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Easy Access to 2,4-Disubstituted Cyclopentenones by a Gold(III)-Catalyzed A3-Coupling/Cyclization Cascade

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c03451 Read Online

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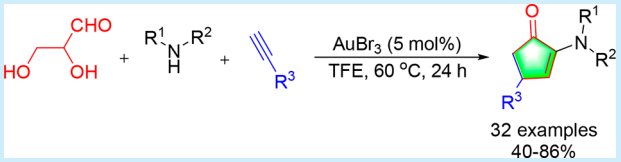
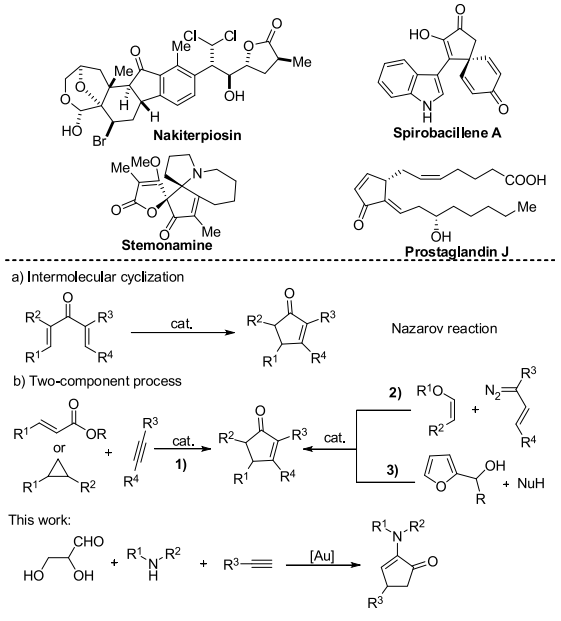
ABSTRACT: An efficient and convenient synthesis of 2,4-disubstituted cyclopentenones has been achieved through a Au(III)-catalyzed isomerization–A3-coupling/cyclization cascade. A possible mechanism involving an initial Au(III)-catalyzed isomerization, A3-type coupling, and cyclization via an enol intermediate is postulated.



Cyclopentenone derivatives are key structural motifs that are widely found in a number of natural products[1] and pharmaceuticals,[2] such as Nakiterpiosin,[3] Spirobacillene A,[4] Stemonamine,[5] and Prostaglandin J (Scheme 1).[6] Often they serve as important synthetic intermediates in complex chemical syntheses.[7] As a result, many efficient strategies for the synthesis of substituted cyclopentenones have been developed.[8] A prominent example that easily gives access to cyclopentenone derivatives by an intramolecular approach is the Nazarov cyclization (Scheme 1a).[9] However, this approach can be challenging due to the occurrence of side reactions derived from the oxyallyl cation intermediate. In addition, difficulties can occur during the preparation of the starting dienones substrates. An alternative method to access cyclopentenone derivatives is a two-component [3 + 2] cycloaddition of unsaturated systems with 1,3-dipolar species, vinyl carbenoid species, or multifunctional cyclopropanes (Scheme 1b).[10] The groups of Ogoshi and Montgomery independently reported on a reductive Ni-catalyzed [3 + 2] annulation of phenyl enoates and alkynes to give cyclopentenones.[11] One of the particularly useful methods for the formation of five-membered carbocycles is the Pauson–Khand reaction. This process enables a rapid and efficient assembly of complex structures from easily available starting materials.[12] In general, such types of multicomponent reactions have emerged as an attractive and powerful strategy.[13] The necessity of stoichiometric metal–carbonyl complexes and/or the use of toxic carbon monoxide in Pauson–Khand reactions still makes the development of alternative processes attractive. Another common strategy is the Piancatelli rearrangement, which furnishes the corresponding cyclopentenones derivatives from 2-furylcarbinols. It has been widely used in the synthesis of many natural products and biologically active molecules.[14] On the other hand, the A3-coupling reaction of terminal alkynes, aldehydes, and amines has already proven to be a powerful tool to access complex compounds from simple starting materials.[15] But, to the best of our knowledge, a divergent synthesis of cyclopentenone derivatives based on an alkyne–amine–aldehyde coupling is not reported in the literature. In continuation of our interest in gold chemistry,[16] we disclose herein a solvent-dependent switch of the chemoselectivity obtained for a gold(III)-catalyzed A3-coupling/cyclization cascade with glyceraldehydes.

