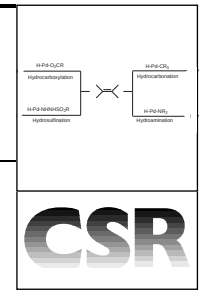
Palladium catalysed pronucleophile addition to unactivated carbon–carbon multiple bonds



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The addition of *nucleophiles* to carbon–carbon multiple bonds coordinated by Pd(II) is one of the most popular processes for palladium promoted organic transformations. However, the palladium catalysed addition of *pronucleophiles* to carbon–carbon multiple bonds has not been investigated widely. The compounds (H–Nu) which are prone to form nucleophilic species (Nu^-) on treatment with either base or transition metals are called pronucleophiles. The additions of carbon pronucleophiles ($H–CR_3$, hydrocarbonation), nitrogen pronucleophiles ($H–NR_2$, hydroamination), carboxyl pronucleophiles (H–OCOR, hydrocarboxylation) and sulfur pronucleophiles (H–S–, hydrosulfination) to C–C multiple bonds are catalysed by palladium complexes. The hydrocarbonation of allenes, enynes, alkynes and methylenecyclopropanes proceeds very smoothly in the presence of palladium catalysts to give the corresponding olefinic derivatives in good to high yields. The hydroamination of allenes, enynes and methylenecyclopropanes affords the corresponding allylic amines. The hydrocarboxylation of allenes gives the corresponding allylic carboxylates in high yields, and the hydrosulfination of allenes with tosylhydrazine produces the corresponding allylic tosylates.

1 Introduction

The construction of the carbon–carbon bond is a fundamentally important process in organic chemistry. Recent years witnessed tremendous growth in a number of reactions and reagents applicable to carbon–carbon bond formation. Among them the carbanionic additions to activated and unactivated carbon–carbon multiple bonds are regarded as one of the most important reactions for carbon–carbon bond formation. In traditional organic chemistry, addition of carbon nucleophiles to activated alkenes and alkynes has been extensively used in the C–C bond forming reactions; the classical example is the Michael reaction. The later reaction involves the addition of the C–H bond of activated methylenes and methynes to activated alkenes in the presence of base (Type A).[1] In modern organic syntheses the use of transition metal catalysts enables the addition of activated methylenes and methynes to activated alkenes (Type B).[2]

The nonfunctionalized carbon–carbon multiple bond systems are recognised as latent functional groups, however, they are generally unreactive towards carbon nucleophiles due to their electron rich π-orbitals. Organic chemists have developed an alternative methodology for the additions of carbon nucleophiles towards such unactivated multiple bonds, which involves either transition metal mediated activation of these unsaturated

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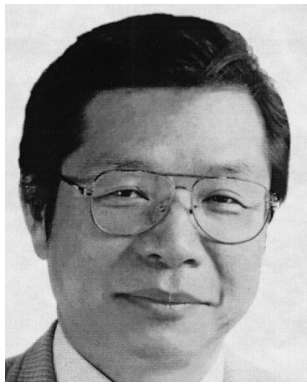

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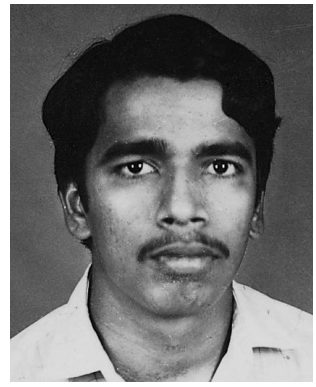

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Ukkiramapandian Radhakrishnan

systems (Type C) or carbometallation reactions (Type D). The activation of unsaturated systems can be achieved by the complexation of electrophilic transition metals to the alkenes or alkynes, which makes the C–C multiple bonds susceptible towards the addition of carbon-nucleophiles (Type C).[3] The reactions of the Type C category are mostly carried out with stoichiometric amounts of the reagents due to various reasons. The addition of a carbon–metal bond of an organometallic species across the carbon–carbon multiple bonds is called a carbometallation reaction (Type D).[4] Most of the organometallics involved in this reaction are polar reagents, such as organomagnesium and organoaluminium species, and several functional groups are not compatible under the reaction conditions. All the C–C bond forming reactions (Types A–D) are shown in Fig. 1.

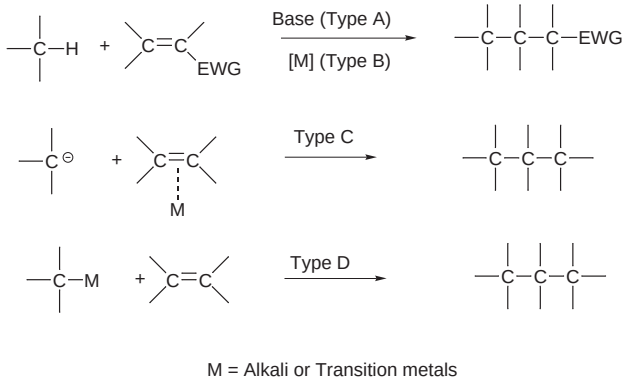


Fig. 1 Carbon–carbon bond forming reactions.

Despite the fact that all the above mentioned reactions (Types A to D) occupy unique positions in the carbon–carbon bond formation reactions, various problems associated with the utilisation of these methods limit their applications. Consequently, there has been a considerable amount of interest in developing newer reagents and methods for carbon–carbon bond formation.

The pioneering efforts by various research groups resulted in the development of catalytic C–C bond forming reactions: the transition metal mediated addition of the C–H bond of active methylene to unactivated carbon–carbon multiple bonds is catalytic and shows functional group compatibility (Fig 2).[5] This reaction consists of the formal addition of a C–H bond across the carbon–carbon multiple bonds and is called a hydrocarbonation reaction.

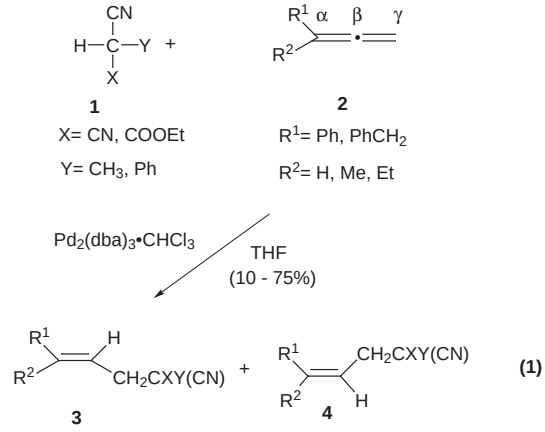
The synthetic applications and mechanistic implications of palladium catalysed hydrocarbonation reactions are described in this review. Also, the discussion is extended to include other reactions which fall into such categories as hydroamination, hydrocarboxylation and hydrosulfination of various unsaturated systems (Fig. 2). The scope of this review does not allow us to present many elegant pieces of work which involve nucleophilic addition to alkenes and alkynes activated by electrophilic metal complexation.

