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Gold(I)-Catalyzed Reactions of 1-(*ortho*-Alkynylaryl)ureas: Highly Selective Heterocyclization and Synthesis of Mixed *N,O*-Acetals

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Dedicated to Prof. A. Laguna on occasion of his 65th birthday.

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Abstract: Readily available 1-(*ortho*-ethynylaryl)urea derivatives undergo a selective gold/silver {[AuCl(IPr)]/$AgSbF_6$} catalyzed *N*-6-*exo*-dig or *N*-5-*endo*-dig heterocyclization process in dimethylformamide (DMF) at 60 °C. Benzoxazine derivatives, i.e., the products of *O*-6-*exo*-dig ring closure through the urea oxygen, could be observed under catalytic conditions only when the *N*-3 basicity was substantially diminished, but were readily isolable in stoichiometric processes carried out at low temperature. The open chain amino *O,O*-acetals and a series of new cyclic mixed *N,O*-acetals containing the trifluoroethyl group were synthesized when the reactions were performed in ethanol or trifluoroethanol, respectively, as solvent. The procedure allows for an easy access to this versatile class of key intermediates in organic synthesis from simple starting materials. The effect of using either DMF or protic solvents on the course of the reactions is reported.

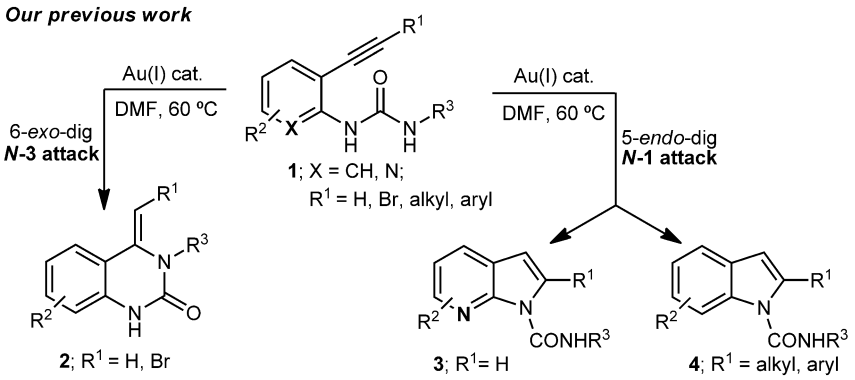
Keywords: alkynes; gold; hydroamination; regioselectivity

Introduction

Homogeneous gold catalysis is a powerful synthetic tool, which is becoming increasingly useful with new transformations being discovered almost on a daily basis.[1] Specifically, the exceptional ability of this metal to activate π systems, especially alkynes, towards nucleophilic attack enables an easy approach to heterocycles,[2] although the desired *endo*/*exo*-dig selectivity in the triple bond activation is not always attained.[3] Alkynyl compounds carrying ambident nucleophiles, such as amides or carbamates, further expand the array of the possible regioisomeric product given that the heterocyclization can now take place either through *O*- or *N*-ring closure processes.[4–6] In some cases, intrinsic geometric restrictions in the substrate framework preclude one or more of these routes resulting in a selective cyclization. Alkynylureas[7–13] constitute a particularly challenging case since three potential nucleophiles and two electrophilic carbon atoms coexist in the molecule, increasing the number of possible regioisomers. The intrinsic potential of this class of transformations prompted us to report in a preliminary communication the distinct cyclization paths followed by the alkynylurea derivatives **1** (Scheme 1).[7] Thus, we found that the [AuCl(IPr)]/$AgSbF_6$ catalytic system was very efficient in promoting in DMF at 60 °C exclusively the *N*-6-*exo*-dig hydroaminative cyclization of a wide variety of 1-(*ortho*-ethynylaryl)ureas **1**[14] carrying electron-donating or electron-withdrawing substituents at the aromatic ring and a variety of alkyl or aryl R^3 groups attached at the N-3 position, to give quinazolin-2-ones **2**.

