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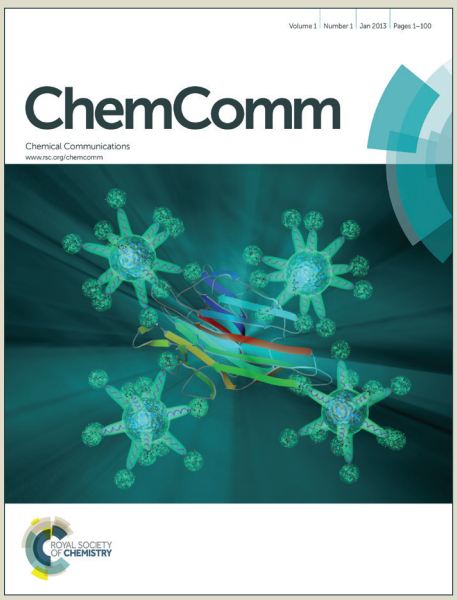

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ARTICLE TYPE

Stereospecific [3+2] Cycloaddition of 1,2-Cyclopropanated Sugars and Ketones Catalyzed by $SnCl_4$: an Efficient Synthesis of Multi-Substituted Perhydrofuro[2,3-*b*]furans and Perhydrofuro[2,3-*b*]pyrans

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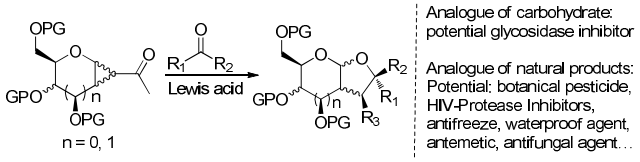
Stereospecific [3+2] cycloaddition of 1,2-cyclopropanated sugars and ketones catalyzed by $SnCl_4$ is described. The method offers multi-substituted perhydrofuro[2,3-*b*]furans (*bis*-THFs) and perhydrofuro[2,3-*b*]pyrans containing a quaternary carbon chiral center in good to excellent yields.

Much effort have been devoted to discovery and study of new stoichiometric or catalytic reactions that employed vicinal donor–acceptor (DA) cyclopropanes in recent years.[1] This powerful and versatile synthon fascinated the synthetic and pharmaceutical chemists not only because they could react with a wide range of nucleophiles and electrophiles.[1b] In the presence of Lewis acid, the doubly activated cyclopropanes could also form 1,3-zwitterionic intermediates which can be trapped by an array of unsaturated bond including carbonyl, imine, nitrone and so on, to form five-, six-, seven-membered carbocycles and heterocycles via [3+n] (n = 2, 3, 4) cycloaddition.[1a, 1c] Among them, the [3+2] cycloaddition between cyclopropanes and carbonyl compounds, especially, the aldehydes,[2] are undoubtedly the strongest and particularly versatile ones, since they offer a powerful strategy to highly stereoselective construction of tetrahydrofurans (THFs). Due to the pioneering works by Johnson and co-workers in 2005,[2j] the [3+2] cycloaddition of D-A cyclopropanes and aldehydes has been extensively investigated.[2] By contrast, only very few researches have been conducted in applying the less reactive ketones, especially, the nonsymmetrical ketones, as the reaction partners for this cycloaddition.[3]

Furthermore, D-A cyclopropanated carbohydrates, which combining the high reactivity of cyclopropanes together with multi-functional group and multi-chiral-centre associated with sugars,[4] were also extensively used to synthesize 2-*C*-branched glycosides,[5] ring expanded to oxepanes[6] or other carbohydrates based heterocyclic compounds.[7] The [3+2] cycloaddition of cyclopropanated carbohydrates, however, much less been mentioned.[8]

Perhydrofuro[2,3-*b*]pyran (and furan) derivatives are broadly found in a large number of structurally complex and bioactive compounds including novaxenicins A, B, C, stemona alkaloids, euplotin C,[9] communiol D,[10] Asteltoxin,[11] and TMC-114.[12] Among them, TMC-114 has been approved by the FDA (named as Darunavir) for AIDS treatment.