2 Hydrocarbonation of carbon–carbon multiple bond systems

The activation of the C–H bonds of alkanes and their addition to carbon–carbon multiple bonds have been sought by organic chemists for a long time. There are very few synthetic methods available for converting a C–H bond into a C–C bond. Recently, Murai *et. al.* found that ruthenium complexes catalyse the addition of *ortho* C–H bonds of aromatic ketones to olefins.[6] Trost *et. al*. reported the palladium catalysed activation of the C–H bonds of terminal alkynes and their addition to allenes and alkynes.[7] Another report which is an important contribution to this hydrocarbonation area is the palladium catalysed addition of the C–H bond of pronucleophiles to 1,3-dienes.[8]

2.1 Hydrocarbonation of mono- and disubstituted allenes

Allenes constitute an important class of organic compounds with unusual chemical properties due to the cumulated double bonds. An interesting example which attracted our attention is the palladium catalysed reaction of activated methylenes with unsubstituted allenes.[9] The synthetic applications of this reaction are very limited, and until recently there were no reports of similar kinds of reactions with substituted allenes. An unprecedented and mechanistically fascinating reaction was encountered between activated methylene (or methynes) and substituted allenes (eqn. (1)).[10] The addition of certain cyano-



activated pronucleophiles **1** to alkyl- and arylallenes **2** was catalysed by $Pd_2(dba)_3 \cdot CHCl_3$ and gave internal alkenes (**3** and/or **4)** in a regio- and stereoselective fashion. In most of the cases, especially with monosubstituted allenes, selective formation of the *E*-isomer was observed and with disubstituted allenes a mixture of *E*- and *Z*-isomers was obtained. However, only γ-adducts were obtained in all cases. The addition reaction became sluggish with allenes containing bulkier substituents.

A tentative mechanism along the following lines may be suggested for the hydrocarbonation of allenes (Scheme 1). The oxidative insertion of Pd(0) into the C–H bond of the activated

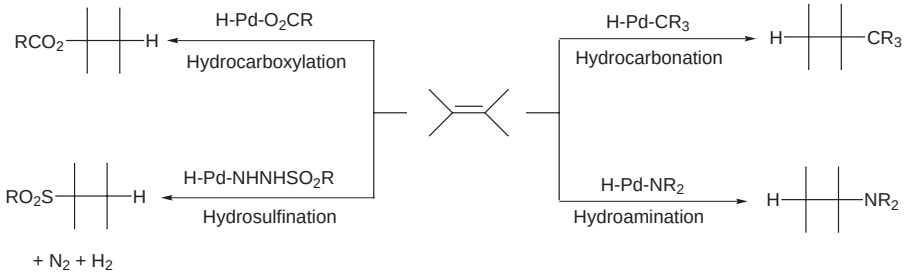
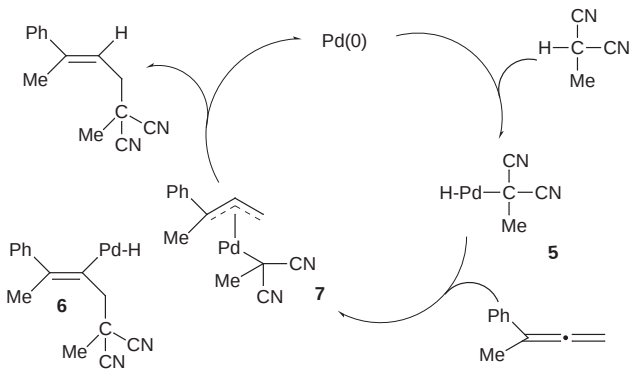


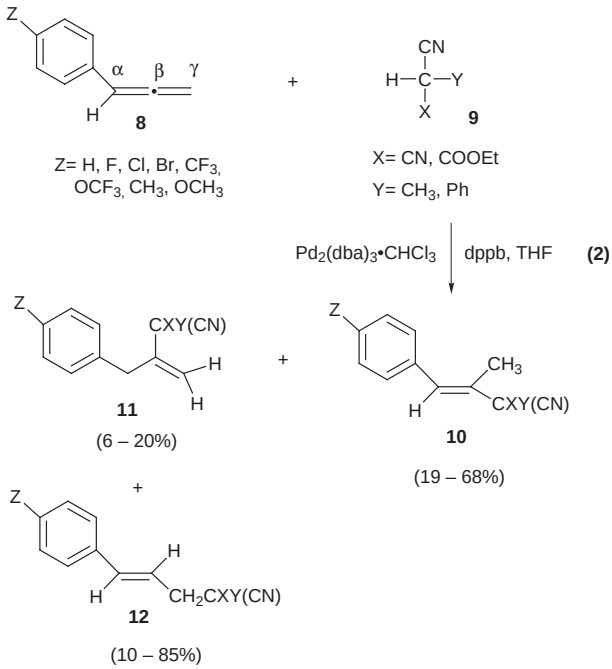
Fig. 2 Carbon–carbon and carbon–heteroatom bond forming reactions.



Scheme 1 Hydrocarbonation of allenes: hydropalladation or carbopalladation mechanism.

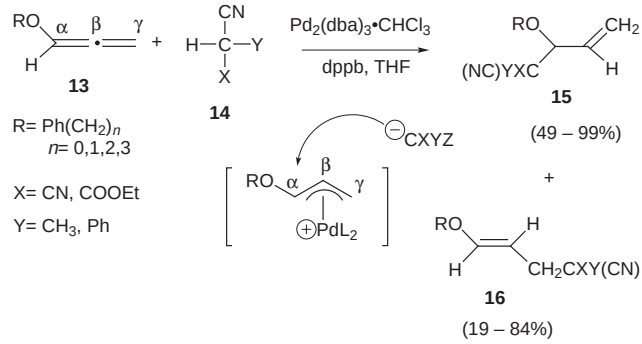
pronucleophiles would produce the Pd(II) species **5** (or alternatively a tautomeric structure $H_3C(CN)C{=}C{=}NPdHL_n$ may be more suitable). Carbopalladation of the allene would afford the alkenylpalladium complex **6** (carbopalladation mechanism), which would undergo reductive coupling to give the addition product and a Pd(0) species. As an alternative mechanism it may be considered that the hydropalladation of allenes with the Pd(II) intermediate **6** gives the π-allylpalladium complex **7** which undergoes reductive coupling to afford the adduct and a Pd(0) species (hydropalladation mechanism). When we found the hydrocarbonation reaction of allenes (eqn. (1)), it was not clear whether the reaction proceeded through either the hydropalladation or carbopalladation mechanism. However, as mentioned below, most pronucleophile additions are well understood by the hydropalladation mechanism, except for the intramolecular addition to alkynes (*vide infra*).

It has been clearly shown that the regioselectivity of the hydrocarbonation of allenes is controlled by the steric effect of pronucleophiles and by the electronic effect of the substituents on the aromatic ring of phenylallenes (eqn. (2)).[11] The



phenylallene substituted at the *para*-position with electron withdrawing groups makes the β-carbon of the allene electrophilic and led to predominantly or exclusively formation of internal β-adducts (**10** and **11**), whereas electron donating substituents such as methyl and methoxy groups at the *para*-position directed the hydrocarbonation reactions in such a way as to give terminal γ-adducts **12**. On the other hand, sterically bulky pronucleophiles, such as ethyl cyanophenylacetate, led to the formation of terminal γ-adducts **12**, regardless of the electronic effect of the substituents at the *para*-position of arylallenes.