Compounds **1** containing a pyridine ring or derived from internal alkynes could, at the same time, also serve as precursors for the pyrrolopyridine **3** or indole **4** rings,[15] through the commonly favored 5-*endo*-dig cyclization process (Scheme 1).[16,17]

In contrast to our results, a similar Au(I)-catalyzed reaction of 1-(*ortho*-ethynylaryl)ureas bearing a terminal alkyne reported by Liu[8] led exclusively to the corresponding indole derivatives **3** under microwave heating. Shortly afterwards, Toste et al.[9] described the Au(I)-catalyzed preparation of propargylic ureas in the three-component reaction of an imine, an



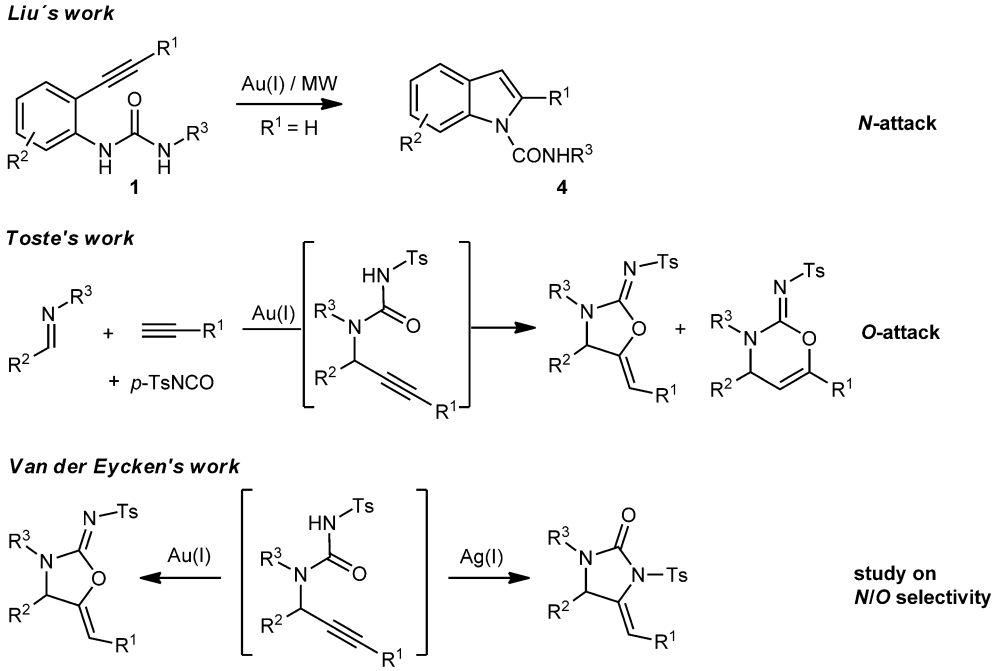
Scheme 1. Gold-catalyzed heterocyclization of 1-(*ortho*-alkynylaryl)ureas **1**.

alkyne and tosyl isocyanate, followed by their subsequent *in situ O*-cyclization (Scheme 2).

Almost simultaneously, Van der Eycken[10] reported the Ag(I)-catalyzed *N*-cyclization of propargylic ureas derived from secondary propargylic amines and, later,[11] a detailed comparative study of the selective *O*- and *N*-cycloisomerization of propargylic ureas with Au(I) and Ag(I) catalysts (Scheme 2). Other studies have confirmed that Ag(I) and other coinage metals catalyze the *O*-cyclization of structurally related *o*-alkynylbenzamides.[5b–d]

Importantly, these reports of the Au(I)-catalyzed *O*-heterocyclization of propargylic ureas and Ag(I)-catalyzed *O*-cyclization of *o*-alkynylbenzamides are in sharp contrast with our findings of the exclusive *N*-cyclization observed for the 1-(*ortho*-alkynylaryl)ureas (Scheme 1).[7]

Hence, the synthetic potential of the heterocyclization reaction of the substituted alkynes, coupled with the somewhat puzzling results summarized above led us to follow up on our preliminary study[7] on the products obtained from (*ortho*-alkynylaryl)ureas in Au(I)-catalyzed reactions in order to clarify in particular the origin of the *N*/*O* selectivity reported and further explore the synthetic scope of these transformations. Here, we update our preliminary report with our study of these reactions at low temperature or in protic solvents leading to the selective synthesis of benzoxazines, acetals or mixed *N,O*-acetals depending on the reaction conditions.

