

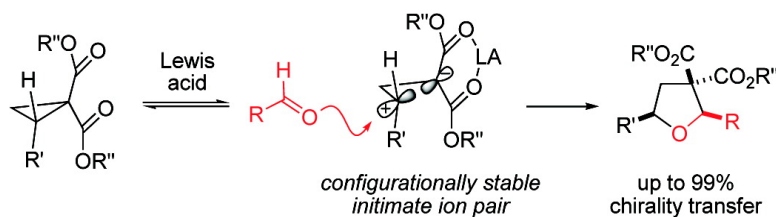
Article

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## Scope and Mechanism for Lewis Acid-Catalyzed Cycloadditions of Aldehydes and Donor–Acceptor Cyclopropanes: Evidence for a Stereospecific Intimate Ion Pair Pathway

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**Abstract:** In this work, the one-step diastereoselective synthesis of *cis*-2,5-disubstituted tetrahydrofurans via Lewis acid catalyzed [3 + 2] cycloadditions of donor–acceptor (D–A) cyclopropanes and aldehydes is described. The scope and limitations with respect to both reaction partners are provided. A detailed examination of the mechanism has been performed, including stereochemical analysis and electronic profiling of both reactants. Experimental evidence supports an unusual stereospecific intimate ion pair mechanism wherein the aldehyde functions as a nucleophile and malonate acts as the nucleofuge. The reaction proceeds with inversion at the cyclopropane donor site and allows absolute stereochemical information to be transferred to the products with high fidelity. The mechanism facilitates the stereospecific synthesis of a range of optically active tetrahydrofuran derivatives from enantioenriched D–A cyclopropanes.

### Introduction

Substituted tetrahydrofurans are important small molecules due to their appearance in a variety of biologically important compounds.<sup>1</sup> Among the myriad methods for the preparation of tetrahydrofurans, cycloadditions are particularly attractive with regard to convergency and atom economy. To this end, several research groups have achieved the synthesis of substituted tetrahydrofurans through the application of donor–acceptor (D–A) cyclopropanes.<sup>2</sup> These versatile three carbon building blocks are useful in organic synthesis due to both their reactivity and ease of preparation.<sup>3</sup> Reissig has demonstrated the use of siloxycyclopropanecarboxylates and TiCl<sub>4</sub> in the synthesis of  $\gamma$ -lactols and homoaldol products.<sup>4–6</sup> The tautomeric  $\gamma$ -lactols can be taken on to substituted tetrahydrofuran derivatives after cleavage of the anomeric hydroxyl group.<sup>7</sup> Oshima has synthesized substituted tetrahydrofurans via the TiCl<sub>4</sub>/tBu<sub>4</sub>NI-

### Scheme 1. General Strategy for THF Synthesis



promoted reaction of cyclopropyl ketones and aldehydes.<sup>8</sup> The proposed mechanism invokes an aldol intermediate that either cyclizes spontaneously or upon treatment with activated alumina. This sequence does not allow for the preparation of tetrahydrofurans substituted at the 5-position. Related work by Sugita has shown that methanochromanones react with aldehydes and ketones under Lewis acid catalysis to give *trans*-fused tetrahydrofurobenzopyranone derivatives in good yields and good diastereoselectivity.<sup>9,10</sup> This paper describes the highly diastereoselective, stereospecific synthesis of *cis*-2,5-disubstituted tetrahydrofurans via the Lewis acid-catalyzed cycloaddition of D–A cyclopropanes and aldehydes (Scheme 1).<sup>11,12</sup> The scope and mechanism are discussed in detail.

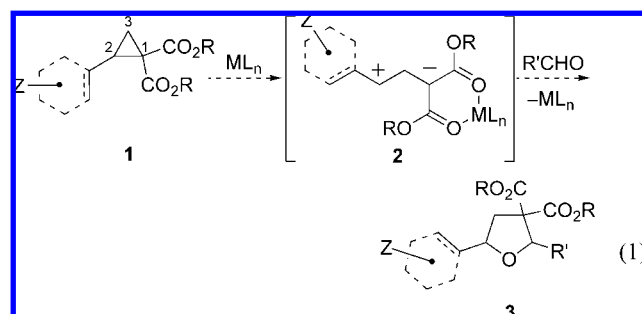
### Results and Discussion

**Reaction Design.** D–A cyclopropanes are the key building blocks in the cycloaddition strategy we pursued. A central goal in our design plan was to develop reactions that could employ a carbon-based donor as the activating group as opposed to the more common heteroatom donor groups that must be cleaved subsequent to cycloaddition.<sup>2</sup> The omission of the anomeric hydroxyl group would allow for the direct synthesis of the 2,5-dialkyl substitution pattern commonly found in naturally oc-

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curing tetrahydrofurans **3** (eq 1). The donor group serves to stabilize the partial positive charge on intermediate **2** that is created as the C1–C2 bond of **1** is cleaved. At the outset it was assumed (erroneously, vide infra) that the achiral zwitterion **2** would be a key intermediate. The donor group can also serve as an additional functional handle on the cycloadducts for further elaboration. Aryl, vinyl, and alkyl groups were targeted to serve in this capacity. The acceptor group is composed of a malonyl dimethyl ester group in most cases. The Lewis acid activates the cyclopropane by association with the acceptor group.<sup>2</sup> Led by the seminal work of Kerr, similarly activated cyclopropanes have been used extensively in recent years.<sup>13a–q</sup>

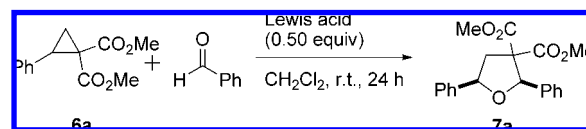


### Cyclopropane Preparation and Cycloaddition Reaction

**Conditions.** The preparation of racemic 2-aryl-cyclopropane-1,1-dicarboxylic acid dimethyl esters **6** was accomplished through the direct cyclopropanation of benzylidene malonates **4** with dimethylsulfonium methylide derived from **5** (eq 2).<sup>14,15</sup> Benzylidene malonates were synthesized from the corresponding aldehydes and dimethyl malonate under Knoevenagel condensation conditions.<sup>14,16,17</sup>

Several Lewis acids were found to promote the [3 + 2] cycloaddition of D–A cyclopropane **6a** and benzaldehyde, albeit

