Organic LETTERS

Letter

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Synthesis of Multiple-Substituted Pyrroles via Gold(I)-Catalyzed Hydroamination/Cyclization Cascade

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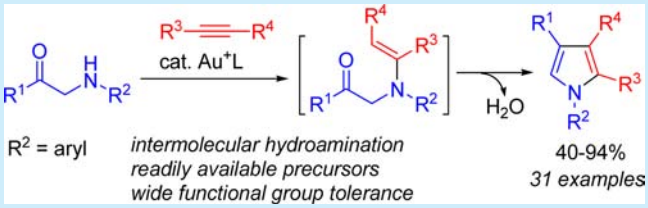
Supporting Information

ABSTRACT: A gold-catalyzed cascade hydroamination/cyclization reaction of α-amino ketones with alkynes to form substituted pyrroles has been developed. The method offers several advantages such as high regioselectivity with the tested cases, wide functional group tolerance, and easily accessible starting materials. The synthetic utility of the obtained pyrrole products was demonstrated by their efficient transformations to 2-vinylated pyrroles via gold-catalyzed intermolecular hydroarylation.

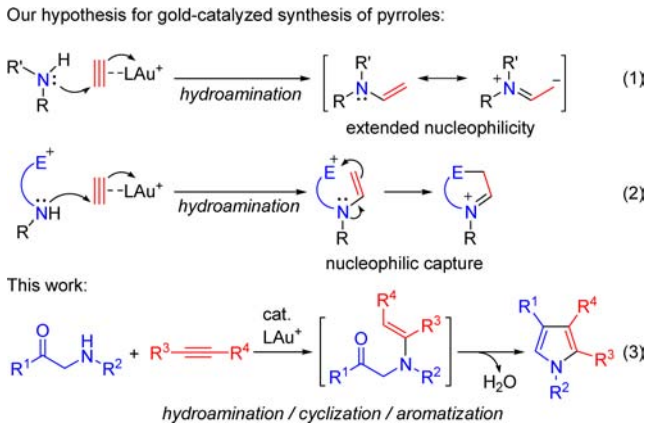


Pyrroles constitute an important class of heteroaromatic compounds, which not only serve as useful building blocks in the synthesis of bioactive molecules[1] but also as key structural units in numerous natural products,[2] pharmaceuticals,[3] and functional materials.[4] For these reasons, a large number of methodologies have been developed for the synthesis of pyrroles. They can be prepared by classical condensation procedures including the Knorr,[5] Paal–Knorr,[6] and Hantzsch pyrrole synthesis,[7] however, these reactions usually proceed with limited substitution patterns of the substrates.

Recently, the transition-metal-catalyzed heteroannulation reaction has come to represent one of the most powerful routes for the preparation of pyrroles.[8] Among these approaches, gold-catalyzed hydroamination of alkynes to pyrroles[9] has received considerable attention due to its high atom-economy and functional group compatibility. However, most of the reactions rely on the intramolecular hydroamination as the key step for ring closure via C–N bond formation.[9a−k] The substrates bearing both of the amino and alkyne groups in these reactions are either preprepared or formed in situ. The preparation of these substrates or their precursors usually requires tedious multistep synthesis. Compared to intramolecular reactions, the intermolecular hydroamination-initialized cascade reaction to pyrroles[9l−n] is not only more attractive for avoiding synthesis of complex substrates but also much more challenging. Pioneering research by Bertrand et al. in 2008 revealed that gold-catalyzed reactions of 1,3- or 1,5-diynes with ammonia could afford symmetrical pyrroles via double hydroamination.[9l] Later, Skrydstrup and coworkers extended the scope to dimerized ynamides and anilines with the same strategy.[9n] Nevertheless, the development of pyrrole synthesis from easily available starting materials with wide diversity via gold-catalyzed intermolecular hydroamination is highly desirable.[10]

Generally, gold-catalyzed hydroamination of alkynes leads to an enamine intermediate or product. It is noticed that the nucleophilicity of the distal carbon of the enamine is increased due to the resonance (Scheme 1, eq 1). We then hypothesized

Scheme 1. Gold-Catalyzed Route to Pyrroles



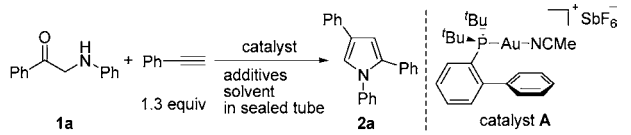
that if an amine tethered with an electrophilic group was employed as the substrate, the nuclophilic enamine moiety might capture the electrophilic group to form nitrogen heterocycles (Scheme 1, eq 2). After many trials, we found that α-amino ketone was an appropriate candidate for realizing this hypothesis. In this paper, we report the gold-catalyzed cyclization of α-amino ketones with alkynes initiated by intermolecular hydroamination to provide pyrroles based on the above strategy. This method can also be viewed as an acetylenic variant of the traditional Knorr pyrrole synthesis.