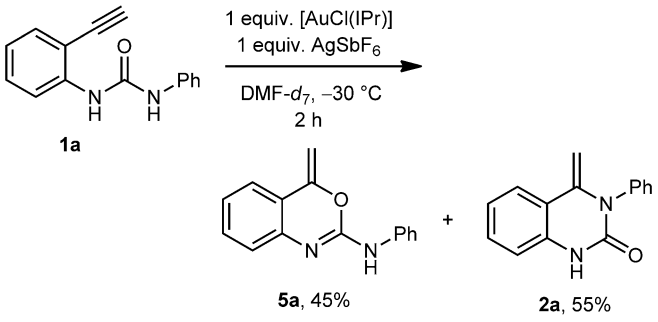


Scheme 2. Other gold(I)-catalyzed cyclization reactions of alkynylureas.

Results and Discussion

N/O Selectivity in the 6-*exo*-dig Cyclization

Products resulting from the nucleophilic attack of the urea oxygen atom in the ring closure reaction of alkynylureas **1** were never observed under our standard conditions ([AuCl(L)]/$AgSbF_6$, DMF, 60 °C)[7] with independence of the ligand present in the Au(I) catalytic species, even though these compounds should be expected to be produced under kinetic control[18] in the heterocyclization reaction. The reaction of **1a** in DMF-d_7 at −30 °C catalyzed with 10 mol% [AuCl(IPr)] and 15 mol% $AgSbF_6$ was selected to follow the evolution of the process by NMR. This catalytic system was selected since it affords exclusively the *N*-6-*exo*-dig heterocyclization product.[7] The starting alkynylurea remained unaltered after 16 h at this low temperature, but was transformed gradually into quinazolin-2-one **2a** when the sample was warmed slowly to 20 °C; the formation of benzoxazine **5a** resulting from the *6-exo*-dig oxygen attack could not even be detected. To accelerate the reaction at low temperature, **1a** was treated with a stoichiometric amount of [AuCl(IPr)]/$AgSbF_6$ in DMF-d_7 at −30 °C in an NMR tube. After 2 h at this low temperature, the formation of an equimolecular mixture of **2a** and **5a** was observed. Compounds **2a** and **5a** could be isolated and fully characterized from this mixture after eliminating the catalyst by filtration on alumina at −30 °C (see Experimental Section) (Scheme 3).

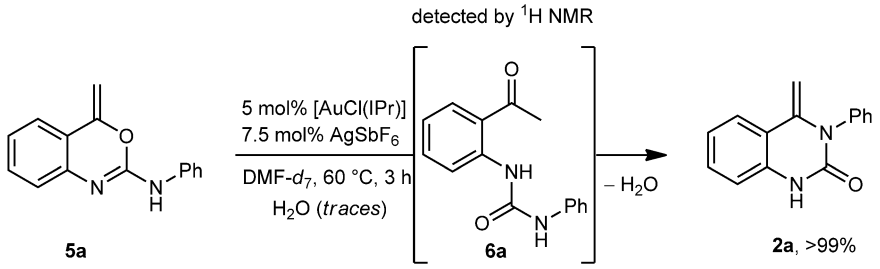


Scheme 3. Stoichiometric cyclization of urea **1a** with [AuCl(IPr)]/$AgSbF_6$ at −30 °C.

