Cycloaddition

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Temporary Generation of a Cyclopropyl Oxocarbenium Ion Enables Highly Diastereoselective Donor–Acceptor Cyclopropane Cycloaddition

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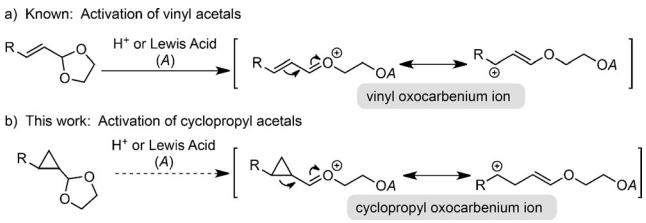
Abstract: *A novel formal [3+2] cycloaddition of cyclopropylacetals and aldehydes was developed, and the resulting trisubstituted tetrahydrofurans display three new chiral centers formed with highly diastereoselectivity. This method is stereocomplementary to most previously reported cycloadditions of malonate diesters, relies on the transient generation of cyclopropyl oxocarbenium ions, proceeds under mild conditions, and is based on the concept of temporary activation of an otherwise inert protecting group.*

Polysubstituted tetrahydrofurans are prevalent cores in various biologically active substances.[1] Over the past few years, perhaps the best developed method for the formation of these moieties has been the [3+2] cycloaddition of donor–acceptor (D–A) cyclopropanes with carbonyl derivatives.[2] Most notably, the groups of Johnson and Waser have intensively investigated this area and have contributed significantly to its development towards a highly efficient and stereoselective method.[3] The quintessential acceptor group in this chemistry is a malonate diester moiety, which is activated by Lewis acid coordination and decisively weakens the central cyclopropyl C–C bond. Nevertheless, the presence of this malonate diester moiety in the final cycloadducts renders the subsequent functionalization of the newly formed products cumbersome.[4]

As shown in Scheme 1a, α,β-unsaturated acetals are known to generate vinyl oxocarbenium ions in the presence of an acid catalyst.[5] These intermediates display a highly polarized double bond as a result of the so-called vinylogy effect[6] and can therefore undergo a broad range of reactions for transforming the C=C double bond.[5]



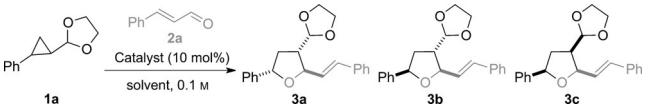
Scheme 1. Cyclopropyl oxocarbenium ions as D–A cyclopopanes.

We envisaged that cyclopropyl oxocarbenium ions, which are potentially accessible from α-cyclopropylacetals, might be prone to a similar electronic activation (Scheme 1b). In particular, we were intrigued by the possibility that appropriately substituted cyclopropyl acetals might behave as entirely new D–A cyclopropanes and thereby enable formal [3+2] cycloaddition reactions. Notably, such a cycloaddition would generate three stereogenic centers at once, a rare occurrence in the D–A cyclopropane literature.[7] As daunting as this prospect may appear, we were also aware that, if the acetal moiety was retained intact in the product, a significant increase in the synthetic versatility of those cycloadducts would result.

Herein, we report the first [3+2] cycloaddition of cyclopropylacetals with aldehydes under mild conditions to stereoselectively afford trisubstituted tetrahydrofuran products that carry an easily functionalizable masked aldehyde.

A preliminary dipolarophile screening showed that cinnamaldehyde (**2**) efficiently undergoes cycloaddition with the phenyl-substituted cyclopropyl acetal **1** (Table 1, entry 5). We thus continued our investigations with **1** and **2** as model

Table 1: Selected examples for optimization of the cycloaddition.



