Sequential Addition/Cyclization Processes of α,β-Ynones and α,β-Ynoates Containing Proximate Nucleophiles.

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Abstract: Sequential processes involving α,β-ynones and α,β-ynoates containing proximate nucleophiles as useful building blocks for the synthesis of heterocyclic derivatives through conjugate-addition type, pericyclic and transition metal-catalyzed transfer hydrogenation/hydroarylation/hydrovinylation/hydroalkynilation reactions followed by heterocyclization are reviewed.

Key words: aminoalkynones; hydroxyalkynoates; sequential reactions; annulation; heterocycles.

1 Introduction

α,β-Ynones/ynoates are prominently employed as valuable building blocks in organic synthesis.[1] A variety of intra- [1a, 2] and inter-molecular[3] reactions have been performed taking advantage of their electronic properties. Transition metal catalyzed processes have been described.[4] α,β-Ynones/ynoates have found wide application as versatile three-carbon building-blocks for the development of new approaches to diversity-oriented syntheses of heterocycles through 1,3-dipolar cycloaddition reactions.[5] Their reaction with bifunctional nucleophiles represented a general strategy to the construction of five-, six-, and seven-membered rings by sequential[6] and consecutive[7] transformations. Catalytic generation of α,β-ynones compatible with following transformations allowing new approaches to the synthesis of heterocycles through multi-component coupling/cycloaddition sequences have been developed.[8] Sequential addition to preformed or *in situ* generated α,β-ynones/ynoates of nucleophiles or heteronucleophiles/cyclocondensation reactions have, also, shown considerable synthetic applications. [9]

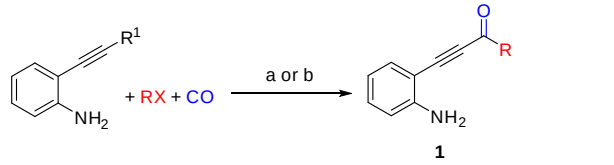
Based on the importance of α,β-ynones/ynoates for their crucial role as key intermediates in organic synthesis and for their key role as interesting structural motif found in numerous biologically active molecules, we have been involved in the development of efficient approaches to their formation[10] and conversion into several heterocyclic derivatives.[11]

This account summarizes investigations on sequential heterocyclization processes involving conjugate addition-type, cycloaddition and transition metal catalyzed transfer hydrogenation/hyroarylation/hydrovinylation/hydroalkynilation reactions over α,β-ynones and α,β-ynoates containing proximate nucleophiles.

2. **Conjugate addition/heterocyclization processes of α,β-ynones and α,β-ynoates containing proximate nucleophiles.**

2.1 *Conjugate Addition/Annulation Reactions of β-(2-Aminoaryl/heteroaryl)-α,β-Ynones.*

Palladium-catalyzed carbonylative Sonogashira reaction represents an efficient methodology for the synthesis of conjugate ynones and the good functional groups compatibility of the procedure has been demonstrated.[12] Interestingly, the carbonylative coupling of *o*-trimethylsilylethynylaniline with aryl iodides and the carbonylative coupling of 2-ethynylanyline with vinyl triflates accomplished an easy entry into β-(2-aminophenyl)-α,β-ynones **1** (Scheme 1).[13]

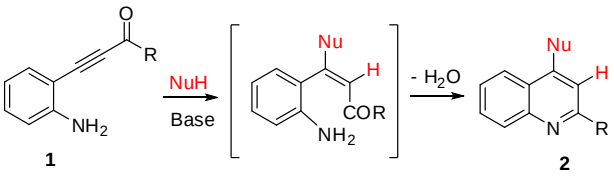


a: (R^1 = $SiMe_3$, R-X = ArI): $PdCl_2$, phosphine ligand; Et_3N, *n*-Bu_4F, THF, rt

b: (R^1 = H, R-X = vinyl triflates): $Pd(OAc)_2$, dppp, Et_3N, DMF, 60 °C

Scheme 1

Work by our group has shown that the ynones **1**, in the presence of suitable nucleophiles, efficiently led to 2,4-disubstituted quinolines **2** through a conjugate addition/cyclization tandem reaction (Scheme 2).[14]



Scheme 2

The reactions were generally carried out at 60-80 °C and accomplished the isolation of 4-heterosubstituted 2-aryl/vinylquinolines derivatives in good to high yields as the sole reaction products (Figure1).

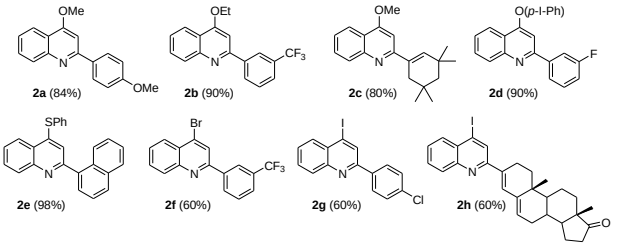
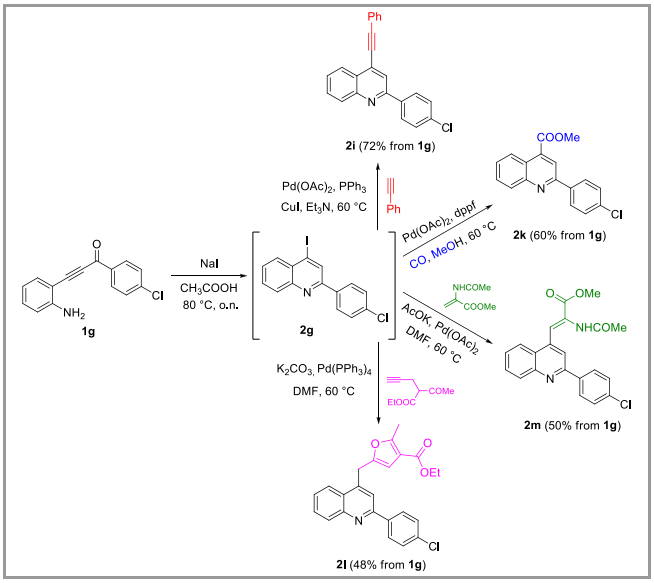


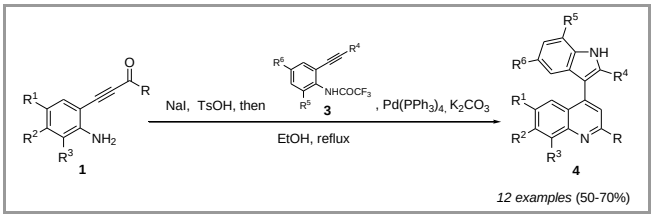
Figure 1

Notably, the reaction of **1g** with sodium iodide in acetic acid allowed the successful synthesis of 2-(4'-chlorophenyl)-4-iodoquinoline **2g** which was further elaborated by means of palladium-catalyzed coupling reactions in a two-step, one pot procedure (Scheme 3).



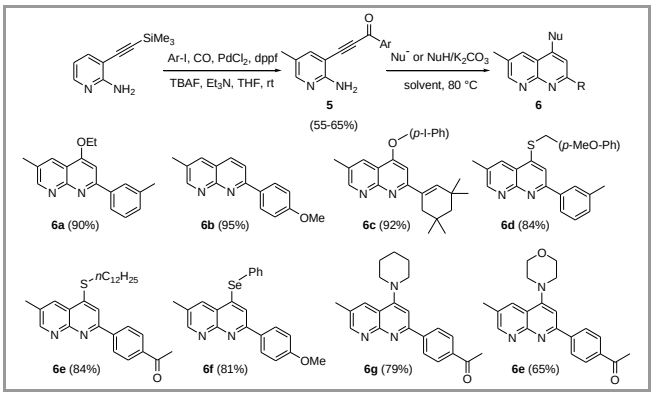
Scheme 3

Following a similar strategy, a concise one-pot approach to the synthesis of 4-(1*H*-indol-3-yl)quinolines **4** was achieved without any intermediate work-up and using ethanol as solvent. The one-flask and operationally simple procedure involved conjugate addition of sodium iodide to β-(2-aminophenyl)-α,β-ynones /cyclization/Pd-catalyzed reaction with 2-alkynyltrifluoroacetanilides **3** (Scheme 4).[15]



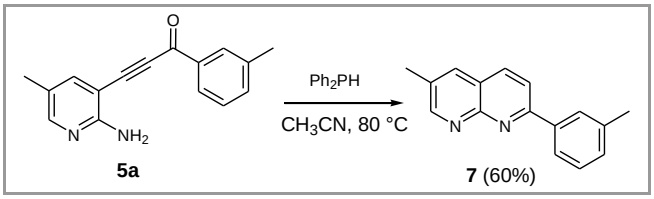
Scheme 4

A variety of [1,8]naphthyridines **6** were regioselectively obtained in high yield by reacting the readily available 3-(2-amino-5-methylpyridin-3-yl)-1-arylprop-2-yn-1-ones **5** at 80 °C in acetonitrile or alcoholic solvents in the presence of a slight excess of nitrogen-, oxygen-, sulfur- and selenium- nucleophile or pronucleophile. The presence of both electron-withdrawing and electron-donating groups in the 2-aryl moiety were tolerated. In the case of amines the solvent was omitted (Scheme 5).[16]



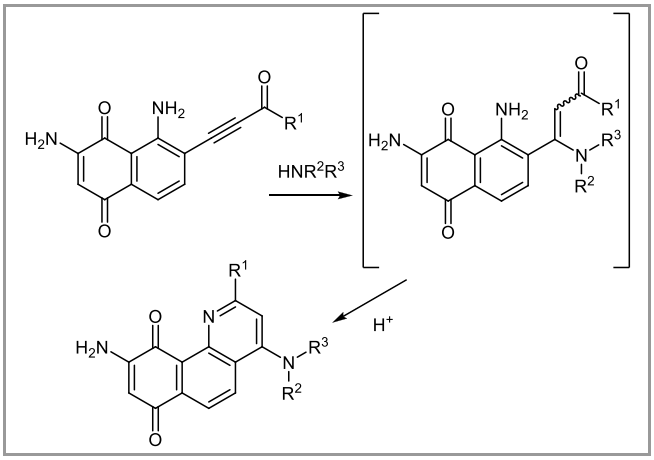
Scheme 5

Surprisingly, the reaction of ynone **5a** with the phosphorus nucleophile Ph_2PH afforded the 4-unsubstituted [1,8]naphthyridine **7** through an unusual sequential reductive cycloamination (Scheme 6).



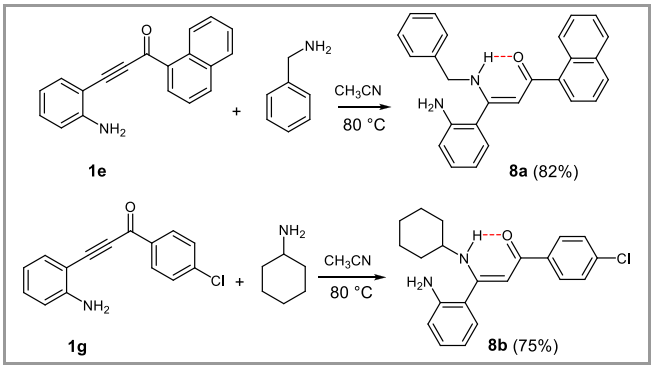
Scheme 6

2- Aryl/alkyl-4,9-bis(dialkylamino)benzo[*h*]quinoline-7,10-diones were prepared through the addition of secondary amine to 6-acylethynyl-5-amino-3-diethylamino-1,4-naphthoquinone followed by cyclization of the resulting adduct (Scheme 7).[17]



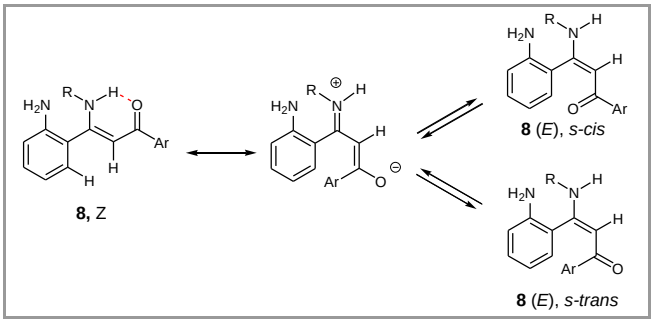
Scheme 7

The reaction of β-(2-aminoaryl/heteroaryl)-α,β-ynone derivatives with nitrogen nucleophiles deserved a deeper investigation. Indeed three major types of products have been observed depending on the reaction conditions and on the nitrogen nucleophiles employed.[18] The reaction of α,β-ynone **1e** with benzylamine in boiling acetonitrile gave the *Z*-3-(2-aminophenyl)-3-benzylamino-1-naphtalen-1-yl-propenone **8a** as the main reaction product. Analogously the α,β-ynone **1g** reacted under the same reaction conditions with cyclohexylamine to lead to the *Z*-3-(2-amino-phenyl)-1-(4-chloro-phenyl)-3-cyclohexylamino-propenone **8b** in 75% yield (Scheme 8).



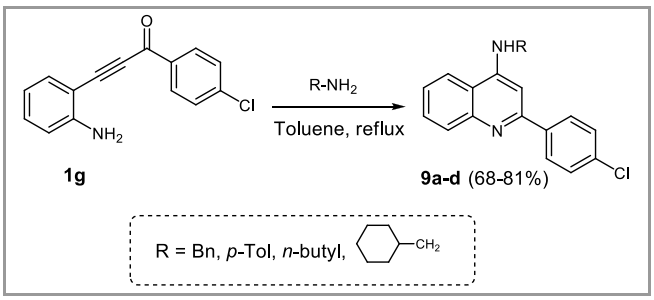
Scheme 8

Monodimensional, bidimensional, and dynamic NMR spectra analysis showed that β-amino-α,β-unsaturated ketones **8** are typical push-pull ethylenes, which can exist in different configurational and conformational isomeric forms (Scheme 9).



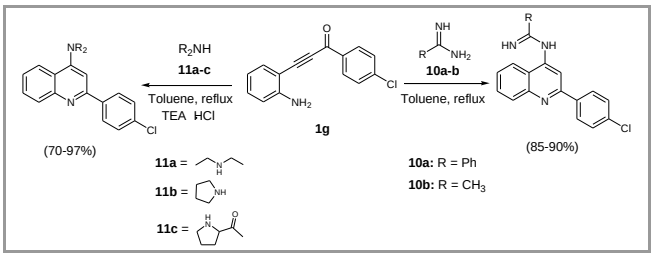
Scheme 9

Moreover, Z→E isomerization of derivatives **8** was experimentally observed by dynamic ^1H NMR experiments performed in DMSO-d_6 at 90°C. As a consequence, the expected 4-amino-quinolines **9a-d** were isolated by carrying out the reaction of ynone **1g** with primary amines in toluene at reflux (Scheme 10).



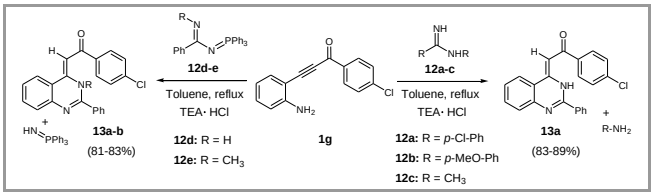
Scheme 10

These typical reaction conditions were ineffective in the presence of primary amines bearing an electron withdrawing group in α-position, such as aminoacetonitrile and methyl esters of glycine, phenyl glycine or valine. The reaction of ynone **1g** with secondary amines **11a-c** under fairly acidic catalysis and with *N,N*-unsubstituted amidines **10a-b** afforded the corresponding quinolines in excellent yields (Scheme 11).



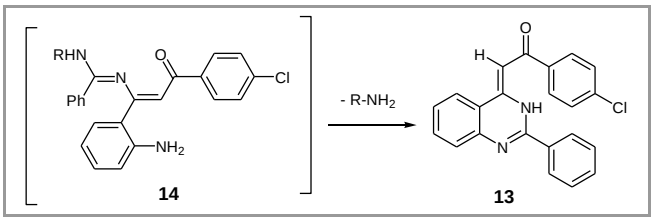
Scheme 11

Conversely, the divergent sequential reaction of **1g** with N-alkyl or N-aryl substituted benzamidines **12a-c**, *N*-imidoylimino-triphenylphosphorane **12d** and *N*-methylimidoylimino-triphenylphosphorane **12e** in the presence of triethylamine hydrochloride achieved the isolation of the vinylidenequinazolines **13a** and **13b** (Scheme 12).



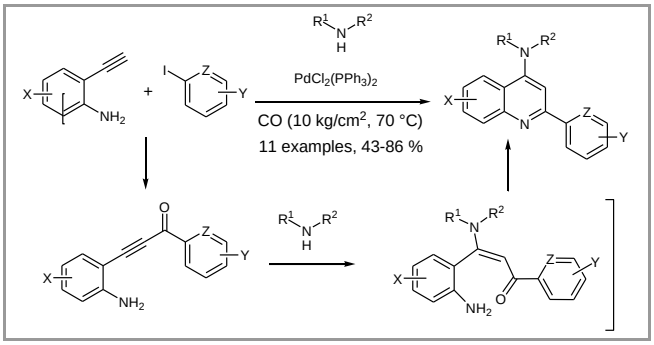
Scheme 12

The formation of the vinylidenequinazolines **13** has been suggested to be the result of the stereoselective *trans*-addition of the amidine moiety over the conjugate triple bond followed by a transamination reaction between the amino group and the amidine function of the intermediate **14** (Scheme 13).



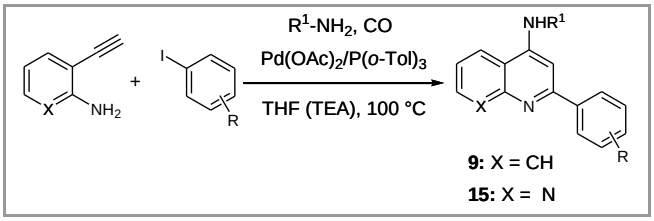
Scheme 13

Torii and co-workers reported a palladium-catalyzed multicomponent domino reaction giving rise to 2-aryl-4-dialkylaminoquinolines in moderate to good yields through tandem conjugate addition/cyclization reactions of the *in situ* generated β-(2-aminoaryl/heteroaryl)-α,β-ynones with amines (Scheme 14).[19] The reaction was performed with 2-ethynylarylamines, aryl iodides, and dialkylamines or dialkylamines/triethylamine, at 70 °C under a carbon monoxide atmosphere (18 bar) in the presence of 5 mol % $PdCl_2(PPh_3)_2$.



