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SEDE DI COMO

Facolta' di Scienze MM.FF.NN.

Dipartimento di Scienze Chimiche e Ambientali

DOTTORATO IN SCIENZE CHIMICHE

XXIII CICLO

GOLD CATALYZED HETEROCYCLIZATION PROCESSES

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1. Introduction

Gold is probably the sole chemical element that literally every person has heard about. Its highly positive potential is responsible for a low reactivity and diffusion in nature in elemental form. One of the most important characteristics of gold is its durability. In fact a lot of ancient art is made of gold. In the past, the monetary system was based on rare gold and as a result this metal was also responsible for gold rushes, wars, conquering of whole continents.

Gold is also used in medicine, such as, in dental healthcare, in arthritis treatments, and recently its anticancer activity has been discovered. Metallic gold is highly biocompatible but gold in ionic form is toxic.[1]

Organic chemists didn't use gold as a catalyst in the past probably because of the low reactivity deduced from the inertness of the elemental gold that only dissolves in *aqua regia* or oxidants such air in presence of strong ligands.

Another reason that prevented the use of gold as potential catalyst, was the high value associated with this metal and the idea that such a catalyst would be unaffordable. This idea is changing for many reasons: monetary systems are not based on gold, the so called "queen of metals" is now less expensive than other metals like rhodium, palladium and platinum. Thousand tons of gold are recycled from stoichiometric technical applications and the same amounts is produced in gold mines every year. This is an advantage compared to rhodium, palladium and platinum because determines a high stability of its price and can justify its use for industrial applications.

Gold catalysts, because of their unique properties have now become well-established best option for many chemical transformations in both heterogeneous and homogeneous processes. Gold salts can promote chemical transformations at room temperature with reaction times of just minutes.[2] This contrasts with other metal-catalyzed reactions that require higher temperatures and reaction times of hours or even days. Furthmore the high reactivity of many metal complexes renders the reactions they catalyze sensitive to both air and moisture and limits their practical utility. Conversely, gold

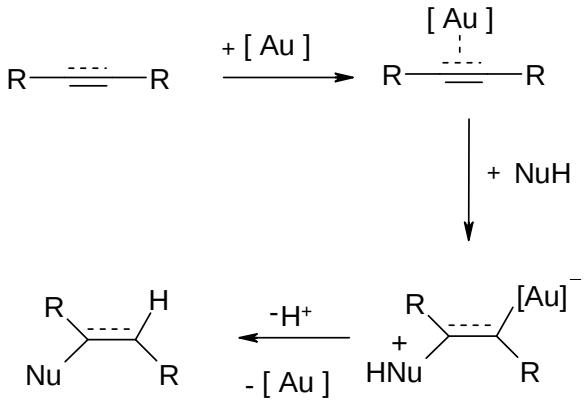
derivatives are robust transition metal catalysts showing air and moisture tolerance and generation only of environmentally safe byproducts.[3] Moreover Au(I) has a good redox stability under ambient conditions and this allows the development of a new way of reactivity without the traditional oxidative addition/reductive elimination cycles so present in late transition-metal catalysts.

Gold catalysts can work very often without ligands under mild conditions and are effective even when very small amounts are used.[4]

1.1 Gold catalyzed nucleophilic additions to C-C multiple bonds

C-C multiple bonds of alkynes, allenes, or olefins coordinate to gold complexes; in this way gold efficiently activates them for the attack of a nucleophile. Other metals like Hg^{2+} are able to activate C-C multiple bonds of alkynes or olefins but the resulting C(sp^3)-Hg bond is usually kinetically stable and requires an extra step to release organic ligand. Thus the overall transformation become stoichiometric in toxic mercury salts.[5,7] Gold catalysis is able to solve this problem because the C-(sp^3)-Au is easily protonated regenerating the active catalyst and releasing the product (Scheme 1).

Scheme 1



As depicted in Scheme 1, gold catalyst coordinates the π-system of the substrate to form an organogold intermediate that undergoes nucleophilic attack. There's evidence that the nucleophile

attacks *anti* to gold to deliver the vinylgold intermediate.[8] Then the organogold intermediate liberates the addition product and the gold catalyst by protodemetallation.

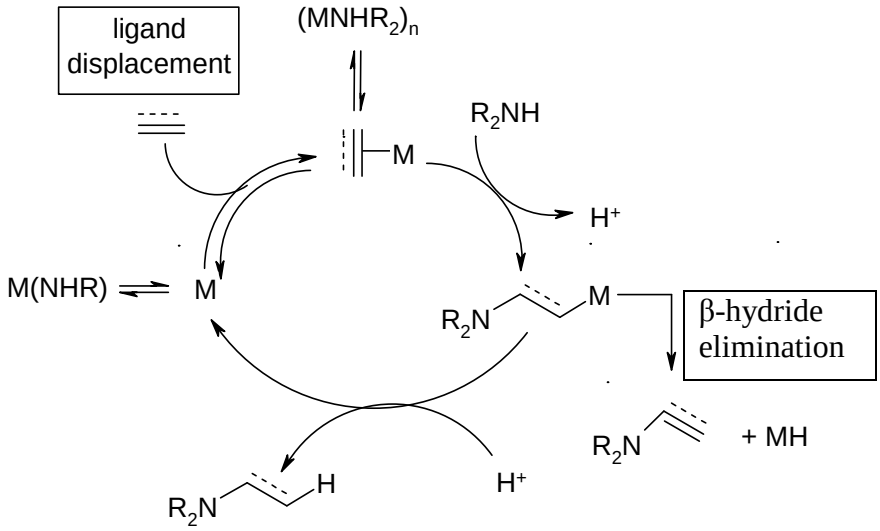
1.2 Gold-catalyzed hydroamination of C-C multiple bonds

Nitrogen-containing heterocycles are a broad and important class of compounds widely spread in nature,[9] often with very high biological activity.[10] Limitations associated to traditional methods for C-N bond formation prompted organic chemists to investigate catalytic addition of N-H bond across a C-C multiple bond as an atom-economical and straightforward route to the synthesis of amine derivatives.

As depicted in Scheme 2, a potential catalytic cycle for hydroamination has been hyphotesized. The C-C multiple bond is activated toward nucleophilic attack by complexation to an electron-deficient, late-transition-metal complex.[11] The following protonolysis releases the amine derivative and regenerates the catalyst.

This approach to hydroamination is suitable for late-transition-metal complexes because they have low oxophilicity and display good tolerance to many functional groups but low air and moisture sensitivity as well. However amines have a very high ligating ability and so they can often poison the metal forming stable complexes without delivering the desired product. Moreover the metal-alkyl complexes formed by nucleophilic attack are often resistant to protonolysis and can give β-hydride elimination, resulting in oxidative amination and hydroamination competitive paths.[12,13]

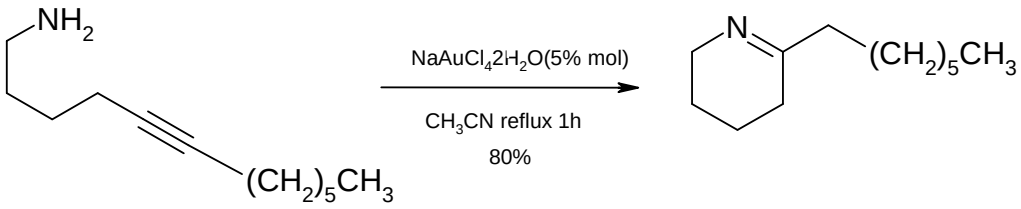
Scheme 2



Au^{III} and cationic Au^{I} are very carbophilic Lewis acids and are able to activate C-C multiple bonds toward nucleophilic attack.[14] These complexes, Au^{I} in particular, being so little oxophilic, display very good functional group compatibility and low sensitivity to air and moisture. Moreover alkylgold complexes are stable to β-hydrogen elimination and are highly reactive with respect to protonolysis of the Au-C bond.[15,16] These are the reasons why Au^{III} and Au^{I} are widely used in hydroamination reactions of alkynes, alkenes, allenes.

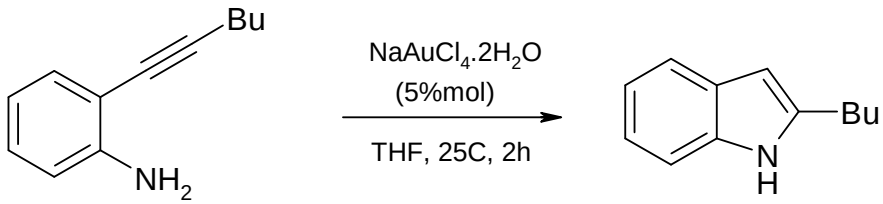
Many examples of gold catalyzed inter and intramolecular hydroamination reactions are present in literature. In particular, gold catalyzed intramolecular cyclization is very interesting. The first example of Au^{III}-catalyzed intramolecular hydroamination to form tetrahydropyridine was reported by Utimoto (Scheme 3).[17]

Scheme 3



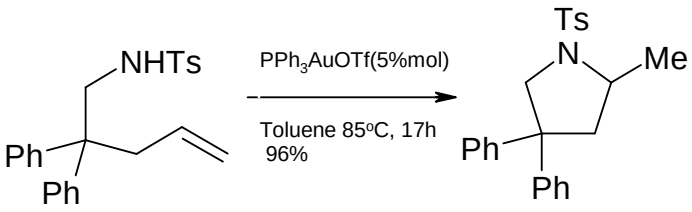
Au^{III} catalyzed hydroamination of 2-(1-alkynyl)-anilines to form 2-(butyl)-indole was also reported by Utimoto (Scheme 4).[18]

Scheme 4



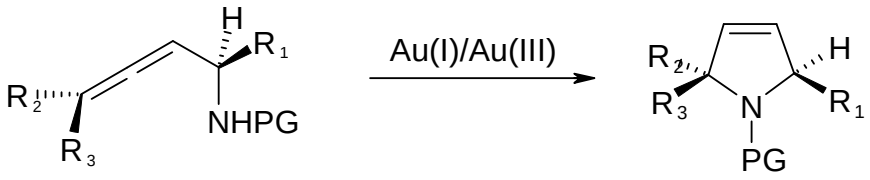
One of the most difficult and challenging goal in homogeneous catalysis is the hydroamination of inactivated alkenes. Au^{I} catalyzed intramolecular hydroamination of unactivated alkenes with sulphonamides as the nitrogen nucleophile has been reported (Scheme 5).[19]

Scheme 5



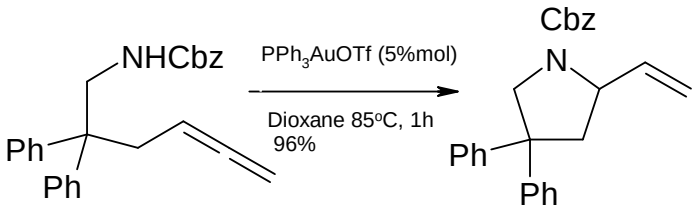
Intramolecular cyclization of allenes with tethered amines, in the presence of a transition metal catalyst represents the most common route to generate nitrogen-containing heterocycles. Allenes are more reactive towards transition metals than alkenes and Au^{I} as well as Au^{III} are able to catalyze at room temperature intramolecular hydroamination of allenes leading to pyrroldines and piperidines (Scheme 5).[20]

Scheme 5



Effective protocols for the *exo*-hydroamination of *N*-allenylcarbamates catalyzed by (phosphane)gold(I) complex has been reported by Widenhoefer (Scheme 6).[21]

Scheme 6

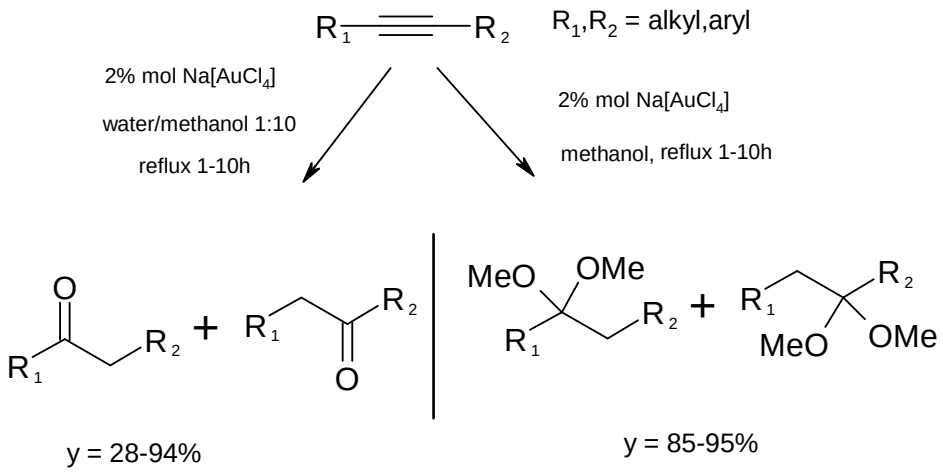


1.3 Gold catalyzed hydroalkoxylation of C-C multiple bonds

Water and alcohol can serve as nucleophiles in inter and intramolecular gold catalyzed hydroalkoxylation reactions of alkynes. These reactions were known to be catalyzed by mercury (II) salts under very acid conditions or by palladium or platinum (II) salts.[22]

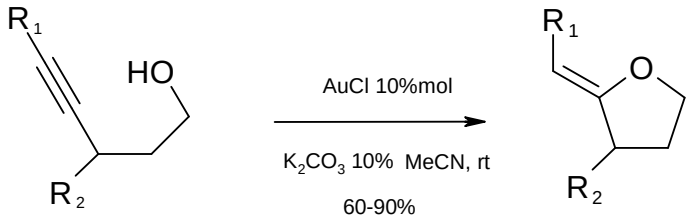
The first catalytic alkynes hydration with gold catalyst ($HAuCl_4$) appeared in 1976.[23] Then Utimoto *et al.* discovered that with 2% mol of $Na[AuCl_4]$ as catalyst, water and alcohols can be used as nucleophiles under mild conditions (Scheme 7).[24]

Scheme 7



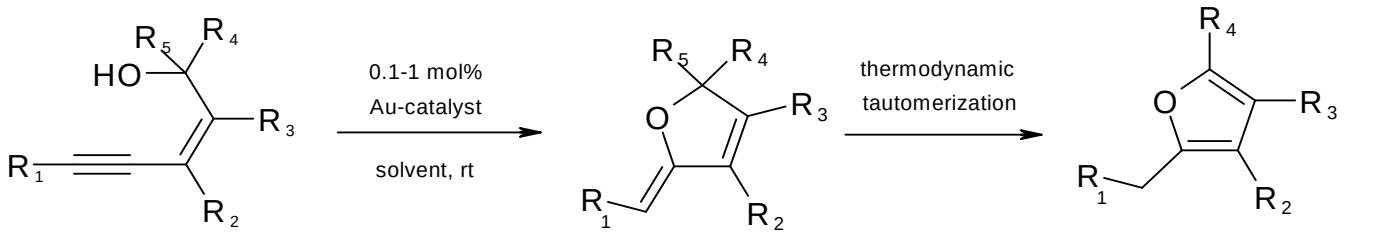
Intramolecular addition of a hydroxyl group to a C-C triple bond was also reported. Catalytic amounts of AuCl and K_2CO_3 are able to convert ω-acetylenic alcohols in α-alkylidene oxygenated heterocycles in a regio- and stereo selective way (Scheme 8).[25]

Scheme 8



(Z)-3-Ethynylallylalcohols can be transformed to furans using both gold(III) and gold(I) in different solvents (Scheme 9).[26,27]

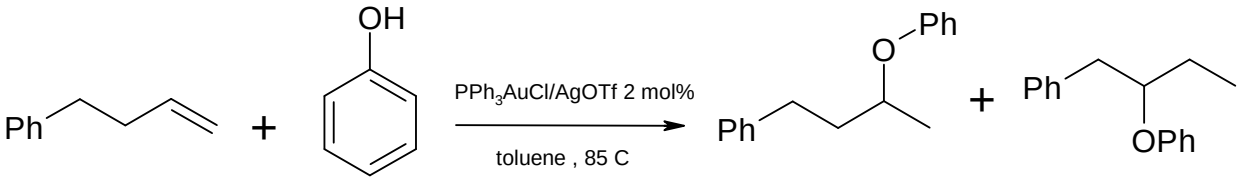
Scheme 9



R_1-R_5 = alkyl,aryl,H (for R_5 not H : 83-97%) (for R_5 = H : 12-100%)

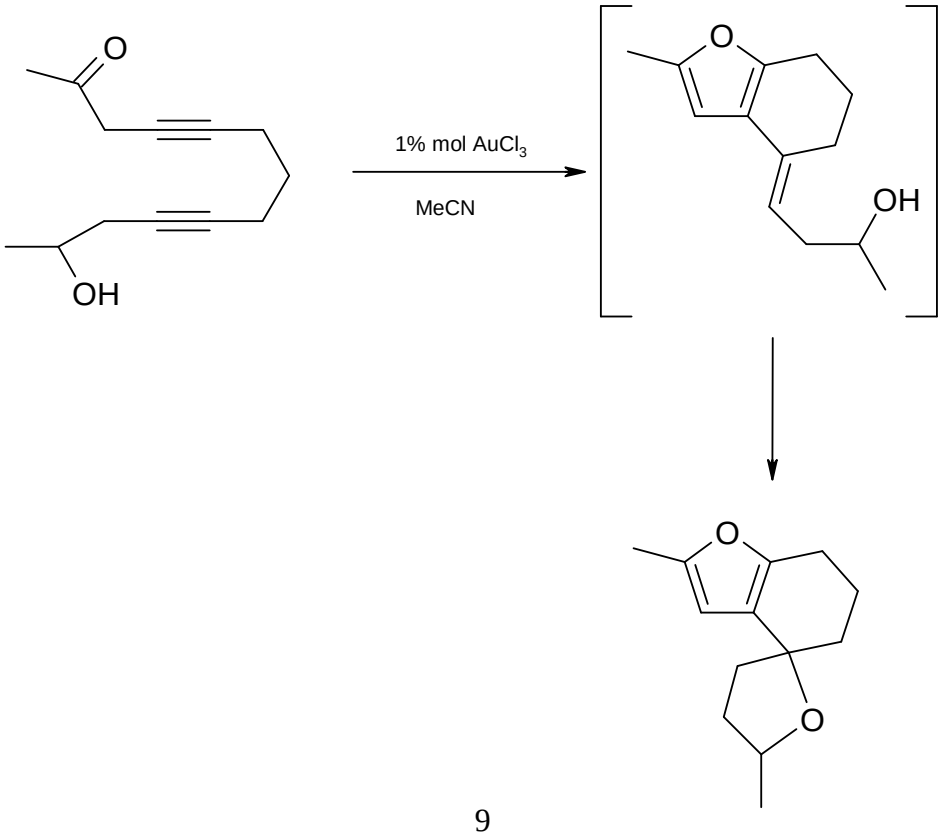
Also simple olefins can be activated by gold toward the inter and intramolecular hydroalkoxylation reactions. An example is the formation of phenyl-alkyl ethers using gold(I) as a catalyst.[28] Cationic gold(I) binds and activates olefins allowing the nucleophilic attack of phenols or carboxylic acid (Scheme 10). This reaction is similar to the palladium(II) catalyzed Wacker process.[29]

Scheme 10



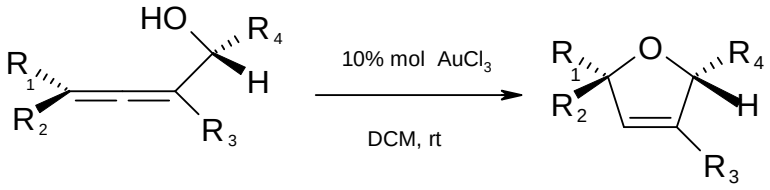
The first intramolecular addition of a hydroxyl group to an activated alkene using gold catalysis was reported by Hashmi in 2000 (Scheme 11).[26]

Scheme 11



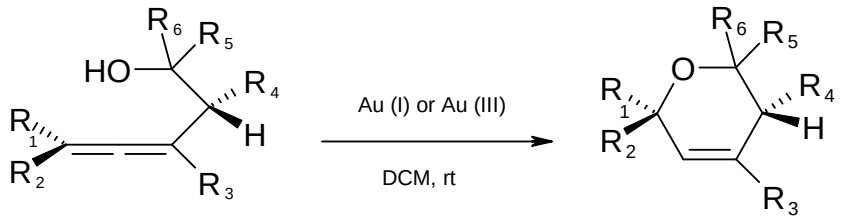
Allenes are not simple substrates because they show problems linked to the chemo, regio and stereo selectivity.[30] The intramolecular hydroalkoxylation of allenes was reported by Krause and Hoffmann-Röder for the cycloisomerisation of allenyl carbinols to give 2,5-dihydrofurans with good stereocontrol.(Scheme 12).[31]

Scheme 12



Both gold(I) and gold(III) are able to cyclomerize β-hydroxyallenes leading to dihydropyrans in good yield, with high regio (no traces of 5-exo-isomer were observed) and stereo-selectivity (Scheme 13).[32]

Scheme 13



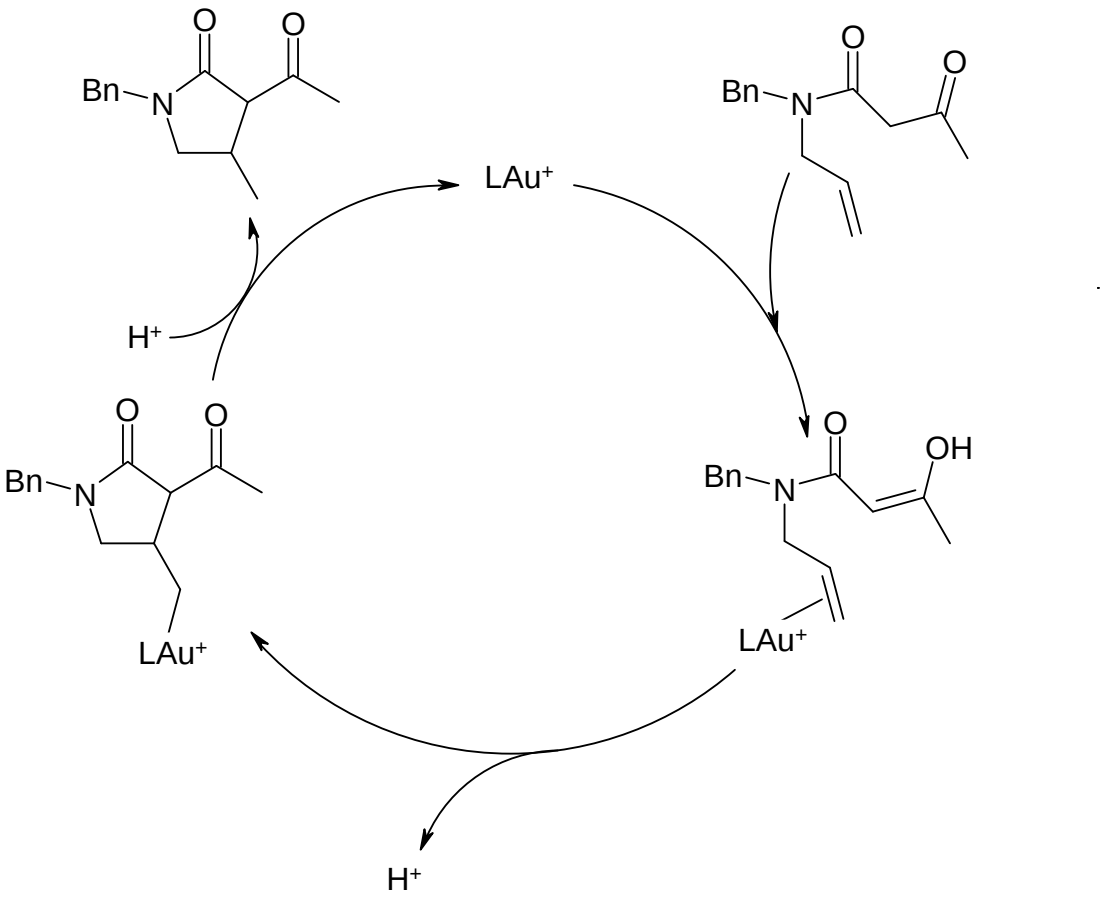
R_1, R_2, R_3 = H, alkyl
R_4 = CO_2Et, OAc
R_5,R_6 = H, Me

1.4 Gold catalyzed functionalization of C_{sp}^3-H, C_{sp}^2-H, C_{sp}-H bonds.

The activation and functionalization of C-H by metal complexes is a very difficult problem in organic chemistry but the importance for this organic transformation encouraged chemists to try new metal catalysts to achieve better results.[33]

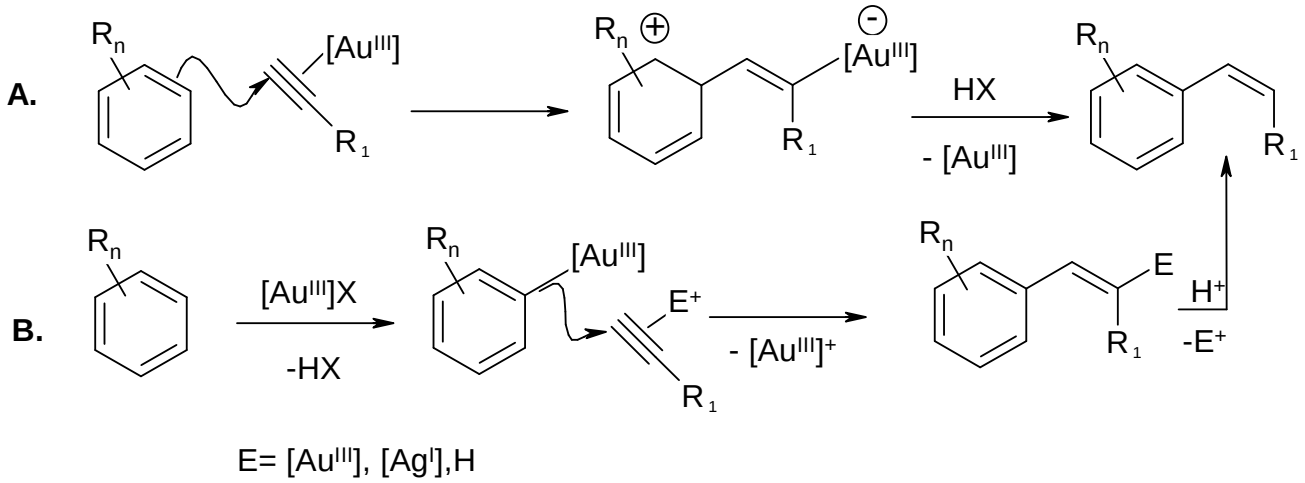
Gold(I) and gold(III) are both able to activate and functionalize C-H bonds. An example of C_{sp}^3-H bond functionalization is the intramolecular alkylation of 1,3-dicarbonyl compounds that is achieved using $AuCl_3$/AgOTf as a catalytic system.[34] In this field an attractive target is the synthesis of substituted lactams by intramolecular addition of β-ketoamide to unactivated alkenes using gold(I) as a catalyst (Scheme 14).[35]

Scheme 14



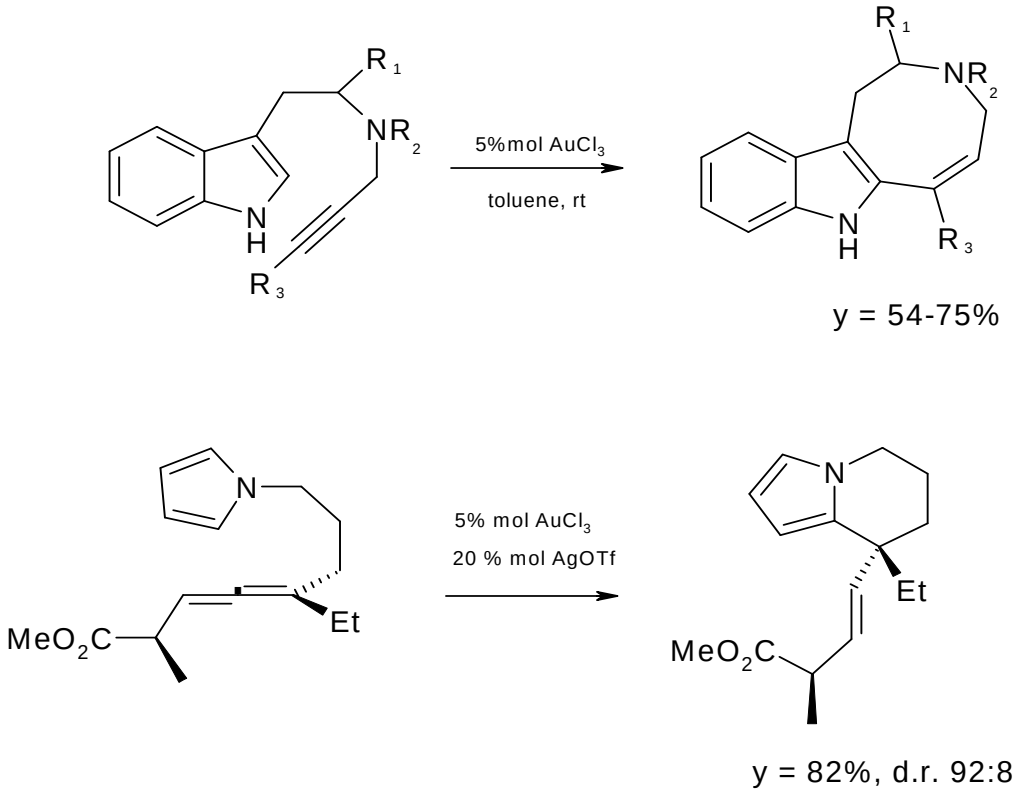
Very interesting is the activation and functionalization of a C_{sp}^2-H bond. The first report of hydroarylation of alkynes by gold was reported by Reetz and Sommer.[36] Hydroarylation mechanism is not well defined. Two different hypothesis have been considered: the first is a Friedel-Craft like-mechanism involving activation of the alkynes by carbophilic gold center (Scheme 15 A).[36] The second one involved the formation of an aureate arene gold intermediate that attacks the activated alkyne (Scheme 15 B).[37] Both of mechanisms furnish the (*Z*)-alkene product.

Scheme 15



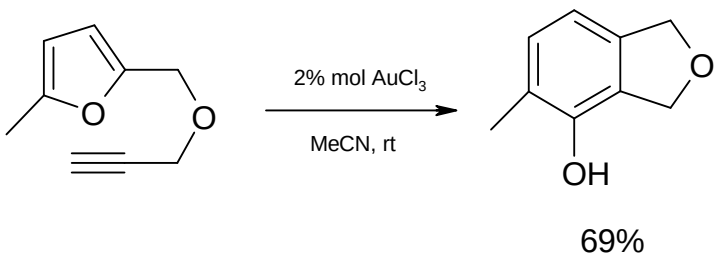
Electron rich arene like pyrrole, indoles, furans, etc. can react, as the nucleophiles, intramolecularly with alkynes, alkenes or allenes in the presence of a gold catalyst to give from six to eight membered ring annulated compounds (Scheme 16).[38,39]

Scheme 16



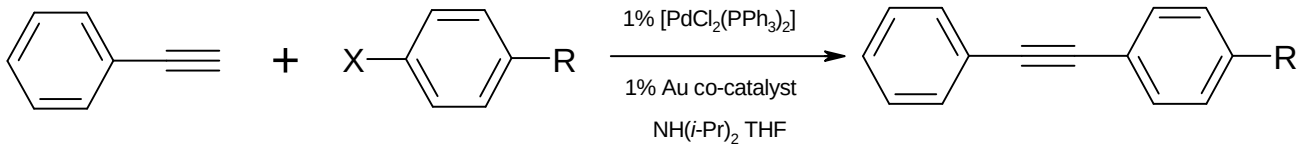
A further example of C_{sp}^2-H bond functionalization is the synthesis of phenols starting from ω-alkynyl furans using $AuCl_3$ as a catalyst reported by Hashmi's group. The reaction showed high selectivity so no side products were detected (Scheme 17).[40]

Scheme 17



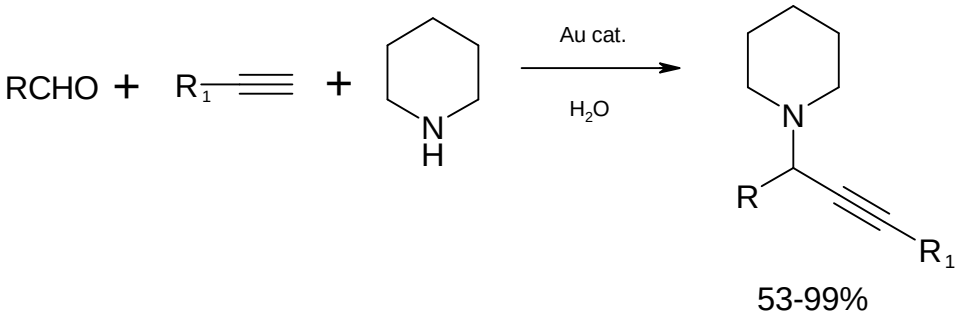
Gold is also able to functionalize C_{sp}-H bond, for example the activation of C-H of 1-alkynes in the Sonogashira coupling with aryl iodide can be accomplished using gold(I) complexes instead of CuI as a cocatalyst.[41] The reactions are cleaner and can be carried out in technical grade solvent without previous purification and in presence of air (Scheme 18).

