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Divergent Construction of Fully Substituted Pyrroles and Cyclopentadiene Derivatives by Ynamide Annulations: 1,2-Cyclopropyl Migration versus Proton Transfer

Wenqing Zang, Yin Wei, and Min Shi*

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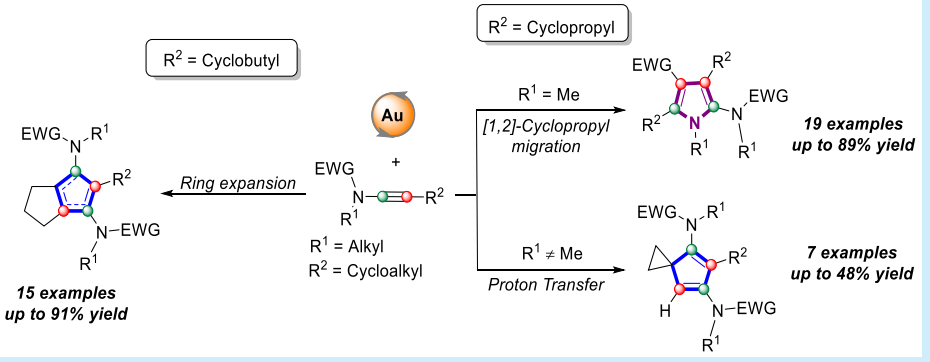

ABSTRACT: A switchable cyclopropyl ynamide cyclization to construct fully substituted pyrroles and cyclopentadiene derivatives in the presence of a gold catalyst was developed. In this version of pyrrole generation, a novel method to furnish gold vinylidenes through [1,2]-cyclopropyl migration was described. On the contrary, the production of cyclopentadienes proceeded through a proton-transfer step. These intriguing mechanisms were proposed based on the structure identification of the alkynyl enamine intermediate and a crossover experiment. The feasibility of cyclobutyl ynamides to specifically construct cyclopentadienes through ring expansion was also investigated.

Owing to their easy availability and high reactivity, ynamide derivatives have been extensively used for the synthesis of versatile *N*-heterocyclic molecules such as pyrroles and quinolines. Ynamides can be regioselectively activated by an electrophile to initiate various intra- or intermolecular cyclizations with either nucleophiles or dipoles in these reactions.[1] During the last several decades, the use of gold catalysis in organic synthesis has been thoroughly investigated due to its unique performance as a Lewis acid catalyst, π-activator, or carbenoid intermediate.[2] In particular, electrophilic gold catalysts have become a powerful and useful synthetic tool for catalyzing a wide variety of cyclization reactions initiated by nucleophilic attack on activated unsaturated bonds such as alkyne,[3] allene,[4] or olefin[5] moieties. Among them, the annulation of ynamides in gold catalysis has attracted considerable attention.[6]

Employing anthranils, 1,2-benzisoxazoles, alkenes, or azide analogues as nucleophiles, the regulation of selectivity has deserved priority in ynamide cyclizations.[7] However, alkynes are rarely treated as counterparts in these transformations.

In 2011, a gold-catalyzed ynamide dimerization to construct a cyclopentadiene structure through a keteniminium intermediate was described by Gagosz, Skrydstrup, and coworkers (Scheme 1a).[8] In 2019, Sahoo's group reported a gold-catalyzed intramolecular cycloisomerization of yne-tethered ynamide to furnish multisubstituted pyrroles based on an umpolung strategy (Scheme 1b).[9] Pioneered by these excellent works as well as upon the consideration of a few investigations of the transformation of cycloalkyl ynamides,[10] we envisioned that the installment of strained small cycloalkyl groups on the alkyne moiety may exhibit diversified reaction pathways upon gold catalysis.[11] In this scenario, we wish to depict the feasibility of cyclopropyl or cyclobutyl ynamide cyclizations to realize the divergent synthesis of fully substituted pyrrole and cyclopentadiene derivatives under gold catalysis. Notably, a possible pattern to generate gold vinylidene species[12] through an unconventional [1,2]-cyclopropyl migration was discovered in this version of pyrrole generation, whereas the cyclopentadienes were produced by proton transfer. In addition,

