## Cyclopropane—Aldehyde Annulations at Quaternary Donor Sites: Stereoselective Access to Highly Substituted Tetrahydrofurans

## ORGANIC LETTERS 2011 Vol. 13, No. 8

1996–1999

Austin G. Smith, Michael C. Slade, and Jeffrey S. Johnson\*

Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290, United States

jsj@unc.edu

## Received February 11, 2011



A diastereoselective synthesis of pentasubstituted tetrahydrofurans via a Lewis acid catalyzed (3 + 2)-annulation of quaternary donor site cyclopropanes and aldehydes is described. The reaction is catalyzed by Sn(OTf)<sub>2</sub>, SnCl<sub>4</sub>, or Hf(OTf)<sub>4</sub> in yields up to 95% and diastereomeric ratios as high as 99:1.

Donor-acceptor (D-A) cyclopropanes are versatile building blocks for the construction of carbocycles and heterocycles via (3+n)-annulation reactions.<sup>1</sup> Their inherent strain energy (27.5 kcal/mol) allows them to react as 1,3-dipolar synthons in the presence of a Lewis acid.<sup>2</sup> We have reported stereoselective (3 + 2)-annulations of D-A cyclopropanes of type **1** (R' = alkyl) and electronically diverse aldehydes **2** (X = O) that provide access to (2, 5-dialkyl) tetrahydrofurans with high *cis*-diastereoselectivity (**3**, Figure 1).<sup>3</sup> Enantioenriched **1** (R' = Ph, er > 99:1) gave (*R*,*R*)-THF **3** with complete chirality transfer (R = Ph, 99:1 er). Carbon-oxygen bond formation occurred at the donor-substituted carbon of 1, with the reaction proceeding with inversion of configuration. The accumulated experimental data were consistent with an unusual substitution mechanism in which 2 acts as a nucleophile toward a configurationally stable intimate ion pair.<sup>3b</sup> Since reaction rates correlated with the stability of the nascent carbenium ion, we questioned whether cyclopropane-1,1-diesters with full substituted-cyclopropane-1,1-diesters have been extensively studied in (3 + n) annulations, analogous reactions with quaternary donxor site cyclopropanes (4, R', R''  $\neq$  H) have not been explored to the same degree.<sup>4</sup>

Annulations with cyclopropanes of this type and aldehyde dipolarophiles would yield (2,2,5-trialkyl) tetrahydrofurans (5, Figure 1), structural motifs present in a number of biologically active natural products.<sup>5</sup> Herein we report a diastereoselective synthesis of pentasubstituted tetrahydrofurans via a Lewis acid catalyzed (3 + 2)-annulation of quaternary donor site cyclopropanes and aldehydes. Results collected from

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Figure 1. Proposed annulation with quaternary donor site cyclopropanes.

chirality transfer experiments with optically active quaternary donor site cyclopropanes provide evidence for the same stereospecific aldehyde nucleophilic attack mechanism as is observed with type 1 D-A cyclopropanes.

The successful application of  $Sn(OTf)_2$  in the (3 + 2)annulation of type 1 D-A cyclopropanes and aldehydes led us to employ this Lewis acid in our initial efforts. Treatment of racemic dimethyl 2-methyl-2-phenylcyclopropane-1,1-dicarboxylate 4a (available in one step via Rhcarbenoid cyclopropanation of  $\alpha$ -methylstyrene<sup>6</sup>) and benzaldehyde with  $Sn(OTf)_2$  (5 mol %) in 1,2-dichloroethane at 23 °C provided tetrahydrofuran 5a in 91% yield and 97:3 diastereoselection; the illustrated diastereomer with the C2and C5-phenyl groups in a cis orientation was preferred (entry 1, Table 1). We next investigated the reactions of different aldehydes in (3 + 2)-annulations with cyclopropane 4a. The reactions were tolerant of a range of electronically diverse aromatic aldehydes, with yields from 82 to 95% (entries 1–6, Table 1). Heteroaromatic (entry 7),  $\alpha$ . $\beta$ -unsaturated (entry 8), aliphatic (entry 9), and branched aliphatic aldehvdes (entry 10) also performed well under identical reaction conditions. In addition to the high yields, we observed high levels of cis-diastereoselection that were competitive with the dr's found in the (3 + 2)-annulation of aldehydes and type 1 D-A cyclopropanes, despite the steric difference between H and Me (dr's up to 99:1, entries 2-10).<sup>7</sup>

