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Gold/Gallium-Catalyzed Annulation of 1,3-Dicarbonyl Compounds and Cyclopropylacetylenes for Synthesis of Substituted Cyclopentenes

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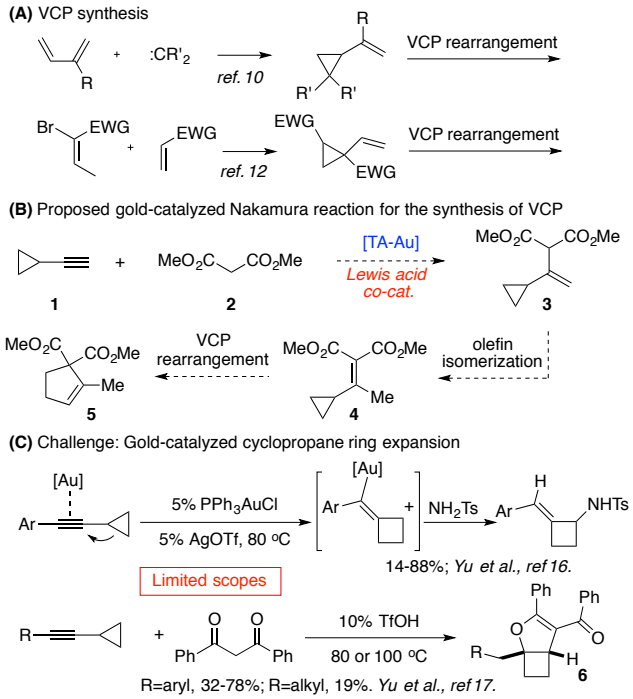
An efficient synthesis of substituted cyclopentenes through gold/gallium-catalyzed annulation of 1,3-dicarbonyl compounds and cyclopropylacetylenes is achieved. This tandem reaction consists of a gold-catalyzed Nakamura reaction, a catalytic dienol-enone tautomerization, and a gallium-catalyzed vinylcyclopropane (VCP) rearrangement.

Vinylcyclopropane (VCP)[1] represents a class of cyclopropane derivatives that possesses high synthetic value.[2] It can participate in various cycloaddition and rearrangement reactions.[3] In particular, VCP rearrangement leads to the formation of cyclopentene, a versatile synthetic building block in organic chemistry,[4] which has been also found in many classes of natural products and drug molecules.[5] However, successful examples of VCP rearrangement catalyzed by transition-metal catalysts remain quite limited.[6] Most of these still require high temperature (60-100 °C)[7] and activated VCPs,[8] thus offering no significant improvements comparing to thermal ones. The N-heterocyclic carbene (NHC) nickel catalyzed VCP isomerization reported by Louie and coworkers is the only system that could facilitate this transformation with electronically unbiased VCP at room temperature.[9]

Typical procedure for synthesis of VCP includes cyclopropanation of 1,3-diene through carbene insertion,[10] and annulation of α,β-unsaturated carbonyl compound[11] and α-bromo-α,β-unsaturated carbonyl compound[12] (**Scheme 1A**). However, these syntheses require multiple steps, and thus largely limit the utility towards cyclopentene synthesis. Thus, an efficient synthesis of VCP followed by preferably a one-pot VCP rearrangement will be highly desirable. Herein, we report a novel strategy that utilizes simple 1,3-dicarbonyl compounds and cyclopropylacetylenes as starting materials to achieve an efficient synthesis of cyclopentenes enabled by gold/gallium tandem catalysis.

