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Rapid Access to Cyclopentadienes Derivatives through Gold-Catalyzed Cycloisomerization of Ynamides with Cyclopropenes by Preferential Activation of Alkene over Alkyne

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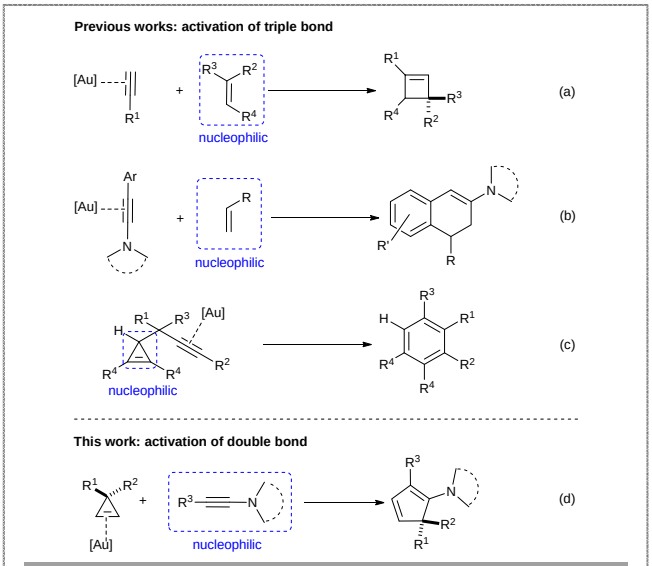
In this communication, the gold-catalyzed intermolecular cycloisomerization of cyclopropenes and ynamides is investigated. The current transformation displayed an activation priority of double bond over triple bond by the cationic gold catalyst, giving the corresponding cyclopentadienes in good to excellent yields. Additionally, this protocol can be expanded to a one-pot two-step procedure for the synthesis of substituted cyclopentones.

Gold-catalyzed cycloisomerization of enynes has received considerable attention in the past decades.[1,2] The state-of-art of this strategy has been showcased by construction of complex molecules from simple building blocks in highly efficient and atom economical fashion. Generally, the cationic gold catalyst would preferentially activate the alkyne moiety instead of the alkenyl tether. Hence, in absence of additional nucleophiles, nucleophilic addition of the alkene to the activated alkyne would take place selectively. Similar priority has also been displayed by gold-catalyzed intermolecular reaction of alkenes with alkynes. For example, Echavarren has implemented an elegant approach to cyclobutenes via gold-catalyzed intermolecular [2+2] cycloaddition of simple alkenes and alkynes (Scheme 1a).[3] More recently, Liu and co-workers reported intermolecular reaction of ynamides[4] with alkenes (Scheme 1b).[5] Liu[6] and we[7] have concurrently reported gold-catalyzed intermolecular nitrene transfer[8] from 2*H*-azirines to ynamides. As a carbo-variant of 2*H*-azirine, cyclopropene also possesses high strain energy, and ready for ring opening under mild conditions.[9] In connection to our interest in gold-catalyzed annulation,[7,10] we were curious about the reactivity of cyclopropene towards ynamide under gold catalysis. In 2010, Wang and co-workers have disclosed a regioselective synthesis



Scheme 1. Examples on gold catalyzed enyne cycloisomerizations.

of benzene derivatives (Scheme 1c).[11] Intriguingly, they have also observed the preferential activation of alkynyl moiety over the strained alkene (cyclopropene) by a gold catalyst. Despite of these elegant achievements, to our knowledge, gold-catalyzed intermolecular reaction of alkyne with cyclopropene has never been realized before.[12] Below, we describe our recent efforts, which led to the newly discovered activation priority of alkene over alkyne by cationic gold catalyst. Guided by this reaction mode, substituted cyclopentadiene derivatives were synthesized in an atom economic fashion (Scheme 1d).