Received: April 30, 2015
Published: June 1, 2015

DOI: 10.1021/acs.orglett.5b01281
Org. Lett. 2015, 17, 2984–2987

Our initial efforts focused on the optimization of the gold-catalyzed reaction of α-amino ketone **1a** and phenylacetylene (Table 1). Echavarren's catalyst (catalyst **A**) bearing a bulky

Table 1. Optimization of Reaction Conditions



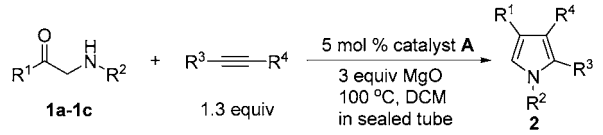
entry	catalyst (5 mol %)	solvent	additives (equiv)	temp (°C)	time (h)	yield (%)[a]
1	A	DCM	none	100	12	75
2[b]	A	DCM	4 Å MS	100	12	81
3	A	DCM	MgO (1.5)	100	3	87
4	A	DCM	MgO (3)	100	2	94
5	A	DCM	$MgSO_4$ (3)	100	3	84
6	A	DCM	MgO (3)	60	12	72
7	A	THF	MgO (3)	100	8	62
8	A	DCE	MgO (3)	100	5	88
9	A	toluene	MgO (3)	100	6	82
10	IPrAuCl/$AgSbF_6$	DCM	MgO (3)	100	3	87
11[c]	PPh_3AuCl/$AgSbF_6$	DCM	MgO (3)	100	8	11
12	A	DCM	MgO (3)	100	14	42[d]
13[e]	$AgSbF_6$	DCM	MgO (3)	100	8	0
14[f]	TfOH	DCM	-	100	12	0

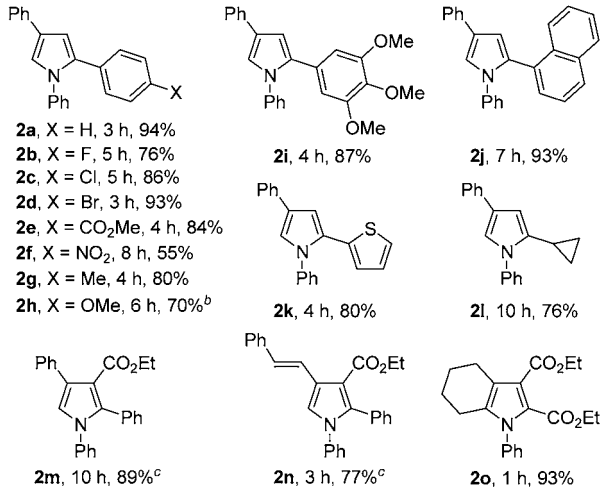
[a]Isolated yields. All the reactions were carried out on 0.3 mmol scale. [b]75 mg 4 Å MS was added. [c]73% **1a** was recovered. [d]3.0 equiv of phenylacetylene was used. 50% of **3a** was also isolated. [e]69% **1a** was recovered. [f]20 mol % of TfOH was used.

