Synthetic Methods

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Scope and Mechanism of the (4+3) Cycloaddition Reaction of Furfuryl Cations**

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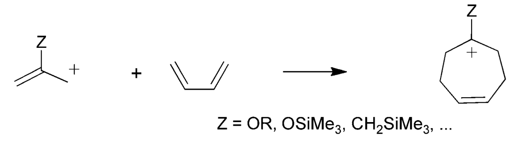
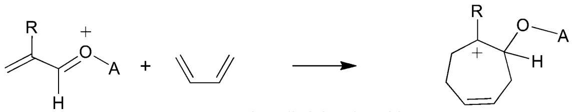
The (4+3) cycloaddition reaction between a conjugated diene and an allylic cation constitutes a convenient and conceptually straightforward method to prepare seven-membered rings.[1,2] In recent years, investigations into this type of cycloaddition, including a number of elegant applications in total synthesis,[3] have demonstrated its potential for development as a synthetic method that could approach the (4+2) cycloaddition (Diels–Alder) reactions in terms of selectivity and efficiency. Of particular interest are allylic cations bearing a cation-stabilizing substituent (Z group) at the 2-position [Eq. (1)][4] and stabilized allylic cations such as vinyloxocarbenium ions [Eq. (2)][5] or, typically, cationic reaction partners incorporating both of these features [Eq. (2), R = Z].[6]



(1)

Z = OR, OSiMe$_3$, CH$_2$SiMe$_3$, ...

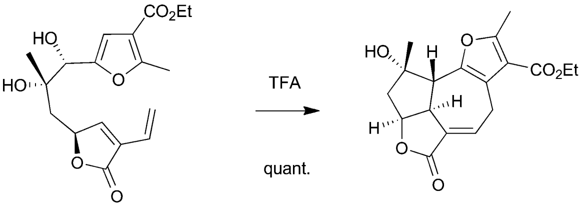


(2)

A = alkyl, Lewis acid

Whereas reactions of vinyloxocarbenium species are believed to proceed by a concerted (4+2) cycloaddition followed by a Wagner–Meerwein-type ring expansion,[5] allylic cations with a Z group at the 2-position have been suggested to undergo "true" (4+3) cycloaddition reactions, either through a concerted or a stepwise process.[7] The synthetic utility of these cycloadditions is limited however by issues concerning the generation of the allylic cation reaction partner. The precursors required for allylic cations can be synthetically challenging, and the carbocationic species themselves are generally quite unstable, thus giving rise to various by-products.

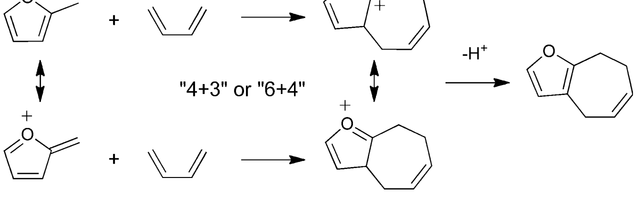
In the course of synthetic studies towards the natural product rameswaralide,[8] Pattenden and Winne uncovered an unexpected smooth intramolecular dehydrative reaction between a diene and a furfuryl alcohol that gave a novel fused polycycle containing a seven-membered ring [Eq. (3), TFA = trifluoroacetic acid].



(3)

We surmised that the mechanism of this intriguing cycloaddition reaction involves the initial formation of a furfuryl cation intermediate,[9] which then undergoes an intramolecular (4+3)-type cycloaddition with the appended diene (cf. Scheme 1). The initially formed bicyclic oxocarbenium ion can then be converted into the observed product through straightforward loss of a proton and regeneration of the furan ring. The cationic reaction partner in this sequence can thus be regarded as an allylic cation with a stabilizing oxygen substituent at the 2-position [cf. Eq. (1)], and moreover, if the oxonium ion resonance structure is considered (Scheme 1, bottom), it can be viewed as a vinylogous vinyloxocarbenium ion [cf. Eq. (2)]. If it is concerted, the observed cycloaddition can then be regarded as a rare example of a "higher order" pericyclic reaction, that is, a [6π + 4π] cycloaddition with an unprecedented 2-oxafulvene-type 6π reactant.[10]

As the prospect of an efficient (4+3) cycloaddition method using simple furfuryl alcohol starting materials is highly attractive from a synthetic point of view, we decided to investigate the scope and mechanism of this unprecedented



Scheme 1. Proposed mechanism of cycloaddition via a furfuryl cation intermediate.

