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Modular approach to non-aromatic and aromatic pyrroles through gold-catalyzed [3 + 2] cycloaddition of 2*H*-azirines and ynamides†

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The developed modular approach to hard-to-reach non-aromatic 3*H*- and 2*H*-pyrroles is based on the integration of 2*H*-azirines and ynamides. Gold-catalyzed [3 + 2] cycloaddition of 2,2-disubstituted 2*H*-azirines and ynamides constitutes a high-yielding route to 5-amino-3*H*-pyrroles. This reaction proceeds under mild conditions ($HAuCl_4$ 5 mol%, DCM, rt) and demonstrates high functional group tolerance (more than 30 examples; yields up to 98%). As a further branch of the proposed synthetic route, we also elaborated a smooth acid-promoted 1,5-shift-based isomerization of the obtained 5-amino-3*H*-pyrroles to fully substituted 5-amino-2*H*-pyrroles (18 examples; yields up to 86%). Furthermore, if 2-substituted 2*H*-azirine-2-carboxylic acid is employed for the cycloaddition with ynamide, a subsequent decarboxylation leads to an aromatic 2-amino-1*H*-pyrrole scaffold.

Introduction

The pyrrole core is an essential structural motif, which is widely presented in a plethora of natural and artificial products.[1–6] While 1*H*-pyrroles are textbook heterocyclic compounds, non-aromatic 2*H*- and, especially, 3*H*-pyrroles are far less studied[7,8] mostly because of their thermodynamic instability that is reflected by the easy aromatization of 2*H*- and 3*H*-pyrroles to 1*H*-isomers.[9–11]

Despite the limited availability and rather small number of obtained and studied 3*H*- and 2*H*-pyrroles, even at this stage it is clear that further development of approaches leading to these heterocyclic species could be beneficial from a medicinal chemistry viewpoint. Indeed, already reported 3*H*- and 2*H*-pyrrole-based systems demonstrate promising therapeutic potential for the treatment of Alzheimer's disease[12] and also function as potent antibiotic[13,14] or antitumor[15] agents. Some plant alkaloids[16,17] (namely, Calyciphylline G[18] and Chamobtusin A[19]) contain the 2*H*-pyrrole motif; both 3*H*- and 2*H*-pyrrole cores are parts of Precorrin-6x[20] – a macrocyclic precursor of vitamin B_{12}. Moreover, the high synthetic potential of 3*H*-pyrroles, which have found application as hetero-dienes in the Diels–Alder reaction, has been convincingly proven.[21–23]

In recent years, significant efforts have been made to construct 3*H*-[24–28] and 2*H*-[24,25,29–35] pyrroles. Some of the reported synthetic schemes are based on the dearomatizations of 1*H*-pyrroles; typically, these reactions proceed under harsh conditions.[31,32] The cyclization of complex prefunctionalized substrates into 3*H*- and 2*H*-pyrroles requires a tedious assembly of the corresponding precursors.[29,34,35] To overcome these limitations, several modular synthetic methods have been proposed; however, they are either of a limited scope,[24,27,30] or employ inconvenient starting materials[25,26] (*e.g.*, malodorous and toxic isocyanides[36]). Considering all these data, one can conclude that the development of expedient modular protocols for the syntheses of these heterocycles comprises a challenging task.

Both 2*H*-azirines and ynamides are convenient molecular building blocks with great potential for the modular synthesis of heterocyclic compounds. In this work, we present a novel methodology, based on the integration of these easily accessible substrates. Our approach provides a full diversity of pyrrole systems, first of all non-aromatic 3*H*- and 2*H*-pyrroles, and also aromatic 1*H*-products (Scheme 1).

