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Palladium-mediated cascade or multicomponent reactions: A new route to carbo- and heterocyclic compounds*

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Abstract: In recent years, new processes based on transition-metal-mediated intramolecular addition reaction of heteronucleophiles and stabilized carbon nucleophiles to unactivated alkenes and alkynes have been developed in our laboratory. In this article, we summarize a number of recent synthetic applications of these new processes. Emphasis is placed on the development of multicomponent reactions based on a Pd-mediated intramolecular cyclization coupled with a carbon–carbon bond-forming reaction. Applications of this methodology to the synthesis of natural lignans are also reported.

Keywords: multicomponent; palladium; heterocycle; synthesis; cascade reactions.

One of the challenging goals in organic chemistry is to discover efficient new routes for the single-step elaboration of a wide range of complex systems from simple and readily available starting materials. In this regard, the development of transition-metal-mediated tandem or cascade reactions has been the subject of intense research over the past several years. Following this trend, our group has recently developed a new Pd-mediated cyclization of unsaturated substrates bearing a nucleophilic substituent and various types of hetero and carbocyclic compounds were then obtained with high regio- and stereoselectivities. This article focuses mainly on research in this field developed in our laboratory over the past four years.

INTRAMOLECULAR ADDITION OF STABILIZED NUCLEOPHILES TO UNACTIVATED ALKENES AND ALKYNES

While the addition of stabilized carbanions to activated unsaturated systems (Michael addition) is one of the most popular methods for the formation of carbon–carbon bonds, rather limited attention has been paid to the intramolecular addition reaction of stabilized carbon nucleophiles to unactivated olefins. Indeed, unactivated olefins are inert toward attack of nucleophiles. When complexed to Pd(II) salts, it is well known that stabilized carbanions may react with these olefin Pd(II) complexes to generate σ-alkylpalladium complexes. One such reaction, an efficient intramolecular carbocyclization of the enolate derived from a malonic compound bearing an unactivated double bond mediated by stoichiometric amounts of inorganic salts of Pd(II) has been reported by Hegedus and coworkers [1]. However, a catalytic process in the presence of a suitable oxidant cannot be realized due to the incompatibility be-

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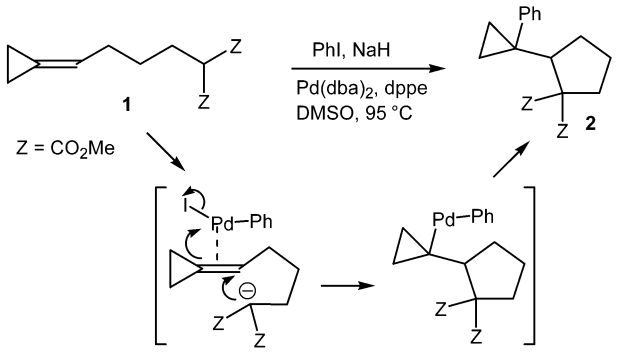
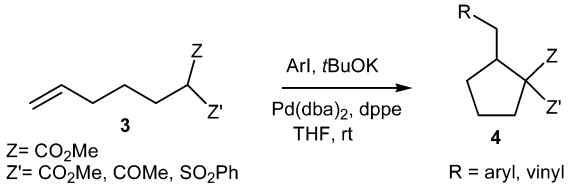
tween the stabilized carbon nucleophile and the stoichiometric oxidant (competitive oxidation of the stabilized carbanion). Recently, Widenhoefer and coworkers developed an interesting $PdCl_2(CH_3CN)_2$-catalyzed intramolecular addition of carbon nucleophiles to olefins that proceeds under neutral conditions and in the absence of a stoichiometric oxidant [2]. This useful Pd(II)-promoted cyclization is, however, restricted to alkenyl-1,3-diones.