**Table 1.** Lewis Acids in [3 + 2] Cycloaddition of Benzaldehyde and D–A Cyclopropane **6a**

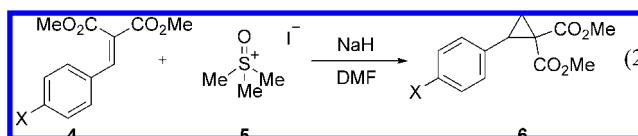


entry	Lewis acid	% yield <sup>a</sup>	d.r. <sup>b</sup>
1	AgOTf	<5	n.d.
2	AgNTf <sub>2</sub>	73	> 100:1
3	AlCl <sub>3</sub>	81	2:1
4	Ce(OTf) <sub>3</sub>	75	> 100:1
5	Cu(OTf) <sub>2</sub>	94	> 69:1
6	Dy(OTf) <sub>3</sub>	28	> 80:1
7	Er(OTf) <sub>3</sub>	20	n.d.
8	Hf(OTf) <sub>4</sub>	30	2:1
9	Ho(OTf) <sub>3</sub>	23	> 71:1
10	Sc(OTf) <sub>3</sub>	96	2:1
11	SnCl <sub>2</sub>	84	> 100:1
12	Sn(OTf) <sub>2</sub>	97	> 100:1
13	Sn(OTf) <sub>2</sub> <sup>c</sup>	98	> 100:1
14	SnCl <sub>4</sub>	90	> 40:1
15	Tb(OTf) <sub>3</sub>	32	> 100:1
16	Tm(OTf) <sub>3</sub>	44	> 100:1
17	Yb(OTf) <sub>3</sub>	74	> 100:1
18	ZnCl <sub>2</sub>	54	> 63:1
19	Zn(OTf) <sub>2</sub>	70	> 61:1

<sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopy using a mesitylene standard.

<sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy. n.d. = not determined.

<sup>c</sup> Catalyst = 5 mol %.

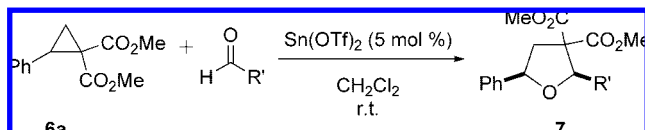


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in a range of conversions and diastereoselectivities (Table 1). Optimal reaction conditions for the cycloaddition of cyclopropane **6a** are 5 mol % of Sn(OTf)<sub>2</sub> in dichloromethane and 3 equiv of aldehyde.

**Substrate Scope and Limitations.** Under the optimized reaction conditions, a variety of electronically and sterically diverse tetrahydrofurans were synthesized in excellent yields and *cis*-diastereoselectivities as determined by NOESY analysis (Table 2). Electron-poor *p*-nitrobenzaldehyde (Table 2, entry 4) required an increased catalyst loading and reaction time but gave similar results under the optimized conditions. The heterocyclic aldehydes furfural and 2-thiophenecarboxaldehyde (Table 2, entries 11 and 12) were also suitable substrates; however, 2-pyridinecarboxaldehyde was completely unreactive, presumably due to coordination of Sn(OTf)<sub>2</sub> with the Lewis basic nitrogen. We previously reported difficulty employing aliphatic aldehydes in this cycloaddition reaction.<sup>11</sup> The use of SnCl<sub>4</sub> solved this problem and allowed for the synthesis of 2-alkyl-substituted tetrahydrofurans in high yields and diastereoselectivities (Table 2, entries 13 and 14).

More synthetically useful *cis*-2,5-disubstituted tetrahydrofurans can be prepared from cyclopropanes where the donor group can be easily manipulated after the cycloaddition. Employing an alkenyl group as the donor substituent supplies an additional functional handle on the cycloadducts. The 2-butenyl cyclopropane **8a** was synthesized via Corey-Chaykovsky cyclopropanation analogous to equation 2. Reactions with these substituted-vinyl species proceed with good yield and excellent diastereoselectivities (Table 3, entries 1 and 2). 2-Vinyl cyclopropanes **8b** and **8c** were prepared from the double

**Table 2.** Aryl Cyclopropane Scope in the [3 + 2] Cycloaddition with Aldehydes

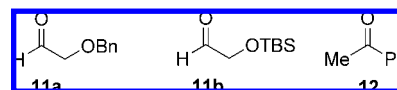
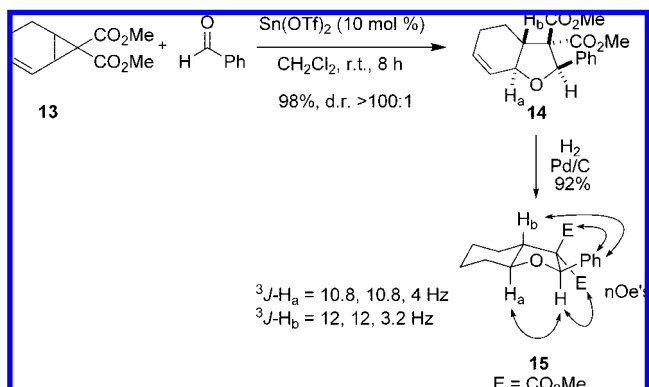
entry	R' (product)	t (h)	yield (%) <sup>a</sup>	d.r.
1	Ph ( <b>7a</b> )	2.5	>98	>100:1
2	4-ClPh ( <b>7b</b> )	4.75	96	>80:1
3	4-MeOPh ( <b>7c</b> )	3.5	98	>86:1
4	4-NO <sub>2</sub> Ph <sup>b</sup> ( <b>7d</b> )	15	89	>19:1
5	( <i>E</i> )-CH=CHPh ( <b>7e</b> )	3.5	96	17:1
6	C≡CPh ( <b>7f</b> )	6	92	1.6:1
7	4-MePh ( <b>7g</b> )	2.25	95	>100:1
8	4-BrPh ( <b>7h</b> )	3	93	>100:1
9	4-AcOPh ( <b>7i</b> )	3.75	90	>100:1
10	4-MeO <sub>2</sub> CPh ( <b>7j</b> )	5.5	87	>100:1
11	2-furyl ( <b>7k</b> )	3.25	82	23:1
12	2-thienyl ( <b>7l</b> )	3.25	98	>83:1
13	Et ( <b>7m</b> )	1.75	>98	>36:1
14	<sup>t</sup> Pr ( <b>7n</b> )	2.5	98	>56:1

<sup>a</sup> Isolated yield. <sup>b</sup> Sn(OTf)<sub>2</sub> (10 mol %) used.

alkylation of the malonate ester with (*E*)-1,4-dibromo-but-2-ene.<sup>18</sup> Reaction of the vinyl cyclopropane **8b** with benzaldehyde and isobutyraldehyde produced the corresponding tetrahydrofurans in yields of 94% and 96% with diastereoselectivities of 8.9:1 and 5.7:1 respectively. The reduced steric demand of the vinyl cyclopropane **8b** in comparison to **8a** may explain the decreased diastereoselectivity of these reactions. Efforts were made to increase the diastereoselectivities of the unsubstituted vinyl cyclopropanes as the *cis* and *trans* isomers were inseparable by flash chromatography. A screen of Lewis acids, solvents, dicarboxyester groups, and temperature led to an increase in the diastereoselectivity for both of these cycloadducts (Table 3, entries 3 and 4). Entry 3 was improved upon by switching the acceptor group to dicarboxybenzyl esters leading to an increase in the diastereomeric ratio (to 24:1). Entry 4 was optimized by changing the solvent from dichloromethane to toluene leading to an increased diastereomeric ratio of 24:1. The final two entries of Table 3 demonstrate the use of ketone dipolarophiles. Acetone was used successfully in the cycloaddition with vinylcyclopropanes **8b** and **8c** with both SnCl<sub>4</sub> and Sn(OTf)<sub>2</sub> to produce the cycloadducts in excellent yields.

