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Complex α–Pyrones Synthesized by a Gold-Catalyzed Coupling Reaction**

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Keywords

α-pyrone; cyclization; gold; rearrangement; tandem reaction

We have been exploring a strategy for the synthesis of small molecules having properties that increase the probability of success in all facets of probe- and drug-discovery pipelines – including discovery, optimization and manufacturing.[1] This strategy involves: 1) the synthesis of building blocks having functionality suitable for subsequent “coupling” and “pairing” steps, 2) intermolecular coupling reactions that join the building blocks in all stereochemical combinations and 3) intramolecular pairing reactions that join different combinations of functional groups yielding diverse skeletons.[2] Here, we describe a multicomponent coupling reaction that we believe will be well suited for the coupling phase of this strategy since, among others, it yields complex and diverse α-pyrones, which are core elements found in many biologically active compounds.[3]

Convergent syntheses[4] of α-pyrones have traditionally involved the lactonization of ketoesters.[5] Transition metal-catalyzed cycloaddition[6] and annulation reactions[7] are recent alternatives that have attracted much attention, but most are limited by the resulting poor regioselectivity or the requirement for harsh reaction conditions. We envisioned that the readily accessible propargyl propiolate **1** could be converted to different products via a cascade process (Figure 1).[8] Late transition-metal catalyzed [3,3]-sigmatropic rearrangement of **1** would generate an enyne allene **A**.[9] A 6-*endo*-dig cyclization would be induced by the activation of the alkyne moiety in **A** to furnish the oxocarbenium intermediate **B**. In one possible pathway, elimination (①, Figure 1) would afford a vinyl α-pyrone **2**. We anticipated that the intermediate **B** could also be trapped by a variety of nucleophiles. We hypothesized that we could control the trapping of electrophilic intermediate **B**, which can in principle be attacked at three distinct sites (②, ③ and ④, Figure 1) by using different nucleophiles and reaction conditions. We describe the successful realization of many of these concepts.

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We dedicate this paper with admiration and affection to Professor Yoshito Kishi on the occasion of his 70th birthday

A similar [3,3]-sigmatropic rearrangement followed by 6-*endo*-dig cyclization cascade has been reported by Toste and coworkers for the synthesis of aromatic ketones.[9a] Stimulated by this result, we attempted to use the reported silver(I) catalysts to achieve the rearrangement of **1a** (Table 1, entry 1). The desired vinyl α-pyrone **2a**, however, was obtained in low yield. In contrast, the widely used cationic Au(I) catalyst (entry 2)[10] at room temperature provided **2a** in 61% yield. At higher temperatures, **2a** was obtained in 81% yield (entry 3) while a comparison experiment using only 5% $AgSbF_6$ afforded a low yield of **2a** (entry 4). Increasing the temperature in 1,2-dichloroethane led to a decreased yield (entry 5). 10% pyridine was added in hope of accelerating the elimination pathway (entry 6), but this resulted instead in the inhibition of the reaction, presumably by inactivation of the cationic gold catalyst by pyridine coordination.[11] Polar or coordinating solvents decreased the reaction efficiency and acetonitrile inhibited the reaction (supporting information).[10b] The reaction mixture converted to a gel when THF was used as the solvent (entry 7), presumably due to the polymerization of THF induced by reactive cationic species.[12] Three other Au(I) species were tested (entries 8–10), but none was superior to $[(Ph_3P)AuCl]/AgSbF_6$ used in the model reaction.