Scheme 1. Synthetic Strategies for the Synthesis of Cyclopentenones

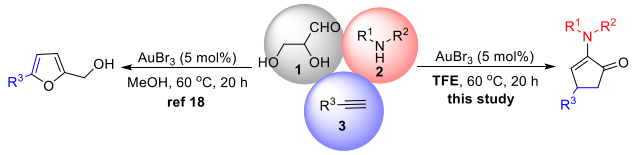


Received: October 15, 2020

https://dx.doi.org/10.1021/acs.orglett.0c03451
Org. Lett. XXXX, XXX, XXX–XXX

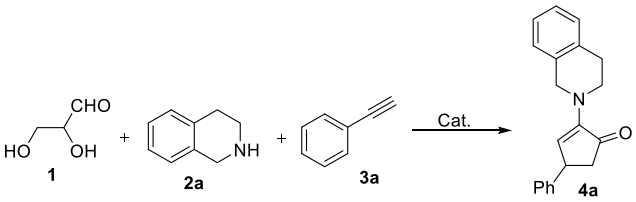
In continuation of our contributions on gold catalyzed furan syntheses,[17] we recently presented an A3-coupling/cyclization sequence between glyceraldehyde, a secondary amine, and a terminal alkyne that delivered furan alcohol as the product (Scheme 2, left).[18] However, during solvent optimization studies for this synthesis of furyl alcohol derivatives, we observed a completely unexpected shift of selectivity by using TFE as solvent. In this case, substituted α-amine cyclopentanones, which belongs to a very particular type α-amino ketone,[19] (Scheme 2, right) were obtained. The chemical value of the obtained products and the interesting but questionable selectivity motivated us to further investigate this chemistry.

Scheme 2. Solvent-Dependent $AuBr_3$-Catalyzed Synthesis of Cyclopentenones



Our studies commenced with the attempt of the reaction of glyceraldehyde **1** with 1,2,3,4-tetrahydroisoquinoline (THIQ) **2a** and ethynylbenzene **3a** in the presence of 5 mol % of $AuCl_3$ in TFE at 60 °C for 24 h. As shown in Table 1, the cyclopentanone product **4a** was obtained in 11% yield (entry 1). When $AuBr_3$ was employed as the catalyst, the target reaction proceeded smoothly in TFE, affording the desired product **4a** in 65% yield (entry 2). However, a decreased yield (7%) was observed when PPh_3AuCl was used. It seemed that the catalysts have great influence on the reaction outcome.

Table 1. Optimization of the Reaction Conditions[a]



Entry	Catalyst	Temp (°C)	Solvent	Yield (%)[b]
1	$AuCl_3$	60	TFE	11
2	**$AuBr_3$**	**60**	**TFE**	**65**
3	PPh_3AuCl	60	TFE	7
4	MesAuCl/$AgSbF_6$	60	TFE	0
5	AgOTf	60	TFE	–
6	$PtCl_2$	60	TFE	–
7	CuI	60	TFE	–
8	$Cu(OTf)_2$	60	TFE	–
9	$AuBr_3$	60	TFE/4A ms	51
10	$AuBr_3$	60	DCE	37
11	$AuBr_3$	60	DMF	–
12	$AuBr_3$	60	THF	–
13	$AuBr_3$	60	Toluene	–
14	$AuBr_3$	60	MeCN	–
15	$AuBr_3$	rt	TFE	–
16	$AuBr_3$	80	TFE	34

[a]Reaction conditions: A solution of **1** (0.3 mmol), **2a** (0.45 mmol), **3a** (0.45 mmol), and catalyst (5 mol %) were stirred in the specified solvent (1.0 mL) and temperature for 24 h. [b]Isolated yield.

Utilizing other multiple bond activated catalysts, such as MesAuCl/$AgSbF_6$, AgOTf, $PtCl_2$, CuI, and $Cu(OTf)_2$, led to negative results (entries 4–8). Then, a screening of solvents was carried out (entries 10–14); typical solvents including DCE, DMF, THF, toluene, and MeCN were employed. In addition, several common alcohol solvents were used, and the relationship between the pK_a value of the reaction solvents and yields was investigated (Figure 1). The results indicated that TFE was the most effective solvent. Thus, our final optimal reaction conditions used 5 mol % $AuBr_3$ in TFE at 60 °C for 24 h.

