A Straightforward Entry to Functionalized Carbo- and Heterocycles Based on Pd-Mediated Cyclizations

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Abstract: The efficient and practical syntheses of functionalized carbo-and heterocyclic compounds have been achieved employing a process based on an intramolecular palladium-mediated cyclization coupled with a carbon-carbon bond forming reaction.

Key words: palladium, cross-coupling, cyclizations, carbocycles, heterocycles

Introduction

The development of new methods for the formation of several carbon-carbon bonds and carbon-heteroatom bonds in a single operation has become an important area of research in organic chemistry.1 Following this trend, the cyclization of unsaturated substrates bearing a carboc- or hetero-nucleophile promoted by an organopalladium complex has recently emerged as a powerful method for the synthesis of complex molecules in one reaction (Scheme 2).2 This cyclization which involves an attack by the nucleophile onto an unsaturation activated by an organopalladium(II) species provides a new route to functionalized five or six membered-rings with the advantage that it proceeds in a completely stereoselective trans-manner. The synthetic potential of this reaction has recently been widely exploited.2 This is due to the wide range of organopalladium species, the accessibility of the cyclization precursors as well as the simplicity of the procedure which make this process highly attractive. In this report, we would like to describe a convenient preparation of

Scheme 1
functionalized 1,3-bis exocyclic dienes (Scheme 1, Procedure 1: reaction involving a carbonucleophile), the utilization of this carbopalladation-cyclization process to the ‘one-pot synthesis’ of stereodefined arylidene tetrahydrofurans by means of a three-component reaction (Scheme 1, Procedure 2) and the preparation under neutral conditions of furo[2,3-b]pyridones (Scheme 1, Procedure 3: reaction involving a heteronucleophile). In marked contrast, the competing Heck reaction is never observed in the cyclization of alkene substrates bearing a cyano group. For the cyclization of the alkynes, a competitive reaction arises with the terminal ones due to the strong tendency to give a direct coupling reaction of the alkyne with the aryl halide. The choice of the base has proven to be crucial for the success of the methodology. The use of a strong base such as KH gives exclusively the cyclized product while the use of a weaker base such as Cs₂CO₃ drastically changes the course of the reaction since only compounds resulting from a Sonogashira coupling reaction are obtained. The efficiency of this palladium-mediated cyclization/coupling reaction has also been shown to be strongly affected by the nature of the catalyst system and best results were obtained in the presence of a palladium(0) catalyst issued from the in situ reduction of PdCl₂(PPh₃)₂ with n-BuLi. A typical example of the formation of cyclohexane derivatives is shown in Procedure 1. The stereodefined conjugated triene 3 is formed through a cyclization/coupling reaction involving the triyne 1 and the conjugated enyne 2 having a stabilizing carbon nucleophile. This procedure can be extended to a wide range of aryl iodides and unsaturated bromides and triflates.

Procedure 2 illustrates the synthesis of the highly substituted tetrahydrofuran 7 by means of a multicomponent reaction based on this palladium-mediated cyclization process. In this reaction, the enolate resulting from the initial 1,4-addition of the propargyl alkoxide 5 to the conjugate acceptor 6 is followed by the palladium-mediated cyclization reaction involving the aryl halide 4. This preparation of furans from easily available and inexpensive starting materials can be applied to a series of propargyl alcohols, gem-diactivated olefins, aryl iodides and vinyl bromides or triflates. To keep the procedure as simple as possible, we developed a protocol involving equal amounts of each partner, the reaction being carried out generally at room temperature in the presence of the palladium catalyst in a mixture of THF and DMSO. The presence of DMSO is needed to inhibit the competitive formation of 3-(4)-methylene tetrahydrofurans as side-products. Temperature above 50°C in the reaction with less reactive substrates such as secondary and tertiary propargyl alcohols or gem-diactivated olefins bearing an arylsulfonyl group is needed. In this last case, the presence of the allylic sulfone moiety provides an opportunity for the introduction of another element of diversity or for other

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RX + Pd(0) \rightarrow RPd(0)X
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R = \text{alkyl, aryl, vinyl, propargyl, allenyl, alkynyl}
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X = \text{AcO, OTs, Cl, Br, I, OTf, OR''}
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**Scheme 2**

**Scope and Limitations**

Procedure 1 represents the reactions involving a carbonucleophile.