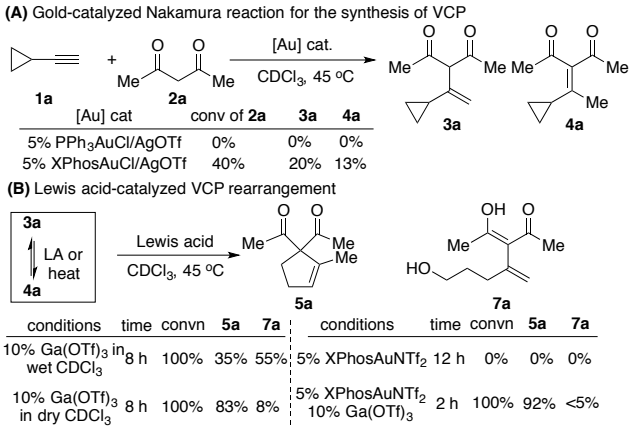
During the last several years, our group has been working on developing novel transition-metal catalytic systems using 1,2,3-triazoles as the ligands.[13] These efforts led to the discovery of triazole-gold complexes (TA-Au) as stable yet active catalysts for alkyne activation. Recently, we reported that the use of our TA-Au catalysts in combination with a catalytic amount of Lewis acid led to a new catalytic system with improved reactivity. With this strategy, some intermolecular additions that were previously challenging were achieved, therefore expanding the scope of cationic gold(I) catalysis.[14] For example, Nakamura reaction—intermolecular Markovnikov addition of 1,3-diketone or β-ketoester across C-C triple bond of alkyne, was accomplished.[15]



Scheme 1. Vinylcyclopropane rearrangement

As shown in **Scheme 1B**, we postulated the formation of vinylcyclopropane **3** through a gold-catalyzed addition of 1,3-dicarbonyl compound **2** to an alkyne. The VCP **4** can be formed through olefin isomerization of **3**. With **4** in hand, the VCP rearrangement could then occur in the presence of catalytic amount of Lewis acids. In fact, the reaction between cyclopropylacetylene

and nucleophiles in the presence of gold or acid catalyst led to the formation of cyclobutane derivatives, which is an undesired pathway for our proposed cyclopentene synthesis (**Scheme 1C**). For example, Yu and coworkers reported the gold-catalyzed addition of tosylamides to cyclopropylacetylenes, where a cyclobutyl cation intermediate was proposed.[16] Although the reaction suffers from harsh conditions (80 °C) and limited substrate scope (and modest yields in many cases), it provides an interesting example of cyclopropylacetylene activation by a gold catalyst. Later, the same group reported triflic acid-catalyzed addition of 1,3-diketones and cyclopropylacetylenes, [17] which further posed the potential challenges for our proposed cyclopentene synthesis. To explore the possibility of the proposed VCP rearrangement, we synthesized the VCP **3a** through gold-catalyzed intermolecular Nakamura reaction. **3a** was then subjected to various Lewis acids to seek conditions for the rearrangement. The results are summarized in **Scheme 2**.



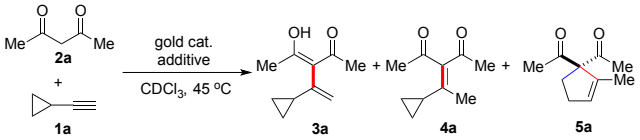
Scheme 2. Lewis acid-promoted VCP rearrangement

As shown in **Scheme 2A**, the reaction of alkyne **1a** and 1,3-diketone **2a** in the presence of catalyst [XPhosAu]OTf provided a mixture of VCP **3a** and **4a**, though in low yields. However, treating either VCP with Lewis acid, such as $Ga(OTf)_3$ and AgOTf, led to interconversion of the two isomers, reaching thermodynamic equilibrium (**3a:4a** ~2:1) within 1 h. As expected, treating these EWG-modified VCPs (pure isomer of **3a**/**4a** or mixtures) with Lewis acid $Ga(OTf)_3$ gave the desired rearrangement product **5a** in 35% yield, along with side product **7a** which was resulted from water addition. The amount of **7a** could be significantly reduced when dry solvent was used. Notably, the cyclobutane derivative **6** (**Scheme 1B**) obtained under Yu's conditions was not observed at all.

