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Chiral Catalyst-Directed Dynamic Kinetic Diastereoselective Acylation of Anomeric Hydroxyl Groups and a Controlled Reduction of the Glycosyl Ester Products

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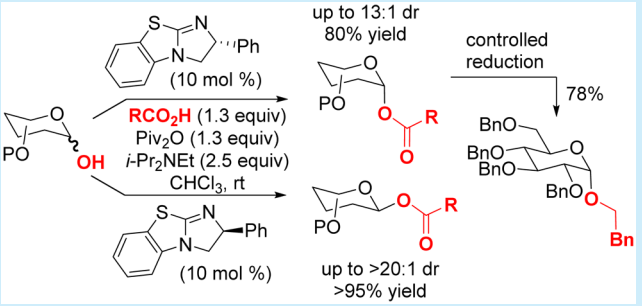
Supporting Information

ABSTRACT: A catalytic method is developed for the diastereoselective acylation of the anomeric hydroxyl group in diverse carbohydrates to form either α- or β-anomeric esters. While exclusive formation of the β-isomer was observed in most sugar substrates with one enantiomer of the chiral catalyst, moderate to high α-selectivity was obtained by using the other enantiomer of the chiral catalyst. The resulting α- and β-anomeric esters have very different reactivity toward a reduction reaction.



The importance of complex carbohydrate-containing natural products continues to stimulate the development of efficient and stereoselective methods for their synthesis. 1-Acyl mono- or oligosaccharides exist in many bioactive natural products, such as QS-21A, phyllanthoside, and phyllanthostatins (Figure 1).[1] Numerous members of the ellagitannin family also have a 1-acylglycoside unit, such as sanguiin H-4 and sanguiin H-5 in Figure 1.[1d] β-1-Acyl glucuronides are the major metabolites of most carboxylic acid containing drugs, and it has become critical to stereoselectively prepare β-1-acyl glucuronides for toxicity evaluation during drug development.[2] Several β-1-acyl glucosides were also identified as metabolites of bile acids and important biomarkers for patients with hepatic diseases.[3] In addition, numerous drugs have been linked to glucose and its derivatives to selectively target cancer cells.[4] Interestingly, the β-1-acyl glucose conjugate showed better activity than the corresponding α-form in the case of glucose−triptolide conjugates in recent studies.[5] However, a general and catalyst-controlled method has not been developed for the stereoselective acylation of the anomeric hydroxyl group to form either isomer.[6]

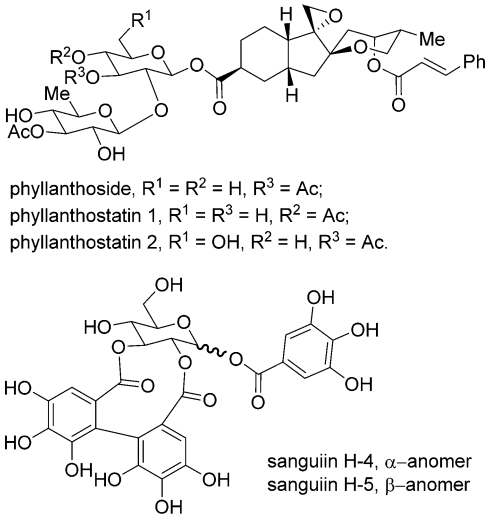


Figure 1. Examples of 1-acyl sugar natural products.

Recently, we[7] and others[8] reported that chiral catalysts could mediate the enantio- and diastereoselective acylation of allylic alcohols in pyranones derived from Achmatowicz rearrangement[9] (Scheme 1A). The resulting allylic esters could then undergo Pd-catalyzed stereospecific *O*-alkylation for de novo synthesis of carbohydrates.[10] Herein, we report that chiral catalysts can also promote the stereoselective acylation of anomeric hydroxyl groups in a variety of carbohydrates to form either the α- or β-anomeric esters (Scheme 1B). The resulting α- and β-anomeric esters showed very different reactivity profiles toward reduction.