biarylphosphine ligand (Johnphos) was first employed (5 mol %) due to its superior catalytic activity in various gold-catalyzed reactions. We were delighted to find that the desired 1,2,4-triphenyl-1*H*-pyrrole **2a** was formed in 75% yield accompanied by ca. 15% of acetophenone in DCM at 100 °C for 12 h in a sealed tube (Table 1, entry 1). Apparently, acetophenone was formed by gold-catalyzed hydration of alkyne.[11] To eliminate the effect of water generated in situ during the reaction process, molecular sieves were added. As expected, the addition of 4 Å MS increased the yield of **2a** to 81% (Table 1, entry 2). Further optimization indicated that addition of MgO not only improved the yields of **2a** to 87−94% but also shorten the reaction time dramatically to 2−3 h (Table 1, entries 3−4). MgO possibly acted as an efficient water scavenger. A screening of Mg(II) additives showed that $MgSO_4$ also afforded high yield of **2a** (84%, Table 1, entry 5). Decreasing the reaction temperature to 60 °C led to lower yield of **2a** and prolonged reaction time (Table 1, entry 6). The reaction could also proceed in various solvents such as THF, DCE, or toluene, leading to **2a** in 62−88% yields (Table 1, entries 7−9). Gold(I)−carbene complexes of IPrAuCl/$AgSbF_6$ (IPr = 2,6-bis(diisopropylphenyl)imidazol-2-ylidene) was also effective for this reaction to afford **2a** in 87% yield (Table 1, entry 10). However, the use of more electrophilic PPh_3AuCl/$AgSbF_6$ only led to 11% yield of **2a** (Table 1, entry 11). It was noted that in some cases, we could also observe the formation of a trace amount of 2-vinylated pyrrole **3a** (1,3,5-triphenyl-2-(1-phenylvinyl)-1*H*-pyrrole) derived from gold-catalyzed hydroarylation[9k,12] of **2a** with alkyne. In the presence of 3 equiv of phenylacetylene, the yield of **3a** was improved to 50% (Table 1, entry 12). The use of $AgSbF_6$ or TfOH as the catalyst did not give the desired product (Table 1, entries 13−14).

Next, we investigated the scope of this gold-catalyzed cascade transformation under the reaction conditions shown in Table 1, entry 4. We first examined the scope of terminal alkynes (Scheme 2) using α-amino ketone **1a** as the reaction partner. In

Scheme 2. Scope of Alkynes[a]





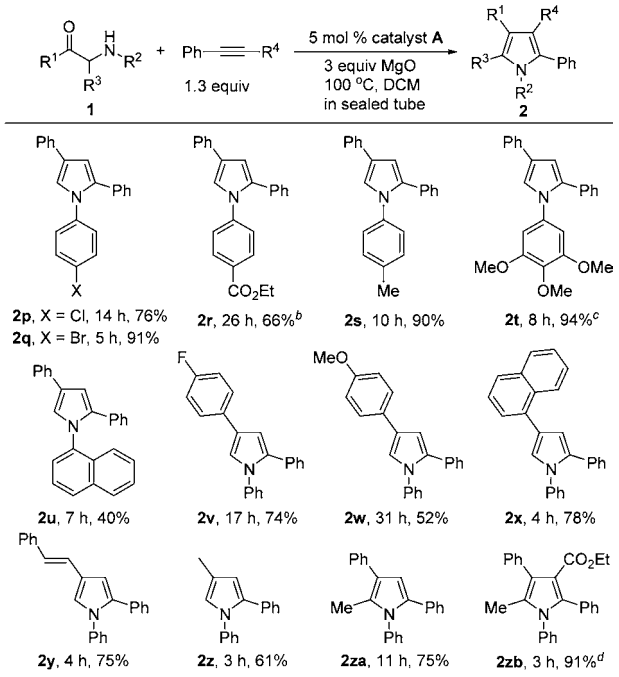
[a]Isolated yields. [b]α-Vinylated pyrrole **3h** was also isolated in 13% yield. [c]Room temperature.

the cases of aryl substituted alkynes, a wide variety of functional groups on the aryl rings are tolerated well. For example, both of the electron-withdrawing (*p*-F, *p*-Cl, *p*-Br, *p*-CO_2Me, *p*-NO_2) and electron-donating (*p*-Me, *p*-MeO, 3,4,5-$(MeO)_3$) substituted aryl alkynes underwent the reaction very well to afford the corresponding pyrroles **2b**−**2i** in 55−93% yields. Generally, the electronic nature of the aryl ring on alkynes had little influence on the efficiency of this reaction. In the case of **2h**, a vinylated product **3h** was also obtained in 13% yield. Sterically encumbered 1-naphthyl-substituted alkyne was converted into **2j** in 93% yield. 2-Thienyl group on the alkyne was also tolerated well to give **2k** in 80% yield. Employing cyclopropylethyne provided the desired pyrrole **2l** in 76% yield. The reaction could be extended successfully to activated internal alkynes, as exemplified by **2m**−**2o**. The products of **2m** and **2n** were formed regioselectively in which EWG group locates at the C-3 position of pyrrole,[13] due to that in the first step, the amino group attacks the alkyne in a fashion of Michael addition.

