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Gold-Catalyzed Aminoalkenylation of β -Amino-1, n -Diynols to Cycloalkyl-, Piperidinyl- and Pyranyl-Fused Pyrroles

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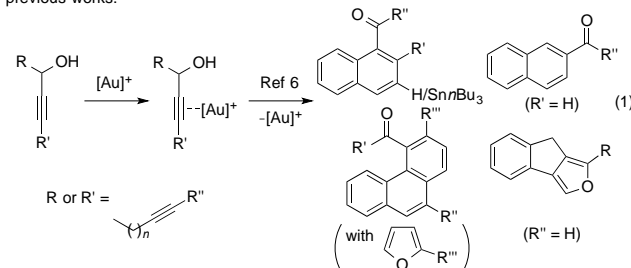
Abstract. A synthetic method to prepare cycloalkyl-, piperidinyl- and pyranyl-fused pyrroles efficiently by gold(I)-catalyzed dehydrative aminoalkenylation of β -amino-1, n -diynols under mild conditions at room temperature is described.

Keywords: 1,2-amino alcohols; gold; homogeneous catalysis; nitrogen heterocycles; synthetic methods

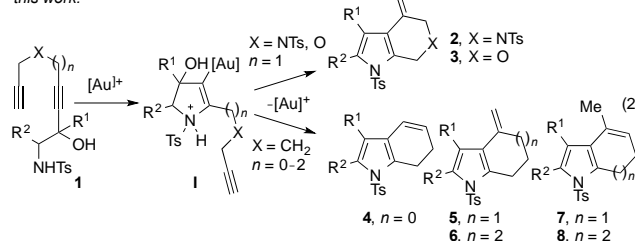
Functionalized pyrroles are present as a structural motif in many bioactive natural products and pharmaceutically interesting compounds.^[1,2] They also feature in many optoelectronic functional materials and are versatile building blocks in organic synthesis and drug discovery programs. For this reason, the development of facile catalytic methods for pyrrole synthesis with selective control of substitution patterns by using readily accessible substrates continues to be actively pursued.

Gold-catalyzed alkyne cycloisomerizations have come to represent one of the most efficient synthetic methods for rapidly increasing molecular complexity and diversity.^[3–6] In the last decade, the field has expanded exponentially, with a myriad of elegant approaches to synthetically valuable compounds being established. Included in this has been the recent emergence of a small handful of examples describing the assembly of 1- and 2-naphthyl ketones, phenanthrenes and 8*H*-indeno[1,2-*c*]furans from the corresponding 1, n -diynols (Scheme 1, eq 1).^[6,7] We envisioned that if 1, n -diynols bearing an appropriately placed β -amino group were explored, such as the type **1** shown in Scheme 1, eq 2, a

previous works:



this work:



Scheme 1. Gold-Catalyzed Reactivities of 1, n -Diynols.

reaction sequence initiated by C–N rather than C–C bond formation might instead prevail to give the putative (4,5-dihydro-1*H*-pyrrol-3-yl)gold species **I**.^[4,8–10] Subsequent dehydrative aromatization followed by trapping of the ensuing cycloadduct by the remaining alkyne moiety may then be anticipated to deliver pyrrole-containing bicyclic molecules **2–8** in a straightforward manner.^[11–14] Achieved under mild conditions at room temperature, we report herein the realization of this unprecedented aminoalkenylation chemistry in gold catalysis that provides a facile and chemoselective approach to cycloalkyl-, piperidinyl- and pyranyl-fused pyrroles in good to excellent yields and as single regioisomers.

Our present study began by examining the gold-catalyzed cycloisomerizations of β -amino-1,6-diynol **1a** in order to establish the reaction conditions (Table 1).^[15] This initially revealed that treating the substrate with 5 mol % of gold(I) phosphine catalyst **A** in THF at room temperature for 1 h afforded piperidinyl-fused pyrrole **2a** in 70% yield (entry 1). The structure of the nitrogen-containing cycloadduct was determined by NMR spectroscopic measurements and X-ray crystallography.^[16] Lower product yields of 14–60% were observed when the transformation was conducted with the gold(I) phosphine complex **B**, AuCl and AuCl₃ as the catalyst (entries 2, 10 and 11). An increase in product yield from 70 to 82 to 90% was subsequently achieved when the reaction was repeated with Ph₃PAuCl/AgOTf and Ph₃PAuNTf₂ in place of gold(I) complex **A** as the catalyst (entries 4 and 5). With Ph₃PAuNTf₂ as the catalyst, changing the solvent from THF to acetone, toluene, dichloro-

methane or 1,2-dichloroethane led to **2a** being obtained in yields of 52–98% (entries 6–9). However, no reaction was detected in control experiments catalyzed by the gold(I) phosphine complex **C** or 10 mol % of the Brønsted acids TfOH or Tf₂NH (entries 3, 13 and 14). In a final control reaction mediated by 5 mol % of AgOTf with THF as the solvent, the exclusive formation of the monocyclic pyrrole **9a** in 80% yield was found (entry 12). On the basis of the above results, the procedure described in entry 6 with 5 mol % of Ph₃PAuNTf₂ as the catalyst in acetone at room temperature for 1 h was deemed to provide the optimum reaction conditions.