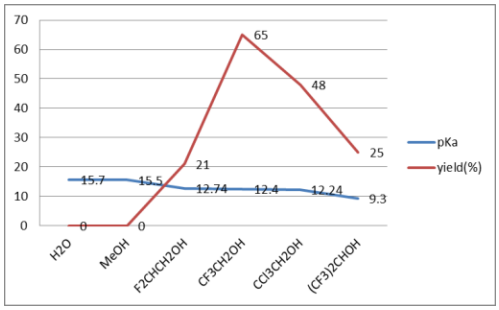
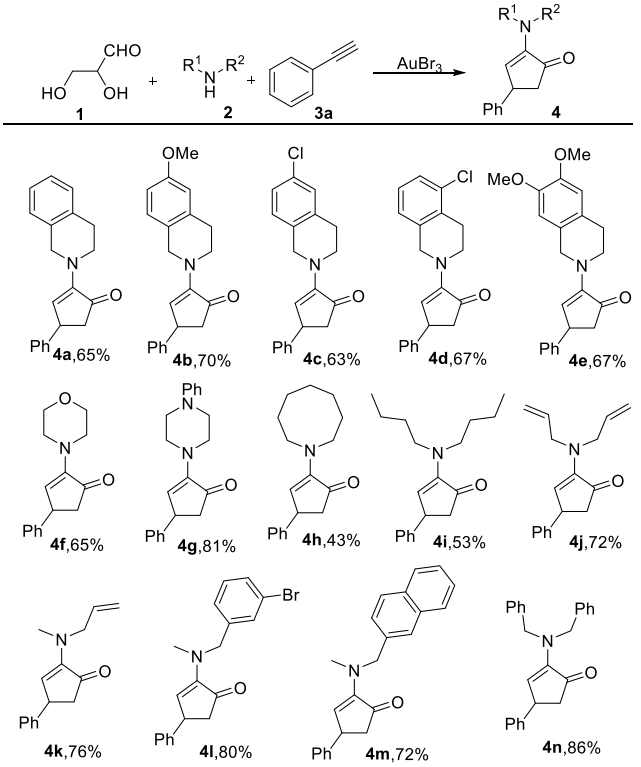


Figure 1. Relationship between the pK_a value and the yields.

With the optimal reaction conditions in hand, we first explored the scope of secondary amines (Scheme 3). As depicted in Scheme 3, a wide range of secondary amines with a diverse set of substituents was tolerated. In general, secondary amines, including cyclic and noncyclic secondary amines, were

Scheme 3. Substrate Scope of Secondary Amines[a,b]



[a]Reaction conditions: A solution of **1** (0.3 mmol), **2** (0.45 mmol), **3** (0.45 mmol), and $AuBr_3$ (5 mol %) were stirred in TFE (1.0 mL) at 60 °C for 24 h. [b]Isolated yield.

https://dx.doi.org/10.1021/acs.orglett.0c03451
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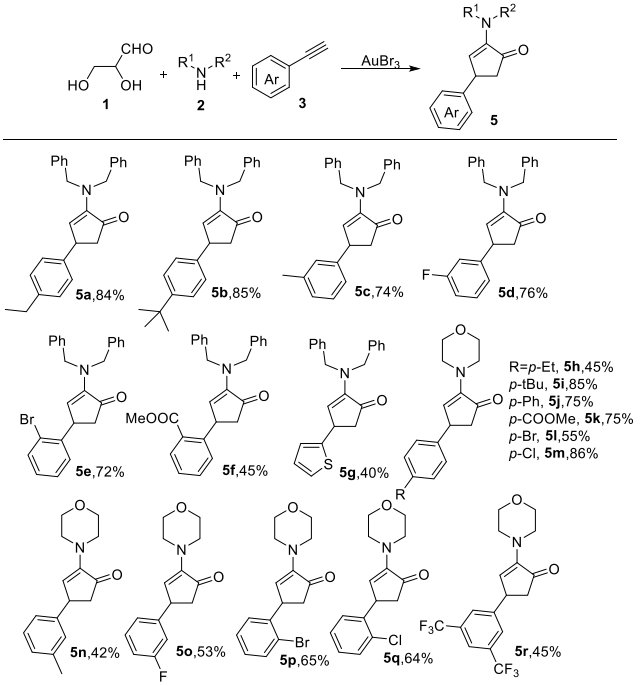
well tolerated in the reactions with glyceraldehydes **1** and alkynes **3**, thus producing the corresponding cycloadducts in 43−86% yields. Notably, the tetrahydroisoquinoline derivatives (**2a**−**2e**) were well-tolerated in the reaction. Besides, the larger ring amine azocane **2h** also provided the product **4h**, though a slightly lower yield was obtained compared to smaller ring sizes. Open chained amines were also suitable substrates, which was demonstrated by the synthesis of products **4i**. Substrates containing terminal olefin groups (**2j**, **2k**) were also suitable in this A3-coupling/cyclization process. In addition, methyl substituted amines can be applied, *N*-methylprop-2-en-1-amine **2k**, 1-(3-bromophenyl)-*N*-methylmethanamine **2l**, and *N*-methyl-1-(naphthalene-2-yl)methanamine **2m** also afforded the expected products **4k**, **4l**, and **4m** in reasonable yields.