In the course of our work in relation with the Pd-mediated reaction of various alkylidenecyclopropanes **1** having a stabilized nucleophile with phenyl iodide [3], we unexpectedly found that the intramolecular carbocyclization reaction of the alkylidenecyclopropane **1** gives the bicyclic compound **2** (Scheme 1). Although the mechanism of the cyclization process was not clear at that time, this was certainly the first reported example of an intramolecular nucleophilic attack on an unsaturation which is electrophilically activated by an organopalladium species. This reaction proceeds via a Wacker-type mechanism in which an organopalladium halide, not a Pd(II) salt, acts as the electrophilic partner of the cyclization. Therefore, this reaction, which only requires catalytic amounts of the metal, results in overall difunctionalization of the olefinic fragment.



Scheme 1

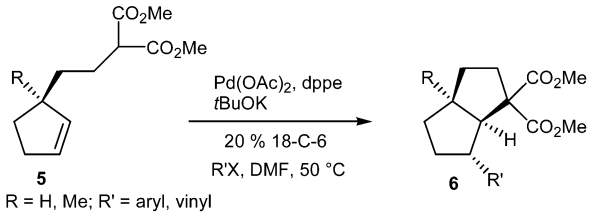
This Pd-catalyzed tandem cyclization-coupling reaction was further applied to linear ethylenic substrates **3** bearing various stabilized carbon nucleophiles, which gave rise to the expected cyclopentanic derivatives **4** [4] (Scheme 2). Strong bases such as KH or *t*-BuOK have to be used to promote the cyclization. With weaker bases, competition with the olefin insertion process on the organopalladium(II) complex (classical Heck reaction) and this cyclization-coupling reaction was generally observed [5].



Scheme 2

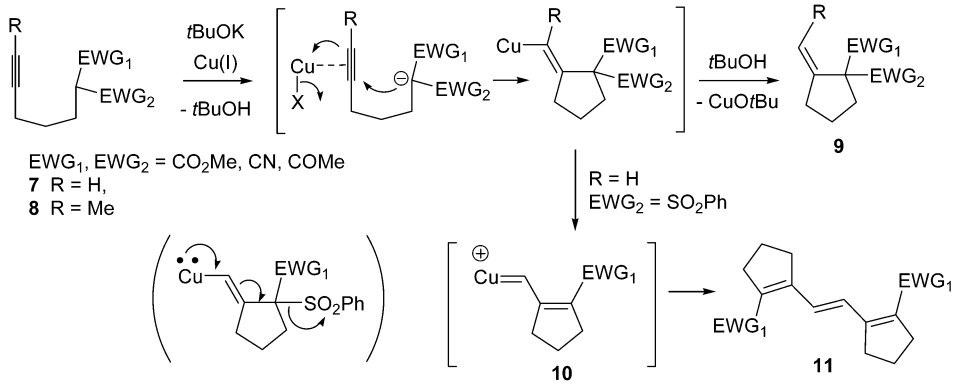
The stereochemical course of this reaction has been probed with functionalized cyclopentene **5** [6]. The Pd-catalyzed reaction of this substrate with phenyl iodide proceeded in a completely stereoselective *trans* manner to give the single diastereoisomer **6**. The stereocontrol observed during the for-

mation of the newly formed stereocenter confirmed that the reaction involves an attack of the nucleophile onto the unsaturation from the opposite side of the activating σ-unsaturated Pd species (Scheme 3).



Scheme 3

The analogous chemistry of alkynes has been far more studied and, in this area, the development of new transition-metal-catalyzed cyclization processes has received a special attention. Several procedures have been reported for cyclization of acetylenic substrates bearing a pendant nucleophile to functionalized methylenecyclopentanes. Some of these reactions proceed under neutral conditions [7]. However, they are generally restricted to β-ketoesters as nucleophiles (Conia-ene type reactions) and could not be applied to a variety of stabilized nucleophiles. Much of the development of this strategy involves the reaction of metal enolates derived from active methine compounds [8]. In line with this, our group has developed a general method allowing the cyclization of a variety of δ-acetylenic stabilized carbanions **7** (R = H) by using catalytic amounts of base and Cu salts. In this reaction, polarization of the triple bond by complexation of the electrophilic Cu salt initiates the nucleophilic attack of the malonate anion. This Cu-catalyzed reaction was applied to internal alkynes such as **8** and converted to the (*Z*)-isomer **9** as the single product. This result further supports a mechanism in which the nucleophile and the Cu species add in a *trans* fashion across the unsaturated bond [9]. The Cu-mediated carbocyclization reaction was also examined with α-sulfonyl ε-acetylenic esters. In this case, the ability of the arylsulfonyl group to act as a leaving group generates the carbenoid Cu complex **10**, which evolves to the formation of the dimeric compound **11** [10] (Scheme 4).