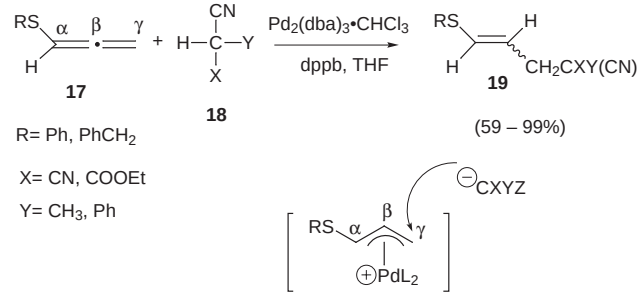
Furthermore the hydrocarbonation of alkoxy- or phenoxyallenes **13** with methylmalononitrile and ethyl cyanomethylacetate gave α-adducts **15** either exclusively or predominantly in good to high yields (Scheme 2).[12] An alkoxy group stabilises



Scheme 2 Hydrocarbonation of alkoxyallenes.

the positive charge formed at the α-position and a nucleophilic attack at the α-position becomes more favorable. Accordingly, it seems that an alkoxy group of the π-allylpalladium directed the nucleophile to the α-carbon of the π-allyl moiety. In contrast, the sterically more bulky pronucleophile, ethyl cyanophenylacetate, gave γ-adducts **16** regioselectively regardless of the electronic nature of the substituents on the allenes. The γ-selectivity in the reaction of sterically bulky pronucleophiles may be due to the steric crowding around the electrophilic carbon center of the π-allylpalladium intermediate.

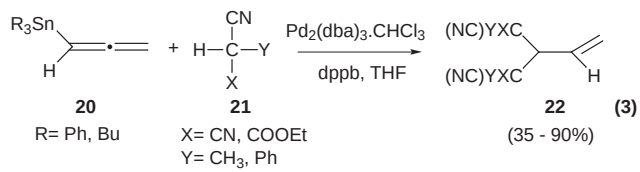
In marked contrast to the oxygen substituted allenes the pronucleophile addition to allenyl sulfides **17** gave the γ-adducts **19** in good to high yields (Scheme 3).[13] It is well



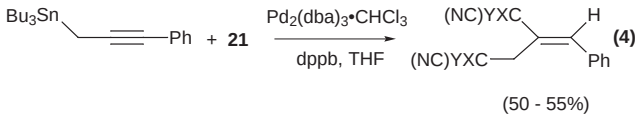
Scheme 3 Hydrocarbonation of allenyl sulfides.

accepted in heteroatom substituted allyl anion and allyl cation chemistry that (1) an oxygen substituent stabilises a neighbouring carbocation and destabilises a neighbouring carbanion due to the electron donating effect of the oxygen atom, and (2) a sulfur substituent destabilises a neighbouring carbocation and stabilises a neighbouring carbanion due to the electron withdrawing effect of the sulfur atom. This may be the reason for the differences in the regioselectivity of pronucleophile addition to oxygen substituted allenes and allenyl sulfides.

Interestingly, the addition of pronucleophiles **21** to allenyl stannanes **20** in the presence of a catalytic amount of $Pd_2(dba)_3{\cdot}CHCl_3$ afforded the addition–substitution products **22** in moderate to high yields (eqn. (3)).[14] The prop-

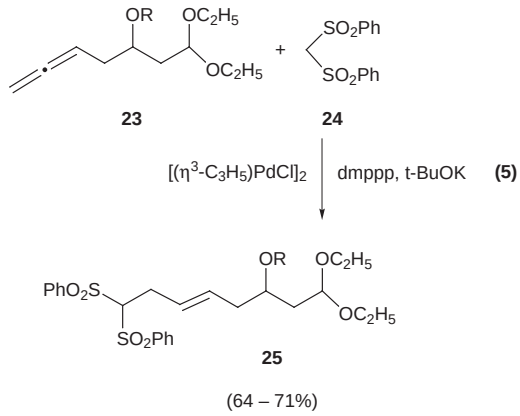


2-ynylstannane derivatives also show a similar kind of reactivity with pronucleophiles and gave addition–substitution products (eqn. (4)). It is worth mentioning that an internal



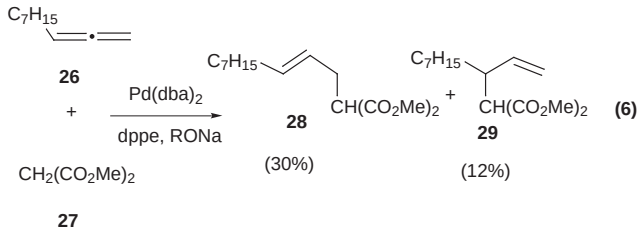
allene, such as 3-phenyl(tributylstannyl)allene also underwent hydrocarbonation in a facile manner under these reaction conditions.

In the above mentioned hydrocarbonation reactions, mostly, cyano activated pronucleophiles were added to simple allenes. Another independent investigation by Trost *et. al*. using a different palladium catalyst system, $[(\eta^3\text{-}C_3H_5)PdCl]_2$–dmppp under basic conditions (t-BuOK) resulted in the addition of Meldrum's acids and sulfonyl activated pronucleophiles to allenes (eqn (5)).[15] This reaction showed excellent chemo-



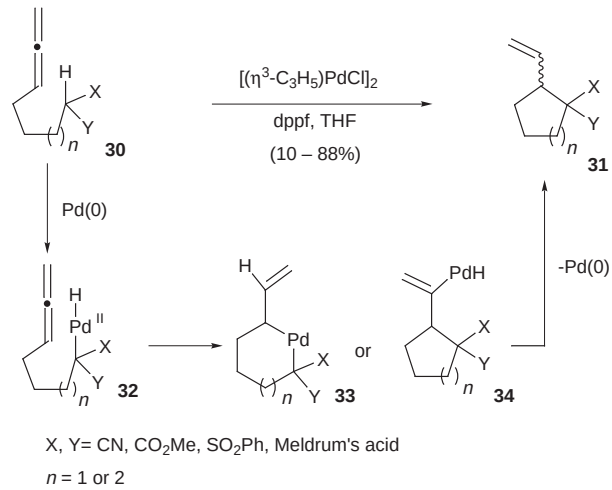
selectivity. The synthetic application of this reaction is shown by preparing a carbocycle *via* intramolecular hydrocarbonation. These authors clearly indicate that the addition of pronucleophiles proceeds through the hydropalladation mechanism.[15]

Gore, Besson and Cazes reported the hydrocarbonation of allenic hydrocarbons **26** under an alternative Pd(0)–base catalytic system (eqn. (6)).[16] This reaction allows the addition



of malonate type methylenes or methines to allenes giving products in moderate yields. The product formation seems to favor a hydropalladation process to form a π-allylpalladium intermediate, which on reductive elimination gives a mixture of products **28** and **29**.

