Article

# Synthesis of a Small Library of Imidazolidin-2-ones using Gold Catalysis on Solid Phase.

Agustina La-Venia, Noelia Soledad Medran, Viktor Krchnak, and Sebastian A. Testero

*ACS Comb. Sci.*, **Just Accepted Manuscript** • DOI: 10.1021/acscombsci.6b00062 • Publication Date (Web): 23 Jun 2016

# Synthesis of a Small Library of Imidazolidin-2-ones using Gold Catalysis on Solid Phase.

*Agustina La-Venia,[†a,b] Noelia S. Medran,[†b] Viktor Krchňák[*a,c] and Sebastián A. Testero[*b]*

[†]These authors contributed equally to this work.

[a]Department of Organic Chemistry, Faculty of Science, Institute of Molecular and Translational Medicine, Palacky University, 771 46 Olomouc, Czech Republic.

[b]Instituto de Química Rosario - IQUIR (CONICET), Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Suipacha 531, Rosario, S2002LRK, Argentina. Fax/Phone: (+54)-341-437-0577; e-mail: testero@iquir-conicet.gov.ar.

[c]Department of Chemistry and Biochemistry, University of Notre Dame, 251 Nieuwland Science Center, Notre Dame, Indiana 46556, United States. Fax: (+1)-574-631-6652, phone: (+1)-574-631-5113; e-mail: vkrchnak@nd.edu.

KEYWORDS: Gold catalysis; Solid-Phase Synthesis; C–N bond formation; Imidazolidin-2-ones; Propargylureas.

ABSTRACT: An efficient and high-yielding solid phase synthesis of a small library of imidazolidin-2-ones and imidazol-2-ones was carried out employing a high chemo- and regio-selective gold-catalyzed cycloisomerization as a key step. Polymer-supported amino acids

derivatized with several alkynes functionalities combined with tosyl- and phenyl-ureas have been subjected to gold-catalysis exhibiting exclusively C–N bond formation. The present work proves the potential of solid phase synthesis and homogeneous gold catalysis as an efficient and powerful synthetic tool for the generation of drug-like heterocycles.

## INTRODUCTION

Application of organometallic chemistry to solid-phase organic synthesis (SPOS) has increased substantially in the last decade.[1] The advantages of SPOS are: easy isolation of resin-bound intermediates and products by simple filtration, excess of reagents can be added to drive reactions to completion, beneficial use of high boiling solvents such as DMF or DMSO and amenability to automate among others.[2] Hence, SPOS allows a rapid synthesis of a large number of compounds in short period of time. On the other hand, in the last years, research in homogeneous gold catalysis has reached a high level of development;[3-14] however, the application of this metal to SPOS is very limited.[15] Gold is a "soft" transition metal that is considered as one of the most powerful activators of a carbon-carbon triple bond due to the high binding energies of the alkyne-gold complexes.[16, 17] As a result, gold is strongly alkynophilic but it is not as oxophilic as most Lewis acids, for instance the interaction with anionic O-ligands provides highly sensitive complexes only.[18] Nitrogen also shows a low affinity as exhibited by the efficiency of the gold-catalyzed hydroaminations and by the fact that only P,N-ligands stable polynuclear bidentate complexes inhibit gold catalysis.[19] This provides a remarkable advantage to the auric chemistry since oxygen, water, and alcohols are often well-tolerated[20, 21] making gold catalysts easy to manipulate and amenable to automate.

The high affinity of gold for alkynes makes them susceptible to nucleophilic attack by heteroatoms such as O, S or N,[22-24] a fully relativistic computational analysis has shown why gold is superior to other relativistic elements in this activation.[25, 26] In the particular case of an intramolecular nucleophilic addition, cyclization can occur in *endo* or *exo* manner (5-*endo*-dig, 5-*exo*-dig, 6-*endo*-dig and 6-*exo*-dig) to form five- or six-membered heterocyclic rings.[27-30]

As part of our research program concerning the application of organometallic chemistry to the solid-phase synthesis,[31-34] herein we report the synthesis of a small library of imidazolidin-2-ones using gold catalysis on propargylureas bonded to solid support. Imidazolidin-2-ones possess a variety of biological activities, including antileishmanil activity,[35] MurB enzyme inhibitors possessing antibacterial activity,[36] antiviral activity,[37] antiarrhythmic,[38] selective high-affinity antagonists for the human dopamine D4 receptor,[39] and anticancer agents.[40, 41, 42]

There are several studies on the cycloisomerization of alkynylureas in solution phase, some of them involving the synthesis of bicyclic heterocycles starting from (*ortho*-arylalkynyl)ureas[43, 44] and others describing the formation of monocyclic heterocycles from *in situ* generated propargylureas.[45, 46] In the case of acyclic propargylureas derived from tosyl isocyanates, *O*-cyclization was predominantly observed under gold catalyzed conditions (Figure 1).[46, 47] On the contrary, when acyclic propargylureas derived from alkyl or aryl isocyanates were subjected to gold catalyzed cycloisomerization C–N bond formation was observed.[48] In the case of internal alkynes ($R^3$= Ar or Alk), the cycloisomerization resulted in the formation of 3,4-dihydropyrimidin-2(1*H*)-ones through a 6-*endo*-dig *N*-cycloisomerization. On the other hand when the alkyne is terminal, imidazol-2-ones are obtained through a 5-*exo*-dig pathway.

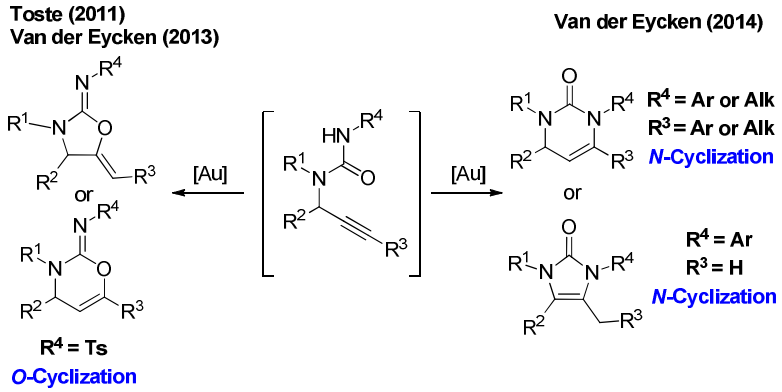
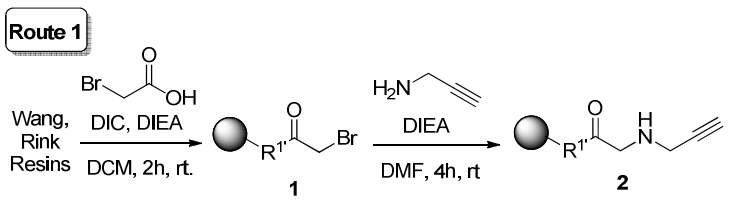



**Figure 1.** Gold-catalyzed cycloisomerizations of *in situ* generated propargylureas in solution.

It is worth noting that while gold catalysis has not been investigated in solid-phase organic synthesis,[15] the inverse approach -heterogenization of gold catalysts for organic synthesis- has been explored in a few cases.[49-51]