Entry	**2** [equiv]	Catalyst	Solvent	*T* [°C]	d.r. [**a**/**b**/**c**][a]	Yield [%][a]
1	1	TfOH	CH_2Cl_2	−78	–	–[b]
2	1	$In(OTf)_3$	CH_2Cl_2	23[c]	–	–[d]
3	1	$Dy(OTf)_3$	CH_2Cl_2	23[c]	–	–[d]
4	1	$SnCl_4$	CH_2Cl_2	23[c]	–	traces
5	1	$Sn(OTf)_2$	CH_2Cl_2	23[c]	47:42:11	65
6	1	$Sc(OTf)_3$	CH_2Cl_2	23[c]	40:40:20	34
7	1	$SnCl_2$	CH_2Cl_2	23[c]	48:30:22	50
8	1	$AuCl_3$	CH_2Cl_2	23[c]	51:46:3	35
9	1	$InCl_3$	CH_2Cl_2	40[c]	71:29:0	66
10	1	TMSOTf	CH_2Cl_2	−78	67:33:0	49
11	1	TMSOTf	CH_3NO_2	−25	87:13:0	56
12	2	TMSOTf	CH_3NO_2	−25	87:13:0	82
13	2	TBSOTf	CH_3NO_2	0 °C	83:17:0	99
14	*2*	*TBSOTf*	*CH_3NO_2*	*−25*	*90:10:0*	*97*

[a] Determined by ^{1}H NMR spectroscopic analysis of the non-purified reaction mixture with 1,3,5-trimethoxybenzene as the internal standard. [b] Degradation. [c] All of the screening experiments were started at −78 °C, and if no conversion was observed, the temperature was slowly raised until some reactivity was observed. [d] No conversion was observed.

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substrates. Weak Brønsted acids were not able to promote any conversion, whereas strong acids such as trifluoromethanesulfonic acid led to the rapid degradation of **1** (Table 1, entry 1) even at low temperature. Hence, we focused our attention on Lewis acid catalysts. Although some of the classically used Lewis acids in cycloaddition chemistry displayed no catalytic activity in this reaction (Table 1, entries 2–4), several others proved to be efficient (Table 1, entries 5–8), including tin-, scandium-, and gold-based species. However, in these early experiments, a distinct lack of diastereoselectivity was observed, with synthetically unappealing mixtures of three out of the four possible diastereoisomers (**3a**, **3b**, **3c**) being routinely observed in varying amounts.

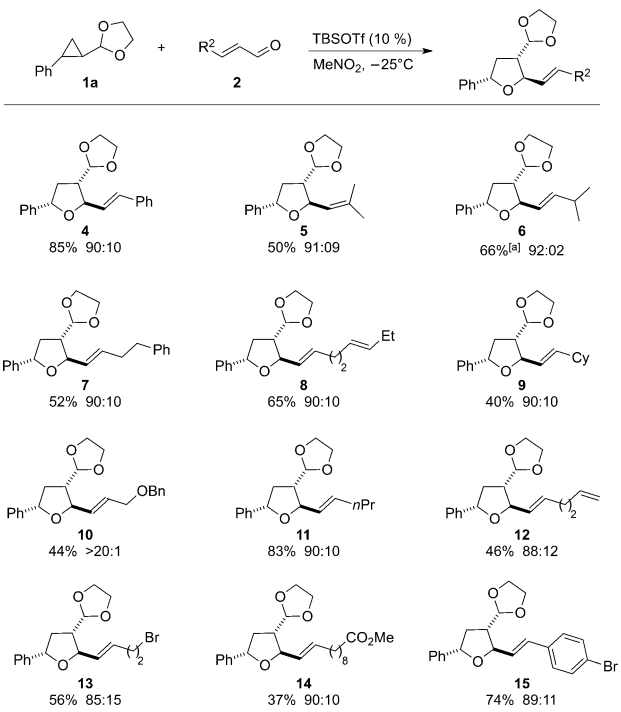
Pleasingly, indium(III) trichloride and trimethylsilyl trifluoromethanesulfonate remarkably improved the diastereoselectivity in favor of the formation of **3a** (Table 1, entry 9). After optimizing the solvent, the temperature, and the stoichiometry of the reaction we found that the best results were reproducibly obtained when using 10 mol% of *tert*-butyldimethylsilyl trifluoromethanesulfonate and 2 equivalents of cinnamaldehyde in nitromethane as the solvent, at −25 °C (Table 1, entry 14). Under these conditions, **3a** was obtained in an excellent 97% yield as measured by NMR (90% yield of isolated product) as a 9:1 mixture of diastereomers.