The rearrangement of propargyl propiolates **1b**–**1f** gave the desired vinyl α-pyrones **2b**–**2g** in 65–84% yields (Table 2). We note that the olefin moiety in **1f** did not interfere with the cascade reaction despite the precedent of reactions involving 1,6-enynes.[10b,13] Substrate **1h** resulted in a less efficient reaction, yielding **2h** in only 40% yield, likely due to an intramolecular attack of the cationic intermediate by the ketal oxygen.[14]

We have also determined that the cationic intermediate **B** can be trapped by electron-rich arenes and heteroarenes in a Friedel-Crafts-type reaction. Performing the model reaction with 5 mol % $[(Ph_3P)AuCl]/AgSbF_6$ at room temperature in the presence of 2 equivalents of trimethoxybenzene afforded the α-pyrone **3a** in 82% yield (Table 3). None of the rearrangement product **2a,** or the products resulting from the nucleophilic attack at the other two positions (③ and ④, Figure 1) was observed. The addition of the aromatic ring to the alkyne[15] does not interfere with the tandem reaction. **3a** was not detected when α-pyrone **2a** was subjected to the reaction conditions, indicating that **2a** is not an intermediate in the formation of **3a**. Electron-rich aromatics and heteroaromatics, such as indole, furan and benzofuran, are also suitable nucleophiles in the Friedel-Crafts-type reaction, affording **3b**–**3h** in 59–85% yields (Table 3). We note that **3a**–**3h** mimic the structure motif of diarylmethanes, which have a broad spectrum of biological activities.[16] The structure of **3d** was verified by X-ray analysis.[17]

When the enantiopure propargyl propiolates (*R*)-**1e** and (*R*)-**1i** were subjected to the same reaction conditions in the presence of electron-rich heteroarenes, racemates of **3e** and **3i** were obtained (Figure 2). This result suggests that the nucleophile bonds to both enantiofaces of the oxocarbenium **B** with equal facility (Figure 2).

When **1j** was subjected to the reaction conditions, tri-substituted α-pyrone **2j** was obtained in only 16% yield, while the major product, tricyclic compound **4**, was obtained in 69% yield (Figure 3). Since **2j** was not converted into **4** when resubjected to the same conditions, **4** apparently results from a 1,2-hydride shift in intermediate **C**, yielding tertiary carbocation **D**, which is trapped by the phenyl group in an intramolecular Friedel-Crafts reaction.[18]

Considering that the propargyl propiolates used in these multicomponent coupling reactions can be readily synthesized from terminal alkynes and aldehydes, which are among the most highly varied and abundant building blocks, we anticipate that this coupling reaction will be well suited for the strategy noted in the Introduction. Two additional observations reinforce this expectation. Our preliminary studies suggest that trapping the intermediate

oxocarbenium ion with alcohol-based nucleophiles results in attack at the lactone carbonyl carbon, resulting in an alternative skeleton (manuscript in preparation). Secondly, strategic placement of suitable functionality in the building blocks allows functional group-pairing reactions that enable further skeletal diversification. To illustrate, coupling product **3k** undergoes a ring-closing metathesis to yield the polycyclic α-pyrone **5** (Figure 4). We are currently exploring the potential of these reaction processes in diversity syntheses and determining the assay performance of the resulting products using many small-molecule screens.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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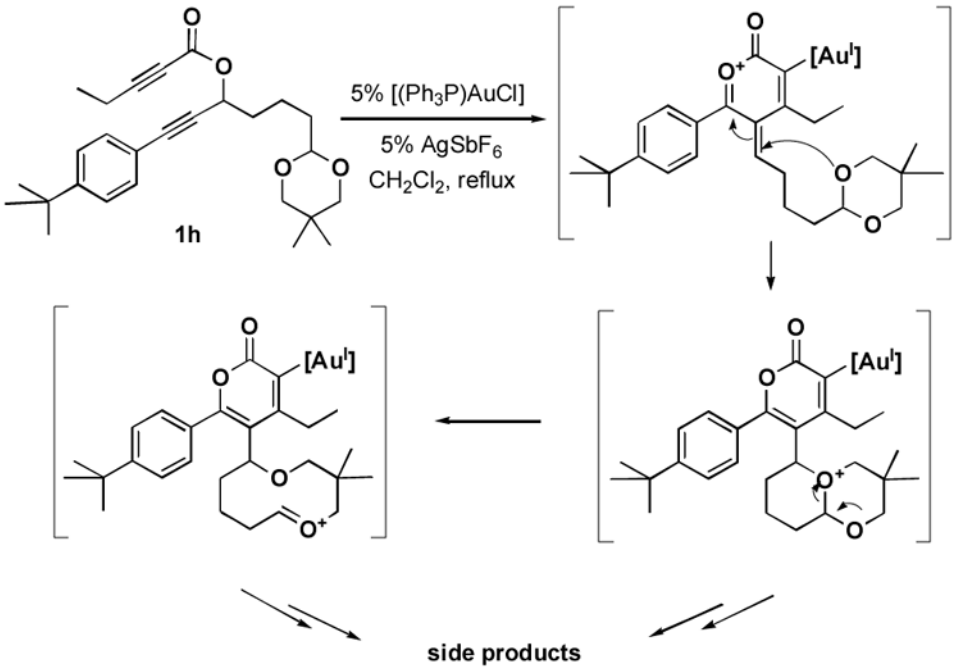
14. A possible pathway for additional reaction products is:



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17. CCDC-650319 (3d) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See the Supporting Information for further details.
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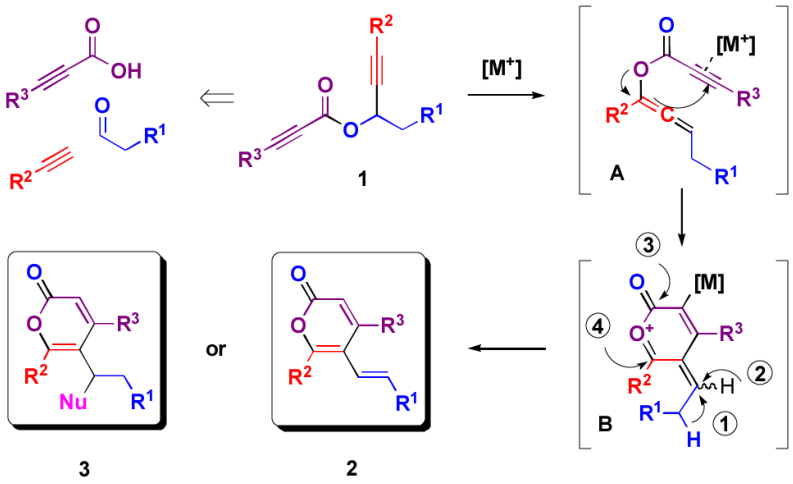


Figure 1.
Syntheses of trisubstituted α-pyrones via transition metal-catalyzed cascade reactions.

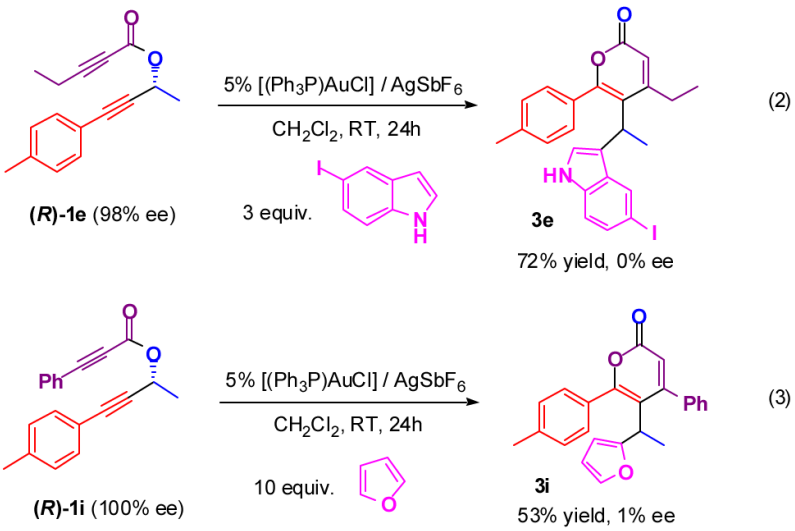


Figure 2.
Racemic products result from non-racemic propargyl propiolates.