With the establishment of **4a** as an effective substrate for aldehyde annulation, we turned our attention to more sterically demanding and functionally useful D–A cyclopropanes. Figure 2 summarizes the range of quaternary donor site cyclopropanes examined with representative aldehydes. Isopropenyl-alkyl (**4b**), aryl-allyl (**4c**), aryl-benzyl (**4d**), electron-withdrawing aryl-alkyl (**4e**), and electron-donating aryl-alkyl (**4f**) cyclopropane 1,1-diesters were all competent substrates for (3 + 2)-annulation with aldehydes. Table 1. Scope of Aldehyde Dipolarophile<sup>4</sup>



entry	R (product)	% yield <sup>b</sup>	$\mathrm{d}\mathbf{r}^c$
1	$C_{6}H_{5}\left(\mathbf{5a}\right)$	91	97:3
2	$4 \cdot MeOC_6H_4$ (5b)	95	96:4
3	$2 - MeC_6H_4$ (5c)	94	97:3
4	$4\text{-MeO}_2\text{CC}_6\text{H}_4$ (5d)	93	99:1
5	$4\text{-ClC}_{6}\text{H}_{4}(5\mathbf{e})$	91	95:5
6	$4-CF_{3}C_{6}H_{4}(\mathbf{5f})$	82	99:1
7	2-thienyl (5g)	91	95:5
8	$(E)$ - $(CH=CH)C_6H_5$ (5h)	87	92:8
9	Et ( <b>5i</b> )	83	96:4
10	<sup><i>i</i></sup> Pr ( <b>5j</b> )	82	96:4

<sup>*a*</sup> Reactions performed with 1.0 equiv of **4a**, 3.0 equiv of **2**, and 5 mol % of Sn(OTf)<sub>2</sub> in 1,2-DCE ([**4a**]<sub>0</sub> = 0.30 M) in a Teflon seal-capped vial. <sup>*b*</sup> Isolated yield after column chromatography, average of at least two trials. <sup>*c*</sup> Determined by <sup>1</sup>H NMR spectroscopy.

Annulations with 4b went with exceptionally high levels of cis-diastereoselection, regardless of the aldehyde substituent (R). Slight modifications to the reaction conditions were necessary for aliphatic aldehydes with 4b: 5 mol % Hf(OTf)<sub>4</sub> at -50 °C in dichloromethane provided 5m, albeit in diminished yield. Reactions with phenyl-allyl cyclopropane 4c proceeded in high yield and moderate dr with both benzaldehyde and 4-chlorobenzaldehyde (5n, 5o). Again, diminished yields were seen with propanal (5p, 32%, dr 90:10), but more sterically hindered isobutyraldehyde provided tertiary THF product in a promising yield (5q, 63%, dr 90:10).<sup>8</sup> We were pleased to observe useful diastereoselectivities in the annulation even when R' and R'' were similar in size. Reactions with 4d proceeded in high yields (up to 87%) and roughly 80:20 dr with each aldehyde (5r-5t). SnCl<sub>4</sub> (10 mol %) in toluene provided the optimal result for the reaction of an aliphatic aldehyde with 4d (5t, 78%, dr 81:19). Cyclopropane 4e was an excellent substrate for annulation, despite the electron-withdrawing nature of the *para*-cyano group (5u-5w, up to 90% yield, dr ~95:5). These results demonstrate the broad electronic tolerance of the donor site on the quaternary cyclopropane. Electrondonating 4-MeOC<sub>6</sub>H<sub>4</sub>-methyl cyclopropane 4f was a particularly fast reacting substrate in this study. Reaction with benzaldehyde was complete within 20 min, providing tetrahydrofuran in 91% yield and 96:4 dr (5x). The product diastereomer ratio eroded with extended reaction times (dr 83:17 after 3.5 h, dr 1:1 after 24 h) due to product equilibration.9

<sup>(6)</sup> Georgakopoulou, G.; Kalogiros, C.; Hadjiarapoglou, L. P. Synlett 2001, 12, 1843–1846.