By taken advantage of the ambivalent nature of ynamide, Gagosz and Skrydstrup have developed a rare approach to substituted cyclopentadiene via the dimerization of the corresponding alkyne.[13] For the gold-catalyzed reaction of ynamides with propargylic carboxylates, Hashmi and co-workers have found that the dimerization of ynamides were completely suppressed once carbenoid intermediate was generated, giving cyclopentadienes exclusively.[14] It is

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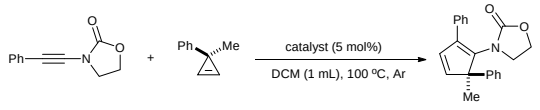
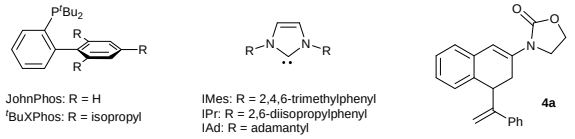
worthwhile to mention that the ynamides employed in these two cases displayed relatively limited substrate scope. The current method complements studies of Gagosz, Skrydstrup and Hashmi. Compared with the intramolecular reaction of cyclopropene and alkyne reported by Wang,[11] this study showed reverse activation priority of cyclopropene over alkyne by gold catalyst, even though ynamide is generally considered to be more reactive than normal internal alkyne.

Table 1. Substrates scope with respects to a variety of triazoles **2**. [a]



1a, 0.2 mmol **2a**, 1.0 mmol **3a**

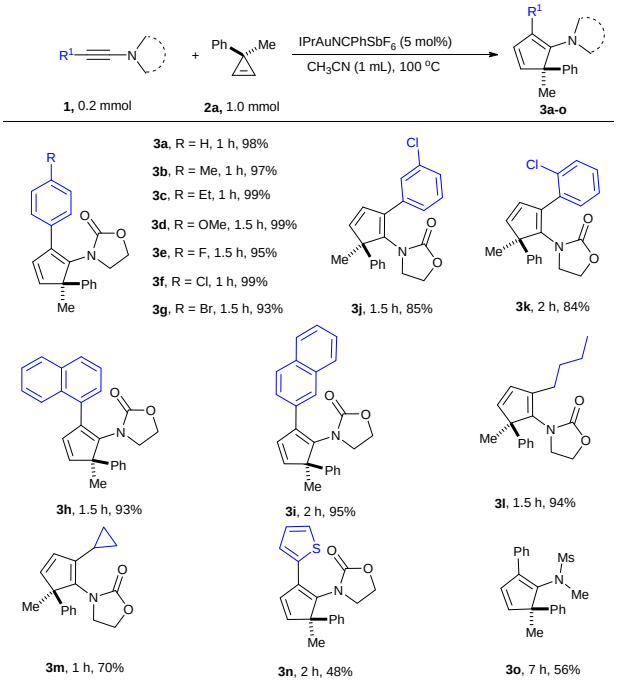
entry	catalyst	time (h)	**3a** (%)[a]	**4a** (%)[a]
1	JohnPhosAu(MeCN)SbF_6	1	47	25
2	^{t}BuXPhosAu(MeCN)SbF_6	4	trace	35
3	PPh_3AuNTf_2	2	70	--
4	$(4\text{-}CF_3C_6H_5)_3PAuNTf_2$	3	62	--
5	IMesAuCl/$AgNTf_2$	2	82	--
6	IAdAu(PhCN)SbF_6	22	61	--
7	IPrAu(PhCN)SbF_6	2.5	97	--
8	IPrAuCl	50	NR	
9	$AgSbF_6$	60	trace	
10[b]	IPrAu(PhCN)SbF_6	1	98	--
11[c]	IPrAu(PhCN)SbF_6	1	95	--



[a] Isolated yield. [b] CH_3CN was selected as solvent instead of DCM. [c] DCE was selected as solvent instead of DCM.

