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Research Article

Saccharide-Assisted Resolution of Bioactive Chiral Carboxylic Acids via NHC-Catalyzed Regioselective Transesterification

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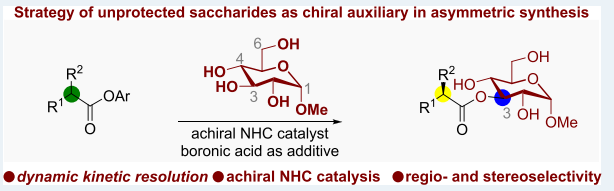
ABSTRACT: The utility of unprotected saccharides as chiral auxiliaries in asymmetric synthesis remains largely undeveloped despite their ready availability, configurational diversity, and chiral purity. Here, we disclose an efficient achiral NHC catalytic strategy to regioselectively install racemic α,α-disubstituted carboxylic esters on specific OH groups of saccharides and simultaneously achieve their dynamic kinetic resolution, which makes unprotected saccharides effective chiral auxiliaries. Multiple controlling parameters, including stereoelectronic and steric effects, are employed to ensure regioselectivity amplification and stereodifferentiation. By varying the structures of NHC catalysts, this strategy is suitable for dynamic kinetic resolution of diverse racemic targets by installing them on different OH sites of structurally diverse unprotected saccharides, greatly expanding the application of saccharides in asymmetric synthesis.



KEYWORDS: *unprotected saccharide, chiral auxiliary, NHC catalysis, dynamic kinetic resolution, regio- and stereoselective*

INTRODUCTION

Chirality is one of the fundamental characteristics of nature's living system.[1] As prominent members of the chiral source, naturally occurring amino acids, nucleotides, and saccharides serve as versatile chirality precursors for diverse chiral catalysts, ligands, and auxiliaries (Scheme 1a).[2] For example, classical chiral reagents such as 2-oxazolidone, aminophosphines and alkaloids are all derived from amino acids.[3] Saccharides, as a major category of natural chiral molecules, contain the highest density of functional groups and defined stereogenic centers in a single small molecule, making them prime chiral pool candidates for controlling asymmetric synthesis.[4] To date, several chiral saccharides have been developed and applied in stereocontrolled chemical reactions.[5] However, compared to amino acids, the utility of saccharides as chiral reagents in asymmetric synthesis and catalysis lags far behind, and is mainly limited to the study of multiprotective saccharides (Scheme 1b). For instance, the well-known Shi epoxidation catalyst, disclosed by Shi and co-workers, is a series of multiprotected D-fructose-derived chiral ketones, which have proven to be an extremely powerful tool for obtaining optically active epoxides.[5a,b] The pre-*O*-pivaloylated galactosyl amine reported by Kunz and Sager[5c] as chiral auxiliary, showed excellent performance in asymmetric reactions, such as Ugi,[5d] Mannich[5e] and Diels−Alder.[5f] Currently, the study of unprotected saccharides as chiral auxiliaries in asymmetric synthesis has been rarely explored, despite their ready availability, configurational diversity and chiral purity. The main obstacle lies in the lack of efficient synthetic tools to ensure good site-selective reactions on many similar OH groups of saccharides while simultaneously guaranteeing good stereoselectivity of the target. Given the multiple similar OH groups of saccharides, introducing more controlling parameters that can provide stereoelectronic or steric effects to achieve effective regioselectivity amplification and stereodifferentiation could offer attractive solutions to make unprotected saccharides good auxiliaries. In recent years, we have been interested in developing a multilayered selectivity-amplification strategy to site-selectively modify certain OH groups in unprotected saccharides.[6] Considering that unprotected saccharides have the advantage of being widely available, abundant, and cheap, site-selectively installing racemic targets on certain OH groups of unprotected saccharides to deliver their dynamic kinetic chiral resolution will greatly expand the application of saccharides in asymmetric synthesis.