Owing to the great structural diversity and wide-ranging biological activity of perhydrofuro[2,3-*b*]pyrans (furans), the construction of these subunits continue to attract the interest of both synthetic and pharmaceutical chemists.[9-12] In this context, and continuation of our previous work on the synthesis of carbohydrate derivatives, we envisioned that the multi-substituted 5/6 or 5/5 fused bicyclic compounds would be used as analogues of the natural products to work as a potential botanical pesticide, antifreeze, waterproof agent, antiemetic and antifungal agent.[9c,-9e] Also, they may be tested as potential glycosidase inhibitor.[13] Recently, started from 2-*C*-branched sugar, we developed a NIS-promoted intramolecular cyclization to synthesize 2-substituted perhydrofuro[2,3-*b*]pyrans.[9c] In continuation of our works to develop new synthetic methodologies, herein, we report our results on synthesis of 2,2,3-tri-substituted perhydrofuro[2,3-*b*] pyrans (furans) via [3+2] cycloaddition of cyclopropanated sugars and ketones (Scheme 1). With excellent diastereoselectivity and wide range of functional groups compatibility, this reaction offers the example that utilizes [3+2] cycloaddition between cyclopropanes and ketones to construct multisubstituted perhydrofuro[2,3-*b*]pyrans and *bis*-THFs, in which containing a quaternary carbon chiral center.[14] To the best of our knowledge, this is the first successful example that utilizes cyclopropanes and ketones as starting material for the [3+2] cycloaddition.[15]



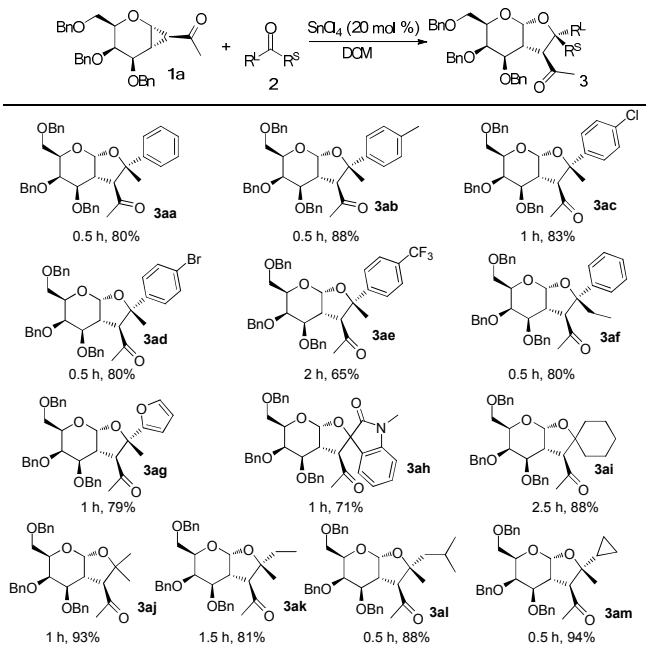
Scheme 1. [3+2] Cycloaddition of 1,2-Cyclopropanated Sugars and Ketones.

Initial studies were performed with Lewis acid in CH_2Cl_2 using cyclopropanated sugar **1a** and acetophenone **2a** as model substrates to screen the reaction conditions. Then, 20 mol % $SnCl_4$ in CH_2Cl_2 at 0-4 °C was chosen as the optimal conditions for the [3+2] cycloaddition. Under these conditions, the cycloaddition product **3aa** was obtained in 80% yield as a single diastereoisomer.

