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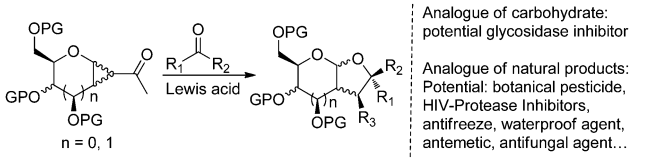
Stereospecific [3+2] cycloaddition of 1,2-cyclopropanated sugars and ketones catalyzed by $SnCl_4$ is described. The method offers multi-substituted perhydrofuro[2,3-*b*]furans (bis-THFs) and perhydrofuro-[2,3-*b*]pyrans containing a quaternary carbon chiral center in good to excellent yields.

Much effort has been devoted to the discovery and study of new stoichiometric or catalytic reactions that employed vicinal donor–acceptor (D–A) cyclopropanes in recent years.[1] These powerful and versatile synthons 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 bonds 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,c] 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 for highly stereoselective construction of tetrahydrofurans (THFs). Due to the pioneering studies of 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 little research has 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 combine the high reactivity of cyclopropanes together with those of multi-functional groups and multi-chiral-centres associated with sugars,[4] were also extensively used to synthesize 2-*C*-branched glycosides,[5] ring expanded oxepanes[6] or other carbohydrate based heterocyclic compounds.[7] The [3+2] cycloaddition of cyclopropanated carbohydrates has, however, been much less 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 (called darunavir) for AIDS treatment.

Owing to the great structural diversity and the wide-range of biological activities of perhydrofuro[2,3-*b*]pyrans (furans), the construction of these subunits continues to attract the interest of both synthetic and pharmaceutical chemists.[9–12] In this context, and in 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 potential botanical pesticides, antifreezes, waterproof agents, antiemetic and antifungal agents.[9c–e] Also, they may be tested as potential glycosidase inhibitors.[13] Recently, starting 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 studies on the development of 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 compatibility of a wide range of functional groups, this reaction offers an example that utilizes [3+2] cycloaddition between cyclopropanes and ketones to construct multi-substituted perhydrofuro-[2,3-*b*]pyrans and bis-THFs, which contain a quaternary carbon



Scheme 1 [3+2] Cycloaddition of 1,2-cyclopropanated sugars and ketones.

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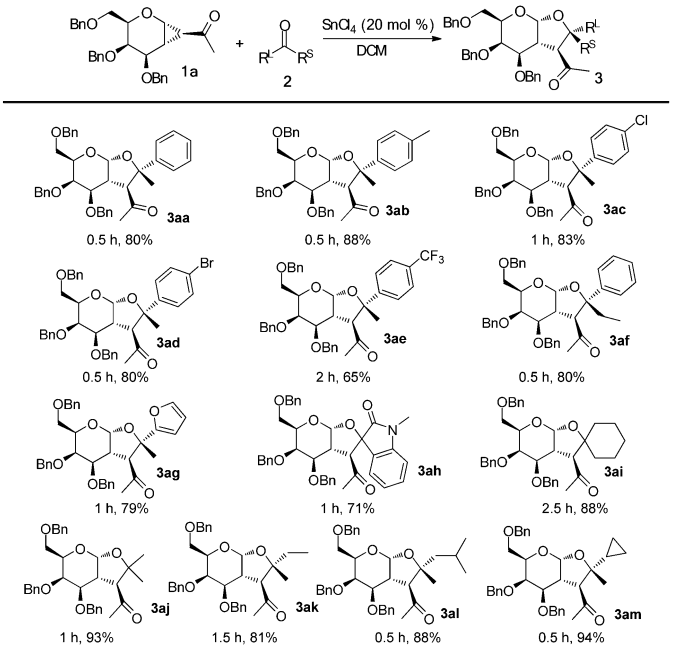
Table 1 $SnCl_4$ catalyzed [3+2] cycloaddition between 1,2-cyclopropanated sugar **1a** and ketones[a,b]



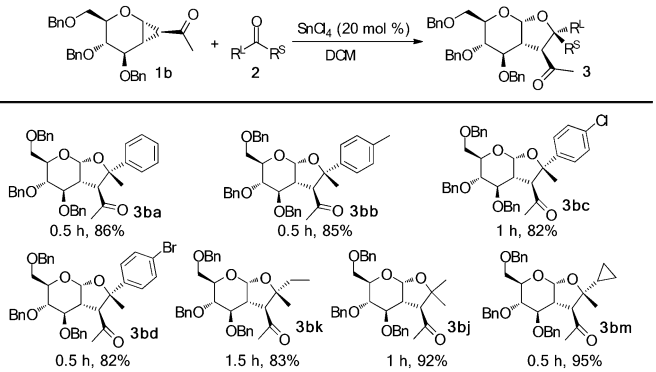
[a] All reactions were performed with cyclopropanated sugar **1a** (0.1 mmol), ketones **2** (0.4 mmol), $SnCl_4$ (0.02 mmol), in CH_2Cl_2 (1 mL) at 0 °C to 4 °C. [b] Isolated yield.