We report herein that, firstly, a facile gold-catalyzed formal [3 + 2] cycloaddition of 2,2-disubstituted 2*H*-azirines and ynamides leads to 5-amino-3*H*-pyrroles. Secondly, a smooth formal 1,5-shift-based isomerization of the obtained 5-amino-

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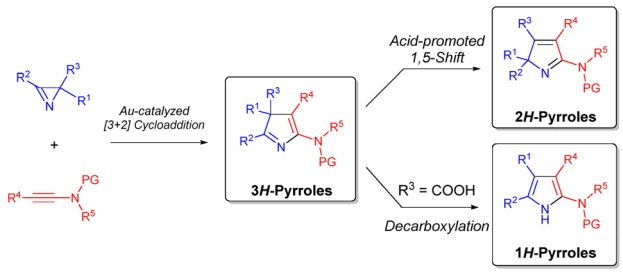
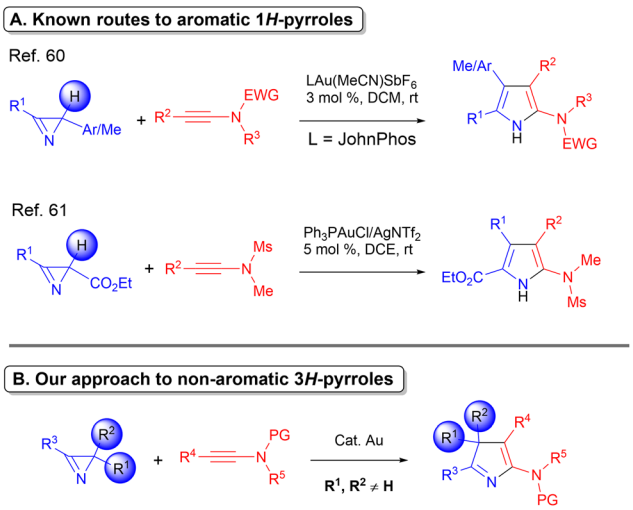


Scheme 1 Our synthetic strategy to achieve non-aromatic and aromatic pyrroles.



Scheme 2 Au-Catalyzed [3 + 2] cycloadditions of 2*H*-azirines and ynamides.

3*H*-pyrroles to 5-amino-2*H*-pyrroles proceeds under acidic conditions; the reaction can be performed in a one-pot manner starting from 2*H*-azirines and ynamides. Thirdly, if 2-substituted 2*H*-azirine-2-carboxylic acid is employed for the gold-catalyzed cycloaddition, a subsequent mild decarboxylation leads to the 2-amino-1*H*-pyrrole scaffold. All our data on this divergent synthetic strategy are discussed in detail in the following sections.

Results and discussion

2*H*-Azirines, as easily accessible building blocks, have been actively employed for an easy increase of the molecular complexity.[37–43] Owing to the intrinsic strain, 2*H*-azirines can undergo a facile ring opening, and thus function as C–C–N or C–N–C triatomic synthons. In turn, ynamides are customizable, highly reactive alkynes, *i.e.* C–C diatomic synthons, and some impressive examples of their synthetic applications have been reported in the chemical literature[44–54] (including our recent works in this direction[55–59]). If the retrosynthetic approach is applied, it would be expected that the integration of 2*H*-azirines and ynamides could lead to pyrrole products formed *via* the formal [3 + 2] cycloaddition.

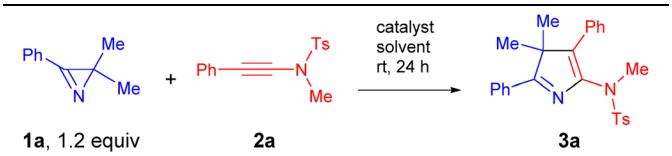
Indeed, two reported methods toward the preparation of *aromatic* 1*H*-pyrroles are based on gold-catalyzed [3 + 2] cycloaddition of 2*H*-azirines and ynamides (Scheme 2A).[60,61] In these reactions, two different types of 2*H*-azirine ring opening occurred, and this diverse reactivity provided different substitution patterns in the formed products. Remarkably, all thus generated 1*H*-pyrroles contained NH-fragments, and the *N*-fixed hydrogens certainly came from the 2nd positions of the starting 2*H*-azirines.