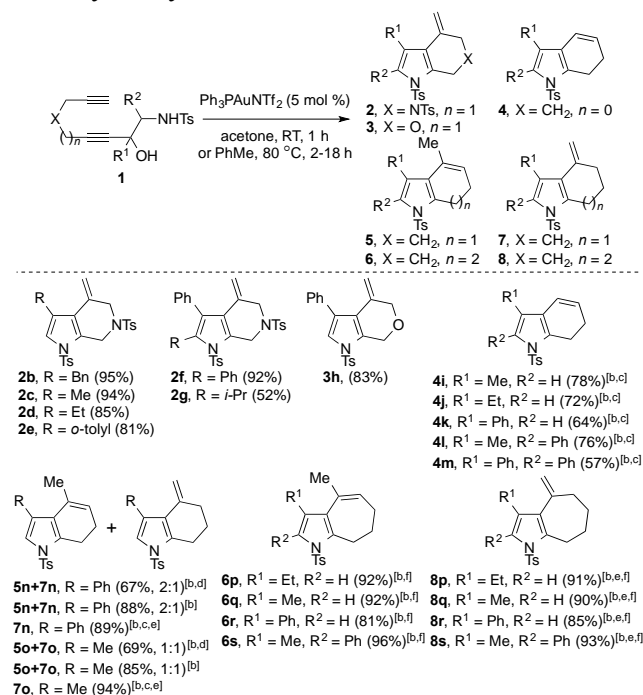
With the reaction conditions established, we next sought to evaluate the generality of the methodology for a series of β -amino-1,*n*-diynols **1b–s**. As illustrated in Table 2, we found the reaction conditions to be broad, with a variety of substituted fused-pyrroles **2–8** furnished in 52–96% yield. Starting β -amino-1,6-diynols (**1b–e**) bearing alkyl or aryl substituents at the carbinol carbon center were found to react well to afford the corresponding piperidinyl-fused pyrrole adducts **2b–e** in up to 95% yield. Likewise, comparable product yields of 92 and 83% were obtained in the reaction of substrates bearing two adjacent phenyl groups (**1f**) or an etheral diyne linker (**1h**). The only instance where a lower product yield of 52% was obtained was when the β -position of the substrate bore an aliphatic isopropyl moiety (**1g**). The reaction of β -amino-1,5-diynols (**1i–m**) containing a -(CH₂)₂- tethered diyne also furnished the corresponding cyclohexenyl-fused pyrroles **4i–m** in up to 78% yield. The β -amino-1,6-diynol homologues **1n** and **1o** were initially found to afford mixtures of **5n** and **7n**, and **5o** and **7o** of the corresponding *endo*- and *exo*-alkenylated products, in 2:1 and 1:1 ratios, and in 67 and 69% yield, respectively. An increase in the product yield of the **5n** and **7n** mixture to 88%, and that of **5o** and **7o** to 85%, was observed when the reaction time was increased from 1 to 3 h. A slight fine-tuning of the conditions in the analogous experiments of these substrates with the introduction of 4 Å molecular sieves (MS) for 2 h subsequently led to the *exo*-alkenylated pyrroles **7n** and **7o** being chemoselectively afforded in respective yields of 89 and 94%. Likewise, in the presence of 4 Å MS, the *exo*-alkenylated pyrroles **8p–s** were exclusively provided from the corresponding β -amino-1,7-diynols **1p–s** in 85–93% yield. Intriguingly, repeating the reactions of these substrates **1p–s** in the absence of 4 Å MS gave the *endo*-alkenylated pyrroles **6p–s** as the sole adduct. The structure of the cycloheptenyl-fused pyrrole **6r** was ascertained by NMR spectroscopic measurements and X-ray crystallography.^[17]

Table 1. Optimization of Reaction Conditions.^[a]

Entry	Catalyst	Solvent	2a [%] ^[b]	9a [%] ^[b]
1	A	THF	70	—
2	B	THF	60	—
3	C	THF	— ^[c]	—
4	Ph ₃ PAuCl/ AgOTf	THF	82	—
5	Ph ₃ PAuNTf ₂	THF	90	—
6	Ph ₃ PAuNTf ₂	acetone	98	—
7	Ph ₃ PAuNTf ₂	toluene	92	—
8	Ph₃PAuNTf₂	CH₂Cl₂	82	—
9	Ph₃PAuNTf₂	(CH₂Cl)₂	52	—
10	AuCl	THF	27	—
11	AuCl ₃	THF	14	—
12	AgOTf ^[d]	THF	—	80
13	Tf ₂ NH ^[d]	THF	— ^[c]	—
14	TfOH ^[d]	THF	— ^[c]	—