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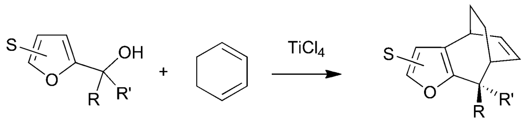
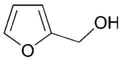
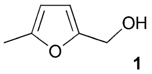
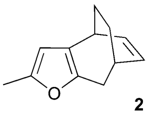
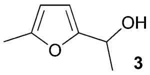
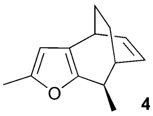
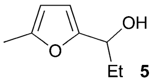
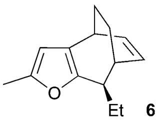
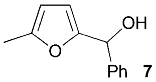
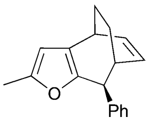
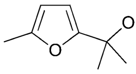
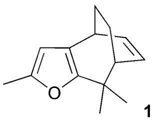
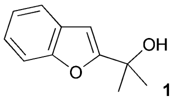
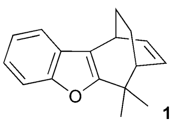
reaction by a joint experimental and theoretical approach. Although the efficiency of the cycloaddition reaction in [Eq. 3] is impressive (the polycycle is obtained as a single diastereomer in quantitative yield), it is definitely helped by the intramolecular nature of the reaction and possibly by the quite specific substitution patterns of the reactants. Thus, we have examined corresponding intermolecular cycloadditions of some simple furfuryl cations with 1,3-cyclohexadiene (CHD) as a model substrate. Our initial results are summarized in Table 1.

Using a number of cation-generating conditions (TFA, $TiCl_4$, or TMSOTf), we were not able to achieve a cycloaddition reaction with furfuryl alcohol itself (Table 1; entry 1). Instead, we invariably observed a swift polymerization reaction to give a black tar. However, when the homologue **1**, in which the highly nucleophilic 5-position of the furan is blocked by a methyl substituent, was used (entry 2) we could isolate the expected adduct **2**, albeit in poor yield. Best results were obtained using a stoichiometric amount of $TiCl_4$, as a Lewis acid. However, poly- and oligomerization reactions still seemed to be the prevalent reaction pathways for compound **1**. By employing an excess of CHD (2 equiv) and by increasing substitution at the carbinol position (entries 3–5), we were able to suppress furfuryl oligomerization and obtained good to excellent yields of cycloadducts **4**, **6**, and **8**. Moreover, these reactions showed moderate to good selectivity for the diastereomer that corresponds to an *exo* (or "extended") mode of addition of the diene to the furfuryl cation (i.e. with the furan oxygen and the diene are at opposite sides of the plane of the forming bonds). Finally, almost quantitative yields of cycloadducts were achieved using the tertiary furfuryl alcohols **9** and **11**, even without resorting to using an excess of diene (entries 6 and 7).

