Organic LETTERS

Letter

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Chiral Catalyst-Directed Dynamic Kinetic Diastereoselective Acylation of Lactols for *De Novo* Synthesis of Carbohydrate

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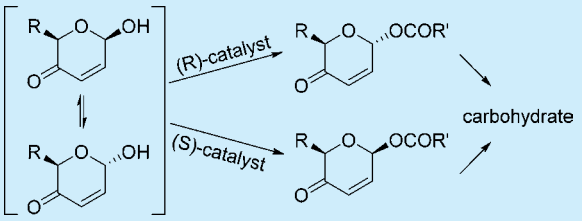
Supporting Information

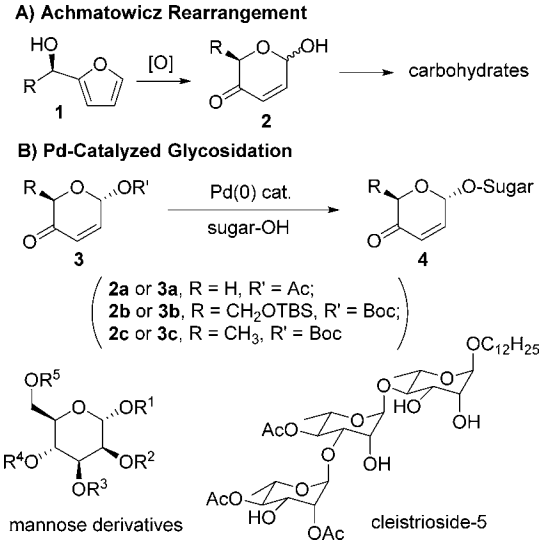
ABSTRACT: The control of the stereochemistry at the anomeric position is still one of the major challenges of synthetic carbohydrate chemistry. We have developed a new strategy consisting of a chiral catalyst-directed acylation followed by a palladium-catalyzed glycosidation to achieve high α- and β-stereoselectivity on the anomeric position. The former process involves a dynamic kinetic diastereoselective acylation of lactols derived from Achmatowicz rearrangement, while the latter is a stereospecific palladium-catalyzed allylic alkylation.



Carbohydrate, one of the four basic macromolecules of life, plays an essential role in numerous important biological processes such as immunological responses, cancer metastasis, and bacterial or viral infections.[1] Efficient and stereoselective synthetic methods, especially *de novo* synthetic methods that do not rely on naturally occurring sugars, may greatly facilitate the study of the biological functions of carbohydrate. It will also enable the development of carbohydrate analogues as novel therapeutic agents.

Since the seminal work by Sharpless and Masamune on *de novo* synthesis of hexopyranoses,[2] a number of new strategies have been developed for the *de novo* synthesis of carbohydrates.[3] However, the stereochemistry at the anomeric position or stereoselective glycosidation remained largely unaddressed in these *de novo* synthesis.[4] Among various *O*-glycosidation methods,[5] Pd-catalyzed Tsuji–Trost allylic alkylation[6] has been recognized by Lee,[7] Feringa,[8] O'Doherty,[9] Liu,[10] and Rhee[11] as a powerful way to link monosaccharides. The *de novo* synthesis of carbohydrate developed by Feringa[8] and O'Doherty[9] relies on Achmatowicz rearrangement[12] and stereoselective Pd-catalyzed glycosidation (Scheme 1). The former converts the biogenic feedstock furan **1** to dihydropyranone **2**, which has been extensively applied in the *de novo* synthesis of carbohydrates since its initial discovery in the 1970s (Scheme 1A).[3a,13] In the latter process, esters or carbonates **3a–c** undergo Pd-catalyzed Tsuji–Trost allylic alkylation[6] to afford product **4** with retention of stereochemistry (Scheme 1B). Feringa and co-workers primarily focused on the glycosidation of ester **3a**, which was derived from lipase mediated resolution.[8,14] In the past decade, O'Doherty and co-workers have applied the Pd-catalyzed glycosidation of **3b** and **3c** to the synthesis of numerous mono- and oligosaccharides, such as mannose derivatives and cleistriosides shown in Scheme 1.[4,15] However, the overall transformation from lactol **2** to product **4** is often not stereoselective because of the low selectivity of the acylation of the lactol.

Scheme 1. *De Novo* Synthesis of Carbohydrates

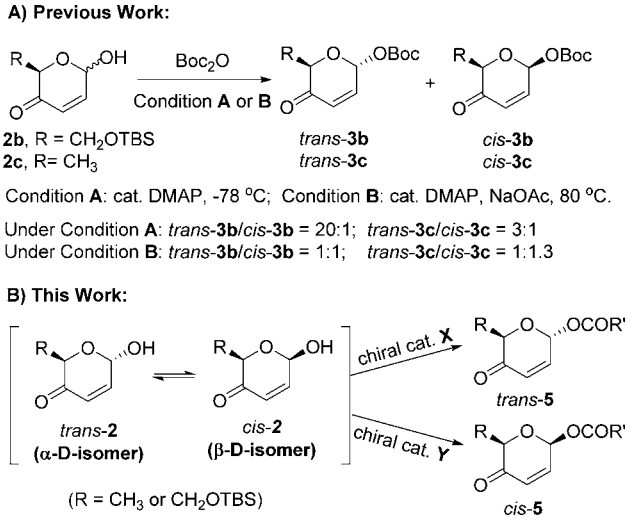


Although *trans*-**3b** could be prepared exclusively from the corresponding Achmatowicz rearrangement product **2b** (Scheme 2A),[9] the best diastereomeric ratio favoring *cis*-**3b** was only 1:1. The ratios for the closely related carbonates *trans*-**3c** and *cis*-**3c** ranged from 3:1 to 1:1.3.[9,16] Chromatographic separation of these isomers is required with the exception of *trans*-**3b**. We recently became interested in the dynamic kinetic diastereoselective transformations of lactol **2** and discovered an Ir-catalyzed dynamic kinetic diastereoselective redox isomer-