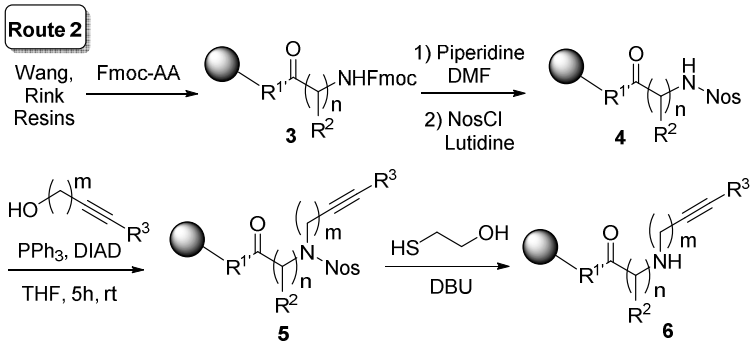
## RESULTS AND DISCUSSION

We validated the feasibility to combine gold catalysis and solid phase synthesizing the immobilized linear propargylamines via two different synthetic routes. Route 1 offers a straightforward procedure to obtain secondary terminal propargylamines (**2**) bound to Wang or Rink resins (Scheme 1). With the aim to synthesize internal alkynes, several Sonogashira conditions were screened on the propargylamines **2** without success. The probable cause of this failure is that polymer-bound propargylamines (**2**) can act as a competing base with the tertiary amine typically employed in classical Sonogashira conditions.[52]



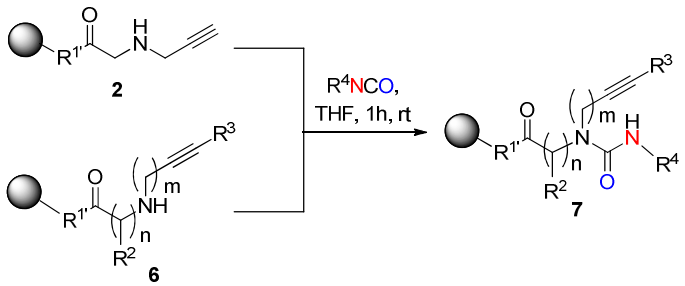
**Scheme 1.** Synthesis of terminal propargylamines bound to the resin.

Alternatively, in Route 2 several Fmoc-protected amino acids were attached to the solid support, followed by Fmoc removal and subsequent amino activation via reaction with 4-Nos-Cl. Then, various alkynes moieties were introduced by the means of a Mitsunobu reaction leading to the versatile propargylamines **6** (Scheme 2). This strategy not only bypasses the use of Sonogashira reactions on polymer-bound propargylamines to introduce variability at $R^3$ position, but also enables additional diversity points based on the use of commercial Fmoc-protected amino acids and alkynyl alcohols.




**Scheme 2**. Synthesis of internal alkynes bound to amino acids.

Having optimized these sequences to obtain the propargylamines **2** and **6**, we proceed with the synthesis of the propargylureas **7** using several isocyanates (Scheme 3).




**Scheme 3.** Synthesis of propargylureas **7** from propargylamines **2** and **6**.

It is important to note that the propargylureas **7** are ambident nucleophiles. Ureas **7** have at least two potential well positioned nucleophilic atoms that can produce gold-catalyzed intramolecular cycloisomerization, the *N* and the *O* of the urea. The potential heterocyclic products **8-11** are detailed in Figure 2.

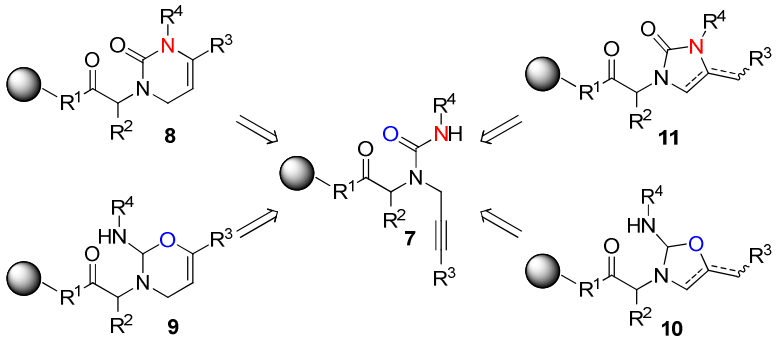
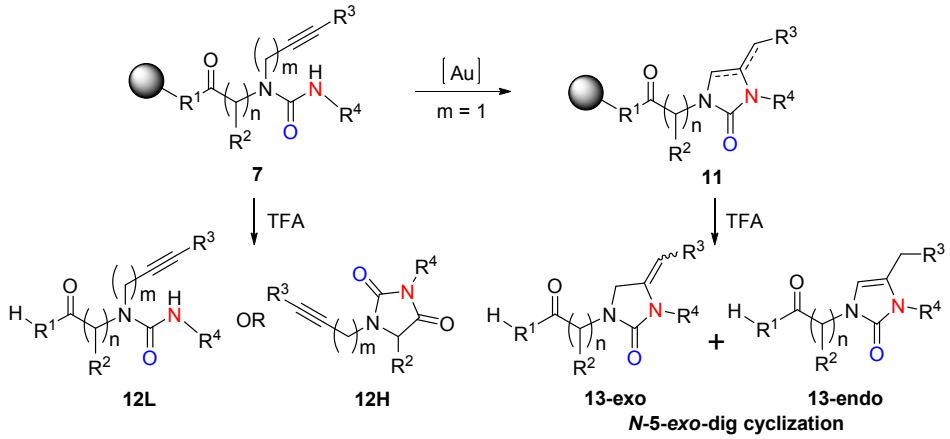



**Figure 2**. Possible modes of cyclization of propargylureas (**7**) bound to resins.

Next, we screened different conditions for the key gold catalysis cycloisomerization (Scheme 4). The reactions were carried out with propargylureas derived from tosyl isocyanates, resin **7** with $R^4$=Ts, using 5 mol% of different gold catalysts, in anhydrous dichloromethane or a mixture of solvents $CH_2Cl_2$:MeCN, varying the time of reactions and the temperature (Table 1). The outcome of the reaction was evaluated by LC/MS analysis (λ=240 nm) after cleavage of the products from the resin with TFA. To prove that TFA was not involved in the alkyne cycloisomerization and to test the yield and purity of the acyclic intermediates, we subjected the acyclic resins **7** to a treatment with the TFA cleavage cocktail isolating the corresponding linear compounds **12L** (**L** by linear) or the corresponding cyclic hydantoins **12H** (**H** by hydantoin). In all cases the alkynes were unaltered.




**Scheme 4.** Gold catalysis cycloisomerization of propargylureas **7**.

**Table 1.** Analytical screening of gold catalysis on propargylureas derived from tosyl isocyanates bound to resin (**7a**).

| Entry | Catalysis conditions | Time (h) | SM | **13a-exo** | **13a-endo** |
|---|---|---|---|---|---|
| 1 | $Ph_3PAuNTf_2$ DCM, RT | 1 | 0 | 81 | 11 |
| | | 2 | 0 | 72 | 24 |
| | | 3.5 | 0 | 69 | 27 |
| | | 16 | 0 | 65 | 33 |
| 2 | $Ph_3PAuCl/AgOTf$ DCM, RT | 1 | 34 | 42 | 19 |
| | | 2 | 0 | 74 | 24 |
| | | 3.5 | 0 | 81 | 19 |
| | | 16 | 0 | 56 | 44 |
| 3 | $Ph_3PAuCl/AgSbF_6$ DCM, RT | 1 | 27 | 39 | 29 |
| | | 2 | 5 | 52 | 38 |
| | | 3.5 | 0 | 58 | 39 |
| | | 16 | 0 | 48 | 48 |
| 4 | $Ph_3PAuCl$ DCM, RT | 1[a] | _ | _ | _ |
| | | 2 | 64 | 31 | 1 |
| | | 3.5 | 51 | 45 | 1 |
| | | 16 | 31 | 57 | 12 |
| 5 | AuCl DCM:MeCN (5:1), RT | 1 | 3 | 65 | 26 |
| | | 2 | 0 | 62 | 34 |
| | | 3.5 | 0 | 63 | 34 |
| | | 16 | 0 | 69 | 31 |
| 6 | $AuCl_3$ DCM:MeCN (5:1), RT | 1 | 0 | 75 | 8 |
| | | 2 | 0 | 77 | 5 |
| | | 3.5 | 0 | 75 | 6 |
| | | 16 | 0 | 77 | 6 |
| 7 | $AuCl_3$ MeCN, 80°C | 1 | _ | _ | _ |
| | | 2 | 0 | 54 | 30 |
| | | 3.5 | 0 | 66 | 23 |
| | | 16 | 0 | 65 | 27 |