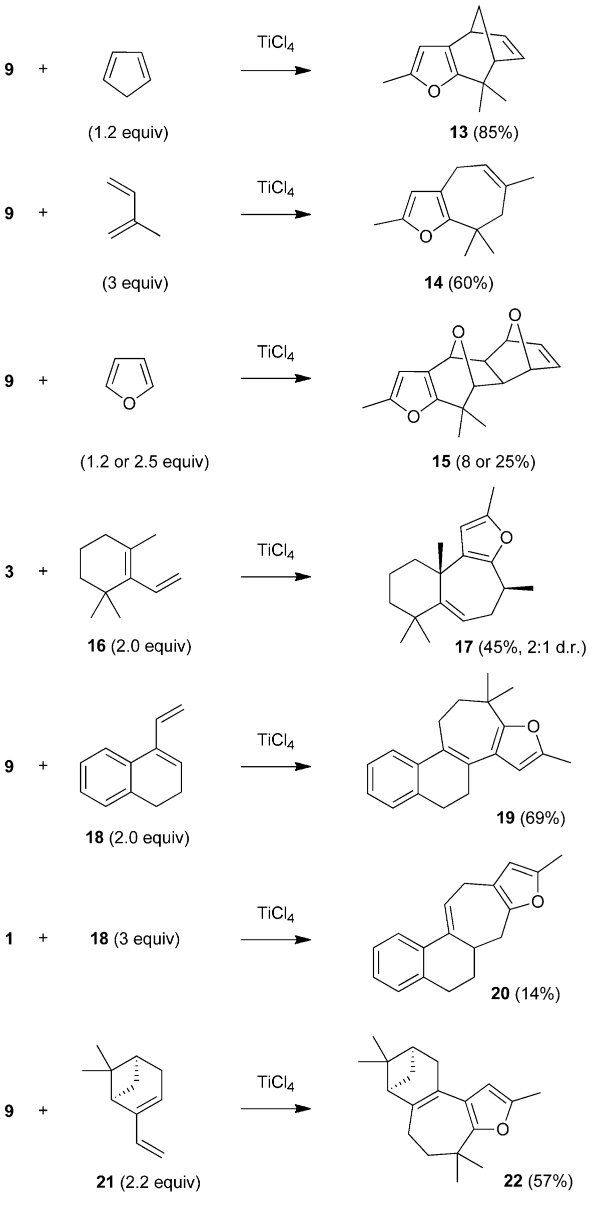
Given the general efficiency of the formation of cycloadducts with CHD, we next examined alternative diene substrates (Scheme 2). The reaction between furfuryl alcohol

Table 1: Reactions of 1,3-cyclohexadiene (CHD) with various furfuryl alcohols.



Entry[a]	Starting material	Product	Yield [%][b]
1		polymers	–
2[c]	 **1**	 **2**	17
3[c]	 **3**	 **4**	82 (4:1)[d]
4[c]	 **5**	 **6**	89 (4:1)[d]
5[c]	 **7**	 **8**	72 (10:1)[d]
6	 **9**	 **10**	96
7	 **11**	 **12**	97

[a] Typical procedure: a solution of the furfuryl alcohol (1.0 equiv) and CHD (1.2 equiv) in CH_2Cl_2 (0.1–0.25 M) was cooled to −78 °C and treated with $TiCl_4$ (1.5 equiv), then warmed to −10 °C over 2 h. [b] Average yield of the isolated product after multiple runs. [c] 2.0 equiv of CHD used. [d] Diastereomer ratio between parentheses in favor of the shown isomer (relative configuration).



Scheme 2. Cycloaddition reactions with alternative dienes.

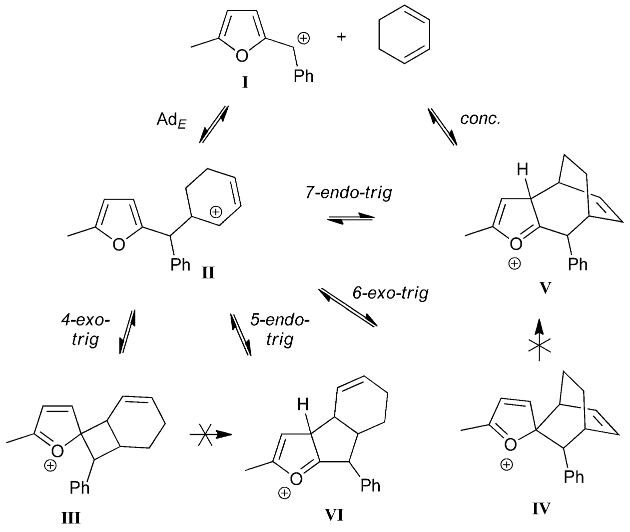
9 and cyclopentadiene smoothly gave the expected cycloadduct **13**. The corresponding reaction with the acyclic diene isoprene proved somewhat less efficient. However, the cyclohepta[b]furan **14** was obtained as a single regioisomer in reasonable yield when an excess of isoprene was used. Surprisingly, reactions with furan, which is one of the most widely used dienes in (4+3) cycloadditions, were quite problematic. The only observed cycloaddition product was the unusual bisadduct **15**, which was isolated as a single diastereomer. To further explore the scope and synthetic potential of this reaction, cycloadditions with some the more challenging dienes **16**, **18**, and **21** were tested. Thus, the tricyclic furan **17**, which incorporates the widdrane sesquiterpene carbon skeleton,[11] was obtained in a single step from the commercially available diene **16**. Reactions with the bicyclic diene **18** gave access to C-homo-D-oxasteroids **19** and **20**,[12] with interesting substrate-dependant regioselectivities. Finally, the novel terpene-like homochiral polycyclic compound **22** was efficiently obtained from a reaction with (+)-nopadiene **21**.

