Cascade Reactions

DOI: 10.1002/anie.200703276

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

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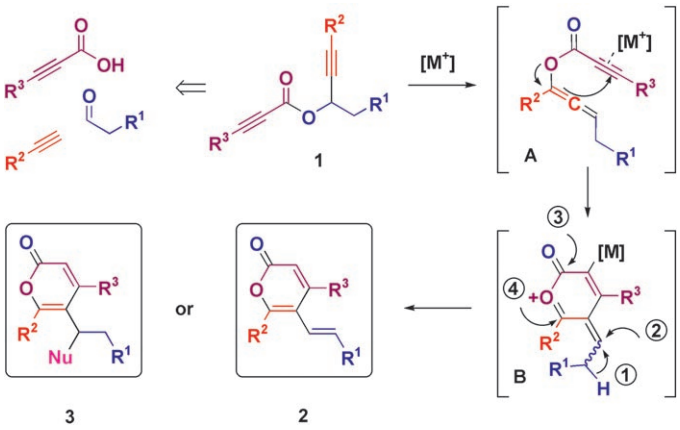
Dedicated to Professor Yoshito Kishi on the occasion of his 70th birthday

We have been exploring a strategy for the synthesis of small molecules with 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 with 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 to yield diverse skeletons.[2] Herein, we describe a multicomponent coupling reaction that we believe is well-suited for the coupling phase of this strategy, as it yields, among other substances, 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 by a cascade process (Scheme 1).[8] The [3,3] sigmatropic rearrangement of **1** catalyzed by a late transition metal 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 give



Scheme 1. Syntheses of trisubstituted α-pyrones by transition-metal-catalyzed cascade reactions.

the oxocarbenium intermediate **B**. In one possible pathway, elimination (①, Scheme 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 the trapping of electrophilic intermediate **B**, which can in principle be attacked at three distinct sites (②, ③, and ④, Scheme 1), could be controlled by using different nucleophiles and reaction conditions. The successful realization of many of these concepts is described.

A similar [3,3] sigmatropic rearrangement followed by a 6-*endo*-dig cyclization cascade reaction has been reported by Toste and co-workers 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). However, the desired vinyl α-pyrone **2a** was obtained in low yield. In contrast, the widely used cationic gold(I) catalyst (Table 1, entry 2)[10] provided **2a** in 61% yield at room temperature. At higher temperatures, **2a** was obtained in 81% yield (Table 1, entry 3), whereas a comparison experiment that used only 5% $AgSbF_6$ afforded a low yield of **2a** (Table 1, entry 4).

Increasing the temperature in 1,2-dichloroethane (DCE) led to a decreased yield (Table 1, entry 5). Pyridine (10 mol%) was added in the hope of accelerating the elimination pathway (Table 1, 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

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[**] The NIGMS-sponsored Center of Excellence in Chemical Methodology and Library Development (Broad Institute CMLD) enabled this research. We thank Ben Stanton, Arturo Vegas, Dr. Weiping Tang, Dr. Thomas Nielsen, and Dr. Xiang Wang for helpful discussions. T.L. thanks Chris Johnson at the Broad Institute for the help with SFC/MS. S.L.S. is an Investigator with the Howard Hughes Medical Institute.

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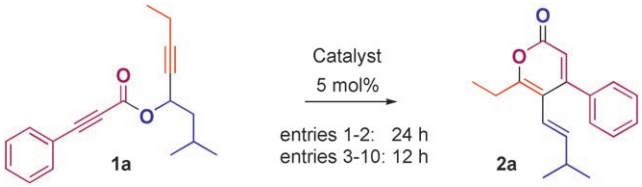
Table 1: Optimization of reaction conditions for the rearrangement of **1a** into **2a**.



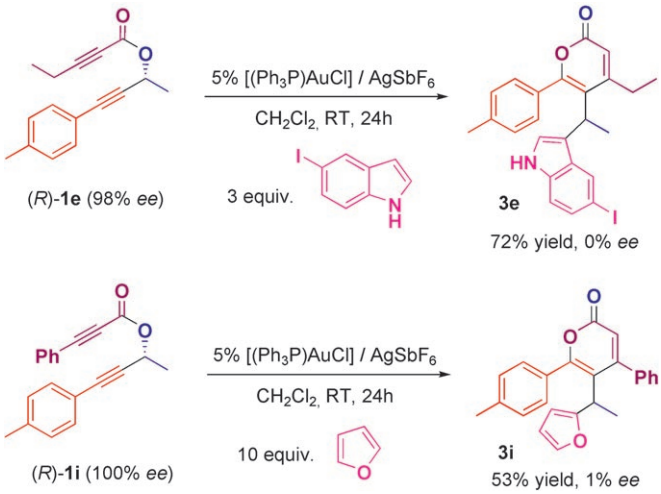
Entry	Catalyst	Conditions	Yield [%][a]	
			1a	**2a**
1	$AgSbF_6$[b]	CH_2Cl_2, RT	95	trace
2	$[(Ph_3P)AuCl]/AgSbF_6$	CH_2Cl_2, RT	0	61
3	$[(Ph_3P)AuCl]/AgSbF_6$	CH_2Cl_2, reflux	0	81
4	$AgSbF_6$	CH_2Cl_2, reflux	25	11
5	$[(Ph_3P)AuCl]/AgSbF_6$	1,2-DCE, 60 °C	0	67
6	$[(Ph_3P)AuCl]/AgSbF_6$[c]	CH_2Cl_2, 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] Yields of isolated product 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.