All tests were carried out using resin **7a** ($R^1$=NH; $R^2$,$R^3$=H; $R^4$=Ts; n,m=1) and 5 mol% of catalyst. The results of the cyclization were analyzed by LC/MS (λ=240nm) and by $^1$H NMR. The numbers in the columns represent the LC/MS ratio of starting material (SM), cyclized *exo* product and cyclized *endo* product. a) Not analyzed.

In most of the cases, the key step catalyzed by gold was remarkable efficient (>84%) and the reaction was complete in 1 hour, except for $Ph_3PAuCl$ in which case the cyclization continued

incomplete despite the increase of the reaction time (Entry 4).[53] The cyclizations promoted by different gold(I) catalysts were successful, but the use of AuCl presented the shortest reaction time (Entry 5). Even though the presence of Au(III) led to the same final heterocycles, the reaction exhibited slightly lower selectivity, producing along with small quantities of unidentified side-products (Entry 6 and 7). Heating the reaction mixture did not present notable modifications in the outcome of the catalysis. In general, the cycloisomerization exhibited an exceptional chemoselectivity towards the *N*-5-*exo*-dig cyclization providing only the imidazolidin-2-ones **13a**. However, a separable mixture of *exo* and *endo* cycled products (**13a-exo** and **13a-endo**, respectively) was observed in all cases, probably as a result of partially double-bond migration promoted by gold or TFA during the cleavage.

After cleavage with TFA, the compounds were purified and fully characterized by $^{1}H$, and $^{13}C$ NMR and using homo and heteronuclear 2D NMR techniques like HSQC and HMBC. Even though a complete analysis was conducted, it was not possible to define at this stage if the products were coming from the *O*-cyclization or *N*-cyclization due to their similarity. Then, we analyzed the compounds by IR spectroscopy following Van der Eycken[47] assignment ranges for oxazolidin-2-imines **14** (1598-1616 $cm^{-1}$) and imidazolidin-2-ones **15** (1727-1745 $cm^{-1}$) but the C=N or C=O stretching IR adsorption peaks for our compounds did not fall in either range (Figure 3). The IR spectroscopic description of other recently disclosed imidazolidin-2-ones are also out of the Van der Eycken's range.[54] Finally, product structures and thus the chemoselectivy of the reaction were unambiguously proven by $^{15}N$ HMBC NMR experiment performed on a 700 MHz NMR spectrometer, which shows that the vinyl proton at 6.35 ppm has a cross peak with each nitrogen and the methyl protons at 2.30 ppm have cross peak with the tosyl nitrogen $N_1$ (see Figure 3b and supporting information). The only structure that explains these correlations it is

structure **13b-endo**. The heterocycles coming from the *O*-ring closure were not observed. This is in sharp contrast to the gold catalyzed cycloisomerization reaction of acyclic propargylureas reported in solution. Van der Eycken and coworkers published a comparative study of the gold- and silver-catalyzed cycloisomerizations of propargylureas derived from tosyl isocyanates[47] and they concluded that the application of cationic gold(I) catalysis generally produces oxazolidin-2-imines **14** as major products while the application of silver(I) triflate selectively provides the corresponding imidazolidin-2-ones **15** (Figure 3a).

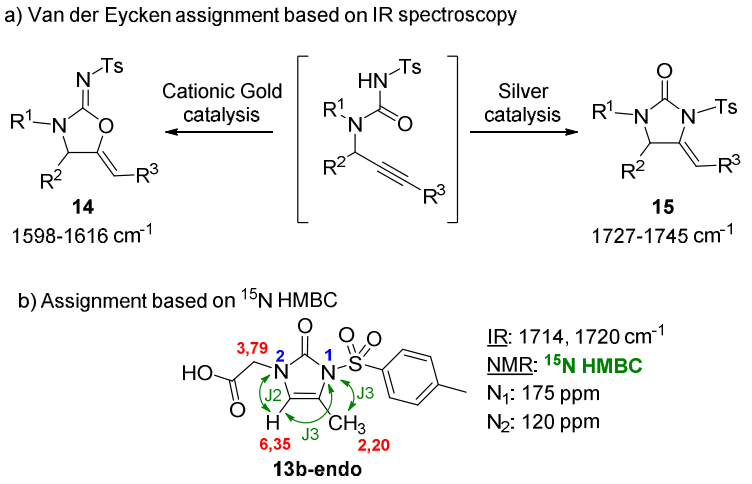
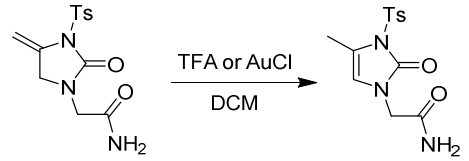



**Figure 3**. Determination of the chemoselectivity of the heterocyclization. Note: green arrows indicate the $^{15}$N HMBC correlations, red numbers are chemical shifts (ppm).

To evaluate which factor is promoting the double-bond migration in the imidazolidin-2-one core, we setup a series of experiments using pure *exo* product **13a-exo** and resin **11a** ($R^1$=$NH_2$; $R^2$,$R^3$=H; $R^4$=Ts; n,m=1). Compound **13a-exo** proved to be stable to treatment with different solvents at high temperature (Entries 1, 2, Table 2). Then, **13a-exo** and resin **11a** were subjected to the presence of TFA at 0°C, RT and 45 °C and the mixture was analysed by LC/MS after 1 h and 17 h. In addition, AuCl salt was added to a solution of pure imidizolidin-2-one **13a-exo** at

RT and 45 °C to evaluate the cationic gold effect. From Table 2, we concluded that the isomerization of the *exo* isomer to the thermodynamically most stable 1,3-dihydro-2*H*-imidazol-2-one (**13a-endo**) is enabled mostly by TFA, increasing the *endo* isomer-percentage with the time, in addition to the isomerization acceleration by the high temperature. On the other hand, AuCl seems not to favour the double-bond migration notably (Entries 8, 9).