These intriguing cycloaddition reactions almost certainly take place by the formation of a furfuryl cation, and we have modelled their reactions with CHD at the DFT level of theory.[13] The phenyl-substituted furfuryl alcohol **7** (see Table 1, entry 5) was chosen for this purpose, as this substrate gives mostly *exo*-selective cycloaddition. Several competing pathways have been investigated in an effort to deduce a plausible mechanism (Scheme 3). Both a stepwise and a concerted process were identified as viable routes for the formation of the observed reaction products, although calculated energies were shown to consistently favor the stepwise pathway at different levels of theory (See the Supporting Information, Tables 1–3).

In the stepwise pathway, a highly reactive allylic cation intermediate **II** is formed, and this intermediate can undergo several very low barrier intramolecular electrophilic additions (Scheme 3). Reactions at the 2-position of the furan—by either a 6-*exo*-trig or a 4-*exo*-trig cyclization process—lead to six- and four-membered ring intermediates **III** and **IV**, respectively. These intermediates are unable to undergo a proton elimination to regain a stable furan ring. Moreover, transition states for low-barrier ring expansions of these intermediates to seven- or five-membered ring intermediates (**V** and **VI**, respectively) could not be located, instead intermediates **III** and **IV** were found to be more likely to re-form intermediate **II**. Low-barrier reactions at the 3-position of the furan lead either to intermediates **V** or **VI** (formation of a seven- or five-membered ring, respectively). The 7-*endo*-trig cyclization was shown to be favored over the 5-*endo*-trig cyclization (see the Supporting Information, Table 1–3), in accordance with Baldwin's rules. Simple deprotonation of this cation (**V**) then leads to the final product **8**. The observed isomers, *exo*-**8** and *endo*-**8**, are derived from the diastereomeric allylic cation intermediates *exo*-**II** and *endo*-**II** (Figure 1). The calculated energy profiles for the formation of the allylic cation (*exo*-**II**/*endo*-**II**) and the subsequent ring closure favor the formation of the experimentally verified major adduct, *exo*-**V** (see Figure 2 and the Supporting Information).

In the pericyclic pathway, the seven-membered-ring intermediate cation **V** is formed directly through a concerted [6π+4π] cycloaddition. The calculated energies for the pericyclic TS's were found to be at least 3.0 kcal mol^{-1} higher than for the corresponding stepwise pathways and favor the formation of the *exo*-adduct (Figure 3 and the Supporting Information). The evolution of furanyl bond distances throughout the reaction suggests that all 6π-electrons of the furfuryl cation are involved in the process (see the Supporting Information).

In conclusion, the reactions reported here uncover a readily available and versatile class of starting materials for the (4+3) cycloaddition reaction between a diene and an allylic cation. The synthetic usefulness of the novel cycloaddition has been shown by a number of illustrative examples and its mechanism has been investigated at the DFT level of



Scheme 3. Possible pathways for the reaction of CHD and furfuryl cation by either a stepwise electrophilic addition (Ad$_E$) pathway or a concerted (conc.) pathway.

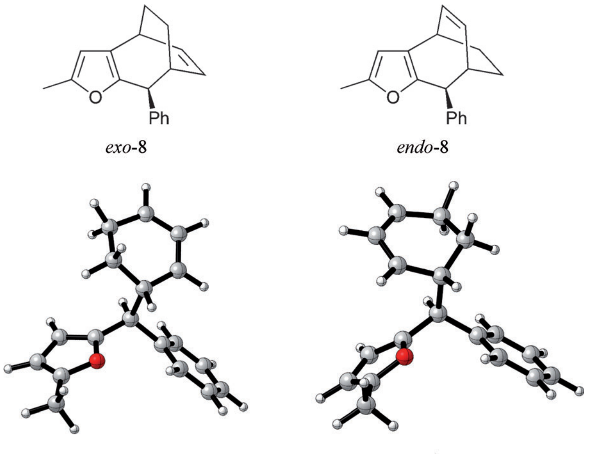


Figure 1. Observed diastereomers for **8** and optimized geometries (BMK/6-311+G(d,p)//B3LYP/6-31+G(d,p)) for the corresponding diastereomeric intermediate allylic cations **II**.