Guided by our interest in the construction of non-aromatic pyrroles, we assumed that the application of 2,2-disubstituted 2*H*-azirines – as the triatomic building blocks in gold-catalyzed [3 + 2] cycloaddition with ynamides – would provide an easy modular access to 3*H*-pyrroles (Scheme 2B). Essentially, in the context of generation of non-aromatic pyrroles, the R^1/R^2-substituents should not be hydrogens, to prevent the tautomerization of the potential 3*H*-products to the corresponding 1*H*-pyrroles.

Gold-catalyzed generation of non-aromatic 3*H*-pyrroles

To validate our hypothesis, we studied an interplay between 2,2-dimethyl-3-phenyl-2*H*-azirine (**1a**) and ynamide **2a** under gold-catalyzed[62–65] conditions (Table 1). In accordance with our expectations, the employment of 5 mol% of $Ph_3PAuNTf_2$ (in DCE at 60 °C for 3 h), as an activator, led to the product of the [3 + 2] cycloaddition, namely non-aromatic 5-amino-3*H*-pyrrole **3a** (85% ^{1}H NMR yield; entry 1). This reaction can also be carried out at room temperature for 24 h (entry 2). Other commonly used gold(I)-based catalysts ($IPrAuNTf_2$ or $JohnPhosAuNTf_2$) were significantly less effective (17–35% yields; entries 3 and 4). We also tested gold(III)-based species

Table 1 Optimization of the gold-catalyzed synthesis of **3a**



1a, 1.2 equiv **2a** **3a**

Entry[a]	Catalyst, mol%	Solvent	Yield,[b] %
1	$Ph_3PAuNTf_2$, 5	DCE	85[c]
2	$Ph_3PAuNTf_2$, 5	DCE	77
3	$IPrAuNTf_2$, 5	DCE	17
4	$JohnPhosAuNTf_2$, 5	DCE	35
5	$PicAuCl_2$, 5	DCE	88
6	$HAuCl_4$, 5	DCE	90
7	**$HAuCl_4$, 5**	**DCM**	**92**
8	$HAuCl_4$, 5	MeCN	82
9	$HAuCl_4$, 5	THF	87
10	$HAuCl_4$, 3	THF	63
11	$HAuCl_4$, 1.5	THF	48
12	TfOH, 100	DCM	None
13	$BF_3{\cdot}Et_2O$, 100	DCM	None

[a] All reactions were carried out on a 0.1 mmol scale (0.2 M). [b] Estimated by ^{1}H NMR spectroscopy using durene as an internal standard. [c] 60 °C, 3 h.

($PicAuCl_2$, $HAuCl_4$; entries 5 and 6) as catalysts for the cycloaddition, and an inexpensive chloroauric acid showed the best result (90% yield). DCM, THF, and acetonitrile can also be used as solvents for the synthesis of **3a** (entries 7–9). The reduced catalytic load of $HAuCl_4$ negatively affected the process (entries 10 and 11). Triflic acid and $BF_3{\cdot}Et_2O$ were completely inactive even at 100 mol% loading (entries 12 and 13); all these indirectly confirmed the essential roles of gold(I) and gold(III) in the studied [3 + 2] cycloaddition.

Summarizing, the best yield of **3a** was achieved with 5 mol% of $HAuCl_4$ in DCM at room temperature after 24 h (92%; entry 7).