Scheme 18



The C-H bond activation of 1-alkynes by gold has been used by Wei and Li as well as in the three components coupling of aldehydes, alkynes and amines (Scheme 19).[42]

Scheme 19



2. Results and Discussion

2.1 Gold catalyzed intramolecular hydroamination of α-aminoallenamides

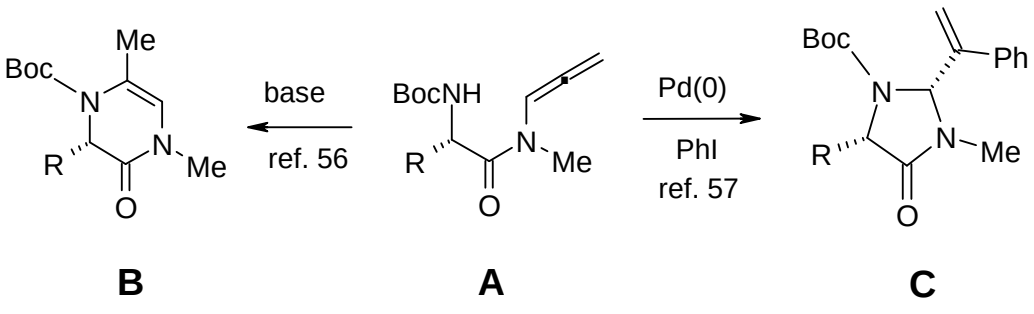
Intramolecular hydroamination, the formal addition of N-H group to carbon carbon multiple bond, is a direct and efficient procedure for the synthesis of nitrogen-containing heterocycles.[43]

Cyclization of allenes with tethered amines represents a fruitful route for this scope. Some alternative strategies based on basic[44] or transition metal-catalysts[45] have been used for this purpose. Among the latter palladium,[46]gold,[47]silver,[48]ruthenium,[49]copper,[50]cobalt,[51] mercury,[52], and titanium,[53] warrant a wide range of procedures such as domino reactions, oxidative cyclizations, cyclocarbonylations, and cycloisomerizations which allow them to differently achieve functional products.

In recent years homogeneous catalysis using gold salts has emerged in organic synthesis as a powerful arm for interesting and useful transformations.[54] The success of the gold catalysis involving allene substrates is related to its ability to coordinate with C-C bonds, thereby allowing the attack of various nucleophiles both in inter- and intramolecular fashion.[55]

Taking into consideration recent works on heterocyclization of α-amino allenamides **A**, under base-promoted[56] and domino palladium-catalyzed[57] conditions to give dihydropyrazinone and imidazolidinone **B** and **C**, respectively (Scheme 20), we thought of undergoing these substrates under reaction in the presence of gold-salts.

Scheme 20



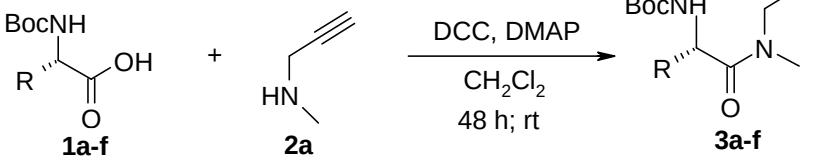
This study was carried out with the double aim *i*) to perform an alternative procedure to enter to optically active nitrogen-containing heterocycles, and *ii*) to investigate the feasibility of gold catalyzed heterocyclization of compounds having amine and allene groups tethered on an amido group.

In the following chapters the results of our research group, concerning gold-catalyzed intramolecular hydroamination of allenamides **A** leading to enantiopure 5-substitued 2-vinylimidazolidinone, are reported. The imidazolidinone derivatives are widespread in several natural products, many of them having biological activities.[58] Moreover, imidazolidinones have proved to be effective in organic catalysis as activators for α,β-unsatured aldehydes through formation of an iminium ion.[59]

2.2 Synthesis of propargylamides 3a-f

Propargylamides **3a-f** were obtained in good yields (Table 1) by the reaction of L-α-aminoacids **1a-f** and *N*-methylpropargylamine **2a** in DCM as a solvent at rt and using DCC as an amido-formation coupling reagents (Scheme 21).

Scheme 21



a: R = *i*-Pr; **b**: R = Me; **c**: R = Bn; **d**: R = *tert*-Bu; **e**: R = Et; **f** = Ph

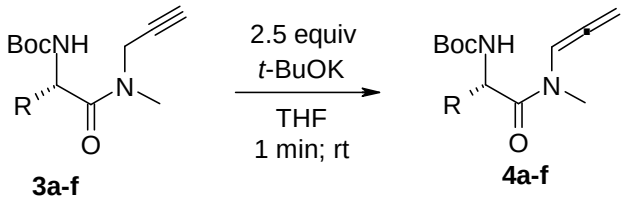
Table 1

R	Yield (%) **3a-f**
i-Pr	95
Me	96
Bn	94
tert-Bu	90
Et	85
Ph	97

2.3 Synthesis of α-aminoallenamides 4a-f

Propargylamides **3a-f** were transformed into α-aminoallenamides **4a-f** by *t*-BuOK promoted isomerization in dry THF (Scheme 22). The exposure time of **3a-f** to the base is crucial and must not exceed 1 minute, so as to prevent the base-promoted cyclization reaction.[56] Yield of products reaction are often near quantitative (Table 2).

Scheme 22



3a-f **4a-f**

a: R = *i*-Pr; **b**: R = Me; **c**: R = Bn; **d**: R = *t*-Bu; **e**: R = Et; **f**: R = Ph

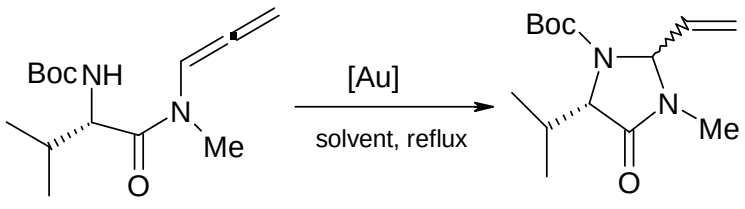
Table 2. Yields of reaction (Scheme 22)

R	Yield (%) **4a-f**
i-Pr	98
Me	94
Bn	95
tert-Bu	98
Et	97
Ph	95

2.4 Optimization of cyclization conditions on α-aminoallenamide 4a with gold catalysts.

The allenamide **4a**, arising from L-valine, was used as the first model-substrate to test the cyclization reaction to give the corresponding 5-isopropyl-2-vinylimidazolidinone **5a** by gold catalysis (Scheme 23). Reaction conditions were optimized by using a variety of Au(I) and Au(III) catalysts (Table 3).

Scheme 23



4a **5a**

Table 3. Optimization of the cyclzation conditions of **4a**

Entry	Catalytic system[a]	Solvent	Reaction products (%)[b]				
			1a	**5a**	**6**	**7**	**8**
1	H_2SO_4[c]	MeCN	-	15	85	-	-
2	AuCl	toluene	95	-	-	5	-
3	AuCl	MeCN	93	-	-	7	-
4	PPh_3AuCl, AgOTf	CH_2Cl_2	90	-	-	10	-
5	PPh_3AuCl, AgOTf, AcOH	CH_2Cl_2	92	-	-	8	-
6	$AuCl_3$	MeCN	-	90[d]	-	10	-
7	$AuCl_3$	dioxane[e]	80	10	-	10	
8	$AuCl_3$	AcOH[f]	-	-	-	10	90
9	$AuCl_3$	CH_2Cl_2[g]	95	-	-	5	-
10	$AuCl_3$, $AgBF_4$	toluene	95	-	-	5	-
11	$NaAuCl_4 \cdot 2H_2O$	MeCN	51	39	-	10	-
12	$NaAuCl_4 \cdot 2H_2O$	CH_2Cl_2[g]	95	-	-	5	-
13	$NaAuCl_4 \cdot 2H_2O$	dioxane	95	-	-	5	-
14	$AuCl_3$, AgOTf	MeCN	90	-	-	10	-
15	$AuCl_3$, AgOTf	AcOH[f]	-	-	-	10	90

[a] Au-catalyst is used in 5 mol%
[b] Ratio determined by HPLC
[c] 5 mol%
[d] As a 2.5:1 *cis/trans* diastereoisomeric mixture
[e] Working on DMF, MeOH and toluene any conversion of **5a** was observed
[f] At 70 °C
[g] At room temperature

First of all, in order to determine the need of a gold species for obtaining the cyclization process, a control investigation was performed submitting the compound **4a** to reaction catalyzed by protic acid. This procedure provided the formation of **5a** in 15% yield beside a large amount of deallenylation by-product **6** (Figure 1) making of no value its applicative interest (entry 1). It should be outlined that $Yb(OTf)_3$ revealed a catalytic behaviour similar to the sulphuric acid while other Lewis acids such as $BF_3.Et_2O$ and $Zn(OTf)_2$ afforded only a tarry mixture.

Treatment of α-amino allenamide **4a** with Au(I)-salts only resulted in the formation of small amounts of the degradation product **7** (entries 2-3). The same behaviour was observed by using PPh_3AuCl complex, also in addition to AgOTf and AcOH (entries 4-5).

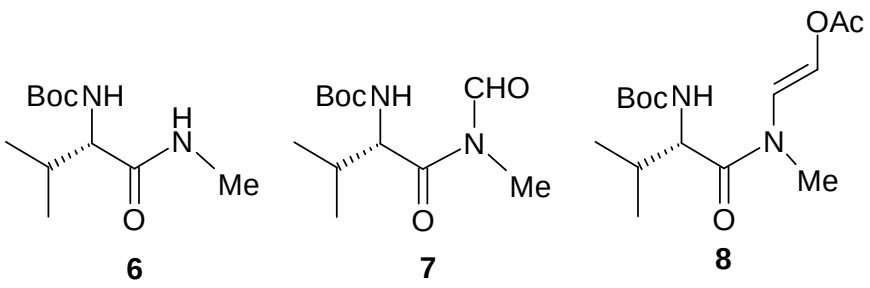


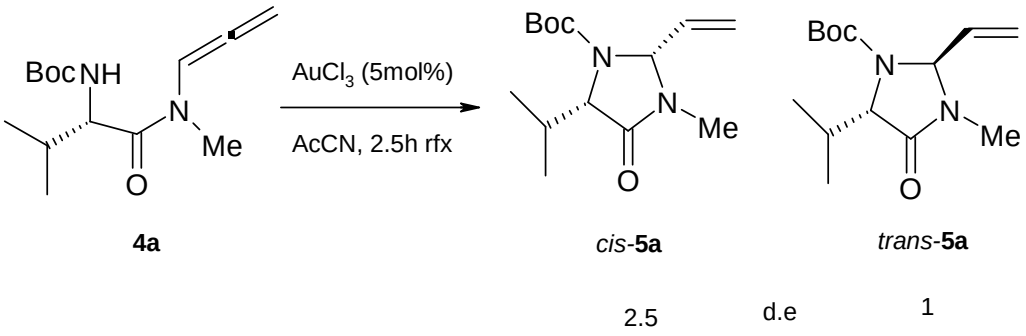
Figure 1. By-products deriving from optimization of reaction conditions reported in Table 3

Working in the presence of $AuCl_3$ (5 mol%) in acetonitrile as solvent at reflux, a mixture of imidazolidinones **5a** was obtained in satisfactory yield (entry 6). Other solvents as dioxane, DMF, MeOH and toluene were tried without improving the cyclization outcome. By performing the reaction in AcOH as solvent at 70°C, only the open chain derivative **8** (Figure 1) was recovered (entries 8 and 15). The use of $NaAuCl_4$ in acetonitrile instead of $AuCl_3$ afforded **5a** in lower yields (entry 11).

2.5 Synthesis of 5-substitued 2-vinylimidazolidinones 5a-f

Having optimized the reaction conditions for the cyclization of allenamide **4a** on a small scale (Table 3, entry 6), we tried to scale-up the reaction in order to isolate reaction products. $AuCl_3$ (5 mol%) was added to a solution of **4a** in acetonitrile dry. The mixture was refluxed for 2 h then solvent was evaporated to dryness. The crude was purified by flash column chromatography affording the 5-*exo*-allylic cyclized products *cis*-**5a** and *trans*-**5a** in a 2.5:1 diastereoisomeric excess (Scheme 24).

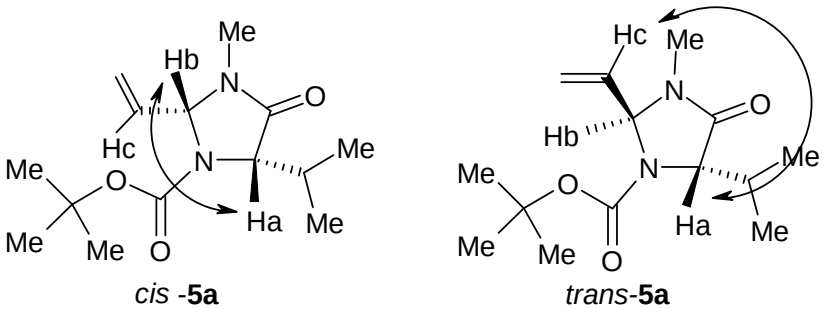
Scheme 24



4a *cis*-**5a** *trans*-**5a**

2.5 d.e 1

The absolute stereochemistry of the *cis* and *trans* diastereoisomers **5a** was assigned by NOE measurements. In particular, NOE enhancement between Hb and Ha has been determinant to identify the *cis*-configuration of the major diastereoisomer. The *trans*-configuration of the minor diastereoisomer was confirmed by the NOE interaction between Hb and Hc (Figure 2).



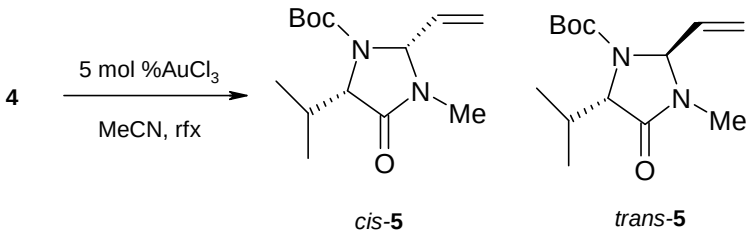
cis -**5a** *trans*-**5a**

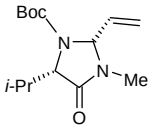
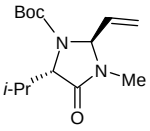
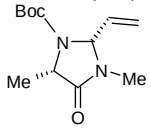
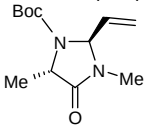
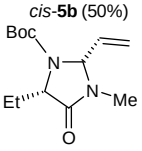
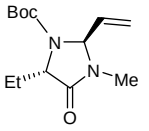
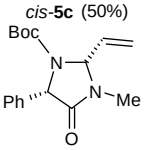
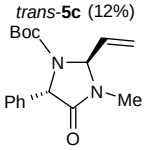
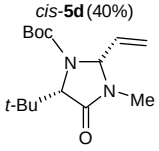
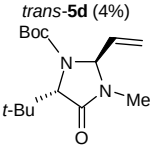
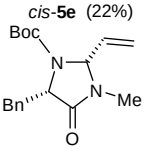
Figure 2. NOE enhancements observed in *cis* and *trans* diastereoisomers.

HPLC analysis (Chiracel ODH column) of *cis*- and *trans*-**5a**, performed in comparison to samples of the corresponding racemic mixture synthesized starting from the (±)-valine, proved an enantiomeric purity better than 99.5%.

Next we explored the scope of the reaction under the conditions of entry 6 Table 3. Thus a selection of the behaviour of allenamides **4** is collected in Table 5.

Table 4. Reaction scope



Entry	Allene	R	Time (h)	Yields of products (%)	
1	**4a**	*i*-Pr	2.5	 *cis*-**5a** (41%)	 *trans*-**5a** (12%)
2	**4b**	Me	1.5	 *cis*-**5b** (50%)	 *trans*-**5b** (12%)
3	**4c**	Et	1	 *cis*-**5c** (50%)	 *trans*-**5c** (12%)
4	**4d**	Ph	1.5	 *cis*-**5d** (40%)	 *trans*-**5d** (4%)
5	**4e**	*t*-Bu	3.5	 *cis*-**5e** (22%)	 *trans*-**5e** (10%)
6	**4f**	Bn	1.5	 *cis*-**5f** (65%)	—

The reactions were completed in 1-3.5 h, always providing the *cis*-imidazolidinone as major product. Allenamides **4a-f** led to *cis* and *trans* products in very similar ratios and yields. The outcome of compound **4e** resulted in a crude tarry mixture that allowed isolating *cis* distererеoisomer in only 22% yield.

Allenamide **4f**, arising from L-phenylalanine, gave rise to cyclization in a higher diastereoselective level that led to the isolation of the sole *cis*-product in 65% yield.

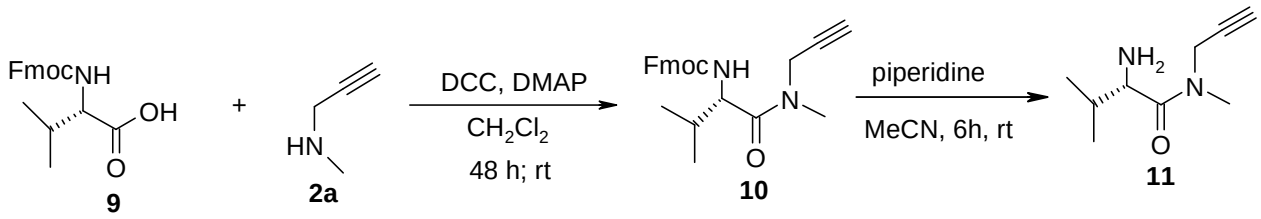
2.6 Synthesis of α-benzylamino allenamide 13

The inertness of Au(I)-catalysts prompted us to study the behaviour of a substrate having a more nucleophilic amino group.

The α-amino allenamide **13** was synthesized for this purpose in four steps.

Starting from the corresponding Fmoc-L-valine **9**, the corresponding propargylamide **10** was synthesized using the usual protocol for the synthesis of propargylamides **3a-f**. The Fmoc protecting group was then removed using piperidine in acetonitrile as solvent at room temperature in 6 h. The crude was purified by flash column chromatography obtaining **11** in 78% yield (Scheme 25).

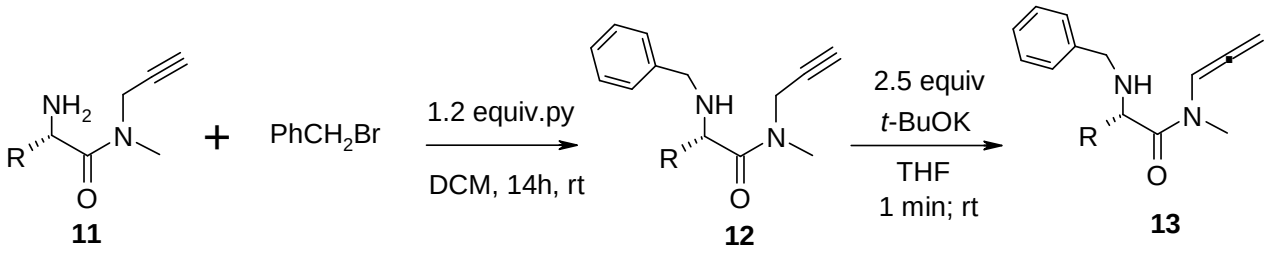
Scheme 25



The intermediate **11** was then alkylated on the free nitrogen using benzylbromide leading to the compound **12** in 50% yield after flash chromatography column. The product **12** was transformed

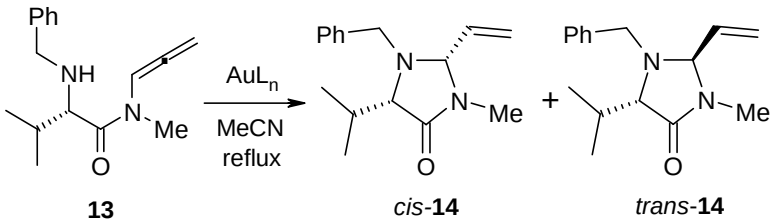
into the corresponding α-benzylaminoallenamide **13** by the same procedure used to obtain allenamide **4a-f** but in lower yield (Scheme 26).

Scheme 26



The α-benzylaminoallenamides **13** underwent to treatment with Au(I) and Au (III) catalysts. Although even in this case the latter turned out to be the most efficient catalyst, PPh_3AuCl was operative in the promotion of the 5-*exo*-allylic cyclization (Table 5).

Table 5. Cyclization of α-benzylaminoallenamide **13**



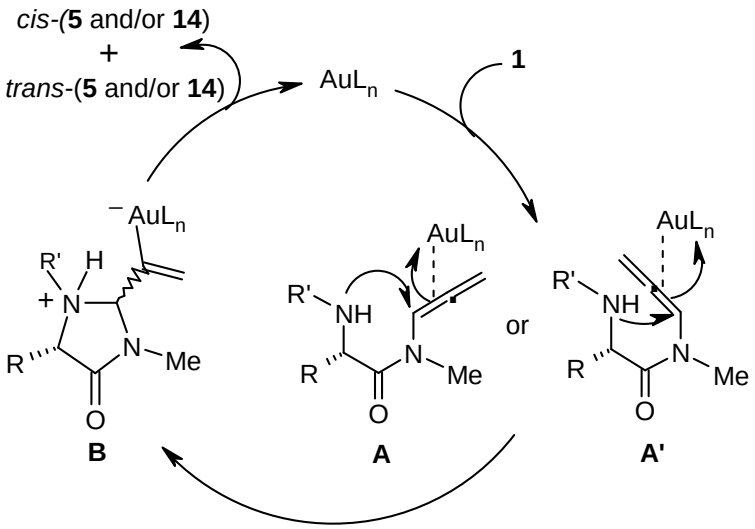
Entry	Catalytic system	Time (h)	Yields of products (%)	
1	$PPh_3AuCl/AgBF_4$	2.5	*cis*-**14** (21%)	*trans*-**14** (14%)
2	$AuCl_3$	0.20	*cis*-**14** (36%)	*trans*-**14** (24%)

The reaction which was carried out in the presence of $AuCl_3$ was faster than cyclization tried on allenamide **4a** (0.20 h *vs* 2.5 h) giving the *cis* isomer as the major product, although with a lower

cis/*trans* ratio. The catalytic system $PPh_3AuCl/AgBF_4$ furnished the *cis* and *trans* imidazolidinones **14** with the same diasteroisomeric ratio found using $AuCl_3$ as catalyst although in lower yield.

A plausible mechanism for the gold-catalyzed heterocyclization is shown in Scheme 27. The inside C-C double bond of the 1,2-diene moiety is activated by the coordination of both Au(I) and Au(III) species (intermediates **A** or **A'**), the so generated π-olefin complex undergoes intramolecular nucleophilic attack by the nitrogen atom of the amino group affording the cyclic vinyl-gold intermediate **B**. However, the development of the C-N bond can be achieved on the π-olefin-Au(III) complex by both Boc and Bn-amino groups, whereas only the more reactive Bn-amino group can interact with π-olefin-Au(I) complex. Protonolysis of the gold-carbon bond **B** gives imidazolidinones derivatives **5** and/or **14** and regenerates the gold-catalyst.

Scheme 27



2.7 Gold catalyzed intramolecular $C_{sp}{}^2$-H alkylation

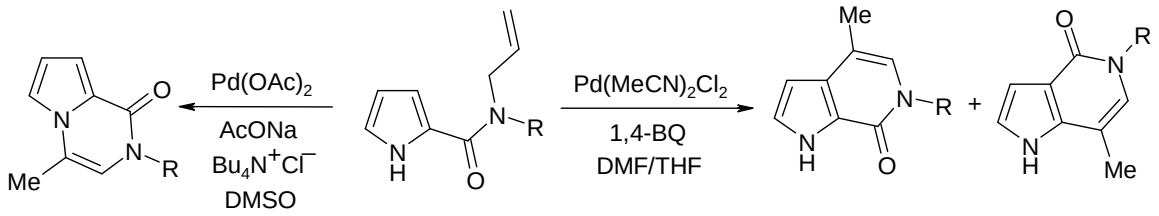
Our following work has been addressed towards studies on cyclization of alkynyl-substituted heterocycles.[60] Homogeneous gold catalysis, has emerged recently as a powerful tool to achieve such a goal, mainly to the chemoselective alkynophilic properties of this attractive metal.[61]

As already mentioned in the introduction, the first example of an intermolecular hydroarylation of alkynes has been reported independently by Reetz[36] and Shi,[37] whilst the development of the first intramolecular version of this reactivity dates back to 2004.[62] From then on, several different reacting partners have been successfully tested under various conditions, developing a large family of gold-catalyzed carbo- and heterocycle synthesis.[63]

However, electron-rich aromatic heterocycles have been under-investigated in comparison to arylic substrates. To the best of our knowledge, only two papers dealing with hydroarylation of indoles have been published,[64] and just one reports the effectiveness of their coupling with internal alkynes.[64b]

The research group I have worked for, elaborated some protocols[65] to obtain complex (poly)heterocyclic system by intramolecular palladium-catalyzed reactions. In particular they reported the cyclization of *N*-allylpyrrolo-2-carboxamides which exhibited also products arising from 1,2-migration of the amide moiety (Scheme 28).[65a]

Scheme 28

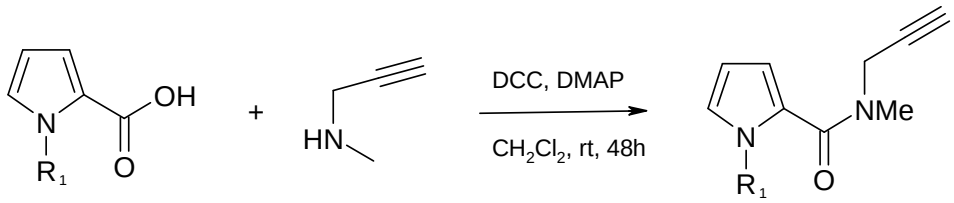


So we were intrigued to investigate the intramolecular hydroarylation of alkynyl pyrrolo-2-carboxamides catalyzed by gold in order to *i*) study the feasibility of gold-catalyzed intramolecular hydroarylation of alkynes tethered via an amido group onto pyrrole skeleton, *ii*) obtain an alternative procedure to access pyrrole fused heterocycles, and *iii*) verify an analogous outcome in terms of rearrangement behaviour.

2.8 Synthesis of 1*H*-pyrrole-2-carboxamides 16a,b

1*H*-Pyrrole-2-carboxamides **16a,b** were synthesized from the corresponding 1*H*-pyrrole-2-carboxylic acids **15a,b** and N-propargyl amine **2a** using DCC as coupling reagent in good yield (Scheme 29).

Scheme 29



15a,b **2a** **16a,b**

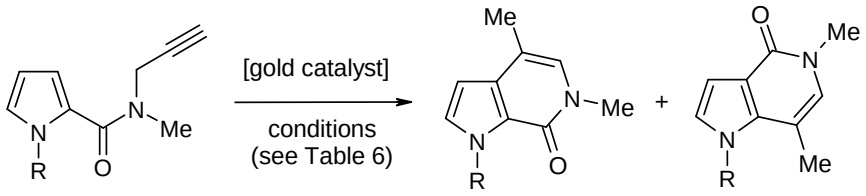
15a: R_1= H
15b: R_1= Me

16a (80%)
16b (**90%)**

2.9 Gold catalyzed cyclization of 1*H*-pyrrole-2-carboxamides 16a,b

The two 1*H*-pyrrole-2-carboxamides **16a,b** were submitted to gold catalyzed cyclization reactions in different conditions (Table 6)

Table 6. Optimization of reaction conditions



16a: R = H
16b: R = Me

17a,b **18a,b**

Entry	Substrate	Gold catalyst[a]	Solvent[b]	**17**[c]	**18**[c]
1	**16a**	$AuCl_3$	MeCN	-	-
2	**16a**	$NaAuCl_4 2H_2O$	MeCN	-	-
3	**16a**	AuCl	DCM	-	-
4	**16a**	$PPh_3AuCl/AgBF_4$	DCM	-	-
5	**16a**	$AuCl_3$	DCM	-	-
6	**16b**	$AuCl_3$	MeCN	63	37
7	**16b**	$NaAuCl_4 \cdot 2H_2O$[d]	MeCN	30	17
8	**16b**	AuCl	DCM	-	-
9	**16b**	$PPh_3AuCl/AgBF_4$	DCM	-	-

[a] Catalyst loading: 5 mol %. [b] All reactions were carried out at reflux for 4 h. [c] HPLC conversion. [d] In this case, 50% of **16b** was also recovered.

At first, it should be noticed that both Au(III) and Au(I) catalysts were unable to cyclize the nitrogen unsubstituted pyrrolo derivative **16a** (entries 1-5). This behaviour was completely different from what was observed in Pd-catalyzed reactions, where *N*-allyl pyrrole-2-carboxamides did not require this substitution to react. Otherwise $AuCl_3$ was able to promote the cyclization of the substrate **16b**, bearing a methyl group on the pyrrolic nitrogen, giving two isomeric bicyclic products. Their structures were unequivocally determined to be the expected 6-*exo*-dig cyclization product **17b** and the cyclized rearranged structure **18b** by ^{1}H NMR, ^{13}C NMR, NOESY1D, gHSQC and ^{1}H-^{13}C long-range correlations (gHMBC) experiments (Figure 3).

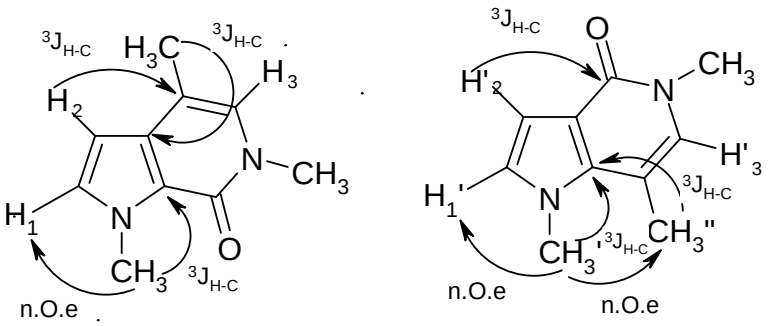


Figure 3. Significant relationships among hydrogen and carbon atoms arising from bidimensional NMR studies

The best result was obtained when the reaction was performed in MeCN at reflux for 4h (entry 6); in this case, the ratio between **17b** and **18b**, determined by HPLC, was 63:17.

$NaAuCl_4.2H_2O$ was also able to cyclize **16b**, but in this case, after 4h in MeCN at reflux, the conversion of the substrate resulted in only 50%, giving a mixture of **17b** and **18b** that the HPLC analysis revealed to be in 30:17 ratio (entry 7). Despite the nitrogen substitution, Au(I) didn't afford any cyclization product of the substrate **16b** (entries 8-9).

2.10 Solvent effect in determining the ratio between compounds 17b and 18b in $AuCl_3$ catalyzed cyclization.

We observed that the catalytic effect of $AuCl_3$ in determining the cyclization of the amide **16b** was influenced by the reaction medium. In particular, the ratio between the cyclization products **17b** and **18b** was strongly affected by the solvent, as shown by the investigated conditions summarized in Table 7.