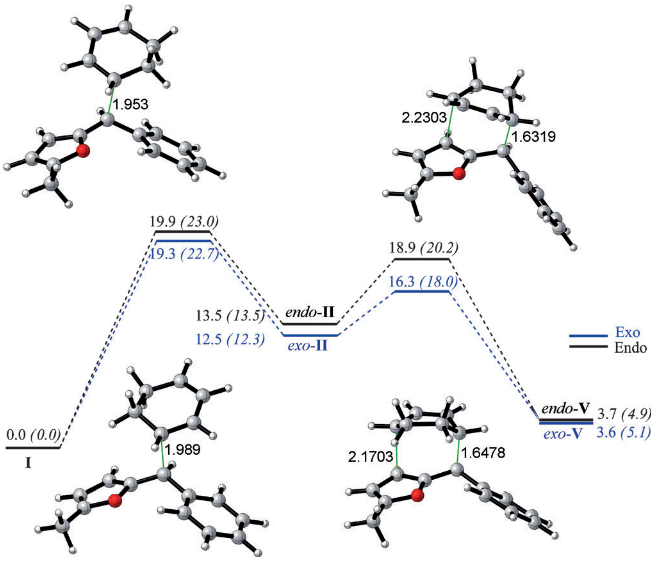
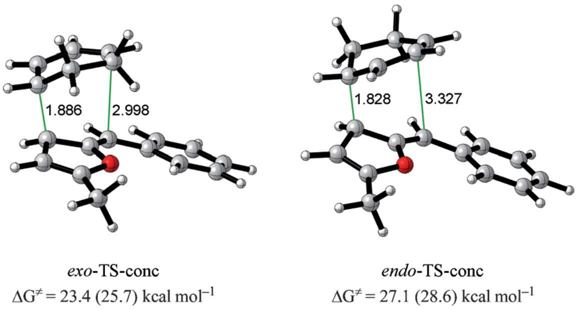


Figure 2. Free-energy profile for the stepwise (4+3) cycloaddition leading to *endo* and *exo* adducts. Free energies in kcal mol^{-1} at the BMK/6-311+G(d,p)//B3LYP/6-31+G(d,p) level of theory, CPCM ($\varepsilon = 8.93$, dichloromethane) results in parentheses, distances in Å.



exo-TS-conc
$\Delta G^{\neq} = 23.4$ (25.7) kcal mol^{-1}

endo-TS-conc
$\Delta G^{\neq} = 27.1$ (28.6) kcal mol^{-1}

Figure 3. Transition-state geometries and Gibb's free energies of activation for the pericyclic [6π+4π] cycloaddition leading to *exo*- and *endo*-adducts. Free energies in kcal mol^{-1} at the BMK/6-311+G(d,p)//B3LYP/6-31+G(d,p) level of theory, CPCM ($\varepsilon = 8.93$, dichloromethane) results in parenthesis, distances are in Å.

theory. The theoretical results point to an efficient and stereoselective two-step cationic cyclization process and are in good qualitative agreement with the experimental results. Further investigations into substrate tolerance and applications in total synthesis, as well as further refinement of the reaction mechanism are now under way and will be reported in due course.

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Keywords: DFT calculations · carbocations · cycloaddition · furans · fused-ring systems

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[11] The observed stereoselectivity is in favor of an *exo* mode of cycloaddition, albeit somewhat less pronounced than in the reactions with CHD.

[12] The isomerization of the double bond to the (more) conjugated position is not unexpected under these reaction conditions, and is also observed for compound **22**.

[13] For recent computational work on related reactions, see: a) E. H. Krenske, K. N. Houk, M. Harmata, *Org. Lett.* **2010**, *12*, 444–447; b) E. H. Krenske, K. N. Houk, A. G. Lohse, J. E. Antoline, R. P. Hsung, *Chem. Sci.* **2010**, *1*, 387–392; c) I. Fernández, F. P. Cossio, A. de Cozar, A. Lledos, J. L. Mascarenas, *Chem. Eur. J.* **2010**, *16*, 12147–12157.