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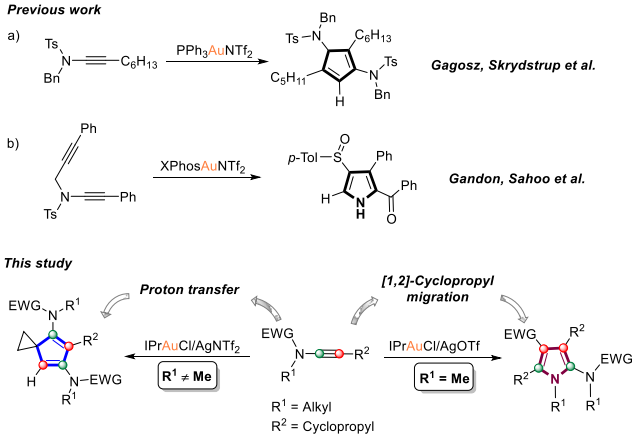
Scheme 1. Gold(I)-Catalyzed Annulation of Ynamides to Construct Cyclic Compounds

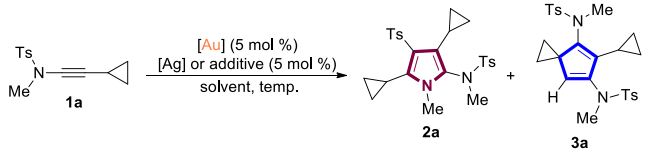


cyclobutyl ynamides could specifically yield a fused cyclopentadiene backbone through the ring expansion process (Scheme 1, this study).

The examination of the optimal reaction conditions was conducted by applying **1a** as a model substrate, and the results are summarized in Table 1. First, using NaBArF as the counterion, we examined the gold catalysts with different phosphine ligands such as PPh_3AuCl (5 mol %) and JohnPhosAuCl (5 mol %) in 1,2-DCE, but we found that the reaction did not afford the desired product (Table 1, entries 1 and 2). However, when IPrAuCl (5 mol %), an NHC-ligated (*N*-heterocyclic-carbene-type ligand) gold complex, was used as the catalyst, the desired pyrrole product **2a** was given in 60% yield within 6 h (Table 1, entry 3). The use of silver salts such as $AgBF_4$, $AgNTf_2$, AgOTf, and $AgSbF_6$ as the additives was examined in the reaction, and we found that adding AgOTf could afford **2a** in a higher yield of 61% (Table 1, entries 4−7).[13] Next, the solvent effect was thoroughly investigated by using toluene, DCM, CH_3CN, dioxane, PhF, and chlorobenzene (PhCl) as the solvents, revealing that PhCl was the best one to deliver **2a** in 70% yield (62% isolated yield) (Table 1, entries 8−13), which was eventually considered to be the optimized conditions (Table 1, entry 13). The yield of **2a** sharply dropped to 52% when the gold catalyst loading was increased to 10 mol %, perhaps due to the fact that the higher catalyst loading accelerated the precipitation of gold(0) in the presence of reducing substrates (Table 1, entry 14).[14] Using prepared IPrAuOTf as the catalyst provided no target product, suggesting that the catalytic process may exhibit a "silver effect" (Table 1, entry 15).[15] The control experiment indicated that no **2a** was generated in the absence of a gold catalyst (Table 1, entry 16). It should also be mentioned that cyclopentadiene derivative **3a** was detected as a byproduct during these screening processes. The structure of **2a** has been unequivocally confirmed by X-ray diffraction. (See the Supporting Information.)