The intramolecular pronucleophile addition to allenes will be synthetically useful for the synthesis of carbocycles. Interestingly, an intramolecular cyclisation of pronucleophile tethered allenes **30** is shown to proceed very well in the presence of palladium catalyst $[(\eta^3\text{-}C_3H_5)PdCl]_2$–dppf under neutral as well as basic conditions (Scheme 4).[17] The use of palladium catalyst under neutral condition gave better yields of carbocycles **31** than the use of of Pd(0) catalyst under basic conditions; $[(\eta^3\text{-}C_3H_5)PdCl]_2$–dppf–t-BuOK. Compared to six membered ring

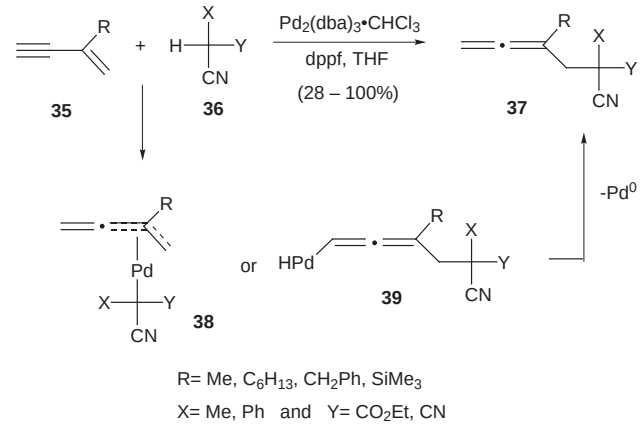


Scheme 4 Intramolecular hydrocarbonation of allenes.

formation the five membered ring formation proceeds smoothly. The formation of the five membered ring proceeds in a 5-*exo-trig* manner and no *endo* product formation was observed. The intramolecular cyclisation can be explained as follows; the oxidative addition of the C–H bond of the pronucleophiles would give the hydridopalladium species **32**, followed by intramolecular hydropalladation **33** or carbopalladation **34** and subsequent reductive elimination, would give the cyclised product.

2.2 Hydrocarbonation of enynes

It was envisioned that pronucleophile addition to conjugated enynes would lead to the formation of allenes, and hence the reaction would serve as an alternative method for the synthesis of allenes. Indeed it was observed. After brief optimisation, the $Pd_2(dba)_3$·$CHCl_3$–dppf combination appeared to be an effective catalyst for the addition of pronucleophiles **36** to enynes **35** (Scheme 5).[18] The palladium catalysed addition of certain



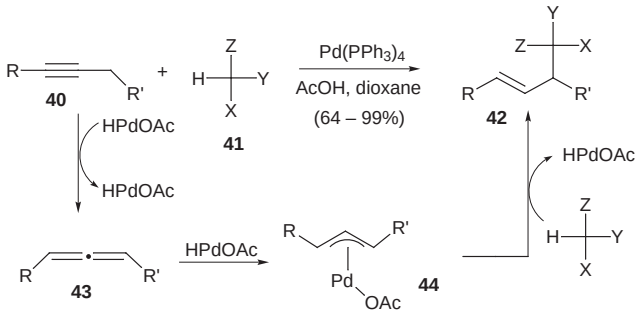
Scheme 5 Hydrocarbonation of enynes.

carbon pronucleophiles **36** to conjugated enynes **35** afforded the corresponding allenes **37** in excellent yields. When an excess of reactive pronucleophiles was added to enynes, further addition to the allenyl double bond took place and the 1,3-bisadducts were isolated. Similarly, the active methylenes in the presence of two equivalents of enynes underwent double addition and gave 1,3-diallenylalkanes. It should be pointed out that in the pronucleophile addition to conjugated enynes the pronucleophiles were selectively added to the double bond rather than the triple bond. Probably, this reaction proceeds through either the

intermediate species **38**, which is formed by hydropalladation to the triple bond, or the intermediate **39** which is produced by the carbopalladation to the double bond.

2.3 Hydrocarbonation of alkynes

The palladium catalysed allylation of carbon nucleophiles using allylic substrates in basic conditions is a well recognised reaction in modern organic chemistry (Tsuji–Trost reaction).[19] This procedure suffers from one serious drawback, *i.e.* it requires a stoichiometric amount of base. An interesting allylation of pronucleophiles **41** with simple alkynes **40** in the presence of $Pd(PPh_3)_4$–AcOH was developed (Scheme 6).[20]

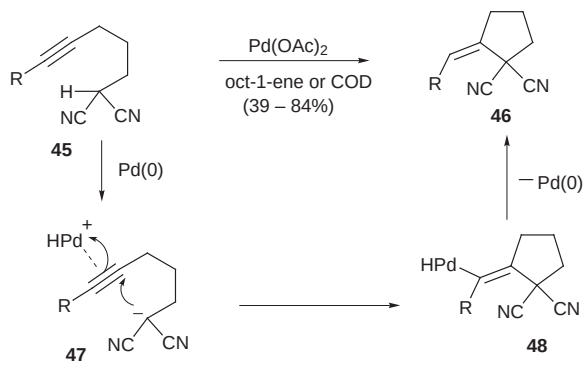


R= Ph, Et R'= H, Me, Et, -CH_2OMe, -CH_2NHCbz, cyclopropyl
X= Me, Ph, MOMO; Y= CN, SO_2Ph; Z= CN, CO_2Et, SO_2Ph

Scheme 6 Hydrocarbonation of alkynes: plausible mechanism.

This reaction is complementary to the Tsuji–Trost reaction, but with significant advantages. The present reaction does not require a stoichiometric amount of base; it works in the presence of catalytic amounts of acetic acid. The reaction carried out in the absence of acetic acid gave only a trace amount of the product. In most of the cases, the products **42** were formed with perfect regioselectivity. A plausible reaction pathway for this allylation may involve the addition–elimination of HPdOAc to internal alkynes which would produce allenes **43** and the active catalyst (HPdOAc). Hydropalladation of allenes with HPdOAc would give the π-allylpalladium complexes **44**, which on reaction with pronucleophiles would give the products.

Also, the intramolecular hydrocarbonation of alkynes with an active methine **45** proceeded very well under neutral conditions using $Pd(OAc)_2$–cycloocta-1,5-diene (or oct-1-ene) catalyst and ethanol as a solvent (Scheme 7).[21] The ε-alkynylmalononitriles **45** indeed underwent cyclisation to give the *Z*-isomers of the corresponding carbocycles **46** in all cases (except when R = trimethylsilyl). It should be pointed out that substrates containing a hydroxy group gave carbocycles in good yields without producing furan or pyran derivatives. The cyclisation reaction for a substrate which bears a terminal alkyne unit (R = H) was sluggish; this may be due to the oxidative addition of Pd(0) into the C–H bond of the terminal alkyne. The formation of the *Z*-isomer suggests that the reaction does not proceed through a π-allylpalladium intermediate; the *E*-isomer must be produced predominantly if it is involved as a reaction intermediate. Probably, the reaction pathway involves the coordination of HPd^+ to the triple bond and subsequent *trans*-carbopalladation of **47**. The reductive elimination of Pd(0) from the resulting vinylpalladium species **48** would lead to the cyclisation product **46**.

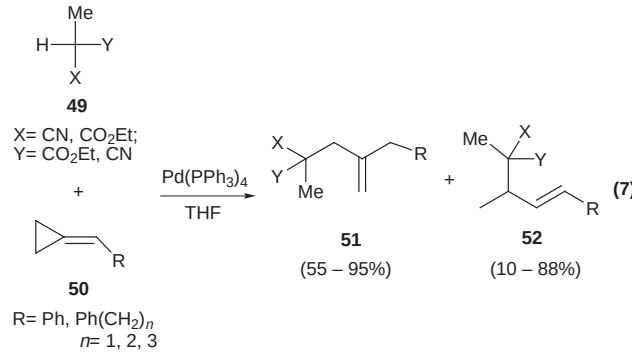


R= H, Me, $HO(CH_2)_3$, TBDMS-$O(CH_2)_n$, Ph, TMS

Scheme 7 Intramolecular hydrocarbonation of alkynes.

