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Two-Step Formal [3+2] Cycloaddition of Enones/Enals and Allenyl MOM Ether: Gold-Catalyzed Highly Diastereoselective Synthesis of Cyclopentanone Enol Ether Containing an All-Carbon Quaternary Center

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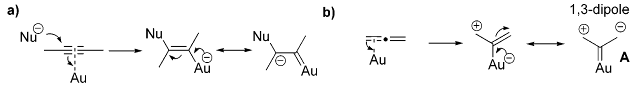
Five-membered carbocycles are of primary importance in organic synthesis, but their synthesis via modular and flexible 1,3-dipolar cycloaddition is hampered by the difficulty accessing all-carbon 1,3-dipoles. Various precursors or synthetic equivalents for the C_3 unit have been developed,[1] but there is still much need to expand their scope and develop new methods leading to highly efficient and stereoselective cycloadditions.

Au catalysts have recently been shown as powerful soft Lewis acids in activating alkynes and allenes toward nucleophilic attack.[2] The alkenylgold intermediate generated can behave as an α-deprotonated gold carbenoid via resonance, reminiscent of an enolate, leading to novel reactivities (Scheme 1a).[3] We speculate that allene, if not immediately attacked by nucleophile upon Au activation, would become all-carbon 1,3-dipole **A** via resonance (Scheme 1b) and participate in concerted 1,3-dipolar cycloaddition. Herein, we disclose our study of this previously unknown concept and report an efficient two-step synthesis of cyclopentanone enol ethers containing an all-carbon quaternary center. An intramolecular [3+2] cycloaddition using allene as 1,3-dipole precursor[4] is proposed, supported by the observed excellent diastereoselectivity.

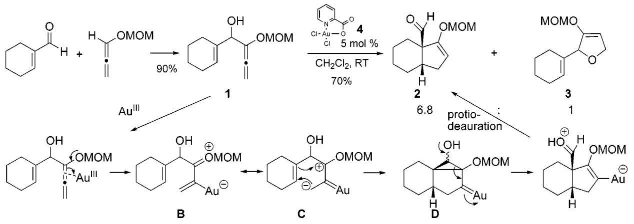
While various useful Au-catalyzed reactions of allenes[5] have been developed, the allene substrates are usually without heteroatom directly attached to the 1,2-diene moiety, and their preparations often require multiple steps. We previously developed an in situ generation of carboxyallenes via Au-catalyzed rearrangement of propargylic esters, which substantially facilitated studies of the chemistry of these functionalized allenes with the very same Au catalyst while avoiding the difficulty in their preparation.[6] In the search for additional approaches toward rapid access to functionalized allenes for the intended [3+2] cycloaddition, we found that allenyl MOM ether, upon α deprotonation, has been used to prepare electron-rich allene derivatives en route to functional structures.[7] To our surprise, no study of these readily available, functionalized allenes in the presence of Au catalyst has been reported.

We began with allenyl carbinol **1**, prepared from cyclohex-1-enecarbaldehyde and allenyl MOM ether in one step (Scheme 2). Compound **1** contains an alkene and an electron-rich allene in close proximity and is ideal for studying Au-catalyzed [3+2] cycloaddition. Gratifyingly, treatment of **1** with 5 mol % of dichloro(pyridine-2-carboxylato)gold (**4**)[8] in CH_2Cl_2 gave cyclopentanone enol ether **2**[9] as the major product and the expected dihydrofuran **3**. The formation of **2** can be rationalized as shown in Scheme 2. Hence, selective Au^{III} activation of the enolic double bond of the allenyl ether moiety gives oxocarbenium **B**, which is in resonance with 1,3-dipole **C**; subsequent intramolecular 1,3-dipolar cycloaddition of **C** forms Au carbenoid **D** with a strained bicyclo[3.1.0]hexane moiety,[10] of which the cyclopropane ring is fragmented with the assistance of the OH group; the final step is protiodeauration.