**13a-exo** **13a-endo**

Both final products come from *N*-5-*exo*-dig cyclization

**Table 2**. Analytical evaluation of double-bond migration in the imidazolidin-2-one core.

| Entry | Compound | Added | T (°C) | Time (h) | **13a-exo** | **13a-endo** |
|---|---|---|---|---|---|---|
| 1 | **13a-exo** | - | 80 | 2 | 99 | 1 |
| 2 | **13a-exo** | - | 80 | 17 | 99 | 1 |
| 3 | **11a** | TFA | 0 | 1 | 99 | 1 |
| 4 | **11a** | TFA | RT | 1 | 99 | 1 |
| 5 | **11a** | TFA | 45 | 1 | 72 | 17 |
| 6 | **13a-exo** | TFA | RT | 17 | 60 | 40 |
| 7 | **13a-exo** | TFA | 45 | 17 | 13 | 87 |
| 8 | **13a-exo** | AuCl | RT | 17 | 99 | 1 |
| 9 | **13a-exo** | AuCl | 80 | 17 | 99 | 1 |

Knowing the differences from the literature for the gold catalyzed cycloisomerization between propargylureas derived from tosyl isocyanates and propargylureas derived phenyl isocyanates (Figure 1), we decided to explore the effect of gold catalysis cycloisomerization on the phenyl-urea family bound to resin (Table 3).

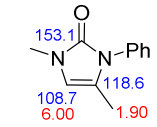
**Table 3.** Analytical screening of gold catalysis on propargylureas derived from phenyl isocyanates bound to resin (**7g**).

| Entry | Catalysis conditions | Time (h) | SM | **13g-exo** | **13g-endo** |
|---|---|---|---|---|---|
| 1 | $Ph_3PAuNTf_2$ DCM, RT | 1 | 6 | 94 | - |
| | | 2 | 6 | 94 | - |
| | | 3.5 | 7 | 93 | - |
| | | 16 | 19 | 81 | - |
| 2 | $Ph_3PAuCl/AgOTf$ DCM, RT | 1 | 8 | 92 | - |
| | | 2 | 8 | 92 | - |
| | | 3.5 | 9 | 91 | - |
| | | 16 | 5 | 95 | - |
| 3 | $Ph_3PAuCl/AgSbF_6$ DCM, RT | 1 | 0 | 100 | - |
| | | 2 | 1 | 99 | - |
| | | 3.5 | 1 | 99 | - |
| | | 16 | 0 | 100 | - |
| 4 | $Ph_3PAuCl$ DCM, RT | 1 | 97 | 3 | - |
| | | 2 | 11 | 89 | - |
| | | 3.5[a] | - | - | - |
| | | 16 | 3 | 97 | - |
| 5 | AuCl DCM:MeCN (5:1), RT | 1 | 4 | 96 | - |
| | | 2 | 4 | 96 | - |
| | | 3.5 | 5 | 95 | - |
| | | 16 | 5 | 95 | - |
| 6 | $AuCl_3$ DCM:MeCN (5:1), RT | 1 | 4 | 96 | - |
| | | 2 | 5 | 95 | - |
| | | 3.5 | 6 | 94 | - |
| | | 16 | 5 | 95 | - |

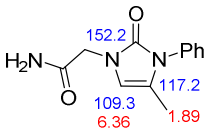
All tests were carried out using resin **7g** ($R^1$=NH; $R^2$,$R^3$ =H; $R^4$=Ph; n,m=1) and 5 mol% of catalyst. The results of the cyclization were analyzed by LC/MS (λ=240nm) and by $^1$H NMR. The numbers in the columns represent the LC/MS ratio of starting material (SM), cyclized *exo* product and cyclized *endo* product. a) Not analyzed.

Gratifyingly, the reaction took place with high yields (>81%) and excellent chemoselectivity and regioselectivity. All the catalysts tested produced the cycloisomerization with almost

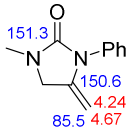
quantitative yields in 1h reaction (entries 1-3, 5 and 6) with the exception of $Ph_3PAuCl$ (entry 4) that needed 2h to provide 89% of product. However, contrary to propargylureas derived from tosyl isocyanates (Table 1), only the isomer **13g-exo** was detected, therefore no migration of the double bond to get the thermodynamically most stable compound **13g-endo** was observed in the analytical testing. According with the literature, when terminal propargylureas derived from phenyl isocyanates are subjected to gold-catalyzed cycloisomerization in solution the conversion proceeds via a 5-*exo*-dig *N*-cyclization mechanism (Figure 1).[48] Our findings in solid phase synthesis are in total agreement with the pathway reported in solution and consequently with the chemoselectivity and the regioselectivity of the reaction. Compound **13g-exo** was fully analyzed by $^{1}H$ and $^{13}C$ NMR, and 2D NMR techniques. However, the chemoselectivy of the reaction could not be determined at this stage. In the preparative scale, we were able to isolate 3% yield of the isomer **13g-endo** (Entry 7, table 4) which was also fully characterized by 1D and 2D NMR experiments. ROESY of **13g-endo** showed one cross peak between the methyl group at 1.89 ppm and one aromatic proton (see supporting information). This interaction evidences that C-N cycloisomerization occurred for propargylureas derived from phenyl isocyanates. Besides, a comparison between the chemical shift of **13g-exo** and **13g-endo** with similar imidazolidin-2-ones and imidazol-2-ones reported in the literature show a complete compatibility (Figure 4).



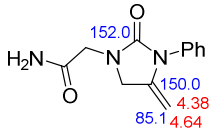

Van der Eycken
JOC 2011, 76, 5867




**13g-endo**




Van der Eycken
Org. Biomol. Chem.
2014, 12, 1741



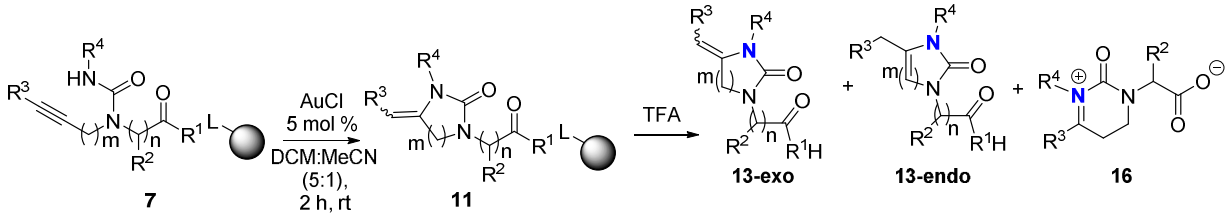

**13g-exo**

**Figure 4.** Comparison of chemical shift of **13g-endo** and **13g-exo** with reported compounds. Note: red numbers are $^{1}H$ chemical shifts (ppm) and blue numbers are $^{13}C$ chemical shifts (ppm).

Based on the efficiency during the annulation, easy handling and economical cost, the salt AuCl was chosen as the optimal catalyst for this transformation. The selected reaction conditions were analogous to the conditions for both tosyl- and phenyl-derivatives using AuCl (5 mol%) as a catalyst in $CH_2Cl_2$:MeCN (5:1) for 2 h at room temperature. Having the optimized conditions at hand, we decided to carry out the synthesis of an array of imidazolidin-2-ones employing various isocyanates, propargyl amines and alcohols, and linkers (Table 4). This strategy furnished the generation of a library of imidazolidin-2-ones **13-exo** and imidazol-2-ones **13-endo** with a high level of diversity. The diversity points involved the use of Wang and Rink resins with different linkers attaching several amino acids as initial step (glycine: $R^2$=H; n=1; alanine: $R^2$=$CH_3$; n=1, β-alanine: $R^2$=H; n=2). The combination of terminal alkynes and tosyl ureas ($R^4$=Ts) provided the final heterocycles with good to excellent total yields up to 97%, moreover, the Au catalysis step exhibited remarkably high efficiency (Entries 1-4). Similarly to the terminal analogous, both internal alkynes ($R^3$=$CH_3$, Ph) reacted with the tosyl urea functionality through 5-*exo*-dig *N*-cyclization, providing only the 1,3-dihydro-2*H*-indazolin-2-ones **13e-endo** and **13f-endo**, respectively. As previously described, double-bond migration took place (Entries 5 and 6). The phenyl urea derivatives ($R^4$=Ph) displayed comparable results in presence of terminal alkynes, obtaining the final 5-membered heterocycles **13** with high overall yields up to 99% (Entries 7, 8). However, in coincidence with the literature, the internal alkynes combined with the phenyl urea functionalities **7j** and **7k** led to 6-membered heterocycles **17** through *N*-6-*endo*-dig mechanism, followed by spontaneous tautomerization towards the corresponding zwitterion species **16j** and **16k** (Scheme 5). Compounds **16j** and **16k** were obtained with moderate to good overall yields

