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Gold(I)-Catalyzed Intra- and Intermolecular Alkenylations of β-Yne-pyrroles: Facile Formation of Fused Cycloheptapyrroles and Functionalized Pyrroles

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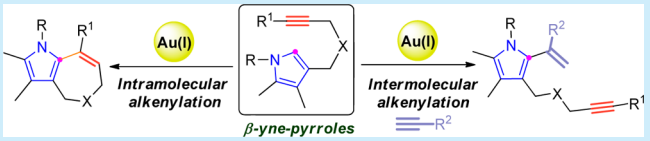
Supporting Information

ABSTRACT: An efficient gold(I)-catalyzed alkenylation of β-alkyne-substituted pyrroles is reported. The intramolecular reaction gives straightforward access to different types of seven-membered-ring-fused pyrroles with *endo*-selectivity, and the intermolecular reaction with alkynes provides functionalized pyrrole derivatives.



A seven-membered-ring fused pyrrole skeleton is a component of many interesting natural products, such as ambiguine K isonitrile, densanins A, and hymenialdisine (Figure 1). From a pharmaceutical point of view, these fused

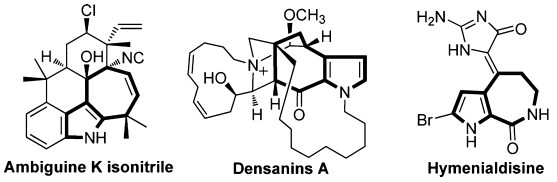


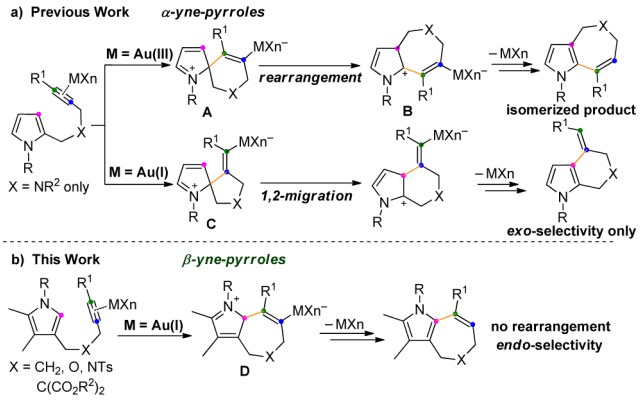
Figure 1. Natural products with seven-membered-ring fused pyrrole.

cycloheptapyrroles and their derivatives selectively inhibited a considerable number of different kinases and cytokines.[1] Therefore, this class of compounds has been considered as a potential lead for the development of promising therapeutic molecules, as well as attractive targets for organic synthesis. Although various methods for the preparation of seven-membered ring systems have been reported,[2] new strategies for the efficient synthesis of seven-membered-ring fused pyrroles are still extremely desirable.

The alkenylation of arenes catalyzed by electrophilic transition-metal complexes has received much attention in the past decade.[3] In particular, gold-catalyzed cyclizations of aromatic and heteroaromatic compounds with alkynes offer a new way for the construction of a polycyclic system,[4−8] including seven-membered-ring fused pyrroles. As the first attempt, Beller and co-workers reported the cyclization of pyrroles tethered to alkynes.[9a,c] Later, Broggini and Van der Eycken developed this strategy to synthesize pyrrolopyridinones and pyrroloazepinones, respectively.[9c−f]

However, it is very difficult to control the chemoselectivity of gold-catalyzed reactions at not fully substituted pyrroles,[8e] including alkyne-substituted pyrroles. Au(III)-catalyzed cyclization involved the cationic spiro intermediate **A**, which might form cation **B** by rearrangement and generated isomerized side product, whereas the substrates cyclized readily with a cationic gold(I) complex but only gave six-membered-ring products by a 6-*exo*-*dig* pathway (Scheme 1, **a**). Such rearrangement or 1,2-

Scheme 1. Gold-Catalyzed Intramolecular Alkenylation of α-Yne-pyrroles and β-Yne-pyrroles



migration via spiro intermediate seemed unavoidable because the α position of pyrrole is normally more nucleophilic than the β position. Considering the uncontrollability of regioselectivity when α-yne-pyrrole substrates were used, a promising solution might be using β-yne-pyrroles. Thus, the annulated intermediate **D** would be formed directly without isomerization (Scheme 1, **b**). Unfortunately, to the best of our knowledge, amide-tethered α-yne-pyrroles[9] were the only option in the intramolecular alkenylation, and a straightforward synthesis of β-yne-pyrroles was proved irrealizable. Very recently, we developed a Ni-catalyzed [3 + 2] cycloaddition of methyleneaziridines and diynes to give pyrroles with the alkyne chain attached at the β position.[10a] This work provided us an

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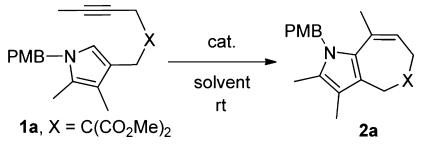
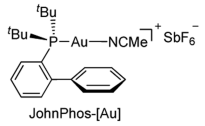
opportunity to study the gold-catalyzed alkenylations of β-yne-pyrroles.