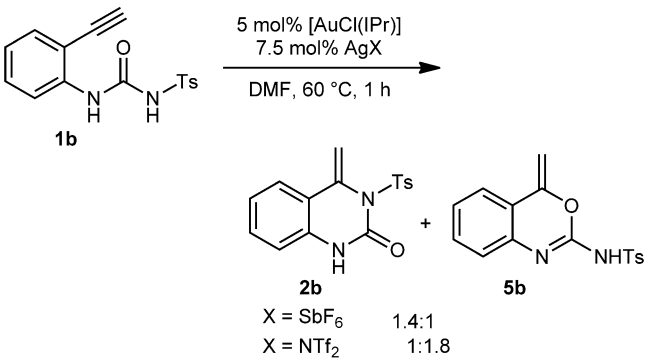
According to these experiments, benzoxazines **5** seem to be the kinetic products in the 6-*exo*-dig cyclization of 1-(*ortho*-alkynylaryl)ureas, which could be observed and isolated only in reactions performed at low temperature but not in catalytic reactions which require higher temperatures to be efficient. Moreover, to reproduce the conditions of the catalytic reaction, benzoxazine **5a** was heated to 60 °C in the presence of 5 mol% [AuCl(IPr)]/7.5 mol% $AgSbF_6$ in DMF; after 3 h, full conversion of **5a** into quinazolin-2-one **2a** was observed (Scheme 4). In contrast, **5a** was recovered intact in the absence of catalyst under similar conditions of solvent and temperature. These experiments would explain why **5a** was never detected in the catalytic heterocyclization reaction of **1a**.

Transient presence of ketone **6a**, generated most probably in the gold-catalyzed hydrolysis of benzoxazine **5a**, was detected when the transformation of **5a** into **2a** was carefully monitored by ^{1}H NMR (Scheme 4).[19] Similar results were observed for reactions promoted with the [Au(PPh_3)]SbF_6 cationic complex under the same conditions. In other words, only formation of benzoxazine **5a** was observed at −30 °C under stoichiometric conditions; but compound **5a** could not be even detected when the reactions were performed under catalytic conditions at 60 °C.[19]

Consequently, the adventitious presence of trace amounts of water in the reaction medium due to the highly hygroscopic nature of silver hexafluoroantimonate used in the catalytic system would justify, at least in part,[20] that the formation of the benzoxazine **5a** was not be observed under catalytic conditions at 60 °C. To minimize the water content in the reaction medium, we explored the cyclization of **1a** promoted by the catalytic cationic complex [Au(IPr)]NTf_2 (5 mol%) in DMF at 60 °C. However, even under these conditions, quinazolin-2-one **2a** was the only product observed.[21] The vinyl ether function in benzoxazine **5a** appeared to be quite reactive under our reaction conditions since **2a** derives from **5a** by hydrolysis and subsequent condensation. It should be noted that water is necessary only in catalytic amount for this isomerization.



Scheme 4. [AuCl(IPr)]/$AgSbF_6$-catalyzed conversion of **5a** into **2a** where ketone **6a** was detected as intermediate.



Scheme 5. Gold-catalyzed heterocyclization of urea **1b**.

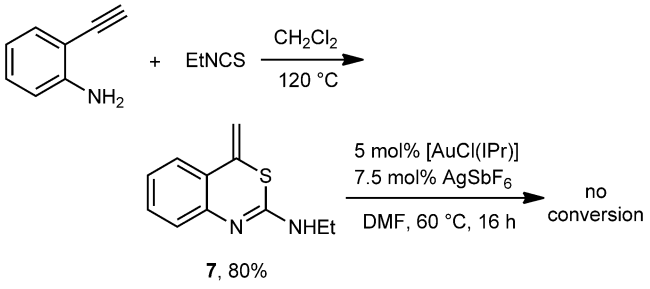
In a further attempt to obtain a benzoxazine less prone to the hydrolysis, we synthetized alkynylurea **1b** from the commercially available tosyl isocyanate.[9–11] The carbonyl oxygen and the N-3 nitrogen atoms should be less basic than in the ureas previously tested. In this case, benzoxazine **5b** was indeed more stable and could be prepared with catalytic [AuCl(IPr)]/$AgSbF_6$ in DMF at 60 °C mixed with quinazolin-2-one **2b** in a 1:1.4 ratio. The dependence of the **5b**:**2b** ratio on the catalytic system used was evidenced by the reverse 1.8:1 value observed when the reaction was promoted with the less hygroscopic cationic complex [Au(IPr)]NTf_2 (Scheme 5).