Table 7. Effect of the solvent on the ratio of the isomeric products

Entry	[Au][a]	Solvent	T (°C)	t (h)	Ratio[b]	**17b**[c]	**18b**[c]
1	$AuCl_3$	Toluene	50	3	7:1	70	8
2	$AuCl_3$	DCM	reflux	3	3:1	41	16
3	$AuCl_3$	MeCN	reflux	4	1.7:1	45	26
4	$AuCl_3$	DMF	90	4	1:1.6	32	50

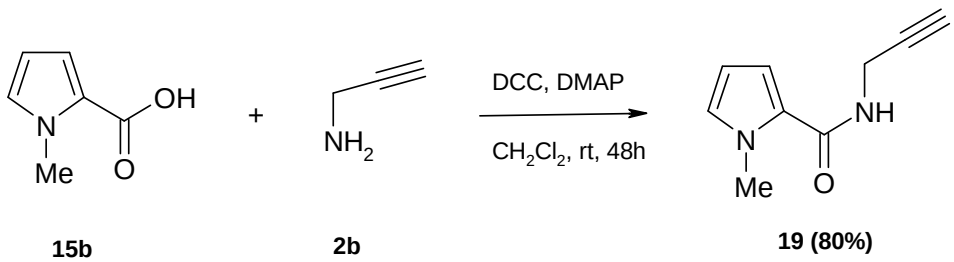
[a] [Au] used at 5 mol %. [b] HPLC-MS ratio between peak areas. [c] Isolated yields after chromatographic column.

In fact, operating in non polar solvents increased the formation of **17b** (entries 1 and 2), whilst changing to polar solvents, an enhanced products ratio until a majority of **18b** was obtained (entry 4). More specifically, the ratio (HPLC-MS) between **17b** and **18b** changed from 7:1 working in toluene to 1:1.6 when DMF was used. This means that less polar solvents favour the expected cyclization product **17b** whereas more the polar ones favour the formation of compound **18b**, arising from the formal 1,2-migration of the amide moiety.

2.11 Synthesis of propargylamides 19 and 20a-d

Other propargylamides were synthesized. Some of these required the previous synthesis of propargylamide **19** as a common intermediate (Scheme 30).

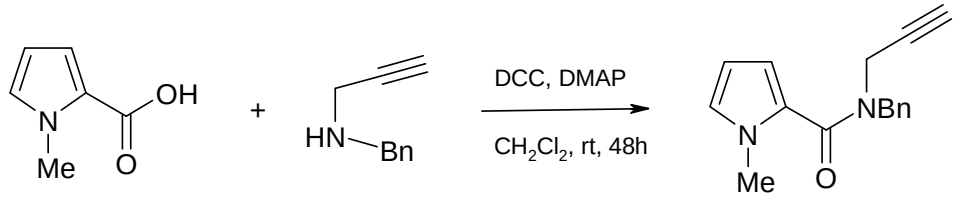
Scheme 30



15b **2b** **19 (80%)**

The propargylamide **20a** was prepared in good yield adopting the same procedure used for propargylamides **15a,b** but using the *N*-benzylprop-2-yn-1-amine **2c** instead of **2a** (Scheme 31).

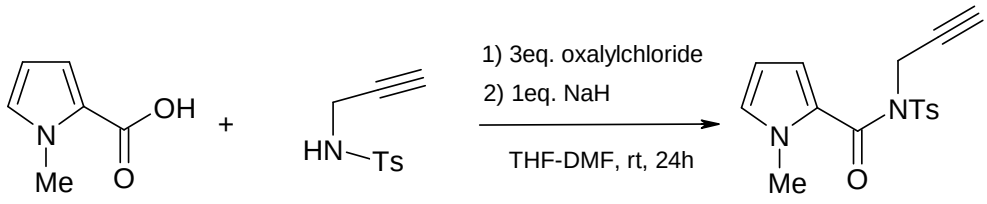
Scheme 31



15b **2c** **20a (85%)**

Propargylamide **20b** was obtained starting from **15b** and using 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide **2d** as coupling partner. In this case because of the low nucleophilicity of the amide **2d**, the formation of **20a** required the synthesis of the corresponding acylchloride from **15b** and the deprotonation of **2d** with NaH (Scheme 32).

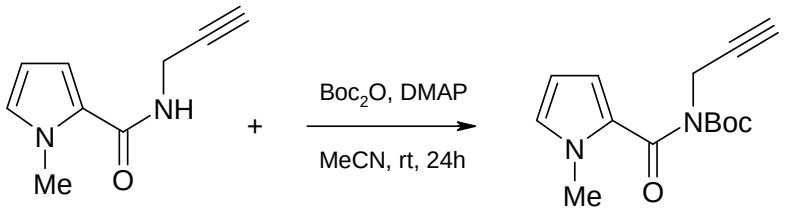
Scheme 32



15b 2.2 eq. **2d** 1eq. **20b (77%)**

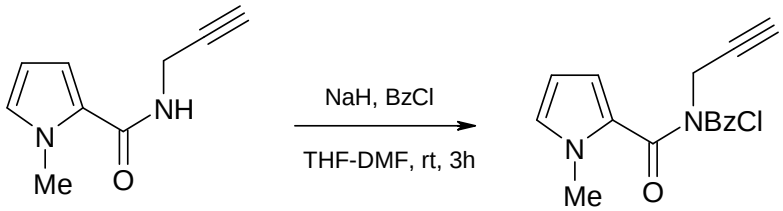
Then we prepared propargylamides **20c** and **20d**, starting from the intermediate **19**. For **20c**, Boc anhydride was added to a solution of **19** in MeCN using a catalytic amount of DMAP. For **20d**, deprotonation of the amidic proton of **19** with NaH was necessary for the efficient acylation with benzoylchloride. Both products were obtained in satisfactory yields (Scheme 33 and 34).

Scheme 33



19 **20c (85%)**

Scheme 34



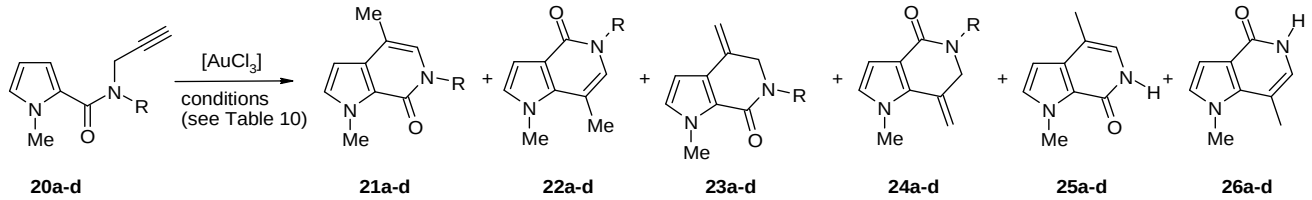
19 **20d (60%)**

2.12 Gold catalyzed cyclizations of *N*-substituted-carboxamides 20a-d

Propargylamides **20a-d** were submitted to the gold-catalyzed cyclization in order to confirm the trend of the observed dependence of the direct and rearranged cyclization products on different solvents already observed for propargylamide **16b**.

The results obtained are summarized in Table 8 where the isolated yields as well as the HPLC-MS areas isomeric ratios are depicted.

Table 8. Scope of the reaction on differently *N*-substituted *N*-propargyl pyrrolo-carboxamides



Entry[a]	Substrate	R	Solvent	T(°C)	t(h)	Yield (%) [b]						HPLC-MS ratio[c]
						21	**22**	**23**	**24**	**25**	**26**	
1	**20a**	Bn	Toluene	45	0.5	84	7	-	-	-	-	7.5 : 1
2	**20a**	Bn	DCM	reflux	0.25	61	12	-	-	-	-	3 : 1
3	**20a**	Bn	MeCN	reflux	0.25	50	25	-	-	-	-	1.6 : 1
4	**20b**	Ts	TBME	RT	1.5	85	7.5	-	-	-	-	9 : 1[d]
5	**20b**	Ts	DCM	reflux	0.5	75	9	-	-	-	-	6 : 1[d]
6	**20b**	Ts	Toluene	45	0.5	65	14	-	-	-	-	4 : 1[d]
7	**20b**	Ts	MeCN	reflux	0.5	70	20	-	-	-	-	3 : 1[d]
8	**20b**	Ts	DMF	90	7	60	25	-	-	-	-	2 : 1
9	**20c**	Boc	Toluene	50	1	-	-	56	14	-	-	2.5 : 1
10	**20c**	Boc	DCM	reflux	1	-	-	20	30	-	5	1 : 1.5 : 0.2
11	**20c**	Boc	MeCN	reflux	3	-	-	-	-	-	65[d]	1
12	**20d**	Bz	Toluene	50	1	51	-	9	-	6	-	30 : 2.3 : 1
13	**20d**	Bz	DCM	reflux	1.5	60	10	-	-	-	-	7 : 1
14	**20d**	Bz	MeCN	reflux	1	50	13	-	-	-	-	5 : 1
15	**20d**	Bz	DMF	90	24	3	-	-	-	40	11	1 : 10[e] : 5

[a] All reactions were carried out using 5 mol % $AuCl_3$. [b] Isolated yield. [c] HPLC-MS ratio between peak areas. [d] After cromatographic column 33% of **20c** was recovered. [e] At the end of the reaction 22% of **20d** was still present.

Substrates **20a** and **20b** underwent $AuCl_3$ catalyzed cyclization in all solvents at different reaction temperatures affording respectively the pyrrolo-pyridines **21a** (entries 1-3) and **21b** (entries 4-8) and the rearranged bicyclic derivatives **22a** (entries 1-3) and **22b** (entries 4-8).

Conversely, substrate **20c**, having a *t*-butoxycarbonyl substituent on the amidic nitrogen, gave two exo-methylenic products **23c** and **24c** (entries 9-10) when the cyclization reaction was carried out in toluene.

Finally, when **20d** underwent $AuCl_3$-catalyzed cyclization in the same solvent at 50°C for 1 hour, only **21d** together with the *exo*-methylenic regioisomer **23d** and the product **25d** lacking in the benzoyl group were obtained.

These outcomes reveal that in all cases, as for products **17b** and **18b**, the HPLC-MS ratio between the different products is strictly dependent on the reaction solvent. In fact, in reactions employing **20a** and **20b**, shifting from unpolar solvents to more polar ones (entries 1-3 and analogously entries 4-6 and 7-8), the HPLC-MS ratio between **21a,b** and **22a,b** slowly decreased. The same behaviour was observed starting from **21c** between the two exo-methylenic regioisomers **23c** and **24c** (entries 9-10), and carrying out the reaction in dichloromethane at reflux for 1 hour afforded also the cyclized rearranged product **26c**. Even more, this latter was the only one detected in the most polar solvent (entry 11).

Carrying out the reaction in dichloromethane at reflux for 1 hour provided also the cyclized rearranged product **26c** (entry 10), lacking in the amidic nitrogen substituent, even if in low yield.

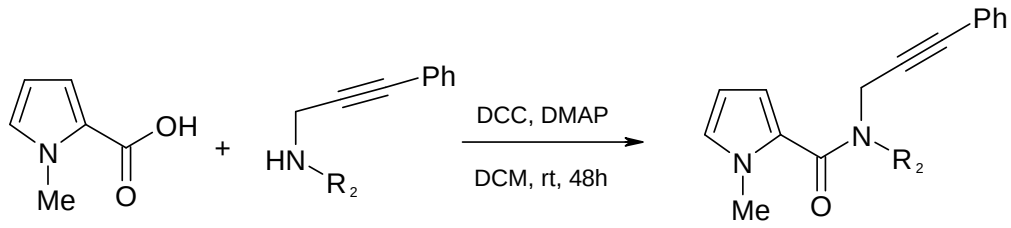
Varying the solvent in **20d**, at last, drove the cyclization completely to the rearranged product 22d, not observed in toluene.

In DMF instead regioisomers **25d** and **26d**, lacking in the benzoyl group, were obtained in almost similar HPLC-MS ratio.

2.13 Synthesis of propargylamides 20e-g

N-Substituted-propargylamides bearing a phenyl substituent at the acetylenic carbon were synthesized. Propargylamides **20e** and **20g** were obtained in excellent yields by reaction of **15b** and the corresponding amines **2e** and **2g** using DCC as the coupling reagent (Scheme 35).

Scheme 35



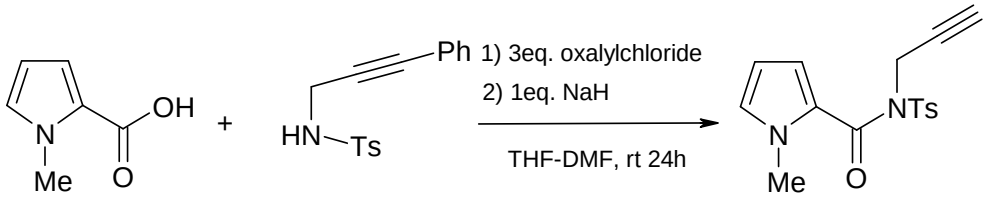
15b

2e : R_2 = Me
2g : R_2 = Bn

20e (90%)
20g (85%)

Propargylamide **20f** was obtained starting from the reaction between the carboxylic acid **15b**, that was transformed in the corresponding acylchloride using oxalylchloride, and the amide **2f**. As for the amide **2d**, also in this case deprotonation of the amidic proton by NaH was necessary to increase nitrogen nucleophilicity (Scheme 36).

Scheme 36



15b 2.2 eq.

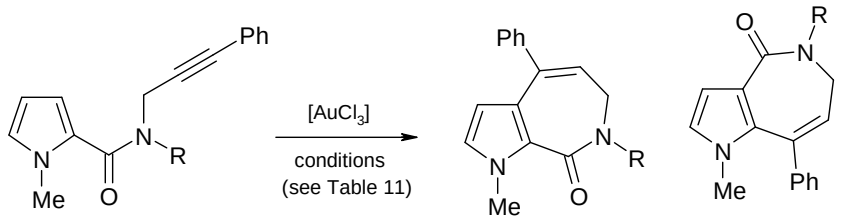
2f 1eq.

20f (90%)

2.14 Gold catalyzed cyclizations of N-substituted-carboxamides 20e-g

We extended then $AuCl_3$ catalyzed cyclization on different solvents to *N*-substituted-proparglylamides **20e-g** bearing a phenyl substituent at the acetylenic carbon. Results are shown in Table 9.

Table 9. Scope of reaction on differently *N*-substituted *N*-propargylamides bearing a phenyl group at the acetylenic carbon



20e-g **27e-g** **28e-g**

Entry[a]	Substrate	R	Solvent	T(°C)	t(h)	HPLC-MS ratio[b]	Yield[c] (%)	
						27:28	**27**	**28**
1	**20e**	Me	DCM	reflux	8	1:3	20	63
2	**20e**	Me	MeCN	reflux	2	1.5:1	43	31
3	**20e**	Me	DMF	90	24	5:1	66	12
4	**20f**	Ts	DCM	rt	0.5	1:2.8	20	60
5	**20f**	Ts	MeCN	40	0.25	3:1	55	17
6	**20f**	Ts	DMF	90	24	10:1	68	7
7	**20g**	Bn	Toluene	80	6	1:5	14	72
8	**20g**	Bn	DCM	reflux	5	1:6	12	74
9	**20g**	Bn	MeCN	reflux	0.5	1:2.5	23	67
10	**20g**	Bn	DMF	90	24	5:1	66	14

[a] All reactions were carried out using 5 mol % $AuCl_3$. [b] HPLC-MS ratio between peak areas. [c] Isolated yield

\

Compared to substrates **20a-d**, that gave only six-membered cyclized products (Table 9), substrates **20e-g** yielded only seven-membered cyclized products in the reaction catalyzed by $AuCl_3$.

No other products were detected in all solvents used. The formation of the seven-membered cyclized products can be found in a stabilizing effect of the phenyl group in the transition state of the reaction.

In addition, Table 9 shows that the HPLC-MS ratio between cyclized products **27e-g** and cyclized rearranged products **28e-g** varied once again passing from less polar to more polar reaction solvents. However, this behaviour is in this case opposite to that observed in Table 8 for six-membered cyclized products, where the HPLC-MS ratio shifted in favour of unrearranged cyclized products decreasing the polarity of the reaction solvent.

2.15 Hypothesis of reaction mechanism for the formation of substrates 20a-d and 20e-g

A proposed mechanism for the hydroarylation of alkynes with pyrroles (substrates **20a-d**) is shown in Figures 4 and 5.

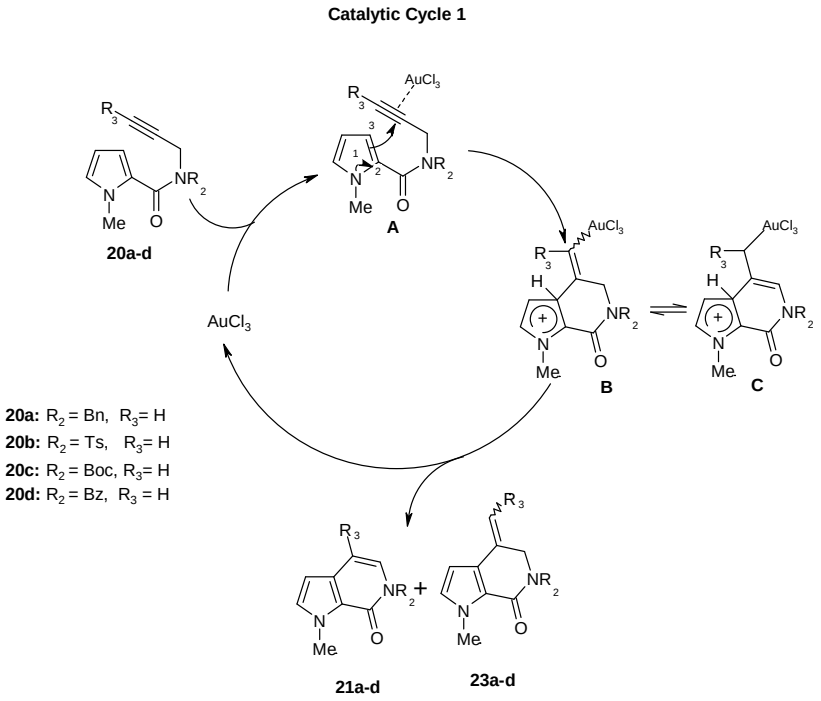


Figure 4. Proposed reaction mechanism for substrates 20a-d (Catalytic Cycles 1)

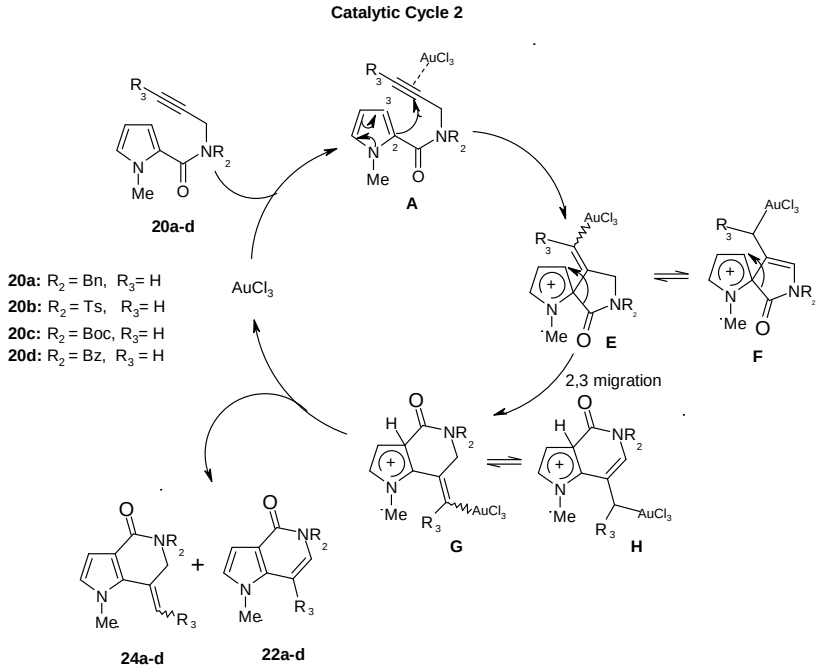


Figure 5. Proposed reaction mechanism for substrates 20a-d (Catalytic Cycles 2)

In the catalytic cycle 1 the alkyne is activated by coordination to $AuCl_3$ (**A**) and undergoes electrophilic aromatic substitution by pyrrolic C-3 to give the vinyl-gold complex (**B**) or the protoisomer (**C**) depending on the reaction condition. Cleavage of the gold-carbon bond in both complexes by pyrrolic proton at C-3 resulted respectively in **21a-d** and **23a-d**.

The catalytic cycle 2 shows the same complex (**A**), described in catalytic cycle 1, which undergoes electrophilic aromatic substitution with the pyrrole at C-2 to give the vinyl-gold complex (**E**) and the protoisomer (**F**) depending on the reaction conditions. Both of these complexes have an instable spirostructure and so they undergo a 2,3-migration of the amide moiety giving respectively the gold-complex (**G**) and (**H**) that are protonated by pyrrolic proton at C-3 affording the cyclized rearranged products **22a-d** and **24a-d**.

To explain the hydroarylation of alkynes with pyrrole for substrates **20e-g**, that gave only seven-membered cyclized products, a similar mechanism was proposed as depicted in Figures 6 and 7.

In the catalytic cycle 3 the alkyne is activated by coordination to $AuCl_3$ (**A**) and undergoes electrophilic aromatic substitution with pyrrole at C-3 to give the seven-membered vinyl-gold complex (**I**) and the protoisomer (**L**). The following cleavage of the gold-carbon bond in the complex (**I**) by pyrrolic proton at C-3 affords products **27e-g** and regenerates the gold catalyst. No product arising from protonolysis of complex (**L**) was observed.

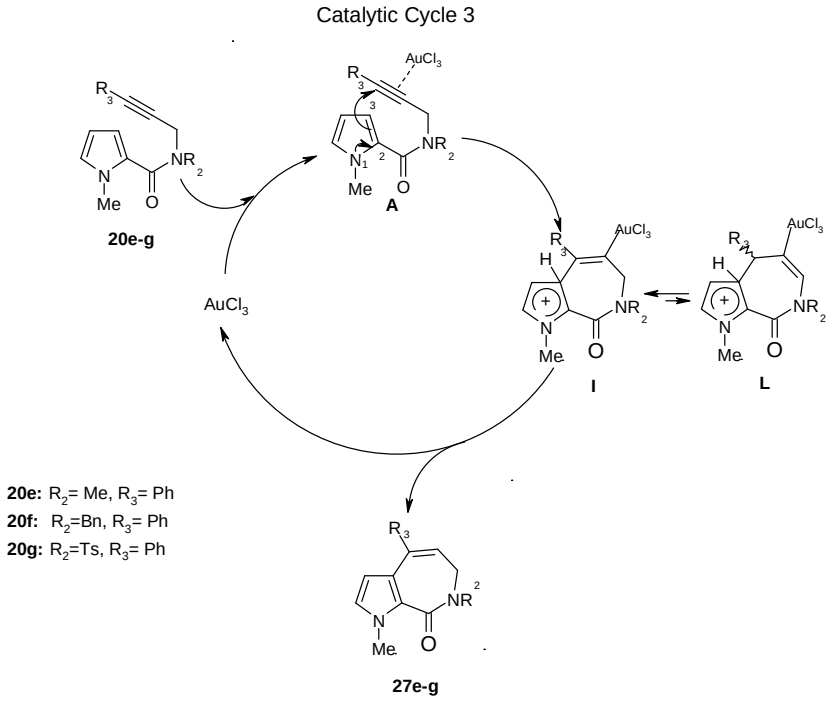


Figure 6. Proposed reaction mechanism for substrates 20e-g (Catalytic Cycles 3)

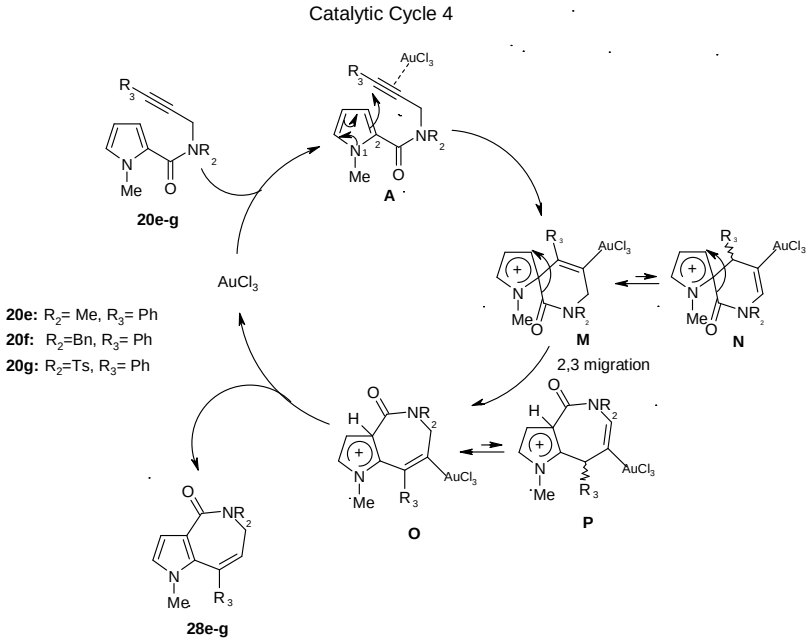


Figure 7. Proposed reaction mechanism for substrates 20e-g (Catalytic Cycles 4)

The catalytic cycle 4 shows the same complex (**A**), described in catalytic cycle 3 that undergoes electrophilic aromatic substitution with the pyrrole at C-2 to give the seven membered vinyl-gold complexes (**M**) and (**F**). Both of these complexes have an instable spirostructure and so they undergo a 2,3-migration of the amide moiety giving respectively the gold-complex (**O**) and (**P**). Only vinyl-gold complex (O) is protonated by pyrrolic proton at C-3 producing the cyclized rearranged product **28e-g**. No product arising from protonolysis of complex (**P**) was observed.

2.16 Gold catalyzed intramolecular hydroalkoxylation of C-C triple bonds.

Traditional methodologies for the synthesis of a number of heterocycles like benzofurans,[66] benzothiophenes,[67] isoquinolines,[68] indoles, [69] isocumarin,[70] isoindolinones,[71] and other polycyclic aromatics[72] are based on the electrophilic cyclization of appropriate functionally-substituted alkynes using iodine, bromine, sulphur and selenium containing electrophiles.

These methodologies show many limitations with regard to atom efficiency and waste formation and in some cases required the remotion of the electrophile used from the molecule skeleton. These and other reasons have stimulated considerable interest in developing new, efficient homogeneous catalytic methods for the synthesis of heterocyclic compounds.[73]

Intramolecular catalytic hydroalkoxylation, the addition of a hydroxyl group to an insatured carbon-carbon bond, is a simple, straightforward and atom-economical route to construct carbon-oxygen bonds creating to huge number of oxygen containing heterocycles that are important structural components of many naturally occurring and pharmacologically active molecules.[74]

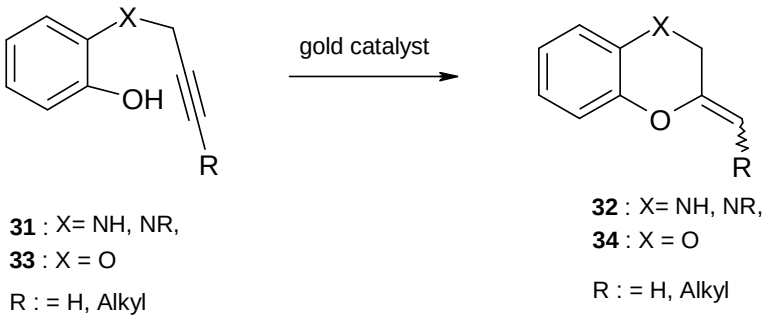
Despite the recent progress of hydroalkoxylation based on transition metal catalysts,[75,76] efficient catalytic transformations remain a challenge due to relatively high enthalpies of typical O-H δ-bonds and low reactivity of electron-rich olefins with nucleophiles.

In this context homogenous gold catalysis has emerged in organic synthesis as a powerful tool due to its unique ability to activate carbon-carbon bonds toward the attack of many nucleophiles.[77] In particular gold catalyzed intramolecular hydroalkoxylation of alkynes represents a fruitful route for the synthesis of oxygenated heterocycles compounds.[78]

As part of our continuing interest on gold catalysis, we were intrigued to investigate the gold catalyzed intramolecular hydroalkoxylation of alkynes tethered with variously 2-substituted amino phenols in order to *i*) develop a different catalytic approach for the synthesis of oxygen-containing heterocycles, *ii*) verify the feasibility of the gold-catalyzed intramolecular hydroalkoxylation of alkynes tethered by the aromatic nitrogen with a 1,2-aminophenol.

In this section we report our results concerning the gold-catalyzed intramolecular hydroalkoxylation of 2-substituted-(prop-2-yn-1-ylamino)phenols **31** and 2-(prop-2-yn-1-yloxy)phenol **33** leading respectively to variously substituted 2,3-dihydro-2-methylene-1,4-benzoxazine **32** and -1,4 benzodioxins **34** (Scheme 37).

Scheme 37



The 1,4-benzoxazines and benzodioxins structure are an integral part of several naturally occurring substances,[79] moreover benzoxazines derivates have been shown to have interesting pharmacological properties.[80]

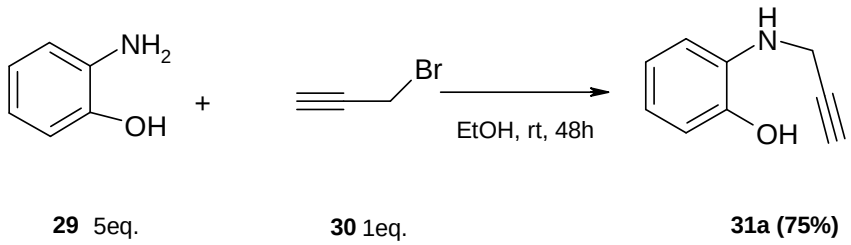
To the best of our knowledge only one paper dealing with metal catalyzed intramolecular synthesis of 1,4-benzoxazines and 1,4-benzodioxines has appeared.[81]

2.17 Synthesis of 2-(prop-2-yn-1-ylamino)phenol 31a

The 2-(prop-2-yn-1-ylamino)phenol **31a**, was prepared from the reaction between 2-aminophenol **29** and propargyl bromide **30** in ethanol at room temperature for 48 hours.

The solvent was then evaporated and the residue was dissolved in TBME, filtered to remove the excess of starting material **31a** and then the solvent was evaporated again to give a crude residue that was purified by flash column chromatography (Scheme 38).

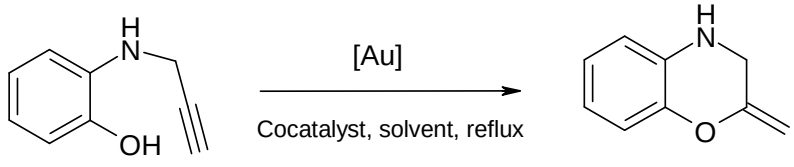
Scheme 38



29 5eq. **30** 1eq. **31a (75%)**

2.18 Optimization of gold catalyzed cyclization conditions on 2-(prop-2-yn-1-ylamino)phenol 31a

Reaction conditions were optimized by using various Au(I) and Au(III) catalysts in the reaction of 2- (prop-2-yn-1-ylamino)phenol **31a** bearing no substituents on the anilinic nitrogen (Table 10).

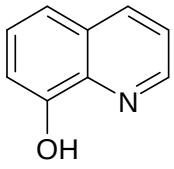


31a **32a**

Table 10. Optimization of reaction conditions

Entry	Catalytic system[a]	Cocatalyst[b]	Solvent	Reaction products (%)[c]		
				31a	**32a**	**35a**
1	$AuCl_3$	-	MeCN	90	-	10
2	$AuCl_3$, $AgBF_4$	-	MeCN	85	-	15
3	$AuCl_3$, AgOTf	-	MeCN	80	-	20
4	$AuCl_3$	-	CH_2Cl_2	100	-	-
5	$AuCl_3$, $AgBF_4$	-	CH_2Cl_2	100	-	-
6	$AuCl_3$, AgOTf	-	CH_2Cl_2	100	-	-
7	$NaAuCl_4 \cdot 2H_2O$	-	MeCN	20	-	80
8	AuCl	-	MeCN	100	-	-
9	AuCl	-	dioxane	100	-	-
10	PPh_3AuCl, AgOTf	-	CH_2Cl_2	100	-	-
11	PPh_3AuCl, AgOTf	-	MeCN	100	-	-
12	PPh_3AuCl, $AgBF_4$	-	MeCN	100	-	-
13	AuI	-	MeCN	100	-	-
14	AuCl	K_2CO_3	MeCN	-	90	10
15	PPh_3AuCl, $AgBF_4$	K_2CO_3	MeCN	60	40	-
16	PPh_3AuCl, AgOTf	K_2CO_3	MeCN	55	45	-
17	$NaAuCl_4 \cdot 2H_2O$	K_2CO_3	MeCN	35	35	30
18	$AuCl_3$	K_2CO_3	MeCN	60	20	20
19	$AuCl_3$, $AgBF_4$	K_2CO_3	MeCN	55	25	20
20	-	K_2CO_3	MeCN	100	-	-

[a]Au-catalyst is used in 5 mol%
[b]K_2CO_3 used in 10% mol
[c]Ratio determined by HPLC



35a

Figure 8. 8-Hydroxyquinoline

Treatment of 2- (prop-2-yn-1-ylamino)phenol **31a** with $AuCl_3$,alone or in addition to $AgBF_4$ and AgOTf, in acetonitrile, at reflux resulted in the recovery of starting material **31a** together with the formation 6-*endo*-dig-cyclized product **35a** (Figure 8) although in very low yield (entries 1-3).