Having established the optimal reaction conditions, we decided to investigate the substrate scope, and the results are summarized in Scheme 2. First, when R^1 was a Me group, employing phenylsulfonyl ynamide **1b** as the substrate, the corresponding fully substituted pyrrole **2b** could be delivered in 73% yield. Then, we examined the reaction outcomes by using **1** with different electron-donating-group (EDG)-substituted phenyls as substrates. As can be seen from Scheme 2, for substrates **1c−i**, the reactions proceeded smoothly in PhCl, furnishing the corresponding products **2c−i** in 48−84% yields. In particular, substrate **1i** bearing a Ph group afforded the desired product **2i** in 84% yield. When an electron-withdrawing group (EWG) was substituted on the phenyl

Table 1. Optimization of the Reaction Conditions for Gold(I)-Catalyzed Transformation of 1a to 2a and 3a



				yield (%)[a]	
entry[b]	Au cat (5 mol %)	[Ag] or additive (5 mol %)	solvent	**2a**	**3a**
1	PPh_3AuCl	NaBArF	1,2-DCE	N.D.	
2	JohnPhosAuCl	NaBArF	1,2-DCE	N.D.	
3	IPrAuCl	NaBArF	1,2-DCE	60	17
4	IPrAuCl	$AgBF_4$	1,2-DCE	48	14
5	IPrAuCl	$AgNTf_2$	1,2-DCE	50	16
6	IPrAuCl	AgOTf	1,2-DCE	61	18
7	IPrAuCl	$AgSbF_6$	1,2-DCE	54	16
8	IPrAuCl	AgOTf	toluene	60	16
9	IPrAuCl	AgOTf	DCM	16	6
10	IPrAuCl	AgOTf	CH_3CN	trace	
11	IPrAuCl	AgOTf	dioxane	trace	
12	IPrAuCl	AgOTf	PhF	57	24
13	**IPrAuCl**	**AgOTf**	**PhCl**	**70 (62)**	**24 (20)**
14	IPrAuCl[c]	AgOTf[c]	PhCl	52	23
15	IPrAuOTf		PhCl	N.D.	
16		AgOTf	PhCl	N.D.	

[a]Yield was determined by ^1H NMR yield using 1-bromo-4-methoxybenzene as an internal standard. [b]Reaction scale is 0.1 mmol of **1a** in anhydrous solvent (0.1 M) at rt for 6 h. [c]10 mol %, 1 h.

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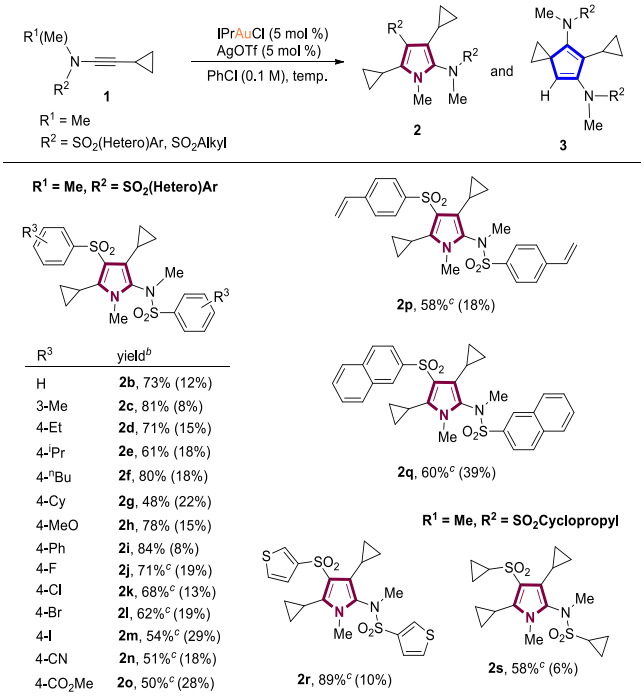
Scheme 2. Substrate Scope of Ynamides 1 to Produce Pyrroles 2 with Cyclopentadienes 3 as Byproducts[a]



