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Letter

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Catalytic Generation of Vinylthionium Ions. (4 + 3)-Cycloadditions and Friedel–Crafts Alkylations

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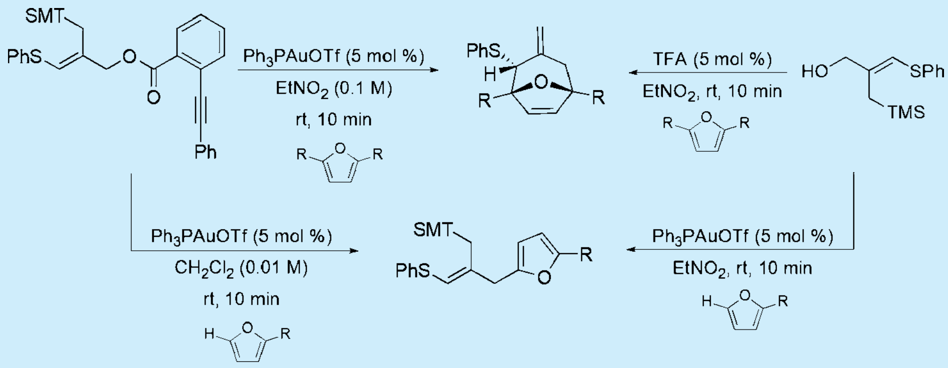
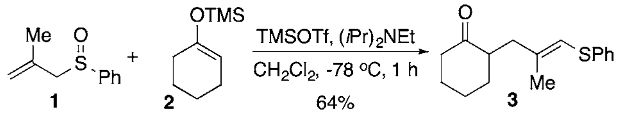
Supporting Information



ABSTRACT: A 3-phenylsulfanyl-substituted allylic alcohol and an ester thereof were treated with Brønsted acids or a gold catalyst, respectively, to generate vinylthionium ions. These species react with dienes, primarily substituted furans, to give products of either (4 + 3)-cycloaddition or Friedel–Crafts alkylation. The results are rationalized on the basis of a stepwise mechanism in which the relative rates of ring closure versus proton loss in the intermediate σ-complex determine the course of the reaction.

The generation of cationic species for carbon–carbon bond formation has a long history in organic chemistry.[1] Vinylthionium ions are a subclass of this rather broad category that offer promise in a number of reactions. For example, Hunter reported that vinylthionium ions generated by the Pummerer rearrangement of allylic sulfoxides could be productively trapped by silyl enol ethers (Scheme 1).[2]

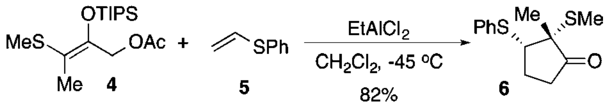
Scheme 1. Generation and Trapping of a Vinylthionium Ion



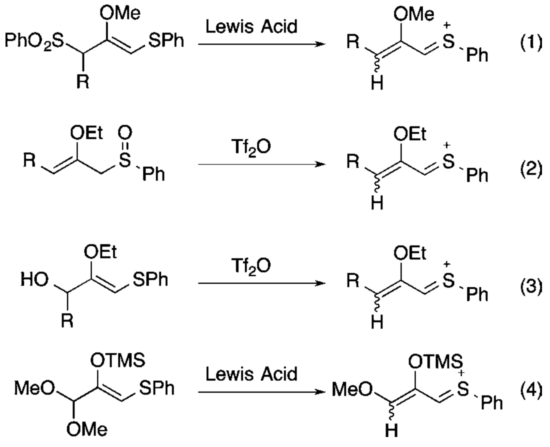
Kuwajima demonstrated the generation of vinylthionium ions from acetates such as **4** and developed their chemistry with respect to formal (3 + 2)-cycloaddition (Scheme 2).[3]

In the context of our studies on (4 + 3)-cycloadditions, we introduced a number of methods for the generation of vinylthionium ions for use as dienophiles. These included the Pummerer rearrangement of allylic sulfoxides,[4] the ionization of allylic sulfones,[4,5] the formation and concomitant ionization of selected allylic alcohols,[6] and the ionization of certain allylic acetals[7] as summarized in Scheme 3. We and others have used some of these methodologies in various applications.[8]