With the optimal conditions in hand, the substrate scopes and limitations of the gold-catalyzed [3 + 2] cycloaddition were examined (Table 2). We first tested diverse ynamides **2** in their reactions with the model azirine **1a** (Table 2, top panel). Various nitrogen-protecting sulfonyl groups were compatible under the optimal conditions and the corresponding 3*H*-pyrroles **3a–d** were obtained in good to excellent isolated yields (77–98%). The methodology was also compatible with protected alcohol fragments (methylenedioxy and *t*-butyldimethylsilyloxy; products **3g** and **3h**). The ynamides bearing both *N*-aliphatic (**2a,e–h**) and *N*-aromatic (**2i**) substituents reacted smoothly. A variety of *o*-, *m*-, *p*-substituted aromatic (**3j–p**) and heteroaromatic (**3q–r**) fragments can be introduced into the 4th position of 3*H*-pyrroles; in these cases, the electronic and steric properties of the substituents insignificantly affected the yields. The method was also applicable for the synthesis of 4-alkenyl- and 4-alkyl-substituted 3*H*-pyrroles **3s** and **3t**, correspondingly. When terminal ynamide **2u** was used, a complex mixture of products was formed, and only traces of the 4-unsubstituted 3*H*-pyrrole **3u** were detected. The [3 + 2] cycloaddition can be carried out in a bidirectional manner, as illustrated by the syntheses of bis-3*H*-pyrroles **3v** and **3w**. Moreover, the reaction was applied to modifications of the natural products: compounds **3x** and **3y**, derived from flavonoid formononetin and steroid estrone, were prepared in high yields.

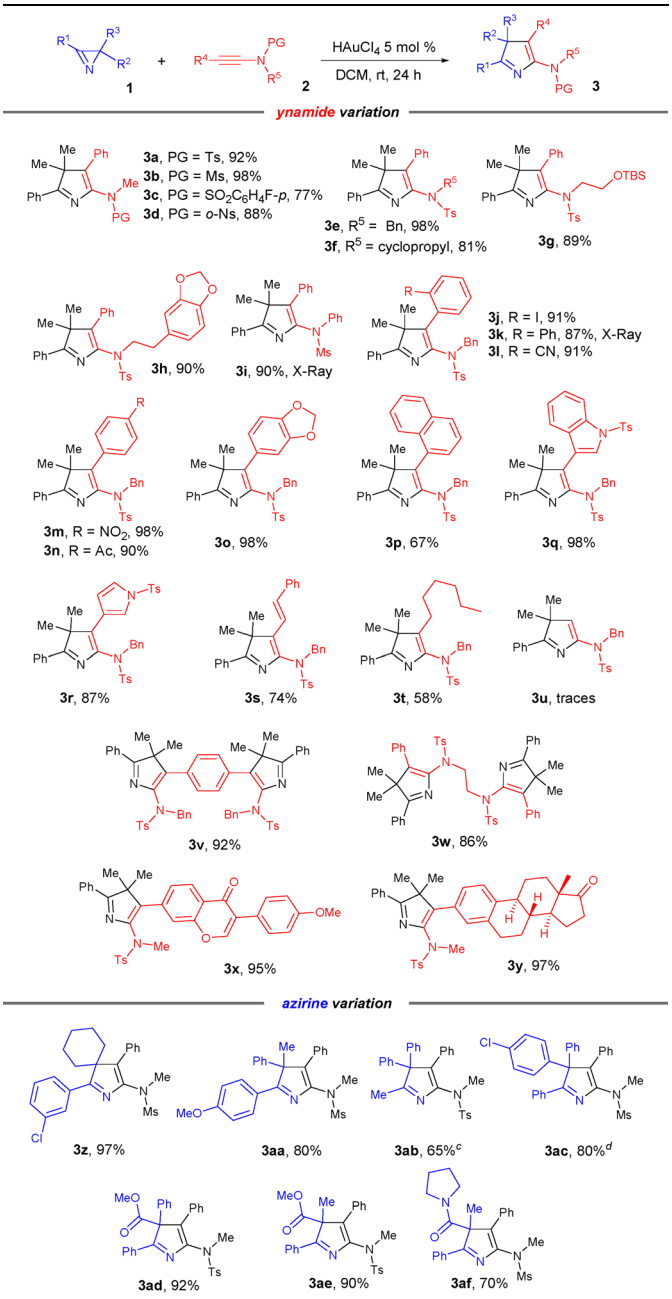
The structures of 3*H*-pyrroles **3i** and **3k** were additionally confirmed by X-ray crystallography (CCDC 2175839 and 2175843,† correspondingly).