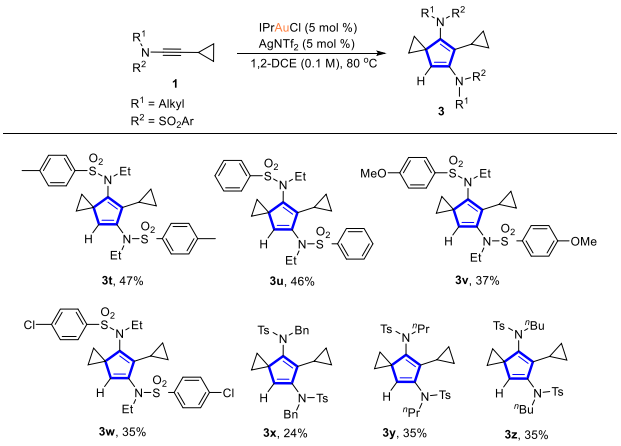
R^3	yield[b]
H	**2b**, 73% (12%)
3-Me	**2c**, 81% (8%)
4-Et	**2d**, 71% (15%)
4-^{i}Pr	**2e**, 61% (18%)
4-^{n}Bu	**2f**, 80% (18%)
4-Cy	**2g**, 48% (22%)
4-MeO	**2h**, 78% (15%)
4-Ph	**2i**, 84% (8%)
4-F	**2j**, 71%[c] (19%)
4-Cl	**2k**, 68%[c] (13%)
4-Br	**2l**, 62%[c] (19%)
4-I	**2m**, 54%[c] (29%)
4-CN	**2n**, 51%[c] (18%)
4-CO_2Me	**2o**, 50%[c] (28%)

[a]General conditions: **1** (0.2 mmol), IPrAuCl (5 mol %), and AgOTf (5 mol %) in PhCl (0.1 **M**) at rt, 12 h. [b]All yields are the isolated yields. (The yields of side product **3** are presented in parentheses.) [c]80 °C.

moiety in substrates **1j** to **1o**, even upon introducing CN and CO_2Me substituents, the desired products **2j−o** were still given in moderate to good yields ranging from 50 to 71% after increasing the reaction temperature to 80 °C. The reaction also performed well when a vinyl group was installed on the phenyl moiety, giving the corresponding product **2p** in a yield of 58%. Changing the phenyl group to a 2-naphthyl group, the desired product **2q** was obtained in 60% yield. A heteroaromatic group was also tolerated, furnishing the desired product **2r** in 89% yield. Moreover, the substrate **1s** bearing an aliphatic sulfonyl group was also compatible, giving the desired product **2s** in 58% yield after increasing the reaction temperature to 80 °C. However, when R^1 was a phenyl group, the reaction afforded no desired pyrrole products. It should also be noted that the isolated yields of the corresponding byproduct cyclopentadienes **3** are summarized in parentheses in Scheme 2.

Interestingly, when an alkyl group other than a methyl group was substituted at the R^1 position, the substrates could undergo a specific reaction pathway to produce cyclopentadiene backbones **3** without the formation of corresponding pyrroles. This may be due to the stronger hyperconjugation of the C−C σ bond than that of the C−H σ bond on the alkyl group (donor orbital) with an *N*-cationic unit (vacant p orbital) (see Scheme 5 for the description), which can provide a more stable keteniminium intermediate for intermolecular dimerization instead of intramolecular rearrangement.[16] After the reaction conditions were screened by using **1t** as a model substrate (see Table S1 in the Supporting Information), we decided to conduct the reaction in 1,2-DCE and apply IPrAuCl/$AgNTf_2$ (5 mol %) as the optimal catalyst to investigate the substrate scope, and the results are summarized in Scheme 3. When R^1 is an ethyl group and R^2 is an aromatic sulfonyl moiety having no substitution or bearing an EDG or