When the same catalytic systems were used in dichloromethane as solvent no cyclization product was observed (Entries 4-6).

To our surprise, the use of $NaAuCl_4$ in acetonitrile instead of $AuCl_3$ afforded the 8-hydroxyquinoline **35a** in high yields (entry 7).

By performing the reaction with the presence of Au(I)-salts in different solvents no trace of cyclized products **32a** and **35a** were detected (entry 8-13).

Working with the presence of AuCl (5 mol %) and K_2CO_3 (10 mol %) as a co-catalyst in acetonitrile at reflux the desidered 6-*exo*-dig-1,4-benzoxazine **32a** was obtained in satisfactory yield with only a very small amount of **35a** (Entry 14).

To test the effectiveness of K_2CO_3 as a co-catalyst we tried it in reaction with others Au(I) catalytic systems but lower yield of compound **32a** were observed (entries 15-16).

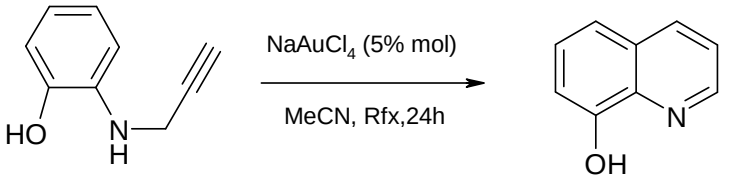
The use of K_2CO_3 (10% mol) with Au(III)-catalysts alone or in the presence of silver salts seems to afford **32a** in lower yield increasing the amount of **35a** (entries 17-19).

To rule out the hypothesis that K_2CO_3 was responsible for the formation of **32a** in absence of any type of gold catalyst, **31a** was heated in acetonitrile at reflux for 24h with a 10% mol of K_2CO_3 recoverying only starting material.

2.19 Synthesis of 8-hydroxyquinoline 35a

With the optimized conditions at hand we tried to reproduce the reaction of formation of **35a** in a bigger scale. $NaAuCl_4$ (5% mol) was added to a solution of **31a** in acetonitrile dry. The mixture was refluxed for 24 hours then solvent was evaporated to dryness. The crude was purified by flash column chromatography affording the 6-*endo*-dig cyclised product **35a** (Scheme 39).

Scheme 39

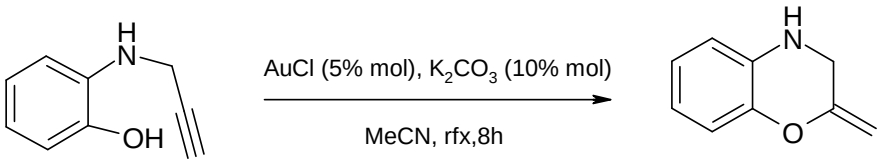


31a **35a (60%)**

2.20 Synthesis of 2,3-dihydro-2-methylene-1,4-benzoxazine 32a

The scale-up of the formation of **32a** required the use of optimized conditions of Table 12 (entry 14). To a solution of **31a** in acetonitrile at room temperature K_2CO_3 (10 % mol) and AuCl (5 % mol) were added. The mixture obtained was stirred at reflux for 8h, and then the solvent was evaporated to dryness. The residue was submitted to flash column chromatography (Scheme 38).

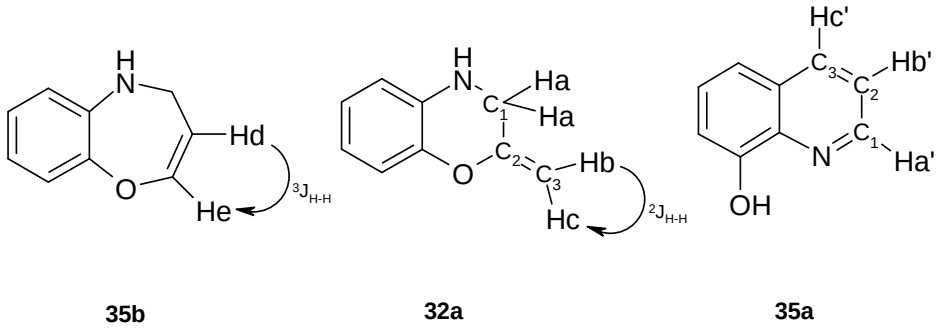
Scheme 38



31a **32a (70%)**

The cyclization ran in the 5-*exo*-methylenic manner leading to the 2,3-dihydro-2-methylene-1,4-benzoxazine **32a** in 70% yield in addition to a 10% of the regioisomer **35a** arising from a 6-*endo*-dig-hydroarylation process.

The structure of the two regioisomeric compounds **32a** and **35a** was unequivocally assigned by ^{1}H NMR. In particular ^{1}H NMR δ chemical shift of the two alkylic protons Ha on carbon C_1 in **32a** is different from that of Ha' on the same carbon C_1 in **35a**. The same happened for ^{1}H NMR chemical shifts δ of aromatic protons Hb' and Hc' respectively on C_2 and C_3 carbons in **35a** that are completely different from the ones observed for vinylic proton Hb and Hc on C_3 in **32a**. The 5-*exo* dig cyclization way observed in **32a** was confirmed by ^{1}H NMR, ^{13}C NMR and edited gHSQC that excluded the formation of the regioisomer **35b** obtained by a 6-*endo* dig cyclization process (Figure 9).



35b **32a** **35a**

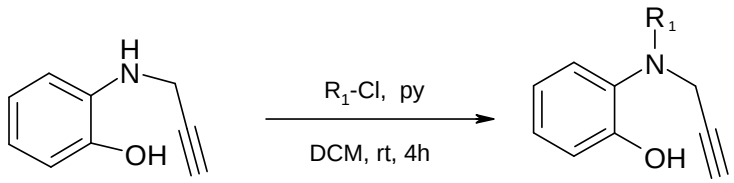
Figure 9. Significantly different ^{1}H NMR chemical shifts among hydrogens in **32a** and **35a-b**

2.21 Synthesis of 2-substitued (prop-2-yn-1-ylamino)phenols 31b-d

To explore the scope of the gold catalyzed cyclization under the conditions of entry 14 of Table 12 we decided to prepare others 2-(prop-2-yn-1-ylamino)phenols but with a substituent on the free nitrogen atom. 2-Substitued (prop-2-yn-1-ylamino)phenols **31b-d** were obtained in good yields

(Table 11) by the reaction between **31a** and the corresponding acylating agent, in dichloromethane as solvent, at room temperature and in the presence of an excess of pyridine.

Table 11. Reaction yields of **31a** with same acylating agents R_1Cl



31a **31b-d**

31b : R_1 = Bz

31c : R_1 = Ac

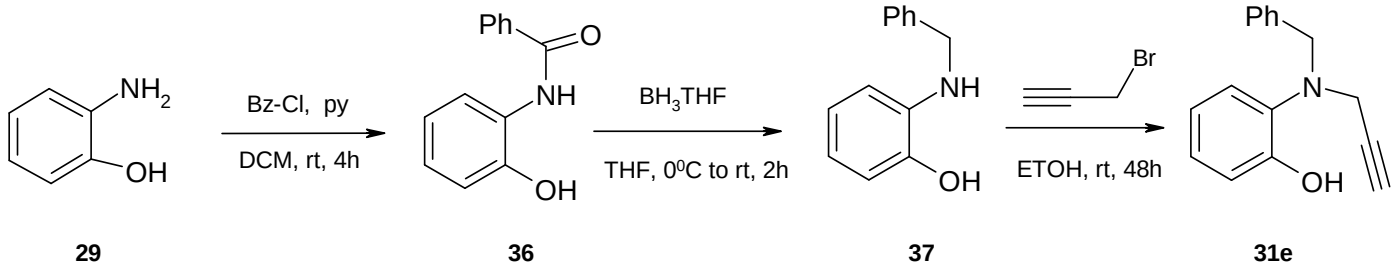
31d: R_1 = Ts

R_1	Yield (%) **31b-d**
Bz	98
Ac	94
Ts	95

2.22 Synthesis of 2-substituted (prop-2-yn-1-ylamino)phenols 31e-g

Different synthetic approaches were adopted for the preparation of 2-substitued (prop-2-yn-1-ylamino)phenols **31e-g**. The substrate **31e** was synthesized in three steps by reaction between the 2-aminophenol **29** and BzCl to give the compound **36** followed by reduction of the amide moiety with BH_3.THF complex. The intermediate **37** so obtained was then alkylated on the nitrogen with propargylbromide (Scheme 40).The total yield of the process was 70%.

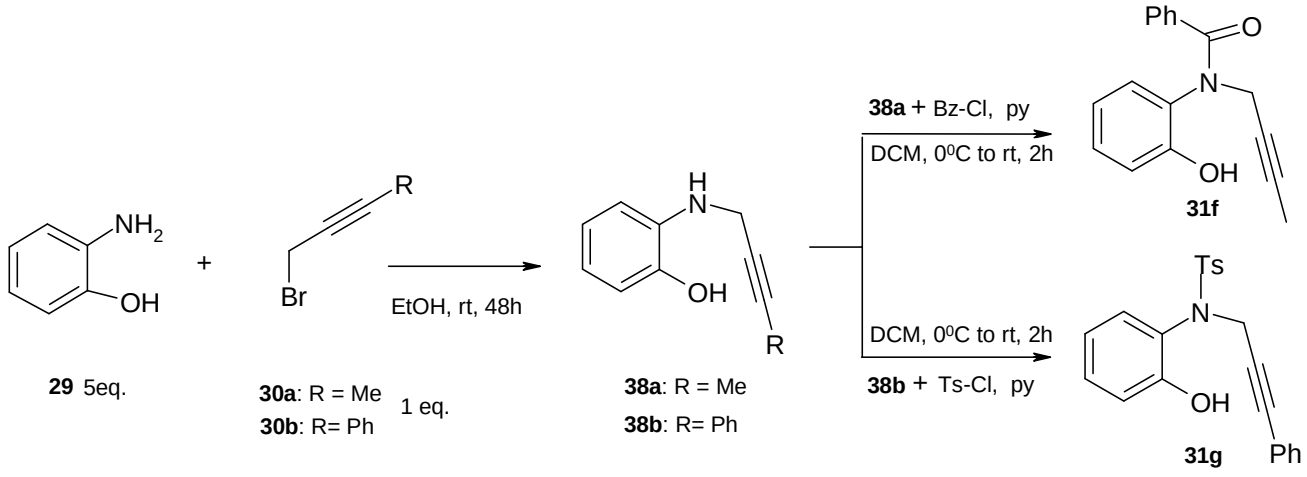
Scheme 40



29 **36** **37** **31e**

The synthesis of **31e** and **31f** required the formation of the corresponding intermediates **38a** and **38b**, obtained by reaction of **31a** with the alkynes **30a** and **30b**, which were then acylated on the nitrogen using benzoylchloride and tosylchloride respectively. Total yield for **31e** was 50% whereas only 36% for **31f** (Scheme 41).

Scheme 41



29 5eq.

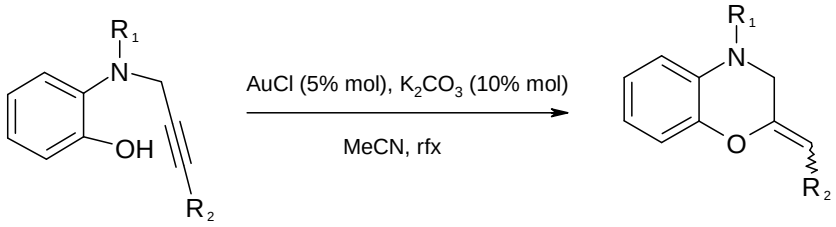
30a: R = Me
30b: R= Ph
1 eq.

38a: R = Me
38b: R= Ph

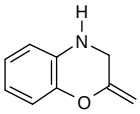
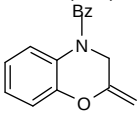
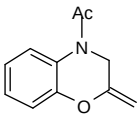
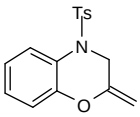
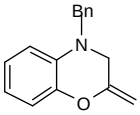
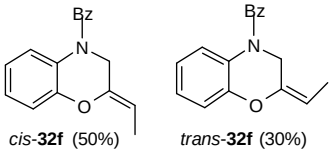
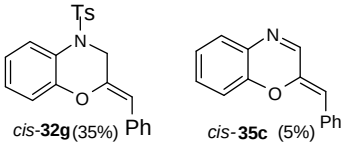
2.23 Synthesis of 2,3-dihydro-2-methylene-1,4-benzoxazines 31b-f by gold catalysis

The substrates **31b-f** were submitted to the gold-catalyzed cyclization under conditions used for the synthesis of **32a** (Scheme 38) and the results are presented in Table 12.

Table 12. Reaction scope



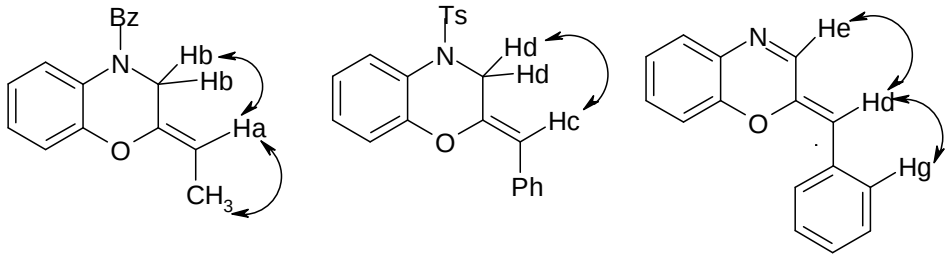
31a-g **32a-g**

Entry	Substrate	R_1	R_2	Time (h)	Yields of products (%)
1[a]	**31a**	H	H	8	 **32a** (70%)
2	**31b**	Bz	H	8	 **32b** (60%)
3	**31c**	Ac	H	5	 **32c** (60%)
4	**31d**	Ts	H	1	 **32d** (90%)
5	**31e**	Bn	H	5	 **32e** (65%)
6[b],[c]	**31f**	Bz	Me	2	 *cis*-**32f** (50%) *trans*-**32f** (30%)
7[b],[c],[d]	**31g**	Ts	Ph	24	 *cis*-**32g** (35%) *cis*-**35c** (5%)

[a] After chromatographyc column 10% of **35a** was isolated
[b] $AuCl_3$ (5% mol) was used instead of AuCl
[c] DMF used as solvent at 95°C
[d] a 5% of *cis*-**35c** was formed

The reactions were completed in 1-24 h, providing the 5-*exo*-methylene-2,3-dihydro-1,4-benzoxazines in a range of yields between 30 and 90%. Only 2-(prop-2-yn-1-ylamino)phenols **31a**, having a free N-H, afforded the cyclized product **32a** in 70% yield in addition to a 10% of regioisomer 8-hydroxyquinoline **35a**.

The presence respectively of a benzoyl and acetyl group on the nitrogen of phenol-acetylenes **31b** and **31c** led smoothly to the same yields of the corresponding cyclized products. The compound **31d**, bearing a tosyl-group on the nitrogen, gave rise to the fastest rate and highest yield of cyclization. The increase of the nitrogen nucleophilicity in **31e**, using a benzyl group, seemed not to change the reaction course giving a 65% yield of the corresponding 1,4-benzoxazine without other side-products. Inertness of substrates **31f** and **31g,** carrying respectively a phenyl and a methyl group on the acetylenic carbon and a tosyl and benzoyl group on the nitrogen, to react under the conditions used for other compounds **31a-d**, prompted us to examine different ways to drive the cyclization. After a short screening of gold catalysts and solvents, we noticed that the use of $AuCl_3$ instead of AuCl was effective to perform the heterocyclization reaction with these substrates only in DMF at 95^{o}C. Under these new conditions compounds **31f** led to a clear mixture of *cis* and *trans* 2,3-dihydro-1,4-benzoxazines, in good yields and with the *cis* isomer as the major product. The behaviour of **31g** was surprisingly different from **31f** resulting in a tarry mixture that provided only the *cis*-disteroisomer in 35% yield in addition to a 5% of the highly conjugate *cis*-**35c** lacking in the tosyl group and with an iminic-double bond. The absolute stereochemistry of the *cis*-diasteroisomer **32f** as well as of *cis*-**32fg** and *cis*-**35c** were assigned by NOE measurements. The stereochemistry of the *trans* diasteroisomers **32g** was assigned only on the basis of the different ^{1}H NMR and ^{13}C NMR chemical shifts from those of the *cis*-diasteroisomer, because of the very broad resonance of the two alkylic protons in α position to the nitrogen atom (Figure 10).



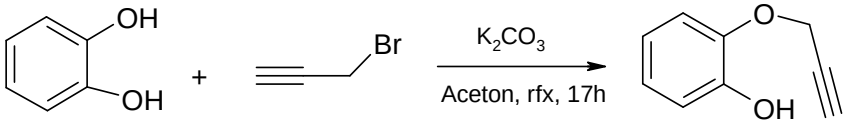
cis-**32f** *cis*-**32g** *cis*-**35c**

Figure 10. NOE enhacements observed in *cis*-isomers of compounds **32f-g** and **35c**

2.24 Synthesis of 2-(prop-2-yn-1-yloxy)phenol 41 and 3-(prop-2-yn-1-yloxy)naphthalen-2-ol 42

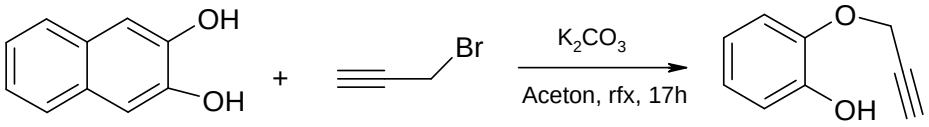
We decided to extend the scope of the reaction to other heterocycles containing the same type of heteroatoms. To do that we prepared the compounds **41** and **42** by reaction of benzene-1,2-diol **39** and naphthalene-2,3-diol **40** with propargylbromide **30** (Schemes 42 and 43).

Scheme 42



39 **30** **41 (60%)**

Scheme 43

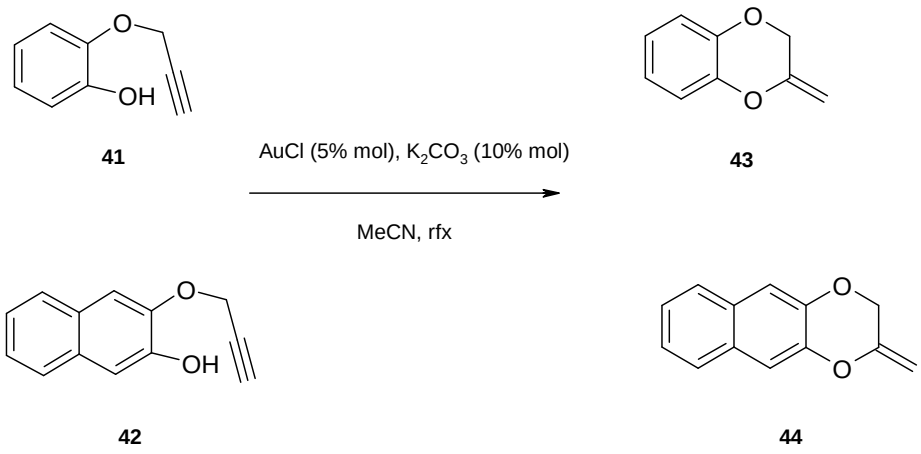


40 **30** **42 (55%)**

2.25 Synthesis of 2-methylidene-2,3-dihydro-1,4-benzodioxines 43 and 44 by gold catalysis

The compounds **41** and **42** were submitted to the gold catalysis under the previous conditions used for the synthesis of 1,4-benzoxazines **32a-g** (Table 13).

Table 13. Cyclization of compounds **41**and **42**



Entry	Substrate	Time (h)	Yields of products (%)
1	**41**	7	**43** (70%)
2[a]	**42**	1.5	**44 (**75%)

[a] Reaction performed in DMF at 100°C

As for substrates **31a-g**, the gold catalyzed cyclization on compounds **41** and **42** ran only in 5-*exo*-methylenic way as confirmed by ^{1}HNMR, ^{13}C NMR and edited gHSQC experiments on cyclized products **43** and **44**.

Substrate **41** smoothly cyclized, in refluxing acetonitrile, to the corresponding 1,4-benzodioxine in 70% yield in 7 hours. Compounds **42** didn't afford the cyclization product **44** under the conditions

used for **41**, so it was necessary to investigate different solvents to find out that only DMF at 100°C was able to give quickly the desired cyclization in good yield.

2.26 Hypothesis of reaction mechanism for the formation of 1,4 benzoxazines 32a-g and 1,4-benzodioxines 43 and 44

A proposed mechanism for the gold catalyzed heterocyclization is shown in Figure 11.

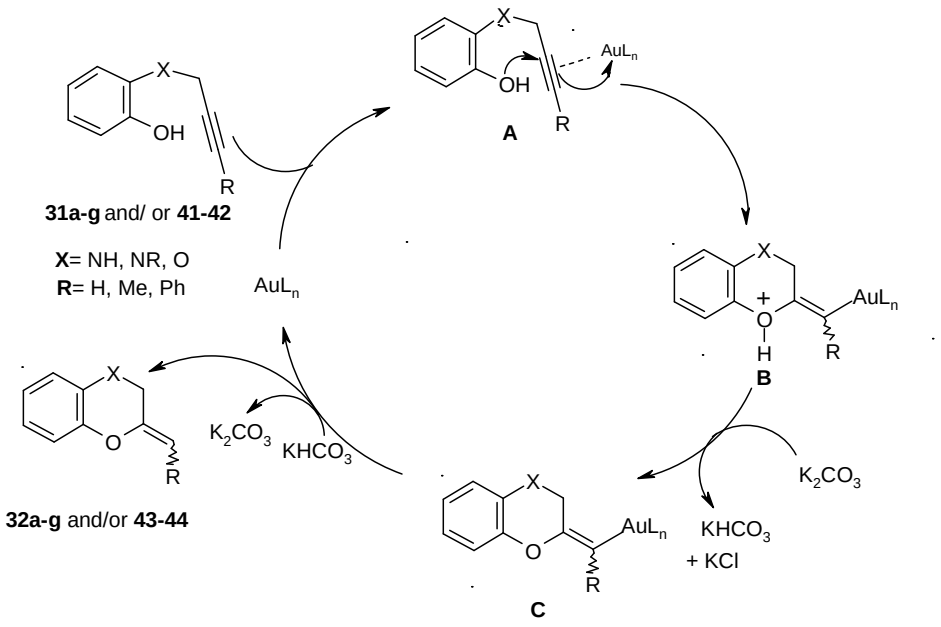


Figure 11. Proposed mechanism for the formation of 1,4-benzoxazines **32a-g** and 1,4-benzodioxines **43** and **44**

The C-C triple bond of the propargylic moiety is activated by the coordination of both Au(I) and Au(III) species (intermediate **A**). The so generated π-alkyne complex undergoes intramolecular nucleophilic attack by the hydroxyl group on the benzene ring affording a protonated intermediates **B** that evolved to the next intermediate **C** by deprotonation with a catalytic amount of K_2CO_3. It's interesting to note that in absence of K_2CO_3 no reaction product was observed.

Protonolysis of the gold-carbon bond of **C** by $KHCO_3$ give rise to the 1,4-benzoxazines **32a-g** and or 1,4-benzodioxines **43** and **44** derivatives regenerating the gold catalyst.

3.Conclusions.

To summarise, new synthetic approaches based on gold catalysis have been developed.

Allenamides were proven to be efficient substrates for gold-catalyzed cyclization, increasing the range of synthetic applications. The procedure generated represents the first example of a gold-catalyzed cyclization on allenes bearing an amido group which, however resulted as inactive. Moreover the obtained oxazolidinones bear a useful vinyl group in position 2 that allow further functionalization in order to investigate their potential effectiveness as organocatalysts.

The intramolecular hydroarylation of *N*-alkynyl pyrrolo-2-carboxamides was accomplished by gold (III)-catalysis giving bicyclic pyrrolo-fused products. The outcome of the reaction led to differently substituted pyrrolo-pyridines and pyrrolo-azepines arising either from direct cyclization or from a formal rearrangement of the carboxamides group. While the substrates having a monosubstituted acetylene afforded pyrrolo[2,3-*c*]pyridine and pyrrolo[3,2-*c*]pyridine structures, the *N*-substituted propargylamides bearing a phenyl substituent at the acetylenic carbon furnished pyrrolo[2,3-*c*]azepines and pyrrolo[3,2-*c*]azepines by a 7-*endo*-dig cyclization products.

Finally a valuable intramolecular gold catalyzed heterocyclization process on 2-substitued (prop-2-yn-1-ylamino)phenols and 2-(prop-2-yn-1-yloxy)phenols was achieved affording 2,3-dihydro-1,4-benzoxazines and 1,4-benzodioxines in good yields and with an excellent regioselectivity with formation of only *exo*-methylenic cyclized products. The presence of an *exo*-vinyl double bond allowed its further functionalization in order to investigate the pharmacologic properties of these important compounds.

4.Experimental Part

Melting points were measured with a Büchi B-540 heating unit and are uncorrected. IR spectra were recorded on a FT-IR spectrophotometer. Optical rotations were measured on a Jasco P-1010 polarimeter. Some ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz on an AVANCE 400 Bruker, other at 600 MHz on a INOVA AS600 Variant. Chemical shifts (δ) are given as ppm relative to the residual solvent peak (chloroform-*d1* 7.25 ppm/77 ppm). Mass spectra were determined on an HPLC-MS LCQ-Advantage Thermo Finnigan instrument. Some protonated molecular mass ion peaks were determined on an HPLC-MS Agilent Technologies 6140 (ESI). Elemental analyses were executed on Perkin-Elmer CHN Analyzer Series II 2400. Column chromatography was performed on a Merck silica gel 60, (mesh size 63-200 µm).

General procedure for the preparation of propargylamides 3a-f

DCC (10 mmol), **2a** (8.3 mmol) and DMAP (0.125 mmol) in anhydrous CH_2Cl_2 (60 mL), cooled at 0 °C, were slowly added to a solution of **1** (10 mmol). The resulting solution was stirred at r.t. for 48 h, then filtered on a path of silica gel. The solvent was evaporated under reduced pressure and the crude residue was purified by flash chromatography (light petroleum / AcOEt 7:3).

(*S*)-2-(*t*-Butoxycarbonylamino)-3-methyl-*N*-methyl-*N*-propargylbutanamide (3a)

Yield: 95%. Colourless oil. IR (nujol): 3304, 3298, 2119, 1703, 1651 cm^{-1}; $[\alpha]^{23}_{D}$ = +29.5 (c = 0.80, $CHCl_3$); Rotamers ratio 2.5:1; ^{1}H NMR (400 MHz, $CDCl_3$, T = 25°C) δ: 0.92 (3H, d, *J* = 6.6 Hz), 0.99 (3H, d, *J* = 6.6 Hz), 1.45 (9H, s), 1.90-2.05 (1H, m), 2.24 (1H, d, *J* = 2.3 Hz), 2.93 (3H, s), 3.75-3.85 (1H, m), 4.15-4.30 (2H, m), 5.33 (1H, d, *J* = 8.9 Hz) (major rotamer); 0.66 (3H, d, *J* = 6.7 Hz), 0.72 (3H, d, *J* = 6.7 Hz), 1.18 (9H, s), 1.70-1.80 (1H, m), 2.22 (1H, d, *J* = 2.3 Hz), 2.76 (3H, s), 3.75-3.85 (1H, m), 4.15-4.30 (2H, m), 5.33 (1H, d, *J* = 8.9 Hz) (minor rotamer); ^{13}C NMR (100

MHz, $CDCl_3$, T = 25°C) δ: 17.6 (q), 19.5 (q), 28.5 (q), 31.5 (d), 34.7 (q), 36.7 (t), 55.2 (d), 72.6 (d), 78.5 (s), 79.3 (s), 156.0 (s), 172.3 (s) (major rotamer); 17.7 (q), 19.8 (q), 28.5 (q), 31.4 (d), 34.7 (q), 39.5 (t), 55.4 (d), 73.6 (d), 78.5 (s), 79.4 (s), 155.9 (s), 172.4 (s) (minor rotamer). MS: *m/z* 268 (M^+). Anal. calcd for $C_{14}H_{24}N_2O_3$: C, 62.66; H, 9.01; N, 10.

(*S*)-2-(*t*-Butoxycarbonylamino)-*N*-methyl-*N*-propargylpropanamide (3b)

Yield: 96 %. Colourless oil. IR: 3306, 3291, 2122, 1705, 1649 cm^{-1}; $[\alpha]^{23}_D$ = +9.7 (c = 1.13, $CHCl_3$); Rotamers ratio 2.3:1; ^{1}H NMR (400 MHz, $CDCl_3$, T = 25°C) δ: 1.33 (3H, d, *J* = 7.2 Hz), 1.45 (9H, s), 2.24 (1H, d, *J* = 2.0 Hz), 3.15 (3H, s), 4.20 (1H, d, *J* = 17.0 Hz), 4.37 (1H, d, *J* = 17.0 Hz), 4.64 (1H, dq, *J* = 7.2, 7.2 Hz), 5.48 (1H, d, *J* = 7.2 Hz) (major rotamer); 1.37 (3H, d, *J* = 7.2 Hz), 1.45 (9H, s), 2.34 (1H, d, *J* = 2.0 Hz), 3.04 (3H, s), 3.96 (1H, d, *J* = 17.0 Hz), 4.40 (1H, d, *J* = 17.0 Hz), 4.64 (1H, dq, *J* = 7.2, 7.2 Hz), 5.41 (1H, d, *J* = 7.2 Hz) (minor rotamer); ^{13}C NMR (100 MHz, $CDCl_3$, T = 25°C) δ: 19.1 (q),28.7 (q), 34.5 (d), 37.1 (t), 46.8 (q), 72.7 (d), 77.8 (s), 79.4 (s), 155.6 (s), 173.1 (s) (major rotamer); 19.5 (q), 28.7 (q), 34.5 (d), 39.5 (t), 46.8 (q), 73.6 (d), 77.8 (s), 79.4 (s), 155.6 (s), 173.1 (s) (minor rotamer). MS: *m/z* 240 (M^+). Anal. calcd for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66. Found C, 60.11; H, 8.22; N, 11.43.44. Found C, 62.41; H, 9.18; N, 10.60.

(*S*)-2-(*t*-Butoxycarbonylamino)-*N*-methyl-3-phenyl-*N*-propargylpropanamide (3c)

Yield: 94%. Colourless oil. IR: 3306, 3295, 2121, 1705, 1650 cm^{-1}; $[\alpha]^{23}_D$ = +38.8 (c = 0.40, $CHCl_3$); Rotamers ratio 3:1; ^{1}H NMR (400 MHz, $CDCl_3$, T = 25°C) δ: 1.43 (9H, s), 2.22 (1H, d, *J* = 2.4 Hz), 2.73 (3H, s), 2.80-3.20 (2H, m), 4.02 (1H, d, *J* = 17.2 Hz), 4.21 (1H, d, *J* = 17.2 Hz), 4.80-4.85 (1H, m), 5.41 (1H, d, *J* = 7.9 Hz), 7.19-7.30 (5H, m) (major rotamer); 1.41 (9H, s), 2.27 (1H, d, *J* = 2.4 Hz), 2.80-3.20 (5H, m), 3.82 (1H, d, *J* = 17.2 Hz), 3.97 (1H, d, *J* = 17.2 Hz), 4.80-4.85 (1H, m), 5.30-5.40 (1H, m), 7.19-7.30 (5H, m) (minor rotamer); ^{13}C NMR (100 MHz, $CDCl_3$, T = 25°C) δ: 28.7 (q), 34.4 (q), 36.9 (t), 40.4 (t), 51.9 (d), 72.6 (d), 78.4 (s), 80.0 (s), 127.3 (d), 128.8 (d), 129.9 (d), 136.6 (s), 155.4 (s), 171.8 (s) (major rotamer); 28.7 (q), 33.8 (q), 39.4 (t), 40.0 (t),

51.9 (d), 73.7 (d), 78.4 (s), 80.2 (s), 127.3 (d), 129.0 (d), 129.6 (d), 136.9 (s), 155.4 (s), 171.8 (s) (minor rotamer). MS: *m/z* 316 (M^+). Anal. calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found C, 68.42; H, 7.50; N, 8.89.