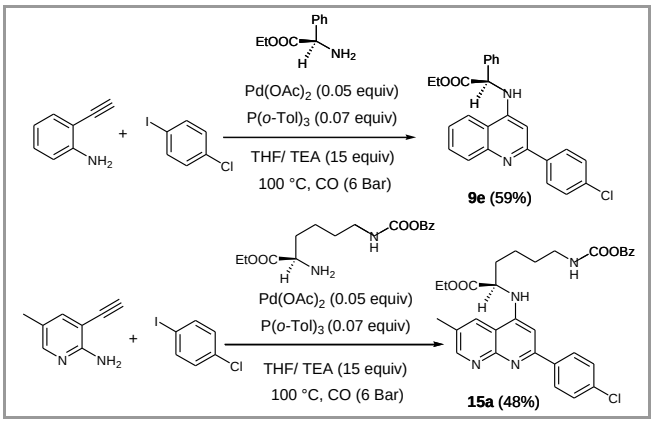
Scheme 14

The Torii's procedure resulted effective only with secondary amines. In the presence of primary amines, a palladium-catalyzed carbonylative amidation reaction, instead of a carbonylative cross-coupling reaction, occurred. Considering that many factors are responsible of the outcome of the reaction of terminal alkynes with aryl iodides under carbonylative conditions,[20] further exploration has been done in this field. Indeed, the carbonylative palladium-catalyzed coupling of 2-ethynylaniline derivatives with aryl iodides, in the presence also of primary amino groups resulted in an efficient multicomponent domino approach to the preparation of the desired quinolines **9** and 2-aryl-4-amino[1,8]naphthyridines **15** through the appropriate choice of catalyst, ligand, solvent, and reaction temperature (Scheme 15).[21]



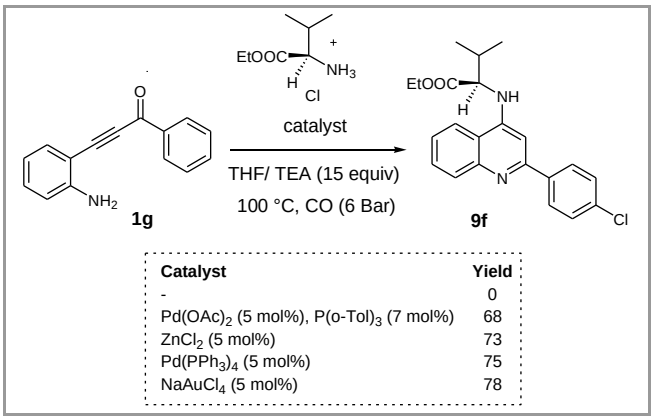
Scheme 15

Notably, this latter domino reaction allowed the extension of the procedure to the use of primary amines bearing an electron-withdrawing group in the α-position (Scheme 16).



Scheme 16

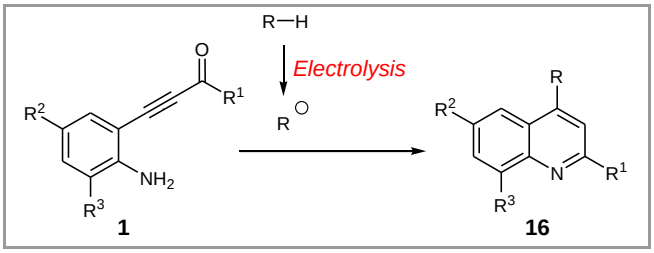
The palladium/phosphine system could play a relevant catalytic role in the intermolecular nucleophilic attack of the amine over the ynone. Indeed, the formation of **9e** was considered the result of the sequential palladium-catalyzed carbonylative coupling followed by the palladium catalyzed aza-Michael addition of phenylalanine ethyl ester to ynone **1g**. The first part of the overall reaction requires palladium(0) as catalyst, while the second one needs palladium(II).[22] Accordingly, by heating the β-(2-aminophenyl)-α,β-ynone **1g** and valine ethyl ester in dioxane at 100 °C with 15 equiv of triethylamine without or in the presence of the standard catalytic system ($Pd(OAc)_2$/TTP), quinoline **9f** was isolated in 68% yield only in the catalyzed reaction (Scheme 17). The experiments performed in the presence either of Pd(0) derivatives or Zinc(II) and Au(III) derivatives demonstrate that the sequential aza-Michael/cyclization reaction of primary amines bearing an electron-withdrawing group in the α-position occurs in the presence of all of these catalysts. Several transition metal salts have been reported to efficiently catalyze aza-Michael reaction of enones by acting as powerful Lewis acids.[23] Au(I)-catalyzed highly efficient intermolecular hydroamination reactions have also been described.[24] So, palladium acting simultaneously both as transition metal catalyst in the Pd(0) oxidation state and as Lewis acid catalyst in the Pd(II) oxidation state could be supposed to achieve the formation the quinoline derivative in the multicomponent process.[25]



Catalyst	Yield
-	0
$Pd(OAc)_2$ (5 mol%), $P(o\text{-}Tol)_3$ (7 mol%)	68
$ZnCl_2$ (5 mol%)	73
$Pd(PPh_3)_4$ (5 mol%)	75
$NaAuCl_4$ (5 mol%)	78

Scheme 17

The tandem addition/annulation reaction of carbonucleophiles with β-(2-aminophenyl)-α,β-ynones was also investigated.[26] A sequential alkylation/heterocyclization of β-(2-aminophenyl)-α,β-ynones **1** promoted by electro-generated carbanions was reported to give a clean and efficient entry to functionalized 4-alkylquinolines (Scheme 18).



Scheme 18

The exploitation of electrochemistry as a tool to generate carbanions which can lead to the target heterocycles **16** appeared very attractive for the development of a more environmentally friendly synthetic protocol.[27] The direct electrolysis of pure nitroalkane was carried out at room temperature under an inert atmosphere and galvanostatic control in a divided cell equipped with Pt electrodes. Then, after addition of a β-(2-aminophenyl)-α,β-ynone **1** to the cathode compartment at the end of the electrolysis, the formation of the corresponding 4-alkylquinolines **16** was observed. Cathodic (pure nitroalkane) and anodic (DMF 0.1 M tetraethylammonium tetrafluoroborate, TEATFB) compartments were separated by a G3-glass diaphragm filled with an agar gel (methyl cellulose in DMF 0.1 M TEAP solution). Moderate gas production was observed, at the cathodic compartment, during the electrolysis. The quinoline derivatives **16** were isolated in best yield when the amount of the electricity supplied during the electrolyses (Q) was 1.2 F mol^{-1}. Interestingly, the reaction works well even with the sterically hindered nitroalkanes (figure 2).

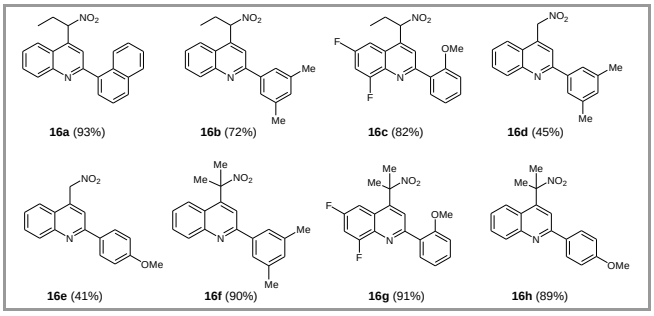
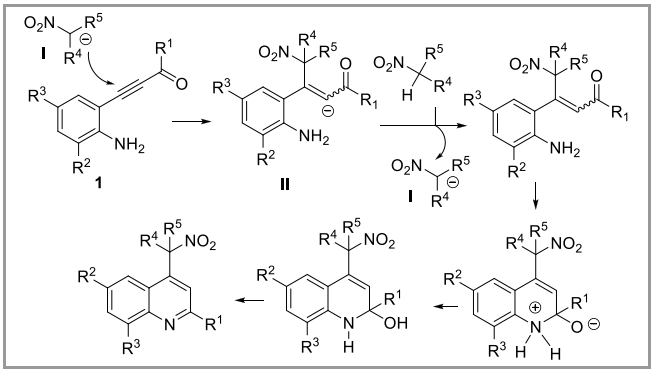


Figure 2

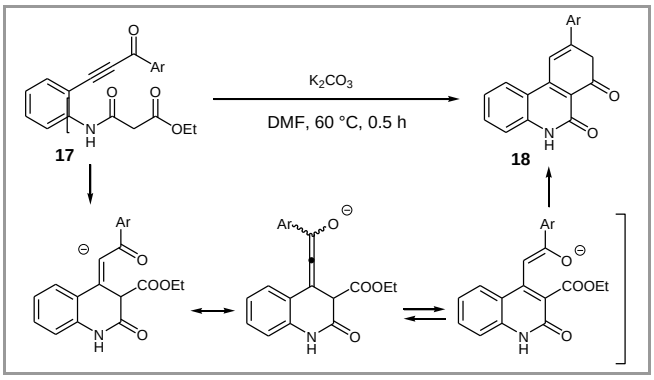
As illustrated in scheme 19, the deprotonation of the starting nitroalkane under solvent free conditions gives anion **I** that adds to the carbon-carbon triple bond to generate a new anion **II**. Then, the reaction of the starting nitroalkane with the anion **II** affords the Michael adduct regenerating **I**. The relative basicity of anions **I** and **II** resulted of pivotal importance for the reaction outcome. The more acidic nitroalkanes (pKa = 8,5 and 7.7 respectively) favoured the fast protonation of **II** leading to the corresponding quinolines in high yields (72-93%). By contrast, the least acidic nitromethane (pKa = 10.2) allowed the formation of the quinolines **16d-e** only in moderate yields (41-45%). Very likely when the anion **II** is not basic enough, the increase of its concentration could determine the formation of side products.



Scheme 19

The solvent- and supporting electrolyte-free electrolysis protocol proved to be effective also for the direct electro-activation of methanol. Conversely, the electrochemically-promoted Michael reaction of active methylene compounds to β-(2-aminophenyl)-α,β-ynones **1** was accomplished in a solution of DMF containing TEATFB 0.1 M as supporting electrolyte.

Interestingly, a K_2CO_3 promoted intramolecular Michael addition/ tautomerisation/ transesterification cascade reaction accomplished the synthesis of the quinolone **18** from β-(2-malonylamidophenyl)-α,β-ynone **17** (Scheme 20).[14]

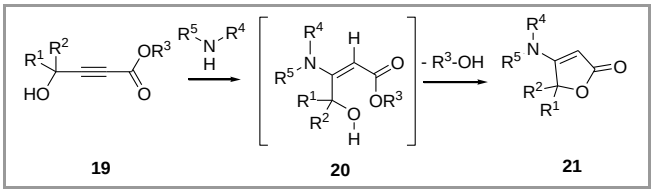


Scheme 20

2.2 *Sequential Reactions of γ-Hydroxy-α,β-Acetylenic Esters with Nucleophilic Reagents.*

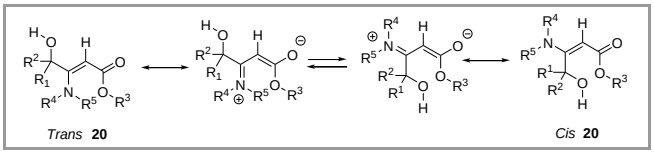
γ-Hydroxy-α,β-acetylenic esters contain three adjacent functional groups displaying different reactivity, namely the alkoxycarbonyl group, the acetylenic unit and the alcoholic moiety. All of them are able to undergo different type of transformations.[28] A variety of approaches to functionalized α,β-unsaturated γ-lactones (Δ^2butenolides, furan-2(5*H*)-ones) starting from γ-hydroxy-α,β-acetylenic esters **19** and a wide range of nucleophiles have been exploited.[29] A series of natural compounds (alkaloids, steroids, tetronic and ascorbic acids, pheromones, and fragrances) contain the Δ^2butenolide fragment[30] and several derivatives are known to act on enzymes and possess bactericidal, fungicidal, or antibacterial properties.[31] 4-Substituted furan-2(5*H*)-ones have been found to be potent antibiotics and have shown cytotoxicity against human colon carcinoma and human melanoma. [32]

First studies performed with esters **19** involved the reactivity toward primary and secondary amines. A conjugate addition/cyclization domino reaction leading to the 4-aminosubstituted-furan-2(5*H*)-ones **21** was prevalent. Under the reaction conditions, the initially formed linear Michael adducts **20** undergo cyclization to give the corresponding furan-2(5*H*)-one derivatives **21** (Scheme 21). Exothermic reactions occurred when the derivatives **19** were treated with secondary aliphatic amines at room temperature; aniline was less reactive and in this case heating to 100 °C was necessary to initiate reaction .[29]



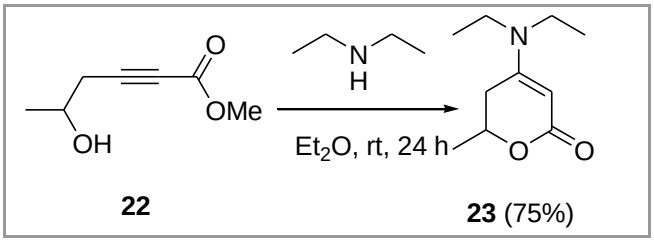
Scheme 21

No products other than 4-amino-lactones were isolated from these addition reaction. This fact appears to support the hypothesis that the initial reaction of primary and secondary amines is a *cis* addition to the activated acetylenic bond, followed by lactone formation through elimination of alcohol from the activated molecule. However, *cis* and *trans* adducts could be in equilibrium through a zwitterionic common resonance structure and the stabilization of the *cis*-adduct by lactonization could be the driving force shifting the reaction toward the formation of **21** as the sole reaction product (Scheme 22).



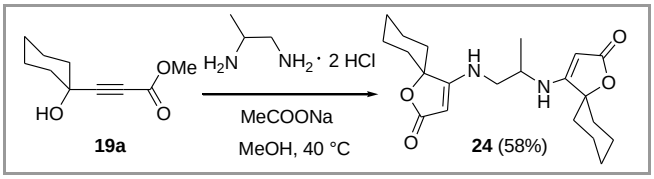
Scheme 22

Analogously, the reaction of the methyl 5-hydroxyhex-2-ynoate **22** with diethylamine efficiently afforded the 4-(diethylamino)-5,6-dihydro-6-methylpyran-2-one **23,** which is formally related to the naturally occurring δ-$\Delta^{\alpha,\beta}$-hexenolactone (Scheme 23).



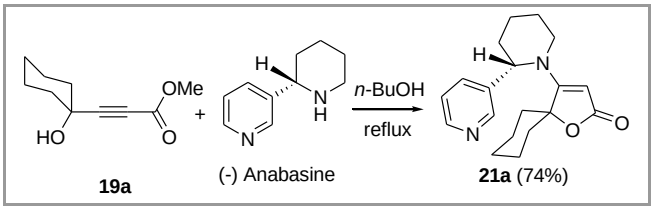
Scheme 23

The procedure was applied to the synthesis of a series of furan-2(5*H*)-one derivatives containing pharmacophoric substituents at the amine moiety.[33] Thus, methyl (1-hydroxycyclohexyl)propiolate **19a** was reacted with various amines in dry diethyl ether or in a 2:1 diethyl ether-methanol mixture at 20-60 °C to give desired amino derivatives **21** in high yields. The reactions with salts of amines were performed in methanol at reflux for 15-20 h in the presence of sodium acetate. Under the above mentioned conditions, both amino groups in 1,2-diaminopropane were involved in the reaction leading to bislactone **24** (Scheme 24).



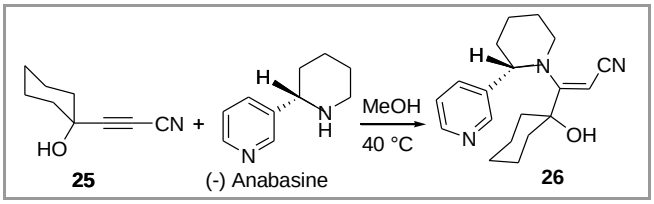
Scheme 24

As expected, the structure of the starting amine, the number of substituents, and their size played a key role on the reaction rate. Benzylic amines were most reactive. Thus, their reactions proceeded readily in diethyl ether at room temperature. Arylhydrazines (*o*-nitro and *o*-methoxyphenylhydrazines) were not involved in the reaction at room temperature, whereas refluxing of these compounds in methanol afforded complex mixtures of products. *N*-nucleophiles, which are components of heterocycles, such as piperidine, piperazine, and some other derivatives, reacted under more drastic conditions. For example, refluxing of (-) anabasine in butanol selectively afforded (in 74% yield) Δ^2-butenolide **21a** containing a chiral center in the α position with the respect to the nitrogen atom (Scheme 25).



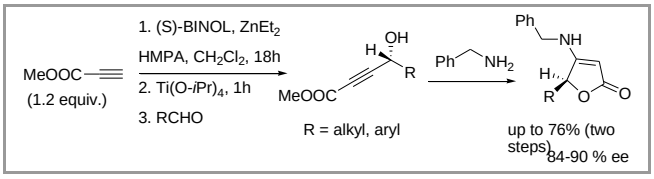
Scheme 25

It should be noted that the analogous reaction of anabasine with 3-(1-hydroxycyclohexyl)propiolonitrile **25** (EtOH, 40 °C) gave only the linear adduct **26** (Scheme 26).