Terminal arylalkynes with both electron-withdrawing and electron-donating substituents on the aromatic moiety are well tolerated (Scheme 4), as demonstrated by the formation of the

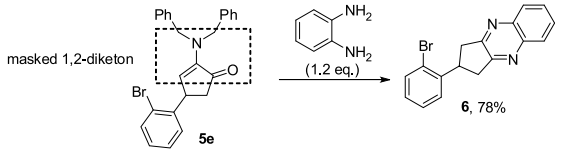
Scheme 4. Substrate Scope of Alkynes[a,b]



[a]Reaction conditions: A solution of **1** (0.3 mmol), **2** (0.45 mmol), **3** (0.45 mmol), and $AuBr_3$ (5 mol %) were stirred in TFE (1.0 mL) at 60 °C for 24 h. [b]Isolated yield.

desired 2,4-substitued cyclopentenone products **5a**−**5r** in moderate to good yields (40−86%). Moreover, substituents can be placed in the *para*-, *ortho*-, or *meta*- position of the aromatic moiety, as shown by the synthesis of products **5a**−**5f** and **5h**−**5r**. A disubstituted 1-ethynyl-3,5-bis(trifluoromethyl)-benzene **3r** gave the corresponding product **5r** in 45% yield. Among the applied aromatic alkynes, it becomes obvious that *para*- substitution in general gives rise to the highest yields, which indicates that steric parameters might play an influential role. Among these systems the best yield was obtained for 1-(*tert*-butyl)-4-ethynylbenzene **3b** that led to the desired cyclopentenone **5b** in excellent 85% yield. Importantly, heterocyclic arylalkynes (2-ethynylthiophene) was also a suitable substrate, providing the thiophene product (**5g**) in 40% yield. Prop-2-ynyl benzene and hex-1-yne, as aliphatic alkynes, were completely unreactive and did not provide the desired cyclopentenones under these conditions. To demonstrate the potential of the product a transformation of 4-(2-bromophenyl)-2-(dibenzylamino) cyclopent-2-en-1-one **5e** was conducted. Due to the enamine substructure, the obtained products can also be regarded as masked 1,2-dicarbonyl compounds, valuable precursors in organic synthesis. A first exploitation of this reactivity was demonstrated by the synthesis of cyclopenta[*b*]quinoxaline derivative **6** that was synthesized from compound **5e** on treatment with benzene-1,2-diamine (Scheme 5).[20]

Scheme 5. 1,2-Diketone Reactivity of Products 5



To gain some mechanistic insight, isotope-labeling experiments using glyceraldehydes **1**, morpholine **2f**, and 1-*tert*-butyl-4-ethynylbenzene **3b** as the model reaction under standard conditions were conducted (see Supporting Information (SI) in detail). Otherwise, propargylamines as the possible reaction intermediate were treated under the standard conditions, but no trace of the target compound was found; only a trace of furan alcohol product could be detected by NMR (see SI in detail). This clearly demonstrates that the reaction cascade toward compounds **4** or **5** is not initiated by an A3-coupling reaction of substrates **1**, **2f**, and **3i**. Furthermore, in order to prove whether the reaction obtained the target product through Piancatelli rearrangement, furan alcohol was investigated with morpholine **2f**, but target compound **5i** was not found after 20 h (see SI in detail).