to a gel when THF was used as the solvent (Table 1, entry 7), probably as a result of the polymerization of THF induced by reactive cationic species.[12] Three other gold(I) species were tested (Table 1, entries 8–10), but none was superior to $[(Ph_3P)AuCl]/AgSbF_6$ used in the model reaction.

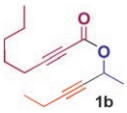
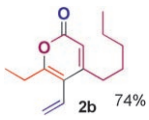
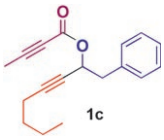
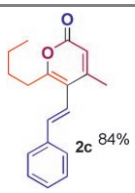
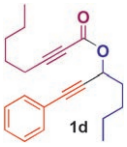
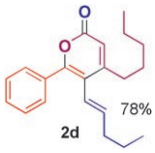
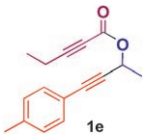
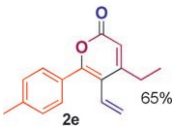
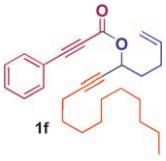
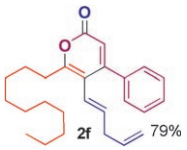
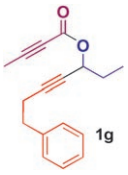
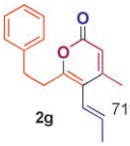
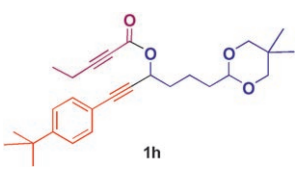
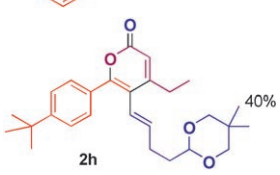
The rearrangement of propargyl propiolates **1b–g** gave the desired vinyl α-pyrones **2b–g** in 65–84% yield (Table 2). The olefin moiety in **1f** did not interfere with the cascade reaction despite the precedent of reactions involving 1,6-enynes.[10b,13] Substrate **1h** resulted in a less efficient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

We 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



Scheme 2. Racemic products result from nonracemic propargyl propiolates.

Table 2: Gold(I)-catalyzed rearrangement of propargyl propiolates to vinyl α-pyrones.[a]

Substrate	Product	Substrate	Product
 1b	 2b 74%	 1c	 2c 84%
 1d	 2d 78%	 1e	 2e 65%
 1f	 2f 79%	 1g	 2g 71%
 1h	 2h 40%		

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

with 5 mol% $[(Ph_3P)AuCl]/AgSbF_6$ at room temperature in the presence of two equivalents of trimethoxybenzene afforded the α-pyrone **3a** in 82% yield (Table 3). None of the rearrangement product **2a**, or the products resulting from nucleophilic attack at the other two positions (③ and ④, Scheme 1), was observed. The addition of the aromatic ring to the alkyne[15] does not interfere with the tandem reaction. Compound **3a** was not detected when α-pyrone **2a** was subjected to these reaction conditions, which indicates 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–h** in 59–85% yields (Table 3). Note that **3a–h** mimic the structure of diaryl methanes, which have a