To validate our hypothesis, β-yne-pyrrole **1a** was prepared as a model substrate for the investigation of alkenylation (Table 1). Disappointingly, $AuCl_3$ and AuCl were completely futile to

Table 1. Optimization of Reaction Conditions[a]



1a, X = $C(CO_2Me)_2$ **2a**

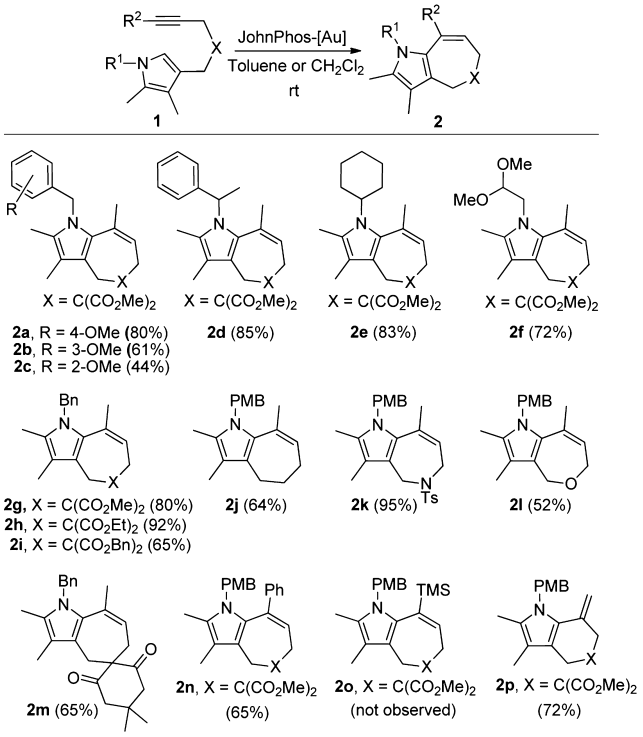
entry	catalyst	solvent	**2a**[b] (%)
1	AuCl	CH_2Cl_2	-NR[c]
2	$AuCl_3$	CH_2Cl_2	-NR
3[d]	$PtCl_2$	toluene	21
4	Au(IPr)Cl[e]/$AgSbF_6$	CH_2Cl_2	50
5	$Au(PPh_3)Cl/AgSbF_6$	CH_2Cl_2	36
6	 JohnPhos-[Au]	CH_2Cl_2	71
7	JohnPhos-[Au]	toluene	80
8	JohnPhos-[Au]	THF	49
9	JohnPhos-[Au]	CH_3CN	35
10	$AgSbF_6$	CH_2Cl_2	-NR

[a]Reaction conditions: **1a** (0.25 mmol), 5 mol % of catalyst, 5 mL of solvent. [b]Isolated yield. [c]No reaction. [d]Under 80 °C. [e]IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

catalyze the reaction. $PtCl_2$, which has been successfully applied in other alkenylations,[7b,8c,9f] only gave the desired fused cycloheptapyrrole **2a** in 21% yield. To our delight, Au(I) complexes bearing *N*-heterocyclic carbene ligands or bulky phosphanes could catalyze the intramolecular reaction of β-yne-pyrroles. The best catalyst for the formation of fused cycloheptapyrrole **2a** is JohnPhos-[Au] (Table 1, entry 6), which allows the cyclizations to be achieved in the absence of Ag(I) salts. Screening of the solvents showed that the reaction proceeded well in toluene, giving the desired product in 80% yield. The identity of **2** was unambiguously secured by X-ray crystallographic analysis of **2n** (Supporting Information).

With the optimal conditions established, we set out to explore the substrate scope of various β-yne-pyrroles in this transformation (Scheme 2). First, substituents on the nitrogen atom did not remarkably influence the final chemical output, providing the corresponding fused cycloheptapyrrole products (**2a**,**b**,**d**−**g**) in good yields. However, the steric effect may be the primary reason for the low yield of **2c**, irrespective of the electronic nature. Subsequently, the tethering unit of pyrroles and alkynes was investigated. To our delight, the link X is not limited to malonate-, substrates containing CH_2- (**2j**), tosylamide- (**2k**), O- (**2l**), and dimedone- (**2m**) tethers could all undergo this cyclization and be transformed into different types of seven-membered-ring fused pyrroles in moderate to good yields. It should be noted that the substituents in the R^2 position played significant roles in this alkenylations. The phenyl group (**2n**) was tolerated, and good yield was obtained. Nevertheless, the less hindered trimethylsilyl (TMS) moiety inhibited this cyclization process, and no identifiable product (**2o**) was detected even when the reaction was performed