We then investigated the scope of α-amino ketones **1** using phenylacetylene as the coupling partner in most cases, and the results are summarized in Scheme 3. It was found that α-amino ketones bearing *N*-aryl substituents such as *p*-Cl, *p*-Br, *p*-CO_2Et, *p*-Me, and 3,4,5-$(MeO)_3$ were all compatible under the catalytic conditions, furnishing **2p**−**2t** in good to high yields. In the case of *p*-CO_2Et-substituted *N*-aryl α-amino ketone, longer reaction time was required, and the resulting product **2r**[14] was formed in a lower yield of 66%, possibly due to the reduced nucleophilicity of the amino group in α-amino ketone and the enamine moiety in the reaction intermediate. α-Amino ketone bearing bulky *N*-(1-naphthyl) substituent afforded **2u** in a low yield of 40%, indicating that the reaction was markedly

DOI: 10.1021/acs.orglett.5b01281
Org. Lett. 2015, 17, 2984−2987

Scheme 3. Scope of α-Amino Ketones[a]

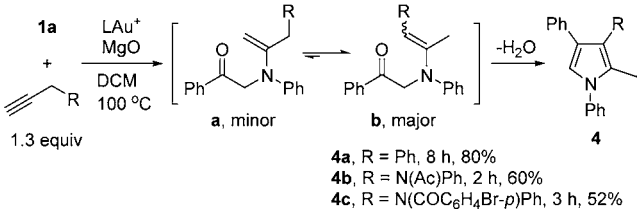


[a]Isolated yields. [b]Containing 7% of the α-vinylated pyrrole **3r**. [c]Containing 6% of **3t**. [d]Room temperature.

influenced by the bulkiness of the *N*-substituent. We next examined the substituent effect (R^1) on the carbonyl group. Both electron-deficient and electron-rich aryl substituents (*p*-F, *p*-OMe, 1-naphthyl) were tolerated well during the reaction, furnishing **2v**−**2x** in 52−78% yields. When R^1 was a vinyl group such as a styryl group, the corresponding pyrrole **2y** was efficiently formed in 75% yield, while the vinyl group remained intact. Aliphatic ketone, as a case study of 1-(phenylamino)-propan-2-one, was also suitable for this reaction, producing **2z** in 61% yield. The substrate bearing a methyl substitutent as R^3 gave tetra- or penta-substituted 2-methylpyrroles **2za** and **2zb** in 75% and 91% yields, respectively. The assembly of 2-methylpyrrole is attractive because the methyl group might be further functionalized[15] via halogenations,[15a] alkyoxylation,[15b] Mannich reactions,[15c] or oxidation reactions.[15d] The structure of pyrroles was unambiguously confirmed by X-ray crystallographic analysis of **2y**.[16] However, the use of *N*-protected α-amino ketones such as *N*-Ts or *N*-Bz protected one failed to produce the desired pyrroles, indicating that the nucleophilicity of the amino group is crucial for successful transformation.[17]

Interestingly, treatment of aliphatic alkynes such as benzyl-substituted alkyne resulted in the formation of tetrasubstituted 2-methylpyrrole **4a** in 80% yield (Scheme 4). We reasoned that

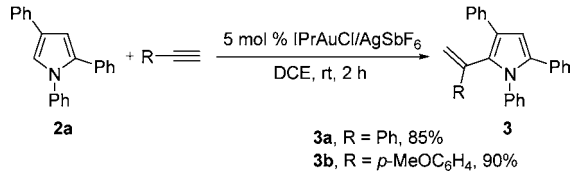
Scheme 4. Reactions with Alkyl-Substituted Terminal Alkynes



the initial formed enamine intermediate **a** might equilibrate with its tautomer **b** via tautomerization. Tautomer **b** might be more stable than **a** and was likely to be the dominant species.[18] Cyclization of **b** led to the formation of **4**. This reaction could be applied to the synthesis of 3-aminopyrroles, a highly useful substance in pharmaceuticals, using propargyl amide as the substrates, in which **4b** and **4c** were formed in 60% and 52% yields, respectively. The above observations also support that the reaction proceeds through the formation of the enamine intermediate.[19]