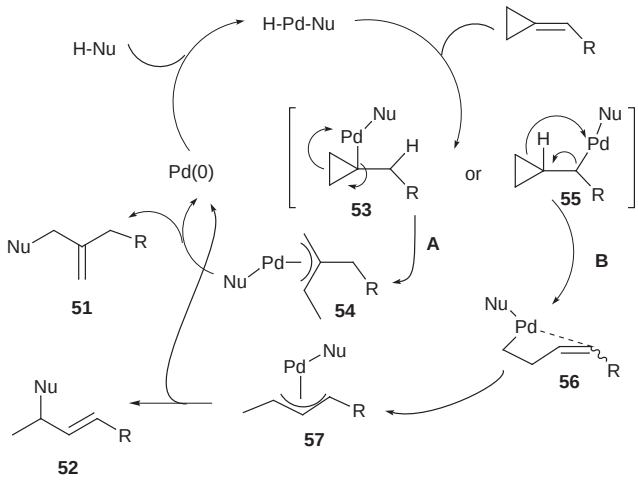
2.4 Hydrocarbonation of methylenecyclopropanes

It can be decided from the foregoing discussion that Pd(0) catalysts are of great value in the hydrocarbonation of allenes and alkynes. Also, the palladium is a useful catalyst for the hydrocarbonation of nonconjugated alkenes such as methylenecyclopropanes (eqn. (7)).[22] The reaction of certain pronucleophiles **49** with methylenecyclopropanes **50** was catalysed by $Pd(PPh_3)_4$ and afforded the hydrocarbonation products, terminal **51** and internal alkenes **52**, either exclusively or as a mixture of both. The selectivity of the product formation depends upon the mode of hydropalladation of alkenes and ring opening of cyclopropane, which in turn depends upon the substituent at the *exo*-methylene carbon and the substituents on the pronucleophiles. In the case of cyanoactivated pronucleophiles the selectivity of the product formation depends upon the chain length of the aliphatic substituents [$Ph(CH_2)_n$]: the addition of methylmalononitrile to (4-phenylbut-1-ylidene)cyclopropane (n = 3) gave **51** as the sole product, whereas the ring opening of (3-phenylprop-1-ylidene)cyclopropane (n = 2) and (2-phenylethylidene)cyclopropane (n = 1) with methylmalononitrile gave a mixture of **51** and **52**. The ester activated pronucleophile, diethyl malonate led to the formation of product **51** exclusively, regardless of the chain length of substituents.



R= Ph, $Ph(CH_2)_n$
n= 1, 2, 3

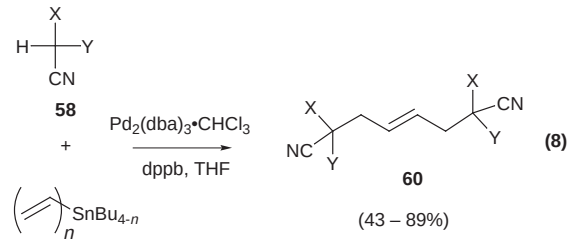
The mechanistic rationale in Scheme 8 may account for the present palladium catalysed ring opening of methylenecyclopropanes with pronucleophiles. Oxidative addition of Pd(0) into the C–H bond of pronucleophiles **49** would generate a hydridopalladium complex which on hydropalladation of methylenecyclopropanes would give either **53** or **55**. The complex **53** would undergo rearrangement to the π-allylpalladium complex **54** (route A). The reductive elimination of Pd(0) from **54** would produce **51**. The palladium complex **55** would isomerise to the π-allylpalladium complex **57** *via* **56** (route B) and the reductive elimination of Pd(0) would give **52**. The reaction with deuterated pronucleophiles substantiated the hydropalladation mechanism.



Scheme 8 Mechanistic pathway: hydrocarbonation of methylenecyclopropane.

2.5 Hydrocarbonation of vinyltin derivatives

In one of the previous sections it has been mentioned that the allenylstannanes underwent substitution–addition reactions with pronucleophiles. Encouraged by this result, we subjected vinyltin derivatives to the palladium catalysed pronucleophile addition reactions. In the presence of a catalytic amount of $Pd_2(dba)_3{\cdot}CHCl_3$–dppb, the reaction of pronucleophiles **58** with vinyltins **59** proceeded through alkylative dimerisation and gave the corresponding 1,4-disubstituted butenes **60** in good yields (eqn. (8)).[23] The reaction proceeded in a stereoselective



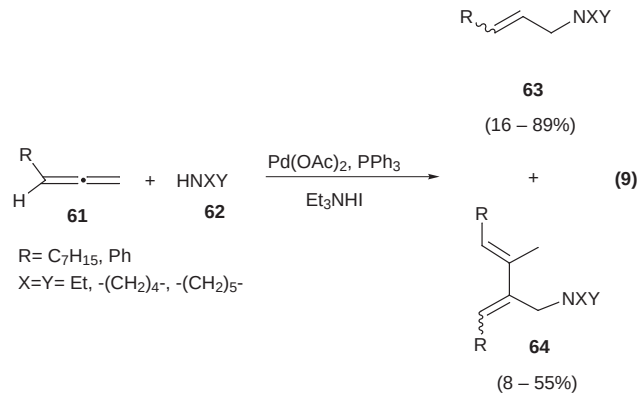
fashion to give *trans* isomers selectively and no *cis* isomers were detected in any reactions. The pronucleophiles, such as malononitrile, diethyl malonate and diethyl phenylmalonate, did not react with vinyltins under the reaction conditions.

3 Hydroamination reactions

The hydroamination reaction of an unactivated unsaturated system consists of the formal addition of an N–H bond across carbon–carbon multiple bonds. It is one of the most useful methods for synthesizing nitrogen containing compounds from unsaturated organic molecules.[24] Therefore, we intended to develop a catalytic process for the hydroamination of unactivated systems, based upon the knowledge and mechanisms obtained from the studies on the hydrocarbonation reactions. Similar to the hydrocarbonation reactions, the hydroamination of unactivated carbon–carbon multiple bonds requires the activation of either unsaturated systems or amines. The activation of carbon–carbon multiple bonds can be effected by the coordination of various electrophilic metals. Most of the amination reactions which are based on nucleophilic addition to the metal activated unsaturated systems are carried out using stoichiometric amounts of the transition metal reagents. On the other hand, the N–H bond can be activated either by deprotonation using electropositive metals or by the oxidative addition of the N–H bond to a transition metal. So far, reports on the oxidative additions of an N–H bond to coordinatively unsaturated metal centers are rare.[24] Remarkably, we could achieve the hydroamination of allenes, enynes and methylenecyclopropanes which proceed most probably through the oxidative addition of N–H bond to palladium(0) under neutral or acidic conditions and the results are described here.

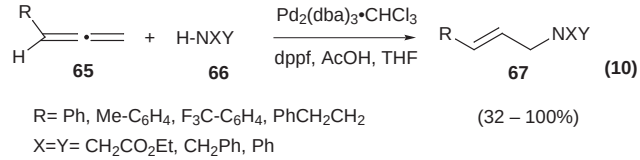
3.1 Hydroamination of mono- and disubstituted allenes

Allylamines are important organic compounds on account of their use as synthetic intermediates and their occurrence as natural substances. The catalytic hydroamination of allenes would be a straightforward method for the synthesis of this useful product. Unsubstituted allenes are known to undergo hydroamination reactions in the presence of a palladium catalyst.[9] The main products of this reaction are alkadienylamines. Cazes *et. al.* reported the palladium catalysed intermolecular hydroamination of substituted allenes **61** using aliphatic amines **62** (eqn. (9)).[25] They utilised the beneficial



effect of adding triethylammonium iodide salt which resulted in the hydroamination of allenes. Under these reaction conditions, in addition to the normal hydroamination product **63**, the allene underwent telomerisation with the amine and gave dienic amine **64** also.