Subsequently, the scope of the methodology was evaluated. The results were summarized in Table 1. Initially, various substituted acetophenone with different substitution patterns and

electronic properties were examined. Gratifyingly, it was found that the stereoselectivity of the [3+2] cycloaddition was not very sensitive to various substrates. In all case, electron-rich (**3ab**) and electron-poor substituted acetophenone (**3ac-3ae**) achieved the products in good to excellent yield, and each product was isolated as a single diastereoisomer. A strong electron-withdrawing group (**3ae**) also provided cycloaddition product in high diastereoselectivity, but led to the yield reduced slightly. The propiophenone was also suitable substrate for this reaction, offered the fused-ring product in 80% yield (**3af**). Heteroaromatic ketone such as 2-acetylfuran (**3ag**) was tolerated, while basic 4-acetylpyridine made the reaction no conversion, only the starting material was recovered. Then, symmetric (**3ai**, **3aj**) and asymmetric (**3ak-3am**) aliphatic ketones were subjected to the [3+2] cycloaddition of cyclopropanated sugar **1a**, and achieved the 2,2-di-alkyl-substituted fused-ring products in good to excellent yields and high stereoselectivity. Especially, when *N*-methyl-isatin was employed in the reaction, we obtained spirocycle oxindole framework (**3ah**), which is a privileged structural motif in a large number of natural products and biological active molecules,[16] in 79% yield.

Table 1. $SnCl_4$ Catalyzed [3+2] Cycloaddition between 1,2-Cyclopropanated Sugar **1a** and ketones. [a,b]

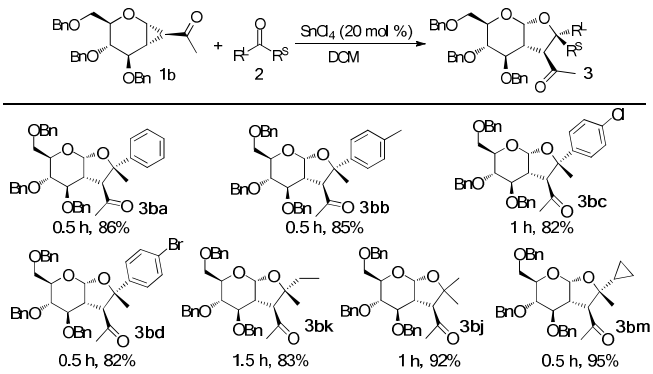


[a]All reactions were performed with cyclopropanated sugar **1a** (0.1 mmol), ketones **2** (0.4 mmol), $SnCl_4$ (0.02 mmol), in CH_2Cl_2 (1 mL) at 0 °C to 4 °C. [b] Isolated yield.

The scope of the [3+2] cycloaddition of cylcopropanated sugar and ketones was further extended to 1,2-cyclopropanated sugar **1b**, and the results are described in Table 2. The cyclopropanated sugar **1b** is also the suitable substrate for the [3+2] cycloaddition. Under the standard reaction conditions, the glucose-based six-five fused ring products were obtained in good to excellent yields. Consistent with the previous results, all of the reaction only offered a single diastereoisomer.

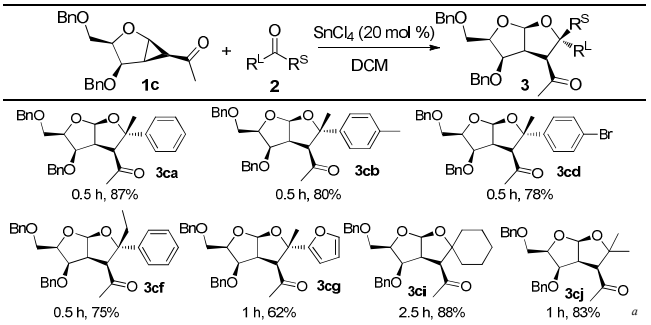
Given the importance of the *bis*-THF framework and the difficulties in the [3+2] cycloadditions of cyclopropanes with ketones, we then turned our attention to furanosyl 1,2-cyclopropanated carbohydrate to synthesize multi-perhydrofuro [2,3-*b*]furans (*bis*-THFs) and further investigate the generality of the cycloaddition. Thus, started from furanosyl 1,2-cyclopropanated sugar **1c** and a series of aromatic, aliphatic, and heteroaromatic ketones, we successfully synthesized a range of *bis*-THF bearing multiple contiguous stereocenters, including a quaternary carbon chiral center (Table 3).