In this sense, we also tested the stability of the sulfur analogous of benzoxazine **5**. However, 1-(2-ethynylphenyl)-3-ethylthiourea could not be isolated upon heating a mixture of *ortho*-ethynylaniline and ethyl isothiocyanate in DCM at 120 °C in a sealed tube. Instead, the thermal 6-*exo*-dig metal-free heterocyclization product **7** was obtained (Scheme 6). The product was found to be very stable and did not isomerize after heating at 60 °C for 16 h in DMF in presence of 5 mol% [AuCl(IPr)]/$AgSbF_6$ (Scheme 6). The different behavior of ethynylureas and thioureas in the heterocyclization reaction, as well as the differences found in the behavior of the cyclic derivatives **5** and **7**, agree well with the usual reactivity shown by carbonyl and thiocarbonyl compounds.[22]

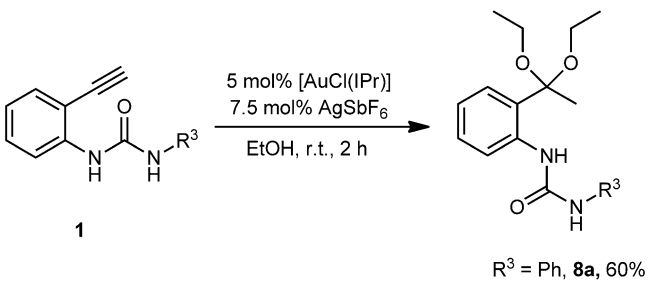
Mixed *N,O*-Acetals

The easy Au(I)-promoted hydrolysis of benzoxazine **5a** prompted us to study the Au(I)-catalyzed heterocyclization of alkynylureas **1** in a protic medium. The reaction of alkynylurea **1a** with 5 mol% [AuCl(IPr)]/7.5 mol% $AgSbF_6$ in EtOH at room temperature gave the open chain acetal **8a** in 60% yield (Scheme 7). Two alternative or simultaneous reaction pathways would account for the formation of the observed acetal, namely (i) the direct Au(I)-catalyzed intermolecular addition of ethanol to the terminal alkyne[23] and/or (ii) the Au(I)-catalyzed solvolysis of the intramolecular benzoxazine **5a**. The open chain acetal derived from alkyl-substituted urea **1c** (R^3 = Et) was detected by ^{1}H NMR but was quite unstable and could not be isolated, giving rise to an inseparable mixture of the corresponding cyclic mixed *N,O*-acetal and quinazoline **2c** which evolved to give pure **2c** after several hours.

However, the reaction of 0.1 M solutions of representative *N*-3 substituted alkynylureas **1** in trifluoroethanol at 40 °C with 5 mol% of [AuCl(IPr)]/$AgSbF_6$ catalyst gave the heterocyclic mixed *N,O*-acetals **9** (see Table 1) in generally satisfactory yields. Mixed *N,O*-acetals are key intermediates in carbon-carbon bond-forming reactions[24] and the method developed herein for these compounds is simple, mild and proceeds with readily available starting materials.[25] Several structural modifications were introduced in ureas **1** to determine the scope of the formation of the fluorine containing mixed acetals **9**. Typical N-3 alkyl-substituted ureas yielded compounds **9** with good yield regardless of the structure of the N-3 alkyl substituent (entries 2, 3 and 4, Table 1). Conversely, the reaction was less efficient with compounds bearing a less nucleophilic N-3 nitrogen such as the phenyl-, benzyl- or allyl-substituted ureas **1a**, **1f** and **1g**, providing lower yields of the corresponding fluorinated mixed acetals **9**. The influence of the substituents on the core aromatic ring was also evaluated. The mixed *N,O*-acetal **9h** was obtained with good yield from the corresponding urea **1h**.