We began our study using readily available ynamide **1a** and cyclopropene **2a** as the model substrates (Table 1). To test the reactivity of **1a** towards cyclopopene **2a**, we first examined the activity of the Echavarren's catalyst [JohnPhosAu(MeCN)SbF_6][15] which has been proved to be active catalyst in our previous reaction of ynamides and 2*H*-azirines.[7] As depicted, when the reaction was carried out in dichloromethane (DCM) at 100 °C for 1h, multi-substituted cyclopentadiene **3a** was isolated in 47% yield. Together with **3a**, dihydronaphthalene **4a** was also obtained in 25% yield (entry 1). Of note, the products resulting from dimerization of **1a**[13] were not observed. Because of self-reaction, an excess of **2a** was required. These reaction outcomes may indicate a preferential coordination of cyclopropene **2a** over ynamide **1a**. The structure of **3a** was further confirmed by single-crystal X-ray analysis. When a catalyst bearing a more bulky ligand (^{t}BuXPhos) was employed, longer reaction time was required. Although **4a** was isolated in slightly higher yield, there was only trace of **3a** could be observed from the reaction mixture (entry 2). Pleasingly, the reaction catalyzed by Gagosz's catalyst ($Ph_3PAuNTf_2$)[16] led to a selective formation **3a**, which was obtained in 70% yield upon isolation (entry 3). Further screening of the catalysts led to the best choice of the cationic gold catalyst bearing an *N*-heterocyclic carbene ligand, with respect of both reaction time and the isolated yield of **3a** (entry 7). Control experiments highlighted the critical role of the cationic nature of gold catalyst (entries 8 and 9). Switching the reaction media to DCE (1,2-dichloroethane) or acetonitrile, resulted in a slightly shorter reaction time, while similar yields were maintained (entries 10 and 11). We have also tried to examine other reaction parameters to enhance the selectivity and the yield of **4a**, however no positive effects were obtained thus far.[17]

Table 2. Scope of Ynamides **1** with Cyclopropene **2a**. [a]

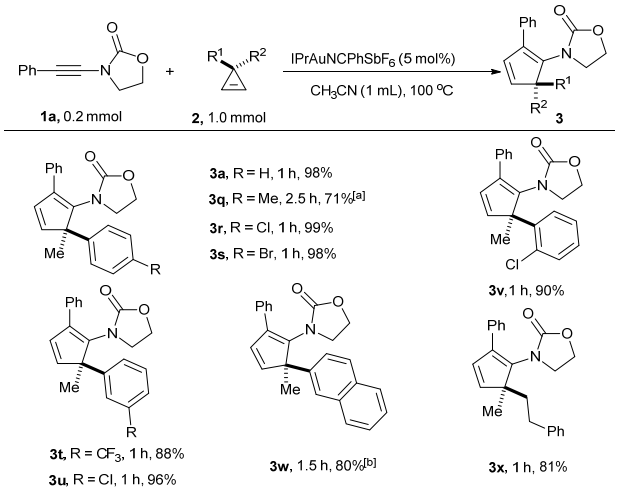


[a] [**1**] = 0.2 M , yields were referred to pure products upon isolation after column chromatography on silica gel.

This new method proved to be versatile, as a wide array of ynamides could participate in current transformation, and the results were shown in Table 2. Specifically, a series of ynamides featuring both electron-donating (methyl, ethyl and methoxy, **3b**-**3d**) and electron-withdrawing (fluoro, chloro, and bromo, **3e**-**3g**) groups at the *para* position of the phenyl ring were well tolerable under the standard conditions, providing the desired products in good to excellent yields (84-99%). The ynamides containing chloro group at the *meta* and *ortho* position of the phenyl ring reacted well with **2a**, affording the corresponding cyclopentadienes (cf. **3j** and **3k**) in high yields (85% and 84%). 1-naphthyl, and 2-naphthyl substituted ynamides were viable substrates as well, leading to the formation of desired product **3h** and **3i** in excellent yields (93% and 95%). Interestingly, the ynamides derived from hex-1-yne and ethynylcyclopropane (**1l** and **1m**) were also amenable to this reaction. Compound **3l** and **3m** were obtained in 94% and 70% yields, respectively. In addition, the reaction of ynamide derived from thienyl acetylene (**1n**) took place well (cf. **3n**). Replacing the oxazolidinone moiety with a sulfonamide group,

resulted in a lower reaction rate, and corresponding cyclopentadiene **3o** was obtained with 56% yield.