From the outset, the observed dominance of *trans*,*trans*-tetrahydrofuran **3a** as a product was striking; the vast majority of the reported examples of [3+2]-cycloadditions between D–A cyclopropanes and aldehydes describe stereoselective access to *cis*-2,5-tetrahydrofuran adducts.[2] This renders our method, which is able to stereoselectively deliver a 2,5-*trans*-configured tetrahydrofuran, stereocomplementary to those prior approaches. Interestingly, the starting cyclopropylacetal features a *trans* relationship between the arene and acetal, which is reversed to *cis* in the cycloaddition product.

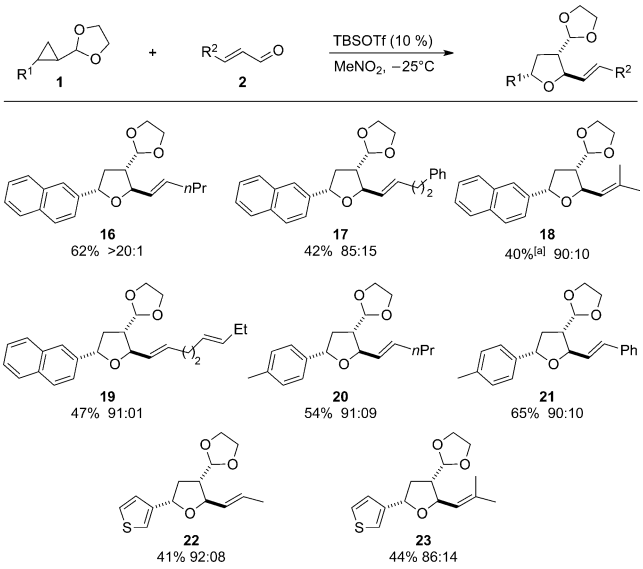
Importantly, control experiments showed that the diastereomeric ratio of product **3** under these conditions remains constant at lower conversions, and is identical to the final value. This suggests that the observed stereoselectivity is not the result of subsequent thermodynamic equilibration.[8]

To explore the generality of the reaction, various unsaturated aldehydes were subjected to [3+2] cycloaddition with **1** (Scheme 2). A wide range of substrates was studied, and smooth cycloadditions occurred within a short reaction time (2 h).[9] The reaction displayed satisfactory functional-group tolerance, and both internal and terminal alkenes (**8** and **12**) were tolerated. Additionally, aliphatic and aromatic halides (**13** and **15**), esters (**14**), and protected alcohols (**10**) proved to be compatible with the mild conditions employed in this transformation. Notably, high diastereoselectivity was obtained in favor of the products shown. As depicted, all products contain the masked aldehyde ultimately responsible for the observed reactivity.

At this juncture, we were eager to examine diverse cyclopropyl acetal derivatives and study their applicability to this transformation, and the results are shown in Scheme 3. Different aromatic residues, including naphthyl, *p*-tolyl, and thienyl residues, were tolerated in the reaction, smoothly delivering the tetrahydrofuran cycloadducts. Although the yields are mostly moderate (a consequence of the somewhat



Scheme 2. Scope of the cycloaddition: variation of the aldehyde partner. Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), TBSOTf (0.01 mmol), nitromethane (1 mL), −25 °C, 2 h. Yields refer to isolated major diastereoisomers; d.r. values were measured by ^{1}H-NMR spectroscopic analysis of the non-purified mixture. [a] TMSOTf was used as a Lewis acid.