Alkenes and acetylenes tethered with a stabilizing carbon nucleophile are good substrates for the palladium-mediated preparation of functionalized five-membered carbocycles. A large variety of stabilized carbanions may be involved in these reactions such as malononitrile, β-diesters, β-keto- or cyano- or sulfonyl esters. (pKₐ in the range of 9–19). Less stabilized anion such as methyl 2-phenylsulfinylacetate does not give the expected cyclization. The use of a strong base such as KH or tert-BuOK is necessary to favor the intramolecular attack of the nucleophile. The yields of carbocycles obtained are independent of the nature of the aryl halide substituents.

The formation of the corresponding six-membered rings proved to be more difficult since competing side reactions occur. To delineate the scope of this reaction, we can make the following observations. For the reactions involving alkene substrates, the course of the reaction is strongly affected by the nature of the nucleophile (Scheme 3). The linear substrate having a β-diester gave only the product of addition of the arylpalladium iodide to the olefin (classical Heck reaction) without the formation of the 6-exo-cyclization product.
ther functionalizations. This procedure can be extended to propargyl amines. Analogously, this type of palladium-initiated cyclization/coupling reactions may be developed on alkynes tethered with heteronucleophiles such as nitrogen or oxygen. Indeed, while a number of examples of intramolecular reactions of stabilized carbon nucleophiles on an alkene coordinated by an organopalladium complex are known, to the best of our knowledge, there is no example of the same reaction performed in the presence of heteronucleophile. This palladium-initiated cyclization/cross-coupling reaction involving heteronucleophiles generally needs the presence of an anionic nucleophile. A typical example is shown in Scheme 4. 

Procedure 3 illustrates the preparation of the furo[2,3-b]pyridone 10 through an intramolecular palladium-mediated cyclization of the 4-benzyloxy-N-methyl-2-pyridone 8 with the 1,4-diiodobenzene (9); the reaction being performed here under neutral conditions as no base is needed. The furo[2,3-b]pyridone 10 results from an attack of the amide onto the palladium-activated triple bond. This is followed by an intramolecular attack of the benzyl ether group, apparently by a Pd(II) species. In this cyclization/coupling reaction, good yields were obtained with aryl halides bearing electron-withdrawing groups while electron-rich arylic halides gave poor results. In this last case, as we have a weak nucleophile, it is necessary to have an organopalladium intermediate able to strongly coordinate to the unsaturated in order to trigger the intramolecular attack of the heteronucleophile to the alkyne. To our knowledge, this cyclization/cross-coupling reaction constitutes the only example of such a reaction performed under completely neutral conditions.

In summary, the procedures described here provide an efficient and practical route for the preparation of a variety of carbo- and heterocyclic compounds. The reactions proceed under mild reaction conditions and various functional groups are well tolerated.

All the reactions were carried out under a positive pressure of nitrogen and with oven-dried glassware. Petroleum ether (PE) refers to 40–60 °C boiling point fraction. All the reaction solvents were distilled prior to use: over Na/benzophenone for THF and over CaH2 for CH3CN and DMSO. All reagents, except commercial products of satisfactory quality, were purified via literature procedures prior to use. KH (35% in mineral oil) was washed with anhyd THF, dried and stored under nitrogen before use. Thin layer chromatography (TLC) was carried out with MERCK 60F254 silica gel plates (supported on aluminum); visualization was done by UV lamp (254 nm and 365 nm) and chemical staining (acidic solution of p-aniisaldehyde in EtOH). Preparative flash chromatography was carried out under medium pressure using Merck silica gel 60 Å (40–63 μm); volumetric composition of the eluent is indicated in parentheses.