We first examined three commercially available chiral catalysts (**4a−c**) for the dynamic kinetic diastereoselective acylation (DKDA) of glucose derivative **1a** using isobutyric

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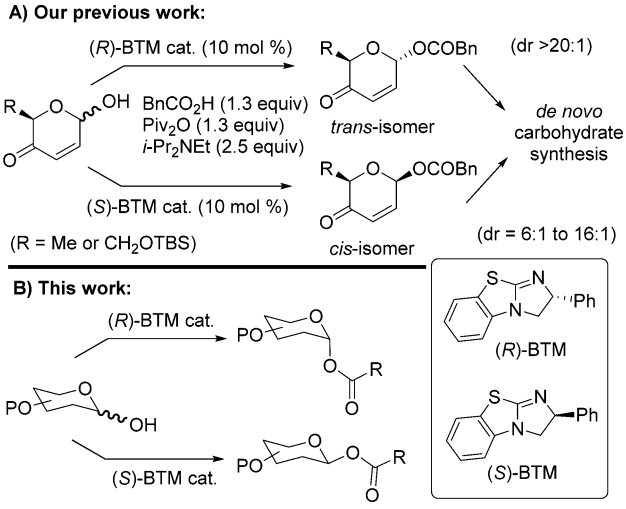
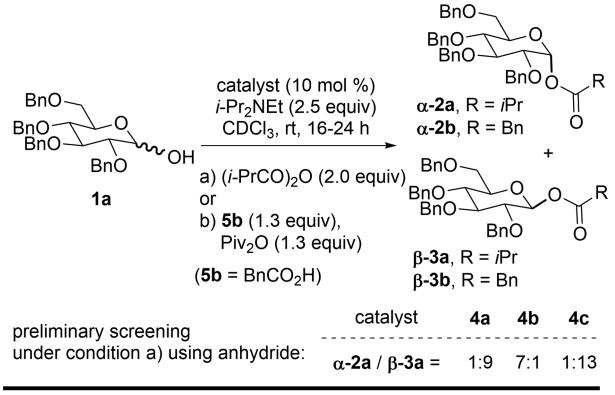
Scheme 1. Stereoselective Acylation of Lactols and Their Further Functionalizations



anhydride (Scheme 2). Both (*S*)-tetramisole[11] and (*S*)-benzotetramisole (BTM)[12] yielded the β-anomer as the major isomer, while (*R*)-BTM mainly provided the α-isomer.

Scheme 2. Screening of Catalysts for DKDA of Glucose



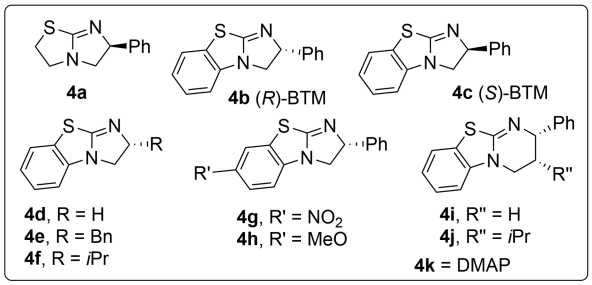
preliminary screening under condition a) using anhydride:

catalyst	4a	4b	4c
α-2a / β-3a =	1:9	7:1	1:13

screening of catalysts under condition b) using mixed anhydride:

catalyst	4b	4c	4d	4e	4f	4g	4h	4i	4j	4k
α-2b / β-3b =	7:1	<1:20	1:2	3:1	3:1	1:1	5:1	3:1	1:1	1:1
conversion (%)	>95	>95	>95	85	80	50	>95	>95	90	>95

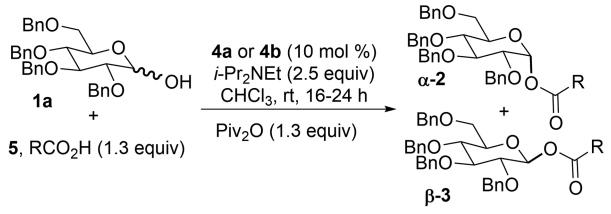
Isolated yield of **α-2b** using catalyst **4b**: 73%
Isolated yield of **β-3b** using catalyst **4c**: 99%



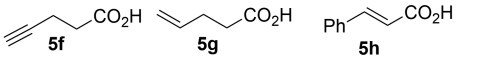
We next turned our attention to the mixed anhydride method[13] due to the availability of diverse carboxylic acids (Scheme 2). Exclusive formation of the β-anomer could be realized using (*S*)-BTM **4c** as the catalyst and phenyl acetic acid as the acylation reagent. We then screened various benzotetramisole catalysts[14] with different steric and electronic properties to further improve the selectivity for the α-isomer. (*R*)-BTM **4b** remained the best catalyst for the highest α-selectivity. We also examined different solvents including toluene, *tert*-amyl alcohol, THF, dichloromethane, and acetonitrile. We found that the highest yield and dr for the α-isomer were obtained in chloroform.

