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Asymmetric Organocatalysis of 4 + 3 Cycloaddition Reactions

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The 4 + 3 cycloaddition reaction of allylic cations and dienes represents a powerful approach to the synthesis of seven-membered rings.[1] Many approaches to the generation of allylic cations and their subsequent cycloadditions have been published. It is only recently, however, that work on asymmetric 4 + 3 cycloaddition reactions has appeared in the literature.[2] All of the approaches are based on a chiral auxiliary approach; no catalytic asymmetric 4 + 3 cycloaddition reactions are known.

As part of a broader program designed to develop catalytic asymmetric 4 + 3 cycloaddition reactions, we have begun examining chemistry developed for the asymmetric catalysis of other reactions. For example, the generation of chiral, unsaturated imminium ions as intermediates in asymmetric Diels−Alder and Friedel−Crafts reactions has recently been published by MacMillan and co-workers.[3] It occurred to us that a system such as **1** should be amenable to similar organocatalysis.[4] An iminium ion derived from **1** should be capable of a productive reaction with a diene via a 4 + 3 cycloaddition reaction, possibly with facial selectivity, depending on the structure of the amine, as shown in Scheme 1. This idea worked, and this report conveys our preliminary study of the process.

We initially explored the reaction of furan with several silyloxypentadienals in the presence of the known chiral amine **4**.[3c] Treatment of pentadienals **1** and **5**−**7** with 20 mol % each of amine **4** and trifluoroacetic acid in the presence of furan at 0 °C for 4 days resulted in the formation of 4 + 3 cycloadduct **8**. Endo selectivity was observed.[5] Although the yields were quite low, the enantiomeric excesses were acceptable,[6] as no optimization was involved. The results are summarized in Table 1. Attempts to separate the enantiomers of the primary cycloadduct on various chiral HPLC columns were not successful. We were fortunate to quickly find that the cycloadduct could be converted to the corresponding *N*-butylpyrrole **9** by treatment with butylamine and that this compound could be resolved on a chiral HPLC column. This behavior was typical for other cycloadducts as well, and we routinely converted cycloadducts to their *N*-butylpyrrole derivatives to obtain enantiomeric excess data.

Unfortunately, 2-methylfuran also did not react well with **1**, appearing to afford complicated mixtures or the alkylation product **11** in variable yields. The isolation of such an alkylation product suggests that the cycloaddition process could be stepwise and provides a rationalization for the poor performance of furan and 2-methylfuran in the cycloaddition reaction. Thus, the formation of an intermediate such as **10** (R = H) is anticipated. The most favorable conformation of this species will be one which does not favor ring closure to give a cycloaddition product, but an extended species which could lose a proton to form a substitution product. Such products are seen in a number of attempted 4 + 3 cycloaddition reactions.

When this problems arises, a way of circumventing it is to use disubstituted furans, so that the conformers resulting from rotation about bond "a" in **10** (R = alkyl) now have similar energies. The conformer needed for ring closure will then be significantly populated, and barriers to rotation to achieve this conformer will be reduced.[7]

Scheme 1

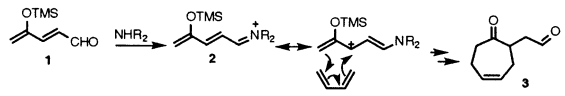
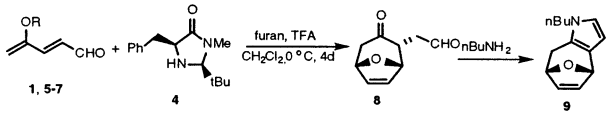


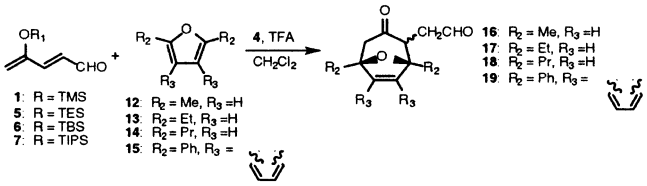
Table 1. Reaction of 4-Trialkylsilyloxypentadienals with Furan in the Presence of Amine **4**



entry	educt, R	yield (%)[a]	ee[b]
1	**1**, TMS	8	50
2	**5**, TES	10	55
3	**6**, TBS	8	65
4	**7**, TIPS	0	

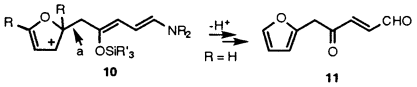
[a] Isolated yields for the endo diastereomer. [b] Enantiomeric excesses were determined by analysis of the *N*-butylpyrrole derivative of **12** using a Chiracel OD-H column.