Carboxylic acids and related carbonyl derivatives bearing two substituents at the stereogenic α-carbon center are widely found in pharmaceutical molecules.[7] For example, *R*-flurbiprofen has been found to offer neuroprotective effects by inhibiting mitochondrial calcium overload in Alzheimer's disease, while *S*-flurbiprofen shows good anti-inflammatory activity.[8] Asymmetric synthesis of such single mirror-image α,α-disubstituted carbonyl compounds is of great significance

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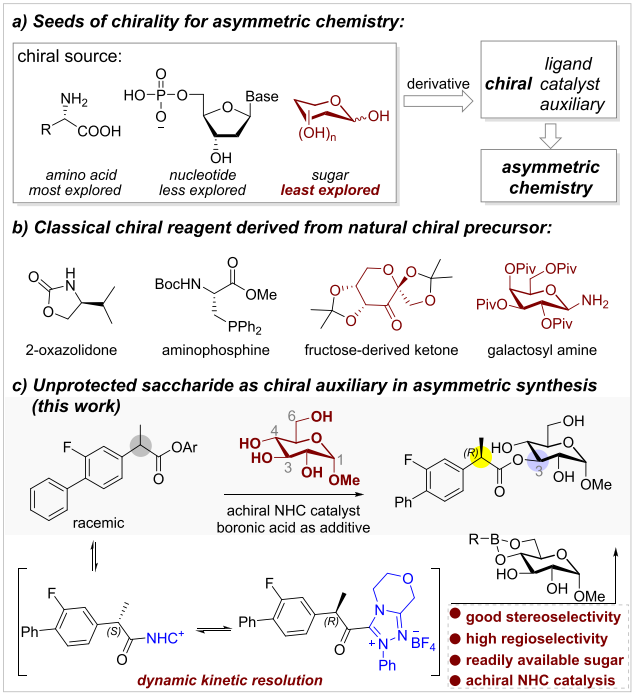
Scheme 1. (a–c) Strategy of Unprotected Saccharides as Chiral Auxiliary in Asymmetric Synthesis

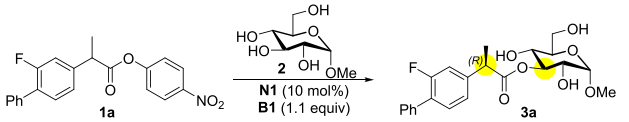


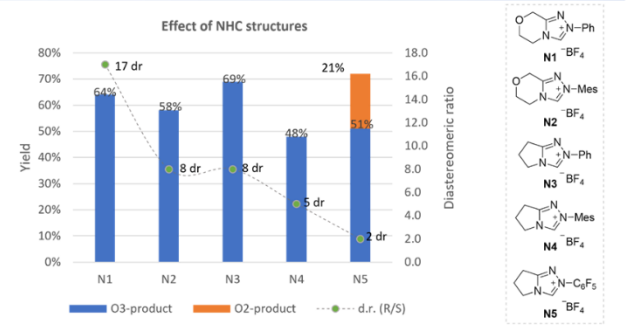
for drug development. Here, we explore unprotected saccharides as chiral auxiliaries and disclose an efficient strategy for the dynamic kinetic chiral resolution of α,α-disubstituted carbonyl compounds through site-selective installation of racemic targets on specific OH groups of unprotected saccharides (Scheme 1c). Using α-methyl glucoside as a model example, flurbiprofen can be site-selectively installed on the C(3)-OH group mediated by *N*-heterocyclic carbene (NHC) and boronic acid to generate the corresponding optically pure flurbiprofen-glucoside ester. The dynamic formation of boronic ester provides transient protection for the C(4,6)-OH groups in glucoside to offer regioselective control[9] and simultaneously facilitates the arrangement of the reacting group relative to shielding or coordinating effects, leading to distinct stereodifferentiation. Additionally, the NHC catalyst reacts with the active ester of flurbiprofen to form an acyl azolium intermediate.[10] The preferred *R*-type optical isomer proceeds with transesterification with the boronic ester, while the *S*-type isomer undergoes racemization under standard conditions. These processes ultimately promote the dynamic kinetic resolution of flurbiprofen, where multiple parameters involving stereoelectronic effects and covalent or noncovalent interactions brought by saccharides, boronic acids, and NHC catalysts synergistically regulate the regio- and stereoselectivity. This strategy can be easily tuned for different OH sites in various configurations of saccharides by varying the structures of boronic acids and NHC catalysts, resulting in the dynamic kinetic resolution of diverse racemic targets.