We then investigated the scope of acids for the DKDA of substrate **1a** (Scheme 3). Diverse carboxylic acids including α-

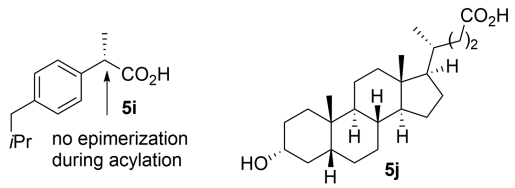
Scheme 3. Scope of Carboxylic Acids for DKDA of Glucose with Mixed Anhydrides[a]



	5a, *i*-PrCO$_2$H	5c, HOAc	5d, EtCO$_2$H	5e, CH$_3$(CH$_3$)$_8$CO$_2$H
	α-2a / β-3a	α-2c / β-3c	α-2d / β-3d	α-2e / β-3e
4b cat.	7:1 [92%]*	6:1 [93%]*	7:1 [94%]*	8:1 [99%]*
4c cat.	<1:20 (95%)	<1:20 (99%)	<1:20 (97%)	<1:20 (89%)



	α-2f / β-3f	α-2g / β-3g	α-2h / β-3h
4b cat.	6:1 [90%]*	6:1 [99%]*	6:1 (61%)
4c cat.	<1:20 (98%)	<1:20 (94%)	<1:20 (73%)



4c cat. α-2i / β-3i < 1:20 (93%) α-2j / β-3j < 1:20 (93%)

[a]Note: The number in parentheses is the isolated yield of the major isomer. The number in brackets is the isolated yield of the mixture of α- and β-isomers.

substituted acid **5a**, acetic acid **5c**, long-chain carboxylic acid **5e**, and unsaturated carboxylic acids **5f**, **5g**, and **5h** all worked well. High selectivity was observed for the formation of all β-isomers. The selectivity for the α-isomer ranges from 6:1 to 8:1. When (*S*)-ibuprofen **5i** was employed as the substrate, we did not observe any epimerization product. The β-glucosidic conjugates of acid **5j** and related bile acids are important biomarkers for patients with hepatic diseases.[3] We were pleased to find that the product β-**3j** was formed with high stereoselectivity under our standard conditions.

The scope of carbohydrates for the DKDA of the anomeric hydroxyl group is examined in Scheme 4. We demonstrated that the preference for the β-isomer **7** remained high for protected D-galactose **1b**, D-xylose **1d**, 2-deoxy-D-glucose **1e**, 2-deoxy-D-galactose **1f**, and L-fucose **1g**. L-Fucose **1g** requires use of the opposite enantiomeric catalyst compared to D-sugars. It is worth mentioning that the intrinsic selectivity for most sugar substrates is low using DMAP as the catalyst. The intrinsic selectivity for mannose derivative **1c** is over 20:1 favoring the α-isomer. We were surprised that (*S*)-BTM catalyst was able to override this strong intrinsic bias and form β-mannoside **7c** as the major isomer. The intrinsic selectivity for xylose derivative

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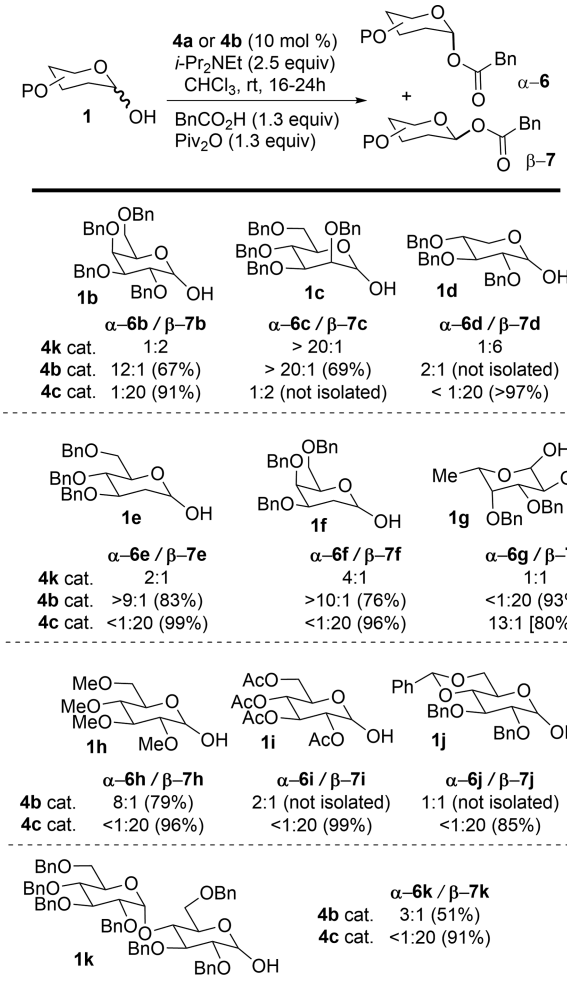
Scheme 4. Scope of Sugar Substrates for DKDA[a]