Then we studied the scope of 2*H*-azirines in the gold-catalyzed [3 + 2] cycloaddition (Table 2, bottom panel). Using the corresponding 2*H*-azirines, both aliphatic and aromatic substituents could be introduced at the 2nd and 3rd positions of the target 3*H*-pyrrole core (**3z–ac**). In the case of 2,2-diaryl-substituted 2*H*-azirines, the reactions were carried out at higher temperatures (40–60 °C; products **3ab** and **3ac**). 3*H*-Pyrroles bearing ester (**3ad** and **3ae**) or amide (**3af**) functionalities were also obtained in high yields.

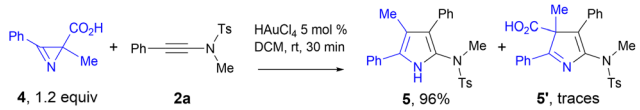
1*H*-Pyrrole from 2*H*-azirine-2-carboxylic acid

Interestingly, when we tested 2*H*-azirine-2-carboxylic acid **4** in the cycloaddition, the only isolated product was the aromatic 1*H*-pyrrole **5** (Scheme 3). In this case, the [3 + 2] cycloaddition was accompanied by spontaneous decarboxylation with the restoration of aromaticity of the pyrrole ring. Traces of the

Table 2 Scope of the gold-catalyzed [3 + 2] cycloaddition. Synthesis of 3*H*-pyrroles **3**[a,b]



[a] All reactions were carried out on a 0.2 mmol scale (0.2 M). [b] Isolated yields. [c] 40 °C, 72 h. [d] 60 °C, 48 h, DCE, Ar, 4 Å MS.



Scheme 3 Synthesis of 1*H*-pyrrole **5** *via* the cycloaddition/decarboxylation sequence.

corresponding 3*H*-pyrrole-3-carboxylic acid were detected by the HRMS assay of the reaction mixture.

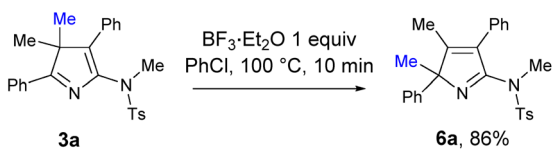
Non-aromatic 2*H*-pyrroles from 1,5-alkyl-shift in 3*H*-pyrroles

Some scattered precedents of acid-[24,66,67] or thermally-[68] induced 1,5-alkyl-shifts in 3*H*-pyrrole-based systems furnishing the 2*H*-isomers have been documented. However, such rearrangements of 5-amino-3*H*-pyrroles have not been described in the chemical literature, to the best of our knowledge. Inspired by the success in the syntheses of 3*H*- and 1*H*-pyrroles, we extended our new methodology to the generation of 2*H*-pyrroles.

When we treated the model 3*H*-pyrrole **3a** with catalytic amounts of Brønsted acids (5–20 mol% of MsOH or TfOH) at 60 °C, only traces of the isomerization product were detected after 24 h. Nonetheless, the desired 2*H*-pyrrole **6a** was obtained in 86% yield when **3a** was treated with a stoichiometric amount of the Lewis acid $BF_3{\cdot}Et_2O$ at 100 °C for 10 min (Scheme 4); 100 mol% of MsOH, as the 1,5-Me-shift activator, also worked smoothly under the same conditions (see the ESI† for details of the optimization studies). In the latter cases, a bright yellow color appeared, when these acids were added to colorless solutions of **3a** in PhCl, and then the reaction mixtures were quickly decolorised on heating. These experimental features are probably associated with the formation of the corresponding salts of **3a**, which are consumed during the isomerization.