Interestingly, while gold catalyst alone could not promote this rearrangement, the rate of the rearrangement catalyzed by the mixture of gold and gallium is faster than that of the rearrangement catalyzed by gallium alone. This increase in reaction rate allowed for the formation of cyclopentene **5a** in excellent yield (92%) even with wet solvent (outcompeted the undesired hydration). The detailed reaction progress was monitored via NMR spectroscopy (see SI). Although the exact reason is unclear at this moment, this result suggested that gallium-catalyzed enol formation and gold-catalyzed alkene activation might occur at the same time to facilitate the rearrangement process. Encouraged by these results, we focused on the exploration of a plausible cascade reaction, combining the Nakamura reaction with gold-catalyzed ring expansion. Thus, combinations of various gold catalysts and Lewis acids were examined with **1a** and **2a** as model reactions. The results are summarized in **Table 1**.

While triazole-gold catalyst [XPhosAu(TA-H)]OTf did not catalyze the reaction of **1a** and **2a** (entry 3), the desired rearrangement product **5a** was formed in 30% yield when catalytic amount of $Ga(OTf)_3$ was added to activate the TA-Au catalyst (entry 4). Changing Au/Ga ratio from 1:1 to 1:2 fur-ther promoted the VCP rearrangement, giving **5a** in higher yield (55%, 76% conversion), which demonstrated that the $Ga(OTf)_3$ was crucial in promoting the rearrangement. Studies of the effect of the phosphine ligand on the reaction yield led to the discovery of phosphite-ligated gold complex $[(ArO)_3PAu(TA\text{-}H)]OTf$ (76% yield, entry 11).

Table 1. Summary of reaction condition screening[a]



entry	gold cat (5 mol %)[b]	additive (mol %)	Time (h)	convn[c] (%)	yield (%)[c] 3a	4a	5a
1	$PPh_3AuCl/AgOTf$	-	8	0	0	0	0
2	XPhosAuCl/AgOTf	-	8	40	20	13	0
3	[XPhosAu(TA-H)]OTf	-	8	0	0	0	0
4	[XPhosAu(TA-H)]OTf	$Ga(OTf)_3$ (5)	8	70	12	10	30
5	[XPhosAu(TA-H)]OTf	$Ga(OTf)_3$ (10)	8	76	0	0	55
6	$[PPh_3Au(TA\text{-}H)]OTf$	$Ga(OTf)_3$ (10)	8	90	0	0	47
7	$Ph_3PAuNTf_2$	$Ga(OTf)_3$ (10)	8	88	0	0	30
8	XPhosAuCl	$Ga(OTf)_3$ (10)	8	45	0	0	11
9	XPhosAuOTf	$Ga(OTf)_3$ (10)	8	100	0	0	40
10	[IPrAu(TA-H)]OTf	$Ga(OTf)_3$ (10)	8	78	0	0	36
11[d]	$[(ArO)_3PAu(TA\text{-}H)]OTf$	$Ga(OTf)_3$ (10)	6	100	0	0	76
12	**$[(ArO)_3PAu(TA\text{-}Me)]OTf$**	**$Ga(OTf)_3$ (10)**	**6**	**100**	**0**	**0**	**90**
13	$[(ArO)_3PAu(TA\text{-}Me)]OTf$	AgOTf (10)	6	0	0	0	0
14	$[(ArO)_3PAu(TA\text{-}Me)]OTf$	$Cu(OTf)_2$ (10)	6	71	25	17	14
15	$[(ArO)_3PAu(TA\text{-}Me)]OTf$	$In(OTf)_3$ (10)	6	100	0	0	49
16	$[(ArO)_3PAu(TA\text{-}Me)]OTf$	$Sc(OTf)_3$ (10)	6	100	0	0	39
17	$[(ArO)_3PAu(TA\text{-}Me)]OTf$	$Yb(OTf)_3$ (10)	6	100	31	29	11
18	-	$Ga(OTf)_3$ (10)	6	0	0	0	0
19	-	TfOH (10)	6	0	0	0	0