Aldehydes containing a heteroatom were also subjected to the [3 + 2] cycloaddition with vinyl cyclopropane **8b**. Aldehyde **11a** (Figure 1) gave only trace amounts of product with SnCl<sub>4</sub> and was not reactive with Sn(OTf)<sub>2</sub> under normal reaction conditions. Aldehyde **11b** was also unreactive with Sn(OTf)<sub>2</sub> under normal reaction conditions. Some product formation could be seen with this dipolarophile in the presence of SnCl<sub>4</sub> but byproduct formation and other inconsistencies hindered optimization of this reaction. Although acetone worked well in the [3 + 2] cycloaddition with vinyl cyclopropane, acetophenone (**12**) displayed variable results. This reaction was plagued by incomplete conversions and byproduct formation. A major byproduct in these reactions is possibly derived from chloride addition to the cyclopropane C2 position.

In this work, C3 of the cyclopropane is usually unsubstituted and reactions occur exclusively at C2. Substitution at the

**Figure 1.** Unsuccessful dipolarophiles.**Scheme 2.** Site Selectivity in 2,3-Disubstituted Malonyl Cyclopropanes and NOESY Analysis of the Derived Cyclohexane

3-position could activate this center resulting in reduced regioselectivity in the cycloaddition. To probe this issue, 2,3-disubstituted malonyl cyclopropane **13** was prepared from the Rh<sub>2</sub>(OAc)<sub>4</sub> catalyzed decomposition of dimethyl diazomalonate in the presence of 1,3-cyclohexadiene.<sup>19</sup> Reaction with benzaldehyde occurs exclusively at the more activated allylic position to form the bicyclic tetrahydrofuran **14** (Scheme 2). In this experiment, complete allylic site selectivity demonstrates the ability to distinguish between C2 and C3 of the cyclopropane based on its electronic character. The *trans* ring junction in the product was supported by NOESY analysis and characteristic coupling constant values for the ring junction protons in the derived cyclohexane **15**. This reaction was also performed with isobutyraldehyde in the presence of SnCl<sub>4</sub>. In this case, product formation was observed but undesired products were present in significant quantities.

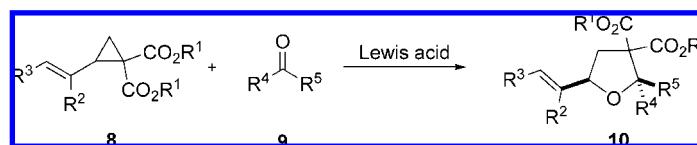
In addition to probing the regioselectivity of the reaction, the requirements of the donor group were explored using *n*-butyl cyclopropane **16**. The alkyl cyclopropane was synthesized through the Rh<sub>2</sub>(OAc)<sub>4</sub>-catalyzed decomposition of dimethyl diazomalonate in the presence of 1-hexene.<sup>20</sup> Reaction with isobutyraldehyde yielded 70% of the cycloadduct **17** in a 4.7:1 diastereomeric ratio. The catalyst loading for this reaction was increased to 30 mol % and the temperature to 45 °C (eq 3). The success of this reaction demonstrates not only that a simple alkyl group can function as an electron-donating group in these reactions, but that alkyl aldehydes can serve as viable dipolarophiles. While the diastereoselectivity is modest, this reaction nonetheless indicates a process where postcycloaddition functionalization of the donor group in target-directed synthesis might not be necessary.  $\beta$ -Keto esters may be employed as the activating group as demonstrated by the cycloaddition of bicyclo[4.1.0]heptanone **18** to give hydroisobenzofuran **19** in 73% yield and good diastereocontrol (eq 4).

The utility of this cycloaddition strategy hinges in part on the ability to manipulate the tetrahydrofuran products. Upon treatment with NaCN in wet DMSO, tetrahydrofuran **7a** underwent decarboxylation in a stereoselective fashion to afford

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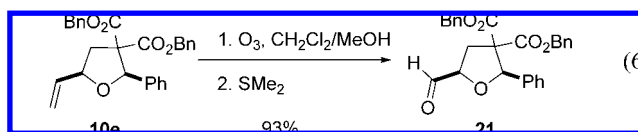
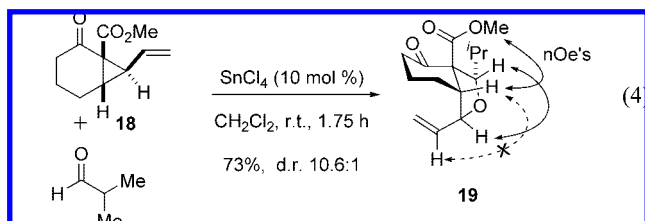
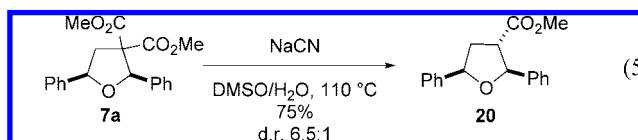
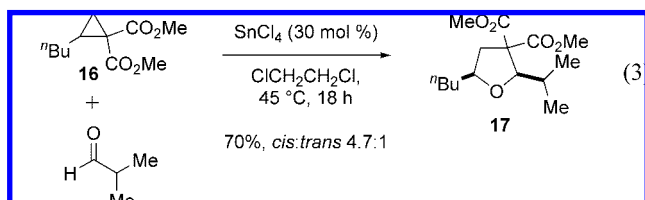
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**Table 3.** Vinyl Cyclopropane Scope in Lewis Acid Catalyzed Cycloadditions of D–A Cyclopropanes with Aldehydes and Ketones

entry	cyclopropane	R <sup>4</sup>	R <sup>5</sup>	solvent	Lewis acid	time (h)	% yield <sup>a</sup> (product)	d.r.
1		H	Ph	CH <sub>2</sub> Cl <sub>2</sub>	Sn(OTf) <sub>2</sub>	5	80 ( <b>10a</b> ) <sup>b</sup>	>100:1
2		H	<sup>i</sup> Pr	CH <sub>2</sub> Cl <sub>2</sub>	Sn(OTf) <sub>2</sub>	6	75 ( <b>10b</b> ) <sup>c</sup>	>100:1
3		H	Ph	CH <sub>2</sub> Cl <sub>2</sub>	Sn(OTf) <sub>2</sub>	8	94 ( <b>10c</b> ) <sup>b</sup>	8.9:1
4		H	<sup>i</sup> Pr	CH <sub>2</sub> Cl <sub>2</sub>	SnCl <sub>4</sub>	8	96 ( <b>10d</b> ) <sup>d</sup>	5.7:1
5		H	Ph	CH <sub>2</sub> Cl <sub>2</sub>	Sn(OTf) <sub>2</sub>	8	60 ( <b>10e</b> ) <sup>c</sup>	24:1
6		H	<sup>i</sup> Pr	C <sub>7</sub> H <sub>6</sub>	SnCl <sub>4</sub>	8	73 ( <b>10d</b> ) <sup>d</sup>	24:1
7		Me	Me	CH <sub>2</sub> Cl <sub>2</sub>	Sn(OTf) <sub>2</sub>	7	90 ( <b>10f</b> ) <sup>c</sup>	NA
8		Me	Me	C <sub>7</sub> H <sub>6</sub>	SnCl <sub>4</sub>	6	99 ( <b>10g</b> ) <sup>e</sup>	NA

