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A gold-catalyzed [4+3]-cycloaddition of functionalized dioxines

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ABSTRACT

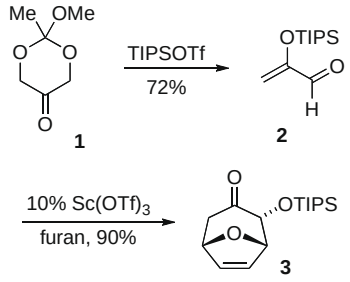
Treatment of 5-silyloxydioxins with 5 mol % $AuCl_3/AgSbF_6$ in the presence of cyclopentadiene or furan results in the rapid formation of [4+3]-cycloadducts at room temperature.

The [4+3]-cycloaddition reaction between allylic cations or their equivalents and dienes represents a powerful approach to the synthesis of seven-membered rings.[1] Further, coupling the process to other reactions such as the quasi-Favorskii rearrangement[2] and ring expansion reactions[3] can lead to the formation of four-membered and eight-membered rings, respectively. The opportunities for using the basic process in combination with other reactions are truly vast.

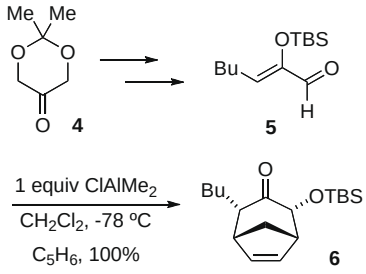
Metal-catalyzed reactions offer viable alternatives to the allylic cation chemistry,[4] but like all other reactions, they have certain limits to their scope. The use of allylic cations or surrogates thus still merits continued investigation from both an applied and a fundamental perspective.

Several years ago, we reported a catalytic version of the [4+3]-cycloaddition reaction in which a silyloxy acrolein functioned as a dienophile. Thus, treatment of **2** with 10 mol % of scandium triflate in the presence of furan resulted in the formation of cycloadduct **3** in 90% yield (Scheme 1).[5] Interestingly, **2** was available directly from **1** simply by treatment with TIPSOTf in the presence of triethylamine. Nearly contemporaneously, Funk reported that a variety of 2-silyloxyalkenals could be prepared from dioxinone **4** and used productively in [4+3]-cycloaddition reactions (Scheme 2).[6] This procedure is ultimately more general than our own, as the acetal function in **4** is less sensitive than the *ortho*-lactone functional group in **1**, allowing for more facile functionalization of **4** and more ready access to substituted silyloxyalkenals like **5**.

In an effort to prepare substrates for the development of catalytic asymmetric [4+3]-cycloaddition reactions, we undertook the preparation of several silyloxyalkenals using the Funk approach. In the course of the work, we became interested in a single specific example of an intramolecular [4+3]-cycloaddition of dioxine **7** mediated by 1 equiv of Lewis acid as shown in Scheme 3. One possible mechanism for this reaction consists of a Lewis acid-mediated retro-hetero-Diels–Alder reaction to afford **8**, which undergoes a



Scheme 1. [4+3]-Cycloaddition of a silyloxyacrolein.



Scheme 2. [4+3]-Cycloaddition of a silyloxyalkenal.

Lewis acid-catalyzed [4+3]-cycloaddition.[7] We wondered if this process could be made general, catalytic and eventually both catalytic and asymmetric. This Letter details our initial, successful studies of the intermolecular version of the reaction.

Given current interest in the field of coinage metals as catalysts for organic reactions,[8] we examined several silver and gold species as potential catalysts for the reaction. For example, attempts were made to catalyze the reaction of dioxine **10** with cyclopentadiene using $AgSbF_6$, $ClAuPPh_3$, $AuCl_3$, and $AgSbF_6/ClAuPPh_3$. All these reactions failed to give evidence for the formation of any product between the two reactants even after 12 h at room temperature.

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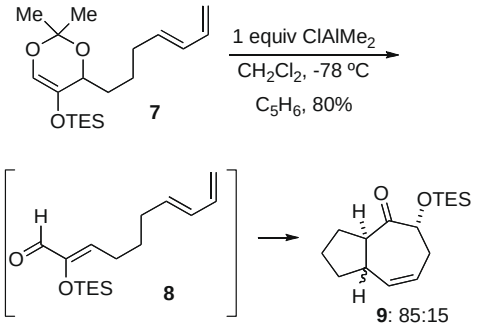
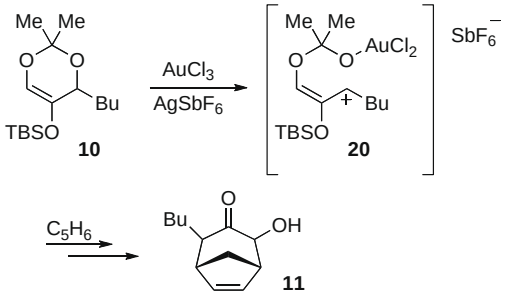


Scheme 3. Intramolecular [4+3]-cycloaddition of a silyloxydioxine.

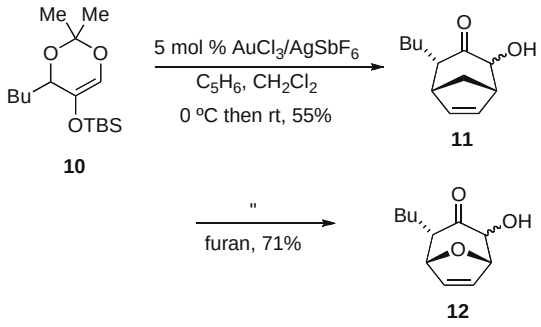


Scheme 5. Intermolecular [4+3]-cycloaddition of a silyloxydioxine.