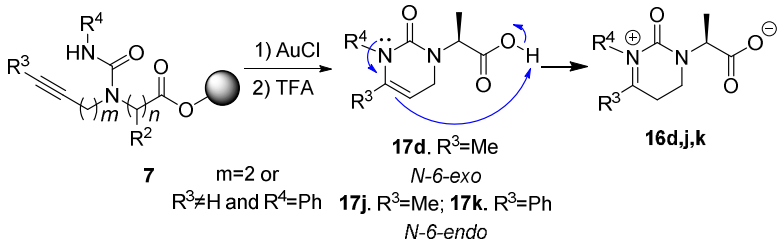
(Entries 10 and 11) The use of extended alkynes **7d** and **7i** (m=2) proceeded via 6-*exo*-dig cyclization with both urea derivatives providing 6-membered heterocycles. Analogous to the process previously detailed, they suffered tautomerization to the zwitterionic species **16d** and **16i** (Entries 4 and 9). It is worthy to highlight that in all the cases we only observed gold-catalyzed C–N bond formation.

**Table 4.** Preparative scale synthesis of substituted imidazolidin-2-ones **13-exo** and **13-endo**




| | Resin | $R^1H$ | $R^2$ | n | m | $R^3$ | $R^4$ | Total Yield[a] (13-exo:13-endo:16) | Au Yield[a,b] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **7a** | $NH_2$ | H | 1 | 1 | H | Ts | 87 (49:38:0) | 93 |
| 2 | **7b** | OH | H | 1 | 1 | H | Ts | 97 (25:72:0) | NA |
| 3 | **7c** | OH | H | 2 | 1 | H | Ts | 75 (65:10:0) | NC |
| 4 | **7d** | OH | $CH_3$ | 1 | 2 | H | Ts | 71 (0:0:71) | NA |
| 5 | **7e** | OH | $CH_3$ | 1 | 1 | $CH_3$ | Ts | 53 (0:53:0) | NA |
| 6 | **7f** | OH | $CH_3$ | 1 | 1 | Ph | Ts | 34 (1:33:0) | 55 |
| 7 | **7g** | $NH_2$ | H | 1 | 1 | H | Ph | 66 (63:3:0) | 70 |
| 8 | **7h** | OH | H | 2 | 1 | H | Ph | 96 (96:0:0) | 99 |
| 9 | **7i** | OH | $CH_3$ | 1 | 2 | H | Ph | 48 (0:0:48) | NA |
| 10 | **7j** | OH | $CH_3$ | 1 | 1 | $CH_3$ | Ph | 30 (0:0:30) | NC |
| 11 | **7k** | OH | $CH_3$ | 1 | 1 | Ph | Ph | 68 (0:0:68) | NA |

a) Yields are referred to isolated products by semi-preparative HPLC. b) Au yield refers to the yield corresponding only to the gold-catalyzed cycloisomerization step, calculated from the ratio between product yield and the yield of the linear compounds **12L** or the cyclic hydantoins **12H** corresponding to the previous step. NA: Not applicable; NC: Not calculated




**Scheme 5**. Zwitterion species **16** derived from 6-membered heterocycles **17** annulated by gold catalysis.

## CONCLUSION

We have demonstrated the potential of the unexplored combination of gold catalysis and solid-phase organic synthesis. In this work, we have disclosed the solid phase synthesis of imidazolidin-2-ones (**13-exo**) with high total yields (>70%) from propargylic ureas (**7**) via Au(I)-catalyzed 5-*exo*-dig and 6-*exo*-dig cyclizations followed, in some cases, by double-bond migration to provide the 1,3-dihydro-2*H*-imidazol-2-one core (**13-endo**). Isomerization experiments demonstrated that the conversion of the **13-exo** cycled products to the thermodynamically most stable **13-endo** compounds is enabled mostly by TFA, increasing the *endo*-percentage with the time. In the case of substrates that combine phenyl ureas functionalities with internal alkynes, the 6-*endo*-dig cycloisomerization was the main pathway leading to 6-membered heterocycles. Interestingly, a tautomerization towards the zwitterionic species **16** was observed for all the products **17** (m=2 or $R^3 \neq H$ in combination with $R^4$=Ph), independently on the cyclization mechanism by which they were originated. It is noteworthy that in all the cases only C-N gold-catalyzed cycloisomerization was detected, as proven by the analysis of $^{15}N$ HMBC and ROESY NMR experiments for selected final compounds. This synthetic strategy has provided a small library of interestingly drug-like heterocycles with several diversity points through gold-promoted cyclizations on solid phase.

EXPERIMENTAL SECTION

**1.-General Information: Material and Methods**

Chemical reagents were purchased from commercial sources and were used without further purification. Solvents were analytical grade and were used without further purification. Commercial Rink amide resin (100-200 mesh, 1% DVB, 0.68 mmol/g) and Wang resin (100-200 mesh, 1% DVB, 1.0 mmol/g) were used. Synthesis was carried out on Domino Blocks (www.torviq.com) in disposable polypropylene reaction vessels.

The volume of wash solvent was 10 mL per 1 g of resin. For washing, resin slurry was shaken with the fresh solvent for at least 1 min before changing the solvent. After adding a reagent solution, the resin slurry was manually vigorously shaken to break any potential resin clumps. Resin-bound intermediates were dried by a stream of nitrogen for prolonged storage and/or quantitative analysis.

For the LC/MS analysis a sample of resin (~5 mg) was treated by 50% TFA in DCM, the cleavage cocktail was evaporated by a stream of nitrogen, and cleaved compounds extracted into 1 mL of MeOH or MeCN. The LC/MS analyses were carried out using two instruments. The first one comprised a 3 x 50 mm C18 reverse phase column, 5 um particles. Mobile phases: 10 mM ammonium acetate in HPLC grade water (A) and HPLC grade acetonitrile (B). A gradient was formed from 5% to 80% of B in 10 min, flow rate of 0.7 mL/min. The MS electrospray source operated at capillary voltage 3.5 kV and a desolvation temperature 300°C. The second instrument comprised a 2.1 x 50 mm C18 reverse phase column, 2.6 µm particles, at 30°C and flow rate of 0.8 mL/min. Mobile phases: 10 mM ammonium acetate in HPLC grade water (A) and HPLC grade acetonitrile (B). A gradient was formed from 10% to 80% of B in 2.5 min; kept for 1.5 min. The column was re-equilibrated with 10% solution B for 1 min. The APCI source

operated at discharge current of 5 μA, vaporizer temperature of 400°C and capillary temperature of 200°C.

Purification was carried out on C18 reverse phase column 19 x 100 mm, 5 μm, a 6 min gradient was formed from 10 mM aqueous ammonium acetate or 0.1 % aqueous TFA and acetonitrile in different proportions depending on the hydrophobicity of compounds (typically from 10-30% acetonitrile for polar compounds up to 50-70% acetonitrile for non-polar compounds), flow rate 15 mL/min.