<sup>a</sup> Isolated yield. <sup>b</sup> Sn(OTf)<sub>2</sub> (10 mol %) was used. <sup>c</sup> Sn(OTf)<sub>2</sub> (20 mol %) was used. <sup>d</sup> Sn(OTf)<sub>2</sub> (5 mol %) was used. <sup>e</sup> SnCl<sub>4</sub> (20 mol %) was used.



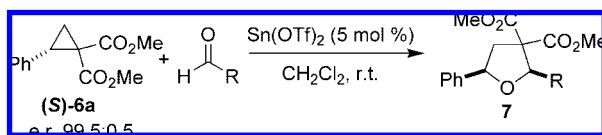
the monoester **20** in good yield (eq 5).<sup>21</sup> This facile process should allow simple functionalization of the ring 3-position. The vinyl tetrahydrofurans can be easily functionalized via ozonolysis as demonstrated in a reaction revealing the aldehyde **21** in 93% yield (eq 6).

**Reaction Stereochemistry.** After successfully performing the [3 + 2] cycloaddition with a range of cyclopropanes and

aldehydes the next step was development of an asymmetric variant. Assuming participation of a ring-opened species such as **2**, it would have been necessary to employ ligand control to effect absolute stereochemical induction. Sibi employed this strategy in the asymmetric cycloaddition of nitrones with D–A cyclopropanes;<sup>22</sup> however, an initial control experiment with (*S*)-**6a** revealed that chirality transfer from the cyclopropane occurred with high fidelity in the cycloaddition. This fortuitous discovery allowed the synthesis of a variety of optically active tetrahydrofurans without the need for ligand control in the

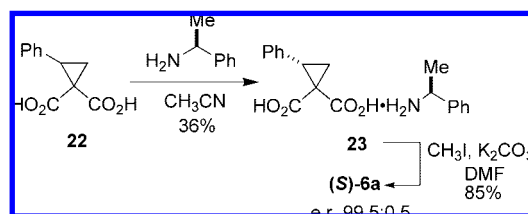
(21) Krapcho, A. P. *Synthesis* **1982**, 805–822.

(22) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 5764–5765.

**Table 4.** Aldehyde Scope in the Lewis Acid-Catalyzed Stereospecific [3 + 2] Cycloaddition of Cyclopropane (**S**)-**6a**

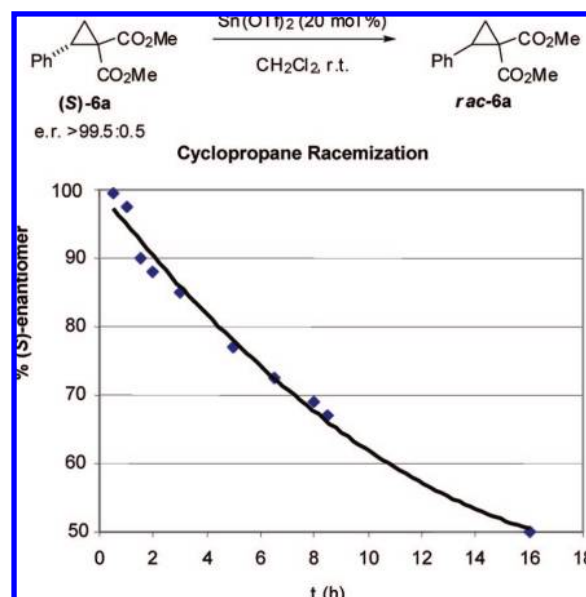
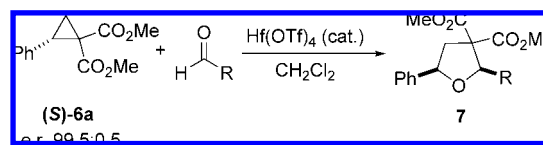
entry	R (product)	t (h)	yield (%) <sup>a</sup>	d.r.	e.r.
1	Ph ( <b>7a</b> )	2.5	100	>100:1	98:2
2	4-ClPh ( <b>7b</b> )	4.75	97	>83:1	98:2
3	4-MeOPh ( <b>7c</b> )	3.5	99	>84:1	99.5:0.5
4	4-O <sub>2</sub> NPh ( <b>7d</b> ) <sup>b</sup>	15	91	>19:1	67:33
5	( <i>E</i> )-CH=CHPh ( <b>7e</b> )	3.5	97	17:1	99.5:0.5
6	C≡CPh ( <b>7f</b> ) <sup>c</sup>	6	90	1.6:1	94:6
7	2-furyl ( <b>7k</b> )	3.25	83	23:1	99.5:0.5
8	2-thienyl ( <b>7l</b> )	3.25	98	>83:1	99:1
9	Et ( <b>7m</b> ) <sup>c</sup>	1.75	100	>36:1	98:2
10	<sup>t</sup> Pr ( <b>7n</b> ) <sup>d</sup>	2.5	98	>56:1	98:2

<sup>a</sup> Isolated yields. <sup>b</sup> Sn(OTf)<sub>2</sub> (20 mol %) was used. <sup>c</sup> Sn(OTf)<sub>2</sub> (10 mol %) was used. <sup>d</sup> SnCl<sub>4</sub> (5 mol %) was used.