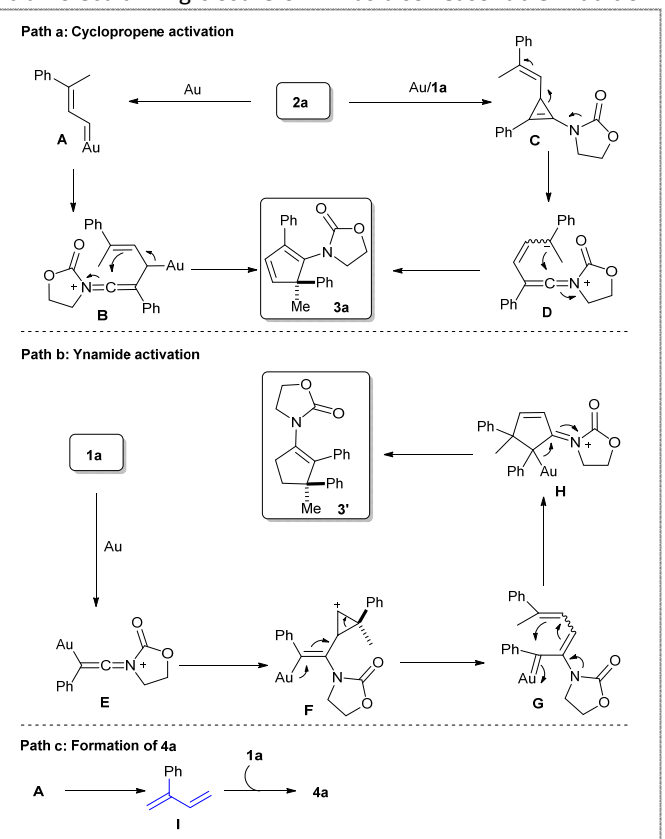
Table 3. Scope of Cyclopropene **2** with Ynamides **1a**. [a]



[a] Cyclopropene 2b was added in four portions (0.5 mmol/0.5 h), after the addition, the reaction was heated for one more hour. [b] Cyclopropene 2h (1 mmol, 5 equiv) was added, after stirred at 100 °C for one hour, another portion of 2h (0.4 mmol, 2 equiv) was added, then the reaction was heated for half an hour.

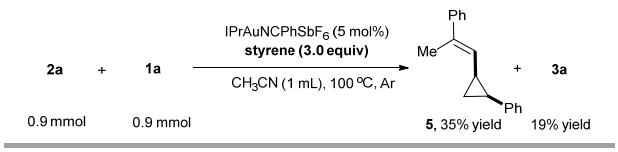
Subsequently, with the ynamide **1a** as the model nucleophile, an array of cyclopropenes **2** were tested under standard conditions. As the results depicted in Scheme 3, by variation of R^2 in cyclopropene **2**, electron-donating groups (methyl) and electron-withdrawing (chloro, and bromo) groups setting at the *para* position of the phenyl ring had negligible effects on the reactions, and all cyclopropenes reacted smoothly with ynamide **1a**, giving the corresponding cyclopentadienes in 71%-99% yields (cf. **3q**, **3r** and **3s**). Similarly, cyclopropenes containing trifluoromenthyl or chloro group at the *meta* position of the phenyl ring exhibited good reactivity as well, affording the desired cyclopentadienes in excellent yields (cf. **3t** and **3u**). Moreover, cyclopropene **2v** bearing steric hindered group (*otho*-chlorophenyl) could also react with **1a** equally well, leading to formation of **3v** in 90% yield upon isolation. 2-Naphthyl, methyl and dialkyl substituted cyclopropenes (**2w** and **2x**) could react with ynamide **1a**, furnishing cyclopentadienes **3w** and **3x** in 80% and 81% yields, respectively.