Table 2. Asymmetric 4 + 3 Cycloaddition Reactions of Substituted Furans



entry	R_1	R_2	R_3	time (h)	T °C	product	yield (%)	endo:exo	ee[a]
1	TMS	Me	H	36	−60	16	64	endo	87
2	TMS	Me	H	96	−78	16	64	endo	89
3	TES	Me	H	96	−60	16	51	endo	81
4	TBS	Me	H	96	−60	16	44	endo	80
5	TIPS	Me	H	96	−60	16	21	endo	90
6	TMS	Et	H	22	−60	17	55	endo	81
7	TBS	Et	H	91	−65	17	18	endo	87
8	TES	Et	H	91	−65	17	46	endo	84
9	TES	Pr	H	95	−65	18	74	endo	85
10	TMS	Pr	H	95	−65	18	33	endo	89
11	TMS	Ph		92	−35	19	56	3.7:1	endo 12% exo 68%

[a] Enantiomeric excesses were determined by analysis of the *N*-butylpyrrole derivative of the cycloadducts using a Chiracel OD-H or Chiralpak AD column.



We thus examined four different 2,5-disubstituted furans to validate this analysis. The results are summarized in Table 2 and

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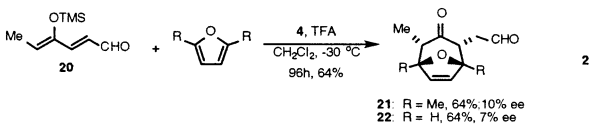
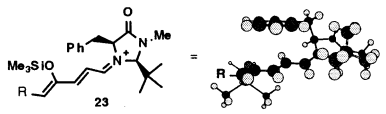
are quite promising. Thus, the reaction of **1** with 2,5-dimethylfuran **12** in the presence of amine **4** and TFA in CH_2Cl_2 for 4 days at −78 °C afforded cycloadduct **16** in 64% yield as a single diastereomer (Table 2, entry 2).[5] Conversion to the corresponding *N*-butylpyrrole and analysis on a Chiracel OD-H column indicated an enantiomeric excess of 89%. Low to good yields of cycloadducts were obtained for furans **12**−**15** with pentadienals **1** and **5**−**7**. Yields tended to be lower as the size of the silyl substituents increased, but no definitive pattern was observed. Enantiomeric excesses were generally good. Interestingly, 2,5-diphenylisobenzofuran afforded a 3.7:1 mixture of endo/exo isomers upon reaction with **1**. The endo isomer was found to have an ee of only 12%. The exo isomer had an ee of 67%. The basis for the difference remains to be determined.

To ascertain whether more substituted dienophiles could be developed in this process, we reacted **20** with 2,5-dimethylfuran in the presence of **4** and TFA.[8] This afforded the cycloadduct **21** in 64% yield.[9] Interestingly, furan also reacted with **20** to produce **22** in 64% yield. Unfortunately, the enantiomeric excesses of **21** and **22** were 10 and 7%, respectively.



2

Although we have no proof of mechanism or absolute configuration at this time, we assume that the iminium ion **23** is produced in accord with proposals by MacMillan.[3] The benzyl group blocks the top face of the ion, while the trialkylsilyloxy group may block the bottom face. When R is an alkyl group, this conformation may be locked and both faces of the iminium ion may be similarly sterically encumbered, leading to low ee's.[10] Further studies will be necessary to determine the stereochemical and other mechanistic features of the reaction.



In summary, we have documented the first examples of the asymmetric organocatalysis of the 4 + 3 cycloaddition reaction. Much remains to be done with respect to optimization, understanding the origin of the stereochemical outcome of the reaction, understanding the mechanism, and applying the results to synthetic problems. Results will be reported in due course.

Acknowledgment. This paper is dedicated to Professor Scott E. Denmark on the occasion of his 50th birthday. This work was supported by the Petroleum Research Fund, sponsored by the American Chemical Society, to whom we are very grateful. Thanks to Paul A. Wender for ongoing, inspiring conversations. Thanks to David MacMillan for sharing some important experimental information at the outset of this project. Thanks to Charles L. Barnes for the acquisition of X-ray data.

Supporting Information Available: Experimental procedures, copies of the proton and carbon spectra of the starting materials and products, and X-ray data for both isomers of **19** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) The pentadienal **1** has been used in 4 + 3 cycloaddition reactions previously, see: Ohno, M.; Mori, K.; Hattori, T.; Eguchi, S. *J. Org. Chem.* **1990**, *55*, 6086−6091.

(5) The assignment was made on the basis of the results of Eguchi and coworkers. See ref 4.

(6) We do not know the absolute configuration of the major enantiomer for this or any other cycloaddition adduct reported here.

(7) Parrill, A. L.; Dolata, D. P. *THEOCHEM* **1996**, *370*, 187.

(8) The stereochemistry of **20** was established by a NOESY experiment.

(9) The assignment of relative stereochemistry was based on chemical shift data of the 4-methyl group and aldehyde proton in **21**. NOESY also supported the assignment. Details are given in the Supporting Information. See ref 4 and (a) Montaña, A. M.; Grima, P. M.; Garcia, F. *Magn. Reson. Chem.* **1999**, *37*, 507. (b) Montaña, A. M.; Ribes, S.; Grima, P. M.; Garcia, F. *Magn. Reson. Chem*. **1998**, *36*, 174.

(10) However, the reaction of **20** with cyclopentadiene produced cycloadducts with enantiomeric excesses in the 50−60% range. Details will be reported later.

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