chiral center.[14] To the best of our knowledge, this is the first successful example that utilizes acetyl-1,2-cyclopropaned sugars and ketones as starting materials for the [3+2] cycloaddition.[15]

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 condition 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 are 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 cases, electron-rich (**3ab**) and electron-poor substituted acetophenones (**3ac**–**3ae**) achieved the products in good to excellent yields, and each product was isolated as a single diastereoisomer. A strong electron-withdrawing group (**3ae**) also provided the cycloaddition product in high diastereoselectivity, but led to a slightly reduced yield. Propiophenone was also a suitable substrate for this reaction, which offered the fused-ring product in 80% yield (**3af**). Heteroaromatic ketone such as 2-acetylfuran (**3ag**) was tolerated, while basic 4-acetylpyridine enabled the reaction to proceed with 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 the 2,2-di-alkyl-substituted fused-ring products were achieved in good to excellent yields and high stereoselectivity. Especially, when

Table 2 [3+2] Cycloaddition between 1,2-cyclopropanated sugar **1b** and ketones[a,b]



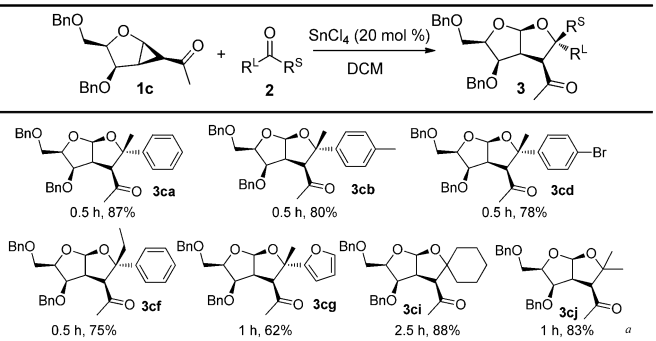
[a] All reactions were performed with cyclopropanated sugar **1b** (0.1 mmol), ketones **2** (0.4 mmol), $SnCl_4$ (0.02 mmol), in CH_2Cl_2 (1 mL) at 0 °C to 4 °C. [b] Isolated yield.

N-methyl-isatin was employed in the reaction, we obtained a spirocycle oxindole framework (**3ah**), which is a privileged structural motif in a large number of natural products and biologically active molecules,[16] in 79% yield.

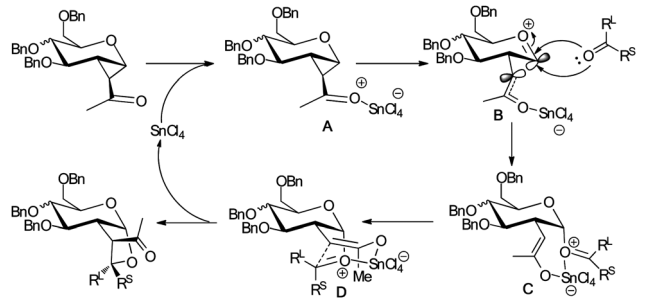
The scope of the [3+2] cycloaddition of cyclopropanated sugar and ketones was further extended to 1,2-cyclopropanated sugar **1b**, and the results are provided in Table 2. The cyclopropanated sugar **1b** is also the suitable substrate for the [3+2] cycloaddition. Under the standard reaction conditions, perhydrofuro[2,3-*b*]-pyran derivatives were obtained in good to excellent yields. Consistent with the previous results, all of the reactions 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-substituted perhydrofuro [2,3-*b*]furans (bis-THFs) and further investigate the generality of the cycloaddition. Thus, starting 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).

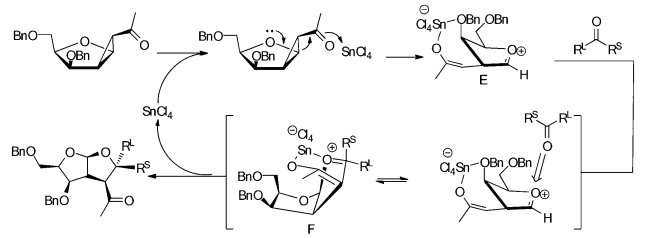
Table 3 $SnCl_4$ catalyzed [3+2] cycloaddition between 1,2-cyclopropanated sugar **1c** and ketones[a,b]



[a] 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.



Scheme 2 Possible reaction mechanism for the formation of perhydrofuro[2,3-*b*]pyrans catalyzed by $SnCl_4$.



Scheme 3 Possible reaction mechanism for the formation of perhydrofuro[2,3-*b*]furans catalyzed by $SnCl_4$.

Based on the 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 working as nucleophiles[2b,d–g] approached the anomeric oxonium ion mainly to gain **C** due to the anomeric effect.[17] Then, intermediate **C** was re-cyclized *via* transition state **D** through aldol-type reaction to afford the fused bicyclic compounds.[18]

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

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 a catalytic amount of tin(IV) chloride. This method offers several advantages, *i.e.*, compatibility of a large range of functional groups and very high diastereoselectivity. Under the reaction 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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