METHODS

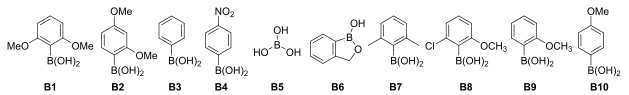
To start, we employed the active ester of flurbiprofen **1a** and glucoside **2** as model substrates to explore the reaction conditions. In accordance with our previous observations,[6a] the use of NHC as a catalyst in association with boronic acid as a cocatalyst successfully led to site-selective transesterification. Summarized in Scheme 2 are the key results of the model reaction from extensive studies on the effects of achiral NHC

Scheme 2. Conditions for Unprotected Saccharides as Chiral Auxiliary in Asymmetric Synthesis





Entry	Variation from standard conditions	Yield [%][b]	dr[c] (*R*/*S*)
1	none[a]	64	17/1
2	**N2** instead of **N1**	58	8/1
3	**N3** instead of **N1**	69	8/1
4	**N4** instead of **N1**	48	5/1
5	**N5** instead of **N1**	72 (O3:O2=5:2)	2/1
6	**B2** instead of **N1**	11	5/1
7	**B3** instead of **B1**	trace	-
8	**B4** instead of **B1**	trace	-
9	**B5** instead of **B1**	5	5/2
10	**B6** instead of **B1**	5	2/5
11	**B7** instead of **B1**	33 (O3:O2:O6=24:4:5)	5/1
12	**B8** instead of **B1**	38 (O3:O2:O6=33:2:3)	7/1
13	**B9** instead of **B1**	8	6/1
14	**B10** instead of **B1**	trace	-
15	Without $ArB(OH)_2$	14 (O3:O2:O6=9:2:3)	4/5



[a]Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2** (0.11 mmol, 1.1 equiv), **N1** (0.01 mmol, 10 mol %), **B1** (0.11 mmol, 1.1 equiv), *t*-BuOLi (0.05 mmol, 0.5 equiv), ethyl acetate (2 mL), 4 Å MS (100 mg), 30 °C, 12 h. [b]NMR yield (paraiodoanisole was used as internal standard). [c]Diastereomeric ratio (dr) determined by ^{1}H NMR of the crude C(3)-OH acylated product.

catalysts and boronic acids on regio- and stereoselectivity. The combination of **N1** and **B1** produced the corresponding product **3a** with high regio- and stereoselectivity (entry 1). Replacing the phenyl group (**N1**) with a trimethylphenyl group (**N2**) in the NHC catalyst (entry 2) or subtly changing the structure from **N1** to **N3** (entry 3) led to a significant drop in the diastereomeric ratio, while the reaction yields and regioselectivity remained basically unchanged. The use of NHC catalyst **N5** produced the product with a higher total yield but extremely lower regio- and stereoselectivity (entry 5).

