfeffer, G. Le Borgne, J. Chem. Soc. Chem. Commun. (1987) 565.

[44] (a) G. Wu, A.L. Rheingold, S.J. Geib, R.F. Heck, Organometallics, 6 (1987) 1941. (b) G. Wu, S.J. Geib, A.L. Rheingold, R.F. Heck, J. Org. Chem. 53 (1988) 3238.

[45] I.R. Girling, D.A. Widdowson, Tetrahedron Lett. 23 (1982) 4281.

[46] K.R. Roesch, R.C. Larock, J. Org. Chem. 63 (1998) 5306.

[47] K.R. Roesch, R.C. Larock, unpublished results.

[48] R.C. Larock, E.K. Yum, unpublished results.

[49] R.C. Larock, M.J. Doty, S. Cacchi, J. Org. Chem. 58 (1993) 4579.

[50] R.C. Larock, Q. Tian, A. Pletnev, J. Am. Chem. Soc. 121 (1999), in press.

[51] (a) R.C. Larock, M.J. Doty, Q. Tian, J. Zenner, J. Org. Chem. 62 (1997) 7536. (b) R.C. Larock, Q. Tian, J. Org. Chem. 63 (1998) 2002.

[52] C.A. Merlic, D.M. McInnes, Tetrahedron Lett. 38 (1997) 7661.

[53] D.S. English, K. Das, J.M. Zenner, W. Zhang, G.A. Kraus, R.C. Larock, J.W. Petrich, J. Phys. Chem. A 101 (1997) 3235.

[54] R.C. Larock, Q. Tian, unpublished results.

[55] R.C. Larock, D. Kadnikov, unpublished results.