Scheme 26

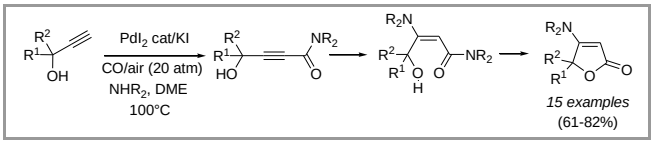
Significantly, optically active 4-amino-2(5*H*)-furanones were efficiently synthesized by combining an asymmetric alkyne addition to aldehydes with a subsequent aliphatic amine addition. Both steps were conducted at room temperature and the products were obtained with high enantioselectivity (84-90% ee) (Scheme 27).[34]



Scheme 27

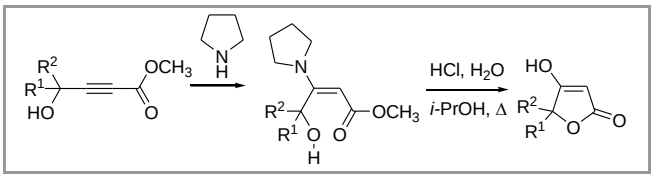
A useful direct, one-pot preparation of 4-dialkylamino-5*H*-furan-2-ones was also achieved starting from 2-yn-1-ols. The formation of the target 4-dialkylamino-5*H*-furan-2-ones occurred through an ordered sequence of steps, namely (a) Pd-catalyzed oxidative mono aminocarbonylation of the starting 2-yn-1-ol to give an

intermediate 4-hydroxy-2-ynamide which can be isolated under appropriate conditions; (b) stereoselective conjugate addition of dialkylamine to the triple bond of 4-hydroxy-2-ynamide with formation of (*E*)-3-dialkylamino-4-hydroxy-2-enamide (not isolated) ; (c) intramolecular alcoholysis of the amide function of the latter to give the final product (Scheme 28).[35]



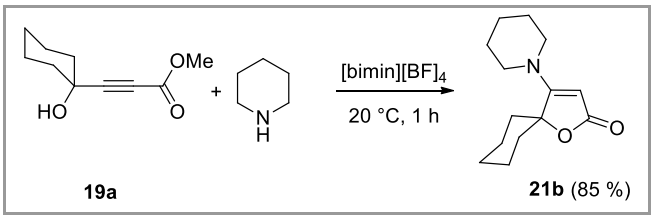
Scheme 28

β-Hydroxybutenolides (tetronics acids) can be easily prepared in good yields by a protocol involving two consecutive chemical events: a Michael addition of pyrrolidine on secondary or tertiary γ-hydroxy-α,β-acetylenic esters to give the corresponding enamine, and the subsequent acid-catalyzed hydrolysis-lactonization of this intermediate. Tetronics acids are object of numerous studies owing to their wide array of biological properties (Scheme 29).[36]



Scheme 29

The domino reaction between γ-hydroxy-α,β-acetylenic esters **19** and amines was significantly accelerated in recyclable ionic liquids (ILs).[37] Commercial 1-butyl-3-methylimidazolium tetrafluoroborate [bmim][BF_4] and hexafluorophosphate [bmim][PF_6], 1-hexyl-3-methylimidazolium tris(pentafluoroethyl) trifluorophosphate [hmim][$PF_3(C_2F_5)_3$], 1-butyl-3-methylpyrrolidinium triflate [bmpl][OTf] and bis(triflyl)amide [bmpl][NTf_2] were used as ILs. The results of the reaction between the alkyne **19a** and piperidine in ILs compared with those attained earlier in Et_2O and under neat conditions showed that in all cases the 4-(piperin-1-yl)-1-oxaspiro[4,5]dec-3-en-2-one **21b** was formed much faster, at lower temperature and in improved yield in ILs than in Et_2O or under solvent-free conditions. As a rule, better results in terms of both the product yield and the reaction rate were observed with the less expensive IL [bmim][BF_4] (Scheme 30). Moreover, ionic liquids were recovered and reused at least five times without any decrease in reaction rates and product yields.



Scheme 30

Positive IL impact was attributed to ion-dipole interactions in the IL medium, which facilitate the charge separation in compounds **19** and **20** and promote the reactions (figure 3).

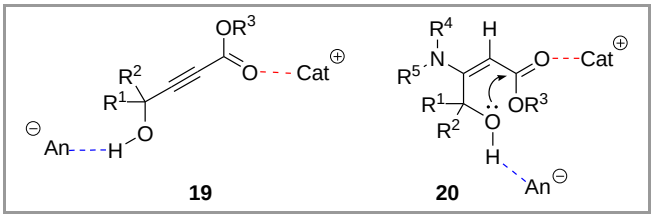
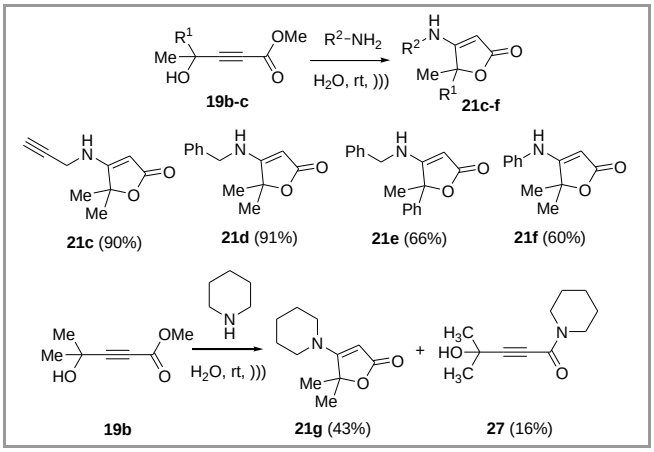


Figure 3

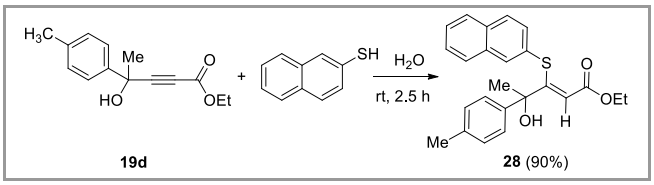
Another alternative procedure entailed with the use of water and ultrasound irradiation instead of ILs.[38] Very likely, the sequential lactonization reaction observed under these latter reaction conditions is a consequence of the role played by water as a Brønsted acid catalyst both in Michael addition and in the transesterification step. The application of ultrasound irradiation significantly increased the reaction rate and yield compared to the traditional stirring. In order to show the general applicability of the method, structurally diverse amines were used. While with primary amines the corresponding 4-amino-2(5*H*)-furanones **21** were isolated as the main reaction products, with a the secondary aliphatic amine, such as piperidine, lack of selectivity was observed due the competitive formation of the amide derivatives **27** (Scheme 31).



Scheme 31

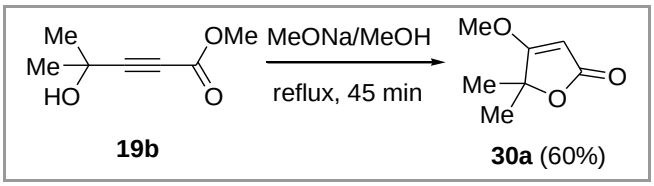
Inverse stereoselectivity was observed with thiols. When 2-napthylthiol was added to a vessel flask containing γ-hydroxy-4-*p*-tolyl-but-2-ynoic acid ethyl ester **19d** in 3 mL of water, immersed in a water bath

(r.t.) and sonicated till completion of the reaction, only the formation, in 90% yield, of the (*Z*)-ethyl 4-hydroxy-3-(naphthalen-2-ylthio)-4-(*p*-tolyl)pent-2-enoate **28** was observed (Scheme 32). Conversely, it was reported that the nucleophilic addition reactions of sulphur nucleophile to β-(2-amino-5-methylpyridin-3-yl)-α,β-ynones proceeded with high *E* stereoselectivity and this stereochemical outcome accomplished the subsequent cyclization reaction. [16]



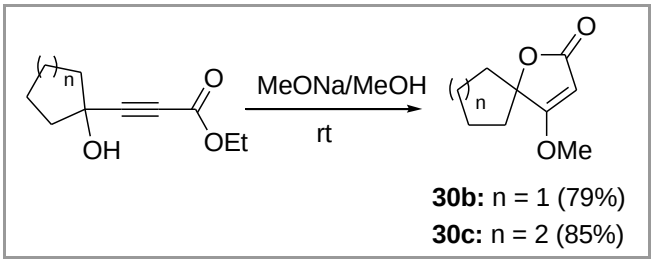
Scheme 32

The conjugate addition/cyclization domino reaction of γ-hydroxy-α,β-acetylenic esters with alcohols/water was, also, extensively investigated. The ester **19b** reacted vigorously with methanol containing sodium methoxide (30-50 mol%) to give the corresponding lactone **30a** (Scheme 33).[29]



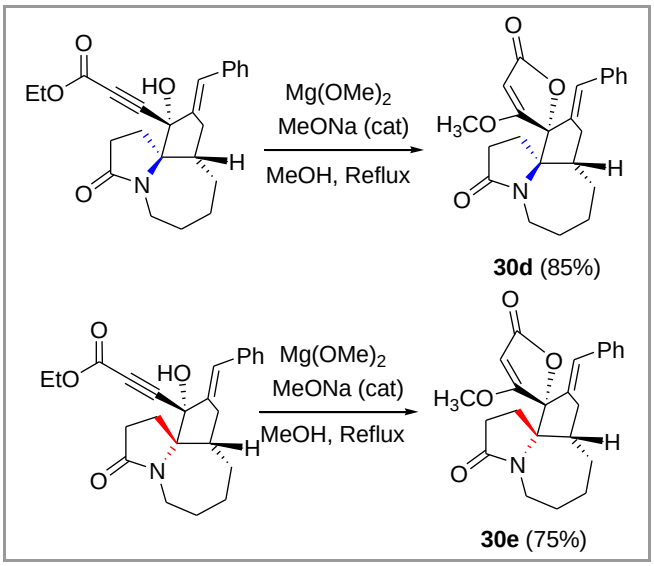
Scheme 33

The method was successfully applied to the synthesis of biologically active 4-spiro-2-hydrotetronic acids **30b-c** (Scheme 34).[39]



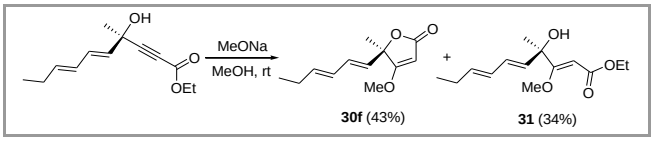
Scheme 34

Analogously, the total synthesis of stenoma alkaloids containing in their structures contiguous spirocyclic quaternary centers was achieved by treatment of suitable spiro γ-hydroxy-α,β-acetylenic ester derivatives with magnesium methoxide in boiling MeOH. The corresponding methyl tetronates **30d-e** were isolated in 85% and 75% yields, respectively (Scheme 35).[40] The formation of compounds **30d-e** occurred in a stereocontrolled fashion through the intermediary of corresponding (*E*)-3-methoxyacrylate derivatives.



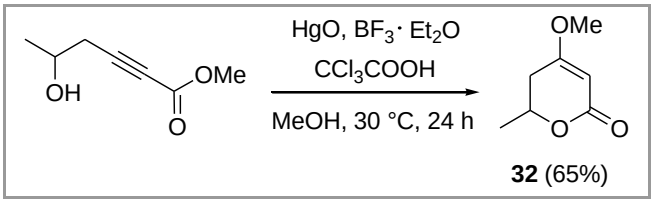
Scheme 35

Lack of stereospecificity was observed in the preparation of lactone **30f**, a key step in the synthesis of the aspertetronin group of natural products (Scheme 36).[41]



Scheme 36

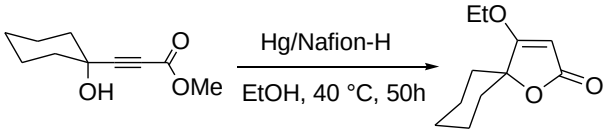
Efficient catalytic systems for the synthesis of alkoxylated lactones from γ- and δ-hydroxy-α,β-acetylenic esters have been developed too. The mercuric oxide-boron trifluoride catalyzed addition of alcohols to acetylenic bonds, not necessarily conjugated to carbonyl or similar groups, has been reported.[42] It was successfully applied to the preparation of β-methoxy-α,β-ethylenic-γ-lactones in good yields.[43] The boron trifluoride-mercuric oxide catalyst was also examined for the domino alkoxylation/lactonization reaction of δ-hydroxy-ester derivatives. The β-methoxy-δ-$\Delta^{\alpha,\beta}$-hexenolactone **32** was obtained in 65% yield under the mercuric oxide-boron trifluoride catalysis, but the formation of **32** failed to occur by using methanolic sodium methoxide (Scheme 37). [29]



Scheme 37

Polymer reagent Hg/Nafion-H resulted effective for the synthesis in good yield of the 4-ethoxy-1-oxaspiro[4,5]dec-3-en-2-one **30g** from methyl (1-

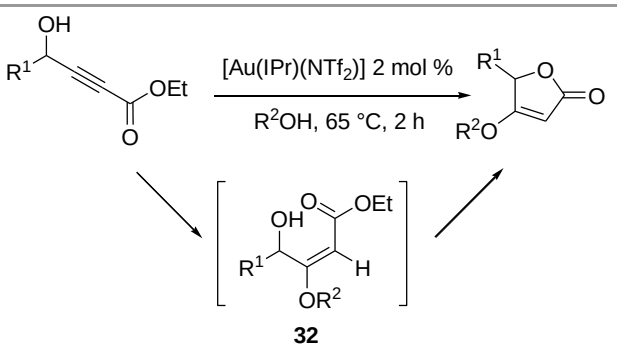
hydroxycyclohexyl)propiolate **19a** dissolved in ethanol (Scheme 38). [44]



19a **30g** (85%)

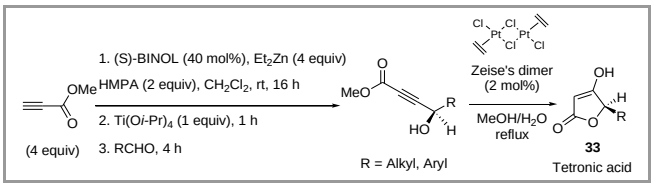
Scheme 38

Teles and co-workers reported, in a seminal work, the highly efficient gold-catalyzed alkoxylation of alkynes.[45] Then, the potential of gold catalysis for the synthesis of 4-alkoxy-2(5*H*)-furanones was examined (Scheme 39).[46] The gold-catalyzed tandem alkoxylation/lactonization of γ-hydroxy-α,β-acetylenic esters was achieved by using 2 mol% of [2,6-bis(diisopropylphenyl)imidazol-2-ylidene]gold bis(trifluoromethanesulfonyl)imidate [Au(IPr)(NTf$_2$)] catalyst. The procedure was applied to a series of various secondary propargylic alcohol derivatives allowing for yields of the desired products of up to 95%. In addition, tertiary propargylic alcohols bearing mostly cyclic substituents were converted into the corresponding spiro derivatives. Both primary and secondary alcohols reacted with the γ-hydroxy-α,β-acetylenic esters at moderate temperatures (65-80 °C) in either neat reactions or using 1,2-dichloroethane as a reaction medium allowing for yields of 23-95% of the desired products. Analysis of the intermediate **32** proved the exclusive formation of the (*E*) isomer which allows for the subsequent lactonization. As a consequence of NOE experiments, the initially envisioned isomerization of (possibly formed) *Z*-isomers does not need to be invoked. This would represent a rare example of *syn*-addition in gold catalysis, which is however strongly related to the unique substrate properties.[47]



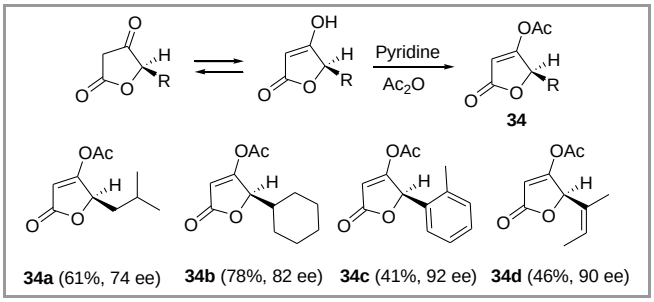
Scheme 39

Readily available optically active γ-hydroxy-α,β-acetylenic esters underwent regiospecific hydration in the presence of Zeise's dimer, [PtCl$_2$(C$_2$H$_4$)]$_2$, to afford the corresponding optically active tetronic acids **33** (Scheme 40).[48]



Scheme 40

In the catalytic hydration, 2 mol% of the Zeise dimer was used. The resulting product **33** was then treated with acetic anhydride and pyridine, which quantitatively converted both the enol and keto tautomers of **33** to the acetate **34** (Scheme 41). The enantiomeric purities of the tetronic acid products were very similar to those of the starting aliphatic γ–hydroxy-α,β-acetylenic esters.



Scheme 41

The electron-withdrawing effect of the ester group, the Lewis acidity of the Pt(II) center, and the chelating effect in the coordination of the acetylenic ester to the Pt(II) center might contribute to the observed regiospecific hydration (Fig. 4).

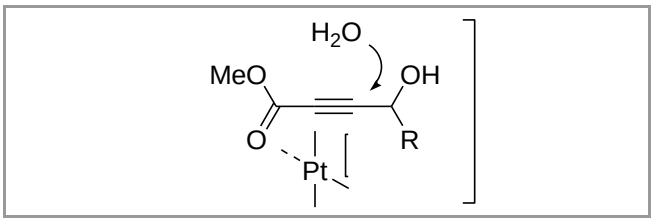
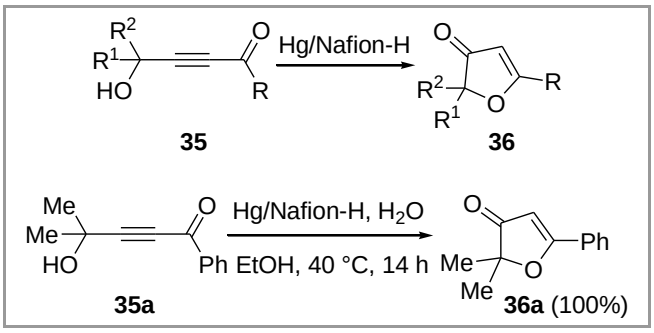


Figure 4

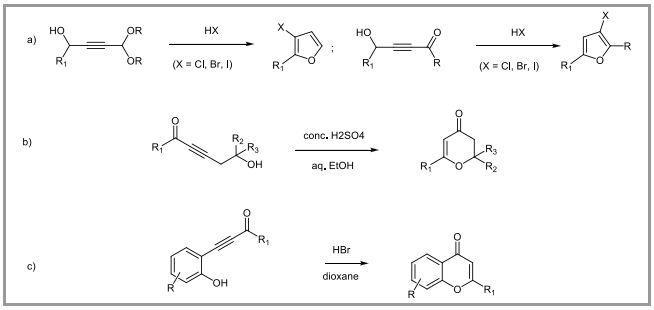
The conjugate addition of water to the triple bond took place efficiently with complete regioselectivity. The hydration reaction of γ-hydroxy-α,β-ynones **35** afforded the corresponding 3(2*H*)-furanones **36** in excellent yields in the presence of Hg/Nafion-H reagent and 5 equivalents of water in ethanol at 40 °C.[44] The process was applied to the synthesis of the natural occurring bullatenone **36a** (Scheme 42).



