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Highly Diastereoselective Synthesis of Tetrahydrofurans via Lewis Acid-Catalyzed Cyclopropane/Aldehyde Cycloadditions

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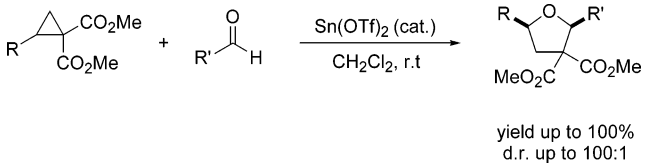
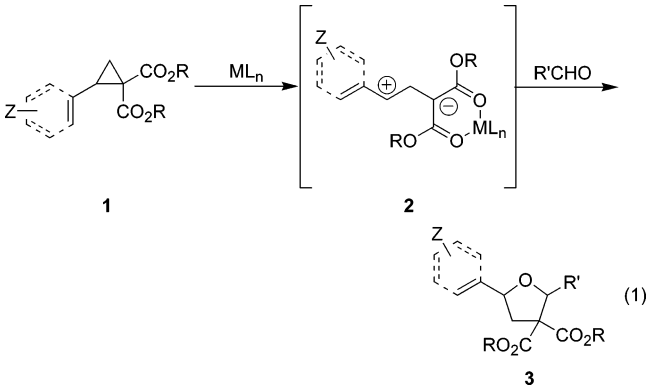


A one-step procedure for the preparation of 2,5-disubstituted tetrahydrofurans from donor−acceptor cyclopropanes and aldehydes has been developed. In the presence of a catalytic amount of $Sn(OTf)_2$, cyclopropanes bearing an aryl or conjugated donor substituent vicinal to a malonyl diester group undergo cycloadditions with diverse conjugated aldehydes furnishing tetrahydrofurans with high cis diastereoselectivity. This method is useful for the preparation of regiodefined tetrahydrofurans.

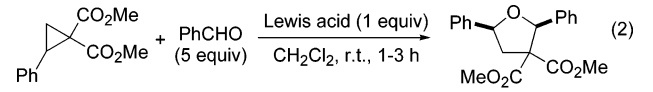
The straightforward preparation of tetrahydrofurans is an important issue in synthetic organic chemistry owing to the repetitive occurrence of these structures in natural products. Among the methods for the preparation of substituted tetrahydrofurans, the use of cyclopropanes in 1,3-dipolar type cycloadditions to carbonyl compounds has not been comprehensively explored, but nonetheless represents a powerful and convergent entry into these types of compounds. The relative ease with which diverse cyclopropanes can be synthesized combined with the inherent ring strain makes the utilization of cyclopropanes as 3-carbon fragments in the synthesis of five-membered heterocycles desirable.[1,2] In this regard, several reports addressing the synthesis of tetrahydrofurans have been described. Reissig has shown the use of silyloxy donor−acceptor (D−A) cyclopropanes in the synthesis of homoaldol products or the tautomeric γ-lactols and the subsequent reduction or substitution of the anomeric hydroxyl group to afford substituted tetrahydrofurans.[3−5] These methods require the use of a stoichiometric amount of Lewis acid or promoter to effect cyclopropane ring cleavage. Oshima has shown that tetrahydrofuran formation can occur in a stereoselective manner from cyclopropyl ketones and aldehydes in the presence of 2 equiv of $TiCl_4$/*n*-Bu_4NI.[6] This methodology is limited to tetrahydrofurans unsubstituted at the 5-position. Under Lewis acid catalysis, Sugita has formed acetal tetrahydrofurans via the cycloaddition of an activated methanochromanone with carbonyl compounds.[7,8] To our knowledge there exists no catalytic one-step synthesis of substituted tetrahydrofurans devoid of an anomeric carbon from simple cyclopropane and carbonyl precursors. We describe herein the highly diastereoselective synthesis of 2,5-disubstituted tetrahydrofurans via the Lewis acid-catalyzed cycloaddition of D−A cyclopropanes and aldehydes.

The majority of D−A cyclopropanes bear either alkoxy or silyloxy donor groups that produce an often unwanted anomeric hydroxyl group in the cycloaddition with a carbonyl compound.[1] In lieu of this, we envisioned, in conjunction with a malonyl diester acceptor group, the use of a carbon-based donor on the D−A cyclopropane (**1**). This donor should stabilize a cationic intermediate (**2**) through resonance after ring cleavage and afford a tetrahydrofuran (**3**) in one step (eq 1). Kerr has successfully employed such cyclopropanes in nucleophilic ring opening/cycloaddition reactions with indoles and nitrones.[9,10] To test the viability of this hypothesis a



1 **2** **3** (1)

number of Lewis acids were screened in the cycloaddition of phenyl cyclopropane **4** and benzaldehyde (eq 2), with



4 **5** (2)

close attention being paid to conversion, cleanliness and diastereoselectivity. Strong Lewis acids such as $TiCl_4$ and $AlCl_3$ gave significant decomposition of the cyclopropane, while several milder Lewis acids such as $SnCl_2$, $ZnCl_2$,