**2.- Synthetic procedures**

**Acylation with bromoacetic acid (1)**

A fritted polypropylene reaction vessel charged with 1 g of DCM-swollen commercial Wang resin or Rink resin (Fmoc-deprotected by 20 min exposure to 50% piperidine in DMF, washed 3 times with DMF and 3 times with DCM). A solution of bromoacetic acid (700 mg; 5 mmol) was made in 10 mL DCM in a fritted syringe and DIC (386 μL; 2.5 mmol) was added. Precipitated *N,N'*-di-*i*-propylurea (DIU) was filtered after 10 min shaking, DIEA (436 μL; 2.5 mmol) was added and the solution was added to the syringe with previously swollen resin. The resin slurry was shaken at ambient temperature for 2 h and then washed 5 times with DCM. In the case of Rink resin the completeness of the acylation was checked using the Bromophenol Blue test.

**Reaction with propargylamine (2)**

A solution of propargylamine (640 μL; 10 mmol) and DIEA (1.74 mL; 10 mmol) in 10 mL DMF was added to resin **1** (1 g) previously swollen in DMF in a fritted polypropylene reaction vessel. The resin slurry was shaken at ambient temperature for 4 h, washed 3 times with DMF and 3 times with DCM.

Quantification of resin loading: a ~10 mg sample of resin was reacted with Fmoc-OSu (160 mg) in 1 mL DCM for 30 min at ambient temperature. The resin was washed 5 times with DCM, dried, exactly weighted and the product was cleaved from resin with TFA:DCM (1:1) for 30 min. The cleavage cocktail was evaporated by a stream of nitrogen, and cleaved compounds extracted into 1 mL of MeOH. These samples of Fmoc derivates were analyzed by LC/MS and the quantified using a standard of Fmoc-Ala-OH; concentration 1-4 mM in MeOH.

**Acylation with Fmoc-amino acid (3)**

A fritted polypropylene reaction vessel was charged with 1 g of DCM-swollen commercial Wang resin or Rink resin (Fmoc-deprotected by 20 min exposure to 50% piperidine in DMF, washed 3 times with DMF and 3 times with DCM). For Rink resin, a solution of amino acid (2 mmol), HOBt (2 mmol, 306 mg), and DIC (2 mmol, 312 mL) in 10 mL DMF:DCM (1:1) was added; for Wang resin the same solution reagents but adding DMAP (0.5 mmol, 61 mg) was added. The resin was shaken at room temperature overnight, and was washed 3 times with DMF and 3 times with DCM.

Quantification of resin loading: An analytical sample or resin **3** was dried, exactly weighted and the product was cleaved from resin with TFA:DCM (1:1) for 30 min. The cleavage cocktail was evaporated by a stream of nitrogen, and cleaved compounds extracted into 1 mL of MeOH. The released Fmoc amino acids were analyzed by LC/MS and quantified using standard of Fmoc-Ala-OH; concentration 1-4 mM in MeOH.

**Sulfonylation with 4-nitrobenzenesulfonyl chloride (4)**

A fritted polypropylene reaction vessel charged with resin **3** (1 g) was swollen with DMF and the Fmoc group was cleaved by 50% piperidine in DMF for 20 min as described above, then resin was washed 3 times with DMF and 3 times with DCM. A solution of 4-nitrobenzenesulfonyl

chloride (667 mg; 3 mmol) and lutidine (380 μL; 3 mmol) in 10 mL DCM was added to the resin and the reaction slurry was shaken at ambient temperature for 4 h. The resin was washed 5 times with DCM. The completeness of the reaction was checked by the Bromophenol Blue test, an analytical amount of resin **4** was cleaved by 50% TFA in DCM and the product was analyzed by LC/MS.

**Mitsunobu Alkylation with Alkynols (5)**

A fritted polypropylene reaction vessel charged with resin **4** (1 g) was swollen with anhydrous THF and then a solution of alkynol (3 mmol), $PPh_3$ (3 mmol, 780 mg) in 6 mL anhydrous THF was added to the reaction vessel. A 10 mL plastic reaction vessel was charged with a solution of DIAD (3 mmol, 600 μL) in 6 mL of anhydrous THF. This syringe was connected to the plastic reaction vessel containing the resin **4**. Connected syringes were left in a freezer for 30 min, and the DIAD solution was drawn into the syringe with the resin. The resin slurry was shaken, gradually warming up to room temperatureand continued shaking at room temperature for 16 h. The resin was washed 3 times with THF, 2 times with MeOH and 3 times with DCM. The resin **5** was checked by analytical cleavage with 50% TFA followed by LC/MS analysis.

**Cleavage of Nosyl Group (6)**

Resin **5** (1 g) was swollen with DMF, and then a solution of 2-mercaptoethanol (6 mmol, 420 μL) and DBU (2 mmol, 300 μL) in 10 mL of DMF was added. The resin was shaken at room temperature for 10 min. The resin was washed 3 times with DMF and 3 times with DCM.

**Urea Formation (7)**

Resins **2** and **6** (1 g) were washed 3 times with anhydrous THF and then solutions of isocyanate (2 mmol) in anhydrous THF (10 mL, 0.2 M) were added. The resin slurry was shaken at room temperature for 1 h. After that time, the resin was washed 3 times with THF and 3 times with

DCM. The completeness of the reaction was evaluated by Bromophenol Blue test, and the samples were checked by 50% TFA cleavage followed by LC/MS analysis. The released compounds were purified by semiprep HPLC and the final compounds were characterized by NMR spectroscopy.

**Gold-catalyzed cyclization (11)**

Resin **7** (0.25 g) was washed 3 times with anhydrous DCM and then a solution of AuCl (5 mol%, 5 μmol, 1.2 mg) in 3 mL anhydrous DCM:acetonitrile (5:1) was added. The reaction slurry was shaken at room temperature for 2 h. The resin was washed 3 times with DCM:acetonitrile and 3 times with DCM. The resins **11** were checked by 50% TFA cleavage followed by LC/MS analysis. The released compounds were purified by semiprep HPLC and the final compounds were characterized by NMR spectroscopy and HRMS.

ASSOCIATED CONTENT

**Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: Analytical Data of Individual Compounds, $^{1}H$, $^{13}C$ and 2D NMR, and IR spectra of the synthesized compounds.

AUTHOR INFORMATION

**Corresponding Authors**

*E-mail: testero@iquir-conicet.gov.ar ; vkrchnak@nd.edu

**Author Contributions**

†These authors contributed equally to this work.

**Funding Sources**

This research has been supported by Palacky University, POST-UP (CZ.1.07/2.3.00/30.0004), Czech Republic-Argentina Mobility project (SPP 463103061/32)- Cooperación bilateral MINCYT-MEYS (ARC/13/06), Agencia Nacional de Promoción Científica y Tecnológica (PICT-2011-0403), Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET, Argentina) and project 1.07/2.3.00/30.0004 from the European Social Fund.

**Notes**

The authors declare no competing financial interest

ACKNOWLEDGMENT

We thank Prof. Rodolfo M. Rasia and Andrea Coscia for the 700 Mhz NMR analyses.