<sup>(7)</sup> The reaction showed broad solvent and Lewis acid tolerance, but the high reactivity observed with  $Sn(OTf)_2$  and 1,2-DCE led us to to use this combination for most substrates.

<sup>(8)</sup> Significant aldehyde decomposition was observed when isobutyraldehyde was used in combination with slower-reacting cyclopropanes (4d, 4e, and 4 g).

<sup>(9)</sup> For examples of Lewis acid catalyzed THF ring opening, see: (a) Sanders, S. D.; Ruiz-Olalla, A.; Johnson, J. S. *Chem. Commun.* **2009**, 5135–5137. (b) Aldous, D. J.; Dalencon, A. J.; Steel, P. G. *J. Org. Chem.* **2003**, *68*, 9159–9161.



<sup>*a*</sup> Reactions performed with 1.0 equiv of **4b-f**, 3.0 equiv of **2**, 5 mol % of Sn(OTf)<sub>2</sub> in 1,2-DCE ([**4**]<sub>0</sub> = 0.30 M) in a Teflon seal-capped vial unless otherwise noted. <sup>*b*</sup> Preparations of **4b-f** are detailed in the Supporting Information. <sup>*c*</sup> Isolated yield after column chromatography, average of at least two trials. <sup>*d*</sup> Determined by <sup>1</sup>H NMR spectroscopy. <sup>*e*</sup> Reaction performed with 5 mol % Hf(OTf)<sub>4</sub> at -50 °C in dichloromethane ([**4**]<sub>0</sub> = 0.30 M). <sup>*f*</sup> Reaction performed with 10 mol % SnCl<sub>4</sub> at 23 °C in toluene ([**4**]<sub>0</sub> = 0.30 M). <sup>*s*</sup> Dr was 96:4 after 20 min, 83:17 after 3.5 h, 1:1 after 24 h. <sup>*h*</sup> Reaction complete in 20 min.

**Figure 2.** (3 + 2)-Annulations of quaternary donor site cyclopropanes.<sup>*a,b*</sup>

A more highly substituted D–A cyclopropane was obtained via intramolecular cyclopropanation of a trisubstituted alkene.<sup>10</sup> Geraniol-derived alkyl–alkyl lactone cyclopropane **4g** emerged as an effective candidate for (3 + 2)-annulation. High yields and diastereoselectivities were observed with aromatic aldehydes, favoring the *endo* product (**5aa** and **5ab**, Table 2). Diminished diastereocontrol was observed with propanal using 10 mol % SnCl<sub>4</sub> in 1,2-DCE (**5ac**, 75%, dr 77:23); the diastereomers in **5ac** were separable by silica gel chromatography. This (3 + 2)-annulation can thus be extended to cyclopropanes of higher substitution and moderate donor ability (alkyl–alkyl).

Enantioenriched 2,2-substituted-1,1-cyclopropane diesters were accessible using a route developed by Davies, Table 2. Pentasubstituted D-A Cyclopropanes<sup>*a,b*</sup>



<sup>*a*</sup> Reactions performed with 1.0 equiv of **4g**, 3.0 equiv of **2**, and 5 mol % of Sn(OTf)<sub>2</sub> in 1,2-DCE ([**4g**]<sub>0</sub> = 0.30 M) in a Teflon seal-capped vial unless otherwise noted. <sup>*b*</sup> Preparation of **4g** is detailed in the Supporting Information. <sup>*c*</sup> Isolated yield after column chromatography, average of at least two trials. <sup>*d*</sup> Determined by <sup>1</sup>H NMR spectroscopy. <sup>*e*</sup> Reaction performed with 10 mol % SnCl<sub>4</sub> in 1,2-DCE, diastereomers separable by column chromatography.