Table 2. [3+2] Cycloaddition between 1,2-Cyclopropanated Sugar **1b** and ketones. [a,b]



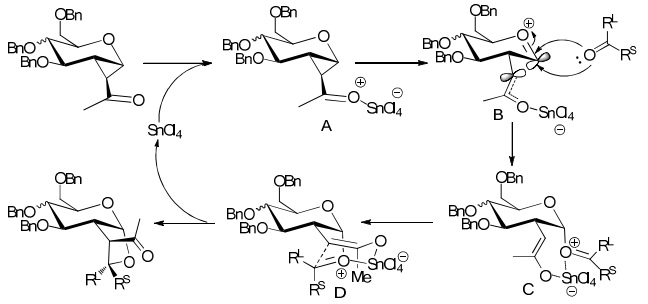
[a]All reactions were performed with cyclopropanated sugar **1b** (0.1 mmol), ketones **2** (0.4 mmol), $SnCl_4$ (0.02 mmol), in CH_2Cl_2 (1 mL) at 0 °C to 4 °C. [b] Isolated yield.

Table 3. $SnCl_4$ Catalyzed [3+2] Cycloaddition between 1,2-Cyclopropanated Sugar **1c** and ketones. [a,b]



All reactions were performed with cyclopropanated sugar **1c** (0.1 mmol), ketones **2** (0.4 mmol), $SnCl_4$ (0.02 mmol), in CH_2Cl_2 (1 mL) at 0 °C to 4 °C. [b] Isolated yield.

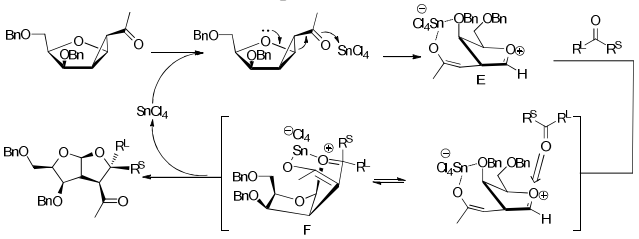
Based on above results, a plausible reaction mechanism is proposed for the formation of perhydrofuro[2,3-*b*]pyrans (Scheme 2). The coordination of $SnCl_4$ to the oxygen of ketone, followed by the ring-opening of the cyclopropane produced the intermediate **B**. Subsequently, ketones worked as nucleophiles[2b,2d-2g] approached the anomeric oxonium ion mainly to gain **C** due to the anomeric effect.[17] Then, intermediate **C** re-cyclized via transition state **D** through aldol-type reaction to



Scheme 2. Possible Reaction Mechanism for the Formation of Perhydrofuro[2,3-*b*]pyrans Catalyzed by $SnCl_4$

afford the fused bicyclic compounds.[18]

The formation of the furan[2,3-*b*]furans can also be explained by the similar process. The coordination of $SnCl_4$ with the keto-carbonyl of the cyclopropane induced the ring-opened to form zwitter-ionic intermediate **E**. Subsequently, ketones attacked to the zwitter-ionic intermediate **E** from the inside,[19] which followed by an intramolecular aldol-type reaction through intermediate **F** furnished the products.



Scheme 3. Possible Reaction Mechanism for the Formation of Perhydrofuro[2,3-*b*]furans Catalyzed by $SnCl_4$

In conclusion, we firstly demonstrated a very simple, efficient and practical method for [3+2] cycloaddition between 1,2-cyclopropanated sugars and ketones in the presence of catalytic amount of Tin (IV) chloride. This method offers several advantages, i.e., a large range of functional group compatibility and very high diastereoselectivity. Under the conditions, the corresponding cyclopropanated sugars underwent stereospecific functionalization with ketones to give the multi-substituted perhydrofuro[2,3-*b*]pyrans and *bis*-THFs bearing a quaternary carbon chiral center in good to excellent yields. The further application of the [3+n] strategy for the synthesis of some other carbohydrate-based fused-ring compounds will be undertaken.

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Notes and references

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† Electronic Supplementary Information (ESI) available: general procedures, spectral data and other supplementary information. See DOI: 10.1039/b000000x/

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