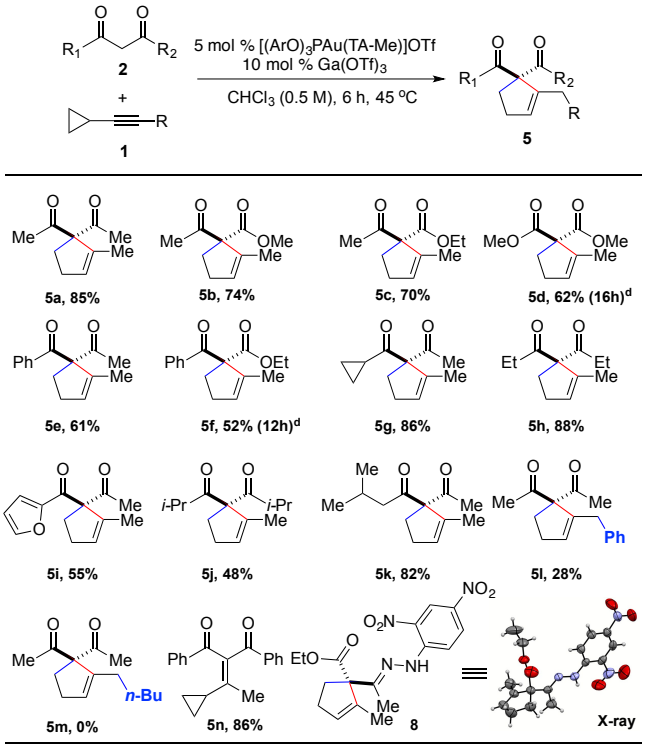
[a] Reaction conditions: **2a** (0.2 mmol), **1a** (2.0 equiv), catalyst and additives in $CDCl_3$ (0.4 mL), 45 °C, 6-8 h; [b] TA-H = benzotriazole, TA-Me = N1-methylbenzotriazole; [c] Determined by ^1H NMR using *p*-xylene as internal standard. [d] Ar = 2,4-di-*tert*-butylphenyl.

Notably, in our previous reported Nakamura reaction, the bulky and electron-rich biarylmonophosphine XPhos ligand gave the best result.[15] The opposite trend in this reaction suggested the critical role of gold in the rearrangement step, which is consistent with the result observed in **Scheme 2B**. Finally, switching 1,2,3-triazole ligand from TA-H (benzotriazole) to TA-Me (N1-methylbenzotriazole) greatly reduced the formation of hydration product **7a**, giving the desired product **5a** in excellent yield (entry 12, 90%). Other tested Lewis acid co-catalysts (entries 13-17) gave either complex reaction mixture or lower yields. Control experiments showed no reaction with $Ga(OTf)_3$ or TfOH alone.

With the optimal conditions in hand, we explored the reaction scope. As shown in **Table 2**, various 1,3-diketones, β-ketoesters and 1,3-diesters were tested. For aliphatic substituted 1,3-diketones, the Au/Ga bimetallic system worked well with terminal alkynes and the reactions occurred in good to excellent yields. Generally longer reaction time is required for β-ketoesters and 1,3-diesters (**5b-5d**), which resulted in slightly reduced yield of **5** (due to competing side reactions). For the aromatic-substituted diketones (**5e** and **5f**), lower yields were observed due to the increased stability of VCP **4**. In the extreme case, with diphenyl-substituted 1,3-diketone, only VCP **5n** was observed with no rearrangement products at all even at prolonged reaction time. Notably, reaction of a cyclopropane-substituted nucleophile **5g** suggested a non-radical mechanism in the rearrangement step. Moreover, furan-substituted nucleophile gave the desired product **5i**, which highlighted the good chemoselectivity of this new bimetallic condition (furan addition to alkyne was not observed). Although internal alkynes like **5m** are generally not

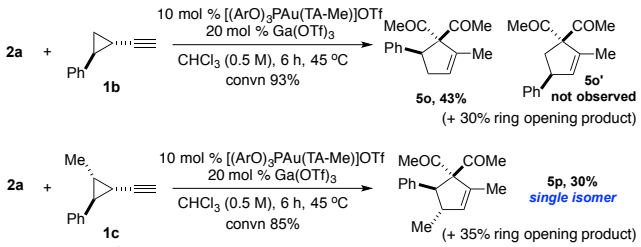
suitable substrates for Nakamura reaction due to the reduced reactivity, the phenyl substituted alkyne afforded desired product **5l** though in modest yield. Finally, the structure of **5c** was unambiguously confirmed by X-ray crystallographic analysis of **8**, a hydrazone derivative of **5c**.