**Scheme 3.** Resolution of Cyclopropane Diacid **22** with (*S*)- $\alpha$ -Methylbenzylamine

cycloaddition (Table 4). The requisite enantiopure phenyl cyclopropane (**S**)-**6a** was prepared according to the asymmetric cyclopropanation strategy developed by Davies in 54% yield and >99.5:0.5 e.r.<sup>23</sup> *N*-Butyl cyclopropane (**R**)-**16** (e.r. 97.5:2.5) was prepared in an analogous fashion. We have also developed a simple resolution of **6a**<sup>13c</sup> using (*S*)- $\alpha$ -methylbenzylamine. Two recrystallizations of the ammonium carboxylate **23** and esterification gives (**S**)-**6a** in >99.5:0.5 e.r. (Scheme 3). Using these enantioenriched substrates, the absolute stereochemical information from the cyclopropanes was regularly transferred to the tetrahydrofuran products in high yields and diastereoselectivities. Only extremely electron-poor aldehydes, which require higher catalyst loadings and longer reaction times, gave products of <96.5:3.5 e.r. To probe this observation the reaction conditions were reproduced in the absence of *p*-nitrobenzaldehyde. After quenching the reaction, complete racemization of (**S**)-**6a** was observed. Next, the cycloaddition reactions in entries 4 and 6 of Table 4 were reproduced but quenched after only 45 and 30 min, respectively. In each case, the tetrahydrofuran products were formed with an e.r. of 96.5:3.5. With these results, it is apparent that there is noticeable loss of stereochemical integrity of the cyclopropane throughout the course of the reaction with these sluggish dipolarophiles. This was confirmed in control experiments performed in the absence of aldehyde (Chart 1).

With the hope of developing a method to carry out cycloadditions with electron-poor aldehydes with high enantiospecificity, we investigated the use of other Lewis acids. From our previous Lewis acid screen (Table 1), it was noted that Hf(OTf)<sub>4</sub> is a highly active catalyst in this system, but significant

**Chart 1.** Sn(II)-Catalyzed Cyclopropane Racemization as a Function of Time**Table 5.** Aldehyde Scope in the Hf(IV)-Catalyzed Stereospecific [3 + 2] Cycloaddition of Cyclopropane (**S**)-**6a**

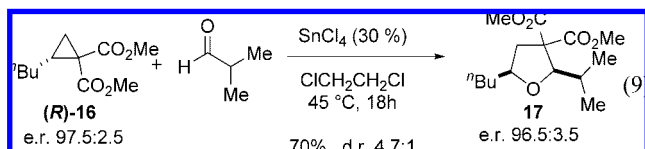
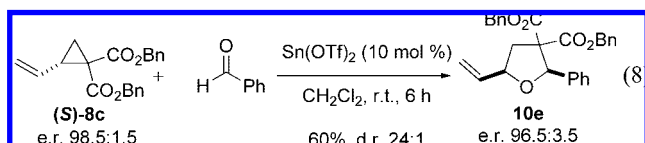
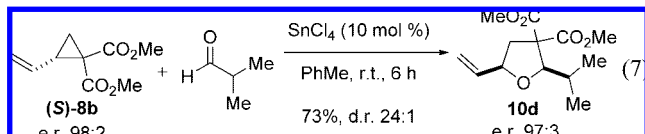
entry	R	mol % cat.	T (°C)	t (h)	yield (%) <sup>a</sup>	d.r. <sup>b</sup>	e.r. <sup>c</sup>
1	Ph	5	r.t.	0.05	99	>100:1	90:10
2	Ph	5	-40	0.75	96	>100:1	99:1
3	Ph	1	r.t.	6	96	>100:1	98:2
4	4-ClPh	5	-40	0.5	95	>100:1	99.5:0.5
5	4-MeOPh	5	-40	3.75	91	>57:1	99.5:0.5
6	4-O <sub>2</sub> NPh	30	-55	72	54	5:1	88.5:11.5
7	( <i>E</i> )-CH=CHPh	5	-40	2	97	>11:1	98.5:1.5
8 <sup>d</sup>	C≡CPh	5	-60	9	87	>9:1	99.5:0.5
9	2-furyl	5	-40	1.5	72	>30:1	98.5:1.5
10	2-thienyl	5	-40	1	83	>100:1	98.5:1.5
11	Et	5	-40	8	99	>30:1	97.5:2.5
12	<sup>t</sup> Pr	5	-40	5	86	>100:1	98.5:1.5

<sup>a</sup> Isolated yields. <sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy. <sup>c</sup> Determined by chiral SFC analysis. <sup>d</sup> With 6.0 equiv of aldehyde.

cyclopropane decomposition and poor diastereoselectivity hampered its utility. We therefore sought to alter the reaction conditions to minimize decomposition while increasing the diastereoselectivity of the reaction and the enantiopurity of the product. When the standard reaction conditions were used with benzaldehyde and Hf(OTf)<sub>4</sub>, the product was obtained in 99% yield and 90:10 e.r. in under five minutes (Table 5, entry 1). Cooling this reaction to -40 °C resulted in an increase of e.r. to 99:1 with a comparable yield (entry 2) and when the reaction was run with a catalyst loading of 1 mol % at room temperature the product was obtained in 98% yield and 98:2 e.r. (entry 3). Problematic aldehydes in the Sn(OTf)<sub>2</sub> system were improved upon in the Hf(OTf)<sub>4</sub> system. The cycloaddition with 4-O<sub>2</sub>NPhCHO resulted in an increase in e.r. to 88.5:11.5 with a drop in d.r. to 5:1 (entry 6), whereas cycloaddition with 3-phenylpropenal resulted in an increase in both e.r. and d.r. to 99.5:0.5 and 9:1, respectively (entry 8).

(23) Davies, H. M. L.; Bruzinski, P.; Hutcherson, D. K.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897–6907.

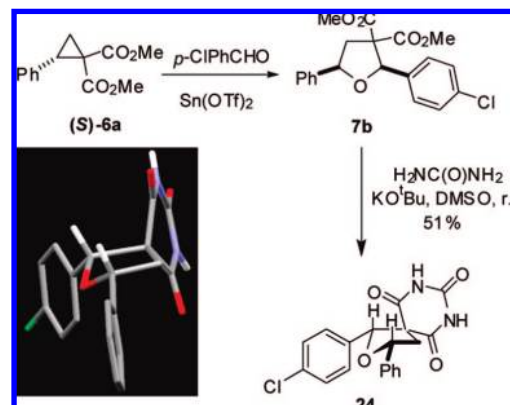
Chirality transfer also occurs in reactions of the vinyl and alkyl D–A cyclopropanes (eq 7–9). Optically active vinyl cyclopropanes (**S**)-**8b** and (**S**)-**8c** were prepared through resolution of the cyclopropane diacid with cinchonidine followed by six recrystallizations.<sup>24</sup> Subjecting the *n*-butyl cyclopropane (**R**)-**16** (e.r. 97.5:2.5) to the reaction conditions yielded the tetrahydrofuran with an e.r. of 96.5:3.5 (eq 9). Thus, racemization occurs very slowly in this system compared to reaction with the aldehyde even at elevated temperatures with a powerful Lewis acid. A likely cause is the diminished capacity of the alkyl group to stabilize the ring-opened zwitterion.