(*S*)-2-(*t*-Butoxycarbonylamino)-*N*-methyl-3,3-dimethyl-*N*-propargylbutanamide (3d)

Yield: 90%. Colourless oil. Rotamers ratio 3:1; ^{1}H NMR (400 MHz, $CDCl_3$, T = 25°C) δ: 0.99 (9H, s), 1.43 (9H, s), 2.21 (1H, dd, *J* = 2.5, 2.5 Hz), 3.21 (3H, s), 3.97 (1H, dd, *J* = 17.2, 2.3 Hz), 4.50 (2H, m), 5.30 (1H, d, *J* = 10 Hz), (major rotamer); 1.02 (9H, s), 1.43 (9H, s), 2.32 (1H, dd, *J* = 2.3, 2.3 Hz), 3.01 (3H, s), 4.11 (1H, dd, *J* = 18.5, 2.1 Hz), 4.50 (2H, m), 5.30 (1H, br.s.), (minor rotamer); ^{13}C NMR (100 MHz, $CDCl_3$, T = 25°C) δ: 26.3 (q), 26.9 (s), 28.3 (q), 36.1 (q), 36.4 (q), 55.9 (d), 71.9 (d), 78.3 (s), 79.5 (s), 155.6 (s), 171.7 (s) (major rotamer); 26.4 (q), 26.9 (s), 28.3 (q), 33.1 (q), 40.0 (t), 55.9 (d), 73.1 (d), 78.3 (s), 79.5 (s), 155.6 (s), 171.7 (s) (minor rotamer). HPLC-MS (ESI): *m/z* 283.38 (MH^+).

(*S*)-2-(*t*-Butoxycarbonylamino)-*N*-methyl-*N*-propargylbutanamide (3e)

Yield: 85%. Colourless oil. Rotamers ratio 1.2:1; ^{1}H NMR (400 MHz, $CDCl_3$, T = 25°C) δ: 0.96 (3H, dd, *J* = 7.4, 7.4 Hz), 1.46 (9H, s), 1.60 (1H, m), 1.78 (1H, m), 2.25 (1H, dd, *J* = 2.3, 2.3 Hz), 3.17 (3H, s), 4.13 (1H, dd, *J* = 17.1, 2.9 Hz), 4.36 (1H, dd, *J* = 17.1, 2.3 Hz), 5.39 (1H, d, *J* = 7.8 Hz), (major rotamer); 0.96 (3H, m), 1.46 (9H, s), 1.60 (1H, m), 1.78 (1H, m) 2.33 (1H, dd, *J* = 2.3, 2.3 Hz), 3.04 (3H, s), 4.0 (1H, dd, *J* = 18.1, 2.1 Hz), 4.42 (1H, m), 5.32 (1H, d, *J* = 7.0 Hz), (minor rotamer); ^{13}C NMR (100 MHz, $CDCl_3$, T = 25°) δ: 9.5 (q),26.3 (t), 28.3 (q), 34.3 (q), 36.6 (t), 51.3 (d), 72.1 (d), 78.2 (s), 79.5 (s), 155.5 (s), 172.0 (s) (major rotamer); 9.6 (q), 26.4 (t), 28.3 (q), 34.3 (q), 36.6 (t), 51.3 (d), 73.1 (d), 78.2 (s), 79.5 (s), 155.5 (s), 172.1 (s) (minor rotamer). HPLC-MS (ESI): *m/z* 255.33 (MH^+).

(*S*)-2-(*t*-Butoxycarbonylamino)-*N*-methyl-2-phenyl-*N*-propargylacetamide (3f)

Yield: 97%. White solid. M. p. 78-80 °C. IR: 3306, 3289, 2115, 1710, 1648 cm^{-1}; $[\alpha]^{23}_{D}$ = +152.2 (c = 0.94, $CHCl_3$); Rotamers ratio 2.7:1; ^{1}H NMR (400 MHz, $CDCl_3$, T = 25°C) δ: 1.43 (9H, s), 2.22 (1H, d, *J* = 2.5 Hz), 2.95 (3H, s), 4.15-4.40 (2H, m), 5.58 (1H, d, *J* = 7.9 Hz), 5.97 (1H, d, *J* = 7.9 Hz), 7.30-7.40 (5H, m) (major rotamer); 1.42 (9H, s), 2.22 (1H, d, *J* = 2.5 Hz), 3.05 (3H, s), 3.82 (1H, d, *J* = 17.5 Hz), 4.12 (1H, d, *J* = 17.5 Hz), 5.60-5.65 (1H, m), 6.00-6.05 (1H, m), 7.30-7.40 (5H, m) (minor rotamer); ^{13}C NMR (100 MHz, $CDCl_3$, T = 25°C) δ: 28.7 (q), 34.6 (q), 37.4 (t), 55.7 (d), 72.7 (d), 78.3 (s), 80.1 (s), 128.1 (d), 128.7 (d), 129.4 (d), 137.9 (s), 155.4 (s), 170.3 (s) (major rotamer); 28.7 (q), 34.0 (q), 39.3 (t), 55.d (q), 73.8 (d), 78.3 (s), 80.1 (s), 128.1 (d), 128.7 (d), 129.4 (s), 137.9 (s), 155.4 (s), 170.3 (s) (minor rotamer). MS: *m/z* 302 (M^+). Anal. calcd for $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33; N, 9.26. Found C, 67.42; H, 7.50; N, 9.47.

General procedure for the preparation of allenamides 4a-f

t-BuOK (2.5 mmol) in THF (10 mL) was added to a solution of **3** (1 mmol). The resulting solution was stirred at r.t. for 1 min, then filtered on silica gel (AcOEt). The solvent was evaporated under reduced pressure and the residue was used without further purification for the next step.

(*S*)-2-(*t*-Butoxycarbonylamino)-3-methyl-*N*-methyl-*N*-(1,2-propadienyl)butanamide (4a)

Yield: 98%. Colourless oil. IR: 3301, 1947, 1719, 1648 cm^{-1}; $[\alpha]^{23}_{D}$ = +55.4 (c = 0.94, $CHCl_3$); Rotamers ratio 1.1:1; ^{1}H NMR (400 MHz, $CDCl_3$, T = 25°C) δ: 0.92 (3H, d, *J* = 6.8 Hz), 1.00 (3H, d, *J* = 6.8 Hz), 1.45 (9H, s), 1.90-2.10 (1H, m), 3.14 (3H, s), 4.50-4.65 (1H, m), 5.25-5.35 (1H, m), 5.43 (2H, d, *J* = 6.4, Hz), 7.54 (1H, dd, *J* = 6.4, 6.4 Hz) (major rotamer); 0.90 (3H, d, *J* = 6.8 Hz), 1.00 (3H, d, *J* = 6.8 Hz), 1.45 (9H, s), 1.90-2.10 (1H, m), 3.04 (3H, s), 4.50-4.65 (1H, m), 5.25-5.35 (1H, m), 5.43 (2H, d, *J* = 6.4 Hz), 6.97 (1H, dd, *J* = 6.4, 6.4 Hz) (minor rotamer); ^{13}C NMR (100 MHz, $CDCl_3$, T = 25°C) δ: 17.5 (q), 19.9 (q), 28.8 (q), 31.9 (q), 33.5 (d), 55.7 (d), 80.0 (s), 87.4 (t),

100.1 (d), 156.2 (s), 171.1 (s), 201.6 (s) (major rotamer); 17.6 (q), 20.0 (q), 28.8 (q), 31.9 (q), 33.5 (d), 56.1 (d), 80.0 (s), 87.8 (t), 101.3 (d), 156.2 (s), 171.1 (s), 203.0 (s) (minor rotamer). MS: *m/z* 268 (M^+). Anal. calcd for $C_{14}H_{24}N_2O_3$: C, 62.66; H, 9.01; N, 10.44. Found C, 62.37; H, 9.19; N, 10.49.

(*S*)-2-(*t*-Butoxycarbonylamino)-*N*-methyl-*N*-(1,2-propadienyl)propanamide (4b)

Yield: 94%. Colourless oil. IR: 3306, 1940, 1705, 1649 cm^{-1}; $[\alpha]^{23}_D$ = +54.5 (c = 1.80, $CHCl_3$); Rotamers ratio 1.1:1; ^1H NMR (400 MHz, $CDCl_3$, T = 25°C) δ: 1.37 (3H, d, *J* = 5.7 Hz), 1.45 (9H, s), 3.11 (3H, s), 4.73 (1H, dq, *J* = 5.7, 5.7 Hz), 5.40-5.50 (3H, m), 7.49-7.52 (1H, m) (major rotamer); 1.35 (3H, d, *J* = 5.7 Hz), 1.45 (9H, s), 3.04 (3H, s), 4.73 (1H, dq, *J* = 5.7, 5.7 Hz), 5.40-5.50 (3H, m), 6.85-6.88 (1H, m) (minor rotamer); ^{13}C NMR (100 MHz, $CDCl_3$, T = 25°C) δ: 19.4 (q), 28.7 (q), 31.9 (q), 47.3 (d), 79.9 (s), 87.8 (t), 100.1 (d), 155.5 (s), 171.5 (s), 201.6 (s) (major rotamer); 19.2 (q), 28.7 (q), 33.0 (q), 46.9 (d), 79.9 (s), 87.3 (t), 100.9 (d), 155.5 (s), 171.5 (s), 202.8 (s) (minor rotamer). MS: *m/z* 240 (M^+). Anal. calcd for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66. Found C, 60.17; H, 8.12; N, 11.50.

(*S*)-2-(*t*-Butoxycarbonylamino)-*N*-methyl-3-phenyl-*N*-(1,2-propadienyl)propanamide (4c)

Yield: 95%. Yellow oil. IR: 3306, 1942, 1701, 1650 cm^{-1}; $[\alpha]^{23}_D$ = +56.7 (c = 0.63, $CHCl_3$); Rotamers ratio 1.4:1; ^1H NMR (400 MHz, $CDCl_3$, T = 25°C) δ: 1.36 (9H, s), 2.72 (3H, s), 2.90-3.06 (2H, m), 4.83-4.90 (1H, m), 5.30 (2H, d, *J* = 6.3 Hz), 5.62-5.69 (1H, m), 7.08-7.35 (5H, m), 7.44 (1H, dd, *J* = 6.3, 6.3 Hz) (major rotamer); 1.36 (9H, s), 2.91 (3H, s), 2.90-3.06 (2H, m), 4.90-4.97 (1H, m), 5.25 (2H, d, *J* = 6.3 Hz), 5.62-5.69 (1H, m), 6.79 (1H, dd, *J* = 6.3, 6.3 Hz), 7.08-7.35 (5H, m) (minor rotamer); ^{13}C NMR (100 MHz, $CDCl_3$, T = 25°C) δ: 28.7 (q), 33.0 (q), 40.2 (t), 52.6 (d), 80.0 (s), 87.6 (t), 100.0 (d), 127.3 (d), 128.8 (d), 129.8 (d), 136.6 (s), 155.5 (s), 170.6 (s), 202.9 (s) (major rotamer); 28.7 (q), 32.0 (q), 39.8 (t), 52.2 (d), 80.0 (s), 87.0 (t), 100.9 (d), 127.1 (d), 128.7

(d), 129.8 (d), 136.6 (s), 155.5 (s), 170.4 (s), 201.7 (s) (minor rotamer). MS: *m/z* 316 (M^+). Anal. calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found C, 68.05; H, 7.82; N, 9.09.

(*S*)-2-(*t*-Butoxycarbonylamino)-3,3-dimethyl-*N*-methyl-*N*-(1,2-propadienyl)butanamide (4d)

Yield: 98%. Colourless oil. Rotamers ratio 1:1; ^{1}H NMR (400 MHz, $CDCl_3$, T = 25°C) δ: 1.01 (9H, s), 1.46 (9H, s), 3.05 (3H, s), 4.61 (1H, d, *J* = 9.9 Hz), 5.30-5.47 (3H, m), 7.57 (1H, dd, *J* = 6.4, 6.4 Hz), (major rotamer); 1.01 (9H, s), 1.47 (9H, s), 3.19 (3H, s), 4.65 (1H, d, *J* =9.9 Hz), 5.30-5.47 (3H, m), 7.12 (1H, dd, *J* = 6.0, 6.0 Hz), (minor rotamer); ^{13}C NMR (100 MHz, $CDCl_3$, T = 25°C) δ: 26.3 (q), 26.3 (q), 26.3 (q), 28.3 (q), 28.3 (q), 28.3 (q), 30.3 (s), 31.4 (q), 56.7 (d), 79.6 (s), 87.2 (t), 99.5 (d), 154.7 (s), 170.5 (s), 201.2 (s) (major rotamer); 26.3 (q), 26.3 (q), 26.3 (q), 28.3 (q), 28.3 (q), 28.3 (q), 30.3 (s), 34.1 (q), 56.3 (d), 79.6 (s), 86.7 (t), 101.8 (d), 154.7 (s), 170.5 (s), 202.8 (s), (minor rotamer). HPLC-MS (ESI): *m/z* 283.38 (MH^+).

(*S*)-2-(*t*-Butoxycarbonylamino)-*N*-methyl-*N*-(1,2-propadienyl)butanamide (4e)

Yield: 97%. Colourless oil. Rotamers ratio 1:1; ^{1}H NMR (400 MHz, $CDCl_3$, T = 25°C) δ: 0.97 (3H, dd, *J* = 13.0, 7.4 Hz), 1.47 (9H, s), 1.63 (1H, m), 1.83 (1H, m), 3.04 (3H, s), 4.65 (1H, m), 5.38 (1H, m), 5.44 (2H, d, *J* = 6.4 Hz), 7.53 (1H, dd, *J* = 6.4, 6.4 Hz) (major rotamer); 0.97 (3H, dd, *J* = 12.5, 7.4 Hz), 1.47 (9H, s), 1.63 (1H, m), 1.83 (1H, m), 3.13 (3H, s), 4.65 (1H, m), 5.38 (1H, m), 5.44 (2H, d, *J* = 6.4 Hz), 6.93 (1H, dd, *J* = 6.0, 6.0 Hz) (minor rotamer); ^{13}C NMR (150.81 MHz, $CDCl_3$, T = 25°C) δ: 9.6 (q), 26.3 (t), 28.3 (q), 28.3 (q), 28.3 (q), 31.5 (q), 51.9 (d), 79.6 (s), 87.4 (t), 79.6 (s), 87.4 (t), 99.6 (d), 155.5 (s), 170.6 (s), 202.4 (s) (major rotamer); 9.6 (q), 26.3 (t), 28.3 (q), 28.3 (q), 28.3 (q), 32.8 (q), 51.6 (d), 79.6 (s), 56.3 (d), 79.6 (s), 86.9 (t), 100.6 (d), 155.5 (s), 170.6 (s), 201.1 (s), (minor rotamer). HPLC-MS (ESI): *m/z* 255.33 (MH^+).

(*S*)-2-(*t*-Butoxycarbonylamino)-*N*-methyl-2-phenyl-*N*-(1,2-propadienyl)acetamide (4f)

Yield: 95%. Yellow oil. IR: 3306, 1946, 1704, 1644 cm^{-1}; $[\alpha]^{23}_D$ = +51.3 (c = 0.89, $CHCl_3$); Rotamers ratio 1.5:1; ^1H NMR (400 MHz, $CDCl_3$, T= 25°C) δ: 1.43 (9H, s), 2.91 (3H, s), 5.27-5.42 (2H, m), 5.64 (1H, d, *J* = 8.0 Hz), 5.95 (1H, d, *J* = 8.0 Hz), 6.77 (1H, dd, *J* = 6.4, 6.4 Hz), 7.25-7.75 (5H, m) (major rotamer); 1.43 (9H, s), 3.03 (3H, s), 5.27-5.42 (2H, m), 5.70 (1H, d, *J* = 8.0 Hz), 5.95 (1H, dd, *J* = 8.0, 8.0 Hz), 7.25-7.75 (6H, m) (minor rotamer); ^{13}C NMR (100 MHz, $CDCl_3$, T = 25°C) δ: 28.7 (q), 33.0 (q), 56.3 (d), 80.3 (s), 88.0 (t), 100.7 (d), 128.1 (d), 128.8 (d), 129.5 (d), 137.6 (s), 155.4 (s), 168.9 (s), 202.7 (s) (major rotamer); 28.7 (q), 32.2 (q), 55.8 (d), 80.3 (s), 87.3 (t), 100.2 (d), 128.1 (d), 128.8 (d), 129.5 (d), 137.9 (s), 154.3 (s), 168.9 (s), 201.6 (s) (minor rotamer). MS: *m/z* 302 (M^+). Anal. calcd for $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33; N, 9.26. Found C, 67.49; H, 7.61; N, 9.42.

General procedure for cyclisation of allenamides 4a-f

A 250 mL round bottomed flask fitted with a magnetic stirrer was charged with **4** (4.2 mmol) and MeCN dry (75 mL) under argon atmosphere. $AuCl_3$ (0.063 g, 0.21 mmol) weighted under argon atmosphere was added to the solution and the mixture was refluxed for 1-3.5h. After this time the mixture was cooled down to room temperature and concentrated in vacuo to dryness. Purification and separation of the two diasteromers by flash column chromatography (toluene / AcOEt 7:3) afforded 5-substituted (2*S*,5*S*) and (2*S*,5*R*)-3-methyl-1-terbutyloxycarbonyl-2-vinylimidazolidin-4-ones **5**.

***tert*-butyl (2*R*,5*S*)-2-ethenyl-3-methyl-4-oxo-5-(propan-2-yl)imidazolidine-1-carboxylate *(cis*-5a)**

Pale yellow oil. IR (nujol): 1645,1706 cm^{-1}. $[\alpha]^{23}_D$ = +52.3 (c = 0.69, $CHCl_3$) ^1H NMR (599.71 MHz, $CDCl_3$, T= 50°C) *δ*: 5.69 (ddd, 1H, *J* = 17.3, 9.9, 8.0 Hz), 5.50 (d, 1H, *J* = 17 Hz), 5.43 (d,

1H, *J* = 10.2 Hz), 5.16 (d, 1H, *J* = 7.7Hz), 4.05 (br.s. 1H), 2.79 (s, 3H), 2.23 (m, 1H), 1.46 (s, 9H), 1.08 (d, 3H, *J* = 7.1 Hz), 1.01 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR (150.81 MHz, $CDCl_3$, T= 50°C) δ 169.5 (C), 154.1 (C), 135.1 (CH), 121.1 (CH_2), 81.1 (C), 76.0 (CH), 64.0 (CH), 31.2 (CH_3), 28.3 (CH_3), 28.3 (CH_3), 28.3 (CH_3), 26.4 (CH), 18.6 (CH_3), 18.2 (CH_3). HPLC-MS (ESI): *m/z* 269.35 (MH^+).

***tert*-butyl (2*S*,5*S*)-2-ethenyl-3-methyl-4-oxo-5-(propan-2-yl)imidazolidine-1-carboxylate *(trans*-5a)**

Pale yellow oil. IR (nujol): 1648, 1714 cm^{-1} . $[\alpha]^{23}_D$ = +10.5 (c = 0.91, $CHCl_3$) ^{1}H NMR (599.71 MHz, $CDCl_3$, T= 50°C) δ: 5.49 (m, 3H), 5.11 (m, 1H), 4.07 (m, 1H), 2.77 (s, 3H), 2.65 (1H, m), 1.46 (s, 9H), 1.16 (d, 3H, *J* = 7.1 Hz), 0.86 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (150.81 MHz, $CDCl_3$, T= 50°C) δ: 169.3 (C), 154.1(C), 135.8 (CH), 121.2 (CH2), 76.7 (CH), 63.2 (CH), 28.5 (CH3), 28.5 (CH3), 28.5 (CH3), 26.6 (CH3), 18.5 (CH3), 16.3 (CH3). HPLC-MS (ESI): *m/z* 269.35 (MH^+).

***tert*-butyl (2*R*,5*S*)-2-ethenyl-3,5-dimethyl-4-oxoimidazolidine-1-carboxylate (*cis*-5b)**

^{1}H NMR (599.71 MHz, CD_3OD, T= 25°C) δ: 5.62 (m, 1H), 5.52 (d, 1H, *J* = 16.8 Hz), 5.46 (d, 1H, *J* = 9.9 Hz), 5.26 (d, 1H, *J* = 8.0 Hz), 4.13 (q, 1H, *J* = 6.8 Hz), 2.80 (s, 3H), 1.47 (s, 9H), 1.47 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (150.81 MHz, CD_3OD , T= 50°C) δ: 173.0 (C), 154.7 (C), 136.5 (CH), 121.9 (CH_2), 82.6 (C), 77.2 (CH), 56.2 (CH), 28.7 (CH_3), 28.7 (CH_3), 28.7 (CH_3), 27.0 (CH_3), 19.1 (CH_3). HPLC-MS (ESI): *m/z* 241.29 (MH^+).

***tert*-butyl (2*S*,5*S*)-2-ethenyl-3,5-dimethyl-4-oxoimidazolidine-1-carboxylate (*trans*-5b)**

^{1}H NMR (599.71 MHz, CD_3OD, T= 25°C) δ: 5.62 (m, 1H), 5.51 (m, 2H), 5.24 (m 1H), 4.13 (m, 1H), 2.78 (m, 3H), 1.47 (m, 12H); ^{13}C NMR (150.81 MHz, CD_3OD , T= 50°C) δ: 172.8 (C), 154.0 (C), 136.0 (CH), 122.3 (CH_2), 82.6 (C), 77.3 (CH), 55.5 (CH), 28.7 (CH_3), 28.7 (CH_3), 28.7 (CH_3), 27.0 (CH_3), 16.9 (CH_3). HPLC-MS (ESI): *m/z* 241.29 (MH^+).

***tert*-butyl (2*R*,5*S*)-5-benzyl-2-ethenyl-3-methyl-4-oxoimidazolidine-1-carboxylate (*cis*-5c)**

^{1}H NMR (599.71 MHz, CD_3OD, T= 50°C) δ 7.24 (m, 3H), 7.09 (m, 2H), 5.23 (d, 1H, *J* = 17.5 Hz), 5.03 (d, 1H, *J* = 10.0 Hz), 5.00 (m, 1H), 4.38 (dd, 1H, *J* = 5.6, 2.5 Hz), 3.74 (m, 1H), 3.27 (m, 1H), 3.15 (dd, 1H, *J* = 13.5, 2.0 Hz), 2.60 (s, 3H), 1.49 (br.s.,9H); ^{13}C NMR (150.81 MHz, CD_3OD , T= 50°C) δ 171.1 (C), 154.6 (C), 137.7 (C), 135.8 (CH), 131.4 (CH), 131.4 (CH), 129.4 (CH), 129.4 (CH), 128.1 (CH), 121.9 (CH_2), 82.6 (C), 77.7 (CH), 61.9 (CH), 37.0 (CH_2), 28.8 (CH_3), 28.8 (CH_3), 28.8 (CH_3), 26.8 (CH_3). HPLC-MS (ESI): *m/z* 317.39 (MH^+).

***tert*-butyl (2*R*,5*S*)-5-*tert*-butyl-2-ethenyl-3-methyl-4-oxoimidazolidine-1-carboxylate (*cis*-5d)**

^{1}H NMR (599.71 MHz, CD_3OD, T= 25°C) δ: 5.82 (ddd, 1H, *J* = 17.0, 10.0, 7.9 Hz), 5.55 (d, 1H, *J* = 16.8 Hz), 5.48 (dt, 1H, *J* = 10.1, 0.9 Hz), 5.27 (d, 1H, *J* = 8.1 Hz), 3.98 (s, 1H), 2.78 (s, 3H), 1.48 (s, 9H), 1.02 (s, 9H); ^{13}C NMR (150.81 MHz, CD_3OD , T= 25°C) δ: 171.3 (C), 157.1 (C), 136.0 (CH), 122.3 (CH_2), 82.7 (C), 78.1 (CH), 68.2 (CH), 36.5 (C), 28.6 (CH_3), 28.6 (CH_3), 28.6 (CH_3), 27.7 (CH_3), 27.7 (CH_3), 27.7 (CH_3), 27.1 (CH_3). HPLC-MS (ESI): *m/z* 283.37 (MH^+).

***tert*-butyl (2*S*,5*S*)-5-*tert*-butyl-2-ethenyl-3-methyl-4-oxoimidazolidine-1-carboxylate (*trans*-5d)**

^{1}H NMR (599.71 MHz, CD_3OD, T= 25°C) δ: 5.52 (m, 3H), 5.19 (dd, 1H, J = 7.7, 2.1 Hz), 4.06 (d, 1H, J = 1.0 Hz), 2.72 (s, 3H), 1.45 (s, 9H), 1.00 (s, 9H); ^{13}C NMR (150.81 MHz, CD_3OD , T= 25°C) δ: 171.2 (C), 155.2 (C), 137.1 (CH), 122.0 (CH_2), 82.6 (C), 78.6 (CH), 66.8 (CH), 39.1 (C), 28.6 (CH_3), 28.6 (CH_3), 28.6 (CH_3), 27.2 (CH_3), 27.2 (CH_3), 27.2 (CH_3), 26.9 (CH_3). HPLC-MS (ESI): *m/z* 283.37 (MH^+).

***tert*-butyl (2*R*,5*S*)-2-ethenyl-5-ethyl-3-methyl-4-oxoimidazolidine-1-carboxylate (*cis*-5e)**

^{1}H NMR (599.71 MHz, CD_3OD, T= 25°C) δ: 5.64 (m, 1H), 5.54 (d, 1H, *J* = 17.0 Hz), 5.48 (d, 1H, *J* = 10.2 Hz), 5.27 (d, 1H, *J* = 8.2 Hz), 4.14 (dd, 1H, *J* = 5.2, 4.5 Hz), 2.79 (s, 3H), 1.95 (m, 1H), 1.81 (m, 1H), 1.46 (s, 9H), 0.90 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (150.81 MHz, CD_3OD , T= 25°C) δ: 171.9 (C), 155.0 (C), 136.1 (CH), 122.4 (CH_2), 82.4 (C), 77.3 (CH), 61.3 (CH), 28.7 (CH_3), 28.7 (CH_3), 28.7 (CH_3), 27.0 (CH_3), 25.4 (CH_2), 9.4 (CH_3). HPLC-MS (ESI): *m/z* 255.32 (MH^+).

***tert*-butyl (2*S*,5*S*)-2-ethenyl-5-ethyl-3-methyl-4-oxoimidazolidine-1-carboxylate (*trans*-5e)**

^{1}H NMR (599.71 MHz, CD_3OD, T= 25°C) δ: 5.58 (m, 3H), 5.23 (m, 1H), 4.20 (m, 1H), 2.79 (m, 3H), 2.27 (m, 1H), 1.85 (m, 1H), 1.46 (m, 9H), 0.77 (m, 3H); ^{13}C NMR (150.81 MHz, CD_3OD , T= 25°C) δ: 171.8 (C), 153.9 (C), 135.7 (CH), 122.6 (CH_2), 82.5 (C), 78.0 (CH), 60.2 (CH), 28.7 (CH_3), 28.7 (CH_3), 28.7 (CH_3), 26.9 (CH_3), 23.7 (CH_2), 7.4 (CH_3); HPLC-MS (ESI): *m/z* 255.32 (MH^+).

***tert*-butyl (2*R*,5*S*)-2-ethenyl-3-methyl-4-oxo-5-phenylimidazolidine-1-carboxylate (*cis*-5f)**

^{1}H NMR (599.71 MHz, CD_3OD, T= 50°C) δ: 7.37 (m, 4H), 7.30 (m, 1H), 5.84 (ddd, 1H, *J* = 17.5, 9.5, 7.9 Hz), 5.60 (d, 1H, *J* = 17.0 Hz), 5.54 (d, 1H, *J* = 10.0 Hz), 5.40 (d, 1H, *J* = 8.1 Hz), 5.13 (s, 1H), 2.83 (s, 3H), 1.38 (br.s., 9H); ^{13}C NMR (150.81 MHz, CD_3OD , T= 50°C) δ: 170.5 (C), 154.8 (C), 139.0 (C), 136.2 (CH), 129.5 (CH), 129.5 (CH), 129.1 (CH), 128.1 (CH), 128.1 (CH), 122.2 (CH_2), 82.7 (C), 77.3 (CH), 64.2 (CH), 28.6 (CH_3), 28.6 (CH_3), 28.6 (CH_3), 27.4 (CH_3). HPLC-MS (ESI): *m/z* 303.36 (MH^+).

***tert*-butyl (2*S*,5*S*)-2-ethenyl-3-methyl-4-oxo-5-phenylimidazolidine-1-carboxylate (*trans*-5f)**

^{1}H NMR (599.71 MHz, CD_3OD, T= 50°C) δ: 7.32 (m, 5H), 5.72 (m, 1H), 5.60 (m, 3H), 5.04 (m, 1H), 2.86 (br.s., 3H), 1.40 (br.s., 9H); ^{13}C NMR (150.81 MHz, CD_3OD , T= 50°C) δ: 170.8 (C), 154.9 (C), 140.8 (C), 135.2 (CH), 129.4 (CH), 129,4 (CH), 129.4 (CH), 128.0 (CH), 128.0 (CH), 122.9 (CH_2), 80.7 (C), 77.4 (CH), 64.2 (CH), 28.4 (CH_3), 28.4 (CH_3), 28.4 (CH_3), 27.0 (CH_3). HPLC-MS (ESI): *m/z* 303.36 (MH^+).

Preparation of (*S*)-2-(9-Fluorenylmethylcarbonylamino)-3-methyl-*N*-methyl-*N*-propargyl-butanamide (10)

DCC (10 mmol), **2a** (8.3 mmol) and DMAP (0.125 mmol) in anhydrous CH_2Cl_2 (60 mL), cooled at 0 °C, were slowly added to a solution of **9** (10 mmol). The resulting solution was stirred at r.t. for

48h, then filtered on a path of silica gel. The solvent was evaporated under reduced pressure and the crude residue was purified by flash chromatography (Cyclohexane / AcOEt 7:3).

Yield: 90%. White foam. Rotamers ratio 4:1; ^{1}H NMR (599 MHz, $CDCl_3$, T = 25°C) δ: 0.95 (3H, d, *J* = 6.6 Hz), 1.01 (3H, d, *J* = 6.6 Hz), 2.03 (1H, dq, *J* = 13.1, 6.6 Hz), 2.24 (1H, t, *J* = 2.3 Hz), 3.19 (3H, s), 4.10 (1H, dd, *J* = 17.3, 2.1 Hz), 4.23 (1H, t, *J* = 6.9 Hz), 4.34 (1H, dd, *J* = 10.5, 7.2 Hz), 4.41 (2H, m), 4.56 (1H, dd, *J* = 9.2, 5.9 Hz), 5.61 (1H, d, *J* = 9.2 Hz), 7.32 (2H, t, *J* = 7.4 Hz), 7.41 (2H, td, *J* = 7.4, 2.6 Hz), 7.61 (2H, dd, *J* = 6.9, 4.3 Hz), 7.77 (2H, d, *J* = 7.6 Hz) (major rotamer); 0.95 (3H, d, *J* = 6.6 Hz), 1.01 (3H, d, *J* = 6.6 Hz), 2.09 (1H, dq), 2.33 (1H, t), 3.04 (3H, s), 4.01 (1H, dd), 4.23 (1H, t, *J* = 6.9 Hz), 4.34 (1H, dd, *J* = 10.5, 7.2 Hz), 4.41 (2H, m), 4.51 (1H, dd), 5.57 (1H, d), 7.32 (2H, t, *J* = 7.4 Hz), 7.41 (2H, td, *J* = 7.4, 2.6 Hz), 7.61 (2H, dd, *J* = 6.9, 4.3 Hz), 7.77 (2H, d, *J* = 7.6 Hz), (minor rotamer); ^{13}C NMR (150.81 MHz, $CDCl_3$, T = 25°C) δ: 17.3 (q), 19.4 (q), 31.6 (d), 34.6 (q), 36.6 (t), 47.1 (d), 55.5 (d), 67.0 (t), 72.1 (d), 78.1 (s), 119.9 (d), 119.9 (d) 125.1 (d), 125.1 (d), 127.0 (d), 127.0 (d), 127.6 (d), 127.6 (d), 141.2 (s), 141.2 (s), 143.7 (s), 143.8 (s), 156.4 (s), 171.7 (s), (major rotamer); 17.4 (q), 19.6 (q), 31.5 (d), 33.3 (q), 39.3 (t), 47.1 (d), 55.7 (d), 67.0 (t), 73.2 (d), 77.6 (s), 119.9 (d), 119.9 (d) 125.1 (d), 125.1 (d), 127.0 (d), 127.0 (d), 127.6 (d), 127.6 (d), 141.2 (s), 141.2 (s), 143.7 (s), 143.8 (s), 156.3 (s), 171.7 (s), (minor rotamer); HPLC-MS (ESI): *m/z* 391.47 (MH^+)

Synthesis of (2*S*)-2-amino-*N*,3-dimethyl-*N*-(prop-2-yn-1-yl)butanamide (11)

Piperidine (4.12 mmol) was added to a solution of **10** (20 mmol) in dry acetonitrile (500ml).The resulting mixture was left under stirring for 6 h then the solvent was evaporated to dryness. The crude residue was purified by flash chromatography (EtOAc / MeOH / TEA 9:0.5:0.5).