Table 2. Reaction scope[a,b,c]



[a] Reaction conditions: **2** (0.2 mmol), **1** (2.0 equiv), catalyst and additives in $CDCl_3$ (0.4 mL), 45 °C, 6 h; [b] Isolated yield. [c] TA-Me = N1-methylbenzotriazole; [d] Reaction time in parenthesis.

To study the reaction mechanism, substituted cyclopropylacetylene **1b** and **1c** were prepared to react with 1,3-diketone **2a** under the TA-Au/Lewis acid catalytic conditions.



Scheme 3 [a,b,c]. [a] Reaction conditions: **2a** (0.2 mmol), **1b** or **2c** (2.0 equiv), catalyst and additives in $CDCl_3$ (0.4 mL), 45°C, 6 h; [b] Isolated yield; [c] TA-Me = N1-methylbenzotriazole.

First, as discussed previously in the literature, it is highly unlikely that this rearrangement will undergo concerted 1,3-CH_2 migration due to the poorly overlapped orbitals in the transition state. As shown in **Scheme 3**, reaction of alkyne **1b** gave **5o** as the only cyclopentene product. Further more, with **1c**, the *trans*-cyclopentene **5p** was observed as the only isomer. The relative stereochemistry of these compounds was confirmed by comprehensive 1D and 2D NMR analysis (see SI for details). Notably, the observation of stereochemistry retention rules out a symmetry-allowed [1,3]-sigmatropic concerted alkyl shift, as the suprafacial orbital recombination occurs with inversion of stereochemistry. Thus, this result potentially disfavors a concerted mechanism.[18]

Conclusions

In summary, we have achieved a mild and efficient synthesis of substituted cyclopentenes through gold/gallium-catalyzed annulation of simple 1,3-dicarbonyl compounds and cyclopropylacetylenes. This tandem reaction consists of a direct addition of 1,3-dicarbonyl compound to cyclopropylacetylene, a catalytic dienol-enone tautomerization, and a gallium-catalyzed VCP rearrangement. Considering the great advantage of preparing VCP from gold-catalyzed cyclopropylacetylene activation, it is expected that applying VCP in complex molecule synthesis will be of general interest for cyclopentene-containing natural product synthesis.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details and NMR spectra. See DOI: 10.1039/c000000x/

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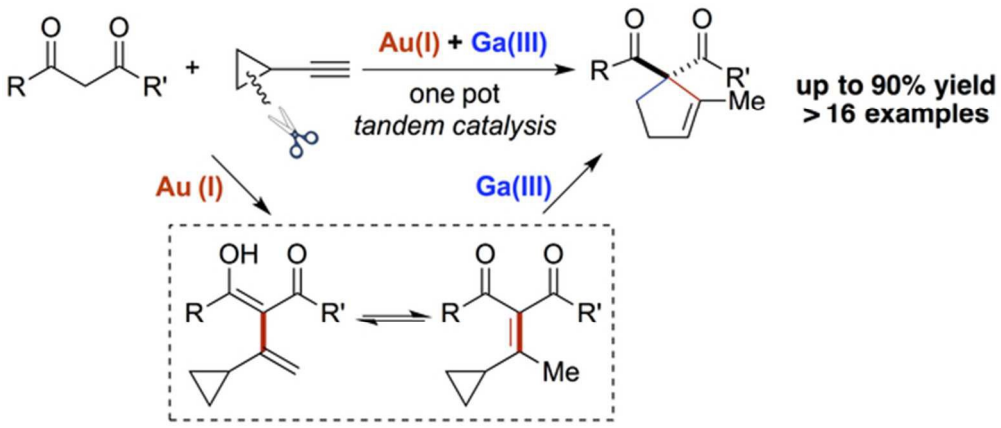

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