However, treatment with 5 mol % of both $AgSbF_6$ and $AuCl_3$ resulted in the formation of cycloadduct **11** in 55% yield *within* 5 min *at room temperature* as a 87:13 mixture of isomers. When the same reaction was conducted with furan as dienophile, cycloadduct **12** was isolated in 71% yield, as a 86:14 mixture of diastereomers as determined by proton NMR (Scheme 4).

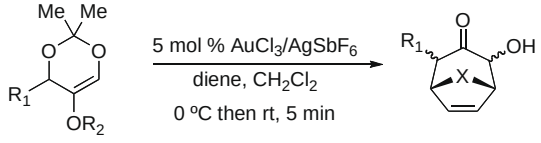
It appears that the diastereomers of **12** are *endo* and *exo* adducts. Thus, treatment of the mixture of **12** with TBSCl produced the corresponding TBS ethers, compounds already prepared by Funk.[6] A comparison of the NMR data with those published indicated that the major isomer was the *endo* compound.[9]

Several other examples of the reaction were performed and the results are summarized in Table 1. Changing the silyl group from TBS to TES had an impact only when furan was used in the reaction (Table 1, entries 1–4). The 'parent' dioxine **14** gave products with both furan and cyclopentadiene that were not substantially different from **10**, though a decrease in the yield of the product derived from furan was noted. Finally, another substituted system (**17**) behaved essentially the same as **10** with respect to the two dienes tested. Stereochemical assignments in this series are based on analogy with **12**.



Scheme 4. Intermolecular [4+3]-cycloaddition of a silyloxydioxine.

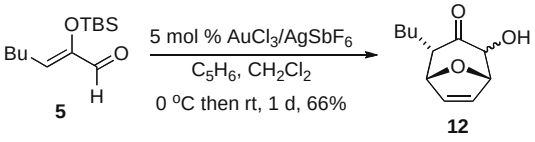
Table 1
Gold-catalyzed [4+3]-cycloadditions



Entry	Educt	R_1	R_2	Diene	Product	Yield[a,b] (%)
1	**10**	Bu	TBS	C_5H_6	**11**	55 (87:13)
2	**10**	Bu	TBS	Furan	**12**	71 (86:14)
3	**13**	Bu	TES	C_5H_6	**11**	50 (83:17)
4	**13**	Bu	TES	Furan	**12**	52 (82:18)
5	**14**	H	TBS	C_5H_6	**15**	65[c]
6	**14**	H	TBS	Furan	**16**	58[c]
7	**14**	H	TBS	Furan	**16**	56[c,d]
8	**17**	Bn	TBS	C_5H_6	**18**	52 (77:23)
9	**17**	Bn	TBS	Furan	**19**	68 (83:17)

[a] Yields are for two steps, enol ether formation and cycloaddition.
[b] (*endo*:*exo*).
[c] Single isomer formed, presumed to be *endo*.
[d] Nitroethane was used as solvent.

Interestingly, it appears that the mechanism for this reaction is more complex than might be expected. For example, if the reaction occurred via a Lewis acid-catalyzed retro-Diels–Alder reaction of **10** to produce **5**, which then proceeded on to product, one might expect that the [4+3]-cycloaddition reaction of **5** would proceed in essentially the same fashion as **10**. This is not the case. When a mixture of **5** and furan was treated with $AuCl_3/AgSbF_6$, a cycloadduct was indeed formed, but the reaction required 24 h at room temperature to go to completion (Eq. 1).



(1)

This suggests that the reaction of **10** with the catalyst produces a reactive intermediate, perhaps **20**, that is trapped by the diene to either directly afford the observed [4+3]-cycloadduct or another intermediate that proceeds to the product (Scheme 5). We have made limited attempts to trap such a reactive intermediate with a simple terminal alkene, allyltrimethylsilane and 1,3-dimethoxybenzene. Both alkenes resulted in the formation of complex reaction mixtures from which no meaningful mechanistic information could be gleaned. In the reaction with dimethoxybenzene, NMR evidence for the formation of **5** was observed, but no other product was apparent.

Regardless of mechanistic ambiguities, we have shown that dioxins can be activated catalytically by mixture of $AuCl_3$ and $AgSbF_6$ in the presence of furan and cyclopentadiene to afford [4+3]-cycloadducts.[10] This demonstrates that dioxines themselves can be viewed as allylic cation equivalents in the context of [4+3]-cycloaddition reactions and suggests that their catalytic activation might be developed into a general and asymmetric process for both inter- and intramolecular versions of the reaction. Studies to realize these goals are in progress and results will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.111.

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7. The use of the term 'cycloaddition' in this context is not meant to be mechanistically rigorous. Indeed, both computational and experimental data suggest that the reaction of silyloxyalkenals with dienes is more complex. See: (a) Davies, H. M. L.; Dai, X. *J. Am. Chem. Soc.* **2004**, *126*, 2692–2693; (b) Arno, M.; Picher, M. T.; Domingo, L. R.; Andres, J. *Chem. Eur. J.* **2004**, *10*, 4742–4749.
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9. We synthesized **11** via the Funk approach and showed that our major cycloadduct was indeed the *endo* isomer.
10. Note that the combination of $AuCl_3$ and silver salts has been used effectively in other contexts. To the best of our knowledge, the precise nature of the reagent in these processes has not been rigorously defined. See, for example: (a) Xiao, Y.-P.; Liu, X.-Y.; Che, C.-M. *J. Organomet. Chem.* **2009**, *694*, 494–501; (b) Yao, X.; Li, C.-j. *J. Am. Chem. Soc.* **2004**, *126*, 6884–6885.