Scheme 4

The synthetic potential of this reaction has recently been exploited by our group for the synthesis of highly substituted methylenetetrahydrofurans [11] and pyrrolidine derivatives [12].

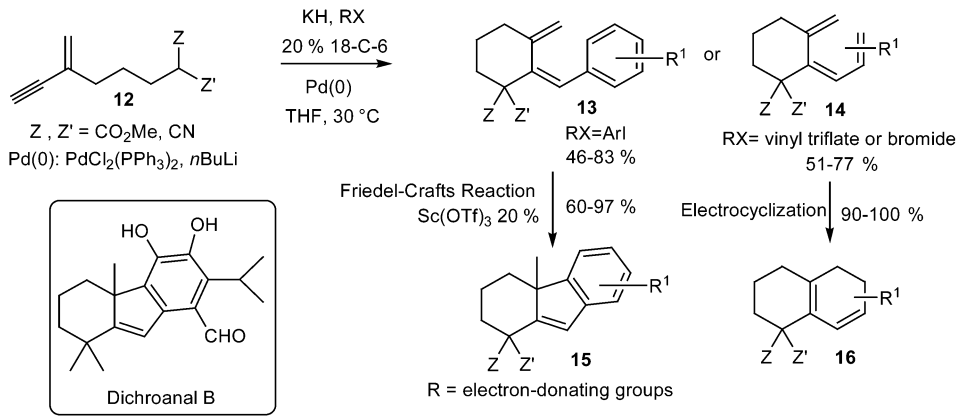
The Pd-catalyzed tandem cyclization-coupling reaction with organic halides developed in our group on olefinic substrates was also applied to acetylenic compounds such as **7** [13]. A major feature of these reactions involving acetylenic substrates is that the configuration of the exocyclic double bond

in the reaction products is always such that the substituent introduced from the unsaturated halide lies *trans* with respect to the bond bearing the stabilized nucleophile.

Recently, this strategy has been extended to the formation of stereodefined functionalized 1,3-bis-exocyclic dienes **13** by cyclization of conjugated enynes **12** having a stabilized carbon nucleophile in the presence of aryl iodides. When the same reaction was performed in the presence of vinyl triflates or bromides as electrophilic partners, the corresponding conjugated trienes **14** were isolated in good yields as single geometric isomers [14].

The synthetic potential of 1,3-bis-exocyclic dienes **13** for the preparation of diverse ring structures was further explored, and their behavior in Diels–Alder reactions was first investigated [15].

An unprecedented Lewis acid-mediated intramolecular Friedel–Crafts alkylation of the exocyclic methylene substituent onto the vicinal aromatic ring was also developed, which takes advantage of the stereodefined configuration of the benzylidene fragment. A wide range of Lewis acids have been tested in this reaction, and the use of $Sc(OTf)_3$ allowed the reaction to proceed catalytically. This new method was very efficient for constructing the 4a-methyltetrahydro-fluorene skeleton **15** bearing electron-donating substituents, an uncommon structure present in some recently isolated natural products such as Dichroanal B [16] (Scheme 5).



