Communication

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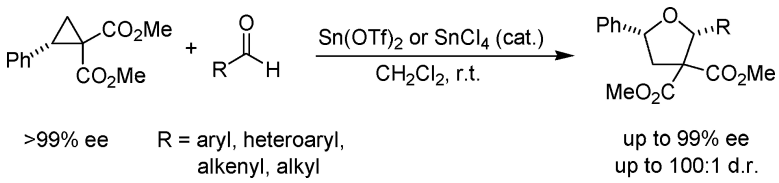

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Enantiospecific Sn(II)- and Sn(IV)-Catalyzed Cycloadditions of Aldehydes and Donor−Acceptor Cyclopropanes

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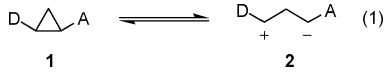
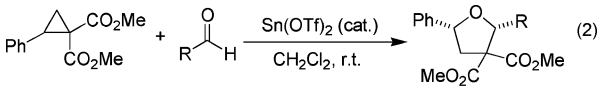
Donor−acceptor (D−A) cyclopropanes are exceptionally useful three-atom building blocks due to their ease of synthesis and high reactivity. The ambiphilic behavior D−A cyclopropanes exhibit toward both electrophiles and nucleophiles has created an extensive array of useful reactions available to organic chemists.[1] In this regard, the view of vicinally substituted donor−acceptor cyclopropanes (**1**) as ring-opened 1,3-zwitterionic equivalents (**2**) implies chirality loss concurrent with reaction progress (eq 1). The purpose of this communication is to demonstrate the unexpected preservation of optical activity in a new family of Lewis acid-catalyzed cyclopropane/aldehyde cycloadditions and to document experiments supporting an unusual S_N2 mechanism accounting for the observed enantiospecificity.



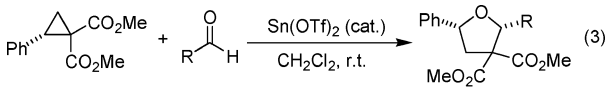
1 **2** (1)

We recently reported a highly diastereoselective synthesis of 2,5-disubstituted tetrahydrofurans (***rac*-4**) via the formal $Sn(OTf)_2$-catalyzed cycloaddition of aldehydes with D−A cyclopropanes (***rac*-3**) bearing a malonyl diester acceptor group and carbon-based resonance donor substituent (eq 2).[2,3] As an extension of this work, we wished to develop an asymmetric version of this new reaction.



***rac*-3** ***rac*-4** (2)

Assuming participation of a species such as **2** in the reaction mechanism, it would have been necessary to employ ligand control to effect absolute stereochemical induction. Indeed, Sibi successfully employed this strategy in the cycloaddition of nitrones with cyclopropanes,[4] a reaction discovered and developed by Kerr.[5] However, our initial control experiment employing cyclopropane (***S*)-3** (>99% ee),[6] benzaldehyde, and $Sn(OTf)_2$ (5 mol %) afforded tetrahydrofuran **4a** in 96% ee (eq 3). This unexpected result indicated that the chiral information contained in the cyclopropane was being transferred in the initial bond-forming event, intermediate **2** was not significant, and that ligand control might not be necessary. To investigate this possibility, the substrate scope was evaluated with a number of aldehydes in the presence of catalytic quantities of $Sn(OTf)_2$ (eq 3).



(*S*)-3
> 99% ee

4a (R = Ph)
96% ee (3)

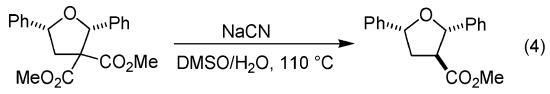
The absolute stereochemical information from the cyclopropane was regularly transferred to the tetrahydrofuran products with high fidelity (Table 1). Only extremely electron-poor aldehydes, which require higher catalyst loading and longer reaction times, gave products of <96% ee (entries 6 and 8). Several experiments were carried out to probe this observation. First, the reaction conditions in entry 6 were reproduced in the absence of *p*-nitrobenzaldehyde. After quenching the reaction, complete racemization of (***S*)-3** was observed. Second, the cycloaddition reactions in entries 6 and 8 were reproduced but quenched after only 45 and 30 min, respectively. In each case, the tetrahydrofuran products were formed in 93% ee. 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 (cf. eq 1).[7] Moreover, in the absence of appreciable cyclopropane racemization, it is likely that the optical purity of the tetrahydrofurans would be as high with these aldehydes as it is with others.

Table 1. Aldehyde Scope in the Lewis Acid-Catalyzed Asymmetric [3 + 2] Cycloaddition of Cyclopropane (*S*)-**3** (eq 3)[a]

entry	R	time (h)	yield (%)[b]	dr	ee (%)
1	Ph	2.25	100	>100:1	96
2	4-ClPh	4.75	97	>83:1	96
3	4-MeOPh	3.5	99	>84:1	99
4	2-furyl	3.25	83	24:1	99
5	2-thienyl	3.25	98	>92:1	98
6	4-NO_2Ph[c]	15	91	> 52:1	34
7	(*E*)-CH=CHPh	3.5	97	17:1	99
8	C≡CPh[d]	6	90	1.6:1	88
9	Et[e]	1.75	100	>36:1	96
10	^{i}Pr[e]	2.5	98	>56:1	96

[a] Cyclopropane (1.0 equiv), aldehyde (3.0 equiv), $Sn(OTf)_2$ (5 mol %), 23−29 °C. [b] Isolated yields. [c] With 20 mol % of $Sn(OTf)_2$ used. [d] With 10 mol % of $Sn(OTf)_2$ used. [e] With 5 mol % of $SnCl_4$ used as Lewis acid.

