## InCl<sub>3</sub> Catalyzed Highly Diastereoselective [3 + 2] Cycloaddition of 1,2-Cyclopropanated Sugars with Aldehydes: A Straightforward Synthesis of Persubstituted *Bis*-Tetrahydrofurans and Perhydrofuro[2,3-*b*]pyrans

XXXX Vol. XX, No. XX 000–000

ORGANIC LETTERS

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## Received August 2, 2013



A mild and efficient strategy for the construction of persubstituted *bis*-tetrahydrofuran and perhydrofuro[2,3-*b*]pyran derivatives has been developed. Persubstituted cyclization products were obtained in good to excellent yields. The [3 + 2] cycloaddition of 1,2-cyclopropanated sugars with aldehydes in the presence of InCl<sub>3</sub> is highly diastereoselective.

Perhydrofuro[2,3-*b*]pyran or furan scaffolds maintain a widespread presence in a host of pharmaceuticals and biologically active natural products.<sup>1–4</sup> The complex skeletons combined with excellent bioactivity continually stimulate many organic and medicinal chemists to develop creative strategies for the construction of such fused-cycle motifs.<sup>5</sup> Although many achievements have been reported, novel synthetic routes suitable for the highly diastereoselective construction of such structural motifs are still highly desired.

The [3 + n] (n = 2, 3, and 4) cycloaddition of Donor– Acceptor (D–A) cyclopropanes provided a large number of five-, six-, seven-membered carbo- and heterocycles that exhibit interesting biological and medicinal properties.<sup>6</sup> Among them, the [3 + 2] cycloadditions between cyclopropanes 1,1-diester and carbonyl compounds have been extensively used to construct substituted tetrahydrofurans (THFs).<sup>6b,7,8</sup> In sharp contrast to these, very few examples using D–A cyclopropanes to construct the perhydrofuro-[2,3-*b*]pyrans or *bis*-THF were reported, especially using monodonor–monoacceptor cyclopropanes as starting materials.<sup>9</sup>

Furthermore, due to their widespread occurrence, lowprice, multifunctional groups, and multichiral centers, carbohydrates offer an irresistible platform for asymmetric

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synthesis. They also provide the key functional subunits for rational drug designs. Cyclopropanated carbohydrates, the combination of cyclopropanes and carbohydrates within a single molecule, have also been widely used to synthesize branched glycosides,<sup>10</sup> oxepanes,<sup>11,12</sup> and some other natural products or carbohydrate-based fused ring compounds.<sup>13</sup> The [3 + n] cycloaddition of 1,2-cyclopropanated sugar, which would be an efficient method to synthesize carbohydrate-based carbo- and heterocyclic compounds, however, still remains almost unknown.<sup>6b,10b</sup> In 2003, excellent work was reported by Pagenkopf and co-workers,<sup>13</sup> which involved the [3 + 2] cycloaddition of carbohydrate-based cyclopropanated ester with nitriles. This method offered densely functionalized 3,4-dihydro-2*H*-pyrroles in high stereoselectivity; however, stoichiometric TMSOTf was required. To the best of our knowledge,

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there have been no reported cycloaddition reactions of cyclopropanated carbohydrates under catalysis conditions until this report.

Given the important role of the substituted perhydrofuro[2,3-*b*]pyrans (and *bis*-THFs), the lack of utility of cyclopropanated carbohydrates in both Lewis acid and transition metal catalyzed cycloadditions, and as part of our continuing interest in the synthesis of carbohydrate analogues,<sup>4c,10c,10d,14</sup> we disclose herein our results on an InCl<sub>3</sub> catalyzed [3 + 2] cycloaddition of cyclopropanated sugars and aldehydes.<sup>15,16</sup> This reaction offers a mild, efficient method to generate multisubstituted perhydrofuro-[2,3-*b*]pyrans (and *bis*-THFs) in high yield with excellent diastereoselectivity (Scheme 1). To our knowledge, this is the first successful example that utilizes the [3 + 2] cycloaddition between cyclopropanes and C=X (X = C, N, O) compounds to synthesize multisubstituted perhydrofuro-[2,3-*b*]pyrans and *bis*-THFs.