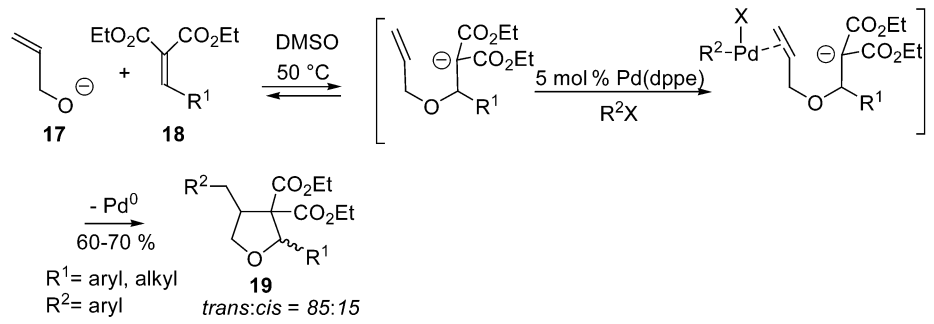
Scheme 5

The stereodefined trienic systems **14** are able to undergo electrocyclic rearrangement to form cyclohexadienes **16**. This thermal 6-π-electrocyclization generally proceeded in refluxing toluene, and the expected compounds were obtained in a range of 90–100 %. It was also possible to develop a one-pot reaction combining the tandem cyclization-coupling reaction and the electrocyclization by carrying out both reactions sequentially in refluxing toluene. It is interesting to note that in this cascade reaction, three carbon–carbon bonds and two rings are formed in one step [17].

DEVELOPMENT OF MULTICOMPONENT REACTIONS FOR THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS

In an effort to explore the potential utility of this novel Pd-mediated cyclization-coupling process, various syntheses of highly substituted heterocycles were developed in our group, by means of multicomponent reactions based on this concept. Pioneering experiments were conducted with readily available allylic alcohols, aryl halides, and *gem*-diactivated olefins as three partners of the reaction [18]. In this three-component reaction, the enolate **17** resulting from the initial 1,4-addition of an allylic alcohol to the conjugate acceptor **18** is followed by the Pd-mediated cyclization reaction involving the unsaturated halide. The best protocol employed a syringe pump addition of a solution of alkoxide in

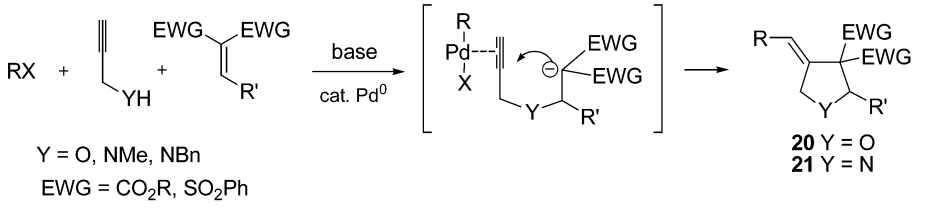
DMSO at 40 °C. This method was successively applied to the simple allylic alcohol, leading to the substituted tetrahydrofurans **19** in a range of 60–70 % yields, whereas secondary or tertiary allylic alcohols gave lower yields (Scheme 6). The aim of this study was to find a methodology that could be applied to combinatorial approaches to libraries of compounds. However, this three-component reaction has been found to have limited versatility since it was restricted to simple allylic alcohol. Moreover, the use of slow addition techniques for the introduction of the allylic alkoxide component proved necessary in order to minimize formation of side products.



Scheme 6

When allylic alcohols were substituted for their propargylic analogs, the above-mentioned three-component reaction became remarkably versatile, giving good yields of stereodefined 3-arylidene (and alkenylidene) tetrahydrofurans **20** with a variety of propargyl alcohols (primary, secondary, and tertiary) and unsaturated halides (aryl iodides, vinyl bromides, and triflates) [19]. The efficiency of this Pd-mediated three-component reaction has been shown to be strongly influenced by the nature of the catalyst, and best results were obtained when using a Pd complex generated in situ by reduction of dichlorobis-(triphenylphosphine)palladium(II) ($PdCl_2(PPh_3)_2$) with *n*-butyllithium. It is important to note that these conditions allowed the simultaneous introduction of no more than one equivalent of each component for optimum yield, and this permitted the avoidance of any recoverage of excess reagents. This three-component reaction is, therefore, ideally suited for generating libraries of small molecules and particularly drug-like heterocyclic compounds.