Scheme 42

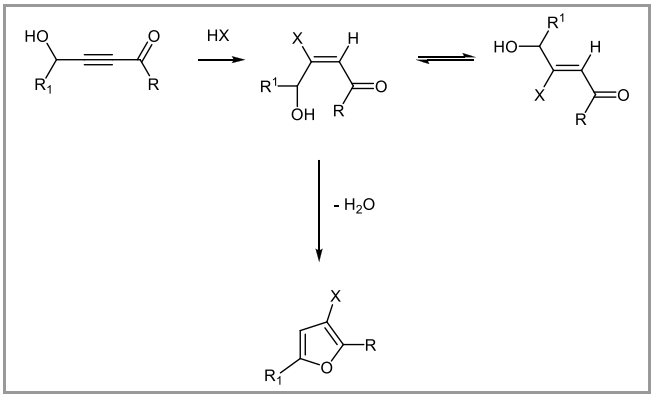
2.3 *Sequential Electrophilic Addition/Annulation Processes of α,β-Ynones Containing Proximate Nucleophiles.*

α,β-ynones may undergo electrophilic addition, and suitably substituted acetylenic ketones were versatile synthetic precursors of various heterocycles through sequential reactions promoted by electrophilic reagents.[49] Hydroxy acetylenic acetals and hydroxy acetylenic ketones led to substituted 3-halofurans (Scheme 43a), flavones(Scheme 43b), and styrylchromones in good-to-excellent yields.[50]



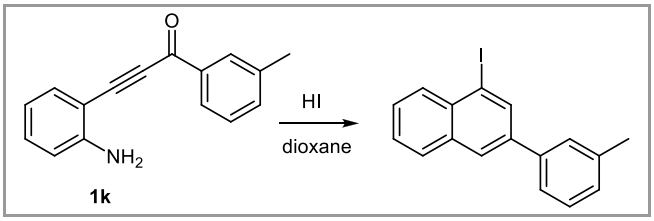
Scheme 43

Hydroxy acetylenic aldehydes derived from hydrolysis of hydroxy acetylenic acetals and hydroxy acetylenic ketones are prone to undergo regioselective addition of HX or H_2O giving rise to a mixture of (*E*)- and (*Z*) adducts. Then rapid interconversion of (*E*)- and (*Z*) adducts under the reaction conditions achieves the formation of the target product after cyclization and dehydration (Scheme 44).



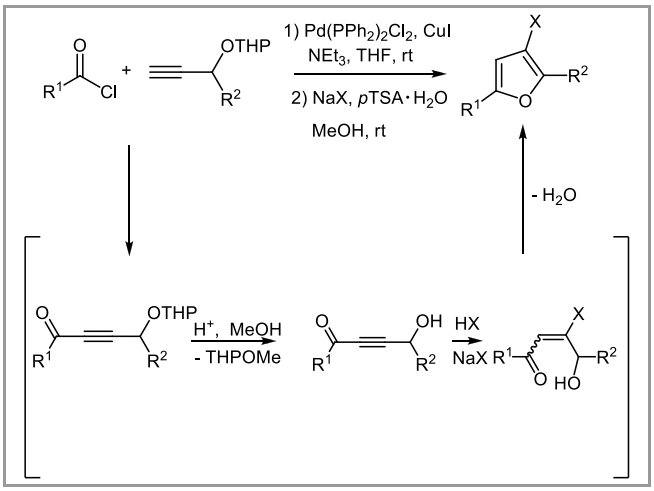
Scheme 44

By this way, the reaction of **1k** with HI gave the expected 4-iodoquinoline derivative in moderate yield (40%) (Scheme 45).[14]



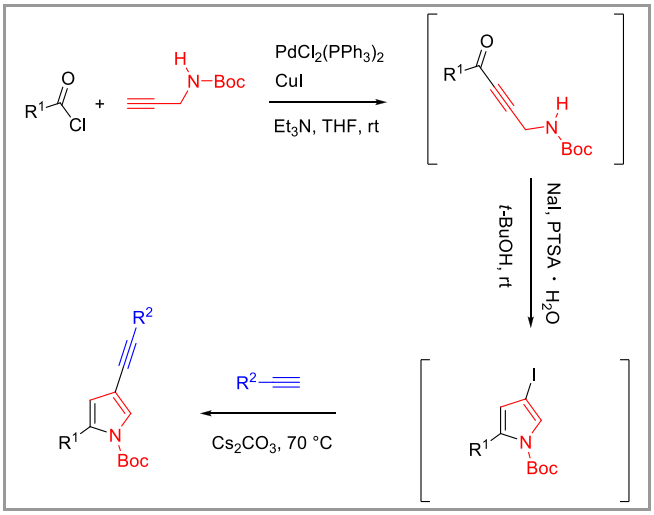
Scheme 45

Moreover, acid-assisted Michael addition of HX over the *in situ* generated γ-hydroxy alkynones played a key role in the one-pot three component synthesis of 3-halofurans (Scheme46).[51] The palladium catalyzed cross-coupling of acyl chlorides with the tetrahydropyranyl propargyl ether was followed by acid catalyzed deprodeprotection of the THP ether with concomitant Brønsted acid mediated Michael addition of the halide to the alkynone intermediate. Hence, the *E*-configured enone derivative subsequently undergoes a cyclocondensation to give the 3-halofuran.



Scheme 46

Analogoulsy, 2-substituted *N*-Boc-4-iodopyrroles were isolated in a one-pot fashion by the palladium-catalyzed cross-coupling of (hetero)aryl-, alkenyl-, and selected alkyl-substituted acid chlorides with *N*-Boc-protected propargylamine which was followed by Michael addition of HI/cyclocondensation reactions (Scheme 47). Interestingly, upon addition of a further alkyne, another coupling can be carried out in a one-pot fashion. [52]



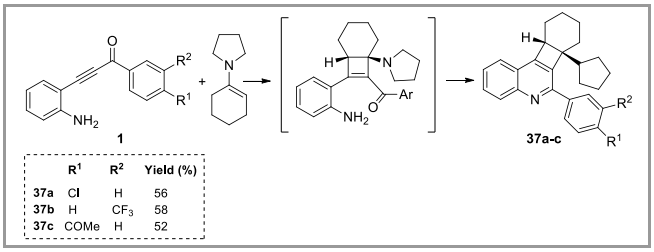
Scheme 47

Sequential Sonogashira-addition-cyclocondensation-Suzuki multicomponent furan synthesis were, also, readily elaborated as a diversity-oriented consecutive multicomponent access to substituted 3-arylfurans.[53] Furthermore, the concept of a sequential alectrophilic addition/heteroannulation process was probed by the conversion of the ynones bearing proximate nucleophiles into dihaloheterocycles.

3. Cycloaddition/Heterocyclization Processes of α,β-Ynones and α,β-Ynoates Containing Proximate Nucleophiles.

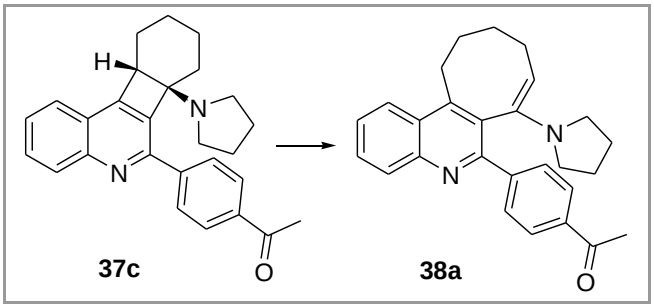
3.1 *[2+2] and [4+2] Cycloaddition/Annulation Reactions*

The [2+2] cycloadditions of enamines with electrophilic acetylenes in apolar solvents are well documented and represent an important strategy for the synthesis of cyclobutene derivatives.[49] However, while the behaviour in these reactions of acetylene mono and dicarboxylates as well as methyl propiolate has received great attention both from the theoretical and applied point of view, less attention has been paid to the cycloaddition reactions with α,β-ynones and related compounds. When β-(2-aminophenyl)-α,β-ynones **1** were treated in toluene under reflux for 4-6 h with 3 equiv. of 1-(cyclohexen-1-yl)pyrrolidine, the 1-(1-pyrrolidino)bicyclo[4.2.0]octane[7,8-*c*]-2-arylquinolines **37a-c** were isolated in moderate yields (Scheme 42).[50]



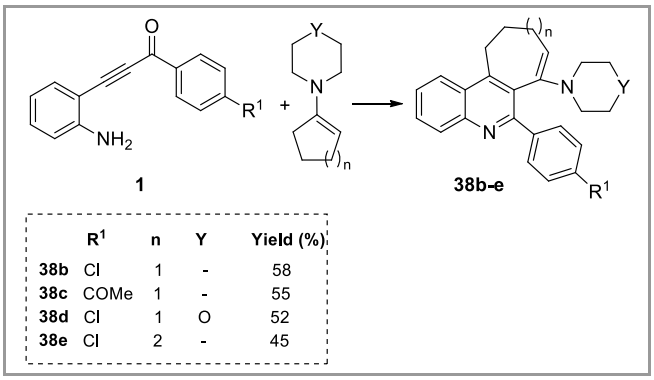
Scheme 42

Thermal rearrangement of this type of cyclobutenes derivatives represents a useful method for ring enlargement with two carbon atoms and has been widely used in the synthesis of medium-sized carbo- and heterocycles.[51] Indeed **37c** was quantitatively converted into the thermodynamically favoured tricyclic quinoline **38a** by heating under reflux in xylene (Scheme 43).



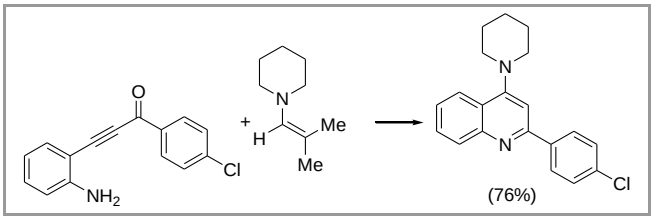
Scheme 43

Interestingly, *c*-fused quinolines **38b-e** were directly isolated, in toluene at reflux, from the reaction of β-(2-aminophenyl)-α,β-ynones **1** with cyclopentanone or cyclohexanone derived enamines (Scheme 44).



Scheme 44

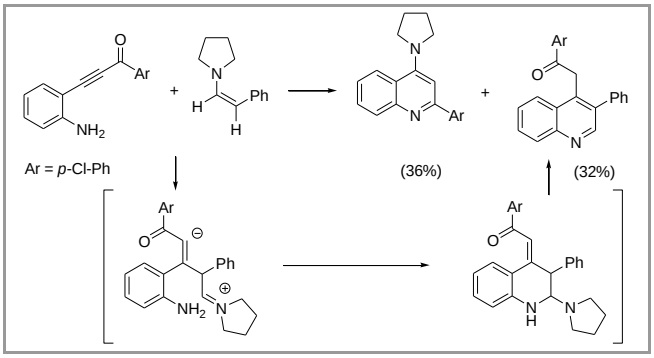
β,β-Disubstituted enamines failed to give cycloaddition reactions and 4-aminoquinolines were isolated after prolonged reaction times (24 h) (scheme 45).



Scheme 45

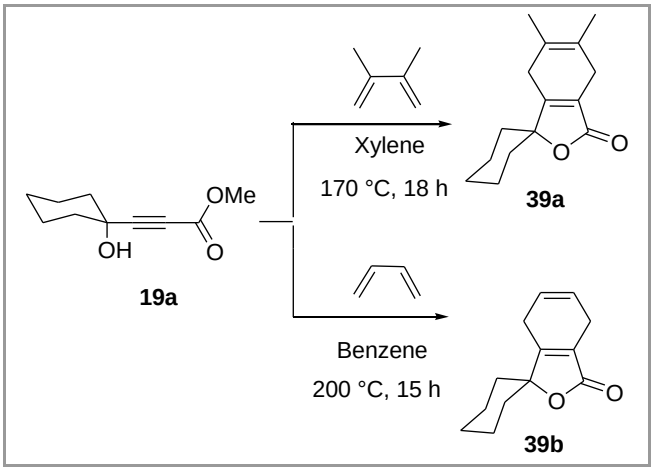
Very likely, the 4-aminoquinolines were formed by domino Michael addition/annulation reaction of amine, which might be generated in situ by the hydrolysis of the starting enamine. β-Monosubstituted enamines gives rise, beside the 4-amino derivative, to a new 3,4-disubstituted quinoline derivative probably through a

nucleophilic attack/annulations/isomerisation /elimination cascade reaction (Scheme 46). The lack of reactivity of these latter enamines towards cycloaddition was attributed to electronic effects.[52]



Scheme 46

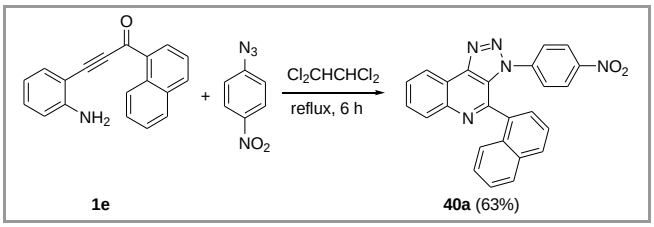
Although, the intramolecular [4+2] cycloaddition reactions of conjugated ynones have been extensively explored,[53] the domino Diels-Alder/annulation reactions of α,β-ynones and α,β-ynoates containing proximate nucleophiles were less investigated. To the best of our knowledge only two examples of this reaction have been reported. Methyl 2-(1'-hydroxycyclohexyl)propiolate **19a** underwent in dry xylene at 170 °C the domino Diels-Alder/ lactonization reaction with 2,3-dimethylbutadiene to give 5,6-dimethyl-3-spirocyclohexyldihydrophthalide **39a**. [54] The same alkyne **19a** reacted with butadiene in benzene at 200 °C giving rise to the lactone **39b** in good yield (Scheme 47).[55]



Scheme 47

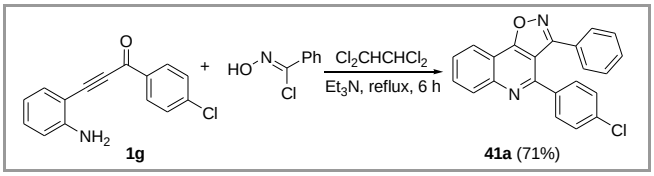
3.2 1,3-Dipolar Cycloaddition /Annulation Reactions

The sequential 1,3-dipolar cycloaddition/annulation reaction of conjugate ynone **1e** with *p*-nitrophenylazide gave the triazolo[4,5-*c*]quinoline **40a** (Scheme 48).[14]



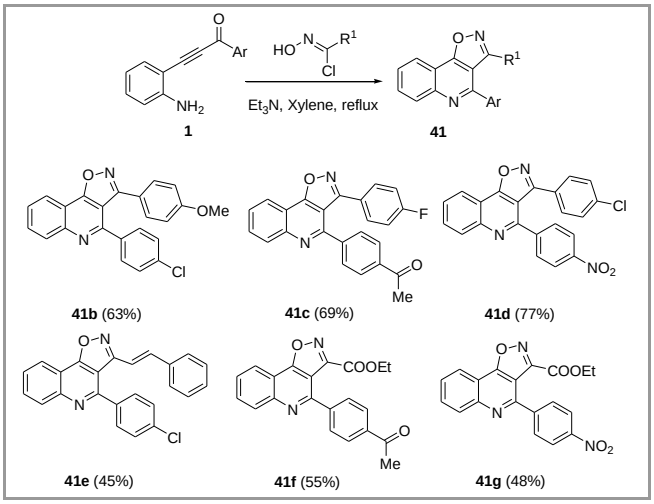
Scheme 48

Analogously, the sequential 1,3-dipolar cycloaddition/annulation reaction of conjugate ynones **1g** with benzonitrile oxide achieved the synthesis of isoxazolo[4,5-*c*]quinoline **41a** (Scheme 49).



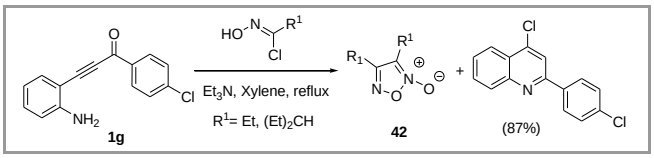
Scheme 49

The synthetic and medicinal importance of isoxazole-annulated ring systems provided enough incentive to devise simple strategies for the generation of these molecular frameworks.[56] A number of isoxazoloquinolines have been identified as MRP1 inhibitors[57] and a class of isoxazoloquinoline derivatives showed anxiolytic activity.[58] For getting through the bottleneck for further studies and developments in medicinal chemistry, the reactivity of β-(2-aminophenyl)-α,β-ynones **1** towards nitrile oxides derived from different substituted aldehydes was investigated providing a clean, mild, and general synthesis of functionalized isoxazolo[4,5-*c*]quinolines. Products **41** were easily prepared by slow drop wise addition of a solution of the appropriate α-chlorooxime (1.2 mmol) in dry xylene to a boiling solution of β-(2-aminophenyl)-α,β-ynone **1** (1.0 mmol) and triethylamine (TEA) (1.5 mmol) in dry xylene(Scheme 50).[59]



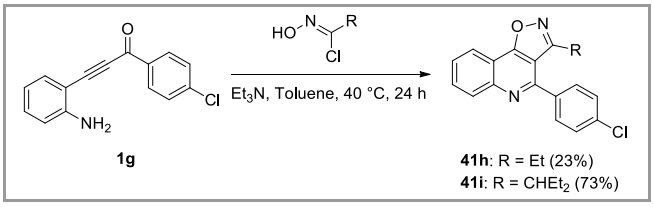
Scheme 50

However, under these standard conditions the alkanenitrile oxides, generated in situ from the corresponding α-chlorooxime, underwent dimerization to furoxanes.[60] Subsequently a competitive nucleophilic addition/annulations reaction promoted by the chloride ion led mainly to the corresponding 4-chloroquinoline derivatives (Scheme 51).