Scheme 1. Lewis Acid (LA) Catalyzed Cycloaddition Reaction of 1,2-Cyclopropanated Sugars with Aldehydes



Our preliminary investigation focused on the cycloaddition reaction of cyclopropanated sugar (1a) and benzaldehyde (2a). After several parameters were screened (Table S1, Supporting Information), the product 3aa was obtained in 86% isolated yield (dr = 18:1) in the presence of 20 mol %InCl<sub>3</sub> in toluene at 0–4 °C for 2 h. Subsequently, to investigate the generality of this reaction, under the optimized reaction conditions, the influence of various substituents on the phenyl ring was first studied (Table 1). The results indicated that the stereoselectivity of the [3 + 2]cycloaddition was not very sensitive to the electron density of the phenyl ring. Both electron-donating (Table 1, entry 2) and electron-withdrawing groups (Table 1, entries 4-11) provided good results. A strong electron-withdrawing group (Table 1, entries 8-11) also provided cycloaddition products in high diastereoselectivity but induced a significant variation in yield. The position of substituents on the phenyl ring also had a negligible effect on the diastereoselectivity (3ad and 3ag vs 3ah: 3ak vs 3al). Then, heteroaromatic aldehydes were subjected to the [3 + 2] cycloaddition with cyclopropanated sugar 1a, and it was found that 2-furaldehyde and 2-thenaldehyde furnished the perhydrofuro[2,3-b]pyrans in high yield with excellent stereoselectivity (Table 1, entries 12, 13); however, 2-pyridylaldehyde did not achieve the conversion (Table 1, entry 16). In addition,

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**Table 1.** InCl<sub>3</sub> Catalyzed [3 + 2] Cycloaddition between 1,2-Cyclopropanated Pyranoses **1a**, **1b** and Aldehydes<sup>*a*</sup>

	+ RH	Ind <sub>3</sub> , 20 mol % Toluene, 0-4 °C	1a: R <sub>1</sub> = OBn, R <sub>2</sub> = H 1b: R <sub>1</sub> = H, R <sub>2</sub> = OBn
OBn		OBn of T	1 · 2
1a or 1b	2	3	

			products	Т	yield	
entry	1	R	(3)	(h)	$(\%)^{o}$	$\mathrm{dr}^c$
1	1a	Ph ( <b>2a</b> )	3aa	<b>2</b>	86	18:1
<b>2</b>	1a	$4\text{-}MeC_{6}H_{4}\left( 2b\right)$	3ab	<b>2</b>	87	>20:1
3	1a	$4\text{-}BrC_{6}H_{4}\left( 2d\right)$	3ad	4	75	20:1
4	1a	$4\text{-}ClC_{6}H_{4}\left( 2e\right)$	3ae	4	72	20:1
5	1a	$2,\!4\text{-}Cl_2C_6H_4(2f)$	3af	<b>5</b>	65	20:1
6	1a	$3\text{-}BrC_{6}H_{4}\left( 2g\right)$	3ag	4	85	20:1
7	1a	$2\text{-}BrC_{6}H_{4}\left( 2h\right)$	3ah	4	83	17:1
8	1a	$4\text{-}NO_{2}C_{6}H_{4}\left(2i\right)$	3ai	16	47	13:1
9	1a	$4\text{-}CNC_{6}H_{4}\left( 2j\right)$	3aj	13	51	19:1
10	1a	$4\text{-}FC_{6}H_{4}\left( 2k\right)$	3ak	14	47	20:1
11	1a	$3\text{-FC}_{6}\text{H}_{4}\left(2l\right)$	3al	14	55	19:1
12	1a	2-furyl ( <b>2m</b> )	3am	<b>2</b>	93	20:1
13	1a	2-thienyl ( $2n$ )	3an	<b>2</b>	81	>20:1
14	1a	n-Pr ( <b>2o</b> )	3ao	1	90	>20:1
15	1a	<i>i</i> -Pr ( <b>2p</b> )	Зар	1	82	>20:1
16	1a	2-pyridyl ( $2q$ )	_	24	0	_
17	1b	Ph ( <b>2a</b> )	3ba	<b>2</b>	71	>20:1
18	1b	$4\text{-}MeC_{6}H_{4}\left( 2b\right)$	3bb	<b>2</b>	82	>20:1
19	1b	$4\text{-}MeOC_{6}H_{4}\left( 2c\right)$	3bc	<b>2</b>	85	>20:1
20	1b	$4\text{-}BrC_{6}H_{4}\left( 2d\right)$	3bd	4	74	>20:1
21	1b	$4\text{-}ClC_{6}H_{4}\left( 2e\right)$	3be	4	81	>20:1
22	1b	2-furyl ( <b>2m</b> )	3bm	4	81	>20:1
23	1b	2-thienyl ( $2n$ )	3bn	4	64	>20:1
24	1b	n-Pr ( <b>2o</b> )	3bo	<b>2</b>	86	>20:1
25	1b	<i>i</i> -Pr ( <b>2p</b> )	3bp	<b>2</b>	70	>20:1