Scheme 3. Substrate Scope of Ynamides 1 to Specifically Deliver Cyclopentadienes 3[a]

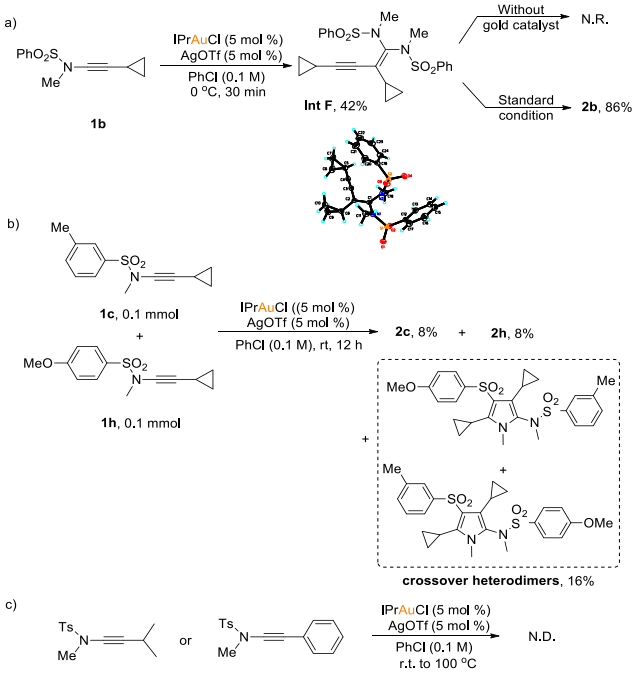


[a]General conditions: **1** (0.2 mmol), IPrAuCl (5 mol %) and $AgNTf_2$ (5 mol %) in 1,2-DCE (0.1 M) with 3 Å MS at 80 °C, 24 h. All yields are the isolated yields.

EWG substituent, the reactions could afford the corresponding products **3t−w** in moderate yields ranging from 35 to 47%. Moreover, the benzyl group was also tolerated, giving the desired product **3x** in 24% yield. The reaction also occurred when the R^2 group was switched to a ^{n}Pr or a ^{n}Bu group, giving the corresponding products **3y** and **3z** in 35% yields, respectively.

To clarify the reaction mechanism, several control experiments were carried out, as shown in Scheme 4. First, we quenched the reaction after 30 min under the standard conditions, and an alkynyl enamine intermediate **F** was isolated in 42% yield, indicating that a [1,2]-cyclopropyl migration

Scheme 4. Control Experiments



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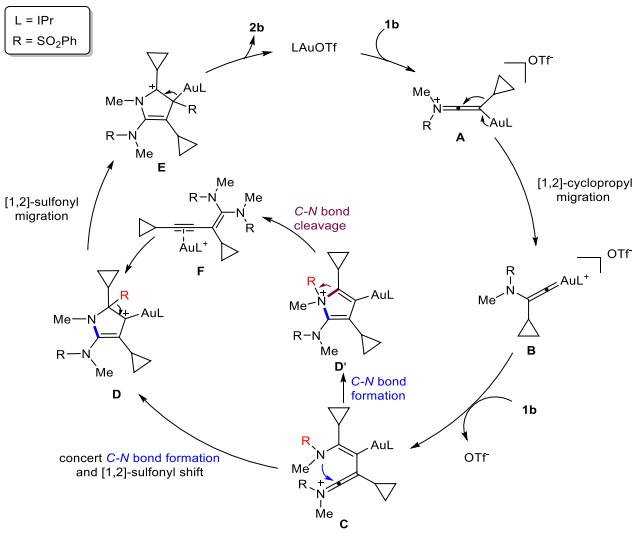
indeed took place in the catalytic cycle, and the reaction may proceed through the corresponding gold vinylidene complexes. The structure of species **F** has been unequivocally confirmed by X-ray diffraction. In addition, the isolated intermediate **F** could be further transformed to the desired product **2b** in 86% yield under the standard conditions, and no **2b** was detected in the absence of gold catalyst (Scheme 4a). A crossover experiment was also conducted upon treating **1c** with **1h** under the standard conditions. We found that the products were afforded with no selectivity, and a mixture of homodimers and crossover heterodimers was produced (Scheme 4b). This result further indicated a dimerization process of ynamides. Moreover, by employing *gem*-dimethyl or phenyl ynamides instead of cyclopropyl ynamides, none of the desired pyrroles were detected as products (Scheme 4c). This result indicated the unique character of the cyclopropane moiety in the reaction.