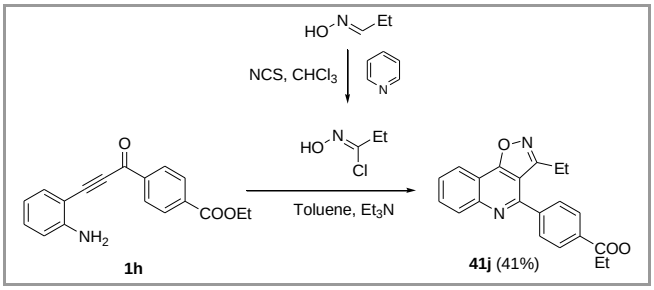
Scheme 51

The dimerization to furoxanes of labile nitrile oxides was minimized by carrying out the reactions in toluene at 40 °C. Under these milder conditions the isoxazolo[4,5-*c*]quinolines **41h-i** were isolated in 23 and 73% yield, respectively (Scheme 52).



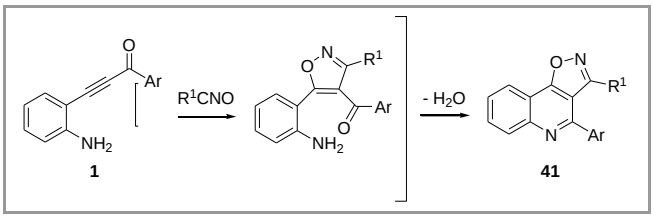
Scheme 52

Further improvement was accomplished by the development of a one-pot procedure starting from β-(2-aminoaryl)-α,β-ynones and generating the α-chlorooxime from the corresponding oxime and, subsequently the nitrile oxide, in the same reaction step. Thus, a solution of the crude α-chloro oxime, obtained by treating the appropriate oxime with *N*-chlorosuccinimide (NCS) at 0 °C in chloroform and in the presence of a catalytic amount of pyridine, was added dropwise at 40 °C, over a period of 30 mins, to a solution of conjugate ynone **1h** and triethylamine in toluene. Under these conditions the isoxazolo[4,5-*c*]quinolines **41j** was isolated in 41% yields (Scheme 53).



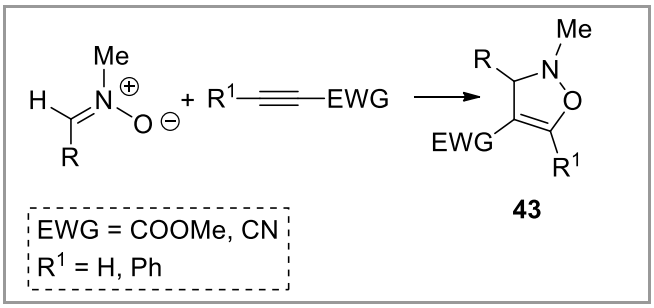
Scheme 53

The suggested reaction mechanism involves a regioselective [3+2] cycloaddition reaction of the ynone with the nitrile oxide, generated in situ from the corresponding α-chlorooxime, followed by an intramolecular addition/elimination reaction between the amino and carbonyl group, with loss of water. The observed regioselectivity is in agreement with the results obtained in the cycloadditions of disubstituted electron-deficient alkynes with nitrile oxides generating isoxazoles carrying the electron-withdrawing group in the 4-position (Scheme 54).[61]



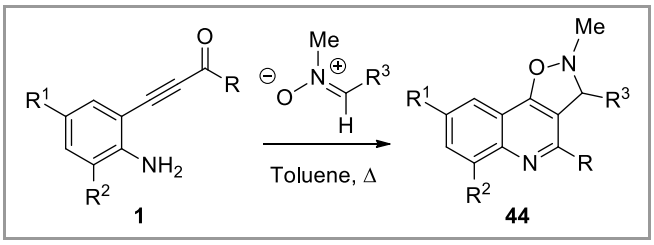
Scheme 54

Nitrones, also, behave as 1,3-dipoles in cycloaddition reactions[62] and are particularly suitable for the construction of structurally complex molecules such as nitrogen-containing biologically active compounds and fused or bridged ring structures.[63] Alkynes undergo facile cycloaddition reactions with nitrones under thermal conditions to give isoxazolines and the regioselectivity is strongly affected by steric and electronic factors.[65] Monosubstituted electron-rich alkynes give 5-substituted 4-isoxazolines as the main products, whereas electron-poor mono substituted alkynes show a strong tendency to afford 4-substituted 4-isoxazolines **43** with high regioselectivity. This is also the case for internal alkynes such as ethyl phenylpropiolate (Scheme 55).[66] This inversion of regioselectivity has been rationalized by FMO theory.[67]



Scheme 55

On the basis of this knowledge, it was envisaged that the cycloaddition reaction of β-(2-aminophenyl) α,β-ynones **1** with nitrones could represent a straightforward entry into isoxazolino[4,5-*c*]quinolines **44** through a sequential one-pot protocol according to scheme 56.



Scheme 56

The isoxazolino[4,5-*c*]quinolines **44** were isolated in moderate-to-high yields as single regioisomers.[68] As shown in figure 5, the reaction tolerates various functional groups, such as the keto (**44a-b**), nitrile (**44d)**, and ester (**44h**) groups; vinylic (**44a-c**) and heteroarylic (**44f**) substituents are also allowed on the isoxazoline moiety. Moreover the isoxazolino[4,5-*c*]-quinoline **44i**, substituted on the benzene ring of the quinoline, was also be obtained in good yield.

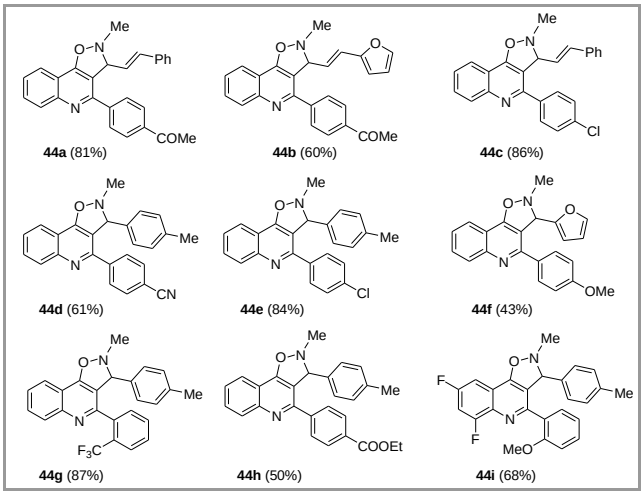
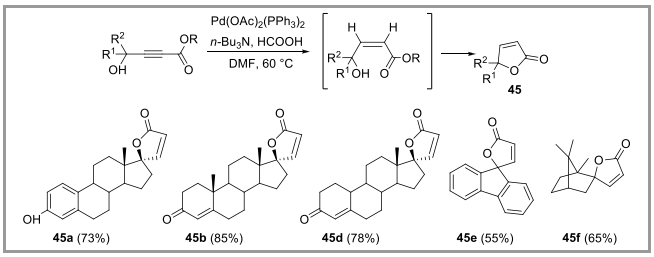


Figure 5

4 Transition Metal-Catalyzed Addition/Heterocyclization Processes of α,β-Ynones and α,β-Ynoates Containing Proximate Nucleophiles.

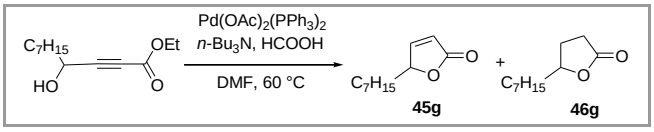
4.1 Palladium-Catalyzed Transfer Hydrogenation / Heterocyclization Processes of α,β-Ynones and α,β-Ynoates Containing Proximate Nucleophiles.

Transition-metal catalysed hydrogenation of alkynes is one of the most important reaction in organic chemistry.[69] This transformation is accomplished by using hydrogen gas in the presence of either a heterogeneous catalyst[70] such as Raney Ni, Lindlar catalyst, Pd/C, or a homogeneous catalyst based on Rh, Ru, or Ir complexes. [71] However, these methods often suffers from the lack of chemo- and stereo-selectivity arising from the *cis/trans* interconversion of the alkenes and the over-reduction of the resulted alkenes to alkanes. Low tolerance with functionalities such as carbonyl, formyl, nitro groups, and C-X bonds (X = O, N, Cl, etc.) due to the competitive hydrogenolysis also narrows its generality. Instead of hydrogen gas, alkynes could also be hydrogenated by using ammonium formate in the presence of a palladium catalyst.[72] A variety of γ-hydroxy-α,β-acetylenic esters containing tertiary hydroxy group reacted selectively with formic acid and tri-*n*-butylamine in the presence of $Pd(OAc)_2(PPh_3)_2$ to give the corresponding butenolides **45** in good to high yield through a sequential *cis*-hydrogenation/cyclization process. Reactions were carried out at 60 °C by using the following molar ratio: γ-hydroxy-α,β-acetylenic ester: HCOOH: *n*-Bu_3N: $Pd(OAc)_2(PPh_3)_2$ = 1: 2.6: 3.4: 0.02 (Scheme 57).[73]



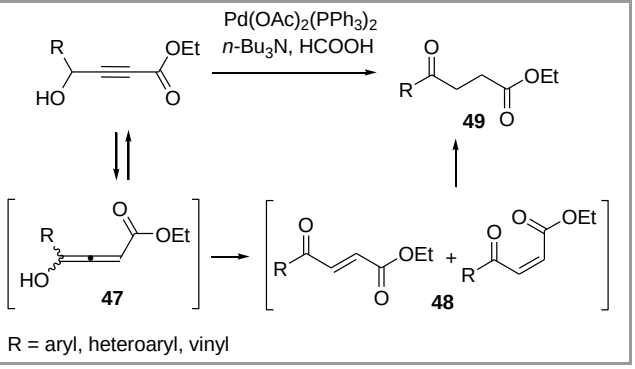
Scheme 57

A 85/15 mixture of butenolide **45g** and saturated γ-lactone **46g** was isolated starting from the corresponding γ-hydroxy-α,β-acetylenic ester containing a secondary hydroxy group (65% total yield) under the same reaction conditions. When formic acid was reduced to about 50% excess it was possible to isolate **45g** in 69% yield and an increase of formic acid to about 300% excess gave **46g** in 64% yield (Scheme 58).



Scheme 58

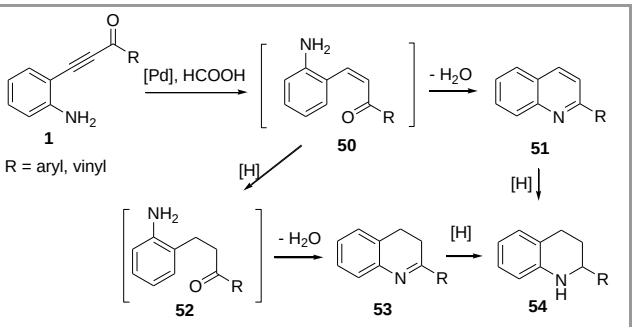
Additional evidences showed that the nature of the formate salt and of the reaction medium can significantly affect the reaction course.[74] Moreover, it was reported that, depending of the feature of the starting γ-hydroxy-α,β-acetylenic ester, the 1,4-dicarbonyl compound **49** could be isolated under the usual hydrogenation conditions, instead of the expected cyclic derivative, through a different isomerization/hydrogenation sequence. In the presence of aryl/heteroaryl/vinyl groups in the starting alkyne the formation of *E/Z* mixture alkene **48** *via* the intermediary allenyl alcohol **47** occurs faster than the palladium-catalyzed hydrogenation of the carbon-carbon triple bond (Scheme 59).[75]



Scheme 59

Further elaboration of ethyl γ-aryl/heteroaryl-γ-hydroxy-2-butynoates with (*S*)-aminoacid benzyl esters in ethanol or dimethylformamide in the presence of triethylamine provided a general, regioselective entry to *N*-(3-aryl/heteroaryl-1-ethoxycarbonyl-3-oxopropyl)-(*S*)-aminoacid esters, useful intermediates for the synthesis of angiotensin converting enzyme inhibitors.[76] Examples of selective *trans* reduction of carbon-carbon triple bonds of γ-hydroxy-α,β-acetylenic esters were also described.[77]

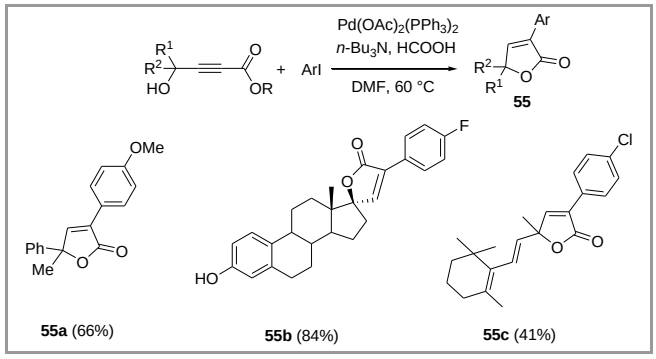
The palladium-catalysed transfer hydrogenation/cyclization of β-(2-aminoaryl)-α,β-ynones **1** afforded 2-aryl- and 2-vinylquinolines **51** in good yield.[78] Heterogeneous conditions (3 equiv of $HCOONH_4$, 10 mol% Pd/C in MeOH (58mL/mmol) at 70 °C) gave **51** in good yield. However, significant amounts of over-reduction derivatives, the tetrahydroquinolines **54**, were sometimes isolated. No attempts were made to establish whether **54** is generated via transfer hydrogenation of **51** and/or reduction of intermediate **50**, cyclization of saturated intermediate **52** followed by reduction of the resultant 3,4-dihydro quinoline **53**. Higher product selectivity has been observed under homogeneous conditions (Scheme 60).



Scheme 60

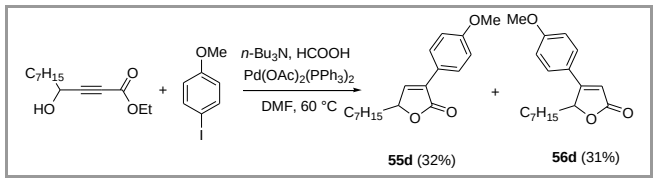
4.2 Palladium-Catalyzed Hydroarylation/ Heterocyclization Processes of α,β-Ynones and α,β-Ynoates Containing Proximate Nucleophiles.

The reaction of aryl iodides with acetylenic systems in the presence of a palladium catalyst, formic acid, and a secondary or tertiary amine, results in the formation of substituted olefinic derivatives.[79] This hydroarylation reaction, which can tolerate various common functional groups, occurs with high stereoselectivity and, depending on the nature of the substituents on the *sp* carbon atoms, with good regioselectivity. Since the *syn* stereochemistry of addition drives the substituents on the same side of the carbon-carbon double bond, it was speculated that the reaction could provide an easy access to a variety of cyclic derivatives by starting from suitable precursors. The hydroarylative lactonization reaction of γ-hydroxy-α,β-acetylenic esters with aryl iodides was applied to the synthesis of functionalized butenolides **55**. The regioselectivity of the reaction was good and appeared determined mainly by steric and coordinating factors (Scheme 61).[73]



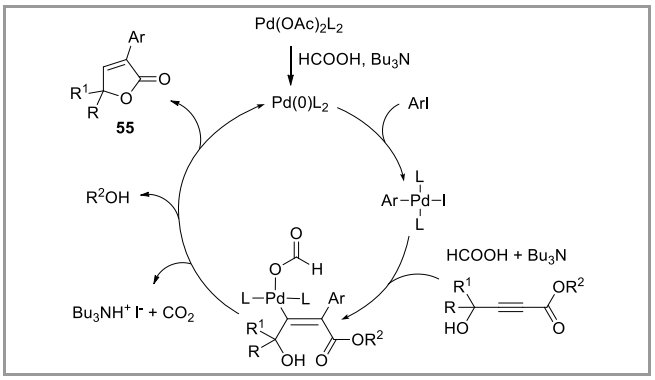
Scheme 61

Accordingly, the isomeric butenolides **56** were isolated in low yield. As expected, when γ-hydroxy-α,β-acetylenic esters containing a less hindered secondary alcoholic group were reacted under usual conditions, a lack of regiochemistry was observed (Scheme 62).



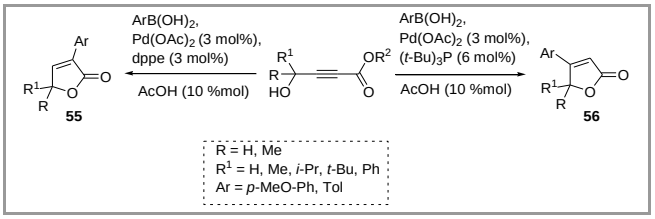
Scheme 62

The sequential hydroarylation/cyclization process, most probably proceeds through the following steps: a) regioselective *syn* addition reaction of the σ-arylpalladium intermediate [generated in situ via oxidative addition of the aryl iodide to Pd(0)] over the starting γ-hydroxy-α,β-acetylenic ester; b) reductive decarboxylative elimination of the resultant σ-alkenylpalladium formate intermediate/ condensation to give the butenolide **55** together with the regeneration of the active palladium catalyst (Scheme 63).