Scheme 2. Gold(I)-Catalyzed Intramolecular Alkenylation of β-Yne-pyrroles[a,b]



[a]Reaction conditions: β-yne-pyrroles **1** (0.3 mmol), JohnPhos-[Au] (5 mol %) in toluene or CH_2Cl_2 (3 mL). [b]Isolated yield.

under 90 °C for 24 h. The low reactivity of substrate **1o** should be attributed to electronic reasons rather than steric hindrance. In particular, a totally different regioselectivity was observed when terminal-alkyne substrate **1p** was introduced, and six-membered-ring fused pyrrole **2p** was isolated as the sole product, corresponding to previous reports of β-yne-furans.[7g] This result suggested that the regioselectivity of cyclization could be tuned by electronic effects of suitable substituents on the alkyne moieties.

Although gold(I)-catalyzed intermolecular alkenylation of alkynes with furans and indoles has been reported,[6b,7g] the intermolecular reaction with pyrroles was less investigated. We were curious whether such reaction could occur on β-yne-pyrroles, which inherently had alkyne moieties after all. To our delight, the intermolecular addition reaction with terminal alkynes proceeded satisfactorily in the presence of 5 mol % of JohnPhos-[Au] and was not affected by the internal alkyne moieties, giving functionalized pyrrole products in moderate to excellent yields (Scheme 3). It should be mentioned that intermolecular reactions of furans[7g] or indoles[6b] with alkynes were not possible to achieve such selective reactions. The substituents in the R position of the terminal alkyne were crucial to the reactivity and regioselectivity. Phenyl group (**3a**) and electron-donating *p*-methoxyphenyl group (**3b**) were tolerated, and high yields were obtained. Notably, the tolerance of the propargyl alcohol with a free hydroxyl group (**3d**) offered the opportunity for further functionalization. It is noteworthy that the electron-withdrawing $-CO_2Me$ group showed different regioselectivity and generated **3e** as a single isomer with *E* configuration. In contrast, the alkyl groups such as cyclohexyl and tertiary butyl were futile in this intermolecular alkenylation, and the intramolecular reaction was dominant, giving seven-

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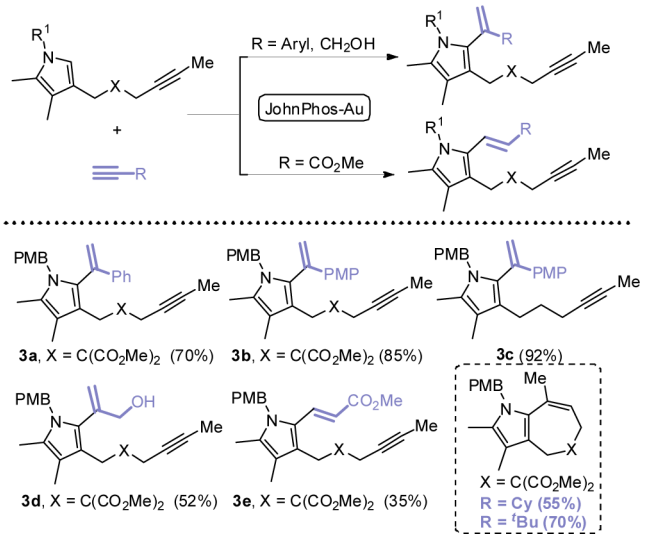
Scheme 3. Gold(I)-Catalyzed Intermolecular Alkenylation of β-Yne-pyrroles with Alkynes[a,b]



[a]Reaction conditions: β-yne-pyrroles **1** (0.3 mmol), terminal alkynes (0.3 mmol), JohnPhos-[Au] (5 mol %) in toluene or CH_2Cl_2 (3 mL). [b]Isolated yield.

membered-ring fused products in good yields. A similar observation was found in the intermolecular reaction with internal alkyne (e.g., 1-phenylpropyne), which may be ascribed to the electronic nature of the external alkynes.

In summary, we describe herein a highly efficient method for the construction of a challenging polycyclic system via gold(I)-catalyzed intramolecular alkenylation of β-yne-pyrroles. This approach exhibits high regioselectivity and functional group tolerance and gives straightforward access to fused cycloheptapyrroles under mild conditions. Six-membered-ring fused pyrroles can also be obtained for substrates with terminal alkynes via *exo*-selective cyclization. Furthermore, intermolecular alkenylation of β-yne-pyrrole with alkyne was investigated to provide functionalized pyrrole derivatives such as **3d**, which would be useful scaffolds for additional annulation processes. With regard to the mechanism, the reactions are straightforward and follow the principles investigated in details by others previously.[11] Further studies on expanding this strategy are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedures, characterization data, ^1H and ^{13}C NMR spectra, and X-ray crystallographic analysis of compound **2n**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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The author names were incorrect in reference 7g in the version published ASAP on March 31, 2014; the correct version reposted April 18, 2014.

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