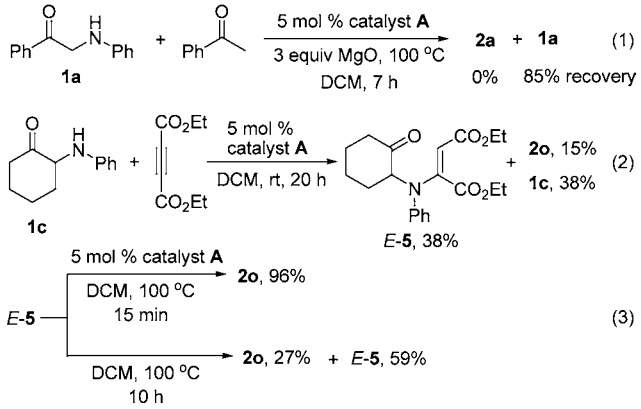
The obtained pyrroles could be alkenylated at its α-position regioselectively via gold-catalyzed intermolecular hydroarylation of alkynes to generate **3a**−**3b** (Scheme 5). It should be noted that intermolecular hydroarylation with substituted pyrroles was less investigated, possibly due to the difficulty of controlling the regioselectivity.[12,20]

Scheme 5. Au(I)-Catalyzed Alkenylation of Pyrroles



To clarify the reaction mechanism, we tried the following control experiments (Scheme 6). It was found that the desired

Scheme 6. Mechanistic Studies

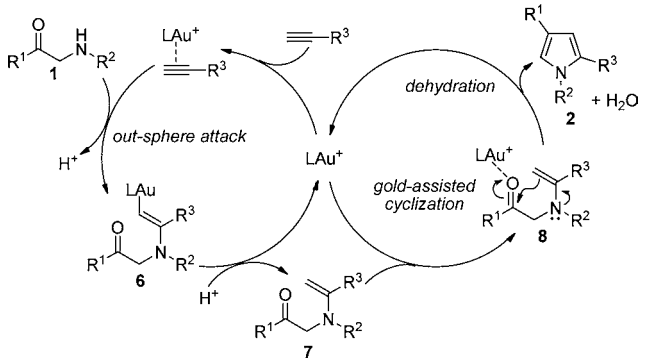


product **2a** was not observed upon stirring **1a** and acetophenone under the standard reaction conditions, implying that the reaction did not proceed via hydration of alkyne followed by condensation with α-amino ketone. In addition, enamine *E*-**5** was isolated in 38% yield by lowering the reaction temperature to room temperature. It was likely that *E*-**5** was formed by gold-catalyzed isomerization of the initially generated *Z*-**5**.[21] *E*-**5** cyclized efficiently within 15 min in the presence of catalyst **A** to afford pyrrole **2o** in 96% yield. However, in the absence of gold catalyst, the reaction efficiency was dramatically decreased (27% yield of **2o**, 10 h). The results indicate that cyclization of the enamine intermediate to pyrrole can be promoted by gold.

On the basis of the above results, we propose the following reaction mechanism for this cascade sequence (Scheme 7). The reaction is initiated by gold-catalyzed regioselective hydroamination of α-amino ketones with terminal alkynes to afford the enamine intermediate **6**. Protodeauration of **6** gives **7**.

DOI: 10.1021/acs.orglett.5b01281
Org. Lett. 2015, 17, 2984−2987

Scheme 7. Proposed Reaction Mechanism



Attack of enamine moiety in **7** to carbonyl group, possible assisted by gold catalyst due to its σ-acidity, followed by elimination of water leads to the final product **2**.

In summary, we have developed a gold-catalyzed hydroamination/cyclization reaction of α-amino ketones with alkynes to multisubstituted pyrroles with high diversity. Gold catalysts are effective to catalyze both processes through activation of the alkyne via π-coordination and carbonyl group via σ-activation. This method offers several advantages such as high regioselectivity with the tested cases, wide substrate scope, and easily accessible starting materials. The synthetic utility of the obtained pyrroles was demonstrated by their efficient transformations to 2-vinylated pyrroles via gold-catalyzed intermolecular hydroarylation. Further studies to extend the scope of this Au-catalyzed cascade reactions are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, spectroscopic characterization of all new compounds, and X-ray crystallography of compounds **2y**, **3a**, and **4a** (PDF, CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01281.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (grant nos. 21125210, 21421091, 21372244), Chinese Academy of Science, and the Major State Basic Research Development Program (grant no. 2011CB808700) for financial support.

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(13) Removing of ester group of **2m** in TFA afforded **2a**. This result confirmed the regiochemistry of **2m**.

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(16) The X-ray crystallography of **2y**, **3a**, and **4a** are shown in the Supporting Information.

(17) See the Supporting Information.

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DOI: 10.1021/acs.orglett.5b01281
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