From mechanistic point of view,[18] two reaction pathways based on distinct activation piority of the π bond systems could be proprosed (Scheme 2). Activation of cyclopropene **2a** (path a) by cationic gold catalyst would furnish vinyl carbenoid intermediate **A**. By taking advantage of the nucleophilic nature of ynamide, addition of **1a** to intermediate **A** would give **B**. Intramolecular cyclization of allylic gold moiety to the most electrophilic carbon center results in the formation of the final product **3a** and with concomitant regeneration of the gold catalyst. Although efforts to isolate transient cyclopropene **C** were not successful thus far, an alternative mechanistic pathway going through cyclopropenation of ynamide **1a**,[19] enamide triggered ring opening of **C**, followed by the intramolecular ring closure of **D** was also reasonable. Addition



Scheme 2. Mechanism rationale.

of styrene to the reaction mixture gave cyclopropane **5** as the major product (Scheme 3).[20] The formation of **5** provides evidence for the generation of carbene intermediate **A**. Because of the observed regioselective of cyclopentadiene **3** (**3a** vs **3'**), the reaction pathway initiated by activation of ynamide could be ruled out (path b). Under certain conditions, a 1,4-hydride migration of **A** might take place, furnishing phenyl-substituted 1,3-diene **I**, which could further serve as a two-carbon unit to participate in Liu's [4+2] cycloaddition with ynamide **1a**,[5] and eventually gave dihydronaphthalene **4a** (path c).

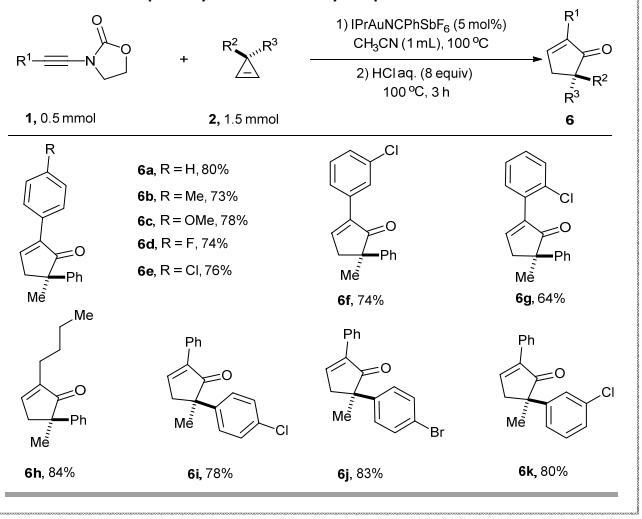


Scheme 3. Mechanistic experiment.

The enamide moiety in **3** has offered a useful synthetic handle for downstream manipulation. After brief condition optimization, **3a** could be transformed to substituted cyclopentenone **6** after simple acidic workup. It is worthwhile to mention that when the reaction was carried out on 0.5 mmol scale, the amount of cyclopropene **2** could be decreased to 3 equiv. without sacrifising the reaction outcome. Encouraged by this result, we sought to develop a one-pot two-step procedure for the direct preparation of **6**. Pleasingly,

when the gold-catalyzed formal [3+2] cycloaddition were complete, without the isolation of **3**, treatment of the reaction mixture with 8 equiv of concentrated HCl aq., and heating for 3 h at 100 °C, a variety of cyclopentenones **6** could be prepared in a straightforward manner (Table 4).

Table 4. One-pot synthesis of cyclopentenones **6**.



In summary, we have described the first gold-catalyzed intermolecular cycloisomerizaition of ynamides with cyclopropenes, furnishing polysubstituted cyclopentadienes in good to excellent yields. Compared with previous gold-catalyzed enyne cycloisomerization, the current work represents a rare example on activation priority of alkenes over alkynes under gold catalysis.[21]

Acknowledgements

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