Yield: 78%. Red oil. ^{1}H NMR (400 MHz, $CDCl_3$, T = 25°C) δ: 0.34 (3H, d, *J* = 6.8 Hz), 1.01 (3H, d, *J* = 6.8 Hz), 1.91 (1H, m), 2.23 (1H, dd, *J* = 2.5, 2.5 Hz), 3.14 (3H, s), 3.51 (1H, d, *J* = 5.4 Hz), 4.19 (1H, dd, *J* = 17.3, 2.5 Hz), 4.13 (2H, br.s.), 4.35 (1H, dd, *J* = 17.3, 2.5 Hz), (major rotamer);

0.92-1.03 (6H, m), 1.91 (1H, m), 2.34 (1H, dd, *J* = 2.1, 2.1 Hz), 3.05 (3H, s), 3.49 (1H, d), 4.13 (2H, br.s.), 4.16-4.39 (2H, m), (minor rotamer). HPLC-MS (ESI): *m/z* 303.36 (MH^+) 169.39

Synthesis of (2*S*)-2-(benzylamino)-*N*,3-dimethyl-*N*-(prop-2-yn-1-yl)butanamide (12)

To a solution of **11** (5.1 mmol) and pyridine (0.45 ml) in dry dichloromethane was slowly added benzylbromide (5.6 mmol) dissolved in dry dichloromethane (4 ml) at 0°C. The resulting mixture was left under stirring overnight at room temperature. The solution was diluted with dichloromethane (30 ml) and washed with water (10 ml). The organic phase was dried over sodium sulphate, filtered, and the solvent evaporated under reduced pressure.The resulting crude was purified by flash chromatography (Cyclohexane / EtOAc 7:3).

Yield: 50%. White solid. Rotamers ratio 2.5:1.^{1}H NMR (400 MHz, $CDCl_3$, T = 25°C) δ: 0.95 (3H, d, *J* = 6.8 Hz), 1.00 (3H, d, *J* = 6.6 Hz), 1.79-1.90 (1H, m), 2.25 (1H, dd, *J* = 2.3, 2.3 Hz), 2.96 (3H, s), 3.22 (1H, d, *J* = 6.4 Hz), 3.51 (1H, d, *J* = 13.2 Hz), 3.85 (1H, d, *J* = 13.2), 4.22 (1H, dd, *J* = 17.1, 2.5 Hz), 4.35 (1H, d, *J* = 17.1, 2.5 Hz), 7.23-7.40 (5H,m), (major rotamer); 0.98-0.99 (6H, m), 1.79-1.90 (1H, m), 2.30 (1H, dd, *J* = 2.3, 2.3 Hz), 3.06 (3H, s), 3.27 (1H, d, *J* = 5.8 Hz), 3.51 (1H, d, *J* = 13.0 Hz), 3.83 (1H, d, *J* = 13.0 Hz), 3.95 (1H, dd, *J* = 18.1, 2.3 Hz), 4.10 (1H, dd, *J* = 18.1, 2.3 Hz), 7.23-7.40 (5H,m), (minor rotamer);^{13}C NMR (100 MHz, $CDCl_3$, T = 25°C) δ: 18.3 (q), 19.7 (q), 31.7 (d), 34.2 (q), 36.5(t), 61.9 (d), 71.8 (s), 78.7 (s), 126.9 (d), 128.2 (d), 128.2 (d), 128.3 (d), 128.3 (d), 140.3 (s), 175.1 (s),(major rotamer); 18.0 (q), 20.1 (q), 31.6 (d), 33.3 (q), 38.8 (t), 52.3 (d), 72.9 (d), 78.1 (s), 126.8 (d), 128.2 (d), 128.2 (d), 128.3 (d), 128.3 (d), 140.4 (s), 174.9 (s), (minor rotamer). HPLC-MS (ESI): *m/z* 259.53 (MH^+)

Synthesis of (2*S*)-2-(benzylamino)-*N*,3-dimethyl-*N*-propadienylbutanamide (13)

t-BuOK (2.5 mmol) in THF (10 mL) was added to a solution of **12** (1 mmol). The resulting solution was stirred at r.t. for 1 min, then filtered on silica gel (AcOEt). The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (Cyclohexane / EtOAc 8:2).

Yield: 50%. Light yellow oil. Rotamers ratio 1:1. ^{1}H NMR (599.7 MHz, MeOD, T = 25°C) δ: 0.91-0.99 (6H, m), 1.80-190 (1H, m), 2.94 (1H, s), 3.51-3.55 (1H,m), 3.53-3.54 (1H, m), 3.68-3.75 (1H, m), 5.44-5.47 (2H, m), 7.21-7.25 (1H, m), 7.28-7.33 (4H, m), 7.49 (1H, m),(first rotamer); 0.91-0.99 (6H, m), 1.80-1.90 (1H, m), 2.99 (1H, s), 3.43-3.45 (1H, m), 3.51-3.55 (1H, m), 3.68-3.75 (1H, m), 5.38-5.44 (2H, m), 6.98 (1H, m), 7.21-7.25 (1H, m), 7.28-7.33 (4H,m), (second rotamer);^{13}C NMR (150.81 MHz, MeOD, T = 25°C) δ: 18.4 (q), 20.04 (q), 32.1 (q), 33.0 (q), 53.3 (t), 63.8 (d), 87.0 (t), 100.20 (d), 128.2 (d), 129.4 (d), 129.4 (d), 129.6 (d), 129.6 (d), 141.1 (s), 175.15 (s), 202.8 (s), (first rotamer); 18.6 (q), 20.0 (q), 33.0 (d), 33.5 (q), 53.5 (t), 63.8 (t) 87.7 (t), 101.7 (d), 128.3 (d), 129.5 (d), 129.5 (d), 129.6 (d), 129.6 (d), 141.1 (s), 175.6 (s), 203.9 (s), (second rotamer). HPLC-MS (ESI): *m/z* 259.53 (MH^+)

Procedures for cyclization of allenamide (13)

a) To a stirred solution of **13** (2.42 mmol) in dry acetonitrile (40 ml) was added $AuCl_3$ (0.121 mmol), under argon atmosphere. The mixture so obtained was refluxed for 20 minutes, then the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (Cyclohexane / EtOAc 7.5:2.5).

b) To a mixture of PPh_3AuCl (0.12 mmol) and $AgBF_4$(0.12 mmol) in dry acetonitrile (30 ml) was added, under argon atmosphere, a solution of **13** (2.59 mmol) in dry acetonitrile (10 ml). The mixture so obtained was refluxed for 2.5h, then the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (Cyclohexane / EtOAc 7.5:2.5).

(*2R*,*5S*)-1-benzyl-2-ethenyl-3-methyl-5-(propan-2-yl)imidazolidin-4-one (*trans*-14a)

Colourless oil. Yield: (using procedure *a*) 24%, (using procedure *b*) 14%. ^{1}H NMR (599.7 MHz, $CDCl_3$, T = 25°C) δ: 1.00 (3H, d, *J* = 6.9 Hz), 1.11 (3H, d, *J* = 7.1 Hz), 2.08 (1H, m, *J* = 14.0, 7.0, 2.8 Hz), 2.70 (3H, s), 3.33 (1H, t, *J* = 2.6 Hz), 3.79 (1H, d, *J* = 14.3 Hz), 3.92 (1H, d, *J* = 14.5 Hz), 4.51 (1H, dd, *J* = 9.0, 2.1 Hz), 5.10 (1H, d, *J* = 17.0 Hz), 5.35 (1H, d, *J* = 10.0 Hz), 5.61 (1H, dt, *J* = 16.9, 9.5 Hz), 7.22 (1H, m), 7.30 (4H, m);^{13}C NMR (150.81 MHz, $CDCl_3$, T = 25°C) δ: 17.3 (q), 18.1 (q), 26.4 (q), 29.0 (d), 50.74 (t), 66.1 (d), 79.4 (d), 122.0 (t), 126.9 (d), 128.0 (d), 128.0 (d), 128.1 (d), 128.1 (d), 134.1 (d), 138.3 (s), 171.8 (s). HPLC-MS (ESI): *m/z* 259.53 (MH^+)

(2*S*,5*S*)-1-benzyl-2-ethenyl-3-methyl-5-(propan-2-yl)imidazolidin-4-one (*cis*-14b)

Light yellow oil. Yield: (using procedure *a*) 36%, (using procedure *b*) 21%.^{1}H NMR (599.7 MHz, $CDCl_3$, T = 25°C) δ: 0.96 (3H, d, *J* = 6.9 Hz), 1.00 (3H, d, *J* = 7.1 Hz), 1.88 (1H, m, *J* = 13.9, 7.0, 3.0 Hz), 2.65 (3H, s), 3.26 (1H, d, *J* = 2.3 Hz), 3.83 (2H, m), 4.22 (1H, d, *J* = 8.4 Hz), 5.05 (1H, d, *J* = 17.3 Hz), 5.10 (1H, d, *J* = 9.9 Hz), 5.47 (1H, ddd, *J* = 17.2, 9.9, 8.5 Hz), 7.23 (5H, m);^{13}C NMR (150.81 MHz, $CDCl_3$, T = 25°C) δ: 17.6 (q), 17.7 (q), 26.3 (q), 29.9 (d), 57.5 (t), 68.8 (d), 82.1 (d), 119.7 (t), 127.1 (d), 127.9 (d), 127.9 (d), 128.9 (d), 128.9 (d), 137.3 (d), 137.6 (s), 171.6 (s). HPLC-MS (ESI): *m/z* 259.53 (MH^+)

1*H*-pyrrole-2-carboxylic acid (15a)

The compound is commercial available by Aldrich.

1-methyl-1*H*-pyrrole-2-carboxylic acid (15b)

The compound is commercial available by Aldrich.

***N*-methylprop-2-yn-1-amine (2a)**

The compound is commercial available by Aldrich.

Prop-2-yn-1-amine (2b)

The compound is commercial available by Aldrich

***N*-benzylprop-2-yn-1-amine (2c)**

The compound is known in literature[82].

4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (2d)

The compound is known in literature[83].

***N*-methyl-3-phenylprop-2-yn-1-amine (2e)**

The compound is known in literature[84].

4-methyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (2f)

The compound is known in literature[85].

***N*-benzyl-3-phenylprop-2-yn-1-amine (2g)**

The compound is known in literature[86].

Synthesis of *N*-methyl-*N*-(prop-2-yn-1-yl)-1*H*-pyrrole-2-carboxamide (16a)

A 100 ml round bottom flask fitted with a magnetic stirrer and a thermometer was charged with 1.5 g (13,5 mmol) of 1*H*-pyrrole-2-carboxylic acid **(15a)** and 30 ml of dry dichloromethane under argon atmosphere.The solution so obtained was stirred at rt for 10 minutes then cooled down to 0°C. To this, a solution of DCC 2.78 g (23.9 mmol) in 8 ml of dry dichloromethane, was slowly dropped in 20 minutes keeping the internal temperature between 0-5°C. To this mixture *N*-methylprop-2-yn-1-amine **(2a)** 0.94 ml (11.1 mmol) was added followed by DMAP 0.020 g (0.16 mmol). The mixture was left at rt under stirring for 48h, then diluted with 100ml of EtOAc, filtered through a small celite pad washed and rinsed with EtOAc, and the filtrate concentrated under reduced pressure The crude residue was then purified by flash column chromatography (Cycloehexane / EtOAc, 6:4).

Yield: 80%. White solid. ^{1}H NMR (599.71 MHz, $CDCl_3$, T= 50°C) δ: 9.85 (1H, br.s.), 6.94 (m, 1H), 6.71 (br.s., 1H), 6.27 (m, 1H), 4.40 (d, 2H, J = 2.5 Hz), 3.31 (br.s., 3H), 2.30 (t, 1H J = 2.6 Hz);^{13}C NMR (150.81 MHz, $CDCl_3$, T= 50°C) δ 162.36 (C), 124.55 (C), 121.40 (CH), 112.86

(CH), 109.81 (CH), 78.86 (C), 72.28 (CH), 38.83 (CH_2), 35.28 (CH_3); HPLC-MS (ESI): *m/z* = 163.18 [MH^+].

Synthesis of *N*,1-dimethyl-*N*-(prop-2-yn-1-yl)-1*H*-pyrrole-2-carboxamide (16b)

A 100 ml round bottom flask fitted with a magnetic stirrer and a thermometer was charged with 3 g (23,9 mmol) of 1-methyl-1*H*-pyrrole-2-carboxylic acid **(15b)** and 45 ml of dry dichloromethane under argon atmosphere.The solution so obtained was stirred at rt for 10 minutes then cooled down to 0°C. To this, a solution of DCC 4.93 g (23.9 mmol) in 15ml of dry dichloromethane, was slowly dropped in 20 minutes keeping the internal temperature between 0-5°C. To this mixture *N*-methylprop-2-yn-1-amine **(2a)** 1.67 ml (19.8 mmol) was added followed by DMAP 0.036 g (0.29 mmol). The mixture was left at rt under stirring for 48h, then diluted with 200ml of EtOAc, filtered through a small celite pad washed and rinsed with EtOAc, and the filtrate was concentrated under reduced pressure The crude residue was then purified by flash column chromatography (Cycloehexane / EtOAc, 6:4).

Yield: 91.6%. Colorless oil. IR = 1672 cm^{-1}. ^{1}H NMR (599.71 MHz, $CDCl_3$, T= 50°C) δ 6.69 (t, 1H, *J* = 2.0 Hz), 6.54 (dd, 1H, *J* = 3.7, 1.1 Hz), 6.09. (dd, 1H, *J* = 3.9, 2.7 Hz), 4.32 (d, 2H, *J* = 2.6 Hz), 3.79 (s, 3H), 3.19 (s, 3H), 2.30 (t, 1H *J* = 2.5 Hz);^{13}C NMR (150.81 MHz, $CDCl_3$, T= 50°C) δ 163.79 (C), 126.68 (CH), 124.70 (C), 113.45 (CH), 106.95 (CH), 79.04 (C), 72.26 (CH), 39.28 (CH_2), 35.76 (CH_3), 34.84 (CH_3); HPLC-MS (ESI): *m/z* = 177.21 [MH^+].Anal.calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found C, 68.32; H, 6.89; N, 15.85.

General procedure for the cyclization of pyrrole-carboxamides: A solution of 2 mmol of the appropriate pyrrole-carboxamide was stirred, under argon atmosphere, with $AuCl_3$ (0.01 mmol) in 30 mL of an appropriate solvent (see Tables 7-8 and 9 for solvents, temperatures and times). At the end of the reaction, the solvent was either removed under reduced pressure (MeCN, DCM, Toluene) or extracted with brine (DMF). The crude residue was purified by flash column chromatography

1,4,6-trimethyl-1,6-dihydro-7*H*-pyrrolo[2,3-*c*]pyridin-7-one (17b)

Yield: 70% (Table 2, entry 1). White solid. M. p.: 76 °C. IR = 1670 cm^{-1}. ^{1}H-NMR (599 MHz, $CDCl_3$, T= 25 °C) δ: 2.13 (s, 3H), 3.49 (s, 3H), 4.13 (s, 3H), 6.17 (d, *J* = 2.9 Hz, 1H), 6.57 (s, 1H), 6.91 (d, *J* = 2.9 Hz, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$, T = 25 °C) δ: 14.75 (q), 35.56 (q), 35.57 (q), 100.06 (d), 110.30 (s), 122.33 (s), 126.21 (d), 130.78 (d), 132.48 (s), 155.64 (s). HPLC-MS (ESI): *m/z* = 177.21 [MH^+]. Anal. calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found C, 68.22; H, 6.80; N, 15.95.

1,5,7-trimethyl-1,5-dihydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one (18b)

Yield: 50% (Table 2, entry 4). Yellow solid. M. p.: 104 °C. IR = 1672 cm^{-1}. ^{1}H-NMR (599 MHz, $CDCl_3$, T = 25 °C) δ: 2.37 (s, 3H), 3.51 (s, 3H), 3.89 (s, 3H), 6.65 (s, 1H), 6.69 (d, *J* = 3.1 Hz, 1H), 6.73 (d, *J* = 3.1 Hz, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$, T= 25 °C) δ 16.11 (q), 35.84 (q), 35.86 (q), 104.39 (d), 104.55 (s), 116.90 (s), 127.39 (d), 129.78 (d), 137.93 (s), 159.63 (s); HPLC-MS (ESI): *m/z* = 177.21 [MH^+]. Anal. calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found C, 68.13; H, 6.81; N, 15.94.

Synthesis of 1-methyl-*N*-(prop-2-yn-1-yl)-1*H*-pyrrole-2-carboxamide. (19)

A 50 ml round bottom flask fitted with a magnetic stirrer and a thermometer was charged with 1 g (7.9 mmol) of 1-methyl-1*H*-pyrrole-2-carboxylic acid **(15b)** and 15 ml of dry dichloromethane under argon atmosphere.The solution so obtained was stirred at rt for 10 minutes then cooled down to 0°C. To this, a solution of DCC 1.64 g (7.9 mmol) in 5 ml of dry dichloromethane, was slowly dropped in 20 minutes keeping the internal temperature between 0-5°C. To this mixture prop-2-yn-1-amine **(2b)** 0.42 ml (6.6 mmol) was added followed by DMAP 0.012 g (0.098 mmol). The mixture was left at rt under stirring for 48h, then diluted with 100ml of EtOAc, filtered through a small celite pad washed and rinsed with EtOAc, and the filtrate concentrated under reduced

pressure. The crude residue was then purified by flash column chromatography (Cycloehexane / EtOAc, 6:4)

Yield: 80%. White solid.^{1}H NMR (599.71 MHz, $CDCl_3$, T= 25°C) δ 6.73 (t, 1H, *J* = 2.2 Hz), 6.59 (dd, 1H, *J* = 3.9, 1.6 Hz), 6.09 (dd, 1H, *J* = 3.7, 2.7 Hz), 6.07 (br.s., 1H), 4.17 (dd, 2H, *J* = 5.4, 2.6 Hz), 3.94 (s, 3H), 2.25 (t, 1H *J* = 2.5 Hz);^{13}C NMR (150.81 MHz, $CDCl_3$, T= 50°C) δ 161.39 (C), 128.25 (CH), 124.91 (C), 112.41 (CH), 107.28 (CH), 79.87 (C), 71.37 (CH), 36.72 (CH_3), 28.87 (CH_2); HPLC-MS (ESI): *m/z* = 163.18 [MH^+].

Synthesis of *N*-benzyl-1-methyl-*N*-(prop-2-yn-1-yl)-1*H*-pyrrole-2-carboxamide (20a)

A 50 ml round bottom flask fitted with a magnetic stirrer and a thermometer was charged with 1 g (8 mmol) of 1-methyl-1*H*-pyrrole-2-carboxylic acid **(15b)** and 15 ml of dry dichloromethane under argon atmosphere.The solution so obtained was stirred at rt for 10 minutes then cooled down to 0°C. To this, a solution of DCC 1.64 g (8 mmol) in 5ml of dry dichloromethane, was slowly dropped in 20 minutes keeping the internal temperature between 0-5°C. To this mixture *N*-benzyllprop-2-yn-1-amine **(2c)** 0.95 g (6.6 mmol) was added followed by DMAP 0.012 g (0.098 mmol). The mixture was left at rt under stirring for 48h, then diluted with 70ml of EtOAc, filtered through a small celite pad washed and rinsed with EtOAc, and the filtrate concentrated under reduced pressure The crude residue was then purified by flash column chromatography (Cycloehexane/Cyclopentilmethylether, 6:4)

Yield: 85%.Colourless oil. IR = 1666 cm^{-1}. ^{1}H NMR (599.71 MHz, $CDCl_3$, T= 25°C) δ 7.37 (m, 2H), 7.33 (m, 2H), 7.30 (m, 1H), 6.73 (m, 1H), 6.60 (br.s., 1H), 6.08 (m, 1H), 4.90 (s, 2H), 4.25 (br.s., 2H), 3.85 (s, 3H), 2.31 (br.s., 1H);^{13}C NMR (150.81 MHz, $CDCl_3$, T= 25°C) δ 164.08 (C), 136.85 (C), 128.74 (CH), 128.74 (CH), 127.78 (CH), 127.78 (CH), 127.55 (CH), 127.00 (CH), 124.69 (C), 113.09 (CH), 107.12 (CH), 79.24 (C), 72.34 (CH), 49.88 (CH_2), 36.67 (CH_2), 35.92

(CH_3); HPLC-MS (ESI): *m/z* = 253.31 [MH^+]. Anal.calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found C, 76.21; H, 6.28; N, 11.12.

Synthesis of 1-methyl-*N*-[(4-methylphenyl)sulfonyl]-*N*-(prop-2-yn-1-yl)-1*H*-pyrrole-2-carboxamide (20b)

To a stirred solution of 1.2 g (9.59 mmol) of 1-methyl-1*H*-pyrrole-2-carboxylic acid **(15b)** in 21ml of dry THF containing 2 drops of N,N-dimethylformamide was added 1.25 ml (14.3 mmol) of oxalylchloride. The resulting mixture was stirred at rt for 3h after wich time the solvent was removed under reduced pressure and then taken up in 15 ml of dry THF.

In a separate flask, to a suspension of 0.137 g of NaH (5.74 mmol) in 10 ml of dry THF cooled to 0°C was added 1g (4.79 mmol) of 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide **(2d)**, dissolved in 10 ml of dry THF, dropping in 15 minutes. The mixture was allowed to stir at 0°C for 30 minutes, after which time, the preformed acid chloride was added *via* siringe and the resulting mixture was allowed to warm to rt overnight. The mixture was quenched at 0°C with 20 ml of water and exctracted with 80 ml of AcOEt. Phase were allowed to separated, the aqueous phase was discharged and the organic phase was washed two times with 20 ml of water, dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude residue was subjected to silica gel chromatography (EtOAc / Cyclohexane, 3:7)

Yield: 77%. White solid. M.p.: 127 ^{0}C. IR = 1674 cm^{-1}. ^{1}H NMR (599.71 MHz, $CDCl_3$, T= 25°C) δ 7.91 (m, 2H), 7.31 (m, 2H), 7.06 (dd, 1H, *J* = 4.1, 1.6 Hz), 6.80 (t, 1H, *J* = 2.1 Hz), 6.13 (dd, 1H, *J* = 4.3, 2.5 Hz), 4.67 (d, 2H, *J* = 2.5 Hz), 3.69 (s, 3H), 2.43 (s, 3H), 2.38 (t, 1H, *J* = 2.5 Hz); ^{13}C NMR (150.81 MHz, $CDCl_3$, T= 25°C) δ 162.15 (C), 144.57 (C), 135.77 (C), 130.73 (CH), 129.31 (CH), 129.31 (CH), 128.67 (CH), 128.67 (CH), 124.16 (C), 118.98 (CH), 108.16 (CH), 78.88 (C), 73.09 (CH), 30.07 (CH_2), 36.21 (CH_3), 21.62 (CH_3); HPLC-MS (ESI): *m/z* =317.37 [MH^+]. Anal. calcd for $C_{16}H_{16}N_2O_3S$: C, 60.74; H, 5.10; N, 8.85. Found C, 60.62; H, 5.14; N, 8.88.

Synthesis of *tert*-butyl [(1-methyl-1*H*-pyrrol-2-yl)carbonyl]prop-2-yn-1-ylcarbamate (20c)

To a stirred solution of 0.81 g (5 mmol) of 1-methyl-*N*-(prop-2-yn-1-yl)-1*H*-pyrrole-2-carboxamide. **(19)**, in 60 ml of acetonitrile was added 1.26 g (5.8 mmol) of di-*tert*-butyl dicarbonate, followed by 0.061 g (0.5 mmol) of 4-dimethylaminopyridine. The resulting solution was allowed to stir at rt overnight and the solvent was removed under reduced pressure. The crude residue was subject to flash column chromatography (Cycloehexane / EtOAc, 8:2)

Yield: 85%. Colourless oil. IR = 1726, 1667 cm^{-1}. ^{1}H NMR (599.71 MHz, $CDCl_3$, T= 25°C) δ 6.80 (t, 1H, *J* = 2.2 Hz), 6.62 (m, 1H), 6.11 (m, 1H), 4.43 (d, 2H, *J* = 2.5 Hz), 3.86 (s, 3H), 2.23 (t, 1H, *J* = 2.4 Hz), 1.36 (s, 8H);^{13}C NMR (150.81 MHz, $CDCl_3$, T= 25°C) δ160.24 (C), 153.14 (C), 129.39 (CH), 127.57 (C), 117.83 (CH), 107.88 (CH), 82.78 (C), 79.32 (C), 70.90 (CH), 36.02 (CH_2), 35.03 (CH_3), 27.73 (CH_3), 27.73 (CH_3) 27.73 (CH_3); HPLC-MS (ESI): *m/z* = 263.30 [MH^+]. Anal. calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found C, 64.15; H, 7.04; N, 10.54.

Synthesis of 1-methyl-*N*-(phenylcarbonyl)-*N*-(prop-2-yn-1-yl)-1*H*-pyrrole-2-carboxamide (20-d)

To a stirred suspension of 0.137 g (5.72 mmol) of NaH in 20 ml of dry THF was slowly added a solution of 0.77 g (4.7 mmol) of 1-methyl-*N*-(phenylcarbonyl)-*N*-(prop-2-yn-1-yl)-1*H*-pyrrole-2-carboxamide **(19)** in 20 ml of dry THF at 0°C followed by 7ml of dry DMF. The mixture was left under stirring at 0°C for 0.5 h then 0.66 ml (5.7 mmol) of benzoylchloride were added. The mixture was allowed to stir for 3h at rt after wich time 10 ml of water were added followed by 30 ml of *tert*-butylmethylether. Phases were allowed to separated, the aqueous phase was discharge and the organic one was washed two times with 10ml of water then dried over sodium sulphate and the solvent evaporated under reduced pressure. The crude residue was then purified by flash column chromatography (Cycloehexane / Cyclopentylmethylether, 6.5:3.5)

Yield: 60%. Colourless oil.^{1}H NMR (599.71 MHz, $CDCl_3$, T= 25°C) δ 7.51 (d, 2H, *J* = 7.9 Hz), 7.32 (m, 1H), 7.26 (m, 2H), 6.62 (dd, 1H, *J* = 3.9, 1.2 Hz), 6.60 (t, 1H, *J* = 2.2 Hz), 5.92 (dd, 1H, *J* = 3.7, 2.7 Hz), 4.72 (d, 2H, *J* = 2.5 Hz), 3.71 (s, 3H), 2.28 (t, 1H, *J* = 2.4 Hz);^{13}C NMR (150.81 MHz, $CDCl_3$, T= 25°C) δ 172.32 (C), 164.93 (C), 136.81 (C), 131.37 (CH), 130.75 (CH), 128.15 (CH), 128.15 (CH), 127.91 (CH), 127.91 (CH), 127.91 (C), 119.66 (CH), 108.50 (CH), 78.72 (C), 72.54 (CH), 35.89 (CH_2), 35.86 (CH_3); HPLC-MS (ESI): *m/z* = 267.29 [MH^+].

Synthesis of *N*,1-dimethyl-*N*-(3-phenylprop-2-yn-1-yl)-1*H*-pyrrole-2-carboxamide (20e)

A 25 ml round bottom flask fitted with a magnetic stirrer and a thermometer was charged with 0.62 g (4.9 mmol) of 1-methyl-1*H*-pyrrole-2-carboxylic acid **(15b)** and 8 ml of dry dichloromethane under argon atmosphere.The solution so obtained was stirred at rt for 10minutes then cooled down to 0°C. To this, a solution of DCC 1.02 g (4.9 mmol) in 4ml of dry dichloromethane, was slowly dropped in 20 minutes keeping the internal temperature between 0-5°C. To this mixture *N*-methyl-3-phenylprop-2-yn-1-amine **(2e)** 0.6 g (19.8 mmol) was added followed by DMAP 0.008 g (0.06 mmol). The mixture was left at rt under stirring for 48h, then diluted with 50ml of EtOAc, filtered through a small celite pad washed and rinsed with EtOAc, and the filtrate concentrated under reduced pressure The crude residue was then purified by flash column chromatography (Cyclopentylmethylether / EtOAc, 1:1)

Yield: 90%.Colourless oil. IR = 1668 cm^{-1} ^{1}H NMR (599.71 MHz, $CDCl_3$, T= 50°C) δ 7.46 (m, 2H), 7.32 (m, 3H), 6.72 (s, 1H), 6.61 (m, 1H), 6.12 (t, 1H), 4.57 (s, 2H), 3.82 (s, 3H), 3.26 (s, 3H);^{13}C NMR (150.81 MHz, $CDCl_3$, T= 50°C) δ 164.02 (C), 131.96 (CH), 131.96 (CH), 128.59 (CH), 128.48 (CH), 128.48 (CH), 126.82 (CH), 125.11 (C), 122.95 (C), 113.65 (CH), 107.17 (CH), 84.58 (C), 84.55 (C), 40.51 (CH_2), 36.01 (CH_3), 34.98 (CH_3); HPLC-MS (ESI): *m/z* = 253.31 [MH^+]. Anal. calcd. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found C, 76.10; H, 6.37; N, 11.22.

Synthesis of 1-methyl-*N*-[(4-methylphenyl)sulfonyl]-*N*-(3-phenylprop-2-yn-1-yl)-1*H*-pyrrole-2-carboxamide (20f)

To a stirred solution of 0.43 g (3.5 mmol) of 1-methyl-1*H*-pyrrole-2-carboxylic acid **(15b)** in 8 ml of dry THF containing 2 drops of N,N-dimethylformamide was added 0.45 ml (5.25 mmol) of oxalylchloride. The resulting mixture was stirred at rt for 3h after wich time the solvent was removed under reduced pressure and then taken up in 8 ml of dry THF.

In a separate flask, to a suspension of 0.049 g of NaH (2.0 mmol) in 7 ml of dry THF cooled to 0°C was added 0.5 g (1.74 mmol) of 4-methyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide **(2f)**, dissolved in 6 ml of dry THF, dropping in 15 minutes. The mixture was allowed to stir at 0°C for 30 minutes, after which time, the preformed acid chloride was added *via* siringe and the resulting mixture was allowed to warm to rt overnight. The mixture was quenched at 0°C with 10 ml of water and exctracted with 40 ml of AcOEt. Phase were allowed to separated, the aqueous phase was discharged and the organic phase was washed two times with 10 ml of water, dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude residue was subjected to silica gel chromatography (Cyclohexane / EtOAc, 7:3)

Yield: 90%. White solid. M.p.: 110 ^{0}C. IR = 1668 cm^{-1}. ^{1}H NMR (599.71 MHz, $CDCl_3$, T= 25°C) δ 8.01 (d, 2H, *J*= 8.4 Hz), 7.31 (m, 7H), 7.09 (dd, 1H, *J* = 4.0, 1.6 Hz), 6.82 (t, 1H, *J* = 2.1 Hz), 6.15 (dd, 1H, *J* = 4.0, 2.6 Hz), 4.93 (s, 2H), 3.73 (s, 3H), 2.40 (s, 3H);^{13}C NMR (150.81 MHz, $CDCl_3$, T= 25°C) δ 162.39 (C), 144.43 (C), 136.08 (C), 131.65 (CH), 131.65 (CH), 130.61 (CH), 129.25 (CH), 129.25 (CH), 128.85 (CH), 128.85 (CH), 128.60 (CH), 128.24 (CH), 128.24 (CH), 124.27 (C), 122.18 (C), 118.67 (CH), 108.18 (CH), 85.05 (C), 84.14 (C), 39.39 (CH_2), 36.27 (CH_3), 21.58 (CH_3); HPLC-MS (ESI): *m/z* = 393.47 [MH^+]. Anal. calcd for $C_{22}H_{20}N_2O_3S$: C, 67.33; H, 5.14; N, 7.14. Found C, 67.26; H, 5.08; N, 7.22.