<sup>*a*</sup> Reaction conditions: cyclopropanated sugar **1a** or **1b** (0.1 mmol), aldehyde (0.4 mmol),  $InCl_3$  (0.02 mmol), toluene (1 mL), 0 to 4 °C. <sup>*b*</sup> Yield of isolated product. <sup>*c*</sup> The dr was determined by <sup>1</sup>H NMR.

the linear aliphatic aldehyde (Table 1, entry 14) and branched aliphatic aldehyde (Table 1, entry 15) were also suitable substrates for the reaction, which offered the 2-al-kyl-substituted perhydrofuro[2,3-*b*]pyrans in good yield and stereoselectivity.

Having successfully achieved the synthesis of glucosebased perhydrofuro[2,3-*b*]pyrans, we next explored the generality of the reaction by using galactose derivatives. Therefore, treatment of 1,2-cyclopropanated galactose **1b** with aromatic (Table 1, entries 17–21), heteroaromatic (Table 1, entries 22 and 23), linear aliphatic (Table 1, entry 24), and branched aliphatic (Table 1, entry 25) aldehydes in the presence of InCl<sub>3</sub> (20 mol %) smoothly afforded the desired cycloaddition products in good yield with excellent diastereoselectivity. Compared to the cyclopropanated glucose, the yields of the reaction between 1,2-cyclopropanated galactose and aldehydes are slightly reduced, which can be rationalized by the high reactivity of the cyclopropanated galactose, <sup>10c</sup> leading to some other byproducts as detected by TLC.

After successful construction of persubstituted perhydrofuro[2,3-*b*]pyrans from 1,2-cyclopropanated pyranose derivatives, we then focused on the synthesis of substituted perhydrofuro[2,3-*b*]furans (*bis*-THFs) via a similar strategy. Based on this, the furanosyl 1,2-cyclopropanated ketone **1c** was prepared,<sup>17</sup> and the scope of the [3 + 2] cycloaddition under the standard conditions was further investigated (Scheme 2). Therefore, a series of substituted *bis*-THFs, which possess a wide occurrence in medicine,<sup>1-3</sup> were obtained from furanosyl 1,2-cyclopropanated ketone **1c**. While the yield of the reaction is moderate, nonetheless, the diastereoselectivity is still excellent. Cycloadditions of 1,2-cyclopropanated ketone **1c** with linear aliphatic and branched aliphatic aldehydes were exceptionally interesting because the products all had similar substituents and stereochemistry as Asteltoxin, which is a latent inhibitor of oxidative phosphorylation.<sup>3</sup>

**Scheme 2.** [3 + 2] Cycloaddition between 1,2-Cyclopropanated Lyxose **1c** and Aldehydes<sup>a-c</sup>



<sup>*a*</sup> Reaction conditions: cyclopropanated sugar **1c** (0.1 mmol), aldehyde (0.4 mmol), InCl<sub>3</sub> (0.02 mmol), toluene (1 mL), 0 to 4 °C. <sup>*b*</sup> Yield of isolated product. <sup>*c*</sup> Unless otherwise noted dr > 20:1.

All products generated in the study have a similar coupling constant (for furan[2,3-*b*]pyrans  $J_{(H7a,H3a)} = 4.0-5.1$  Hz, for furan[2,3-*b*]furans  $J_{(H6a,H3a)} = 5.1-5.9$  Hz), which suggested the fused ring systems have [2,3-*b*]-*cis*-bicyclic stereochemistry.<sup>1a,4</sup> The structure of bicycles was determined by the <sup>1</sup>H NMR, <sup>1</sup>H-<sup>1</sup>H COSY, and NOESY<sup>17</sup> and was further confirmed by X-ray crystallographic analysis of compound **3bb**.<sup>18</sup>

<sup>(17)</sup> See the Supporting Information for details.