Scheme 2. (3 + 2)-Cycloaddition with a Vinylthionium Ion



Scheme 3. Generation of Vinylthionium Ions Used in (4 + 3)-Cycloadditions



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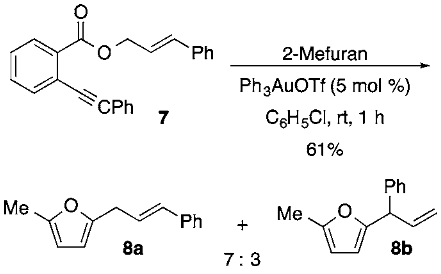
Recently, we became interested in the possibility of generating dienophilic allylic cations in a chiral environment in the hopes of developing a new method for the asymmetric, catalytic (4 + 3)-cycloaddition reaction.[9] Vinylthionium ions were appealing within this conceptual framework for at least two reasons. The sulfanyl group can be easily removed from the product of the reactions by standard desulfurization protocols. More importantly, we viewed the sulfanyl substituent as a potential point of noncovalent interaction between the vinylthionium ion and chiral counterions such that the structural and stereochemical integrity of the ion pair might be enhanced. Toward this ultimate goal, we have conducted preliminary investigations on the catalytic reaction of certain substrates to evaluate mechanistic issues and reveal the scope of the process as a prelude to further work. This letter summarizes our efforts to date.

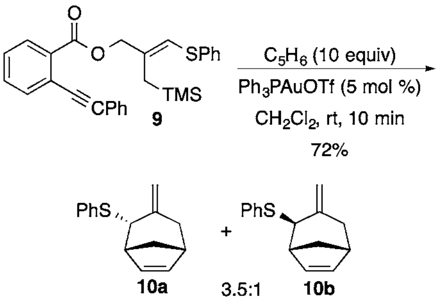
Our initial interest was in performing a catalytic (4 + 3)-cycloaddition under the mildest conditions possible. We were particularly intrigued by various reports involving the gold-catalyzed ionization of certain esters to form oxocarbenium, benzylic, or allylic cations.[10] For example, treatment of **7** with triphenylphosphine gold(I) triflate in the presence of 2-methylfuran was reported to afford the alkylation products **8a** and **8b** in 61% yield in a ratio of 7:3 (Scheme 4). This reaction likely proceeded via an allylic cation.

Scheme 4. Gold-Catalyzed Alkylation of 2-Methylfuran



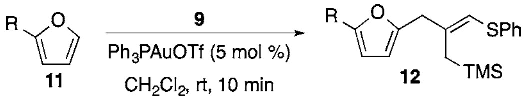
We used this and other examples as inspiration for the design of a gold-catalyzed (4 + 3)-cycloaddition reaction. The ester **9**, prepared from the corresponding known alcohol[11] and acid,[12] was treated with 5 mol % of triphenylphosphine gold(I) triflate in the presence of cyclopentadiene (10 equiv) in dichloromethane at room temperature. This afforded the cycloadducts **10a** and **10b** in 72% yield as a 3.5:1 inseparable mixture of *endo* and *exo* diastereomers (Scheme 5). The stereochemical assignment of each isomer was based on past results with related cycloadditions as well as on spectral data (^{1}H and ^{13}C NMR, COSY, NOESY, HMQC).

Scheme 5. Gold-Catalyzed (4 + 3)-Cycloaddition



To expand the scope of the reaction, we decided to examine the process with furan and a series of simple 2-substituted analogues thereof. The results are summarized in Table 1. As can be seen, the only products we obtained were those from Friedel−Crafts alkylation, not cycloaddition.[13] We attributed this outcome to a stepwise process in which initial carbon−carbon bond formation was followed by either loss of a proton to give the observed products (Scheme 6, path a) or ring closure to afford a cycloadduct (Scheme 6, path b) .