Synthesis of *N*-benzyl-1-methyl-*N*-(3-phenylprop-2-yn-1-yl)-1*H*-pyrrole-2-carboxamide (20g)

A 25 ml round bottom flask fitted with a magnetic stirrer and a thermometer was charged with 0.63 g (5 mmol) of 1-methyl-1*H*-pyrrole-2-carboxylic acid **(15b)** and 8 ml of dry dichloromethane under argon atmosphere.The solution so obtained was stirred at rt for 10minutes then cooled down to 0°C. To this, a solution of DCC 1.04 g (5 mmol) in 4ml of dry dichloromethane, was slowly dropped in 20 minutes keeping the internal temperature between 0-5°C. To this mixture *N*-benzyl-3-phenylprop-2-yn-1-amine **(2g)** 0.93 g (4.2 mmol) was added followed by DMAP 0.008 g (0.06 mmol). The mixture was left at rt under stirring for 48h, then diluted with 50ml of EtOAc, filtered through a small celite pad washed and rinsed with EtOAc, and the filtrate concentrated under reduced pressure The crude residue was then purified by flash column chromatography (Toluen / EtOAc, 9:1)

Yield: 80%. Yellow oil. IR = 1667 cm^{-1}.^{1}H NMR (599.71 MHz, $CDCl_3$, T= 50°C) δ 7.44 (m, 2H), 7.38 (m, 4H), 7.32 (m, 4H), 6.74 (t, 1H, *J* = 1.7 Hz), 6.67 (br.s., 1H), 6.10 (t, 1H, *J* = 3.2 Hz), 4.96 (s, 2H), 4.49 (s ,3H), 3.86 (s, 3H);^{13}C NMR (150.81 MHz, $CDCl_3$, T= 50°C) δ164.07 (C), 137.12 (C), 131.80 (CH), 131.80 (CH), 128.72 (CH), 128.72 (CH), 128.40 (CH), 128.30 (CH), 128.30 (CH), 127.89 (CH), 127.89 (CH), 127.50 (CH), 126.92 (CH), 124.90 (C), 122.79 (C), 113.12 (CH), 107.14 (CH), 84.61 (C), 84.51 (C), 49.98 (CH_2), 37.92 (CH_2), 35.94 (CH_3); HPLC-MS (ESI): *m/z* = 329.40 [MH^+]. Anal. calcd for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53. Found C, 80.32; H, 6.21; N, 8.58.

1,4-dimethyl-6-[(4-methylphenyl)sulfonyl]-1,6-dihydro-7*H*-pyrrolo[2,3-*c*]pyridin-7-one (21b)

Yields: 85% (in TBME), 75% (in dichloromethane), 65% (in Toluene), 70% (in acetonitrile), 60% (in DMF). White solid. M.p.: 201^{0}C. IR = 1673cm^{-1}. ^{1}H NMR (599.71 MHz, $CDCl_3$, T= 25°C) δ 7.98 (m, 2H), 7.55 (q, 1H, *J* = 1.4 Hz), 7.33 (m, 2H), 6.98 (d, 1H, *J* = 2.8 Hz), 6.21 (d, 1H, *J* = 2.6 Hz), 4.01 (s, 3H), 2.43 (s, 3H), 2.23 (d, 3H, *J* = 1.5 Hz); ^{13}C NMR (150.81 MHz, $CDCl_3$, T= 25°C)

δ153.95 (C), 144.96 (C), 135.34 (C), 133.72 (C), 132.82 (CH), 129.35 (CH), 129.35 (CH), 128.99 (CH), 128.99 (CH), 121.45 (C), 119.77 (CH), 111.83 (C), 101.42 (CH), 36.15 (CH_3), 21.68 (CH_3), 15.30 (CH_3); HPLC-MS (ESI): *m/z* = 317.37 [MH^+]. Anal. calcd for $C_{16}H_{16}N_2OS_3$: C,60.74; H, 5.10; N, 8.85. Found C, 60.78; H, 5.11; N, 8.77

1,7-dimethyl-5-[(4-methylphenyl)sulfonyl]-1,5-dihydro-4H-pyrrolo[3,2-c]pyridin-4-one (22b)

Yield: 7.5% (in TBME), 9% (in dichloromethane), 14% (in toluene), 20% (in acetonitrile), 25% (in DMF). Yellow solid. M.p.: 215^{0}C. IR = 1673 cm^{-1}.^{1}H NMR (599.71 MHz, $CDCl_3$, T= 25°C) δ7.98 (m, 2H), 7.59 (q, 1H, *J* = 1.3 Hz), 7.30 (m, 2H), 6.66 (m, 2H), 3.90 (s, 3H), 2.44 (d, 3H, *J* = 1.3 Hz), 2.40 (s, 3H); ^{13}C NMR (150.81 MHz, $CDCl_3$, T= 25°C) δ157.42 (C), 145.19 (C), 138.13 (C), 134.94 (C), 129.28 (CH), 129.28 (CH), 129.28 (CH), 129.28 (CH), 128.14 (CH), 122.73 (CH), 116.69 (C), 106.59 (C), 106.01 (CH), 36.19 (CH_3), 21.65 (CH_3), 16.73 (CH_3); HPLC-MS (ESI): *m/z* = 317.37 [MH^+]. Anal calcd for $C_{16}H_{16}N_2OS_3$: C, 60.74; H, 5.10; N, 8.85. Found C, 60.61; H, 5.18; N, 8.87.

6-benzyl-1,4-dimethyl-1,6-dihydro-7*H*-pyrrolo[2,3-*c*]pyridin-7-one (21a)

Yields: 86% (in Toluene), 61% (in dichloromethane), 50% (in acetonitrile).Yellow solid.M.p.: 76 ^{0}C. IR = 1670 cm^{-1}.^{1}H NMR (599.71 MHz, $CDCl_3$, T= 25°C) δ 7.33 (m, 2H), 7.28 (m, 3H), 7.00 (d, 1H, *J* = 2.8 Hz), 6.67 (q, 1H, *J* = 1.4 Hz), 6.25 (d, 1H, *J* = 2.8 Hz), 5.19 (s, 2H), 4.21 (s, 3H), 2.18 (d, 3H, *J* = 1.3 Hz);^{13}C NMR (150.81 MHz, $CDCl_3$, T= 25°C) δ155.54 (C), 137.89 (C), 132.65 (C), 131.20 (CH), 128.64 (CH), 128.64 (CH), 127.55 (CH), 127.55 (CH), 127.39 (CH), 125.43 (CH), 122.49 (C), 111.02 (C), 100.38 (CH), 50.42 (CH_2), 35.90 (CH_3), 15.06 (CH_3); HPLC-MS (ESI): *m/z* = 253.31 [MH^+]. Anal.calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found C, 76.21; H, 6.44; N, 11.07.

5-benzyl-1,7-dimethyl-1,5-dihydro-4H-pyrrolo[3,2-c]pyridin-4-one (22a)

Yields: 7.3% (in toluene), 12% (in dichloromethane), 25% (in acetonitrile).White solid. M.p.: 106 ^{0}C. IR = 1671 cm^{-1}. ^{1}H NMR (599.71 MHz, $CDCl_3$, T= 25°C) δ 7.26-7.30 (m, 5H), 6.81 (d, 1H, *J* = 3.1 Hz), 6.74 (d, 1H, *J* = 3.0 Hz), 6.69 (br.s., 1H), 5.19 (s, 2H), 3.91 (s, 3H), 2.36 (s, 3H);^{13}C NMR (150.81 MHz, $CDCl_3$, T= 25°C) δ159.37 (C), 137.86 (C), 137.83 (C), 128.73 (CH), 128.59 (CH), 128.59 (CH), 127.77 (CH), 127.77 (CH), 127.57 (CH), 127.41 (CH), 116.93 (C), 105.34 (C), 104.94 (CH), 50.44 (CH_2), 35.94 (CH_3), 16.31 (CH_3); HPLC-MS (ESI): *m/z* = 253.31 [MH^+]. Anal. calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found C, 76.20; H, 6.48; N, 11.06.

***tert*-butyl 1-methyl-4-methylidene-7-oxo-1,4,5,7-tetrahydro-6*H*-pyrrolo[2,3-*c*]pyridine-6-carboxylate. (23c)**

Yields: 56% (in toluene),20%(in dichloromethane). White solid. M.p.: 92 ^{0}C. IR = 1723, 1671 cm^{-1}. 1H NMR (599.71 MHz, $CDCl_3$, T= 25°C) δ 6.77 (d, 1H, *J* = 2.8 Hz), 6.21 (d, 1H, *J* = 2.8 Hz), 5.28 (t, 1H, *J* =1.3 Hz), 5.08 (t, 1H, *J* = 1.8 Hz), 4.56 (t, 2H, *J* = 1.6 Hz), 3.95 (s, 3H), 1.57 (s, 9H);^{13}C NMR (150.81 MHz, $CDCl_3$, T= 25°C) δ158.73 (C), 152.72 (C), 133.27 (C), 131.20 (CH), 129.84 (C), 121.41 (C), 108.09 (CH), 102.00 (CH_2), 82.73 (C), 51.77 (CH_2), 36.64 (CH_3), 28.12 (CH_3), 28.12 (CH_3) 28.12 (CH_3); HPLC-MS (ESI): *m/z* = 263.30 [MH^+]. Anal. calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found C, 64.20; H, 6.95; N, 10.61.

***tert*-butyl 1-methyl-7-methylidene-4-oxo-1,4,6,7-tetrahydro-5*H*-pyrrolo[3,2-*c*]pyridine-5-carboxylate. (24c)**

Yields: 14% (in toluene), 30% (in dichloromethane). Colourless oil. IR = 1724, 1671 cm^{-1}. ^{1}H NMR (599.71 MHz, $CDCl_3$, T= 25°C) δ 6.55 (d, 1H, *J* = 3.1 Hz), 6.51 (d, 1H, *J* = 3.0 Hz), 5.21 (m, 2H), 4.45 (s, 2H), 3.68 (s, 3H), 1.45 (br.s. 9H);^{13}C NMR (150.81 MHz, $CDCl_3$, T= 25°C) δ161.73 (C), 152.72 (C), 133.47 (C), 130.20 (CH), 127.04 (CH), 117.38 (C), 109.61 (CH_2), 107.62 (CH), 82.33

(C), 52.40 (CH_2), 35.80 (CH_3) 27.87 (CH_3), 27.87 (CH_3), 27.87 (CH_3); HPLC-MS (ESI): *m/z* = 263.30 [MH^+]. Anal. calcd for $C_{14}H_{18}N_2O_3$ C, 64.10; H, 6.92; N, 10.68. Found C, 64.16; H, 6.94; N, 10.59.

1,7-dimethyl-1,5-dihydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one (26c)

Yields: 5% (in dichloromethane), 65% (in acetonitrile).Yellow solid. M.p.: 75 ^{0}C. IR = 1675 cm^{-1}. ^{1}H NMR (599.71 MHz, $CDCl_3$, T= 25°C) δ 11.19 (br.s., 1H), 6.82 (br.s., 1H), 6.81 (d, 1H, *J* = 3.1 Hz), 6.78 (d, 1H, *J* = 3.1 Hz), 3.97 (s, 3H), 2.44 (s, 3H);^{13}C NMR (150.81 MHz, $CDCl_3$, T= 25°C) δ 161.31 (C), 139.21 (C), 127.69 (CH), 125.34 (CH), 116.60 (C), 105.20 (C), 104.12 (CH), 36.12 (CH_3), 16.30 (CH_3); HPLC-MS (ESI): *m/z* = 263.30 [MH^+]. Anal. calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found C, 66.63; H, 6.11; N, 17.34.

1,4-dimethyl-6-(phenylcarbonyl)-1,6-dihydro-7*H*-pyrrolo[2,3-*c*]pyridin-7-one. (21d)

Yields: 51% (in toluene), 60% (in dichloromethane), 50% (in acetonitrile), 3% (in DMF). Yellow solid. M.p.: 93 ^{0}C. IR = 1674, 1668 cm^{-1}.^{1}H NMR (599.71 MHz, $CDCl_3$, T= 25°C) δ 7.81 (d, 2H, *J* = 7.9 Hz), 7.58 (m, 1H), 7.46 (m, 2H), 7.06 (d, 1H, *J* = 2.8, Hz), 7.03 (m, 1H), 6.30 (d, 1H, *J* = 2.8, Hz), 4.07 (s, 3H), 2.25 (s, 3H);^{13}C NMR (150.81 MHz, $CDCl_3$, T= 25°C) δ173.55 (C), 155.56 (C), 134.28 (C), 133.75 (C), 133.13 (CH), 132.57 (CH), 129.39 (CH), 129.39 (CH), 128.47 (CH), 128.47 (CH), 121.92 (CH), 121.60 (C), 112.24 (C), 101.48 (CH), 36.15 (CH_3), 15.05 (CH_3); HPLC-MS (ESI): *m/z* = 267.29 [MH^+]. Anal. calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found C, 72.19; H, 5.41; N, 10.46.

1,7-dimethyl-5-(phenylcarbonyl)-1,5-dihydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one. (22d)

Yield: 10% (in dichloromethane), 13% (in acetonitrile). Yellow solid. M.p.: 165 ^{0}C. IR = 1673, 1669 cm^{-1}.^{1}H NMR (599.71 MHz, $CDCl_3$, T= 25°C) δ 7.78 (d, 2H, *J* = 7.6 Hz), 7.56 (t, 1H, *J* = 7.6

Hz), 7.44 (t, 2H, *J* = 7.9 Hz), 7.13 (s, 1H), 6.76 (m, 2H), 3.97 (s, 3H), 2.46 (s, 3H);^{13}C NMR (150.81 MHz, $CDCl_3$, T= 25°C) δ 173.53 (C), 159.42 (C), 138.30 (C), 134.14 (C), 133.00 (CH), 129.42 (CH), 129.42 (CH), 128.39 (CH), 128.39 (CH), 128.05 (CH), 125.16 (CH), 116.74 (C), 107.00 (C), 106.18 (C), 36.20 (CH_3), 16.49 (CH_3); HPLC-MS (ESI): *m/z* = 267.29 [MH^+]. Anal. calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found C, 72.21; H, 5.25; N, 10.49.

1-methyl-4-methylidene-6-(phenylcarbonyl)-1,4,5,6-tetrahydro-7*H*-pyrrolo[2,3-*c*]pyridin-7-one. (23d)

Yield: 9% (in toluene).White solid. M.p.: 127 ^{0}C. IR = 1670 cm^{-1}. ^{1}H NMR (599.71 MHz, $CDCl_3$, T= 25°C) δ 7.60 (dd, 2H, *J* = 8.1, 1.0 Hz), 7.48 (m, 1H), 7.40 (m, 2H), 6.85 (d, 1H, *J* = 2.8 Hz), 6.32 (d, 1H, *J* = 2.6 Hz), 5.41 (s, 1H), 5.21 (s, 1H), 4.71 (s, 2H), 3.86 (s, 3H);^{13}C NMR (150.81 MHz, $CDCl_3$, T= 25°C) δ 173.47 (C), 159.94 (C), 136.79 (C), 133.13 (C), 131.96 (CH), 131.27 (CH), 131.13 (CH), 127.99 (CH), 127.99 (CH), 127.92 (CH), 127.92 (CH), 120.58 (C), 109.03 (CH_2), 102.67 (CH), 51.88 (CH_2), 36.56 (CH_3); HPLC-MS (ESI): *m/z* = 267.29 [MH^+]. Anal. calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found C, 72.21; H, 5.42; N, 10.46.

1,4-dimethyl-1,6-dihydro-7*H*-pyrrolo[2,3-*c*]pyridin-7-one. (25d)

Yield: 6% (in toluene), 40% (in DMF). Yellow solid. M.p.: 116 ^{0}C. IR = 1671 cm^{-1}. ^{1}H NMR (599.71 MHz, $CDCl_3$, T= 25°C) δ 11.34 (br.s., 1H), 7.09 (d, 1H, *J* = 2.8 Hz), 6.77 (s, 1H), 6.34 (d, 1H, *J* = 2.8 Hz), 4.20 (s, 3H), 2.26 (d, 3H, *J* = 0.8 Hz);^{13}C NMR (150.81 MHz, $CDCl_3$, T= 25°C) δ 156.54 (C), 133.89 (C), 131.18 (CH), 122.24 (C), 121.10 (CH), 111.11 (C), 100.79 (CH), 35.73 (CH_3), 14.88 (CH_3); HPLC-MS (ESI): *m/z* = 163.18 [MH^+]. Anal. calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found C, 66.59; H, 6.16; N, 17.32.

For **26d** see **26c**

1,7-dimethyl-4-phenyl-6,7-dihydropyrrolo[2,3-*c*]azepin-8(1*H*)-one. (27e)

Yields: 20% (in dichloromethane), 43% (in acetonitrile), 66% (in DMF). White solid. M.p.; 118 ^{0}C. IR = 1673 cm^{-1}. ^{1}H NMR (599.71 MHz, $CDCl_3$, T= 25°C) δ 7.39 (m, 2H), 7.35 (m, 3H), 6.73 (d,

1H, *J* = 2.8 Hz), 6.07 (t, 1H, *J* = 6.9 Hz), 5.95 (d, 1H, *J* = 2.8 Hz), 4.00 (s, 3H), 3.78 (d, 2H, *J* = 6.9 Hz), 3.17 (s, 3H);^{13}C NMR (150.81 MHz, $CDCl_3$, T= 25°C) δ162.21 (C), 142.64 (C), 140.52 (C), 128.57 (CH), 128.57 (CH), 128.10 (CH), 128.10 (CH), 127.78 (CH), 127.14 (C), 126.78 (CH), 126.68 (C), 119.60 (CH), 107.73 (CH), 47.53 (CH_2), 36.62 (CH_3), 34.65 (CH_3); HPLC-MS (ESI): *m/z* = 253.31 [MH^+]. Anal. calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found C, 76.24; H, 6.35; N, 11.04.

1,5-dimethyl-8-phenyl-5,6-dihydropyrrolo[3,2-*c*]azepin-4(1*H*)-one. (28e)

Yields: 63% (in dichloromethane), 31% (in acetonitrile), 12% (in DMF). White solid. M.p.: 130 ^{0}C. IR: = 1676 cm^{-1}. ^{1}H NMR (599.71 MHz, $CDCl_3$, T= 25°C) δ 7.34 (m, 3H), 7.22 (d, 2H, *J* = 6.4 Hz), 6.77 (d, 1H, *J* = 2.8 Hz), 6.63 (d, 1H, *J* = 2.8 Hz), 6.13 (t, 1H, *J* = 7.4 Hz), 3.74 (d, 2H, *J* = 7.1 Hz), 3.17 (s, 3H), 3.07 (s, 3H);^{13}C NMR (150.81 MHz, $CDCl_3$, T= 25°C) δ166.02 (C), 139.38 (C), 137.87 (C), 131.50 (C), 128.67 (CH), 128.67 (CH), 128.04 (CH), 127.51 (CH), 127.51 (CH), 124.74 (CH), 124.31 (CH), 123.28 (C), 109.68 (CH), 47.55 (CH_2), 36.44 (CH_3), 35.38 (CH_3); HPLC-MS (ESI): *m/z* = 253.32 [MH^+]. Anal. calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found C, 76.23; H, 6.30; N, 11.04.

1-methyl-7-[(4-methylphenyl)sulfonyl]-4-phenyl-6,7-dihydropyrrolo[2,3-*c*]azepin-8(1*H*)-one (27f)

Yields: 20% (in dichloromethane), 55% (in acetonitrile), 68% (in DMF). White solid. M.p.: 190 ^{0}C. IR: = 1673 cm^{-1}.^{1}H NMR (599.71 MHz, $CDCl_3$, T= 25°C) δ 7.85 (d, 2H, *J* = 8.2 Hz), 7.37 (m, 5H), 7.25 (d, 2H), 6.78 (d, 1H, *J* = 2.6 Hz), 6.34 (t, 1H, *J*= 7.0 Hz), 5.93 (d, 1H, *J* = 2.8 Hz), 4.54 (br.s., 2H), 3.91 (s, 3H), 2.39 (s, 3H);^{13}C NMR (150.81 MHz, $CDCl_3$, T= 25°C) δ160.72 (C), 144.33 (C), 143.35 (C), 140.08 (C), 136.22 (C), 129.56 (CH), 129.38 (CH), 129.38 (CH), 128.98 (C), 128.57 (CH), 128.57 (CH), 128.56 (CH), 128.56 (CH), 128.26 (CH), 128.26 (CH), 128.14 (CH), 124.60

(C), 121.46 (CH), 109.05 (CH), 43.35 (CH_2), 37.13 (CH_3), 21.63 (CH_3); HPLC-MS (ESI): *m/z* = 393.47 [MH^+]. Anal. calcd for $C_{22}H_{20}N_2O_3S$: C, 67.33; H, 5.14; N, 7.14. Found C, 67.37; H, 5.19; N, 7.09.

1-methyl-5-[(4-methylphenyl)sulfonyl]-8-phenyl-5,6-dihydropyrrolo[3,2-*c*]azepin-4(1*H*)-one (28f)

Yield: 60% (in dichloromethane), 17% (in acetonitrile), 7% (in DMF). White solid. M.p.: 154 ^{0}C. IR = 1674 cm^{-1}. ^{1}H NMR (599.71 MHz, $CDCl_3$, T= 25°C) δ 7.90 (d, 2H, *J* = 8.2 Hz), 7.39 (m, 3H), 7.26 (d, 2H, *J* = 8.2 Hz), 7.22 (m, 2H), 6.71 (d, 1H, *J*= 3.0 Hz), 6.62 (d, 1H, *J* = 3.0 Hz), 6.42 (t, 1H, *J* = 7.6 Hz), 4.87 (br.s.,1H), 3.88 (br.s., 1H), 3.06 (s, 3H), 2.40 (s, 3H);^{13}C NMR (150.81 MHz, $CDCl_3$, T= 25°C) δ164.12 (C), 144.20 (C), 138.99 (C), 138.66 (C), 136.51 (C), 132.37 (C), 129.27 (CH), 129.27 (CH), 128.91 (CH), 128.91 (CH), 128.57 (CH), 128.57 (CH), 128.48 (CH), 127.49 (CH), 127.49 (CH), 126.19 (CH), 125.51 (CH), 121.48 (C), 110.88 (CH), 43.31 (CH_2), 36.83 (CH_3), 21.60 (CH_3); HPLC-MS (ESI): *m/z* = 393.47 [MH^+]. Anal. calcd for $C_{22}H_{20}N_2O_3S$: C, 67.33; H, 5.14; N, 7.14. Found C, 67.25; H, 5.26; N, 7.06.

7-benzyl-1-methyl-4-phenyl-6,7-dihydropyrrolo[2,3-c]azepin-8(1H)-one (27g)

Yields: 12% (in dichloromethane), 23% (in acetonitrile), 66% (in DMF). Light yellow solid. M.p.: 106 ^{0}C. IR = 1675 cm^{-1}.^{1}H NMR (599.71 MHz, $CDCl_3$, T= 25°C) δ 7.35 (m, 9H), 7.26 (m, 1H), 6.76 (d, 1H, *J* = 2.8 Hz), 5.96 (d, 1H, *J* = 2.6 Hz), 5.89 (t, 1H, *J* = 6.9 Hz), 4.79 (s, 2H), 4.05 (s ,3H), 3.75 (d, 2H, *J* = 6.92 Hz);^{13}C NMR (150.81 MHz, $CDCl_3$, T= 25°C) δ162.32 (C), 142.42 (C), 140.59 (C), 138.08 (C), 128.59 (CH), 128.59 (CH), 128.56 (CH), 128.56 (CH), 128.08 (CH), 128.08 (CH), 127.89 (CH), 127.89 (CH), 127.72 (CH), 127.29 (CH), 127.05 (CH), 126.88 (C), 126.81 (C), 120.25 (CH), 107.87 (CH), 50.36 (CH_2), 45.21 (CH_2), 36.80 (CH_3); HPLC-MS (ESI): *m/z* = 329.40 [MH^+]. Anal. calcd for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53. Found C, 80.41; H, 6.18; N, 8.61.

5-benzyl-1-methyl-8-phenyl-5,6-dihydropyrrolo[3,2-c]azepin-4(1H)-one (28g)

Yield: 74% (in dichloromethane), 67% (in acetonitrile), 14% (in DMF). Light yellow solid. M.p.: 80 ^{0}C. IR = 1676 cm^{-1}.^{1}H NMR (599.71 MHz, $CDCl_3$, T= 25°C) δ 7.29 (m, 10H), 6.85 (d, 1H, *J* = 3.0 Hz), 6.67 (d, 1H, *J* = 3.0 Hz), 5.95 (t, 1H, *J* = 7.4 Hz), 4.81 (br.s., 2H), 3.70 (d, 2H, *J* = 7.2 Hz), 3.08 (s ,3H);^{13}C NMR (150.81 MHz, $CDCl_3$, T= 25°C) δ 166.03 (C), 139.57 (C), 138.36 (C), 137.83 (C), 131.51 (C), 128.70 (CH), 128.70 (CH), 128.48 (CH), 128.02 (CH), 127.95 (CH), 127.95 (CH), 127.95 (CH), 127.58 (CH), 127.58 (CH), 127.17 (CH), 125.10 (CH), 124.79 (CH), 110.02 (CH), 50.60 (CH_2), 44.94 (CH_2), 36.50 (CH_3); HPLC-MS (ESI): *m/z* = 329.40 [MH^+]. Anal. calcd for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53. Found C, 80.34; H, 6.25; N, 8.48.

2-aminophenol (29)

The compound is commercial available by Sigma Aldrich.

Propargylbromide (30)

The compound is commercial available by Sigma Aldrich.

1-bromo-2-butyne (30a)

The compound is commercial available by Sigma Aldrich.

(3-bromoprop-1-yn-1-yl)benzene (30b)

The compound is known in literature[87].

Preparation of 2-(prop-2-yn-1-ylamino)phenol (31a)

To a solution of 2-aminophenol **(29)** (45.8 mmol) in EtOH (130 ml) was slowly dropped propargylbromide **(30)** (9.16 mmol) at room temperature.The mixture was left under stirring at rt for 4 days. Solvent was evaporated under reduced pressure. The residue was washed with TBME (100 ml) and the solid preicipitate was filtered-off. The solution was then evaporated under reduced pressure. The crude residue was purified by flash chromatography column. (Cyclohexane / EtOAc, 7.5:2.5)

Yield: 75%. Pale yellow solid. M. p.: 96-97 °C. IR = 2132, 3305, 3388, 3495 cm^{-1}. ^1H NMR (599 MHz, $CDCl_3$, T= 25°C) δ: 2.25 (1H, t, *J* = 2.39 Hz), 3.96 (2H, d, *J* = 2.31 Hz), 4.56 (2H, br.s.), 6.74 (1H, m), 6.76 (1H, m), 6.84 (1H, m), 6.91 (1H, m);^{13}C NMR (150.81 MHz, $CDCl_3$, T = 25°C) δ: 34.4 (CH_2), 71.6 (C), 81.3 (C), 114.2 (CH), 114.8 (CH), 119.7 (CH), 121.7 (CH), 135.6 (C), 144.6 (C); HPLC-MS (ESI): *m/z* = 148.17 [MH^+]. Anal. Calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52; found: C, 73.61; H, 5.90; N, 9.44.

Synthesis of *N*-(2-hydroxyphenyl)benzamide (36)

To a stirred solution of 2-aminophenol **(29)** (81.5 mmol) and pyridine (32.4 ml) in dry dichloromethane (816 ml) was slowly dropped a solution of benzoylchloride (85.5 mmol) in dry dichloromethane (80 ml) at 0°C. The mixture was allowed to rt and left at this temperature for further 3 hours. The organic phase was then washed three times with an aqueous solution of HCl 2N (3x 80 ml), then two times with an aqueous solution of $NaHCO_3$ sat.(2x100 ml) and other two times with water (2x 100 ml). The aqueous phase was discharged and the organic one was dried over Na_2SO_4, filtered on a gouch and the solvent evaporated under reduced pressure. The crude residue was triturated in TBME (80 ml), filtered and the solid dried in the oven at 40 ^{0}C.

Yield: 97%. White solid. ^1H NMR (599 MHz, $CDCl_3$, T= 25°C) δ: 6.94 (1H, m), 7.09 (1H, d, *J* = 8.2 Hz), 7.18 (1H, m), 7.21 (1H, d, *J* = 7.9 Hz), 7.53 (2H, t, *J* = 7.9 Hz), 7.62 (1H, m), 7.92 (2H, d, *J* = 7.6 Hz), 8.12 (1H, br.s.), 8.62 (1H, br.s.);^{13}C NMR (150.81 MHz, $CDCl_3$, T = 25°C) δ: 119.9 (CH), 120.6 (CH), 122.3 (CH), 125.6 (C), 127.3 (CH), 127.3 (CH), 127.3 (CH), 128.9 (CH), 128.9 (CH), 132.5 (CH), 133.1 (C), 148.8 (C), 167.1 (C); HPLC-MS (ESI): *m/z* = 214.23 [MH^+].

Synthesis of 2-(benzylamino)phenol (37)

To a solution of BH_3THF 1M (19 ml) diluted with THF dry (10 ml), was slowly dropped a solution of *N*-(2-hydroxyphenyl)benzamide **(36)** (4.7 mmol) in THF dry (10 ml) keeping the internal

temperature at rt. The solution was left under stirring for 1.5h then cooled down to 0°C and quenched dropping MeOH (20 ml) in 20 minutes. Temperature was raised to rt and the solution was stirred for further 0.5h. Methanol was evaporated under reduced pressure to dryness.

Yield: 95%. Gray solid.^{1}H NMR (599 MHz, $CDCl_3$, T= 25°C) δ: 4.37 (2H, s), 4.70 (1H, br.s.), 6.64 (1H, t, *J* = 7.6 Hz), 6.69 (1H, d, *J* = 7.6 Hz), 6.73 (1H, d, *J* = 7.6 Hz), 6.84 (1H, t, *J* = 7.58 Hz), 7.29 (1H, t, *J* = 7.2 Hz), 7.36 (2H, t, *J* = 7.6 Hz), 7.41 (2H, d, *J* = 7.6 Hz);^{13}C NMR (150.81 MHz, $CDCl_3$, T = 25°C) δ: 48.5 (CH_2), 112.3 (CH), 114.2 (CH), 117.6 (CH), 121.6 (CH), 127.1 (CH), 127.5 (CH), 127.5 (CH), 128.5 (CH), 128.5 (CH), 136.9 (C), 139.4 (C), 143.4 (C); HPLC-MS (ESI): *m/z* = 200.24 [MH^+].

Synthesis of *N*-(2-hydroxyphenyl)-*N*-(prop-2-yn-1-yl)benzamide (31b)

To a stirred solution of 2-(prop-2-yn-1-ylamino)phenol **(31a)** (6.7 mmol) and pyridine (2.7 ml) in dry dichloromethane (68 ml) was slowly dropped a solution of benzoylchloride (7.1 mmol) in dry dichloromethane (6,7 ml) at 0 C. The mixture was allowed to rt and left at this temperature for further 3 hours. The organic phase was then washed three times with an aqueous solution of HCl 2N (3x 16 ml), then two times with an aqueous solution of $NaHCO_3$ sat.(2x20 ml) and other two times with water (2x 30 ml). The aqueous phase was discharged and the organic one was dried over Na_2SO_4, filtered on a gouch and the solvent evaporated under reduced pressure. The crude residue was triturated in TBME (20 ml), filtered and the solid dried in the oven at 40°C.