<sup>(18)</sup> CCDC 914931 (**3bb**) contains the supplementary crystallographic data for this study. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam. ac.uk/ data request/cif.

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Based on the results of the experiments, a plausible mechanism is proposed for the InCl<sub>3</sub>-catalyzed [3 + 2] cycloaddition between 1,2-cyclopropanated sugars and aldehydes (Scheme 3). First, InCl<sub>3</sub> coordinated to the keto-carbonyl of the cyclopropane and induced the ring opening of cyclopropane to form zwitterionic intermediate **A**, which is expected to form the indium enolate (**pathway A**).<sup>19</sup> Subsequently, aldehydes trapped the anomeric oxocarbenium ion from either the  $\beta$ - or  $\alpha$ -face producing the intermediate **B** and **C** respectively.<sup>13</sup>

Scheme 3. Plausible Mechanism of InCl<sub>3</sub> Catalyzed [3 + 2] Cycloaddition between Cyclopropanated Pyranoses and Aldehydes



Then, intermediate **B** isomerizes to **C** via zwitterionic **A** due to the anomeric effect,<sup>20</sup> and intermediate **C** was ultimately recyclized via transient state **D**, through an intramolecular aldol-type reaction to form the bicyclic compound.<sup>21,22</sup>

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(22) It is also possible that after the ring opening of the cyclopropanes, the aldehydes reacted with the formed zwitterionic via an aldol-type reaction to form the oxygen anions, which were further reacted with the anomeric oxonium ion to generate the fused-ring products, as Yokoe and co-workers reported (see ref 9). However, in this case, the electron poor aldehydes should react faster than the electron rich aldehydes. Thus, this process can be ruled out. Whereas, if the aldehydes reacted with the anomeric oxonium ion to generate another oxonium ion first, then the produced intermediate carried out the intramolecular aldol-type reaction; the rate-limiting step for this reaction would be the reaction between the aldehyde and the oxoium ion. This coincides with the results of our experiments.

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Alternatively, after  $InCl_3$  coordinated to the keto-carbonyl of cyclopropane, aldehydes can act as a nucleophile to assist the cyclopropane ring opening (**pathway B**).<sup>7b-d</sup> This pathway could form the intermediate **B** mainly due to steric hindrance. For pyranosyl cyclopropane ketones, both of the two pathways perhaps exist in our reaction system. However, for the furanosyl cyclopropane, we favor **pathway A** over **pathway B** due to the lack of equilibrium between intermediate **B** and **C**.

Therefore, for the furanosyl 1,2-cyclopropanated lyxose, after  $InCl_3$  activated the cyclopropane, the ring opening of 1,2-cyclopropane followed and formed a furanbased zwitterionic intermediate **E**, in which the C3-OBn group resided in a pseudo axial position and the alkoxymethyl group at C-4 and the C-branch in C-2 were in a pseudo equatorial position. Then, aldehydes approached intermediate **E** via an inside attack model,<sup>23</sup> followed by recyclization through an aldol-type reaction process as shown in Scheme 4, to obtain the *bis*-THF products.

**Scheme 4.** Plausible Mechanism of InCl3 Catalyzed [3 + 2] Cycloaddition between 1,2-Cyclopropanated Lyxose and Aldehydes



In summary, we have developed a novel [3 + 2] cycloaddition reaction catalyzed by InCl<sub>3</sub> using 1,2-cyclopropanated sugars as a new type of reagent. The cycloaddition between cyclopropanated sugars and aldehydes is efficient and provides a general method to construct substituted perhydrofuran[2,3-*b*]pyrans and *bis*-THFs. This method offers several advantages, i.e., excellent diastereoselectivity, a large range of functional group compatibility, and simplicity in operation, making it a useful and attractive strategy for the synthesis of some natural products and other carbohydrate analogues. Further investigations of the scope of this reaction and of the biological activities of these compounds will be undertaken.

Acknowledgment. This work was supported by the Chinese Academy of Sciences (Hundreds of Talents Program) and the National Science Foundation of China (20972151 and 21372215).

Supporting Information Available. Experimental procedures; characterization data for all new compounds;  ${}^{1}H-{}^{1}H$  COSY for **3an**; and NOESY for **3an**, **3bn**, and **3cb**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.