We previously reported difficulty employing aliphatic aldehydes in this cycloaddition reaction.[2] The use of $SnCl_4$ solved this problem and allowed the synthesis of 2-alkyl-substituted tetrahydrofurans in high yield, diastereoselectivity, and enantiomeric excess (entries 9 and 10).



***rac*-4** **5** 75%
d.r. = 6.5:1 (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 ***rac*-4** underwent decarboxylation in a stereoselective manner to afford monoester **5** in good yield (eq 4).[8] This facile process should allow simple functionalization of the ring 3-position.

The cycloadduct with *p*-chlorobenzaldehyde (entry 2) was converted to its derived barbituric acid, and the absolute stereochemistry was determined by a single-crystal X-ray diffraction study

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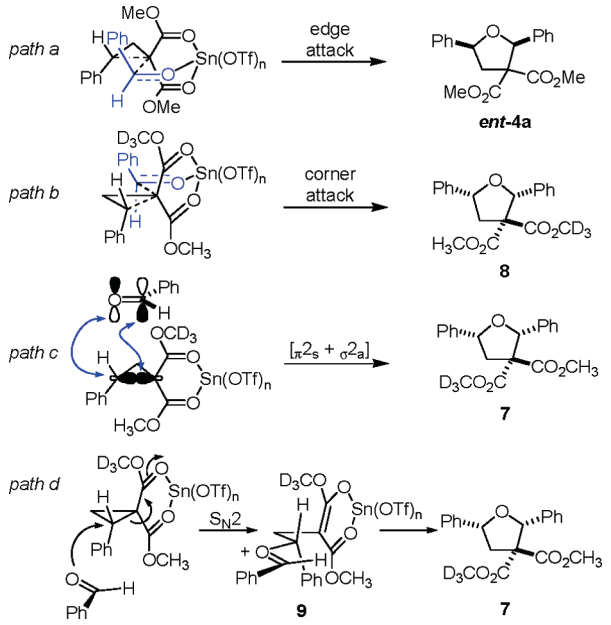
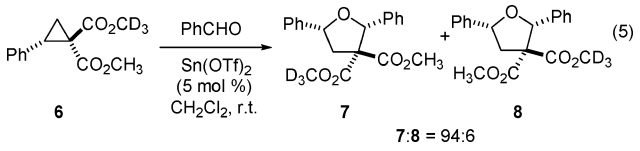
Scheme 1



to be (2*R*,5*R*), as shown in eq 3.[9] Insight into the mechanism of this cycloaddition can be gained from both the absolute stereochemistry of the product and an additional labeling study in which one of the diastereotopic carboxymethyl groups of the cyclopropane was deuterated (**6**) and subjected to the normal reaction conditions (eq 5). In this reaction, 94% of the label was found *cis* to the phenyl groups in the tetrahydrofuran. Four reasonable mechanisms for the cyclopropane/aldehyde cycloaddition can be evaluated in the context of these experimental observations (Scheme 1).



An S_E2 process in which the cyclopropane undergoes "edge" attack by the aldehyde would occur with retention of configuration at the 1-position (path a).[10] Placing the large group of the aldehyde away from the phenyl group on the cyclopropane would lead to the incorrect absolute stereochemistry (***ent*-4a**). An S_E2 process occurring by a "corner" attack mechanism would proceed with inversion at the cyclopropane 1-position and afford tetrahydrofuran **8** (path b);[11,12] however, this is the minor diastereomer observed from the labeling experiment. If a concerted mechanism is considered, the reaction would need to occur via a symmetry allowed [$_\pi2_s$ + $_\sigma2_a$] pathway.[13] There is only one coplanar orientation of reactants that is consistent with the observed relative and absolute stereochemistry and would not suffer from large unfavorable steric interactions (path c). Last, an unusual S_N2 process, where the aldehyde acts as a nucleophile inverting the stereochemistry at the activated C-2 carbon of the cyclopropane, is entirely consistent with all experimental evidence (path d).[14−16] In this mechanism, little rotation occurs about the enolate carbon−methylene carbon σ-bond in intermediate **9** before the oxocarbenium ion is internally quenched to form the heterocycle. Since the reaction of (*S*)-**3** affords **4a** in 96% ee, 2% of the scrambling in the labeling study reaction (eq 5) can be assumed to arise from racemization. Thus, only 4% of intermediate **9** undergoes bond rotation before ring closure.

With respect to the two possible mechanisms that correctly predict the observed product, we favor an S_N2 displacement over a concerted reaction pathway. First, in the concerted reaction, the primary orbital interaction is between the HOMO of the cyclopropane and 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. Second, every dipolarophile studied afforded the product in very similar enantiomeric excess regardless of the size of the aldehyde substituent (except for very electron-poor dipolarophiles, which we have shown is not a steric effect), a fact that is more consistent with an enantiospecific reaction than an enantioselective reaction.

In summary, we have developed the synthesis of 2,5-disubstituted tetrahydrofurans in excellent yield, diastereoselectivity, and a very high degree of absolute stereochemical control from a formal cyclopropane/aldehyde cycloaddition. The tetrahydrofuran products can be further manipulated to allow for the preparation of more complex optically active heterocycles. This reaction is believed to proceed through an initial S_N2 attack on the activated cyclopropane, and through this process, absolute stereochemical information is transferred to the product.

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

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