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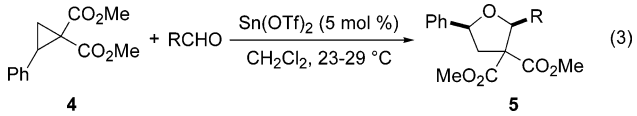
TABLE 1. Aldehyde Scope Study in the [3+2] Cycloadditon with Cyclopropane 4 (Eq 3)[a]

entry	R	time (h)	yield (%)[b]	dr
1	Ph	2.5	100	>100:1
2	4-ClPh	4.75	96	>80:1
3	4-OMePh	3.5	98	>86:1
4	2-furyl	3.25	82	23:1
5	2-thienyl	3.25	98	>83:1
6	4-NO_2Ph[c]	15	89	>19:1
7	(*E*)-CH=CHPh	3.5	96	17:1
8	C≡CPh[d]	6	92	1.6:1

[a] Cyclopropane (1.0 equiv), aldehyde (3.0 equiv), $Sn(OTf)_2$ (5 mol %). Room temperature varied between 23 and 29 °C. [b] Isolated yields. [c] 20 mol % of $Sn(OTf)_2$ used. [d] 10 mol % of $Sn(OTf)_2$ used.

$Mg(OTf)_2$, and $La(OTf)_3$ exhibited no reactivity toward the cyclopropane. $Cu(OTf)_2$ provided clean cycloadduct **5** in 89% conversion after 3 h with a diastereomeric ratio of 59:1. $Sc(OTf)_3$ and $SnCl_4$ cleanly produced **5** in 100% conversion after 3 h, with diastereomeric ratios of 3.1:1 and 31:1, respectively. After 1 h, $Sn(OTf)_2$ afforded only the tetrahydrofuran adduct with 100% conversion and >100:1 cis:trans selectivity. In light of this, subsequent studies employed $Sn(OTf)_2$ as the Lewis acid catalyst.

The conditions for the cycloaddition with **4** were optimized to 5 mol % of $Sn(OTf)_2$ and 3 equiv of aldehyde. Under these conditions a range of aldehydes was studied to determine the scope of this reaction (eq 3). A number

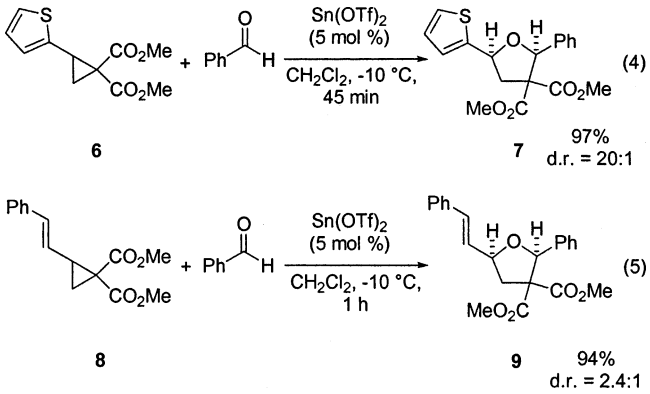


(3)

4 **5**

of electronically and sterically diverse 2,5-disubstituted tetrahydrofurans (**5**) were successfully prepared in excellent yields and diastereoselectivities (Table 1). Electron-rich, electron-neutral, and slightly electron-poor aldehydes underwent cycloaddition affording the tetrahydrofuran derivatives smoothly in a matter of hours (entries 1−3). The rather electron-poor *p*-nitrobenzaldehyde required an increased catalyst loading and reaction time, but under these conditions gave the product in excellent yield and stereoselectivity (entry 6). The heterocyclic aldehydes furfural and 2-thiophenecarboxaldehyde were suitable substrates for this chemistry (entries 4 and 5); however, 2-pyridinecarboxaldehyde was completely unreactive, presumably due to coordination of $Sn(OTf)_2$ with the Lewis basic nitrogen. Alkyl aldehydes proved to be difficult substrates, with sluggish and somewhat messy reactions observed, but α,*β*-unsaturated aldehydes in conjugation with an aryl system were effective dipolarophiles (entries 7 and 8). The effective use of unsaturated aldehydes should allow for further functionalization of the tetrahydrofuran products. With the exception of entry 8, in which the diastereomeric ratio was quite low, the 2,5-disubstituted tetrahydrofurans were synthesized in excellent yields and cis diastereoselectivity.