Extending this concept to propargylamines gave rise to the formation of a new class of stereodefined arylidene-(or alkenylidene)pyrrolidines **21** in high yields [20] (Scheme 7).

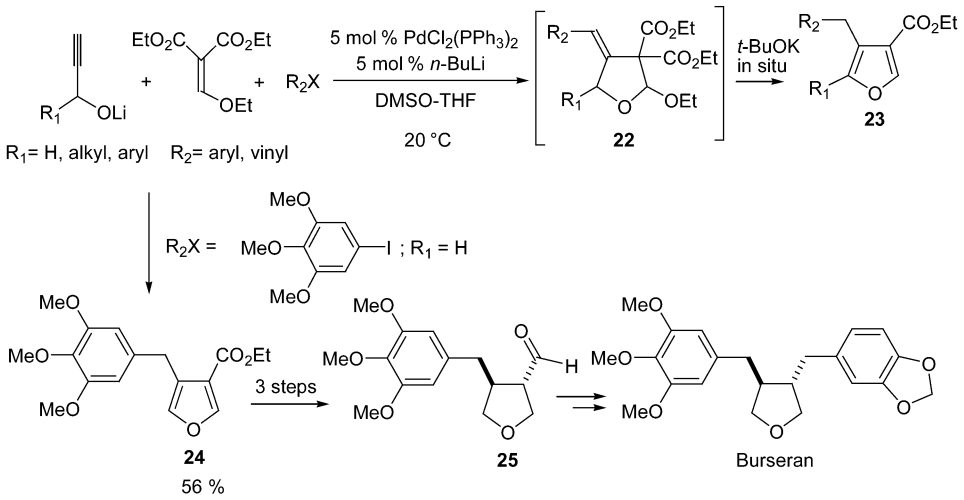


Scheme 7

We have recently shown that this sequential hetero-Michael conjugate addition-carbopalladation-reductive elimination process may also involve allylamines as nucleophilic partners [21]. In this case, in marked contrast with what was observed with their corresponding allylic alcohols, it was possible to introduce all components simultaneously at the start of the reaction with no side reaction occurring.

This multicomponent reaction allows the clean and selective assembling of diversely functionalized 4-benzyl (and 4-allyl) pyrrolidines in moderate to good yields.

An interesting extension of this methodology to the one-pot preparation of furan derivatives has been achieved using the commercially available diethyl ethoxymethylenemalonate as Michael acceptor. In this case, the resulting 2-ethoxy-4-arylidene tetrahydrofurans **22** were converted to the expected furans **23** by in situ addition of a slight excess of potassium *t*-butoxide. The entire process involved a sequence of a conjugate addition, a Pd-catalyzed cyclization-coupling reaction, an alkoxide-induced eliminative decarboxylation and, finally, an isomerization of the exocyclic double bond. A formal synthesis of the lignan antitumor burseran employing this process as a key step illustrated the potential utility of this concept for the preparation of some natural products of the 3,4-benzyltetrahydrofuran lignans family [22]. The 4-benzylfuran-3-carboxylate **24** prepared in a single step from three readily available starting materials was transformed into the known 4-benzyltetrahydrofuran-3-carboxaldehyde **25** by the following three steps: reduction of the ester group into the corresponding alcohol, hydrogenation of the furan ring, and oxidation (Scheme 8).