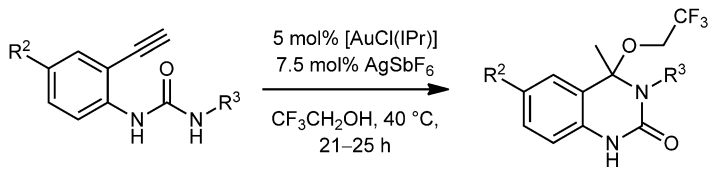


Scheme 6. Direct cyclization of *ortho*-ethynylaniline with ethyl isothiocyanate.

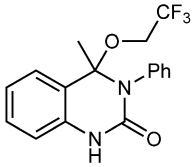
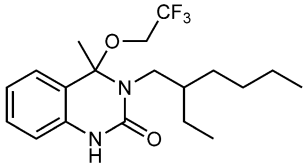
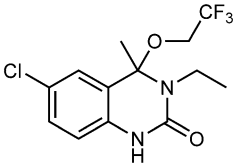
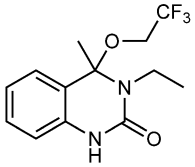
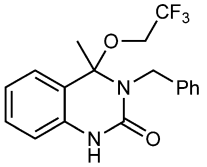
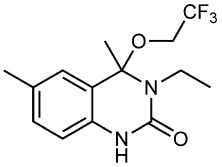
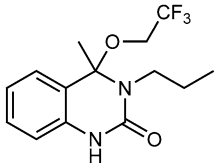
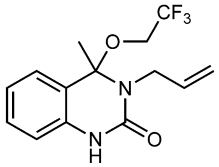
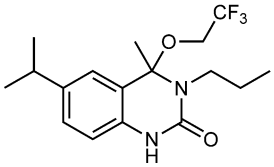


Scheme 7. Gold(I)-catalyzed reactions of alkynylureas **1** in EtOH.

Table 1. Synthesis of fluorinated mixed acetals **9** through Au(I)-catalyzed intramolecular hydroamination reactions of 1-(*o*-ethynylaryl)ureas **1** in CF_3CH_2OH.



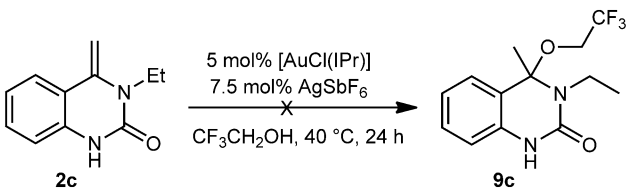
1 **9**

Entry	Mixed acetals **9**	Entry	Mixed acetals **9**	Entry	Mixed acetals **9**
1	 **9a**,[b] 23% R^2 = H, R^3 = Ph	4	 **9e**, 64% R^2 = H, R^3 = 3-ethylheptyl	7	 **9h**, 67% R^2 = Cl, R^3 = Et
2	 **9c**, 61% R^2 = H, R^3 = Et	5	 **9f**,[b] 27% R^2 = H, R^3 = Bn	8	 **9i**,[b] 30% R^2 = Me, R^3 = Et
3	 **9d**, 65% R^2 = H, R^3 = Pr	6	 **9g**,[b] 37% R^2 = H, R^3 = allyl	9	 **9j**,[b] 42% R^2 = *i*-Pr, R^3 = Pr

[a] Isolated yields.
[b] Formation of the corresponding open chain acetals **10** (13–25% yields) was observed.