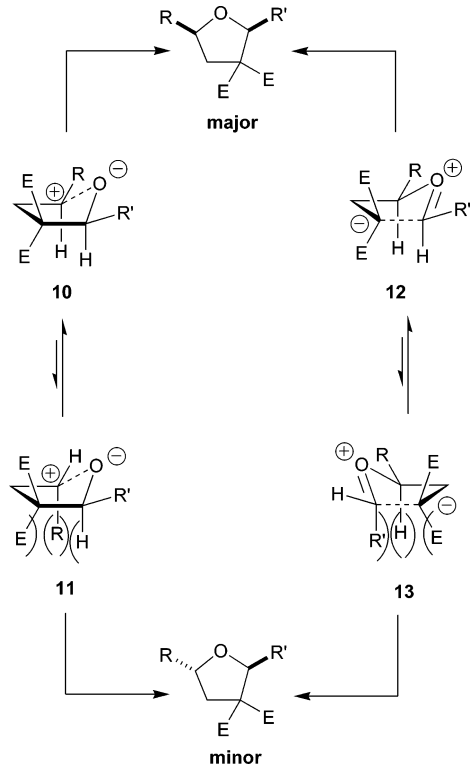
Simple manipulation of the donor substituent on the cyclopropane ring allows for the formation of a wider range of tetrahydrofuran derivatives. Substituted tetrahydrofurans **7** and **9** were prepared in high yields employing thienyl cyclopropane **6** (eq 4) and styrenyl cyclopropane **8** (eq 5) in the $Sn(OTf)_2$-catalyzed cycloaddition with benzaldehyde. These are adducts regioisomeric to



those synthesized from **4** using 2-thiophenecarboxaldehyde and (*E*)-cinnamaldehyde (Table 1, entries 5 and 7).

The 2,5-relative stereochemistry of the major isomer in each reaction was determined by NOESY analysis. This was invariably shown to be cis.[11] We have proposed a stereochemical model for the favorable formation of the cis isomer (Scheme 1). The stereochemical outcome is

SCHEME 1. Model for the Observed Cis Stereoselectivity



assumed to arise in the final step of two possible limiting mechanisms. The left half of the scheme depicts the final bond formation after aldol-type addition has taken place. Placing the large donor group pseudoequatorial (**10**) should be more favorable owing to the interactions in the pseudoaxial arrangement (**11**), thus leading to the ob-

(11) For **9**, the diastereomers were inseparable. The major isomer is assumed to be cis by analogy.

served cis product. In a similar fashion, the right half of the scheme depicts final bond formation following nucleophilic cyclopropane ring opening by the aldehyde. In this case the large group on the aldehyde can be placed in a pseudoequatorial (**12**) or pseudoaxial position (**13**), the former being more sterically favored and leading to the 2,5-cis tetrahydrofuran.

In conclusion, a catalytic synthesis of 2,5-disubstituted tetrahydrofurans from carbon donor substituted (D−A) cyclopropanes and aldehydes has been developed. This practical one-step synthesis is effective for aldehydes of varying electronics and typically produces tetrahydrofurans in very high yields with excellent cis diastereoselectivities. Furthermore, it has been shown that 2,5-regiochemistry is easily managed through the appropriate choice of a cyclopropane donor substituent and the aldehyde employed as a dipolarophile.

Experimental Section

Representative Procedure for Cycloaddition Reactions: 2,5-Diphenyltetrahydrofuran-3,3-dicarboxylic Acid Dimethyl Ester (5a, Table 1, entry 1). In an inert atmosphere glovebox a flame-dried vial was charged with $Sn(OTf)_2$ (7.1 mg, 0.017 mmol, 0.050 equiv), cyclopropane **4** (80.0 mg, 0.342 mmol, 1.0 equiv), and a magnetic stir bar. Outside of the glovebox, the vial was placed under Ar and charged with 0.5 mL of CH_2Cl_2 followed by benzaldehyde (110 mg, 1.03 mmol, 3.0 equiv) via syringe. The reaction was stirred at room temperature. After 2.25 h the reaction was passed over a small plug of silica with 50 mL of Et_2O, the solvent was removed with a rotary evaporator, and the residue was placed under vacuum (<0.1 Torr) overnight. ^{1}H NMR analysis of the unpurified product (δ 5.79 vs δ 5.98) gave the diastereomeric ratio >100:1. The crude product was purified by flash chromatography (7.5% EtOAc/petroleum ether) to afford 116 mg (100%) of the product as a colorless oil. Analytical data for title compound: IR (thin film, cm^{-1}) 3064, 2953, 1732, 1606, 1497, 1456, 1435, 1360, 1271, 1232, 1209, 1176, 1093, 1064, 1028, 943, 902, 812, 750, 700; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58−7.47 (m, 4H), 7.44−7.23 (m, 6H), 5.79 (s, 1H), 4.95 (dd, J = 10.5, 6.0 Hz, 1H), 3.82 (s, 3H), 3.09 (s, 3H), 3.00 (dd, J = 13.5, 10.8 Hz, 1H), 2.73 (dd, J = 13.2, 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 169.3, 140.0, 137.8, 128.6, 128.22, 128.17, 127.9, 127.1, 126.6, 84.6, 80.0, 66.5, 53.0, 52.2, 42.9; TLC (80% CH_2Cl_2/petroleum ether) R_f 0.34. Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.64; H, 6.00.

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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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