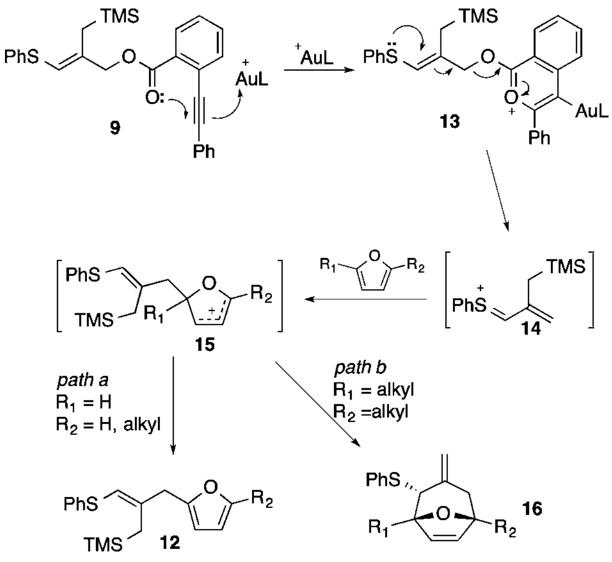
Table 1. Gold-Catalyzed Alkylation of Furans by 9



entry[a]	R	product	yield **12** (%)
1	H	**12a**	93
2	Me	**12b**	93
3	Et	**12c**	95
4	*n*-Pr	**12d**	91
5	*n*-Bu	**12e**	75
6	*n*-pentyl	**12f**	70
7	*n*-hexyl	**12g**	68
8	*n*-heptyl	**12h**	66
9	*n*-octyl	**12i**	60

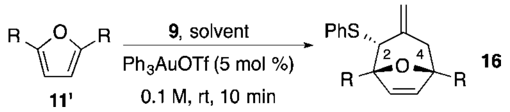
[a] 1 equiv of **11** was used.

Scheme 6. Putative Mechanism for the Formation of Friedel-Crafts or Cycloaddition Products



In an attempt to circumvent the former process, we examined 2,5-disubstituted furans as substrates. We anticipated that both blocking the proton loss and favoring conformations conducive to cyclization[14] would yield positive results in this case. The results are summarized in Table 2. Studies of solvents suggested that polar solvents were more effective than relatively nonpolar ones (Table 2, entries 1−5). Lowering the concentration of the furan was detrimental (Table 2, entry 6). We settled on using 1 equiv of a furan at a concentration of 0.1 M in nitroethane (Table 2, entries 5, 8−12). In these cases, cycloadducts were obtained quickly, stereoselectively, and in good yields. The assignment of stereochemistry was based on a

Table 2. Gold-Catalyzed (4 + 3)-Cycloadditions of 9 with 2,5-Disubstituted Furans



entry	R	solvent	product	yield 16 (%)
1	Me	CH_2Cl_2	**16a**	*a*
2	Me	toluene	**16a**	*a*
3	Me	THF	**16a**	*a*
4	Me	MeCN	**16a**	81
5	Me	$EtNO_2$	**16a**	85
6	Me	$EtNO_2$[b]	**16a**	32
7	Me[c]	$EtNO_2$	**16a**	62
8	Et	$EtNO_2$	**16b**	82
9	*n*-Pr	$EtNO_2$	**16c**	79
10	*n*-Bu	$EtNO_2$	**16d**	76
11	*n*-pentyl	$EtNO_2$	**16e**	71
12	*n*-hexyl	$EtNO_2$	**16f**	65

[a] Complex mixture by TLC. [b] 0.01 M. [c] 10 equiv of **11′a**.

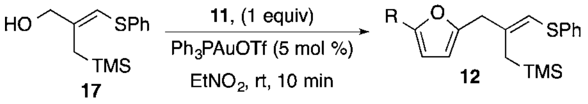
NOESY analysis of **16a**, which indicated that the proton on C-2 (3.85 ppm) exhibited stronger NOE with the more downfield proton on C-4 (2.55 ppm), suggesting a *cis* relationship between the two protons. Further, the other proton on C-4 (2.34 ppm) showed NOE with the olefinic proton at 5.90 ppm, indicating that it is spatially proximal to this proton and thus must be endo.

A question that typically arises in metal catalysis of this type is whether treatment with a Brønsted acid also results in the reactions observed.[15] Treatment of **9** with either triflic acid or trifluoroacetic acid (5 mol %) in the presence of **11′a** did not afford products seen in the corresponding gold-catalyzed reactions.