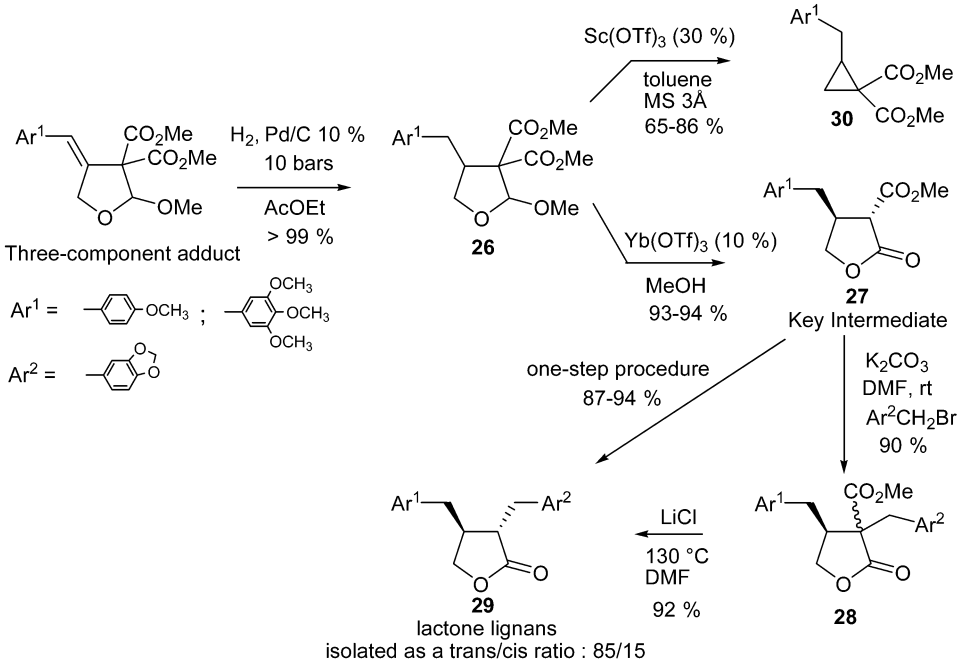
Scheme 8

A short synthesis of lactone lignans exploiting this three-component coupling strategy was recently developed in our group using a new Lewis-acid-catalyzed ring-opening/cyclization reaction of 2-methoxytetrahydrofuran derivatives **26** leading to γ-butyrolactones **27** as a key step [23]. The reaction proceeds through Lewis activation of the acetal that promotes ring cleavage of the 2-methoxytetrahydrofuran and generates a stabilized malonic enolate and an oxonium species. This latter could be captured by methanol or water, present as contaminant in the reaction mixture, and the resulting alcohol then attacks one of the ester groups to give **27**.

Due to the presence of the ester group, alkylation of lactones **27** with a benzyl halide such as 3,4-methylenedioxybenzyl bromide was readily accomplished in good yield, the reaction being performed in DMF at room temperature in the presence of K_2CO_3 as base. Decarbalkoxylation of the resulting lactones **28** under Krapcho's condition (NaCl, DMF, 130 °C) afforded the trans alkylated product **29** predominantly (85:15) in high yield. A more direct alkylation-decarbalkoxylation method was also developed. The two steps were conducted sequentially in the same reaction vessel without isolation of the intermediate by adding LiCl (5 equiv) and water (2 equiv) to the alkylated product (Scheme 9). We have then developed a convergent, high-yielding, and practical synthesis of dibenzyl-

butyrolactone lignans since these natural products have been obtained in only four synthetic steps and in excellent overall yield.

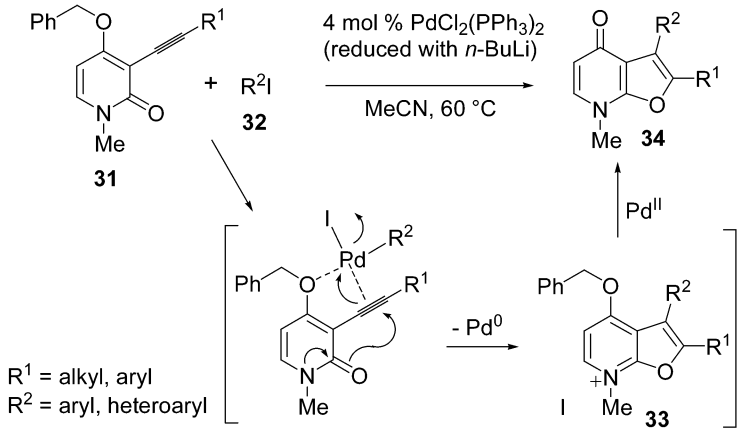
It has also been discovered that this strategy could be applied to the synthesis of cyclopropanic compounds **30**. Indeed, the treatment of 2-methoxytetrahydrofuran derivatives **26** with 30 mol % of $Sc(OTf)_3$ in toluene at reflux, under strictly dried conditions, resulted in the exclusive formation of the corresponding cyclopropanic substrates in rather good yields (Scheme 9).