IR spectra were recorded on a Perkin-Elmer FT-IR PARAGON 500 spectrometer. NMR spectra were recorded at r.t. on BRUKER AM 300, ALS 300, DRX 300 and BRUKER AC 200 apparatus. Internal references are tetramethylsilane (δ = 0.00 ppm) or residual protons of deuterated solvents (δ = 7.26 ppm for 1H NMR and δ = 77.16 ppm for 13C NMR for CDCl3). Letters s, d, t, q, quint, hept, m and br, respectively, refer to singlet, doublet, triplet, quadruplet, quintuplet, heptuplet, multiplet and broad. Low- and high-resolution mass spectra were recorded with a Thermoquest Finnigan MAT 95 XL apparatus operating at 70eV (for chemical ionizations, isobutane was used). Melting points were measured on a Büchi B-540 apparatus and are uncorrected. Elemental analyses were performed by the Service Central d’Analyses du CNRS, Solaize France.

(E)-1-Cyano-2-cyclohex-1-enyl-methylene-3-cyclohexancarboxylic Acid Methyl Ester (3); Typical Procedure
Few drops of n-BuLi (2.6 M in hexanes) were added to a stirred suspension of PdCl2(PPh3)2 (35 mg, 0.05 mmol) in THF (2 mL) until the solution turned dark red. The resulting solution was heated with a heat gun until the solution turned dark red.

In a separate flask, KH (48 mg, 1.2 mmol) and 18-crown-6 (53 mg, 0.2 mmol) were suspended in THF (6 mL). Enyne 1 (191 mg, 1 mmol) in THF (2 mL) was added dropwise followed by cyclohexenyl trflate 2 (345 mg, 1.5 mmol) and the resulting solution was stirred during 15 min. Then, palladium catalyst solution was added to the reaction mixture. The reaction conversion was monitored by TLC until the disappearance of the starting enyne 1. The crude product was directly filtered onto a pad of cellite, and concentrated under vacuum. The residue was purified by chromatography on silica gel (petroleum ether–Et2O, 70:30) to yield 3 as a yellow pale solid; yield: 208 mg (77%); mp 81–82 °C.


1H NMR (CDCl3): δ = 5.34 (m, 4 H), 1.81–2.17 (m, 7 H), 2.29 (t, J = 6.3 Hz, 2 H), 2.49 (ddd, J = 13.4, 6.8, 4.4 Hz, 1 H), 3.82 (s, 3 H), 4.88 (d, J = 2.2 Hz, 1 H), 5.10 (s, 1 H), 5.84 (br s, 1 H), 6.09 (s, 1 H).

13C NMR (CDCl3): δ = 22.0, 22.9, 23.6, 26.1, 28.2, 35.3, 35.5, 53.3, 53.5, 116.8, 118.4, 131.7, 133.0, 134.7, 142.6, 142.7, 167.6.

Anal. Calcld for C17H21NO2: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.50; H, 7.63; N, 5.18.

Scheme 4
Methyl (±)-3-Benzenesulfonyl-4-benzylidene-2-phenyltetrahydrofuran-3-carboxylate (7); Typical Procedure

*n*-BuLi (2.0 M in hexanes, 550 µL, 1.1 mmol) was slowly added to an ice cooled solution of propargyl alcohol (5) (75 µL, 1.1 mmol) in THF (2.5 mL) under N₂, and stirring was continued for 5 min, at which time the ice bath was removed. Methyl trans-n-benzenesulfonyl cinnamate (6) (234 mg, 1.0 mmol) was then added and the resulting enolate solution was stirred at r.t. for an additional 5 min. Meanwhile, in a separate flask, *n*-BuLi (2.0 M in hexanes, approx 50 µL, 0.1 mmol) was added dropwise to a well stirred suspension of PdCl₂(PPh₃)₂ (35 mg, 0.05 mmol) in DMSO (2.5 mL) under N₂ until a dark red homogeneous solution was obtained. Iodobenzene (225 mg, 1.1 mmol) was then added and the resulting palladium complex solution was subsequently transferred via cannula to the enolate solution. The reaction mixture was stirred at 50 °C for 1 h and then partitioned between EtOAc and aq NH₄Cl solution. The aqueous phase was extracted with EtOAc (3 ×), and the combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The residue was subjected to silica gel chromatography (EtOAc–petroleum ether, 1:4) to afford the tetrahydrofuran 7 (265 mg (61%) as a mixture of diastereomers (cis:trans = 15:85). A pure sample of the trans isomer was obtained for analysis; solid; mp 122–124 °C (EtOH).