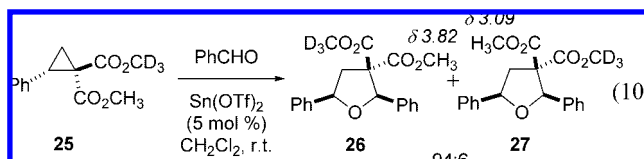
**Reaction Mechanism.** A key piece of mechanistic evidence was gained from the control experiment employing enantioenriched cyclopropanes. The products were obtained without any significant loss in the stereochemical information from the enantioenriched cyclopropane. Racemic products would be expected if the reaction proceeded through a ring opened zwitterion (**2**). The results suggested that this zwitterion was not significant in this cycloaddition. Therefore, it was of interest to elucidate the mechanism and the origin of chirality transfer. Further investigations required knowledge of the absolute stereochemistry of the reaction products. The cycloadduct **7b** was converted to its derived barbituric acid **24**, and a single-crystal X-ray diffraction analysis determined the absolute stereochemistry as (*2R*, *5R*) (Scheme 4). The X-ray analysis also revealed that inversion occurs at the cyclopropyl stereocenter (*C2*) during the course of the reaction. Inversion at the cyclopropane donor site was also confirmed in the cycloaddition results with bicyclo[4.1.0]heptanes **13** and **18**.

An additional labeling study was conducted in which one of the diastereotopic carboxymethyl groups of the cyclopropane was selectively labeled. It was prepared by selective hydrolysis of the ester group *trans* to the phenyl substituent of **6a**.<sup>23</sup> Subsequent reesterification with perdeuterated dimethyl sulfate yielded the labeled cyclopropane **25**.<sup>25</sup> Reaction with benzaldehyde gave a mixture of products in which 94% of the label in the major product **26** was found *cis* to the phenyl groups (eq 10). A significant upfield shift in the <sup>1</sup>H NMR spectrum is regularly observed for the methyl group *cis* to the *C2* phenyl

**Scheme 4.** Barbituric Acid Derivative Synthesis for Absolute Stereochemistry Determination by X-Ray Analysis



group of the tetrahydrofuran due to shielding ring currents. This spectral characteristic allows facile assignment of the ester groups.



Four reasonable mechanisms for the [3 + 2] cycloaddition can be evaluated in the context of these experimental observations (Scheme 5). First, an unusual substitution process was considered wherein the aldehyde acts as a nucleophile, causing inversion of the stereochemistry at the activated *C-2* carbon of the cyclopropane (mechanism A).<sup>26–28</sup> Inversion has been observed for the methanolysis<sup>28</sup> and aminolysis<sup>29</sup> of activated cyclopropanes at elevated temperatures. Cram has proposed carbanion-carbonium ions as transient configurationally stable intermediates in reactions with D–A cyclopropanes of this type.<sup>30,31</sup> Next, an *S<sub>E</sub>2*-process occurring by a “corner” attack mechanism would proceed with inversion at the cyclopropane 1-position and afford the tetrahydrofuran (mechanism B); however, this is the minor diastereomer observed from the labeling experiment.<sup>32–35</sup> The cyclopropane could also undergo “edge” attack by the aldehyde (mechanism C). This *S<sub>E</sub>2* process would occur with retention of configuration at the 1-position.<sup>6</sup> Placing the large group of the aldehyde away from the phenyl group on the cyclopropane would lead to the incorrect absolute stereochemistry. If a concerted mechanism is considered, the reaction would need to occur via a symmetry allowed [ $\pi_2s + \sigma_2a$ ] pathway (mechanism D).<sup>36–38</sup> There is only one coplanar orientation of reactants that is consistent with the observed relative and absolute stereochemistry and would not suffer from

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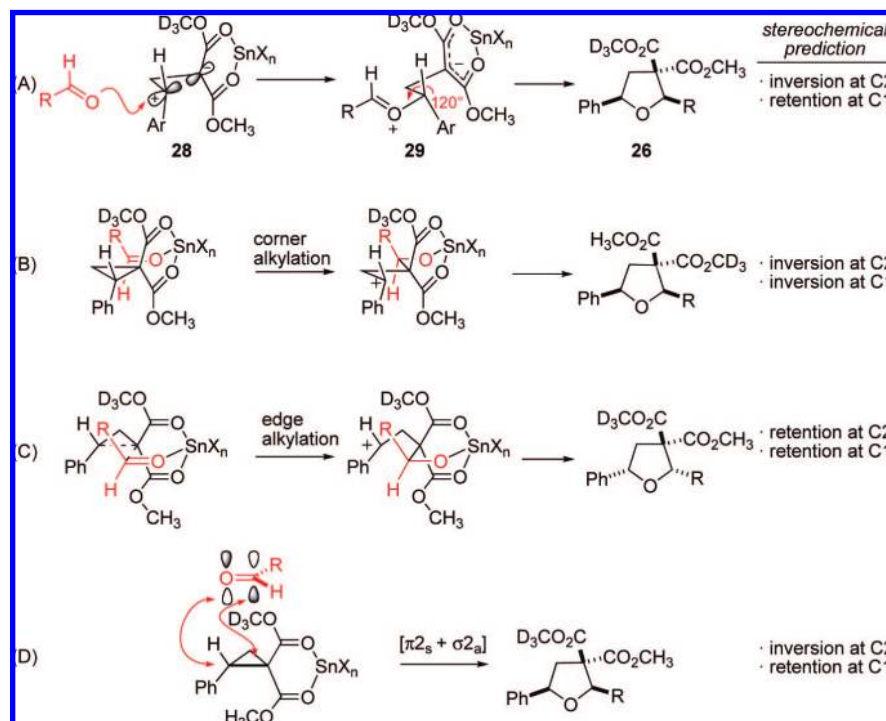
(34) Graziano, M. L.; Cimminiello, G. *J. Chem. Res. (S)* **1989**, 42–43.

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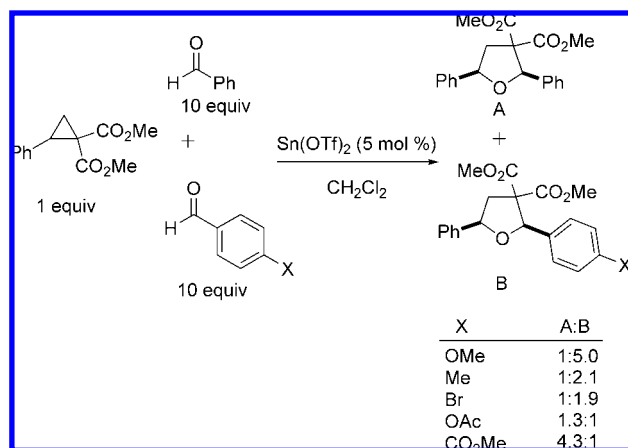
(24) This resolution has also been achieved with brucine: Quinkert, G.; Schwartz, U.; Stark, H.; Weber, W.-D.; Adam, F.; Baier, H.; Frank, G.; Dürner, G. *Lieb. Ann. Chem.* **1982**, 1999–2040.

(25) Corey, E. J.; Gant, T. G. *Tetrahedron Lett.* **1994**, *35*, 5373–5376.