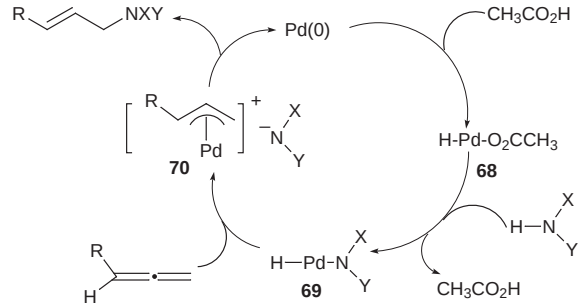
By employing a different palladium catalyst system under acidic conditions, the hydroamination reaction with wider synthetic scope was observed. In the presence of $Pd_2(dba)_3{\cdot}CHCl_3$–dppf with acetic acid in THF, allylamines **67** were obtained as the only product in good to excellent yields (eqn. (10)).[26] This catalytic system was very effective for the



intermolecular hydroamination of various monosubstituted allenes **65** with protected amines **66** to afford the *E*-isomer of the corresponding allylamines **67**. In contrast to the hydrocarbonation reactions, here the regioselectivity was not affected by either the bulkiness of the nucleophile or the electronic properties of *para*-substituents of arylallenes. In all cases γ-adducts were obtained as the only product. In fact, the aliphatic

allenes gave lower yields of products than the corresponding aromatic allenes.

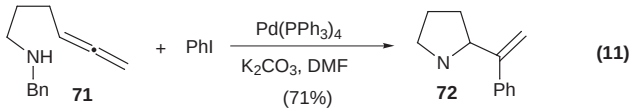
A possible reaction pathway for this palladium(0) catalysed hydroamination is shown in Scheme 9. The oxidative addition



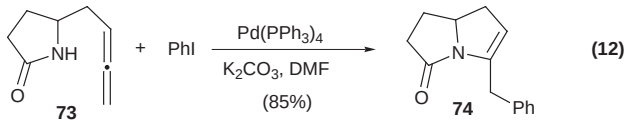
Scheme 9 Hydroamination of allenes: plausible mechanism.

of acetic acid to Pd(0) would produce hydridopalladium species **68**, which on reaction with amine would give intermediate **69** and acetic acid. The species **69** would form the π-allylpalladium intermediate **70** with allenes which after reductive elimination would give the hydroamination product with γ-selectivity.

An efficient intramolecular cyclisation of tethered aminoallenes is a potentially useful method for constructing nitrogen heterocycles bearing the key substituents present in naturally occurring compounds. Gallagher *et al.*[27] and Hiemstra *et al.*[28] reported palladium catalysed intermolecular coupling/intramolecular cyclisation sequences based on allenes as the π-component for the synthesis of nitrogen heterocycles (eqns. (11) and (12)). In these reactions, the organopalladium(II) iodide



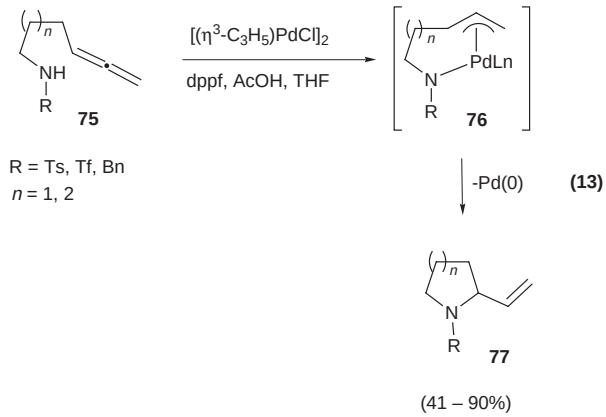
(11)



(12)

formed *in situ* activates the allenic double bond to undergo intramolecular cyclisation to give five membered ring heterocycles **72** and **74**.

An entirely new type of hydroamination which proceeds through the insertion of an M–H bond (M = Pd) into an allenic double bond has been developed in this laboratory.[29] Amines or sulfonylamides bearing an allene **75** at the terminus of the carbon chain underwent a facile intramolecular reaction in the presence of a catalytic amount of $[(\eta^3\text{-}C_3H_5)PdCl]_2$–dppf and acetic acid (eqn. (13)). In the absence of acetic acid the reaction

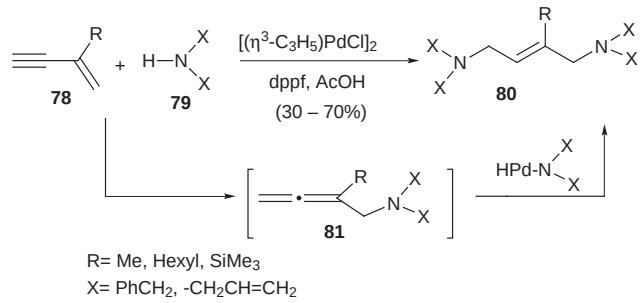


(13)

was very sluggish. The tethered aminoallenes cyclised smoothly in 5-*exo*-*trig* or 6-*exo*-*trig* modes to afford the corresponding vinylpyrrolidines and vinylpiperidines, respectively. The protecting group at the amine moiety of allenylamines plays an important role. The tethered allenylamines protected with triflate, toluene-*p*-sulfonate and benzyl groups gave the corresponding products **77** in good yields, but other protecting groups did not give the desired products.

3.2 Hydroamination of enynes

The hydoamination of conjugated enynes **78** in the presence of a palladium catalyst was reasonably facile and gave the *E*-isomer of alkenic 1,4-diamine **80** (Scheme 10).[30] Unlike the



Scheme 10 Hydroamination of enynes.

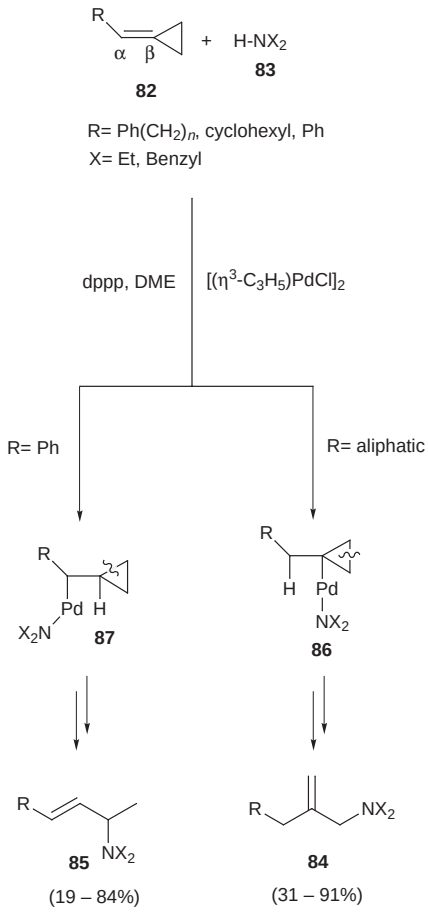
hydrocarbonation of enynes, aminoallenes **81** (through monohydroamination) were not obtained as the products. Probably, the aminoallenes **81** are very reactive and underwent further addition of the amine to give the dihydroamination products, alkenic 1,4-diamines **80**. It should be pointed out that the unsymmetrically substituted 1,4-diaminobut-2-enes could also be obtained using two different amines. Unfortunately, the reaction did not give fruitful results with aliphatic amines and sulfonamides. These types of alkenic 1,4-diamines **80** are important organic compounds on account of their use as synthetic intermediates and as inhibitors.