Yield: 70%. White solid. M.p.: 156-158 °C. IR (nujol): 2133, 1698, 3290, 3325 cm^{-1}. ^{1}H NMR (599 MHz, $CDCl_3$, T= 25°C) δ: 2.32 (1H, d, br.s.), 4.58 (2H, d, br.s.), 6.09 (1H, br.s.), 6.77 (1H, br.s.), 6.94 (2H, m), 7.27 (6H, m);^{13}C NMR (150.81 MHz, $CDCl_3$, T = 25°C) δ: 38.6 (CH_2), 72.8 (CH), 79.0 (C), 116.9 (CH), 121.1 (CH), 127.8 (CH), 127.9 (CH), 127.9 (CH), 129.6 (CH), 129.7 (CH), 129.7 (CH), 130.0 (C), 130.3 (CH), 134.5 (C), 151.8 (C), 171.5 (C); HPLC-MS (ESI): *m/z* = 252.27 [MH^+]. Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57; found: C, 76.27; H, 5.43; N, 5.75.

Synthesis of *N*-(2-hydroxyphenyl)-*N*-(prop-2-yn-1-yl)acetamide (31c)

To a stirred solution of 2-(prop-2-yn-1-ylamino)phenol **(31a)** (6.7 mmol) and pyridine (2.7 ml) in dry dichloromethane (68 ml) was slowly dropped a solution of acetylchloride (0.5 ml) in dry dchloromethane (6,7 ml) at 0°C. The mixture was allowed to rt and left at this temperature for further 1 hour. The organic phase was then washed three times with an aqueous solution of HCl 2N (3x 16 ml), then two times with an aqueous solution of $NaHCO_3$ sat.(2x20 ml) and other two times with water (2x 30 ml). The aqueous phase was discharged and the organic one was dried over Na_2SO_4, filtered on a gouch and the solvent evaporated under reduced pressure. The crude residue was triturated in TBME (20 ml), filtered and the solid dried in the oven at 40°C.

Yield: 75%. White solid. M.p.: 158-159 °C. IR (nujol): 2120, 1675, 3296 cm^{-1}. ^1H NMR (599 MHz, $CDCl_3$, T= 25°C) δ: 1.89 (3H, s), 2.27 (1H, t, *J* = 2.3 Hz), 4.48 (2H, m), 6.69 (1H, br.s.), 6.98 (1H, t, *J* = 7.5 Hz), 7.07 (1H, d, *J* = 8.2 Hz), 7.21 (1H, m), 7.32 (1H, m);^{13}C NMR (150.81 MHz, $CDCl_3$, T = 25°C) δ: 22.0 (CH_3), 37.5 (CH_2), 72.6 (CH), 79.0 (C), 117.5 (CH), 121.2 (CH), 128.4 (C), 129.0 (CH), 130.5 (CH), 152.6 (C), 171.8 (C); HPLC-MS (ESI): *m/z* = 190.21 [MH^+]. Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40; found: C, 69.81; H, 6.01; N, 7.23.

Synthesis of *N*-(2-hydroxyphenyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (31d)

To a stirred solution of 2-(prop-2-yn-1-ylamino)phenol **(31a)** (6.8 mmol) and pyridine (2.7 ml) in dry dichloromethane (68 ml) was slowly dropped a solution of tosylchloride (7.1 mmol) in dry dchloromethane (6,7 ml) at 0°C. The mixture was allowed to rt and left at this temperature for further 1 hour. The organic phase was then washed three times with an aqueous solution of HCl 2N (3x 16 ml), then two times with an aqueous solution of $NaHCO_3$ sat.(2x20 ml) and other two times with water (2x 30 ml). The aqueous phase was discharged and the organic one was dried over Na_2SO_4, filtered on a gouch and the solvent evaporated under reduced pressure. The crude residue was purified by flash chromatography column (Cyclohexane / EtOAc 8:2)

Yield: 80%. Pale yellow solid. M.p.: 165-166 °C. IR (nujol): 2135, 3266, 3415 cm^{-1}.^{1}H NMR (599 MHz, $CDCl_3$, T= 25°C) δ: 2.21 (1H, t, *J* = 2.4 Hz), 2.44 (3H, s), 4.39 (2H, d, *J* = 1.32 Hz), 6.54 (1H, s), 6.71 (2H, m), 7.06 (1H, m), 7.23 (1H, m), 7.27 (2H, s), 7.59 (2H, d, *J* = 8.24 Hz);^{13}C NMR (150.81 MHz, $CDCl_3$, T = 25°C) δ: 21.6 (CH_3), 41.7 (CH_2), 74.1 (CH), 77.5 (C), 117.4 (CH), 120.4 (CH), 125.7 (C), 128.1 (CH), 128.4 (CH), 128.4 (CH), 129.4 (CH), 129.4 (CH), 130.5 (CH), 133.8 (C), 144.5 (C), 154.4 (C); HPLC-MS (ESI): *m/z* = 302.36 [MH^+]. Anal. calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65; found: C, 63.92; H, 4.83; N. 4.69.

Synthesis of 2-[benzyl(prop-2-yn-1-yl)amino]phenol (31e)

To a solution of 2-(benzylamino)phenol **(37)** (80 mmol) in EtOH (400 ml) was slowly dropped propargylbromide **(30)** (16 mmol) at room temperature.The mixture was left under stirring at rt for 4 days. Solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography column. (Cyclohexane / Cyclopentylmethylether, 9:1)

Yield: 70%. Red oil. IR (nujol): 2112, 3312, 3392 cm^{-1}. ^{1}H NMR (599 MHz, $CDCl_3$, T= 25°C) δ: 2.33 (1H, m, *J* = 1.3 Hz), 3.58 (2H, d, *J* = 2.3 Hz), 4.16 (2H, s), 6.88 (1H, t, *J* = 7.7 Hz), 6.94 (1H, d, *J* = 8.2 Hz), 7.11 (1H, t, *J* = 7.7 Hz), 7.29 (1H, m), 7.34 (4H, m), 7.41 (1H, d, *J* = 7.6 Hz);^{13}C NMR (150.81 MHz, $CDCl_3$, T = 25°C) δ: 42.7 (CH_2), 57.2 (CH_2), 73.8 (CH), 78.8 (C), 114.1 (CH), 119.8 (CH), 124.0 (CH), 127.1 (CH), 127.7 (CH), 128.5 (CH), 128.5 (CH), 129.26 (CH), 129.26 (CH), 136. 8 (C), 137.0 (C), 151.9 (C); HPLC-MS (ESI): *m/z* = 238.29 [MH^+]. Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90; found: C, 81.14; H, 6.20; N, 5.96.

Synthesis of 2-[(3-phenylprop-2-yn-1-yl)amino]phenol (38a)

To a solution of 2-aminophenol **(29)** (93.5 mmol) in EtOH (200 ml) was slowly dropped (3-bromoprop-1-yn-1-yl)benzene **(30a)** (18.7 mmol) at room temperature.The mixture was left under stirring at rt for 4 days. Solvent was evaporated under reduced pressure. The residue was washed

with TBME (100 ml) and the solid preicipitate was filtered-off. The solution was then evaporated under reduced pressure. The crude residue was purified by flash chromatography column. (Cyclohexane / EtOAc, 8 :2)

Yield: 63%. Light yellow solid. ^{1}H NMR (599 MHz, $CDCl_3$, T= 25°C) δ: 4.17 (2H, s), 4.25 (2H, q, *J* = 2.31 Hz), 4.56 (2H, br.s.), 6.72 (1H, m), 6.75 (1H, m), 6.82 (1H, dd, *J* = 7.9, 1.3 Hz), 6.90 (1H, m);^{13}C NMR (150.81 MHz, $CDCl_3$, T = 25°C) δ: 3.5 (CH_3), 34.6 (CH_2), 76.1 (C), 79.2 (C), 113.9 (CH), 114.5 (CH), 119.1 (CH), 121.5 (CH), 135.8 (C), 144.4 (C); HPLC-MS (ESI): *m/z* = 151.81 [MH^+].

Synthesis of 2-(but-2-yn-1-ylamino)phenol (38a)

To a solution of 2-aminophenol **(29)** (93.5 mmol) in EtOH (200 ml) was slowly dropped 1-bromo-2-butyne **(30a)** (18.7 mmol) at room temperature.The mixture was left under stirring at rt for 4 days. Solvent was evaporated under reduced pressure. The residue was washed with TBME (100 ml) and the solid preicipitate was filtered-off. The solution was then evaporated under reduced pressure. The crude residue was purified by flash chromatography column. (Cyclohexane / EtOAc, 7.5:2.5)

Yield: 60%. Light brown solid. ^{1}H NMR (599 MHz, $CDCl_3$, T= 25°C) δ: 1.82 (3H, t, *J* = 2.47 Hz), 3.88 (2H, q, *J* = 2.31 Hz), 4.56 (2H, br.s.), 6.72 (1H, m), 6.75 (1H, m), 6.82 (1H, dd, *J* = 7.9, 1.3 Hz), 6.90 (1H, m);^{13}C NMR (150.81 MHz, $CDCl_3$, T = 25°C) δ: 3.5 (CH_3), 34.6 (CH_2), 76.1 (C), 79.2 (C), 113.9 (CH), 114.5 (CH), 119.1 (CH), 121.5 (CH), 135.8 (C), 144.4 (C); HPLC-MS (ESI): *m/z* = 151.81 [MH^+].

***N*-(but-2-yn-1-yl)-*N*-(2-hydroxyphenyl)benzamide (31f)**

To a stirred solution of 2-(but-2-yn-1-ylamino)phenol **(38a)** (5.4 mmol) and pyridine (2.1 ml) in dry dichloromethane (54 ml) was slowly dropped a solution of benzoylchloride (5.7 mmol) in dry dichloromethane (5.3 ml) at 0°C. The mixture was allowed to rt and left at this temperature for further 3 hours. The organic phase was then washed three times with an aqueous solution of HCl 2N (3x 16 ml), then two times with an aqueous solution of $NaHCO_3$ sat.(2x20 ml) and other two times

with water (2x 30 ml). The aqueous phase was discharged and the organic one was dried over Na_2SO_4, filtered on a gouch and the solvent evaporated under reduced pressure. The crude residue was triturated in TBME (15 ml), filtered and the solid dried in the oven at 40°C.

Yield: 80%. White solid. M.p.: 142-143 °C. IR (nujol): 2208, 1715, 3275 cm^{-1}.^{1}H NMR (599 MHz, $CDCl_3$, T= 25°C) δ: 1.81 (3H, t, *J* = 2.3 Hz), 4.53 (2H, m), 6.72 (1H, br.s.), 6.91 (2H, m), 7.11 (1H, m), 7.15 (2H, br.s.) 7.24 (1H, br.s.), 7.37 (2H, br.s.);^{13}C NMR (150.81 MHz, $CDCl_3$, T = 25°C) δ: 3.58 (CH_3), 39.0 (CH_2), 74.3 (C), 80.8 (C), 117.0 (CH), 120.7 (CH), 127.7 (CH), 127.7 (CH), 127.8 (CH), 127.8 (CH), 129.5 (CH), 129.8 (CH), 130.0 (C), 130.0 (CH), 134.8 (C), 152.2 (C), 171.6 (C); HPLC-MS (ESI): *m/z* = 266.30 [MH^+]. Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28; found: C, 76.99; H, 5.83; N, 5.21.

Synthesis of 2-[(3-phenylprop-2-yn-1-yl)amino]phenol (38b)

To a solution of 2-aminophenol **(29)** (93.5 mmol) in EtOH (200 ml) was slowly dropped (3-bromoprop-1-yn-1-yl)benzene **(30b)** (18.7 mmol) at room temperature.The mixture was left under stirring at rt for 4 days. Solvent was evaporated under reduced pressure. The residue was washed with TBME (100 ml) and the solid preicipitate was filtered-off. The solution was then evaporated under reduced pressure. The crude residue was purified by flash chromatography column. (Cyclohexane / EtOAc, 8 :2)

Yield: 63%. Light yellow solid. ^{1}H NMR (599 MHz, $CDCl_3$, T= 25°C) δ: 4.17 (2H, s), 4.25 (1H, br.s.), 5.21 (1H, br.s.), 6.76 (2H, m), 6.93 (2H, m), 7.31 (3H, m), 7.42 (2H, m);^{13}C NMR (150.81 MHz, $CDCl_3$, T = 25°C) δ: 35.1 (CH_2), 83.43 (C), 86.4 (C), 114.2 (CH), 114.5 (CH), 119.5 (CH), 121.5 (CH), 122.8 (C), 128.1 (CH), 128.2 (CH), 128.2 (CH), 131.7 (CH), 131.7 (CH), 135.6 (C), 144.6 (C); HPLC-MS (ESI): *m/z* = 224.26 [MH^+].

Synthesis of *N*-(2-hydroxyphenyl)-4-methyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (31g)

To a stirred solution of 2-[(3-phenylprop-2-yn-1-yl)amino]phenol **(38b)** (5.4 mmol) and pyridine (2.1 ml) in dry dichloromethane (54 ml) was slowly dropped a solution of tosylchloride (5.7 mmol) in dry dichloromethane (5.3 ml) at 0°C. The mixture was allowed to rt and left at this temperature for further 3 hours. The organic phase was then washed three times with an aqueous solution of HCl 2N (3x 16 ml), then two times with an aqueous solution of $NaHCO_3$ sat.(2x20 ml) and other two times with water (2x 30 ml). The aqueous phase was discharged and the organic one was dried over Na_2SO_4, filtered on a gouch and the solvent evaporated under reduced pressure. The crude residue was triturated in TBME (15 ml), filtered and the solid dried in the oven at 40°C.

Yield: 60%. Pale yellow solid. M.p.: 168 °C. IR (nujol): 2215, 3324 cm^{-1}.^{1}H NMR (599 MHz, $CDCl_3$, T= 25°C) δ: 2.41 (3H, s), 4.63 (2H, br.s.), 6.63 (1H, s), 6.75 (1H, m), 6.84 (1H, dd, *J* = 8.0, 1.5 Hz), 7.09 (1H, dd, *J* = 8.2, 1.3 Hz) 7.27 (7H, m), 7.65 (2H, d, *J* = 8.2 Hz);^{13}C NMR (150.81 MHz, $CDCl_3$, T = 25°C) δ: 21.6 (CH_3), 42.7 (CH_2), 82.9 (C), 85.9 (C), 117.4 (CH), 120.4 (CH), 122.0 (C), 126.1 (C), 128.2 (CH), 128.2 (CH), 128.5 (CH), 128.5 (CH), 128.6 (CH), 129.4 (CH), 129.4 (CH), 130.5 (CH), 130.5 (CH), 131.5 (CH), 131.5 (CH), 134.2 (C), 144.3 (C), 154.5 (C); HPLC-MS (ESI): *m/z* = 378.45 [MH^+]. Anal. Calcd for $C_{22}H_{19}NO_3S$: C, 70.00; H, 5.07; N. 3.71; found: C, 70.18; H, 4.81; N. 3.52.

Synthesis of 2-(prop-2-yn-1-yloxy)phenol (41)

The compound is known in letterature[88].

Synthesis of 3-(prop-2-yn-1-yloxy)naphthalen-2-ol (42)

The compound is known in letterature[88].

White solid. . ^{1}H NMR (599 MHz, $CDCl_3$, T= 25°C) δ: 2.62 (1H, t, *J* = 2.3 Hz), 4.90 (2H, d, *J* = 2.3 Hz), 5.88 (1H, s), 7.26 (1H, s), 7.31 (1H, s), 7.34 (1H, m) 7.37 (1H, m), 7.68 (1H, d, *J* = 7.9 Hz),

7.71 (1H, d, *J* = 7.58 Hz);^{13}C NMR (150.81 MHz, $CDCl_3$, T = 25°C) δ: 56.7 (CH_2), 76.5 (CH), 77.6 (C), 107.5 (CH), 109.9 (CH), 123.9 (CH), 124.7 (CH), 126.3 (CH), 126.6 (CH), 128.6 (C), 130.0 (C), 145.2 (C), 145.5 (C); HPLC-MS (ESI): *m/z* = 199.21 [MH^+].

Synthesis of 2-methylidene-3,4-dihydro-2*H*-1,4-benzoxazine (32a)

To a solution of 2-(prop-2-yn-1-ylamino)phenol **(31a)** (3.98 mmol) in dry acetonitrile (120 ml) , K_2CO_3 (0.39 mmol) and AuCl (0.19 mmol) were added. The mixture was refluxed for 8h. At the end of this time the solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography (Cyclohexane / Cyclopentylmethylether 7:3).

Yield: 70%. Red oil. IR (nujol): 3352 cm^{-1}. ^{1}H NMR (599 MHz, $CDCl_3$, T= 25°C) δ: 3.68 (2H, d, *J* = 1.9 Hz), 4.25 (1H, d, *J* = 0.6 Hz), 4.48 (1H,d, *J* = 0.6 Hz), 5.91 (1H, br.s.), 6.61 (1H, td, *J* = 7.7, 1.6 Hz), 6.69 (1H, dd, *J*= 7.9, 1.65 Hz), 6.76 (1H, td, *J* = 7.9, 1.3 Hz), 6.80 (1H, d, *J* = 7.9 Hz);^{13}C NMR (150.81 MHz, $CDCl_3$, T = 25°C) δ: 41.9 (CH_2), 88.3 (CH_2), 115.1 (CH), 115.2 (CH), 118.1 (CH), 121.8 (CH), 135.2 (C), 142.0 (C), 152.5 (C); HPLC-MS (ESI): *m/z* = 148.17 [MH^+]. Anal. calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52; found: C, 73.62; H, 6.02; N, 9.43

Synthesis of quinolin-8-ol (35a)

To solution of **(31a)** (3 mmol) in dry acetonitrile (80 ml), $NaAuCl_4$ was added (0.15 mmol). The mixture was refluxed for 24 hours, At the end of this time, the solvent was evaporated under reduced pressure and the residue was purified by chromatographic column (Toluene / EtOAc 6.5:3.5)

Yield: 60%. White solid. The product is commercial available by Aldrich.

Synthesis of (2-methylidene-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)(phenyl)methanone (32b)

To a solution of *N*-(2-hydroxyphenyl)-*N*-(prop-2-yn-1-yl)benzamide **(31b)** (3.98 mmol) in dry acetonitrile (120 ml) , K_2CO_3 (0.39 mmol) and AuCl (0.19 mmol) were added. The mixture was refluxed for 8h. At the end of this time the solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography (Cyclohexane / EtOAc 9:1).

Yield: 60%. Light yellow solid. M.p.: 115-116 °C. IR (nujol): 1694 cm^{-1}.^{1}H NMR (599 MHz, $CDCl_3$, T= 25°C) δ: 4.33 (1H, d, br.s.), 4.46 (2H, s), 4.73 (1H, d, *J* = 1.3 Hz), 6.71 (2H, br.s.), 7.05 (2H, m), 7.35 (2H, t, *J* = 6.9 Hz), 7.44 (1H, t, *J* = 6.9 Hz), 7.48 (2H, d, *J* = 7.9 Hz);^{13}C NMR (150.81 MHz, $CDCl_3$, T = 25°C) δ: 43.9 (CH_2), 90.7 (CH_2), 116.8 (CH), 121.2 (CH), 124.2 (CH), 125.9 (CH), 127.2 (C), 128.3 (CH), 128.3 (CH), 128.6 (CH), 130.8 (CH), 130.8 (CH), 134.5 (C), 145.3 (C), 151.6 (C), 168.4 (C); HPLC-MS (ESI): *m/z* = 252.27 [MH^+]. Anal calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57; found: C, 76.36; H, 5.32; N, 5.84.

Synthesis of 1-(2-methylidene-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)ethanone (32c)

To a solution of *N*-(2-hydroxyphenyl)-*N*-(prop-2-yn-1-yl)acetamide **(31c)** (5.3 mmol) in dry acetonitrile (100 ml) , K_2CO_3 (0.53 mmol) and AuCl (0.26 mmol) were added. The mixture was refluxed for 5h. At the end of this time the solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography (Cyclohexane / EtOAc 7:3).

Yield: 60%. Red oil. IR (nujol): 1680 cm^{-1}. ^{1}H NMR (599 MHz, $CDCl_3$, T= 25°C) δ: 2.29 (3H, s), 4.33 (1H, br.s), 4.38 (1H, d, br.s.), 4.66 (1H, d, *J* = 1.6 Hz), 7.01 (1H, dt, *J* = 7.6, 1.3 Hz), 7.05 (1H, d, *J* = 7.9 Hz), 7.16 (2H, m);^{13}C NMR (150.81 MHz, $CDCl_3$, T = 25°C) δ: 22.2 (CH_3), 41.8 (CH_2), 90.5 (CH_2), 117.0 (CH), 121.6 (CH), 123.8 (CH), 126.7 (CH), 127.4 (C), 146.2 (C), 151.7 (C), 168.8 (C); HPLC-MS (ESI): *m/z* = 190.21 [MH^+]. Anal. calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40; found: C, 69.67; H, 6.07; N, 7.26.

Synthesis of 2-methylidene-4-[(4-methylphenyl)sulfonyl]-3,4-dihydro-2*H*-1,4-benzoxazine (32d)

To a solution of *N*-(2-hydroxyphenyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide **(31d)** (3.3 mmol) in dry acetonitrile (100 ml) , K_2CO_3 (0.33 mmol) and AuCl (0.16 mmol) were added. The mixture was refluxed for 1h. At the end of this time the solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography (Cyclohexane / EtOAc 9:1).

Yield: 90%. White solid. M.p.: 172-173 °C. ^{1}H NMR (599 MHz, $CDCl_3$, T= 25°C) δ: 2.36 (3H, s), 4.06 (1H, s), 4.28 (2H, s), 4.32 (1H, s), 6.85 (1H, d, *J* = 8.2 Hz), 7.04 (1H, t, *J* = 7.7 Hz), 7.12 (2H, d, *J* = 7.9 Hz), 7.18 (1H, t, *J* = 7.7 Hz), 7.35 (2H, d, *J* = 7.91 Hz), 7.74 (1H, d, *J* = 8.2 Hz);^{13}C NMR (150.81 MHz, $CDCl_3$, T = 25°C) δ: 21.5 (CH_3), 46.0 (CH_2), 91.3 (CH_2), 116.6 (CH), 122.0 (CH), 124.2 (C), 126.8 (CH), 127.6 (CH), 127.6 (CH), 127.6 (CH), 129.2 (CH), 129.2 (CH), 134.4 (C), 144.1 (C), 147.1 (C), 148.5 (C); HPLC-MS (ESI): *m/z* = 302.36 [MH^+]. Anal. calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65; found: C, 63.85; H, 4.88; N. 4.46.

Synthesis of 4-benzyl-2-methylidene-3,4-dihydro-2*H*-1,4-benzoxazine (32e)

To a solution of 2-[benzyl(prop-2-yn-1-yl)amino]phenol **(31e)** (4.97 mmol) in dry acetonitrile (140 ml) , K_2CO_3 (0.49 mmol) and AuCl (0.24 mmol) were added. The mixture was refluxed for 5h. At the end of this time the solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography (Cyclohexane / Cyclopentylmethylether 9.3:0.7).

Yield: 65%. Red oil. ^{1}H NMR (599 MHz, $CDCl_3$, T= 25°C) δ: 3.60 (2H, s), 4.13 (1H, d, *J* = 0.66 Hz), 4.37 (2H, s), 4.62 (1H, d, *J* = 1.32 Hz), 6.80 (1H, m), 6.81 (1H, m), 6.89 (1H, m), 6.96 (1H, dd, *J* = 7.7, 1.32 Hz), 7.31 (1H, m), 7.37 (4H, m);^{13}C NMR (150.81 MHz, $CDCl_3$, T = 25°C) δ: 48.4 (CH_2), 54.7 (CH_2), 88.8 (CH_2), 113.8 (CH), 115.8 (CH), 119.6 (CH), 122.0 (CH), 127.3 (CH), 127.6 (CH), 127.6 (CH), 128.6 (CH), 128.6 (CH), 135.7 (C), 137.2 (C), 143.7 (C), 152.0 (C); HPLC-MS

(ESI): *m/z* = 238.29 [MH^+]. Anal. calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90; found: C, 81.15; H, 6.16; N. 5.73.

Synthesis of [(2*Z*)-2-ethylidene-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl](phenyl)methanone (32f-*cis*) and [(2*E*)-2-ethylidene-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl](phenyl)methanone (32f-*trans*)

To a solution of *N*-(but-2-yn-1-yl)-*N*-(2-hydroxyphenyl)benzamide **(31f)** (2.5 mmol) in dry DMF (90 ml) , K_2CO_3 (0.25 mmol) and $AuCl_3$ (0.12 mmol) were added. The mixture was refluxed for 2h. At the end of this time the the mixture was diluted with TBME (200ml), washed with water (3x100ml). The organic phase was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude residue was purified by flash chromatography (Cyclohexane / EtOAc, 9:1).

Yield: 50% (**32f-*cis***). White solid. M.p.: 129-131 °C. IR (nujol): 1705 cm^{-1}. ^1H NMR (599 MHz, $CDCl_3$, T= 25°C) δ: 1.78 (3H, d, *J* = 6.9 Hz), 4.38 (2H, br.s.), 4.69 (1H, m), 6.70 (1H, br.s.), 6.70 (1H, br.s.), 7.05 (1H, m), 7.08 (1H, m), 7.35 (2H, m), 7.43 (1H, m), 7.48 (2H, d, *J* = 6.9 Hz);^{13}C NMR (150.81 MHz, $CDCl_3$, T = 25°C) δ: 9.3 (CH_3), 44.7 (CH_2), 101.7 (CH), 116.9 (CH), 120.8 (CH), 124.3 (CH), 125.8 (CH), 127.2 (C), 128.2 (CH), 128.2 (CH), 128.6 (CH), 128.6 (CH), 130.7 (CH), 134.7 (C), 144.5 (C), 145.5 (C), 168.3(C). HPLC-MS (ESI): *m/z* = 266.30 [MH^+]. Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28; found: C, 77.14; H, 5.51; N, 5.39.

Yield: 30% (**32f-*trans***). White solid. M.p.: 144-145 °C. ^1H NMR (599 MHz, $CDCl_3$, T= 25°C) δ: 2.02 (3H, d, br.s.), 4.51 (2H, m), 4.78 (1H, br.s.), 6.68 (1H, br.s.), 6.80 (1H, br.s.), 7.10 (2H, m), 7.17 (2H, m), 7.24 (1H, m), 7.33 (2H, d, *J* = 7.2 Hz);^{13}C NMR (150.81 MHz, $CDCl_3$, T = 25°C) δ: 22.2 (CH_3), 44.4 (CH_2), 100.4 (CH), 121.2 (CH), 124.4 (CH), 127.7 (CH), 127.7 (CH), 128.1 (CH), 128.1 (CH), 128.2 (CH), 129.1 (CH), 129.8 (CH), 135.4 (C), 135.5 (C), 151.0 (C), 152.9 (C), 169.7 (C); HPLC-MS (ESI): *m/z* = 266.30 [MH^+]. Anal. Calcd for $C_{22}H_{19}NO_3S$: C, 70.01; H, 5.07; N. 3.71; found: C, 70.11; H, 5.11; N. 3.63.

Synthesis of (2*Z*)-2-benzylidene-4-[(4-methylphenyl)sulfonyl]-3,4-dihydro-2*H*-1,4-benzoxazine (32g)

To a solution of *N*-(2-hydroxyphenyl)-4-methyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide **(31g)** (2.5 mmol) in dry DMF (90 ml) ,K_2CO_3 (0.25 mmol) and $AuCl_3$ (0.12 mmol) were added. The mixture was refluxed for 24h. At the end of this time the the mixture was diluted with TBME (200ml), washed with water (3x100ml). The organic phase was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude residue was purified by flash chromatography (Cyclohexane / EtOAc, 9:1).

Yield: 35% (**32g-*cis***). White solid. M.p.: 144-145 °C. ^{1}H NMR (599 MHz, $CDCl_3$, T= 25°C) *δ*: 2.02 (3H, s), 4.33 (2H, s), 5.18 (1H, s), 6.89 (2H, d, *J* = 7.91 Hz), 7.02 (1H, d, *J* = 7.9 Hz), 7.11 (1H, t, *J* = 7.7 Hz), 7.17 (1H, m), 7.26 (5H, m), 7.29 (2H, s), 7.76 (1H, dd, *J* = 7.9, 0.9 Hz);^{13}C NMR (150.81 MHz, $CDCl_3$, T = 25°C) δ: 21.1 (CH_3), 47.7 (CH_2), 107.8 (CH), 116.8 (CH), 122.4 (CH), 124.9 (C), 126.5 (CH), 127.4 (CH), 127.4 (CH), 127.5 (CH), 127.9 (CH), 128.0 (CH), 128.0 (CH), 128.5 (CH), 128.5 (CH), 129.2 (CH), 129.2 (CH), 133.9 (C), 133.9 (C), 141.0 (C), 144.3 (C), 147.2 (C); HPLC-MS (ESI): *m/z* = 378.45 [MH^+]. Anal. Calcd for $C_{22}H_{19}NO_3S$: C, 70.01; H, 5.07; N. 3.71; found: C, 70.11; H, 5.11; N. 3.63.

(2*Z*)-2-benzylidene-2*H*-1,4-benzoxazine (35c)

Yield: 5%. Yellow solid. M.p.: 112-113 °C. ^{1}H NMR (599 MHz, $CDCl_3$, T= 25°C) δ: 5.79 (1H, s), 7.05 (1H, dd, *J* = 8.0, 1.1 Hz), 7.07 (1H, m), 7.22 (1H, td, *J* = 7.7, 1.3 Hz), 7.30 (1H, m), 7.38 (1H, dd, *J* = 7.6, 1.3 Hz), 7.41 (2H, t, *J* = 7.7 Hz), 7.77 (2H, d, *J* = 7.6 Hz), 7.81 (1H, s);^{13}C NMR (150.81 MHz, $CDCl_3$, T = 25°C) δ: 112.5 (CH), 115.3 (CH), 123.9 (CH), 127.8 (CH), 128.1 (CH), 128.5 (CH), 128.5 (CH), 129.0 (CH), 129.0 (CH), 129.5 (CH), 132.5 (C), 134.0 (C), 143.4 (C), 145.5 (C), 154.5 (C); HPLC-MS (ESI): *m/z* = 222.25 [MH^+]. HRMS (EI): m/z calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33; found: C, 81.67; H, 4.84; N, 6.27.

Synthesis of 2-methylidene-2,3-dihydro-1,4-benzodioxine (43)

To a solution of 2-(prop-2-yn-1-yloxy)phenol **(41)** (6.1 mmol) in dry acetonitrile (100 ml) , K_2CO_3 (0.61 mmol) and AuCl (0.30 mmol) were added. The mixture was refluxed for 7h. At the end of this time the solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography (Cyclohexane / EtOAc, 9.7:0.3).

Yield: 70%. Colourless oil. ^{1}H NMR (599 MHz, $CDCl_3$, T= 25°C) δ: 4.36 (1H, d, *J* = 1.9 Hz), 4.51 (2H, s), 4.75 (1H, d, *J* = 1.9 Hz), 6.90 (3H, m), 6.97 (1H, m);^{13}C NMR (150.81 MHz, $CDCl_3$, T = 25°C) δ: 64.6 (CH_2), 91.2 (CH_2), 116.4 (CH), 117.2 (CH), 122.1 (CH), 122.2 (CH), 142.6 (C), 143.7 (C), 150.0 (C).

Synthesis of 2-methylidene-2,3-dihydronaphtho[2,3-*b*][1,4]dioxine (44)

To a solution of 3-(prop-2-yn-1-yloxy)naphthalen-2-ol **(42)** (5.0 mmol) in dry DMF (80 ml) , K_2CO_3 (0.50 mmol) and AuCl (0.25 mmol) were added. The mixture was refluxed for 2h. At the end of this time the mixture was diluted with TBME (200 ml) and washed four times with water (4x80 ml). The aqueous phase was discharged and the organic one was dried over Na_2SO_4, filtered on a gouch and the solvent evaporated under reduced pressure.The crude residue was purified by flash chromatography (Cyclohexane / EtOAc, 9.7:0.3).

Yield: 75%. Light yellow solid. ^{1}H NMR (599 MHz, $CDCl_3$, T= 25°C) δ: 4.43 (1H, d, *J* = 0.6 Hz), 4.60 (2H, s), 4.83 (1H, d, *J* = 0.9 Hz), 7.33 (1H, s), 7.35 (2H, m), 7.37 (1H, s), 7.70 (2H, m);^{13}C NMR (150.81 MHz, $CDCl_3$, T = 25°C) δ: 64.8 (CH_2), 91.4 (CH_2), 112.0 (CH), 112.8 (CH), 124.6 (CH), 124.7 (CH), 126.6 (CH), 126.7 (CH), 129.6 (C), 129.8 (C), 142.6 (C), 143.9 (C), 150.1 (C).

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