Scheme 5. Mechanistic Analysis of the [3 + 2] Lewis Acid-Catalyzed D–A Cyclopropane/Aldehyde Cycloaddition



Scheme 6



significant unfavorable steric interactions. Only mechanism A and D predict a stereochemical outcome that matches the experimental observation.

Further experimentation was used to distinguish mechanisms A and D. Competition experiments were performed using substituted benzaldehydes of varying electronic character versus benzaldehyde (Scheme 6). When electron-rich aldehydes were used the product ratio favors the species from the electron rich aldehyde, product **B**; however, when electron poor aldehydes are used the product ratio reverses and favors the tetrahydrofuran **A** derived from benzaldehyde. In mechanism A (Scheme 5), electron rich aldehydes should react faster if the key step is nucleophilic attack of the oxygen lone pair on the activated cyclopropane (mechanism A, Scheme 5), thus the competition experiments' ratios support this mode of action. This piece of evidence disfavors a concerted mechanism (mechanism D, Scheme 5). In the concerted reaction, the primary orbital interaction would be between the HOMO of the cyclopropane and the LUMO of the aldehyde. This is not congruent with the

sluggish reactivity of electron-poor aldehydes, which have lower LUMO energies and should therefore react faster if such a mechanism were operative. It would also be predicted that Lewis acid coordination to the malonate would lower the HOMO ( $\sigma_{C1-C2}$ ) and not provide rate acceleration. Computational studies for this and related systems have identified viable stepwise pathways.<sup>39,40</sup>

Simple variation of the donor substituents on the D–A cyclopropane ring allows for the preparation of electronically different tetrahydrofurans at the 5-position. Substituted tetrahydrofurans in entries 1–10 of Table 6 were prepared in high yields from the corresponding substituted cyclopropanes of varying electronic character. There was a significant drop in the rate of the reaction as the donor substituents became more electron withdrawing as in entries 3–5 of Table 6. This trend is in line with the proposed mechanism since the electronics of the cyclopropane govern the ease of formation of the ring-opened species **28**. In these highlighted cases, the electron-poor C2 donor group destabilizes the polarized species **28**. Higher catalyst loadings as well as longer reaction times were needed in these cases; however, under the optimized conditions these heterocycles could be obtained in good yields and stereoselectivities.

Viewing the initial attack of the cyclopropane in terms of the C1–C2  $\sigma$ -bond stability allows further insight into the mechanism. Reactions between the *p*-methoxyphenylcyclopropane **30a** (PMP-cyclopropane) and aldehydes of varying electronic character including *p*-nitrobenzaldehyde proceed with high diastereoselectivities in less than 30 min with 5 mol % catalyst

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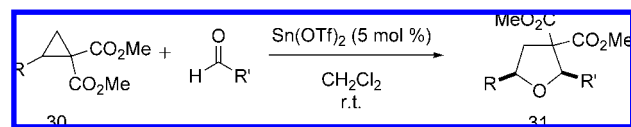
(37) Graziano, M. L.; Chiosi, S. *J. Chem. Res. (S)* **1989**, 44–45.

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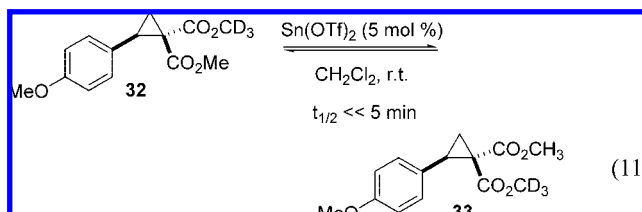


**Table 6.** Substituted-Aryl Cyclopropane Scope in Lewis Acid-Catalyzed [3 + 2] Cycloaddition of D–A Cyclopropanes and Aldehydes

entry	R	R'	Time (h)	% yield <sup>a</sup> (product)	d.r.
1	4-OMePh ( <b>30a</b> )	Ph	0.1	85 ( <b>31a</b> )	>63:1
2	4-MePh ( <b>30b</b> )	Ph	1.25	60 ( <b>31b</b> )	>100:1
3 <sup>b</sup>	4-BrPh ( <b>30c</b> )	Ph	25	61 ( <b>31c</b> )	>100:1
4 <sup>c</sup>	4-OAcPh ( <b>30d</b> )	Ph	24	91 ( <b>31d</b> )	>100:1
5 <sup>c</sup>	4-MeO <sub>2</sub> CPh ( <b>30e</b> )	Ph	24	83 ( <b>31e</b> )	>100:1
6	2-thienyl ( <b>30f</b> )	Ph	0.75	97 ( <b>31f</b> )	20:1
7	( <i>E</i> )-CH=CHPh ( <b>30g</b> )	Ph	1	94 ( <b>31g</b> )	2.4:1
8	4-OMePh ( <b>30a</b> )	4-MeOPh	0.1	90 ( <b>31h</b> )	>100:1
9	4-OMePh ( <b>30a</b> )	4-MeOPh	3.75	90 ( <b>31h</b> )	12:1
10	4-OMePh ( <b>30a</b> )	4-O <sub>2</sub> NPh	0.4	82 ( <b>31i</b> )	>83:1

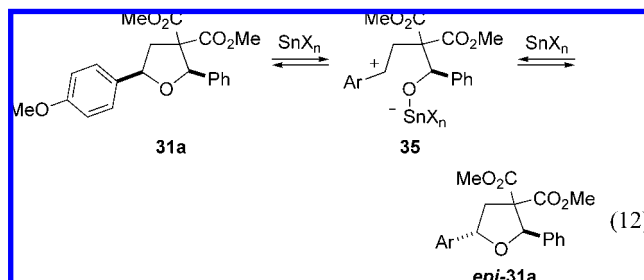
<sup>a</sup> Isolated yield. <sup>b</sup> Sn(OTf)<sub>2</sub> (10 mol %) was used. <sup>c</sup> Sn(OTf)<sub>2</sub> (30 mol %) was used.

(Table 6). By way of comparison, the reaction of *p*-nitrobenzaldehyde with cyclopropane **6a** requires 15 h and 30 mol % catalyst loading. In contrast to the configurational stability of **25** (and thence **6a**), a labeling study with the diastereomerically pure PMP-cyclopropane **32** revealed complete scrambling of the carboxyester groups in less than five minutes in the presence catalytic quantities of Sn(OTf)<sub>2</sub> (eq 11). The ability of the *p*-methoxy group to stabilize any cationic charge at C2 facilitates ring-opening of the cyclopropane. Reactions with this species proceed swiftly regardless of the electronics of the aldehyde as can be seen with *p*-nitrobenzaldehyde and probably point to a carbenium ion electrophile that more closely resembles **2** than **28**.