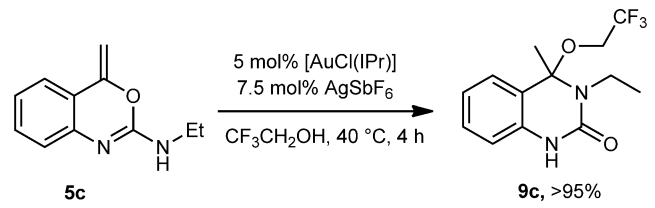
However, the presence of electron-donating substituents (R^2 = Me and R^2 = *i*-Pr) on this ring of the starting urea **1** decreased the efficiency of the formation of the mixed acetals **9i** and **9j** (see entries 8 and 9 Table 1).[26] The formation of the aforementioned new mixed *N*,*O*-acetals **9** should be attributed most probably to the poor nucleophilic character of trifluoroethanol compared to water or ethanol, and the efficiency of their preparation is also a function of the nucleophilic character of the N-3 urea nitrogen. In addition, to proceed efficiently the reaction requires neat trifluoroethanol as solvent. The use of a 4:1 or 2:1 TFE/DMF solvent under similar conditions only gave the corresponding quinazolin-2-ones **2**.

To get a better insight into the mechanism of the formation of compounds **9**, several experiments were performed. First, we heated a solution of quinazolin-2-one **2c** in TFE at 40 °C in the presence of 5 mol% [AuCl(IPr)]/7.5 mol% $AgSbF_6$; after 24 h compound **2c** was recovered unchanged. This experiment allowed us to exclude the protodemetallated compounds **2** as precursors in the formation of *N*,*O*-acetals **9** (Scheme 8).

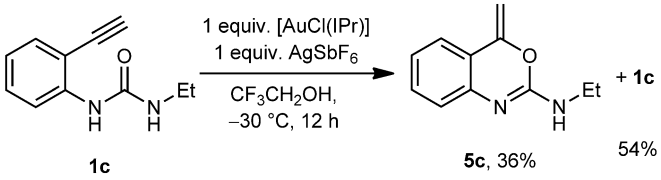


2c **9c**

Scheme 8. Attempted transformation of **2c** into **9c**.



Scheme 9. Catalytic conversion of **5c** into **9c**.



Scheme 10. Stoichiometric cyclization of urea **1c** with [AuCl(IPr)]/$AgSbF_6$ at −30 °C in TFE.

Then, we decided to explore compounds **5** as possible reaction intermediates in this transformation. The trifluoroethoxydihydroquinazolin-2-one **9c** was obtained with >95% yield when a TFE solution of **5c** was heated for 4 h with 5 mol% [AuCl(IPr)]/7.5 mol% $AgSbF_6$ (Scheme 9).

This fact strongly suggests that benzoxazines **5**, the kinetic cyclization products from alkynylureas **1**, react with TFE under our reaction conditions to give the corresponding mixed *N*,*O*-acetals **9**.[27] Thus, to detect a possible kinetic intermediate in this reaction, equimolecular amounts of urea **1c** and the gold complex [AuCl(IPr)]/$AgSbF_6$ in TFE were allowed to react at −30 °C and the mixture was left standing for 12 h at this low temperature (Scheme 10) (for additional details see the Supporting Information). Formation of benzoxazine **5c** mixed with the starting material was observed by ^{1}H NMR while the generation of quinazolin-2-one **2c** was inhibited under these conditions.

These results would explain the fact that the formation of compounds **9** is favored when the basicity of the urea N-3 position is increased with the introduction of alkyl substituents. Accordingly, the less basic N-3 substituted ureas **1a**, **1f** and **1g** allow the competitive incorporation of a second molecule of TFE with formation of the corresponding open chain acetals **10**.[28]