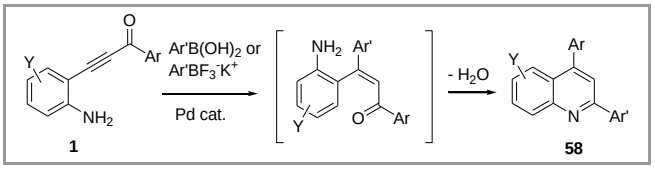
Scheme 63

Highly regioselective *sin* hydroarylation/cyclization sequences were also achieved *via* palladium catalyzed addition of arylboronic acids to γ-hydroxy-α,β-acetylenic esters. The hydroarylation of simple unsymmetrical alkynes with a variety of organoboronic acids, under palladium catalysis, was reported to give mixture of the corresponding regioisomeric alkenes.[80] However, it was found that incorporation of a specific functional group such as a keto, hydroxy, or 2-pyridyl groups could play a role in controlling the site of addition. Mechanistically, it is expected that oxygen or nitrogen atoms present in the alkyne substrate would bind the Lewis acidic $RB(OH)_2$ and thereby direct the addition site.[81] On the other hand, bulky substituents might block addition to one end of the alkyne. The regioselectivity can also be controlled by employing a various types of ligands. [82] Hence, it was reported that the palladium-catalyzed arylative lactonization of γ-hydroxy-α,β-acetylenic esters with boronic acids could be achieved with a high control of regioselectivity and *syn*-stereoselectivity under two different conditions (Scheme 64).[83]



Scheme 64

The palladium-catalyzed hydroarylation/cyclization reactions of β-(2-aminoaryl)-α,β-ynones **1** with organoboron derivatives were also investigated (Scheme 65).[84] The process led to the regioselective formation of the quinoline **58** under all reaction conditions tested.



Scheme 65

Higher yields were observed in the presence of an excess of the organoboron reagent. Interestingly, the environmentally benign ethanol was a suitable reaction medium and this solvent was used when the process was extended to the reaction of various ynones **1** and boron derivatives to afford quinolines **58** in good to excellent yields (Figure 6). Various substituents are allowed both on the boron derivative and on the alkynone. Aryltrifluoroborate salts gave results comparable with arylboronic acids. Moreover, the reaction of **1a** with the aryltrifluoroborate could proceed also without adding acetic acid. Although these reaction conditions resulted less effective than the standard protocol (that requires 0.15 equiv. of AcOH), the possibility of carrying out the palladium-catalyzed hydroarylation under neutral conditions is undoubtedly worth of interest. $Pd(OAc)_2$/dppe was generally used as the catalytic system. Slightly better yields were observed in some examples by increasing the amount of the dppe to 0.1 equiv (Pd:P = 1:2); however, no systematic investigation was carried out on this aspect. When $Pd(OAc)_2$ alone or a combination of $Pd(OAc)_2$/*t*-Bu_3P were tested in place of the $Pd(OAc)_2$/dppe, it was observed a dramatic loss of efficiency together with a less pronounced decrease in the selectivity. Conversely, the $Pd(OAc)_2$ /tricyclohexylphosphine catalytic system gave good results, showing that the use of a bidentate ligand is not compulsory. The hydroarylation was also catalyzed by Pd(0) precatalysts. The catalytic system $Pd_2(dba)_3$/dppe gave nearly the same yield of $Pd(OAc)_2$/dppe, while $Pd(PPh_3)_4$ was much less effective.

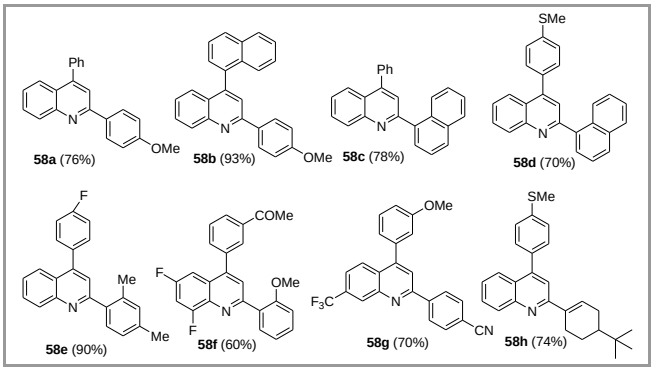
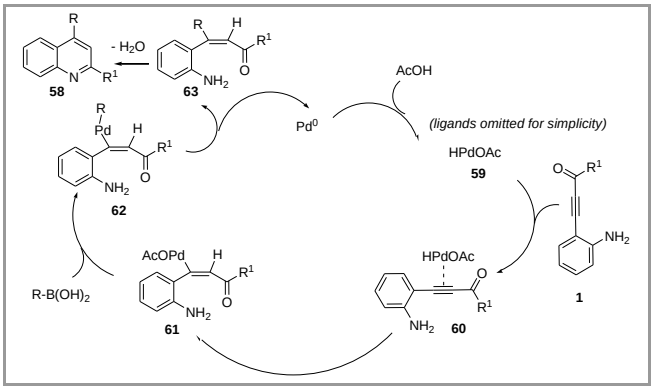


Figure 6

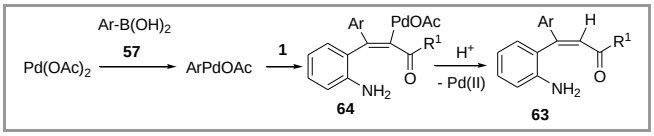
A plausible catalytic cycle for the hydroarylation is depicted in Scheme 66. The active Pd(0) catalyst can be generated *in situ* from Pd(II) species in several ways, including oxidation of dppe[85] and homocoupling of arylboronic acid.[86] The oxidative addition of Pd(0) to AcOH affords the hydride complex **59** (likely, under neutral conditions this step can take place through the insertion of Pd(0) into the O-H bond of ethanol).[87] Then, **59** coordinates the ynone **1** to give the π-complex **60**. Subsequent hydropalladation followed by trans-metallation with arylboronic acid (or potassium trifluoroborate) generates the species **62**, from which

the hydroarylation product **63** is obtained through reductive elimination of Pd(0). Subsequent sequential cycloamination results in the formation of the quinoline ring **58**. A similar catalytic cycle was probed by ESI-FTMS in the related hydroarylation of allenes with arylboronic acids in the presence of acetic acid.[88]



Scheme 66

An alternative pathway for the hydroarylation could also be considered. Initial trans-metallation[89] of $Pd(OAc)_2$ with boron derivatives generates an ArPdOAc complex; carbopalladation of **1** by this species gives the intermediate **64**; protonolysis of **64** affords the alkene **63** and regenerates the catalyst (Scheme 67).

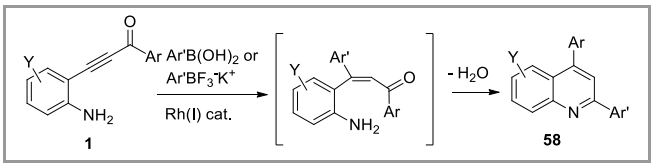


Scheme 67

This latter cycle can be however ruled out when the reaction is carried out using Pd(0) precatalyst. The regiochemical outcome of the present reaction also suggest that the formation of the product via ArPdOAc is unlikely. Indeed, on the basis of experimental[90] and theoretical[91] results concerning the insertion of α,β-alkynones and alkynals into Ar-Pd bond, the isolation of 3-arylquinolines as main product should be expected. A third possibility, involving the initial oxidative addition of arylboronic acid to Pd(0) to give an Ar-Pd-$B(OH)_2$ species that carbopalladates the triple bond, seems in contrast with the results showing that such oxidative addition does not take place.[92] Assuming therefore that the catalytic cycle depicted in Scheme 66 is operating, in order to shed some light on the observed regioselectivity, quantum-chemical calculations in the framework of Density Functional Theory were carried out leading to conclusion that electronic factors provide the main explanation for the observed regioselectivity, since the more electrophilic β-carbon atom conceivably shows larger affinity for the palladium.

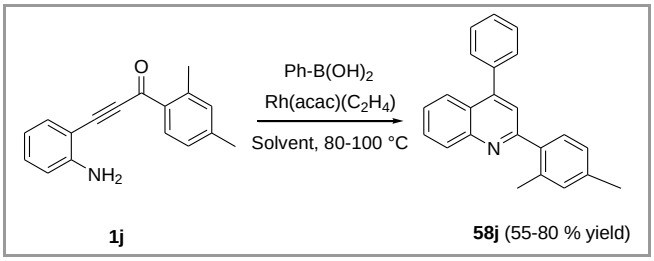
4.3 Rhodium-Catalyzed Hydroarylation/ Heterocyclization Processes of α,β-Ynones and α,β-Ynoates Containing Proximate Nucleophiles.

The rhodium-catalyzed hydroarylation of alkynes with arylboronic acids is a well established functionalization methodology. The reaction shows the same stereochemical outcome of the palladium-catalyzed process (*sin*-addition), but electronic factors seem to play a more important role in determining the regioselectivity. In particular, methyl trimethylsilylpropynoate was selectively arylated at the C3 carbon atom, despite of the presence of a bulky trimethylsilyl group on that position.[93] The same regiochemical outcome was observed in the sequential reaction of α,β-ynones **1** with arylboronic acids giving rise to the corresponding 2,4-diarylquinolines **58** through a rhodium-catalyzed hydroarylative cycloamination process (Scheme 68).[94]



Scheme 68

The reaction of phenylboronic acid with ynone **1j** was chosen as a model system to screen the best reaction conditions for the synthesis of 2,4-diarylquinolines (Scheme 69).

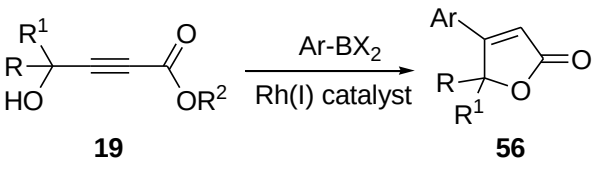


Scheme 69

By using $Rh(acac)(C_2H_2)$/dppf as catalyst, **58j** was always isolated as the main reaction product in good to high yield. The regioselectivity, determined via ^1H NMR and GC-MS analysis, was showed to be higher than 96%. The highest yields were obtained with a fivefold excess of boronic acid. The use of a 2:1 ratio between Rh and dppf seemed preferable to a 1:1 ratio. The replacement of dioxane with a greener solvent such as aqueous ethanol is also possible, although the former gave better yields. Dppp was slightly less effective than dppf in dioxane/water whereas in ethanol the two ligands gave similar yields. When the methodology was extended to different α,β-ynones/ boron derivatives, quinolines **58** were isolated in moderate to high yields. The process tolerates electron-withdrawing as well as electron-donating substituents on the α,β-ynone and arylboronic acid moieties. Substituents on

the benzenic ring of quinoline could also be introduced, and heteroarylboronic acids were used as well.

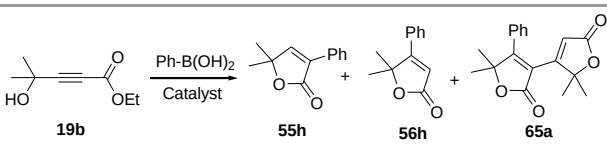
Furthermore, Rh(I) complexes were efficient catalysts for the regioselective synthesis of 4-substituted-2(5*H*)-furanones **56** (Scheme 70).[95]



19 **56**

Scheme 70

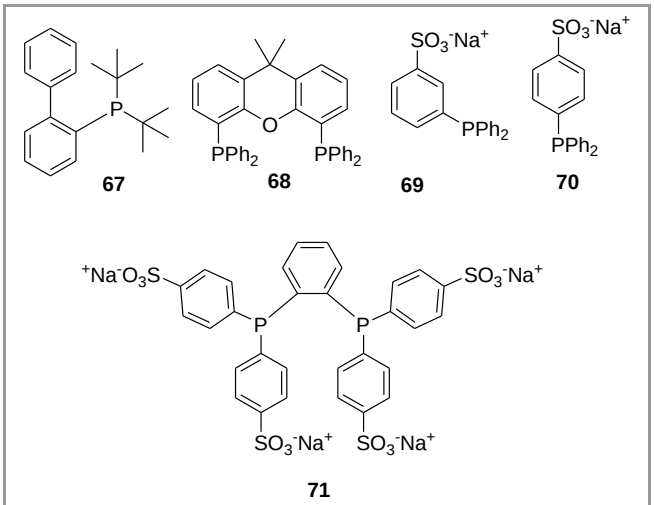
The reaction selectivity was strongly influenced by the reaction medium, the temperature and the precatalyst feature. Indeed, by reacting 1 equiv. of 4-hydroxy-4-methyl-pent-2-ynoic acid ethyl ester **19b** with 5 equiv. Ph–$B(OH)_2$ the 5,5-dimethyl-4-phenyl-5*H*-furan-2-one **56h** was isolated in 69% yield together with the regioisomer **55h** in 10% yield in the presence of $[Rh(cod)(OH)]_2$/1,1'-bis(diphenylphosphino)ferrocene (dppf) as the catalytic system in dioxane/water 10/1 (V/V). The formation of **65a** (20% yield) as by-product was also observed (Scheme 71) .



19b **55h** **56h** **65a**

Scheme 71

The use of $[Rh(cod)OH]_2$/ dppf resulted in a more active catalytic system with respect to $[Rh(cod)Cl]_2$/dppf and $Rh(acac)(C_2H_4)_2$/dppf even if the latter combination resulted highly selective. The use of $[Rh(cod)OH]_2$ without the addition of phosphine ligands also promoted the reaction however with no improvements in terms of selectivity. The combination of $[Rh(cod)OH]_2$ with PPh_3 has proven to be unsuitable and generally resulted in low selectivity. The choice of the bulky, electronrich 2-(di-*t*-butylphosphino)biphenyl as ligand (Figure 7, **67**), which was reported to have beneficial effects on the rhodium-catalyzed addition of alkynes to 1,2-diketones, 1,2-ketoesters and aldehydes,[96] did not ensure improved selectivity. Chelating bisphosphine ligands gave discrepant results. The features of the bisphosphine ligands played a pivotal role in determining the outcome of the reaction. Even if it has been reported that excellent catalytic activities could arise from diphosphine ligands based in xantene backbone,[97] experiments performed under usual reaction conditions in the presence of $[Rh(cod)OH]_2$/9,9-dimethyl-4,5-bis(diphenylphosphino)xantene (Figure 7, **68)** led to a complex reaction mixture. Whereas, the formation of **65a** (53% yield) prevailed with 1,2-bis(diphenylphosphino)ethane (dppe) improved yields of the target **56h** were observed by increasing the distance between the two phosphorous atoms in the series dppe, 1,3-bis(diphenylphosphino)propane (dppp) and 1,4-bis(diphenylphosphino)butane (dppb) . Among the examined bisphosphine ligands, dppb was significantly more effective.



67 **68** **69** **70**

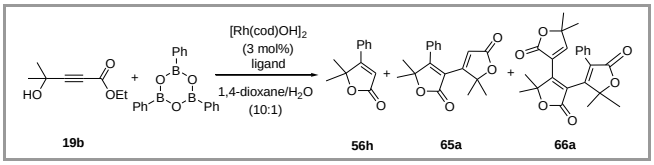
71

Figure 7

The screening of the solvent system resulted in the observation that the use of ethanol instead of 1,4-dioxane was detrimental to the reaction selectivity. The reaction was also carried out in neat water and in a biphasic water/toluene system by associating the $[Rh(cod)OH]_2$ with water-soluble ligands (Figure 7, **69-71**). Surprisingly, even if disappointing results were observed from a synthetic point of view the reaction in water led to the formation of **56h** as a single regioisomer. Conversely, in the biphasic water/toluene system, a lack of regioselectivity was observed.

The role played by the phenylboroxine in the reaction outcome was explored (Scheme 72).[98] It is presumed that in solution arylboronic acids are in equilibrium with the corresponding arylboroxines and water. This equilibrium should influence the reaction stoichiometry and prevent the coupling process. Results clearly point out the drastic effect of the triphenylboroxine besides **19b**/triphenylboroxine ratio, ligand and the temperature on the resulting reaction.[99] Indeed the reaction of an equimolecular amount of **19b** with phenylboroxine**,** in the presence of rhodium-dppe catalytic system in 1,4-dioxane/H_2O at 100 °C for 2 h gave a 45% yield of the dibutenolide derivative **65a** together with the derivative **56h**. The formation of **65a** in a better yield was observed by reacting the boroxine with excess alkyne **19b**. A similar effect of the boron reagent has also been reported in the nickel-catalyzed 1,2-addition of arylboroxines to aromatic aldehydes.[100] The formation of the tributenolide derivative **66a** was observed when the **19b** excess was

increased or in dry solvent, using 1,4-dioxane (dried with molecular sieves).

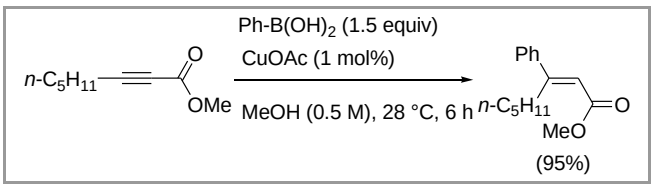


Scheme 72

The subsequent investigation on the scope and limitations of the rhodium-catalyzed alkylative lactonization showed that the reaction of the γ-hydroxy-α,β-acetylenic ester bearing a tertiary propargylic group resulted in reversal of the regioselectivity compared to that observed in the palladium-catalyzed process. Moreover, by contrast with the results obtained in the palladium-catalyzed alkylative lactonization of **19** with organoboronic acids the bulkiness of groups near the triple bond did not affect the regioselectivity of the rhodium-catalyzed reaction which was directed by the ester group.[73, 82] According to the results observed with the model system, the use of [RhOH(cod)]$_2$/dppb as catalytic system accomplished the formation of the target 4-substituted-2(5*H*)-furanones in good yield with excellent regioselectivity. Multiple addition derivatives were detected as by-products. The best selectivity was observed by using Rh(acac)(C_2H_4)$_2$/dppf. As far as organoboron derivatives are concerned, the process tolerates aryl- and heteroaryl-boronic acids, their corresponding pinacol esters, and aryl- and vinyl-trifluoroborate salts. The latter derivatives have emerged as promising compounds that can overcome certain limitations of other organoboron derivatives.[101] According to literature,[102] the yield of 4-aryl/heteroaryl/2(5*H*)-furanones starting from pinacol esters derivatives**,** resulted lower than that observed starting from boronic acids.