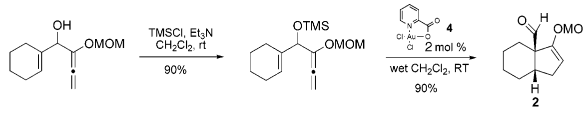
Scheme 1. Proposed Generation of All-Carbon 1,3-Dipoles from Allenes in the Presence of Au Catalyst



Scheme 2. Au-Catalyzed Formation of Cyclopentenone Enol Ether **2** and the Proposed Mechanism



With this encouraging result, we examined extensively the parameters of this reaction aiming to improve the yield of **2** while curbing the formation of dihydrofuran **3**. Although none of the other catalysts (e.g., $Ph_3PAuNTf_2$, AuCl, and $PtCl_2$) nor different solvents (e.g., THF, CH_3CN, and toluene) helped, masking the free hydroxyl group in **1** with a TMS group led to a dramatic increase of selectivity, and aldehyde **2** was isolated in 90% yield using 2 mol % of catalyst **4** while dihydrofuran **3** was not observed (eq 1). In this case, the small amount of water in wet CH_2Cl_2[11] was necessary to convert TMS^+ into proton for protiodeauration.



(1)

The scope of this reaction was then probed using the optimal protocol shown in eq 1. We first examined the case of methacrolein (Table 1, entry 1). It was found that the TMS ether intermediate could be prepared in one-pot by quenching the in situ-formed lithium allenyl alkoxide with TMSCl; the silyl ether was formed rather pure in the crude residue, which could be used directly without further purification. As a result, aldehyde **6a** was isolated in 89% yield over two steps. This substantially simplified two-step procedure not only circumvents potential decomposition of the rather delicate silyl ether during column purification but also constitutes a formal intermolecular [3+2] cycloaddition between enals and allenyl MOM ether.

Using the simplified procedure, cyclic enals with different ring sizes (entries 2 and 3) coupled with allenyl MOM ether efficiently, yielding cis-fused bicyclic aldehydes in excellent yields. While diastereocontrol by a remote stereogenic center in the case of (−)-perillaldehyde was minimal (entry 4), the double-bond geometry in acyclic enals seems to dictate the stereochemical outcome of the adduct. Hence, *trans*-α-methylcinnamaldehyde (i.e., **5e**) led to exclusive observation of **6e** with the phenyl group *trans* to

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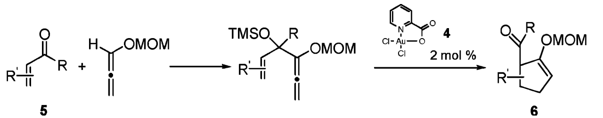
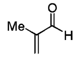
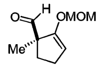
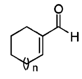
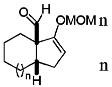
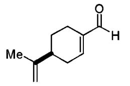
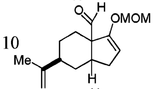
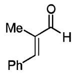
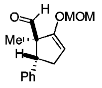
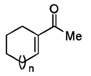
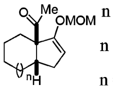
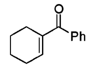
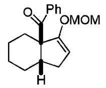
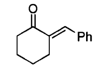
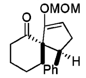
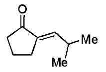
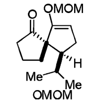
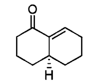
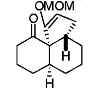
Table 1. Two-Step Formal [3+2] Cycloadditions



Entry	Enal/Enone 5^a		Reaction conditions	Time (min)	Adduct 6^b		Yield^c (%)
1		a	wet CH_2Cl_2, rt	10		a	89
2		n = 0; b	wet CH_2Cl_2, rt	10		n =0; b	90
3		n = 2; c	wet CH_2Cl_2, rt	10		n = 2; c	85
4		d	wet CH_2Cl_2, rt	10		d	73^d
5		e	anhyd. CH_2Cl_2 AcOH (2 eq), rt	30		e	60^e
6		n = 0; f	anhyd. CH_2Cl_2 AcOH (2 eq), 0°C	30		n = 0; f	99
7		n = 1; g		30		n = 1; g	90
8		n = 2; h		30		n = 2; h	83
9		i	anhyd. CH_2Cl_2 AcOH (2 eq), 0°C	30		i	44^e
10		j	anhyd. CH_2Cl_2 AcOH (2 eq), 0°C	30		j	90
11		k	wet CH_2Cl_2, rt	10		k	79
12		l	anhyd. CH_2Cl_2 AcOH (2 eq), rt	30		l	83^e