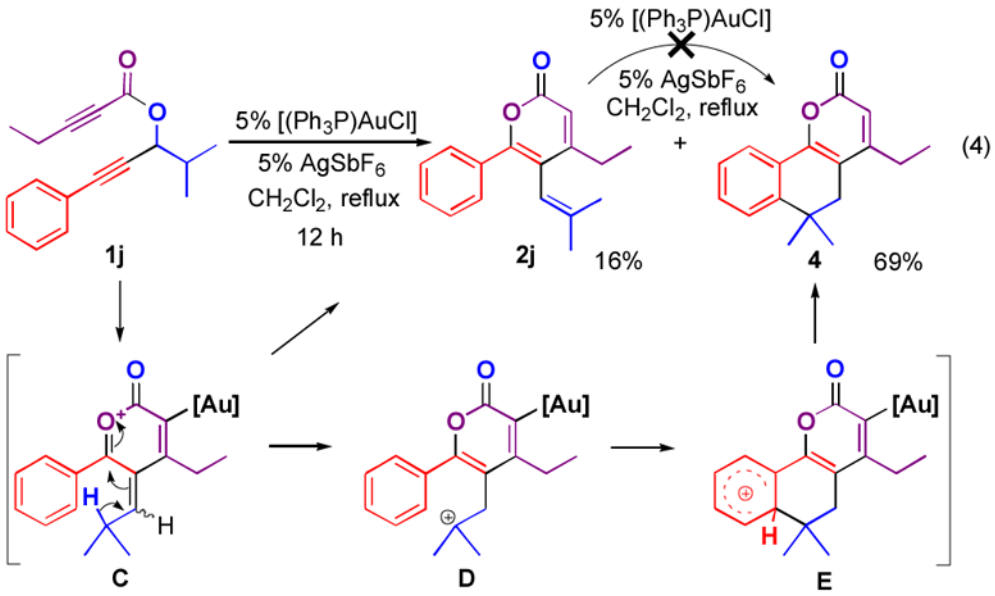


Figure 3.
Cascade process yielding a tricyclic α-pyrone.

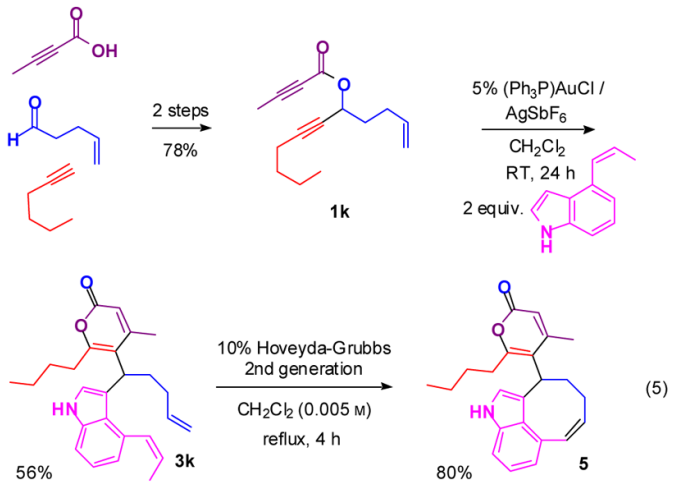
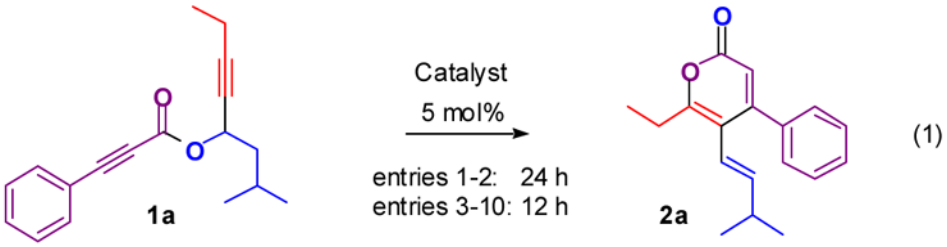