Nevertheless, we were intrigued with the possibility that both the ester of **9** was not necessary for the reaction and the alcohol precursor to **9** might function well in the processes we had been developing. To examine both of these questions, we treated alcohol **17** with $Ph_3PAuOTf$ in the presence of various furans, under essentially the same conditions as for the reaction of **9** with **11**, save for a switch in solvent to $EtNO_2$. The results are summarized in Table 3, and they do parallel the results shown in Table 1.

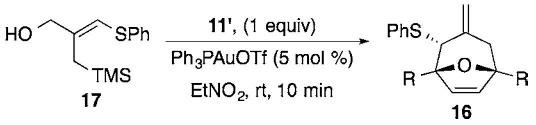
We next decided to test the ability of **17** to engage in (4 + 3)-cycloadditions under essentially the same conditions that gave rise to the FC adducts shown in Table 3. This was successful, and the results are summarized in Table 4.

Table 3. Gold-Catalyzed Alkylation of Furans by 17



entry	R	product	yield 12 (%)
1	H	**12a**	86
2	Me	**12b**	84
3	Et	**12c**	83
4	*n*-Pr	**12d**	80
5	*n*-Bu	**12e**	67
6	*n*-pentyl	**12f**	64
7	*n*-hexyl	**12g**	63
8	*n*-heptyl	**12h**	61
9	*n*-octyl	**12i**	61

Table 4. Gold-Catalyzed (4 + 3)-Cycloadditions of 17 with 2,5-Disubstituted Furans

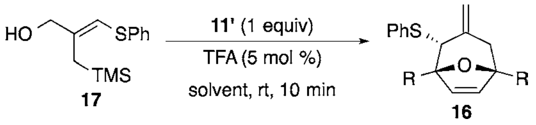


entry	R	product	yield 16 (%)
1	Me	**16a**	82
2	Et	**16b**	82
3	*n*-Pr	**16c**	79
4	*n*-Bu	**16d**	75
5	*n*-pentyl	**16e**	73
6	*n*-hexyl	**16f**	67

Interestingly, the reaction of **17** with **11′a** in the presence of $Ph_3PAuOTf$ failed in the presence of 4 Å molecular sieves or 2,6-lutidine. Moreover, the reaction of **17** with **11′a** catalyzed by silver triflate produced the cycloadduct **16a** in 66% yield (rt, 10 min). There is no reaction of **17** and **11′a** under thermal conditions (refluxing acetonitrile). Finally, the reaction of **9** with **11′a** in the presence of $Ph_3PAuOTf$ did afford cycloadduct **16a** in the presence of 4 Å molecular sieves or 2,6-lutidine. These data suggest that while the reactions of **17** are not metal-catalyzed, they are catalyzed by protic acid.

We examined this idea using trifluoroacetic acid as a catalyst, which is much cheaper than triflic acid.[16] The results are shown in Table 5. As can be seen, the results parallel those from all of the other studies. Overall, all of the results suggest that the reactions of ester **9** are indeed gold-catalyzed, while those of the corresponding alcohol **17** are catalyzed by protic acid, even in the presence of gold(I).

Table 5. Acid-Catalyzed (4 + 3)-Cycloadditions of 2,5-Disubstituted Furans



entry	R	solvent	product	yield 16 (%)
1	Me	CH_2Cl_2	**16a**	57
2	Me	toluene	**16a**	46
3	Me	acetone	**16a**	60
4	Me	MeCN	**16a**	76
5	Me	$EtNO_2$	**16a**	78
6	Et	$EtNO_2$	**16b**	78
7	*n*-Pr	$EtNO_2$	**16c**	77
8	*n*-Bu	$EtNO_2$	**16d**	64
9	*n*-pentyl	$EtNO_2$	**16e**	73
10	*n*-hexyl	$EtNO_2$	**16f**	68

In summary, we have developed a new route to what appear to be vinylthionium ions that are capable of either (4 + 3)-cycloaddition or alkylation reactions with selected dienes. Understanding the mechanism of these reactions in order to favor cycloaddition and applying chiral acids to the process could result in the creation of new asymmetric methodology, including a (4 + 3)-cycloaddition reaction. Further results will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and analytical data for new compounds and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(13) The *Z* stereochemical assignment of the products was based on a NOESY spectrum of **12d**, which clearly showed an NOE interaction between the olefinic proton and the methylene group attached to the furan ring.

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