REFERENCES

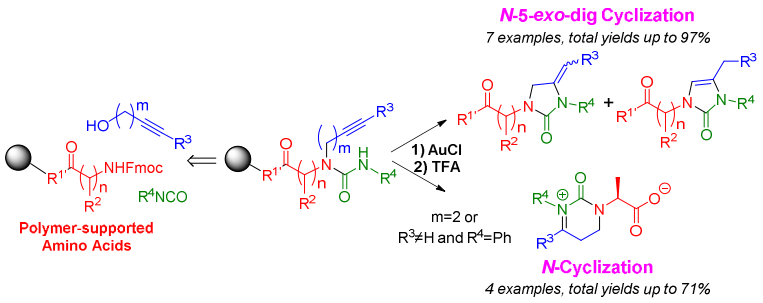
1. Testero, S. A.; Mata, E. G., Prospect of metal-catalyzed C-C forming cross-coupling reactions in modern solid-phase organic synthesis. *J. Comb. Chem.* **2008**, *10*, 487-497.
2. Zaragoza Dörwald, F., *Organic Synthesis on Solid Phase, 2nd ed.* Wiley-VCH: Weinheim, Germany, 2002.
3. Hashmi, A. S. K., Dual Gold Catalysis. *Acc. Chem. Res.* **2014**, *47*, 864-876.
4. Hashmi, A. S. K.; Hutchings, G. J., Gold catalysis. *Angew. Chem. Int. Ed.* **2006**, *45*, 7896-7936.
5. Furstner, A.; Davies, P. W., Catalytic carbophilic activation: Catalysis by platinum and gold pi acids. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410-3449.
6. Hashmi, A. S. K., Gold-catalyzed organic reactions. *Chem. Rev.* **2007**, *107*, 3180-3211.
7. Jimenez-Nunez, E.; Echavarren, A. M., Gold-catalyzed cycloisomerizations of enynes: A mechanistic perspective. *Chem. Rev.* **2008**, *108*, 3326-3350.
8. Li, Z. G.; Brouwer, C.; He, C., Gold-catalyzed organic transformations. *Chem. Rev.* **2008**, *108*, 3239-3265.
9. Gorin, D. J.; Sherry, B. D.; Toste, F. D., Ligand effects in homogeneous Au catalysis. *Chem. Rev.* **2008**, *108*, 3351-3378.
10. Hashmi, A. S. K.; Rudolph, M., Gold catalysis in total synthesis. *Chem. Soc. Rev.* **2008**, *37*, 1766-1775.
11. Furstner, A., Gold and platinum catalysis-a convenient tool for generating molecular complexity. *Chem. Soc. Rev.* **2009**, *38*, 3208-3221.
12. Das, A.; Abu Sohel, S. M.; Liu, R. S., Carbo- and heterocyclisation of oxygen- and nitrogen-containing electrophiles by platinum, gold, silver and copper species. *Org. Biomol. Chem.* **2010**, *8*, 960-979.

13. Rudolph, M.; Hashmi, A. S. K., Gold catalysis in total synthesis-an update. *Chem. Soc. Rev.* **2012**, *41*, 2448-2462.
14. Shen, H. C., Recent advances in syntheses of carbocycles and heterocycles via homogeneous gold catalysis. Part 2: Cyclizations and cycloadditions. *Tetrahedron* **2008**, *64*, 7847-7870.
15. La-Venia, A.; Testero, S. A.; Mischne, M. P.; Mata, E. G., Gold catalysis on immobilized substrates: a heteroannulation approach to the solid-supported synthesis of indoles. *Org. Biomol. Chem.* **2012**, *10*, 2514-2517.
16. Corma, A.; Leyva-Perez, A.; Sabater, M. J., Gold-Catalyzed Carbon-Heteroatom Bond-Forming Reactions. *Chem. Rev.* **2011**, *111*, 1657-1712.
17. Hashmi, A. S. K., Homogeneous gold catalysts and alkynes: A successful liaison. *Gold Bull.* **2003**, *36*, 3-9.
18. Ibrahim, N.; Vilhelmsen, M. H.; Pernpointner, M.; Rominger, F.; Hashmi, A. S. K., Gold Phenolate Complexes: Synthesis, Structure, and Reactivity. *Organometallics* **2013**, *32*, 2576-2583.
19. Khin, C.; Hashmi, A. S. K.; Rominger, F., Gold(I) Complexes of P,N Ligands and Their Catalytic Activity. *Eur. J. Inorg. Chem.* **2010**, 1063-1069.
20. Shen, H. C., Recent advances in syntheses of heterocycles and carbocycles via homogeneous gold catalysis. Part 1: Heteroatom addition and hydroarylation reactions of alkynes, allenes, and alkenes. *Tetrahedron* **2008**, *64*, 3885-3903.
21. Hashmi, A. S. K., Homogeneous Gold Catalysis Beyond Assumptions and Proposals-Characterized Intermediates. *Angew. Chem. Int. Ed.* **2010**, *49*, 5232-5241.
22. Arcadi, A., Alternative synthetic methods through new developments in catalysis by gold. *Chem Rev* **2008**, *108*, 3266-325.
23. Jimenez-Nunez, E.; Echavarren, A. M., Molecular diversity through gold catalysis with alkynes. *Chem. Commun.* **2007**, 333-346.
24. Rudolph, M.; Hashmi, A. S. K., Heterocycles from gold catalysis. *Chem. Commun.* **2011**, *47*, 6536-6544.
25. Pernpointner, M.; Hashmi, A. S. K., Fully Relativistic, Comparative Investigation of Gold and Platinum Alkyne Complexes of Relevance for the Catalysis of Nucleophilic Additions to Alkynes. *J. Chem. Theory Comput.* **2009**, *5*, 2717-2725.
26. Lein, M.; Rudolph, M.; Hashmi, S. K.; Schwerdtfeger, P., Homogeneous Gold Catalysis: Mechanism and Relativistic Effects of the Addition of Water to Propyne. *Organometallics* **2010**, *29*, 2206-2210.
27. Shen, H. C.; Graham, T. H., Gold-catalyzed formation of heterocycles – an enabling new technology for medicinal chemistry. *Drug Discov Today: Technol* **2013**, *10*, e3-e14.
28. Arcadi, A., Gold Catalyzed Synthesis of Heterocycles. In *Gold Catalysis: An Homogeneous Approach*, Toste, F. D.; Michelet, V., Eds. Imperial College Press: 2014; pp 175-224.
29. Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W., Gold catalysis: Mild conditions for the synthesis of oxazoles from N-propargylcarboxamides and mechanistic aspects. *Org. Lett.* **2004**, *6*, 4391-4394.
30. Hashmi, A. S. K.; Schuster, A. M.; Gaillard, S.; Cavallo, L.; Poater, A.; Nolan, S. P., Selectivity Switch in the Synthesis of Vinylgold(I) Intermediates. *Organometallics* **2011**, *30*, 6328-6337.