The experiments described above gave us valuable information on the mechanism of the reaction (Figure 2). A

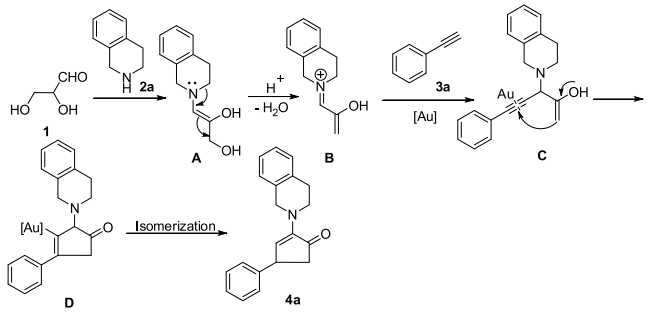


Figure 2. Proposed mechanism for the cyclopentenone formation.

possible reaction mechanism using substrate **1**, **2a**, and **3a** as an example is depicted in Figure 1. Initially, glyceraldehyde **1** and morpholine **2a** gives rise to the condensation product **A**; this could be followed by dehydration to afford the iminium ion enol **B** catalyzed by the acidic TFE. Phenyl acetylene **3a**, which would be activated by the gold catalyst to generate the corresponding gold acetylide,[16a] reacts with the iminium ion **B** to give the corresponding propargylamines **C**, which can be detected with Mass Spectrometry (MS). Nucleophilic attack of the enol onto the gold activated triple bond then affords **D** which after elimination of a proton under release of the catalyst delivers the final product **4a**.

https://dx.doi.org/10.1021/acs.orglett.0c03451
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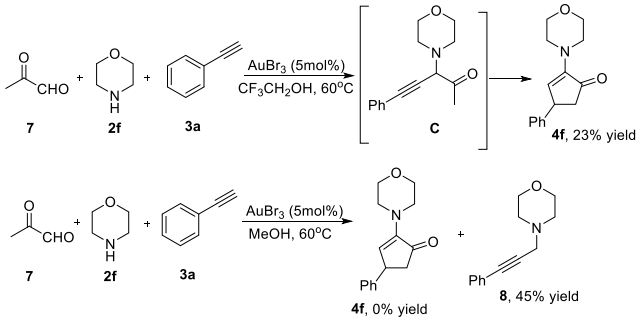
To verify this mechanism, pyruvic aldehyde **7** (35% dissolved in water) was utilized for the A3-coupling reaction under the standard conditions (Scheme 6). The reaction

Scheme 6. Test Experiment with Pyruvic Aldehyde



further proceeded to deliver the final **4f** in 23% yield, and the intermediate **C** could be detected by MS. Moreover, if MeOH was chosen as the solvent, the reaction did not afford **4f** in the absence of TFE. Instead a 45% yield of 4-(3-phenylprop-2-ynyl)morpholine **8** was collected, and the intermediate **C** also could be found from MS, which means TFE is necessary for the second step from intermediate **C** to target product **4f**. This result is completely in line with our mechanistic hypothesis. The only difference is that in the above-mentioned case glyceraldehyde serves as a synthetic equivalent of pyruvic aldehyde.

In summary, we have established a new Au(III)-catalyzed solvent-dependent isomerization−A3-coupling/cyclization cascade to afford 2,4-disubstituted cyclopentenones. The transformation proposes a straightforward and versatile protocol that employs readily available alkynes, aldehydes, and amines as starting materials and operates under mild reaction conditions. The reaction proceeds through a possible mechanism involving an initial Au(III)-catalyzed isomerization followed by an A3-type coupling. The reaction is then terminated by cyclization via an enol intermediate. The addition of slightly acidic TFE as the reaction solvent is crucial in order to change the chemoselectivity of the starting materials from the common furan systems pathway, toward the yet unknown cyclopentenone pathway. Due to the additional enamine substructure, the obtained cyclopentenones can be regarded as masked diketones which makes them extremely attractive as valuable synthetic intermediates. The opportunity to use pyruvic aldehyde as a starting precursor as well should enable easy further functionalization, and further studies are ongoing in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03451.

Spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Jiangsu Key Laboratory of Advanced Catalytic Materials and Technology (BM 2012110), Advanced Catalysis and Green Manufacturing Collaborative Innovation Center in Changzhou University.

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