3.3 Hydroamination of methylenecyclopropanes

Analogously to the hydrocarbonation of methylenecyclopropanes, the hydroamination also proceeded smoothly in the presence of $[(\eta^3\text{-}C_3H_5)PdCl]_2$–dppp and gave either **84** or **85** (Scheme 11).[31] The regioselectivity clearly depends upon the substituent on the double bond of methylenecyclopropanes **82**. The palladium catalysed hydroamination of alkyl substituted methylenecyclopropanes mainly proceeds through the Markovnikov type addition to give **86** followed by distal bond cleavage to give the product **84**, whereas in the case of benzylidenecyclopropanes the reaction goes through anti-Markovnikov addition followed by proximal bond cleavage and gives the product **85** exclusively. This regiochemical difference may be due to the following reason; the alkyl substituent decreases the electron density at the α-carbon of the alkene and the phenyl group increases the electron density at the α-carbon.[31] Hence, the hydropalladation and ring opening mode changes accordingly. The Markovnikov and anti-Markovnikov hydropalladation mechanisms were confirmed by carrying out the reactions of deuterated amines with alkyl and phenyl substituted methylenecyclopropanes.

4 Hydrocarboxylation of allenes

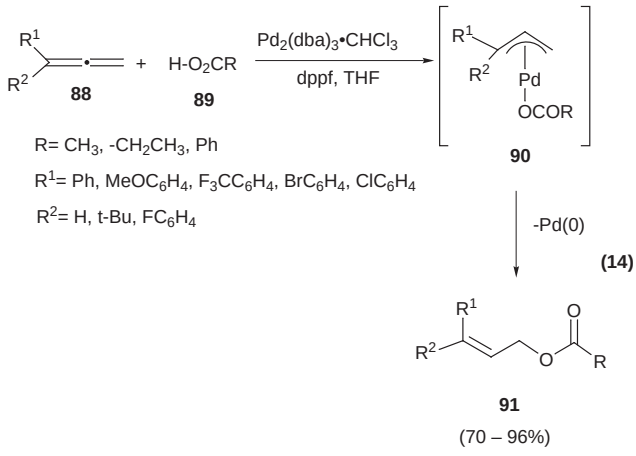
Hydrocarboxylation of carbon–carbon multiple bonds is one of the most important processes for the synthesis of unsaturated and saturated carboxylic esters. In a classical organic reaction, carboxylic esters are produced by the addition of carboxylic



Scheme 11 Hydroamination of methylenecyclopropanes.

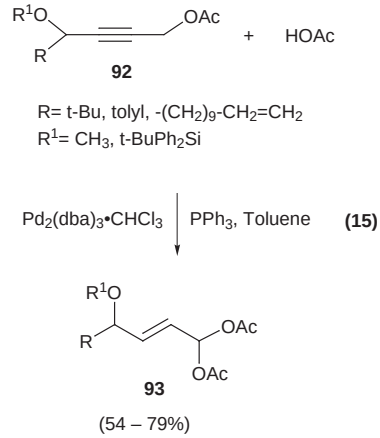
acids to olefins mediated by protonic acids.[1] In modern organic synthesis, transition metal catalysts have replaced protonic acid catalysts. A number of other workers have contributed to this area which involves the nucleophilic addition of carboxylic groups to the metal coordinated carbon–carbon multiple bonds.[32] We were interested in the reactions which involve the activation of carboxylic acids to form H–M–OOCR and proceed through insertion of the double bond into the H–M bond. An interesting example which demonstrates the synthetic potential of this methodology has been observed in our laboratory.[33]

The $Pd_2(dba)_3$•$CHCl_3$–dppf complex catalysed the hydrocarboxylation of aromatic allenes **88** to give allyl esters **91** in excellent yields with perfect regio- and stereoselectivities (eqn. (14)).[33] Regardless of the electronic nature of substituents at the



para-position of aromatic allenes, the γ-adducts were obtained as the only product. In contrast to the classical electrophilic addition reaction, the new version of the hydrocarboxylation reaction of allenes most probably proceeds through the π-allylpalladium species **90**. It is worth mentioning that various types of carboxylic acids **89** and an amino acid smoothly reacted with allenes affording the corresponding allyl esters in excellent yields. In general the monosubstituted allenes gave *E*-isomers exclusively and the disubstituted allenes provided *E*/*Z* mixtures. Unfortunately, in the case of aliphatic allenes, no hydrocarboxylated products were obtained, instead, buta-1,3-diene derivatives were formed.

Propargylic (propargyl = prop-2-ynyl) derivatives are known to undergo isomerisation to give allenes. Trost *et al.* reported a palladium catalysed hydrocarboxylation of *in situ* generated allenes from propargyl derivatives (eqn. (15)).[34] The

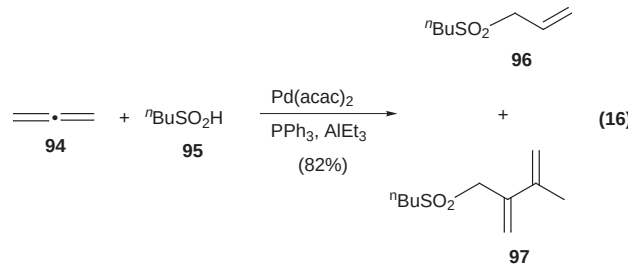


propargyl acetates **92** on treatment with acetic acid in the presence of a Pd(0) catalyst resulted in the formation of geminal diacetates **93**. Remarkably, the intramolecular version of this reaction proceeded efficiently to give macrocycles in moderate yields.

5 Hydrosulfination of allenes

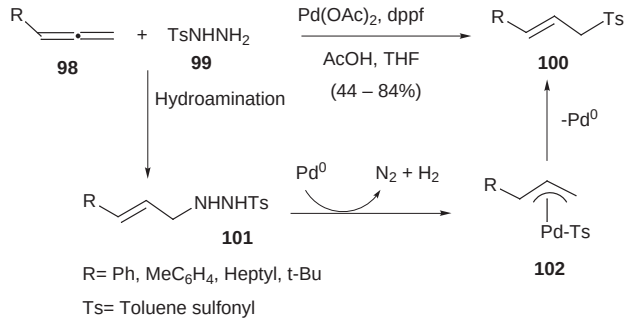
Some organosulfur compounds are considered to be an important class of pharmacological agents. Until recently, the transition metal mediated synthesis of organic sulfur compounds attracted much less attention. It was reasoned that organic sulfur compounds were considered to be catalytic poisons. However, several transition metal mediated syntheses of organic sulfur compounds have been reported in recent years. Among various transition metals, palladium complex catalysts have been found to be useful in the direct addition of organosulfur compounds to unactivated carbon–carbon multiple bonds.[35]