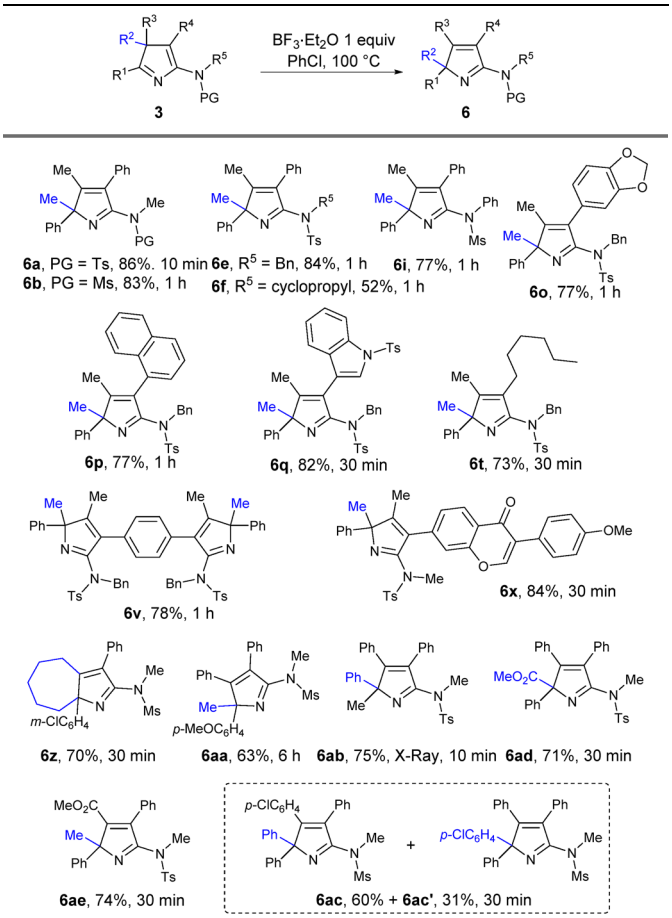
Under the verified optimal conditions ($BF_3{\cdot}Et_2O$ 1 equiv., PhCl, 100 °C), we studied the scope of the isomerization of 5-amino-3*H*-pyrroles **3** to 5-amino-2*H*-pyrroles **6** (Table 3). The 1,5-Me shift proceeded smoothly in the case of 3,3-dimethyl-substituted substrates **3**. Spiro-3*H*-pyrrole **3z** provided the corresponding cyclohepta-annulated 2*H*-pyrrole **6z** through the cycle expansion. When substrates with $R^2 \neq R^3$ and R^2 = Me were tested, exclusively the methyl migrations were observed (products **6aa** and **6ae**). Notably, the complete conversion of **3aa** was achieved only after 6 h. 3*H*-Pyrrole **3ad** was transformed into 2*H*-pyrrole **6ad** as a result of the migration of the ester group. The structure of 2*H*-pyrrole **6ab**, originating from the 1,5-Ph-shift, was additionally confirmed by X-ray crystallography (CCDC 2175759†). In the case of an unsymmetrically substituted 2,2-diaryl 3*H*-pyrrole **3ac**, two isomeric 2*H*-pyrroles **6ac** and **6ac′** were obtained. Thus, the relative migratory aptitude for the studied compounds was Alk > CO_2Me > Ar.

The synthesis of 2*H*-pyrrole **6a** could be carried out in a modular one-pot format on a 1.0 mmol scale starting directly from 2*H*-azirine **1a** and ynamide **2a** (Scheme 5).

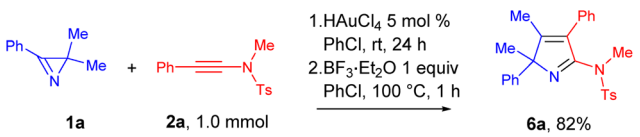


Scheme 4 Synthesis of 2*H*-pyrrole **6a** *via* the acid-promoted 1,5-Me-shift.