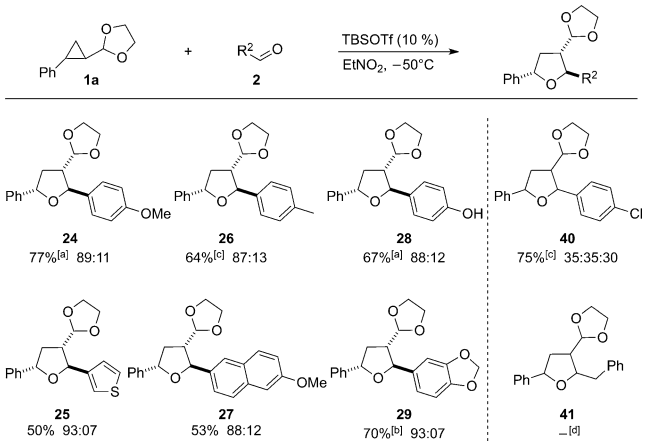


Scheme 3. Scope of the cycloaddition: variation of the cyclopropane partner. Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), TBSOTf (0.01 mmol), nitromethane (1 mL), −25 °C, 2 h. Yields refer to isolated major diastereoisomers; d.r. values were measured by ^{1}H-NMR spectroscopic analysis of the non-purified mixture. [a] The reaction was performed at −15 °C.

lower stability of cyclopropane acetals **1** under these conditions), the increase in structural and stereochemical complexity enabled by this highly stereoselective cycloaddition reaction is noteworthy.

In spite of the considerable synthetic potential provided by using α,β-unsaturated aldehydes as dipolarophiles (see below), given the novelty of this system, we were interested in studying the behavior of aromatic aldehydes in our cycloaddition reaction. In the event, these were considerably more reactive than their enal analogues. Indeed, electron-rich aromatic aldehydes afforded satisfying yields and diastereoselectivity under even milder conditions (−50 °C).

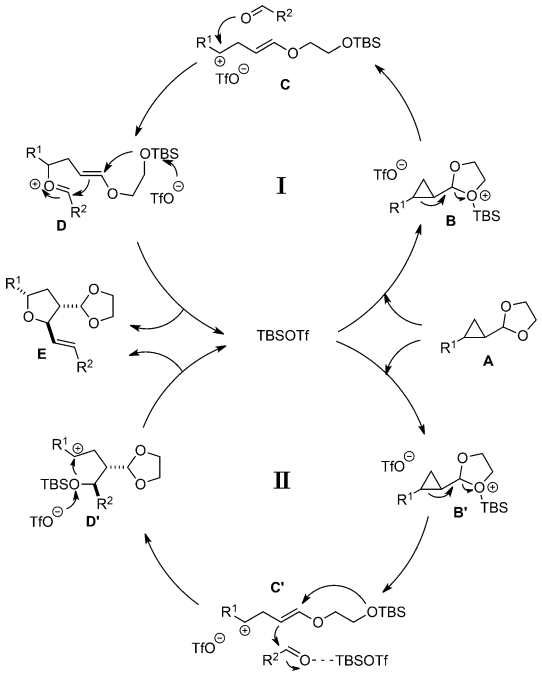
The reaction enabled the use of a thiophene carbaldehyde (**25**, Scheme 4), and even a free phenol (**28**) was tolerated under these conditions. However, the use of electron-neutral or electron-poor substrates afforded lower stereoselectivity,



Scheme 4. Scope of the cycloaddition with aryl-substituted aldehydes. Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), TBSOTf (0.01 mmol), nitroethane (1 mL), −50 °C, 2 h. Yields refer to isolated major diastereoisomers; d.r. values were measured by ^{1}H-NMR spectroscopic analysis of the non-purified mixture. [a] The reaction was performed in nitromethane at −25 °C. [b] The reaction was performed at −40 °C. [c] Yield refers to the isomer mixture. [d] The temperature was raised to 50 °C.

although we observed faster conversion of the cyclopropane acetal (**40**, Scheme 4), and aliphatic aldehydes were not reactive enough, even at higher temperatures (**41**, Scheme 4).