Figure 4.
Intramolecular functional group-pairing reaction involving substituents attached to distinct building blocks prior to the intermolecular coupling reaction (c.f., “Build/Couple/Pair strategy”[2]).

Table 1

Optimization of reaction conditions for the rearrangement of **1a** into **2a**



Entry	Catalyst	Conditions	Yield [%][a]	
			1a	2a
1	$AgSbF_6$[b]	CH_2Cl_2, RT	95	trace
2	$[(Ph_3P)AuCl]/AgSbF_6$	CH_2Cl_2, RT	0	61
3	$[(Ph_3P)AuCl]/AgSbF_6$	CH_2Cl_2, reflux	0	81
4	$AgSbF_6$	CH_2Cl_2, reflux	25	11
5	$[(Ph_3P)AuCl]/AgSbF_6$	1,2-DCE, 60°C	0	67
6	$[(Ph_3P)AuCl]/AgSbF_6$[c]	CH_2Cl_2, RT	96	0
7	$[(Ph_3P)AuCl]/AgSbF_6$	THF, 40°C	--	--[d]
8	$[(Ph_3PAu)_3O]BF_4$[e]	CH_2Cl_2, reflux	95	0
9	$[(Ph_3P)AuNTf_2]$	CH_2Cl_2, reflux	0	45
10	$[(Ph_3P)AuCl]/AgOTf$	CH_2Cl_2, reflux	0	48

[a] Isolated yields after column chromatography.

[b] 2 mol % PPh_3, 1.5 equiv. MgO as additive.

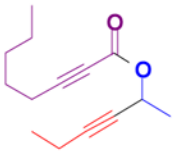
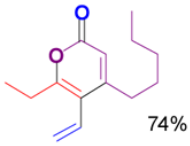
[c] 10 mol % pyridine as additive.