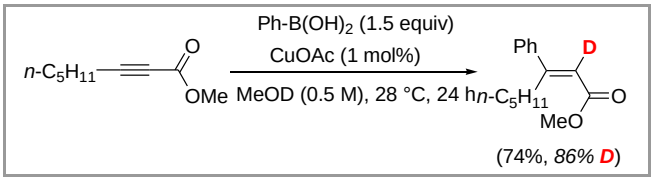
4.4 Copper-Catalyzed Hydroarylation/Heterocyclization Processes of α,β-Ynones and α,β-Ynoates Containing Proximate Nucleophiles.

The copper catalyzed conjugate addition of arylboronates to alkynoates proceeded in MeOH under mild conditions to yield trisubstituted cinnamates with precise *syn*-selectivity (Scheme 73).[103]



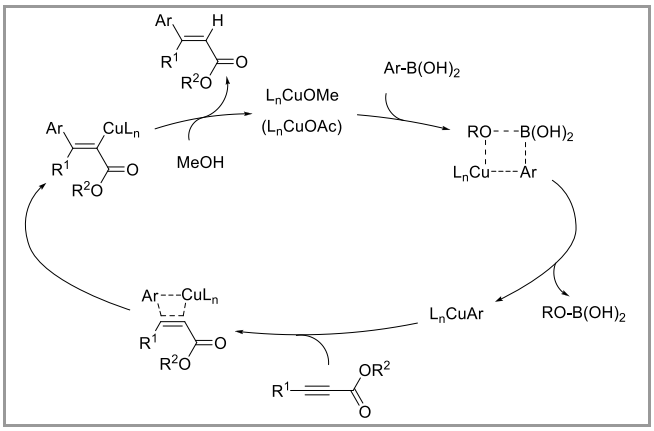
Scheme 73

A variety of copper salts were examined but none of them were superior to the acetates. CuCl and CuBr gave the desired products in comparable yields, although their reactions were only complete after prolonged reaction time. In contrast, CuI, $CuCl_2$, and $CuBr_2$ hardly exhibited any catalytic activity. Electron-donating ligands such as 2,2'-bipyridine (bipy) and N-heterocyclic carbenes [1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene: IPr; or 1,3-dimesitylimidazol-2-ylidene: IMes] did not show any positive effect. The protocol was compatible with phenylboronic acids bearing carbon-halogen bonds as well as carbonyl functional groups. To obtain further insight into the reaction mechanism, the reaction was carried out in MeOD. As a result, mono-deuterated product was obtained, indicating that the hydroxyl group of methanol behaved as a proton donor. Insufficient deuteration might be attributed to the H-D exchange between MeOD and PhB(OH))$_2$ or direct proton transfer from PhB(OH)$_2$ to an alkenylcopper intermediate (Scheme 74).



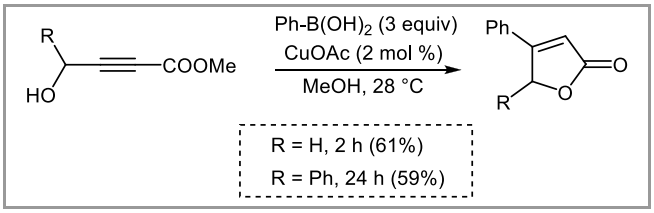
Scheme 74

Scheme 75 outlines a plausible mechanism of the Cu-catalyzed conjugate addition of arylboronic acids to alkynoates. Transmetallation from the arylboronic acids to copper methoxide (or acetate) proceeds via a four-centered transition state to yield reactive arylcopper species. Subsequent carbocupration of the alkynoates produces vinylcopper intermediates, which then undergo protonolysis by methanol to yield the final cinnamates with the concomitant restoration of copper methoxide. Because the protocol employs methanol as a solvent, the vinylcopper intermediates undergo facile protonolysis before isomerization, resulting in the stereoselective formation of the *syn*-hydroarylation products even at ambient temperature. In previous cuprate-based methods, a low reaction temperature was required to prevent the isomerization of the initially formed *syn*-carbocupration adducts to *anti*-isomers via allenolate intermediates.[104]



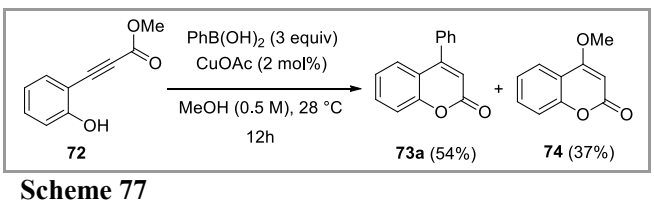
Scheme 75

The efficient copper-catalyzed addition reaction of bis(pinacolato)diboron to α,β-acetylenic esters has been also developed to give corresponding β-borylated-α,β-ethylenic esters in high yields under mild reaction conditions.[105] On the basis of the success of above studies, it was envisaged that applying the carbocupration procedure to alkynoate substrates with a hydroxyl terminal should allow an easy approach to unsaturated lactones via concomitant cyclization between the hydroxyl and ester carbonyl groups. The Cu-catalyzed hydroarylation of methyl 4-hydroxy-2-butynoate with phenylboronic acid gave 3-phenylbutenolide in 61% yield. When the reaction was carried out using phenyl substituted butynoate derivative, the corresponding 4,5-diphenylbutenolide was also obtained in comparable yield (scheme 76).



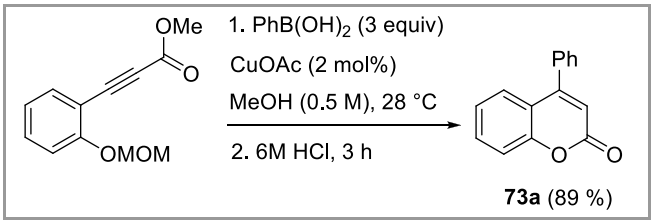
Scheme 76

Moreover, as an extension of this sequential hydroarylation/lactonization process, it was developed a synthetic approach to 4-arylcoumarines, which constitute a subgroup of flavonoids.[106] When the building block **72** was first subjected to hydroarylation conditions, 4-phenylcoumarin **73a** was obtained in 54% yield; however, unexpectedly, 4-methoxycoumarin **74** was also formed in 37% yield (Scheme 77).



Scheme 77

It was reasonable to assume that the *o*-hydroxy group played a key role in facilitating the addition of methanol. In fact, the MOM-protected derivative underwent smooth hydroarylation within 6h under the same conditions, and upon treatment with 6M HCl in refluxing MeOH in the same pot, the desired coumarin **73a** was formed in 89% yield as an exclusive product (Scheme 78).



Scheme 78

The scope of the method in terms of arylboronic acids was checked. Neither electrondonating nor electronwithdrawing groups gave a deleterious effect on the formation of coumarins **73** (figure 8).

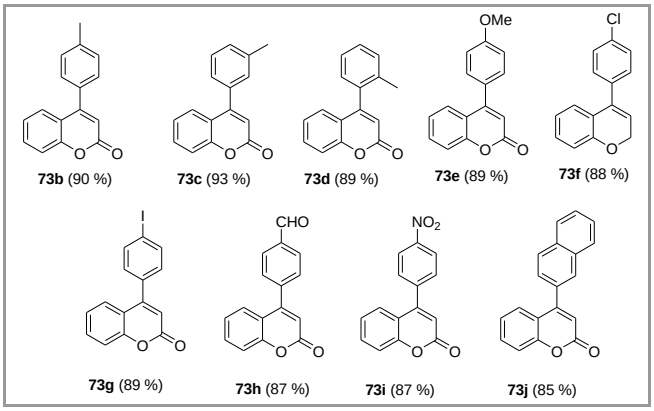
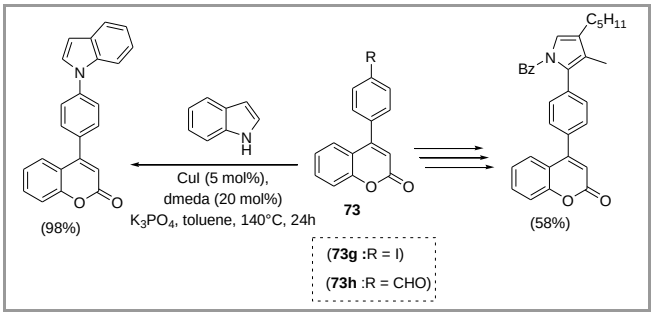


Figure 8

More importantly, the protocol was applied to arylboronic acids having a labile functional group, efficiently affording the corresponding coumarins **73g-h** without the loss of the reactive C-I bond or the formyl group. These functional groups are useful synthetic handles for further derivatizations (Scheme 79).



Scheme 79

The application of the method to the synthesis of natural products belonging to the Dalbergia family

highlights its utility (figure 10). The plants belonging to the Dalbergia family have been known to possess unique medicinal properties.

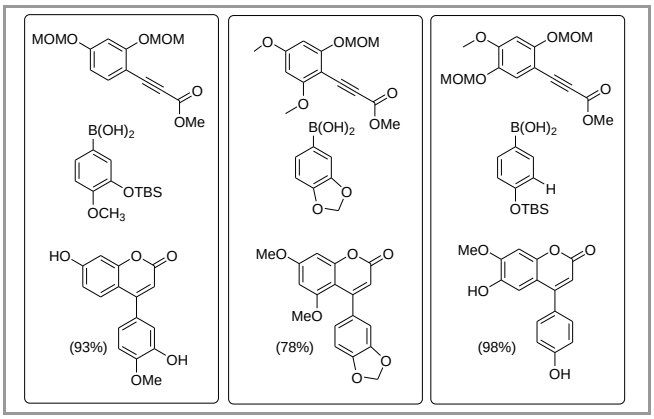
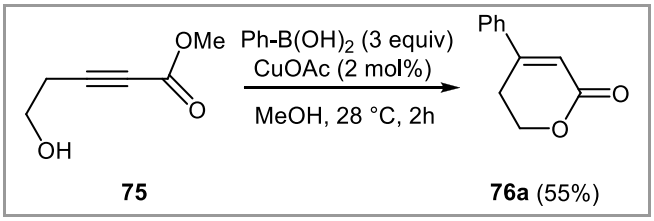


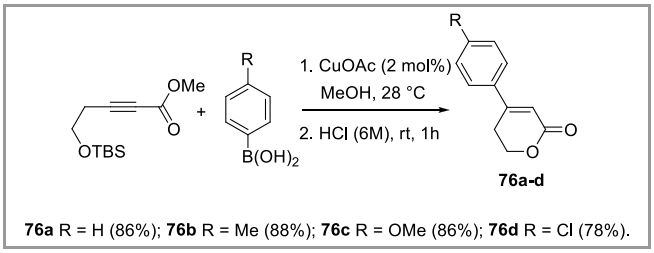
Figure 10

In order to examine the effect of the tether length between the alkyne and hydroxyl moieties on the reaction, it was carried out the copper-catalyzed hydroarylation of 5-hydroxy-2-pentynoate **75**. In contrast to the result obtained from 3-(2-hydroxyhethyl)propiolate, only the 4-phenylpentenolide **76a** was isolated, the corresponding 4-methoxypentenolide was not formed from **75** (Scheme 80).[107]



Scheme 80

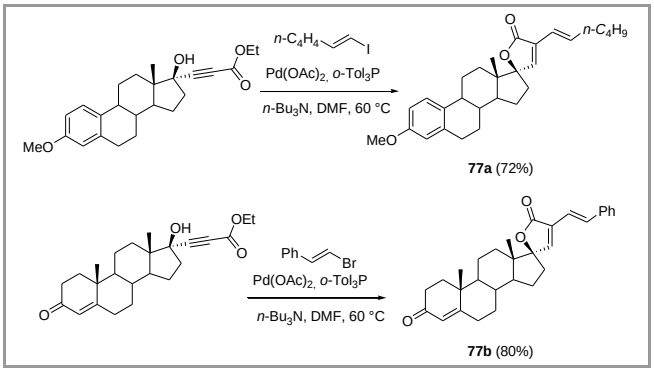
Very likely, the product selectivity depends on the distance of the hydroxyl group from the carbomethoxy moiety. Nevertheless, the use of the *tert*-butyldimethylsilyl (TBS) as protecting group increased the overall yield of products **76** (Scheme 81).



Scheme 81

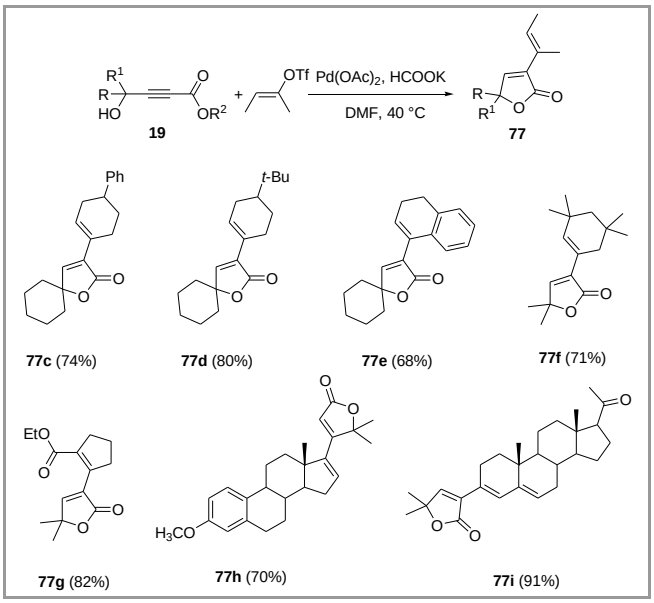
4.5 Transition Metal-Catalyzed Hydrovinylation/Heterocyclization Processes of α,β-Ynones and α,β-Ynoates Containing Proximate Nucleophiles.

Vinyl halides reacted with disubstituted acetylenes in the presence of the palladium-formate reducing system to give stereoselective formation of functionalized 1,2,4-trisubstituted-1,3-dienes in good to high yields.[108] The nature of the base and the temperature affected the regiochemical outcome of the reaction. A high degree of regioselectivity was observed in the hydrovinylation of steroidal γ-hydroxy-α,β-ynoates. In these cases, sequential hydrovinylation/heteroannulation occurred to give the corresponding 3-alkenyl-spirobutenolides **77a-b** in good yields (Scheme 82).



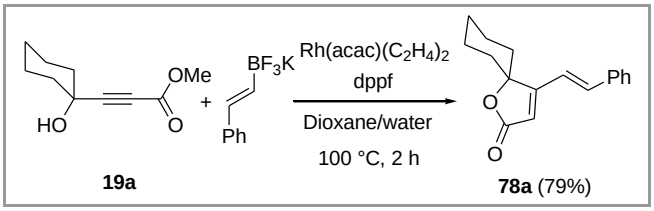
Scheme 82

Based on the concept of sequential hydrovinylation/cyclization of γ-hydroxy-α,β-acetylenic ester **19**, a general regioselective synthesis of 3-vinylfuran-2(5*H*)-ones **77** from vinyl triflates was also explored.[109] The reactions were carried out in DMF at 40 °C using the following molar ratios: vinyltriflates:**19**:HCOOK:$Pd(OAc)_2$ = 1:1.2:2:0.05. The omission of the phosphine ligands resulted the key to direct the outcome of the reaction towards the desired hydrovinylation product by hampering the competitive palladium-catalyzed reduction of triflates to the corresponding alkenes (Scheme 83).



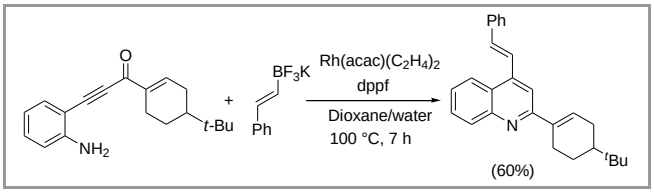
Scheme 83

The regioisomeric 4-vinylfuran-2(5*H*)-ones **78** can be readily available by means of the sequential rhodium-catalyzed stereo- and regio-selective addition of vinyl organoboron derivatives to the alkyl 4-hydroxy-2-alkynoates/lactonization reaction. The formation of the derivatives **78** occurred by reacting the ynoate **19** with an excess (5 equiv) of the potassium β-styryltrifluoroborate in the presence of the catalytic system Rh(acac)(C_2H_4) (0.03 equiv.)/dppf (0.06 equiv) in dioxane/water 10/1 at 100 °C for 2 h (Scheme 84).[95]



Scheme 84

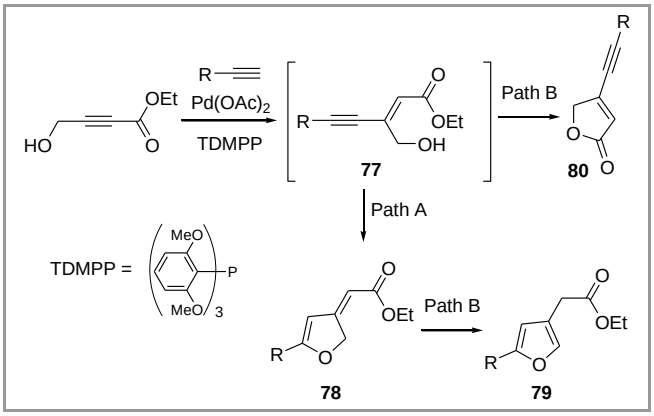
The rhodium-catalyzed process was also applied to the regioselective preparation of 4-vinylquinolines (Scheme 85).[94]



Scheme 85

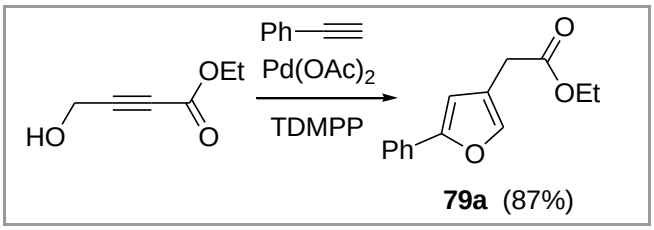
4.6 Transition Metal-Catalyzed Hydroalkynylation/ Heterocyclization Processes of α,β-Ynones and α,β-Ynoates Containing Proximate Nucleophiles

While the Michael reaction of stabilized carbon nucleophiles constitutes one of the fundamental C-C bond forming processes, this process does not generally extend to acetylide anion. Effecting such additions by use of a transition metal catalyst may have the advantage of (a) extending the reaction to acceptors that may not otherwise participate, (b) controlling stereochemistry (geometry) where applicable, (c) promoting further useful transformations of the initial adducts, and (d) enhancing synthetic efficiency by not requiring stoichiometric amounts of reagents like bases or metals. Trost reported that the addition of terminal alkynes to γ-hydroxy ynoates may be readily directed to form either furans **79** in two tandem palladium-catalyzed reactions or butenolides **80** in a palladium tin co-catalyzed event (scheme 86).[110]



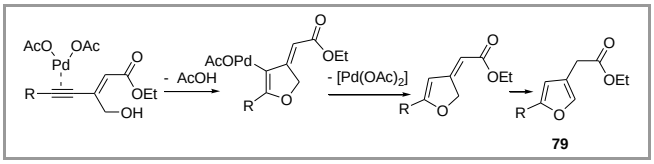
Scheme 86

Addition of 1 equiv of alkyne and 1 equiv of alkynoate to 2 mol% TDMPP, 5 mol% $Pd(OAc)_2$ in benzene at room temperature followed by 0.75-1.5 equiv of DBU gave furan **79a** in 87% yield after direct column chromatography of the reaction mixture (Scheme 87).