These observations, along with the qualitatively higher reactivity of aromatic aldehydes versus enals, allow two possible interpretations concerning the actual mechanism of this cycloaddition (Scheme 5). Assuming that cyclopropylacetal **1** undergoes Lewis acid triggered ring opening to give stabilized carbenium ion **C**, attack by the aldehyde carbonyl would lead to the intermediate **D** (Scheme 5, cycle I), from which cyclisation to product **E** could take place. While this pathway is attractive, given our success with electron-rich aromatic aldehydes, the observed *trans,trans*-diastereoselectivity is not easily rationalized on this basis. Alternatively, Mukaiyama-type aldol reaction (**C′**→**D′**) followed by ether–carbenium ion cyclisation (Scheme 5, cycle II) might also account for the formation of **E**. Additional mechanistic studies will be required to distinguish between these two

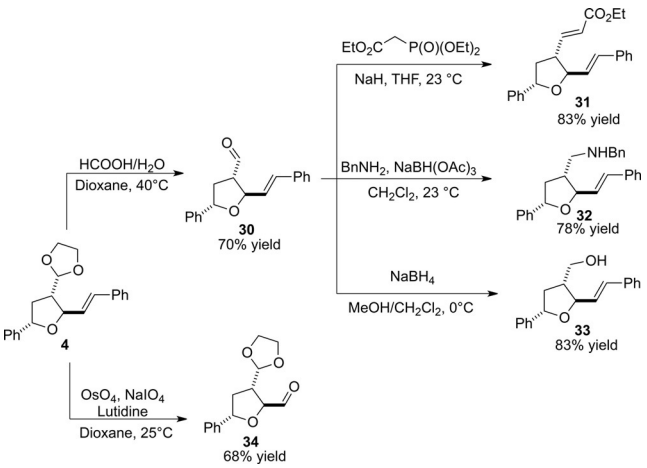


Scheme 5. Possible mechanisms for the cycloaddition of cyclopropylacetals and aldehydes.

pathways, as well as to clarify whether the substitution step is SN_1- or SN_2-like (via an intimate ion pair, as originally proposed by Johnson).[2j]

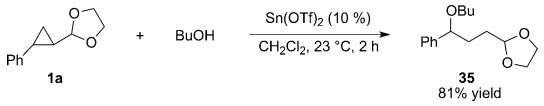
These reactions deliver densely functionalized tetrahydrofuran products that can be readily modified through standard synthetic procedures. As shown in Scheme 6, acetal removal to give the aldehyde is easily achieved without noticeable epimerization and in good yield. Once revealed, the aldehyde moiety can readily engage in olefination, reduction, or reductive amination reactions. Additionally, the olefinic moiety of product **4** can itself be used as a surrogate for an aldehyde, generating the differentiated (through protection) dialdehyde **34** by oxidative cleavage.

It should be noted that this mode of activation of the cyclopropane C–C bond is not limited to cycloaddition



Scheme 6. Functionalization of tetrahydrofuran **4**.

reactions, and the nucleophilic addition of a simple alcohol can also be achieved at room temperature under tin(III) tin(II) catalysis. This gives the ether **35** in high yield (Scheme 7).



Scheme 7. Ring opening of cyclopropane **1a** with butanol.

In summary, we present herein the first examples of the generation and exploitation of cyclopropyl oxocarbenium ions as reagents in synthesis. Suitably substituted derivatives thereof can serve as donor–acceptor cyclopropane building blocks that engage aldehydes in highly diastereoselective formal [3+2] cycloaddition. This chemistry enables the de novo generation of three stereogenic centers with high diastereoselectivity and proceeds in a stereocomplementary fashion to the known chemistry of cyclopropane diesters. Notably, the use of an acetal as the acceptor moiety leads to the interesting feature of having a protecting group serve as a platform for the temporary generation of an electrophile, an interesting concept for which there are only scattered examples in the literature to date[10] and which is bound to find growing utility in organic synthesis.

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Keywords: cycloaddition · cyclopropane · donor–acceptor systems · oxocarbenium ions · tetrahydrofuran

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