**Trans**-isomer

1H NMR (300 MHz, CDCl₃); δ = 8.05 (d, J = 8.5 Hz, 2 H), 7.75–7.25 (m, 11 H), 7.12 (d, J = 8.5 Hz, 2 H), 6.83 (s, 1 H), 5.98 (s, 1 H), 4.23 (dd, J = 13.5, 2.6 Hz, 1 H), 4.00 (dd, J = 13.9, 2.6 Hz, 1 H), 3.94 (s, 3 H).

13C NMR (50 MHz, CDCl₃); δ = 160.2, 137.1, 136.3, 135.7, 134.4, 133.3, 131.8, 131.5, 128.9, 128.7, 128.6, 128.5, 128.4, 128.2, 127.1, 126.8, 121.8, 129.8, 129.4, 130.4, 131.3, 133.2, 134.2, 137.8, 138.1, 143.5, 154.7, 166.5, 174.9.


**Cis**-isomer

Deduced from mixture of isomers. 1H NMR (300 MHz, CDCl₃); δ = 7.97 (d, J = 8.5 Hz, 2 H), 7.75–7.25 (m, 11 H), 7.12 (d, J = 8.5 Hz, 2 H), 6.40 (s, 1 H), 6.05 (s, 1 H), 5.21 (dd, J = 13.9, 2.3 Hz, 1 H), 4.92 (dd, J = 13.9, 2.6 Hz, 1 H), 3.94 (s, 3 H).

4-[3-(4-Iodophenyl)-7-methyl-4-oxo-4,7-dihydrofuro[2,3-b]pyridin-2-yl]-benzoic Acid Methyl Ester (10)

*n*-BuLi (2.5 M in hexanes) was added dropwise to a suspension of PdCl₂(PPh₃)₂ (0.5 mg, 0.009 mmol) in THF (1 mL) until the mixture turned dark green. A heat gun was then used to gently heat the mixture and obtain a homogeneous dark red solution. MeCN (3 mL), the pyridone derivative 8 (0.19 mmol) and the aromatic halide 9 (0.27 mmol) were then successively added. The reaction mixture was left to stir for 48 h at 60 °C and concentrated in vacuo. The residue was purified by chromatography on silica gel (acetone) to yield 10 as a yellow solid; yield: 85 mg (93%); mp 272 °C (decomp.).

1H NMR (300 MHz, DMSO-<d>δ</d>); δ = 3.85 (s, 3 H), 3.86 (s, 3 H), 6.01 (d, J = 7.5 Hz, 1 H), 7.25 (d, J = 8.3 Hz, 2 H), 7.55 (d, J = 8.3 Hz, 2 H), 7.62 (d, J = 7.5 Hz, 1 H), 7.77 (d, J = 8.3 Hz, 2 H), 7.92 (d, J = 8.3 Hz, 2 H).

13C NMR (75 MHz, DMSO-<d>δ</d>); δ = 37.2, 53.0, 95.2, 112.0, 115.4, 121.8, 126.8, 129.8, 130.4, 131.3, 133.2, 134.2, 137.8, 138.1, 143.5, 154.7, 166.5, 174.9.

HRMS (CI): m/z [MH⁺] calcd for C₂₂H₁₇INO₄+: 486.0203; found: 486.0202.

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