The PMP-cyclopropane **30a** exhibited time-dependent diastereoselectivity in the transformation to tetrahydrofurans. These reactions proceed in high initial diastereoselectivities (Table 6, entry 8), but epimerization occurs if the reaction is not quenched promptly upon completion (Table 6, entry 9). A mechanism was proposed that allows for epimerization at C5 of the tetrahydrofuran through a postcycloaddition ring opening wherein the cation is stabilized by the electron releasing donor group. Lewis acid coordination to the ring oxygen would facilitate this process (eq 12).<sup>41</sup>

The origin of the *cis*-diastereoselectivity in these cycloaddition reactions can be analyzed in the context of the proposed mechanism (Scheme 7). The more accessible *trans* lone pair on the carbonyl oxygen most likely attacks the configurationally stable carbenium-/carbanion **28** in the initial substitution reaction. The rate of this capture is directly related to the nucleo-



philicity of RCHO. The attack produces (*E*)-oxocarbenium ion **29**. From the staggered conformation, a 120° rotation about the C2–C3  $\sigma$ -bond would place the zwitterion in an envelope conformation **38**. The substituents from the cyclopropane and aldehyde occupy pseudoequatorial positions in this conformation.<sup>42</sup> The enolate then quenches the oxocarbenium ion leading to ring closure. It is apparently the case that little bond rotation about the C1–C3  $\sigma$ -bond occurs in oxocarbenium ion **29**, affording tetrahydrofuran **26** with the labeled carbomethoxy group *cis* to the 2'- and 5'-substituents.<sup>43</sup> This retention of configuration is reasonable considering that scrambling of the ester groups would require a 180° C1–C3 bond rotation to be faster than the 120° C2–C3 bond rotation. Additionally, this 180° rotation would involve an eclipsing butane interaction between C2 and one carboxyester group, while the 120° rotation would not suffer similar torsional strain.

As demonstrated in the reactions with 2,3-disubstituted D–A cyclopropanes, regioselectivity is well-controlled. All of the cycloaddition reactions studied produce substituted tetrahydrofurans as a single regioisomer in which the oxygen atom of the aldehyde has become bonded to the tertiary carbon of the cyclopropane and the carbonyl carbon atom has become bonded to the quaternary carbon of the cyclopropane. This results from nucleophilic attack by the aldehyde at the more electrophilic site on the cyclopropane ring. Coordination of the Lewis acid to the cyclopropane ester groups is expected to break the C1–C2 cyclopropane  $\sigma$ -bond in analogy to Cram's thermal cleavage reactions, providing a configurationally stable carbenium/carbanion pair (**28**).<sup>28,31</sup> The presence of an electron-releasing group in the donor position stabilizes the positive charge, and hence, the bond between the substituted carbon and the quaternary carbon is preferentially broken.

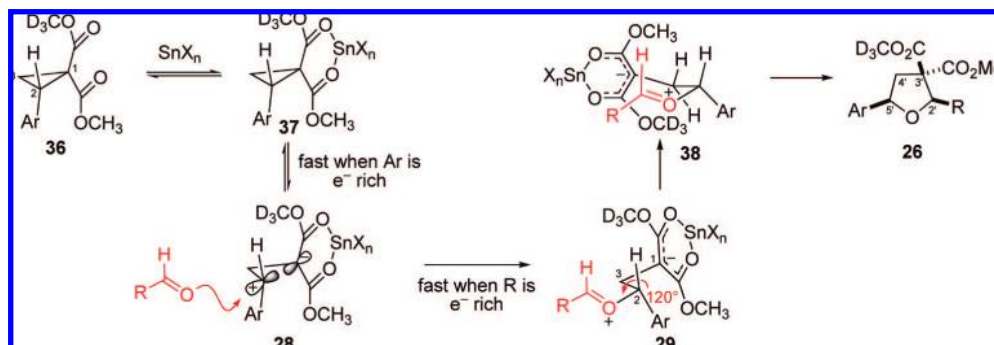
## Conclusion

In summary, a Lewis acid-catalyzed [3 + 2] cycloaddition reaction of carbon-based D–A cyclopropanes and aldehydes has been developed. This methodology achieves the facile synthesis of *cis*-2,5-disubstituted tetrahydrofurans from readily accessible starting materials. This synthesis is effective for both alkyl and aryl aldehydes of varying electronics and typically produces tetrahydrofurans in very high yields with excellent *cis*-diastereoselectivities. Furthermore, both unsaturated and aliphatic substituents on the D–A cyclopropane provide the necessary stabilization for successful reactivity, allowing access to a diverse array of tetrahydrofuran derivatives. Mechanistic studies have shown that this formal [3 + 2] cyclopropane/aldehyde cycloaddition occurs via an unusual nucleophilic

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(42) A transition structure with the oxygen on the flap of the envelope and the C2' and C5' substituents in the equatorial positions would provide the same product. See ref 11a.

(43) The numbering scheme changes from the cyclopropane starting material going to the tetrahydrofuran product. The prime (') denotes an atom in the product.

Scheme 7. Origin of *cis*-2,5-Diastereoselectivity in [3 + 2] Cycloaddition Reactions

substitution mechanism in which the aldehyde acts as a nucleophile toward a configurationally stable intimate ion pair. Our original characterization of this process as an S<sub>N</sub>2 reaction<sup>12</sup> accurately describes the stereochemical outcome, but the study detailed herein reveals that the reaction carries all of the hallmarks of one proceeding via an *ionic* electrophile: substitution at the more highly substituted carbon atom and faster reaction rates with electron releasing groups on both the nucleophile and electrophile.<sup>44</sup> The stereospecificity of this reaction mechanism mediates the efficient transfer of absolute stereochemical information from aryl-, vinyl-, and alkyl-substituted cyclopropanes to the products, allowing the facile synthesis of optically active *cis*-2,5-disubstituted tetrahydro-

furans from enantioenriched cyclopropanes. Effective decarboxylation of a tetrahydrofuran derivative has demonstrated that the products can be manipulated to allow for the synthesis of more complex optically active heterocycles. Additional work in our group has suggested the application of this process to the facile synthesis of substituted tetrahydrofurans containing an even greater degree of substitution and stereochemical complexity is possible.

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(44) A reviewer suggested that our results may still be interpreted as an S<sub>N</sub>2 mechanism. We believe that the high site selectivity in the cycloaddition of compound **16** provides the best evidence against the S<sub>N</sub>2 mechanism. Because the S<sub>N</sub>1/S<sub>N</sub>2 continuum contains reactions proceeding via intimately associated ion pairs, the most complete description consistent with the IUPAC nomenclature for such reactions would be D<sub>N</sub>\*A<sub>Nint</sub>. For excellent reviews of substitution mechanisms, see: (a) Guthrie, R. D.; Jencks, W. P. *Acc. Chem. Res.* **1989**, *22*, 343–349. (b) Katritzky, A. R.; Brycki, B. E. *Chem. Soc. Rev.* **1990**, *19*, 83–105.

**Supporting Information Available:** Experimental procedures and analytical data for all new compounds; structural and stereochemical proofs for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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