Scheme 9

INTRAMOLECULAR ADDITION OF HETERONUCLEOPHILES TO UNACTIVATED ALKYNES

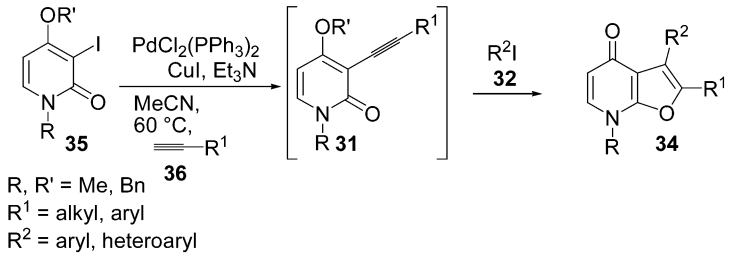
All reactions discussed previously involved the reaction of stabilized carbon nucleophiles onto unactivated olefins and alkynes. Analogously, this type of Pd-initiated cyclization-coupling reaction may be developed on alkynes tethered with heteronucleophiles such as oxygen or nitrogen. This cyclization-coupling reaction has been developed by us and others into a very efficient and straightforward route for the synthesis of a wide range of useful, functionally substituted heterocycles [24]. This reaction involving heteronucleophiles generally needs the presence of an anionic nucleophile. Recently, a practical synthesis of furo[2,3-b]pyridones **34** through an intramolecular Pd-mediated cyclization of 4-benzyloxy-*N*-methyl-2-pyridone **31** with various arylic halides **32** was developed in our laboratory, the reaction being performed here under neutral conditions as no base is needed [25]. The furo[2,3-b]pyridones **30** result from an attack of the amide onto the Pd-activated triple bond. The heteroannulative coupling produces furopyridinium salts **33** which collapse to form the desired pyridones **34** through subsequent cleavage of the benzyl ether group, apparently by a Pd(II) species (Scheme 10). In this cyclization-coupling reaction, good yields were obtained with aryl halides bearing electron-withdrawing groups, while electron-rich aryl iodides gave poor results. Indeed, in this case, as we have a weak nucleophile, it is necessary to have an organopalladium intermediate able to strongly coordinate to the unsaturation so as to trigger the intramolecular attack of the heteronucleophile to the



Scheme 10

alkyne. To our knowledge, this cyclization-coupling reaction constitutes the only example of such a reaction performed under completely neutral conditions.

The successful participation of *N*-substituted-3-alkynyl-2-pyridones **31** in this Pd-catalyzed cyclization-coupling reaction encouraged us to explore a more direct access to substituted furo[2,3-b]pyridones. These bicyclic heterocyclic systems were thus prepared in a single, practical operation through the sequential coupling of three readily available starting materials, 3-iodo-2-pyridones **35**, terminal alkynes **36**, and aryl iodides **32**. This new multicomponent approach is based on the sequential one-pot combination of a Sonogashira coupling reaction with the Pd-mediated cyclization-coupling process discussed above, the organic halide entering the sequence once the first reaction has gone to completion since competitive coupling reaction may occur. It is interesting to note that in this process a single Pd catalyst intervenes in three different transformations acting alternatively as an organometallic reagent or as a Lewis acid: Sonogashira coupling, cyclization, and fragmentation (Scheme 11).



Scheme 11

In summary, the Pd-catalyzed reaction of nucleophiles bearing a tethered unactivated double or triple bond with organic halides or triflates has been developed by our group into a versatile and efficient method to access diversely substituted carbo- and heterocyclic systems. By further combination of the process with an initial hetero-Michael addition reaction or Sonogashira coupling reaction, we have developed efficient new multicomponent reactions that could be applied to the synthesis of a wide variety of heterocyclic systems as well as of natural products of the lignans family.

ACKNOWLEDGMENTS

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