On the basis of these mechanistic studies and previous works, a plausible mechanism[17] for the transformation of **1** to **2** is outlined in Scheme 5. As for substrate **1b**, the coordination

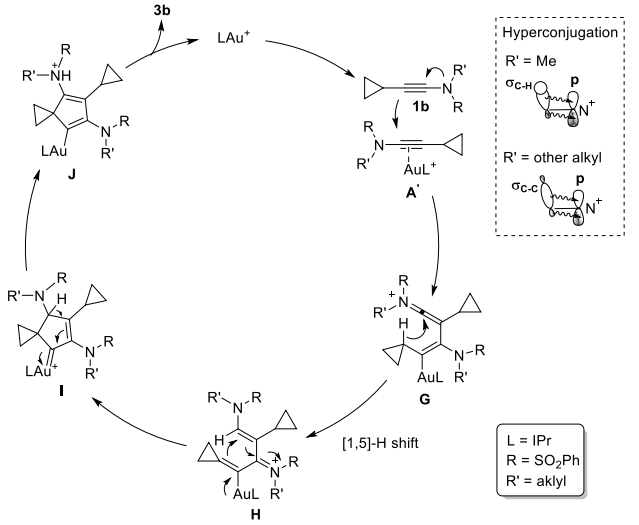
Scheme 5. Plausible Reaction Mechanism for the Transformation of Ynamides 1 to Pyrroles 2



with the employed gold catalyst gives intermediate **A**, which undergoes a [1,2]-cyclopropyl migration, affording vinyl gold carbenoid intermediate **B**, followed by the nucleophilic addition of another molecule of substrate **1b** to this gold vinylidene complex, leading to the formation of the keteniminium species **C**. Next, an intramolecular C−N bond formation and 1,2-sulfonyl shift process occur in concert to render an intermediate **D**.[18] Subsequently, 1,2-migration of the sulfonyl group takes place again to form pyrrolyl intermediate **E**. Finally, species **E** undergoes a gold elimination to afford the desired product **2b** along with the regeneration of the gold catalyst. During this catalytic cycle, the existence of intermediate **F**, which is derived from an *N*-nucleophilic attack on the keteniminium unit from intermediate **C** followed by another C−N bond cleavage, also contributes to the generation of intermediate **D** under gold catalysis. (See the Supporting Information for more details.)

In terms of the dimerization of cyclopentadiene compounds **3** from ynamides **1**, an alternative mechanism is demonstrated in Scheme 6.[8] Instead of the intramolecular cyclopropyl

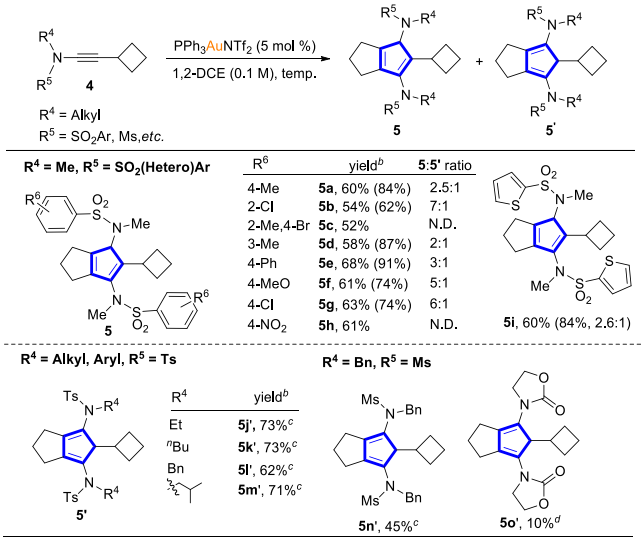
Scheme 6. Plausible Reaction Mechanism for Substrates 1b Dimerization to Give Cyclopentadienes 3b