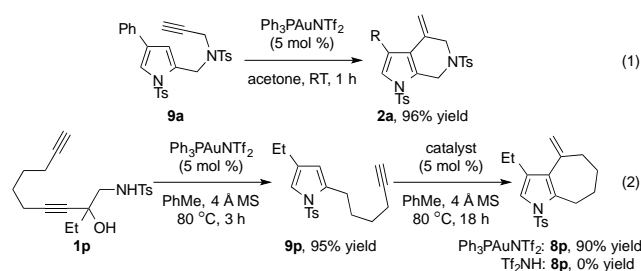
[a] All reactions were performed at the 0.18 mmol scale with catalyst:**1a** ratio = 1:20 at room temperature for 1 h. [b] Isolated yield. [c] No reaction based on TLC and ¹H NMR analysis of the crude mixture. [d] Reaction performed with 10 mol % of the catalyst.

Table 2. Aminoalkenylation of β -Amino-Diynols **1b**–**s** Catalyzed by $\text{Ph}_3\text{PAuNTf}_2$ [a]



[a] All reactions were performed at the 0.18 mmol scale with a $\text{Ph}_3\text{PAuNTf}_2$:**1** ratio of 1:20 in acetone at room temperature for 1 h. Values in parentheses denote isolated yields and product ratios for mixtures. [b] Reaction conducted in toluene at 80 °C. [c] Reaction time = 2 h. [d] Reaction time = 3 h. [e] Reaction with 4 Å MS. [f] Reaction time = 18 h.

The mechanistic premise outlined in Scheme 1, eq 2, predicted that the gold(I)-catalyzed cycloisomerization may proceed through an aminoalkenylation pathway comprised of tandem hydroamination and alkenylation steps. While the isolation of **9a** in Table 1, entry 12, under catalysis by AgOTf was fortuitous, the outcome suggests that this may be an intermediate in the gold(I)-catalyzed transformation. This was corroborated by the formation of fused-pyrrole **2a** in 96% yield from the aromatic *N*-heterocycle under the optimized gold(I) catalysis conditions (Scheme 2, eq 1). The likelihood of this catalytic reaction pathway was further exemplified by the isolation of **9p** on repeating the Au(I)-mediated rearrangement of β -amino-1,7-diynol **1p** under the conditions described in Scheme 2, eq 2 for 3 h. Resubmission of the pyrrole intermediate to the same reaction conditions for a further 18 h afforded the fused-pyrrole adduct **8p** in 90% yield. In contrast, repeating the analogous transformation of **9p** with 5 mol % of Tf_2NH instead of $\text{Ph}_3\text{PAuNTf}_2$ as the catalyst was found to the near quantitative recovery of the pyrrole substrate.



Scheme 2. Control Experiments with **1p** and **9a**.

A tentative mechanism for the present gold(I)-catalyzed aminoalkenylation of β -amino-1,*n*-diynols is outlined in Scheme 3. We postulate that this could involve the initial activation of the internal alkyne moiety in the substrate to give the organogold complex **II**. This might consequently trigger the formation of vinyl gold intermediate **I** by an intramolecular C–N bond-forming hydroamination step. Ensuing protodemetalation and Brønsted acid-assisted dehydrative aromatization of the resultant 2,3-dihydro-1*H*-pyrrol-3-ol adduct **III** would deliver isolable pyrrole **9** via the iminium species **IV**.^[10] Further activation of the pendant alkyne in this newly formed compound may afford the gold(I)-coordinated complex **V**. In the instances of 1,5-diynol substrates (**1i–m**), this may lead to 5-*endo-dig* alkenylation to the spirocyclic gold species **VI** and succeeding 1,2-alkyl migration to give the second vinyl gold intermediate **VII**.^[13] Rearomatization and protodemetalation would then furnish the cyclohexenyl-fused adduct **4**. In contrast, 1,6- and 1,7-diynol substrates (**1a–h** and **1n–s**) may undergo the respective preferential 5-*exo-dig* and 6-*exo-dig* cyclizations to produce spirocyclic vinyl gold adduct **VIII** from Au(I)-activated complex **V**. Subsequent 1,2-alkyl migration of this adduct to give the bicyclic gold species **IX** followed by rearomatization and protodemetalation would deliver the *exo*-alkenylated pyrroles **2**, **3**, **7** and **8**. For the piperidinyl- and pyranyl-fused adducts **2** and **3**, we propose that stabilization through non-conjugation of the heteroatom lone pair may rationalize the exclusive isolation of these *exo*-alkenes.^[18] However, without this heteroatomic interaction, the greater stability offered by an internal alkene moiety may explain the isolation of pyrroles **7** and **8**, and isomerization to the *endo*-tautomers **5** and **6** under the mild acidic conditions generated when in the presence of water. A redistribution of product isomers in control experiments with the *exo*-alkenylated pyrrole **8p** under the various conditions described in Scheme 4 would support this latter posited role of water. Treatment of **8p** with an equivalent of water for 18 h was found to give a 1:1 mixture of **6p** and **8p**, which

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