Table 3 Scope of the 1,5-shift-based isomerization of 3*H*-pyrroles **3**. Synthesis of 2*H*-pyrroles **6** [a,b]



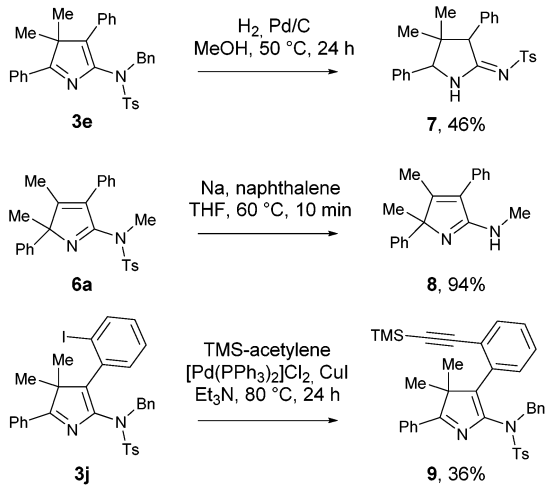
[a] All reactions were carried out on a 0.2 mmol scale (0.2 M). [b] Isolated yields.



Scheme 5 One-pot synthesis of 2*H*-pyrrole **6a** on a mmol scale.

Synthetic values of the non-aromatic pyrroles

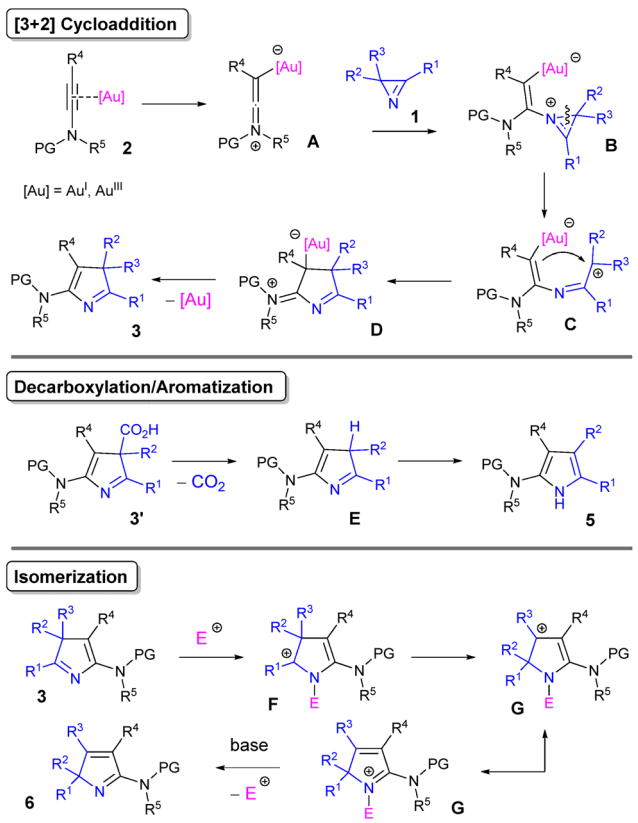
Considering the potential synthetic and medicinal chemistry values[12–15] of non-aromatic pyrroles, we performed some post-modifications of the obtained products (Scheme 6). 3*H*-Pyrrole **3e** was converted into pyrrolidine **7** under catalytic hydrogenation conditions. Sodium naphthalene smoothly excised the tosyl protective group from the 5-amino-substituent of 2*H*-pyrrole **6a**. In addition, a modification of a peripheral fragment was illustrated by the Sonogashira coupling of **3j** with TMS–acetylene. These model transformations emphasized the usefulness and the flexibility of the reported methodologies.



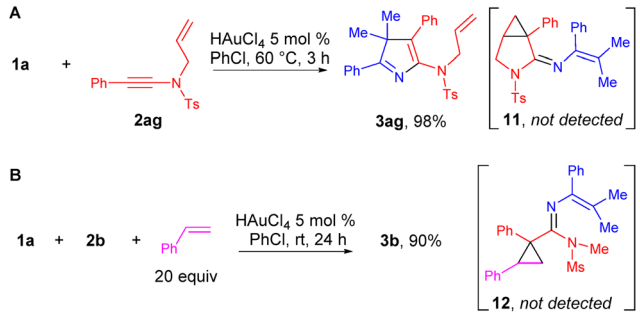
Scheme 6 Post-modifications of products **3** and **6**.