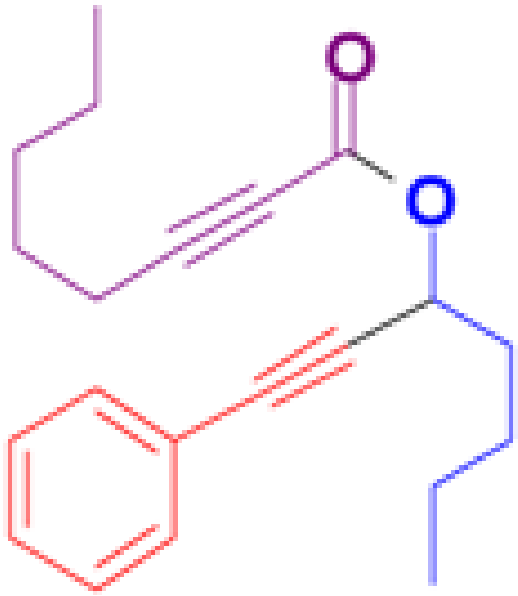
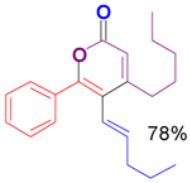
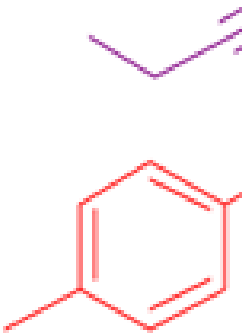
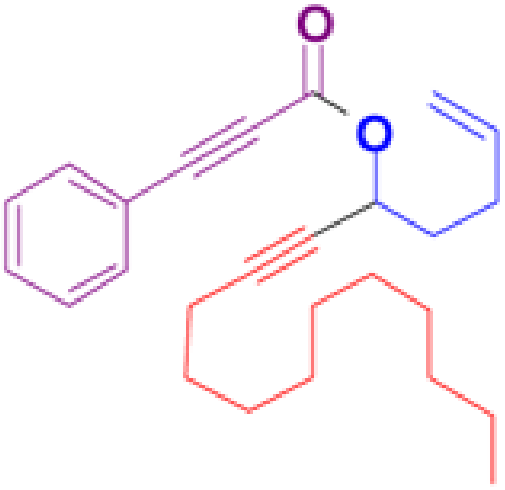
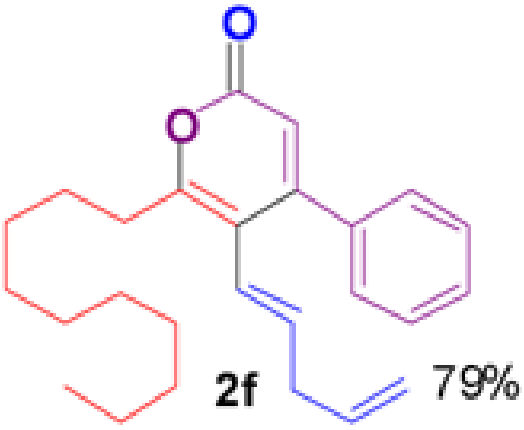
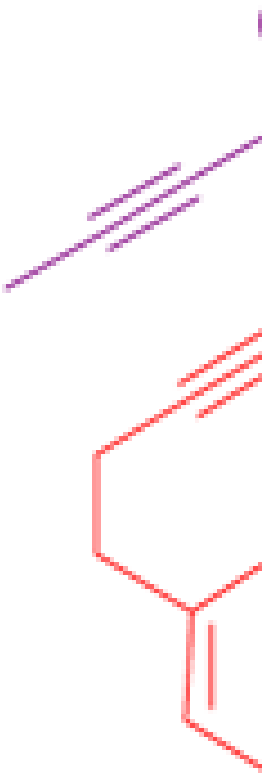
[d] The reaction mixture became vigorous and solidified.

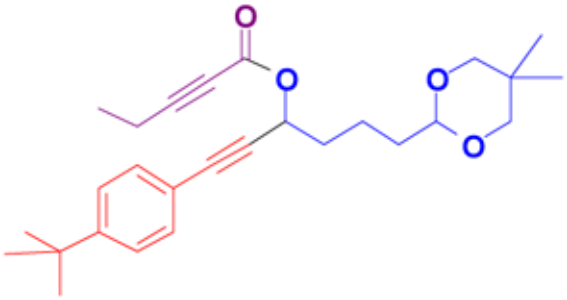
[e] 2 mol % catalyst.

Table 2

Gold(I)-catalyzed rearrangement of propargyl propiolates to vinyl α-pyrones[a]

Substrate	Product	Su
 **1b**	 74% **2b**	

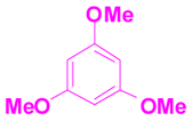
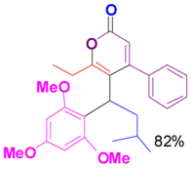
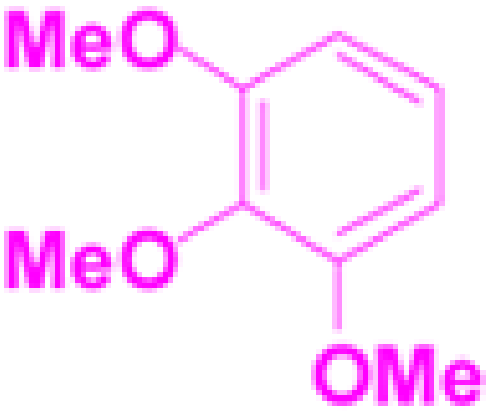
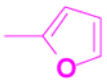
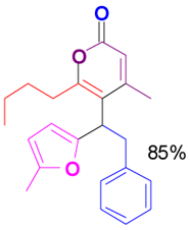
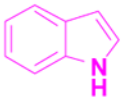
Substrate	Product	Su
 1d`	 78% 2d	
 1f	 2f 79% 2f	