Conclusions

In conclusion, Au(I)-catalyzed hydroamination of the readily available 1-(*ortho*-ethynylaryl)ureas at 60 °C in DMF allows the selective preparation of quinazolin-2-one and indole derivatives through a 6-*exo*-dig or a 5-*endo*-dig *N*-heterocyclization process, respectively, with high to good yields. Alkyl or aryl substituents at N-3 have little influence on the course of the reaction, but internal alkynes undergo exclusively 5-*endo*-dig *N*-heterocyclization. The benzoxazine ring, the kinetic framework expected from a 6-*exo*-dig ring closure through the urea oxygen, is only partially formed under catalytic conditions when the basicity at N-3 is substantially diminished by tosyl substitution. Conversely, benzoxazines were isolated in the processes carried out at low temperature. Reactions were slow under these conditions and were accelerated by using Au(I) in stoichiometric amount to achieve an acceptable conversion. The adventitious presence of trace amounts of water in the reaction medium, difficult to avoid due to the highly hygroscopic nature of solvent and catalyst, justifies why benzoxazine derivatives are never observed in the reactions of the normal ureas under catalytic conditions at 60 °C. However, a transient presence of the ketone resulting from hydrolysis of the benzoxazine ring could be detected by ^{1}H NMR. Carrying out the catalytic reactions in ethanol, instead of DMF the corresponding open chain amino *O*,*O*-acetals were isolated. Use of trifluoroethanol, a less basic alcohol, as solvent allows us to modify the outcome of the solvolysis reaction and obtain, in this manner, a series of new mixed *N*,*O*-acetals containing the trifluoroethyl group a simple manner from readily available starting materials.

Experimental Section

Representative Procedure for the Gold(I)-Mediated Hydroaminative Cyclization of 1-(*ortho*-Ethynylphenyl)-3-phenylurea (1a); Synthesis of Benzoxazine 5a

A solution of 1-(2-ethynylphenyl)-3-phenylurea **1a** (0.062 mmol) in DMF-d_7 (30 μL) was added to an NMR tube containing a solution of [Au(IPr)]SbF_6 (0.062 mmol) (generated from a stoichiometric mixture of [AuCl(IPr)] and $AgSbF_6$) in DMF-d_7 (0.5 mL) at −30 °C. The tube was shaken and placed in the probe of an NMR spectrometer precooled at −30 °C and the reaction was monitored by ^{1}H NMR. ^{1}H NMR analysis after 2 h revealed complete conversion of urea **1a** in the corresponding quinazolin-2-one **2a** and benzoxazine **5a** in a 1.2:1 ratio.

Representative Procedure for Gold(I)-Catalyzed Heterocyclization of Ureas 1 in TFE: Synthesis of Mixed *N,O*-Acetals 9

An oven-dried resealable test tube with a Teflon stirring bar was charged with 1-(*ortho*-ethylaryl)urea **1** (0.5 mmol) dissolved in dried CF_3CH_2OH (4 mL). Subsequently, [AuCl(IPr)] (5 mol%) and $AgSbF_6$ (7.5 mol%) were added. The tube was sealed with a Teflon screw-cap and placed in an oil bath at 40 °C. The reaction mixture was heated at this temperature and stirred for 20 h. Next, the mixture was cooled

to room temperature, diluted with dichloromethane (2–3 mL), and filtered over activated aluminum oxide. The solvent was removed under reduced pressure and the fluorinated mixed *N,O*-acetals **9** were isolated by silica gel column chromatography (hexane/ethyl acetate).

Further experimental details, characterization of all new isolated compounds, and copies of ^{1}H and ^{13}C NMR spectra for quinazolin-2-ones **2**, indoles **3** and **4**, benzoxacines **5**, acetals **8** and fluorinated compounds **9** are available in the Supporting Information.

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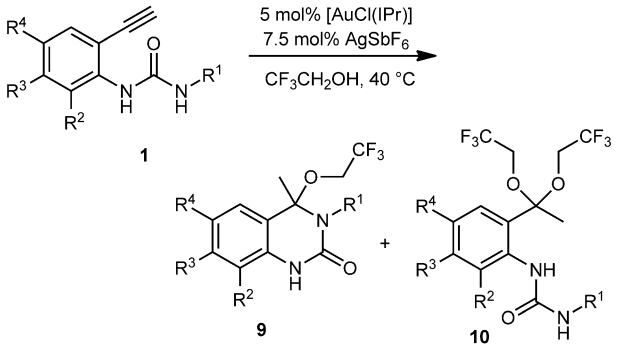

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