Plausible mechanisms

Postulated mechanisms for the developed routes to non-aromatic 3*H*-, 2*H*-, and aromatic 1*H*-pyrroles are shown in Scheme 7. First of all, the activation of ynamide **2** by gold complexes leads to the keteneiminium intermediate **A** (Scheme 7, top panel). Then, **A** reacts with 2*H*-azirine **1**, to give the azirinium intermediate **B**, which undergoes a three-membered ring opening at the N–C^2 bond. The resulting acyclic intermediate **C** cyclizes to pyrroline **D**, which is converted into 3*H*-pyrrole **3**, as a result of deauration with the regeneration of the gold catalyst. When **3** bears a carboxyl group at the 3rd position, a smooth decarboxylation provides the corresponding 3*H*-pyrrole **E**, which immediately tautomerizes into the 1*H*-pyrrole **5** (Scheme 7, central panel). The isomerization of 3*H*-pyrroles **3** to 2*H*-pyrroles **6** (Scheme 7, bottom panel) proceeds as a result of the attack on the pyrrole nitrogen by an electrophile (Brønsted or Lewis acids). The resulting cation **F** undergoes an alkyl- or an aryl-1,5-shift, furnishing a more thermodynamically favorable cation **G**. Finally, the electrophile is ejected from **G**, thus providing 2*H*-pyrrole **6**, under basic work-up conditions. Reducing the load of Brønsted or Lewis acids negatively affects the isomerization efficiency (see section 2.5 of the ESI† for details). Most likely this is associated with the basic nature of non-aromatic pyrroles, which easily form salts on treatment with strong acids.[7,8] Therefore, an equivalent amount of an acid should be used for the complete isomerization. Probably, the isomerization of the 3*H*-pyrrole **6aa** proceeds slowly (6 h), since the electron-donating *p*-methoxyphenyl-substituent R^1 reduces the effective positive charge in the corresponding cation **F**.



Scheme 7 Plausible mechanisms.



Scheme 8 Control experiments.

The generation of carbene intermediates in gold-catalyzed *O*- and *N*-transfer reactions is a controversial issue.[69] We did not detect any cyclopropanation[56] products, when the ynamide substrate **2ag**, featuring an alkene fragment, was employed (Scheme 8A), or when styrene was added in the reaction mixture containing **1a** and **2b** (Scheme 8B). In addition, any products derived from CH-insertions[70] or 1,2-shifts[71] were not detected in the gold-catalyzed reaction occurring between hexyl-substituted ynamide **2t** and azirine **1a** (Table 2). These observations do not validate the hypothesis of the involvement of α-imino gold carbenes in the studied [3 + 2] cycloaddition.

Conclusions

Summarizing, we developed a modular and divergent approach to otherwise hard-to-reach non-aromatic 3*H*- and 2*H*-pyrroles; this synthetic method is based on the gold-catalyzed integration of 2,2-disubstituted 2*H*-azirines and ynamides.

Initially, this reaction proceeds through [3 + 2] cycloaddition furnishing 5-amino-3*H*-pyrroles. The latter compounds undergo smooth isomerization to 5-amino-2*H*-pyrroles under acidic conditions; the synthesis of the 2*H*-products can be carried out starting from 2*H*-azirines and ynamides in a one-pot manner. Moreover, aromatic 2-amino-1*H*-pyrroles can also be obtained by the gold-catalyzed cycloaddition of 2-substituted 2*H*-azirine-2-carboxylic acids and ynamides. The obtained 3*H*- and 2*H*-pyrroles were successfully involved in further transformations, including the modifications of the pyrrole cores and peripheral substituents. We believe that our new synthetic strategy can promote new discoveries in the attractive but still quite poorly explored chemistry of non-aromatic 3*H*- and 2*H*-pyrroles.

Author contributions

A. Yu. D. conceptualized the research project. N. V. S., G. D. T., E. I. C., I. P. F., and A. Yu. D. conducted the experiments and prepared the ESI.† N. V. R., V. Yu. K., and A. Yu. D. designed the experiments and wrote the paper. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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