A good amount of information has been accumulated on the use of palladium catalysts for the syntheses of allyl sulfones from 1,3-dienes and sulfinic acids. Furthermore it was reported that the unsubstituted allenes **94** reacted with *n*-butanesulfinic acid **95** to give high yields of vinyl **96** and butadienyl sulfones **97** (eqn. (16)).[35]



In our continued interest in the direct addition reaction of carbon-pronucleophiles and heteroatom-nucleophiles, we be-

came interested in the syntheses of organosulfur compounds using a palladium catalyst. It was envisioned that in the presence of palladium catalysts tosylhydrazine would act as a sulfinic acid equivalent by losing one equivalent of N_2 and H_2. As we expected, a new type of hydrosulfination reaction of substituted allenes **98** with tosylhydrazine **99** in the presence of palladium catalyst was observed (Scheme 12).[36] Unlike the hydro-



Scheme 12 Hydrosulfination of allenes.

carbonation of allenes, the regioselectivity of the product formation was not influenced by the electronic effect of the *para*-substituent on arylallenes. Generally, the tosyl group added regioselectively to the γ-position of allenes and *trans*-allyl sulfones were obtained without the formation of *cis*-allyl sulfones. The reaction pathway may involve the formation of intermediate **101** *via* the hydroamination of allenes with tosylhydrazine. Subsequently, the intermediate **101** would be converted to allyl sulfones **100** *via* the π-allylpalladium complex **102** with releasing N_2 and H_2.

6 Conclusions

Until recently, there has been dearth of catalytic methods for C–C bond formation involving *pronucleophiles* and unactivated unsaturated systems. We were surprised by this fact and entered this field several years ago with the aim of developing suitable catalytic systems for pronucleophile based carbon–carbon bond forming reactions. We have discovered many synthetically useful reactions and they are reported in this short review. The palladium catalysed hydrocarbonation of allenes and allylation of pronucleophiles using alkynes constitutes on important breakthrough. This methodology has also been successfully applied to the hydrocarbonation of non-conjugated alkenes such as methylenecyclopropanes. In addition to the hydrocarbonation reactions, considerable progress has also been made in hydroamination, hydrocarboxylation and hydrosulfination reactions also. The hydroamination reactions were utilised efficiently to obtain biologically important allylic amines and important classes of nitrogen containing heterocycles.

It can be discerned from the foregoing discussion that palladium has proved to be a useful catalyst for carbon–carbon and carbon–heteroatom bond formation involving unactivated unsaturated systems and pronucleophiles. Many additional applications of the reactions and procedures discussed in this review will be forthcoming. For the future, investigations aimed at promoting additional methodologies, mechanistic investigations and further efforts to increase the turnover number of catalyst will be of useful to both academic and industrial synthetic chemists.

7 References

1 J. March, *Advanced Organic Chemistry*, Wiley Interscience, New York, 4th Edition, 1992, pp. 795–797.
2 T. Naota, H. Taki, M. Mizuno and S.-I. Murahashi, *J. Am. Chem. Soc.*, 1989, **111**, 5954.
3 L. S. Hegedus, *Comprehensive Organic Synthesis*, B. M. Trost and I. Fleming, Eds. Pergamon Press, Oxford, 1990, vol. 4, pp. 571–583.
4 P. Knochel, *Comprehensive Organic Synthesis*, B. M. Trost and I. Fleming, Eds. Pergamon Press, Oxford, 1990, vol. 4, pp. 865–911.
5 Y. Yamamoto, *Pure Appl. Chem.*, 1996, **68**, 9, and references cited therein.
6 S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonada and N. Chatani, *Nature (London)*, 1993, **366**, 529.
7 B. M. Trost, M. T. Sorum, C. Chan, A. E. Harms and G. Ruhter, *J. Am. Chem. Soc.*, 1997, **119**, 698.
8 K. Takahashi, A. Miyake and G. Hata, *Bull. Chem. Soc. Jpn.*, 1972, **45**, 1183.
9 D. R. Coulson, *J. Org. Chem.*, 1973, **38**, 1483.
10 Y. Yamamoto, M. Al-Masum and N. Asao, *J. Am. Chem. Soc.*, 1994, **116**, 6019.
11 Y. Yamamoto, M. Al-Masum, N. Fujiwara and N. Asao, *Tetrahedron Lett.*, 1995, **36**, 2811.
12 Y. Yamamoto and M. Al-Masum, *Synlett*, 1995, 969.
13 Y. Yamamoto, M. Al-Masum and A. Takeda, *Chem. Commun.*, 1996, 831.
14 Y. Yamamoto, M. Al-Masum and N. Fujiwara, *Chem. Commun.*, 1996, 381.
15 B. M. Trost and V. J. Gerusz, *J. Am. Chem. Soc.*, 1995, **117**, 5156.
16 L. Besson, J. Gore and B. Cazes, *Tetrahedron Lett.*, 1995, **36**, 3853.
17 M. Meguro, S. Kamijo and Y. Yamamoto, *Tetrahedron Lett.*, 1996, **37**, 7453.
18 V. Gevorgyan, C. Kadowaki, M. M. Salter, I. Kadota, S. Saito and Y. Yamamoto, *Tetrahedron*, 1997, **53**, 9097.
19 J. Tsuji, *Palladium Reagents and Catalysts; Innovations in Organic Synthesis*, John Wiley, Chichester, 1995, p. 297.
20 I. Kadota, A. Shibuya, Y. S. Gyoung and Y. Yamamoto, *J. Am. Chem. Soc.*, 1998, **120**, 10262.
21 N. Tsukada and Y. Yamamoto, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2477.
22 N. Tsukada, A. Shibuya, I. Nakamura and Y. Yamamoto, *J. Am. Chem. Soc.*, 1997, **119**, 8123.
23 I. Nakamura, N. Tsukada, M. Al-Masum and Y. Yamamoto, *Chem. Commun.*, 1997, 1583.
24 T. E. Muller and M. Beller, *Chem. Rev.*, 1998, **98**, 675.
25 L. Besson, J. Gore and B. Cazes, *Tetrahedron Lett.*, 1995, **36**, 3857.
26 M. Al-Masum, M. Meguro and Y. Yamamoto, *Tetrahedron Lett.*, 1997, **38**, 6071.
27 I.W. Davies, D. I. C. Scopes and T. Gallagher, *Synlett*, 1993, 85.
28 W. F. J. Karstens, F. P. J. T. Rutjes and H. Hiemstra, *Tetrahedron Lett.*, 1997, **38**, 6275.
29 M. Meguro and Y. Yamamoto, *Tetrahedron Lett.*, 1998, **39**, 5421.
30 U. Radhakrishnan, M. Al-Masum and Y. Yamamoto, *Tetrahedron Lett.*, 1998, **39**, 1037.
31 I. Nakamura, H. Itagaki and Y. Yamamoto, *J. Org. Chem.*, 1998, **63**, 6458.
32 C. Bruneau and P. H. Dixneuf, *Chem. Commun*, 1997, 507, and references cited therein.
33 M. Al-Masum and Y. Yamamoto, *J. Am. Chem. Soc.*, 1998, **120**, 3809.
34 B. M. Trost and W. Brieden, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 1335.
35 U. M. Dzhemilev and R. V. Kunakova, *J. Organomet. Chem.*, 1993, **455**, 1.
36 S. Kamijo, M. Al-Masum and Y. Yamamoto, *Tetrahedron Lett.*, 1998, **39**, 691.

Review 8/06581K