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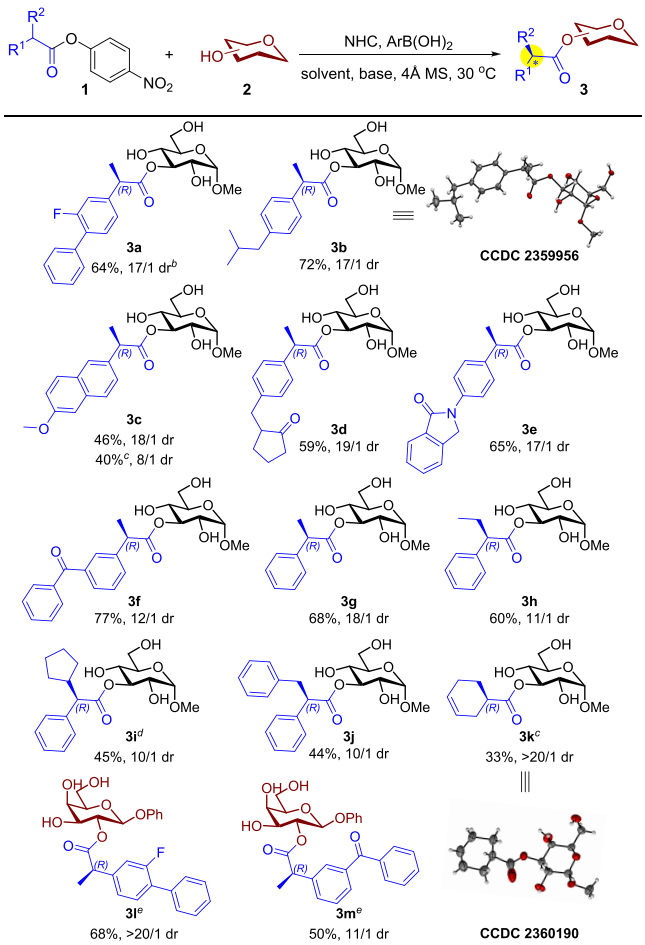
Additionally, adjusting the position of substituents on the phenyl ring of boronic acid (**B1** to **B2**) led to a profound decrease in yield and diastereomeric ratio (entry 6). Removing one or both methoxy substituents on the phenyl ring of boronic acid (**B1** to **B3**, **B9**) resulted in no or very small amounts of product (entry 7, 13). While keeping the substituent position unchanged, simply modulating the type of substituents in boronic acid (**B1** to **B7**, **B8**) also had a serious impact on the results (entry 11, 12). The absence of boronic acid led to minimal product with low yield and selectivity (entry 15). These findings clearly show that the structures of both NHC catalysts and boronic acids dramatically affect reaction yields and selectivity. Therefore, it is feasible to engineer these effects in a combinatorial manner to realize unprotected saccharides as chiral auxiliaries in asymmetric synthesis.

The scope and applications of our strategy using active esters of racemic α,α-disubstituted carbonyl compounds as targets were evaluated (Scheme 3). Using D-glucoside as a model saccharide, the combination of **N1** and **B1** worked effectively for selective C(3)-OH esterification of glucoside and dynamic kinetic resolution of various α,α-disubstituted carbonyl substrates to obtain optically pure *R*-type products. A series of nonsteroidal anti-inflammatory and analgesic drugs, such as ibuprofen, loxoprofen, indoprofen, and ketoprofen, were successfully installed on the C(3)-OH group of glucoside with good yield and diastereomeric ratio (**3a**-**3f**). Various commonly encountered functional groups such as halides, ether, carbonyl, and amide were well tolerated. Notably, the employment of optically pure *S*-type naproxen also resulted in the formation of the *R*-type product (**3c**), albeit with a slightly lower diastereomeric ratio, indicating the presence of racemization and dynamic kinetic resolution process in the reaction. Additionally, we were pleased to find that the α-methyl group can be replaced by more sterically demanding substituents such as ethyl (**3h**), cyclopentyl (**3i**), and benzyl groups (**3j**), demonstrating the generality of the reaction. Of note, the *S*-type cyclohexenyl-substituted carbonyl substrate was also compatible with the reaction conditions, affording the corresponding *R*-type product **3k**. Among these products, the structure of **3b** and **3k** were unambiguously assigned by X-ray diffraction analysis.[11] To verify the flexibility of the strategy, we also explored the conditions for the selective reaction between galactoside and flurbiprofen. To our delight, when the combination of **N3** and **B2** was employed, flurbiprofen was successfully installed on the C(2)-OH group of galactoside, resulting in the corresponding product **3l** with excellent regio- and stereoselectivity. Based on these results, it is reasonable to expect dynamic kinetic resolution of diverse racemic targets through site-selective transesterification on different OH groups of various types of saccharides.