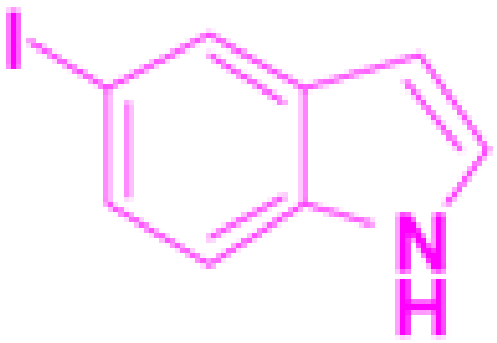
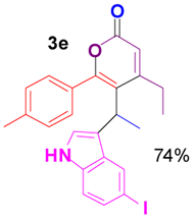
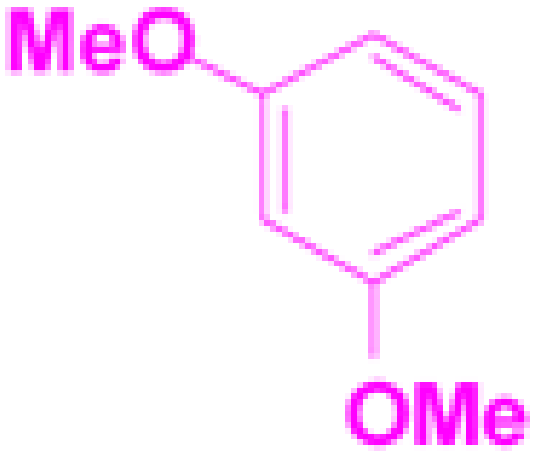
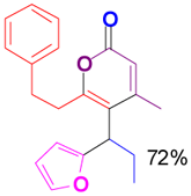
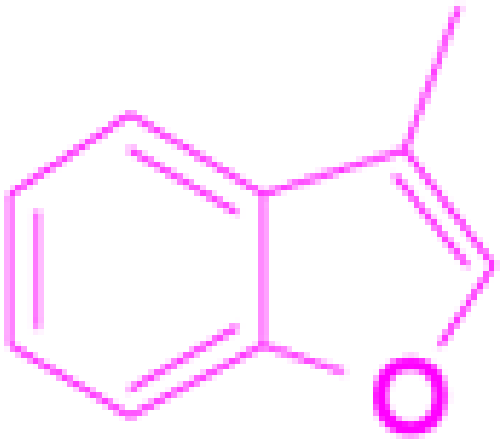
Substrate	Product	Su
	**1h**	

[a] Reaction conditions: propargyl propiolate (0.05 M), $[(Ph_3P)AuCl]/AgSbF_6$ (5 mol %), CH_2Cl_2, reflux, 12 h.

Table 3

Gold(I)-catalyzed syntheses of trisubstituted α-pyrones from propargyl propiolates[a]

Substrate/Nu	Product	Substrate/Nu
 2 equiv. **1a+**	 82% **3a**	 5 equiv. **1b+**
 5 equiv. **1c+**	 85% **3c**	 3 equiv. **1d+**

Substrate/Nu	Product	Substrate/Nu
 3 equiv. **1e+**	 74% **3e**	 10 equiv. **1f+**
 5 equiv. **1g+**	 72% **3g**	 5 equiv. **1h+**

[a] Reaction conditions: propargyl propiolate (0.05 M), nucleophile, $[(Ph_3P)AuCl]/AgSbF_6$ (5 mol %), CH_2Cl_2, room temperature, 24 h.