31. Testero, S. A.; Mata, E. G., Synthesis of 3-(aryl)alkenyl-beta-lactams by an efficient application of olefin cross-metathesis on solid support. *Org. Lett.* **2006**, *8*, 4783-4786.
32. Poeylaut-Palena, A. A.; Testero, S. A.; Mata, E. G., Solid-supported cross metathesis and the role of the homodimerization of the non-immobilized olefin. *J. Org. Chem.* **2008**, *73*, 2024-2027.
33. Poeylaut-Palena, A. A.; Testero, S. A.; Mata, E. G., The non-metathetic role of Grubbs' carbene complexes: from hydrogen-free reduction of alpha,beta-unsaturated alkenes to solid-supported sequential cross-metathesis/reduction. *Chem. Commun.* **2011**, *47*, 1565-1567.
34. Poeylaut-Palena, A. A.; Mata, E. G., Cross Metathesis on Solid Support. Novel Strategy for the Generation of beta-Lactam Libraries Based on a Versatile and Multidetachable Olefin Linker. *J. Comb. Chem.* **2009**, *11*, 791-794.
35. Robert, J. M. H.; Sabourin, C.; Alvarez, N.; Robert-Piessard, S.; Le Baut, G.; Le Pape, P., Synthesis and antileishmanil activity of new imidazolidin-2-one derivatives. *Eur. J. Med. Chem.* **2003**, *38*, 711-718.
36. Bronson, J. J.; DenBleyker, K. L.; Falk, P. J.; Mate, R. A.; Ho, H. T.; Pucci, M. J.; Snyder, L. B., Discovery of the first antibacterial small molecule inhibitors of MurB. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 873-875.
37. Chang, C. S.; Lin, Y. T.; Shih, S. R.; Lee, C. C.; Lee, Y. C.; Tai, C. L.; Tseng, S. N.; Chern, J. H., Design, synthesis, and antipicornavirus activity of 1- 5-(4-arylphenoxy)alkyl -3-pyridin-4-ylimidazolidin-2-one derivatives. *J. Med. Chem.* **2005**, *48*, 3522-3535.
38. Blass, B. E.; Fensome, A.; Trybulski, E.; Magolda, R.; Gardell, S. J.; Liu, K.; Samuel, M.; Feingold, I.; Huselton, C.; Jackson, C. M.; Djandjighian, L.; Ho, D.; Hennan, J.; Janusz, J. M., Selective Kv1.5 Blockers: Development of (R)-1-(Methylsulfonylamino)-3- 2-(4-methoxyphenyl)ethyl -4-(4-methoxyphe nyl)-2-imidazolidinone (KVI-020/WYE-160020) as a Potential Treatment for Atrial Arrhythmia. *J. Med. Chem.* **2009**, *52*, 6531-6534.
39. Carling, R. W.; Moore, K. W.; Moyes, C. R.; Jones, E. A.; Bonner, K.; Emms, F.; Marwood, R.; Patel, S.; Fletcher, A. E.; Beer, M.; Sohal, B.; Pike, A.; Leeson, P. D., 1-(3-cyanobenzylpiperidin-4-yl)-5-methyl-4-phenyl-1,3-dihydroimidazol-2- one: A selective high-affinity antagonist for the human dopamine D-4 receptor with excellent selectivity over ion channels. *J. Med. Chem.* **1999**, *42*, 2706-2715.
40. Xue, N.; Yang, X. C.; Wu, R.; Chen, J.; He, Q. J.; Yang, B.; Lu, X. Y.; Hu, Y. Z., Synthesis and biological evaluation of imidazol-2-one derivatives as potential antitumor agents. *Bioorg. Med. Chem. Lett.* **2008**, *16*, 2550-2557.
41. Sharma, V. K.; Lee, K. C.; Joo, C.; Sharma, N.; Jung, S. H., Importance of Imidazolidinone Motif in 4-Phenyl-N-arylsulfonylimidazolidinone for their Anticancer Activity. *Bull. Korean Chem. Soc.* **2011**, *32*, 3009-3016.
42. Abdel-Aziz, A. A. M.; El-Azab, A. S.; El-Subbagh, H. I.; Al-Obaid, A. M.; Alanazi, A. M.; Al-Omar, M. A., Design, synthesis, single-crystal and preliminary antitumor activity of novel arenesulfonylimidazolidin-2-ones. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2008-2014.
43. Gimeno, A.; Cuenca, A. B.; Medio-Simon, M.; Asensio, G., Gold(I)- Catalyzed Reactions of 1-(ortho-Alkynylaryl)ureas: Highly Selective Heterocyclization and Synthesis of Mixed N,O-Acetals. *Adv. Synth. Catal.* **2014**, *356*, 229-236.
44. Ye, D. J.; Wang, J. F.; Zhang, X.; Zhou, Y.; Ding, X.; Feng, E. G.; Sun, H. F.; Liu, G. N.; Jiang, H. L.; Liu, H., Gold-catalyzed intramolecular hydroamination of terminal alkynes in aqueous media: efficient and regioselective synthesis of indole-1-carboxamides. *Green Chem.* **2009**, *11*, 1201-1208.

45. Peshkov, V. A.; Pereshivko, O. P.; Sharma, S.; Meganathan, T.; Parmar, V. S.; Ermolat'ev, D. S.; Van der Eycken, E. V., Tetrasubstituted 2-Imidazolones via Ag(I)-Catalyzed Cycloisomerization of Propargylic Ureas. *J. Org. Chem.* **2011**, *76*, 5867-5872.
46. Campbell, M. J.; Toste, F. D., Enantioselective synthesis of cyclic carbamimidates via a three-component reaction of imines, terminal alkynes, and p-toluenesulfonylisocyanate using a monophosphine gold(I) catalyst. *Chem. Sci.* **2011**, *2*, 1369-1378.
47. Pereshivko, O. P.; Peshkov, V. A.; Jacobs, J.; Van Meervelt, L.; Van der Eycken, E. V., Cationic Gold- and Silver-Catalyzed Cycloisomerizations of Propargylic Ureas: A Selective Entry to Oxazolidin-2-imines and Imidazolidin-2-ones. *Adv. Synth. Catal.* **2013**, *355*, 781-789.
48. Pereshivko, O. P.; Peshkov, V. A.; Peshkov, A. A.; Jacobs, J.; Van Meervelt, L.; Van der Eycken, E. V., Unexpected regio- and chemoselectivity of cationic gold-catalyzed cycloisomerizations of propargylureas: access to tetrasubstituted 3,4-dihydropyrimidin-2(1H)-ones. *Org. Biomol. Chem.* **2014**, *12*, 1741-1750.
49. Carrettin, S.; Blanco, M. C.; Corma, A.; Hashmi, A. S. K., Heterogeneous gold-catalysed synthesis of phenols. *Adv. Synth. Catal.* **2006**, *348*, 1283-1288.
50. Jaimes, M. C. B.; Bohling, C. R. N.; Serrano-Becerra, J. M.; Hashmi, A. S. K., Highly Active Mononuclear NAC-Gold(I) Catalysts. *Angew. Chem. Int. Ed.* **2013**, *52*, 7963-7966.
51. Lothschutz, C.; Szlachetko, J.; van Bokhoven, J. A., Heterogenized Gold(I)-Carbene as a Single-Site Catalyst in Continuous Flow. *ChemCatChem* **2014**, *6*, 443-448.
52. Leikoski, T.; Kallonen, S.; Yli-Kauhaluoma, J., The Sonogashira Coupling of Polymer-Supported Propargylamine with Aryl Iodides. *Helv. Chim. Acta* **2010**, *93*, 39-47.
53. Longer reaction times did not affect the outcome of the reaction
54. Ranjan, A.; Yerande, R.; Wakchaure, P. B.; Yerande, S. G.; Dethe, D. H., Base-Mediated Hydroamination of Propargylamine: A Regioselective Intramolecular 5-exo-dig Cycloisomerization en Route to Imidazole-2-thione. *Org. Lett.* **2014**, *16*, 5788-5791.

Table of Contents Graphic and Synopsis




A small solid-phase library of imidazolidin-2-ones and imidazol-2-ones has been synthesized from propargylureas employing a high chemo- and regio-selective gold-catalyzed cycloisomerization. In all the cases only C-N gold-catalyzed functionalization was observed.