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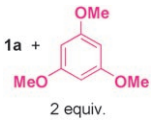
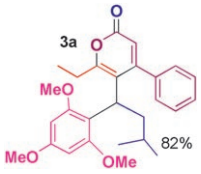
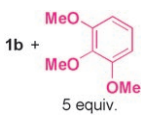
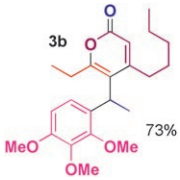
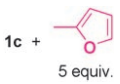
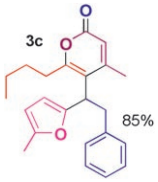
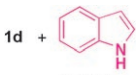
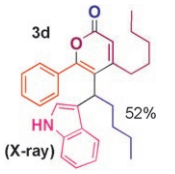
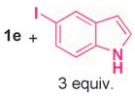
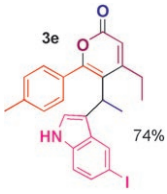
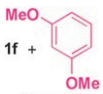
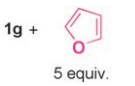
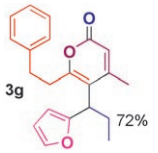
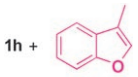
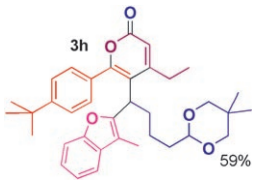
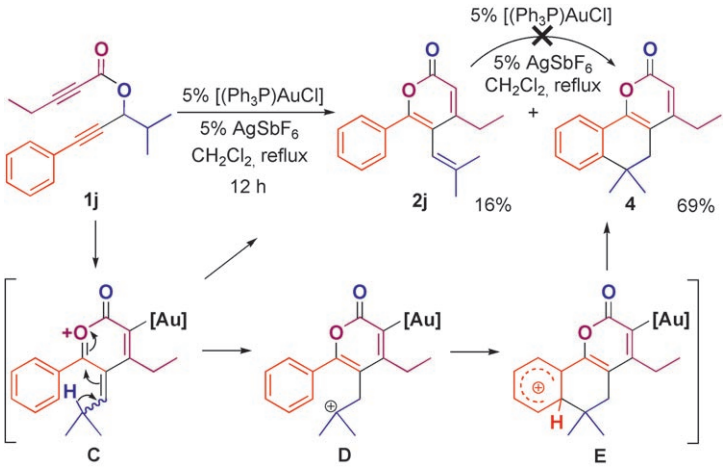
Table 3: Gold(I)-catalyzed syntheses of trisubstituted α-pyrones from propargyl propiolates.[a]

Substrate/Nu	Product	Substrate/Nu	Product
			
			
			
			

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



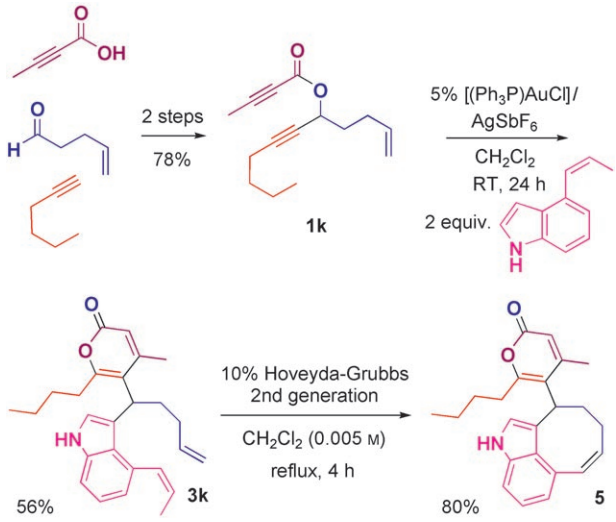
Scheme 3. Cascade process yielding a tricyclic α-pyrone.

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 (Scheme 2). This result suggests that the nucleophile bonds to both enantiofaces of the oxocarbenium **B** with equal facility.

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

As 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. First, our preliminary studies suggest that trapping the intermediate oxocarbenium ion with alcohol-based nucleophiles results in attack at the lactone carbonyl carbon atom, which results in an alternative skeleton. Second, strategic placement of suitable functionality in the building blocks allows functional-group pairing reactions that enable further skeletal diversification. To illustrate this concept, coupling product **3k** undergoes a ring-closing metathesis to yield the polycyclic α-pyrone **5** (Scheme 4). We are currently exploring the potential of these reaction processes in diversity syntheses and determining the assay



Scheme 4. Intramolecular functional-group pairing reaction involving substituents attached to distinct building blocks prior to the intermolecular coupling reaction (cf. "build/couple/pair strategy"[2]).

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performance of the resulting products using many small-molecule screens.

Received: June 22, 2007
Published online: September 24, 2007

Keywords: cascade reactions · cyclization · gold · pyrones · rearrangement

[1] For examples, see: a) N. Kumagai, G. Muncipinto, S. L. Schreiber, *Angew. Chem.* **2006**, *118*, 3717 – 3720; *Angew. Chem. Int. Ed.* **2006**, *45*, 3635 – 3638; b) D. A. Spiegel, F. C. Schroeder, J. R. Duvall, S. L. Schreiber, *J. Am. Chem. Soc.* **2006**, *128*, 14766 – 14767.

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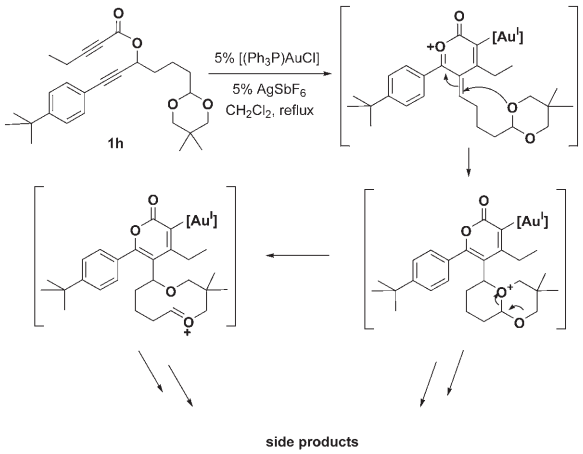
[14] A possible pathway for additional reaction products is:



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