with slight modifications.<sup>11</sup>  $\alpha$ -Methylstyrene was treated with styryldiazoacetate and the Rh<sub>2</sub>(*S*-DOSP)<sub>4</sub> catalyst at -50 °C in pentanes. The monoester was taken directly to the desired diester via ozonolysis with NaOH/MeOH, affording (-)-4a in 76:24 er.<sup>12</sup> (3 + 2)-Annulation with anisaldehyde and (-)-4a at 23 °C with 5 mol % of Sn-(OTf)<sub>2</sub> provided the desired tetrahydrofuran (+)-5b in low enantioenrichment (58:42 er). Racemization of the starting cyclopropane was slowed by performing the reaction at decreased temperatures with 5 mol % Hf(OTf)<sub>4</sub>. Reaction with anisaldehyde at -78 °C in dichloromethane gave (+)-5b with improved enantioselectivity (66:34 er, Figure 3).





Electron poor (–)-4e was also selected for chirality transfer studies. (–)-4e was accessed in 95:5 er using the Davies protocol. Annulation with anisaldehyde under standard conditions (5 mol %  $Sn(OTf)_2$ , 1,2-DCE, 23 °C) gave tetrahydrofuran (+)-6 in 93:7 er. These results implicate a reaction mechanism analogous to that previously proposed

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Scheme 1. Mechanistic Rationale



for this reaction family (Scheme 1). Lewis acid coordination to the diester facilitates intimate ion pair formation (7), thereby enabling aldehyde nucleophilic attack that results in inversion at the more substituted site. 120° bond rotation about the C2–C3 bond (8), followed by diastereoselective ring closure via an envelope transition state, in which the R group on the aldehyde and the larger R' group on the cyclopropane are oriented pseudoequatorially (9), provides the *cis*-THF adduct **5-(major**). As R' and R" become similar in size (cyclopropanes **4c** and **4d**), ring flip to envelope **10** potentially becomes competitive due to an increased steric penalty in **9** (H and R" both pseudoaxial). Ring closure at this stage provides *trans*-THF **5-(minor)**. An alternative but equally plausible explanation for **5-(minor)** posits a 180° reversal in aldehyde approach because of diminished steric

differentiation. Aldehyde attack (giving 12) and 120° bond rotation provide envelope 10 directly, where R and R" are pseudoequatorial. The need for lower temperatures to promote any sort of chirality transfer in the reaction with (-)-4a is consistent with an increasingly stabilized carbenium ion at C3 and fast racemization at room temperature. (-)-4e is sufficiently electron-withdrawing to disfavor competitive racemization and, thus, reacts with a high transfer of stereochemical information under the standard reaction conditions.

In conclusion, we have developed an intermolecular (3+2)-annulation of guaternary donor site cyclopropanes and aldehydes that provides access to highly substituted tetrahydrofuran adducts. Aromatic and aliphatic aldehydes can participate, resulting in THF products in promising to high yields and moderate to excellent cisdiastereoselectivity. The enhanced carbenium ion stability at the donor site allows for a diverse array of nucleophile-electrophile coupling partners. Experiments with enantionenriched cyclopropanes demonstrate that stereochemical information can still be transferred from the starting cyclopropane to the products, despite the heightened ability of the quaternary donor site cyclopropanes to racemize when treated with a Lewis acid. This mechanistic feature allows for access to optically active pentasubstituted tetrahydrofurans in one step from enantioenriched cyclopropanes. Efforts in our laboratory to expand the reactivity profile of quaternary donor site cyclopropanes are currently underway.

**Acknowledgment.** This work was supported by the NSF (CHE-0749691) and Novartis.

**Supporting Information Available.** Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.