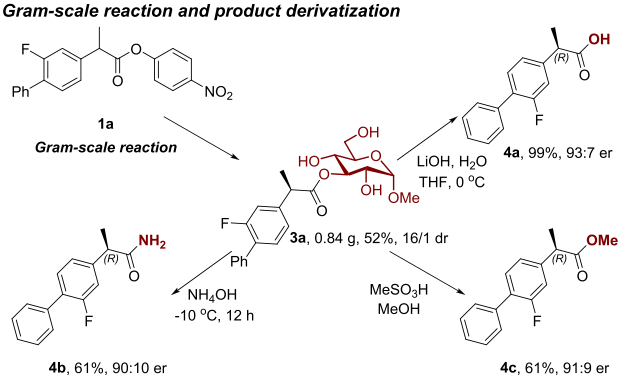
The practicality of the protocol was evidenced by the efficient Gram-scale synthesis of optically pure flurbiprofen-glucoside compound **3a** with good regio- and stereoselectivity under standard conditions (Scheme 4). To assess the synthetic utility of the product, various transformations of the ester bond were carried out. For example, *R*-type flurbiprofen **4a** with high enantiomeric ratio (er) can be obtained by hydrolysis of ester **3a** under alkaline conditions.[12] Amine exchange of **3a** with ammonium hydroxide gave amide **4b** in good yield,[13] and ester exchange of **3a** in a methanol solution of methylsulfonic acid was feasible, resulting in the corresponding ester **4c** with good efficiency.[14]

Scheme 3. Scope of α,α-Disubstituted Carbonyl Substrates[a]



[a]General reaction conditions: **1** (0.1 mmol, 1.0 equiv), **2** (0.11 mmol, 1.1 equiv), **N1** (10 mol %), **B1** (0.11 mmol, 1.1 equiv), *t*-BuOLi (0.05 mmol, 0.5 equiv), ethyl acetate (2 mL), 4 Å MS (100 mg), 30 °C, 12 h. [b]Diastereomeric ratio (*R*/*S*). [c]*S*-type optical isomer substrates were used. [d]**1i** (0.15 mmol, 1.5 equiv), **2** (0.1 mmol, 1.0 equiv). [e]Reaction conditions: **1** (0.1 mmol, 1.0 equiv), β-D-phenylgalactoside (0.11 mmol, 1.1 equiv), **N3** (10 mol %), **B2** (0.11 mmol, 1.1 equiv), K_2CO_3 (0.05 mmol, 0.5 equiv), 1,4-dioxane (2 mL), 4 Å MS (100 mg), 30 °C, 12 h.

Scheme 4. Synthetic Utility and Product Derivatization



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CONCLUSIONS

In summary, we have developed an efficient asymmetric synthesis strategy to utilize unprotected saccharides as chiral auxiliaries and achieve dynamic kinetic resolution of α,α-disubstituted carbonyl compounds by their regioselective installation on unprotected saccharides mediated by NHC catalysts and boronic acids. The formation of boronic ester transiently shields certain OH groups in saccharides, providing a prominent regulatory effect for controlling the regio- and stereoselectivity of the reaction. The covalent and noncovalent interactions as well as steric effects generated between boronic ester and NHC catalysts can be systematically and modularly adjusted to achieve dynamic kinetic resolution of diverse racemic targets by installing them on different OH sites in various configurations of saccharides. The utility of this strategy has enabled the facile preparation of a wide range of chiral carbonyl molecules through further transformations of the ester group. Given the ready availability and configurational diversity associated with unprotected saccharides, we expect our approach to enrich and expand the application of saccharides as chiral auxiliaries in asymmetric synthesis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.4c04076.

Experimental procedures and spectral data for all new compounds (PDF)
CIF file of CCDC 2359956 (CIF)
CIF file of CCDC 2360190 (CIF)

Accession Codes

CCDC 2359956 and 2360190 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: + 44 1223 336033.

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Author Contributions

#S.D., J.Z., and H.W. contributed equally.

Notes

The authors declare no competing financial interest.

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(11) Deposition numbers 2359956 (for **3b**), and 2360190 (for **3k**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre.

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