migration, the intermediate **A′** would undergo an intermolecular nucleophilic attack of **1b**, giving rise to keteniminium species **G**. A subsequent [1,5]-H shift followed by a metalla-Nazarov cyclization would lead to a gold carbenoid intermediate **I** through intermediate **H**. Then, a proton transfer could furnish intermediate **J**, and the cyclopentadiene **3b** would be finally produced through the protodeauration of the gold catalyst.

To further extend the reaction scope, the examination of cyclobutyl ynamides **4** was performed as the last part of this scenario (Scheme 7). Substituted by a methyl group at the R^4 position, either an EWG or an EDG on the phenylsulfonyl moiety, the reactions efficiently proceeded, affording the corresponding cyclopentadiene products **5a−h** through ring

Scheme 7. Substrate Scope of Ynamides 4 to Cyclopentadienes 5 and 5′[a]



[a]General conditions: **4** (0.2 mmol), PPh_3AuNTf_2 (5 mol %) in 1,2-DCE (0.1 M) at rt, 12 h. [b]All yields are the isolated yields. (The total yields of isomers **5** and **5′** are presented in parentheses.) [c]60 °C. [d]80 °C.

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expansion in moderate to good yields ranging from 52 to 68%. (The detailed mechanism is depicted in Scheme S1.) A heteroaromatic group was also tolerated, furnishing the desired product **5i** in 60% yield. Moreover, the ratios of products **5′**, which are the regioisomers of **5**, are also listed in Scheme 7. The reaction also proceeded smoothly when R^4 was switched to other alkyl groups, giving **5j′−m′** in 62−73% yields as single regioisomers after increasing the reaction temperature to 60 °C. The reaction also proceeded smoothly when R^5 was a Ms group, producing **5n′** in 45% yield. The structures of **5a′**, **5i**, and **5l′** have been unequivocally confirmed by X-ray diffraction. (See the Supporting Information.) It should also be mentioned that the cyclopentyl ynamide only gave rise to a complex mixture.

In summary, we have discovered gold-catalyzed cyclopropyl ynamide cyclizations to selectively synthesize fully substituted pyrroles and cyclopentadiene derivatives. In this version of pyrrole construction, an unconventional pattern to generate gold vinylidene species through [1,2]-cyclopropyl migration was proposed. On the contrary, the cyclopentadienes were produced through proton transfer. Moreover, the dimerization of cyclobutyl ynamides could specifically produce cyclopentadienes through ring expansion. Further investigations of the mechanistic details and exploration of new methodologies based on this new gold carbene generation process are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01819.

Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for new compounds (PDF)

Accession Codes

CCDC 1907300, 1919649, 1948342, 1952765, and 1995246 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Min Shi − *State Key Laboratory of Organometallic Chemistry, Center for Excellence in Molecular Synthesis, University of Chinese Academy of Science, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*; orcid.org/0000-0003-0016-5211; Email: mshi@mail.sioc.ac.cn; Fax: 86-21-64166128

Authors

Wenqing Zang − *State Key Laboratory of Organometallic Chemistry, Center for Excellence in Molecular Synthesis, University of Chinese Academy of Science, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*

Yin Wei − *State Key Laboratory of Organometallic Chemistry, Center for Excellence in Molecular Synthesis, University of Chinese Academy of Science, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*; orcid.org/0000-0003-0484-9231

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01819

Notes

The authors declare no competing financial interest.

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