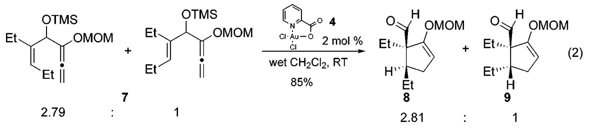
[a] The substrate concentration was 0.05 M. [b] No other diastereomer was observed. [c] Isolated yield over two steps based on the enal/enone starting material. [d] Value represents a 1:1 mixture of diastereomers. [e] Reaction run using 5 mol % of catalyst **4**.

the aldehyde moiety. Notably, **5e** is a difficult substrate, and **6e** was formed in only 37% yield using wet CH_2Cl_2. Fortunately, using AcOH as the proton source led to much improved reaction, and **6e** was isolated in 60% yield using 5 mol % of **4** (entry 5). Surprisingly, cinnamaldehyde did not participate in this reaction.

We were delighted to find that this efficient reaction applied well to enone substrates. In general, AcOH was the preferred proton source, and the reactions proceeded well at 0 °C. For example, without purification of intermediate TMS ethers, 1-acetylcycloalkenes of different ring sizes underwent smooth reactions, and the cis-fused bicyclic ketones were formed in excellent yields (entries 6−8). Notably, phenyl enone **5i** participated in this two-step reaction as well, albeit in a low yield (entry 9). Remarkably, α-ylidenecycloalkanones such as **5j** and **5k** were good substrates, leading to spiral adducts with complete diastereoselectivity in good to excellent yields (entries 10 and 11). With bicyclic enone **5l** (entry 12), tricyclic ketone **6l** was isolated pure in 83% yield. The excellent stereoselectivity is due to the excellent diastereoselectivities in both the formation of the TMS ether intermediate and the Au-catalyzed [3+2] cycloaddition.

The observed high diastereoselectivities can be readily explained using the 1,3-dipolar cycloaddition mechanism proposed in Scheme 2 instead of alternative stepwise mechanisms involving carbon cation formation in the enal/enone double bond.

Further support for the proposed concerted, if not synchronous, mechanism was obtained: a crude mixture of TMS ether **7**[12] with a *Z*/*E* ratio of 2.79/1 was treated with catalyst **4**, and a mixture of diastereomeric aldehydes **8** and **9** with a practically identical ratio (2.81/1) was isolated in 85% overall yield (eq 2). NOESY-1D experiments confirmed that the major product, **8**, has the aldehyde moiety *cis* to the vicinal ethyl group.



Several features of this two-step cycloaddition sequence are noteworthy: it is operationally simple and no purification of the TMS ether intermediate is necessary; the adduct possesses an all-carbon quaternary center with readily functionalizable and well differentiated aldehyde/ketone and enol ether substituents; beside the excellent diastereoselectivity, it is regiospecific; synthetically useful spirobicyclic compounds (e.g., **6j** and **6k**) can be readily prepared; moreover, with stereocontrol on the formation of the intermediate allenyl carbinol silyl ether, the configuration of the all-carbon quaternary center can be readily controlled and predicted (e.g., entry 12, Table 1).

In summary, a highly diastereoselective, two-step formal [3+2] cycloaddition between allenyl MOM ether and an enal/enone is developed. An intramolecular 1,3-dipolar cycloaddition using allene as 1,3-dipole precursor is proposed. Synthetically versatile cyclopentanone enol ethers containing an all-carbon quaternary center can be readily prepared with excellent stereocontrol.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Extensive NMR studies including NOESY-1D experiments were used to establish its structure.

(10) A stepwise mechanism was proposed in a related case, see: Buzas, A.; Gagosz, F. *J. Am. Chem. Soc.* **2006**, *128*, 12614−12615.

(11) Generated by shaking CH_2Cl_2 with H_2O followed by phase separation.

(12) The starting enal had a *Z*/*E* ratio of 2.3/1. The increase of *Z*/*E* ratio in **7** is likely due to the slightly different reactivities of the *Z*- and *E*-enal toward α-lithiated allenyl MOM ether.

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