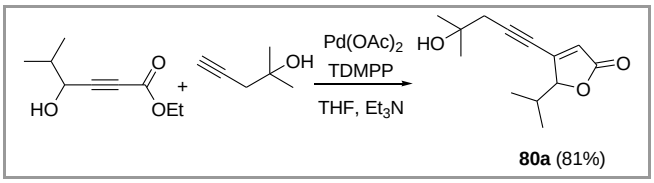
Scheme 87

The role of the ratio of the rather basic phosphine TDMPP relative to palladium acetate in promoting furan formation was investigated. Increasing the amount of palladium acetate relative to TDMP dramatically improved its formation. Thus, the use of a 1:2 or preferably 2:5 TDMPP:$Pd(OAc)_2$ ratio effects complete addition and cyclization to the isofuran derivative. The following tautomerisation is completed upon addition of DBU at this point. (Scheme 88).



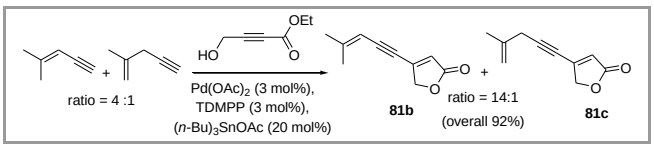
Scheme 88

Since uncomplexed palladium acetate enhances furan formation, it was taught that the addition of a base like triethylamine may reduce the Lewis acidity of palladium acetate as well as serve as a general base catalyst for lactonization. Indeed, furan formation was completely suppressed and butenolide **80a** was isolated in 81% yield by using a 1:1 THF:Et_3N mixture as solvent (Scheme 89).



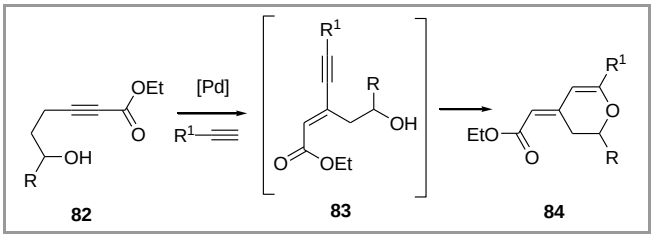
Scheme 89

A much more effective approach involved addition of a catalytic amount (10-40 mol%) of tri-*n*-butyltin acetate as a transesterification catalyst. The addition of 20 mol% of tri-*n*-butyltin acetate to 3 mol% palladium acetate and 3 mol% TDMPP in THF followed by 1 equiv of hydroxy ynoate and 1 equiv of terminal alkyne for 16h at room temperature accomplished the formation of the butenolide derivative after direct column chromatography of the reaction mixture. The utility of this protocol was examined in the synthesis of the natural product cleviolide **81b** which by virtue of the sensitivity of the polyunsaturation within a small molecular framework demands very mild methods. Interestingly, a 92% yield of a 14:1 ratio of cleviolide **81b** to isocleviolide **81c**, from which pure cleviolide can be crystallized, was isolated by reacting an excess of a 4: 1 ratio of the conjugated and unconjugated enynes with ethyl 4-hydroxybutynoate (Scheme 90).



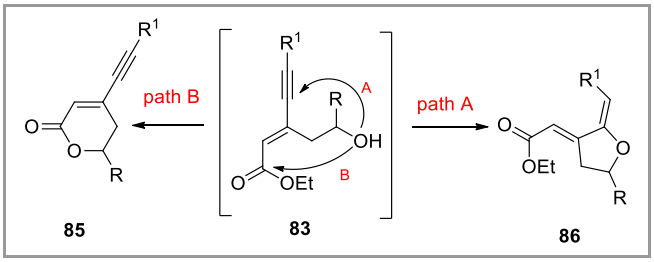
Scheme 90

Strategies based upon the 6-*endo-dig* cyclization of intermediate adducts **83** derived by palladium-catalyzed addition of terminal alkynes onto ynoates **82** have been explored with the aim of accessing the synthesis of bryostatins and other natural products showing promising antitumor activity (Scheme 91).[111]



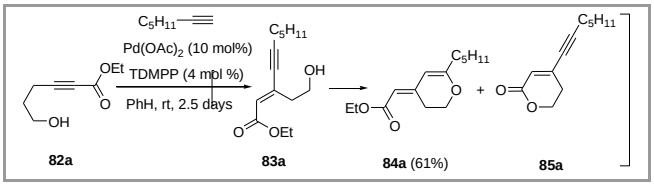
Scheme 91

Two potential competing processes to the 6-*endo-dig* cyclization were immediately evident: a lactonization to δ-pentanolactone **85** (Scheme 92, path B) or a 5-*exo-dig* cyclization to diene **86** (Scheme 92, path A).



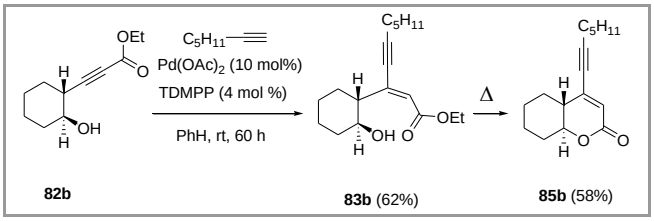
Scheme 92

The reaction of 1-heptyne and methyl 5-hydroxy-2-pentynoate **82a** catalyzed by palladium acetate with tris-(2,6-dimethoxyphenyl)phosphine as ligand gave the dihydropyran **84a** in satisfactory yield as the only detectable product (Scheme 93). Following the reaction by thin-layer chromatography revealed that formation of the simple adduct **83a** occurred completely within 24 h; but cyclization proceeded very slowly. Increasing the reaction temperature to 50°C when the formation of adduct **83a** was clomplete or simply running the reaction at 50°C led to a significant reduction in reaction time with about the same yield but gave rise to competitive formation of lactone **85a**. A workable solution was found by increasing the catalyst loading whereby a 61% isolated yield of dihydropyran **84a** was isolated as the only product.



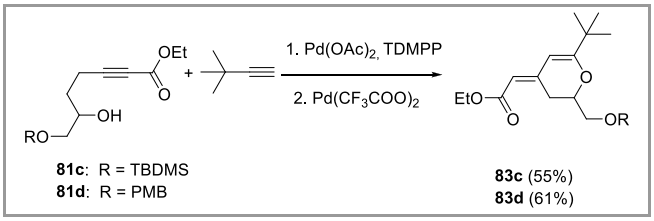
Scheme 93

On the other hand, the *trans*-hydroxyalkynoate **82b** gave the expected adduct within 2 days (50% isolated yield). Use of more forcing conditions gave no dihydropyran but only lactone **85b**, which was isolated in 58% overall yield (Scheme 94).



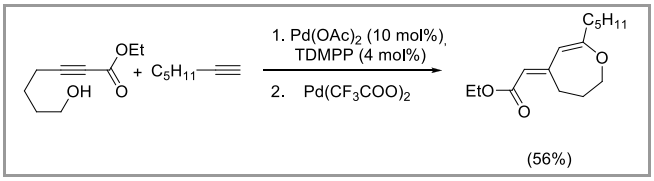
Scheme 94

Based on the previously observed dramatic enhancement of rate in formation of π-allylpalladium complexes from less nucleophilic alkenes upon using palladium trifluoroacetate, a one-pot protocol achieving the rapid conversion of the two alkyne **81c,d** directly to the dihydropyran was developed. A 1:1 mixture of palladium acetate and TDMPP for the initial addition (stage one) followed by addition of palladium trifluoroacetate for the cyclization (stage two) were used. The effectiveness of this protocol is highlighted by the successful synthesis of the dihydropyrans **83c,d** (Scheme 95). Placing a conjugating substituent like phenyl on the terminal alkyne makes the 5-*exo-dig* cyclization now compete with the 6-*endo-dig* product.



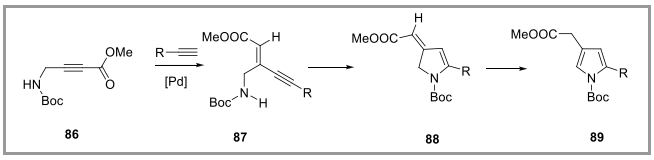
Scheme 95

The two-stage one-pot catalytic system employing the combination of palladium acetate and palladium trifluoroacetate allowed the extension to the formation of seven-membered rings, a cyclization that completely fails in the absence of the palladium trifluoroacetate (Scheme 96).



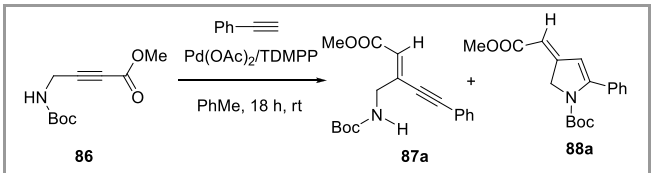
Scheme 96

The addition of terminal alkyne to suitably activated propargyl amine **86** resulted in ynenoate **87**, whose isomerization via a 5-*endo-dig* cyclization and tautomerisation then provided pyrrole **89** (Scheme 97). [112]



Scheme 97

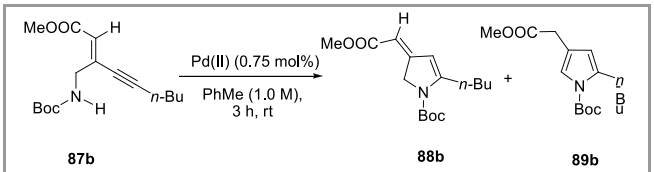
Initial investigations employing phenyl acetylene as the donor alkyne with toluene as the solvent revealed that product distributions depend on the ratio of Pd(OAc)$_2$ to the *tris*-(2,6-dimethoxyphenyl)phosphine (TDMPP) ligand. Accordingly, an equimolar amount of ligand and metal cleanly afforded ynenoate **87a** as a single geometrical isomer, whereas decreasing the amount of TDMPP resulted in competitive formation of isopyrrole **88a** (Scheme 98).



Entry	Pd(OAc)$_2$ (mol %)	TDMPP (mol %)	Ratio **87a/88a**	Conversion (%)
1	3.0	3.0	20/1	100
2	3.0	1.5	3/2	100
3	3.0	0.8	1/5	100

Scheme 98

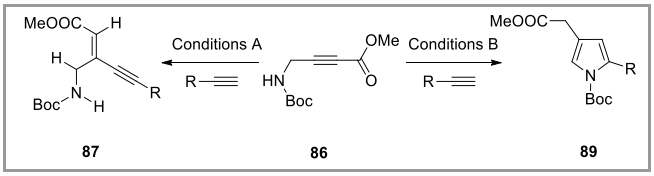
Importantly, pyrrole formation was not observed under the reaction conditions, and increasing either the reaction time or temperature resulted in complex mixtures and poor mass recovery. While both free and phosphine-ligated Pd(OAc)$_2$ were ineffective at promoting isomerization to the pyrrole product, Pd(OTFA)$_2$ resulted in clean formation of pyrrole **89b** from ynenoate **87b**. In this case, both acetonitrile and benzonitrile complexes of $PdCl_2$ were not as effective as Pd(OTFA)$_2$, which promoted the desired cyclization and tautomerisation in near quantitative yield. Once again, TDMPP was found to inhibit both of these transformations suggesting that a nonphosphine-ligated Pd species is responsible for catalysis (Scheme 99).



Entry	Pd(II)	TDMPP (mol %)	Ratio **88b/89b**	Conversion (%)
1	Pd(OTFA)$_2$	-	1/20	100
2	Pd(OTFA)$_2$	0.4	1/20	95
3	Pd(OTFA)$_2$	0.8	1/2	72
4	$PdCl_2$(MeCN)$_2$	-	1/1	47
5	$PdCl_2$(PhCN)$_2$	-	1/20	52

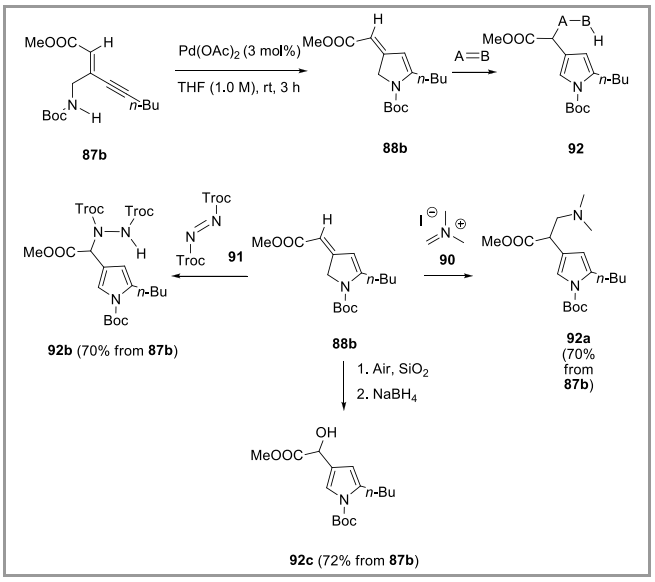
Scheme 99

Thus, treatment of **86** with a variety of aromatic alkynes in the presence of $Pd(OAc)_2$ (0.75 mol%) and TDMPP (0.75 mol%) in toluene at room temperature afforded the corresponding ynenoate **87** in 77-97% isolated yields after 6h (Scheme 100, conditions A). Nonaromatic donor alkynes generally required slightly longer reaction times (12-24 h), and provided ynenoates **87** in 64-97% isolated yields. Alternatively, pyrroles **89** can be obtained in yields ranging from 60 to 99% in a two-stage, one-pot process (Scheme 100, conditions B). For aromatic donors, addition of $Pd(OTFA)_2$ (1.5 mol%), following complete conversion to the ynenoate, resulted in the cyclized/isomerized product after only 6h. Once again, nonaromatic donors require slightly longer reaction times and higher catalyst loadings (5 mol% $Pd(OTFA)_2$) but nevertheless returned good to excellent yields of the desired products after 24h. Importantly, these reactions are performed in screw-cap vials under an ambient atmosphere, with commercial grade alkynes and benchtop solvents. Furthermore, yields remain consistent upon scale-up. The method tolerates a wide range of substituted donor alkynes. *Ortho*-, *meta*-, and *para*-substituted aromatic alkynes with both electrondonating and electronwithdrawing groups participate effectively. Given the involvement of Pd(II) species throughout both the coupling and the isomerization steps, aryl bromides do not interfere with the reaction. The basic nitrogen of an unprotected aniline is also tolerated in the coupling portion of the cascade. In addition to aromatic donors, aliphatic alkynes undergo efficient coupling and isomerization. Importantly, both free and acetylated propargyl alcohols react smoothly under the standard conditions. Interestingly, the use of a 1,3-enyne as a donor provided an efficient synthesis of desirable C-vinyl pyrroles.



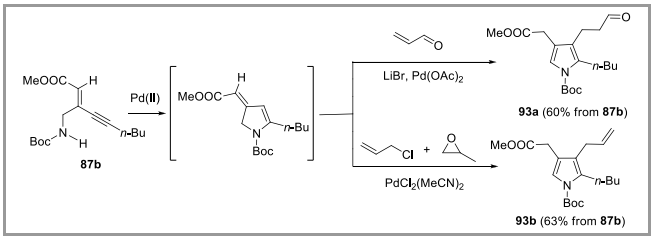
Scheme 100

The use of Pd catalysis to effect the cyclization of **87** offered additional avenues for substitution of the pyrrole nucleus. The ynenoate **87b** was cyclized to isopyrrole **88b** in quantitative yield in the presence of $Pd(OAc)_2$ (3 mol%) in THF. Gratifyingly, **88b** underwent addition to both Eschenmoser's salt **90** and diazene **91**, affording products of C-C and C-N bond formation, **92a** and **92b** respectively. In addition, oxygenation affording the hydroxy derivative **92c** could be effected by simply stirring **88b** overnight open to the atmosphere in the presence of SiO_2 (Scheme 101).



Scheme 101

The ability to intercept isopyrrole **88** provided attractive, atom-economical avenue for further derivatizations of the pyrrole side chain. The palladium-catalyzed cyclization of **87b** in the presence of acrolein and LiBr afforded **93a** via a reductive Heck-type addition reaction. Alternatively, allylation in the 3-position was effected with allyl chloride in the presence of $PdCl_2(CH_3CN)_2$ and propylene oxide as a suitable acid scavenger (Scheme 102).



Scheme 102

Conclusion

Research activities aimed to the employment of valuable synthetic building blocks for the development of increasingly efficient synthetic processes, demonstrated that addition reactions over α,β-ynones and α,β-ynoates containing proximate nucleophiles can be interfaced with subsequent cyclization to generate more complex functional molecules. The synthetic approaches to heterocyclic derivatives from these starting building blocks based on sequential processes involving conjugate addition-type, pericyclic and transition metal-catalyzed transfer hydrogenation/hyroarylation/hydrovinylation/hydroal kynylation reactions followed by annulation have been summarized. These methodologies benefit from the ability to conduct multiple chemical transformations in a single reaction vessel, providing their intended targets while minimizing waste associated with traditional isolation and purification protocols.

Acknowledgment

The authors are grateful for financial support from the Università degli Studi dell'Aquila and Università degli Studi di Milano.

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