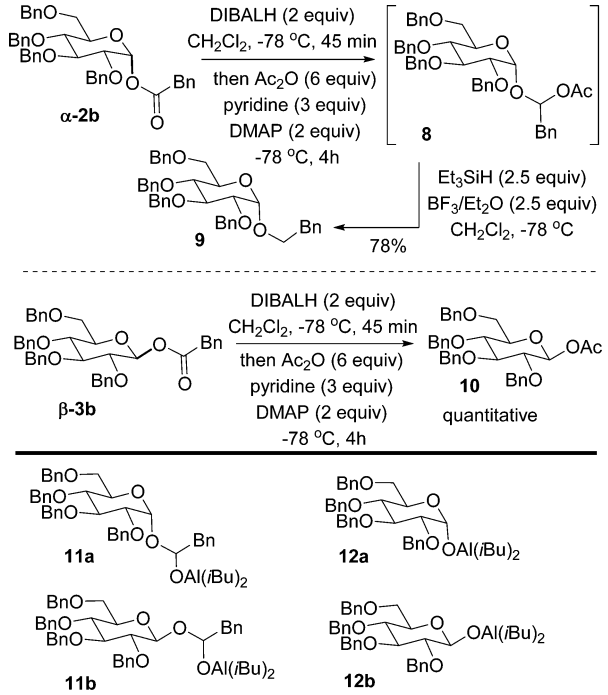
[a]Note: The number in parentheses is the isolated yield of the major isomer. The number in brackets is the isolated yield of the mixture of α- and β-isomers.

1d is about 6:1 favoring the β-isomer. (*R*)-BTM catalyst is able to override the intrinsic bias, and α-xyloside **6d** is formed as the major isomer.

We also briefly examined the effect of the protecting group on the diastereoselectivity using D-glucose as the example. The results for methyl ether **1h** are similar to those for benzyl ether **1a**. Interestingly, acetyl- and benzylidene-protected **1i** and **1j** showed decreased selectivity for the formation of α-esters, while the selectivity for the formation of the β-ester remained the same. A similar trend was also observed for disaccharide **1k**. The change of anomeric ratios by varying the protecting group is common in glycosylation reactions.[15] The mechanism for this intriguing selectivity change in acylation will be further investigated.[12c,d]

Reduction of the anomeric esters to ethers has been reported by Barrett via the formation of thionoester intermediates and desulfurization.[16] We investigated the possibility of one-pot reduction of esters to ethers based on a protocol reported by Rychnovsky (Scheme 5).[17] We found that α-glucoside **9** could be prepared from α-isomer **2b** efficiently and there was no scrambling of stereochemistry. To our surprise, β-isomer **3b** afforded simple acetyl ester **10** after the first step. The above results suggest that aluminum complex **11a** is stable under the reaction conditions and does not undergo further reduction to

Scheme 5. Reduction of Anomeric Esters



form **12a**, while aluminum complex **11b** is further reduced under the reaction conditions to form **12b**.

In summary, we have developed a chiral catalyst-directed dynamic kinetic stereoselective method for the acylation of anomeric hydroxyl groups in a variety of sugar substrates. The resulting α- or β-1-acylsugars have very different reactivity profiles in a reduction reaction. The detailed mechanism for the catalyst-directed acylation and the full scope of the intriguing reduction of anomeric esters is under investigation and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03683.

Detailed experimental procedures, characterization data, and spectra (^{1}H, ^{13}C NMR, IR, and HRMS) (PDF)

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Notes

The authors declare no competing financial interest.

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