Received: September 11, 2015
Published: October 20, 2015

DOI: 10.1021/acs.orglett.5b02641
Org. Lett. 2015, 17, 5272–5275

Scheme 2. DKDA of Lactols



ization of lactol **2** to its lactone.[17] We envisioned that chiral catalysts could either reinforce or override the intrinsic diastereoselectivity for the acylation of lactol **2** and provide a general solution for the synthesis of either *trans*-**5** or *cis*-**5** via chiral catalyst-directed dynamic kinetic diastereoselective acylation (DKDA) (Scheme 2B).

After we analyzed chiral organocatalysts that are known to mediate enantioselective acylation of alcohols,[18] commercially available levamisole **6** with an (*S*)-configuration became attractive to us because of its broad utility in many different reactions (Table 1).[19] This type of tetramisole-based catalyst has been extensively used by Birman and co-workers for the kinetic resolution of secondary alcohols,[20] azlactones,[21] and α-thiolcarboxylic acids.[22] Wiskur and co-workers also applied them to the asymmetric silylation of alcohols.[23]

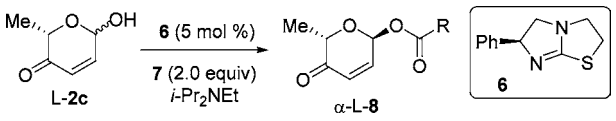
Chiral lactol L-**2c** was prepared enantioselectively in two steps from 2-acetylfuran via catalytic asymmetric hydrogenation (98% ee) and Achmatowicz rearrangement according to known protocols.[17,24] Using **6** as the catalyst, no reaction was observed when $(Boc_2)O$ was employed. We were pleased to find that simple acetic anhydride provided product **8b** with a dr of 8:1 favoring the *trans*-α-isomer. Higher selectivity was observed by using more hindered anhydrides **7c** and **7d**. A similar trend was also observed by Birman and co-workers for the acylation of alcohols.[20]

Since only one enantiomeric isomer was commercially available for catalyst **6**, we prepared substrate D-**2c** to explore the mismatched acylation. The dr dropped from 8:1 to 1:1 when D-**2c** was employed as the substrate using acetic anhydride as the acylation reagent. Under the conditions of entry 7 in Table 1, a dr of 8:1 favoring the mismatched *cis*-isomer with a β-D configuration was observed, and this *cis*-isomer could be isolated in 76% yield. We then tried to acylate mismatched substrate D-**2b** with a silyloxymethylene group on the 5-position under the conditions of entry 4 in Table 1. Unfortunately, low conversions and low dr's were observed. No improvement was obtained by changing the TBS group to benzyl or benzoyl protecting groups.

While we were optimizing conditions for these challenging mismatched substrates, Ortiz and co-workers reported the dynamic kinetic asymmetric transformation (DYKAT) of lactol **2a** (R = H) and four related lactols with either two hydrogen or two methyl substituents on the 5-position to the corresponding esters with up to 88% ee.[25] Commercially available (−)-levamisole was also employed as the chiral organocatalyst. The method was then applied to an elegant synthesis of anti-HIV drug BMS-986001. Although the DYKAT of lactol **2a** was nicely demonstrated by Ortiz and co-workers, it was not obvious that the DKDA of substrates **2b** and **2c** could be easily achieved. In fact, our results have indicated that it is challenging to override the intrinsic diastereoselectivity for mismatched substrates.

We also tried to acylate substrates L-**2c** and D-**2c** under the conditions in entry 4 of Table 1 using benzotetramisole (BTM) catalyst **9** (Table 2), which was first introduced by Birman for the kinetic resolution of alcohols.[20] We obtained products with dr's ranging from 8:1 to 1:7 for matched and mismatched substrates. We were then attracted by Shiino's mixed anhydride conditions for the kinetic resolution of alcohols because a wide variety of carboxylic acids are readily available.[26] We explored different carboxylic acids for the acylation of matched substrate

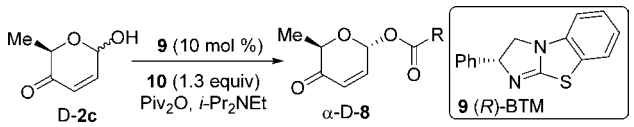
Table 1. Screening of Anhydride for DKDA[a]



entry	anhydride **7**	conversion[b] (%)	product[b] (dr)
1	**7a**, Boc_2O	0	
2	**7b**, Ac_2O	>99	α-L-**8b** (8:1)
3	**7c**, $(EtCO)_2O$	>99	α-L-**8c** (11:1)
4	**7d**, $(i\text{-PrCO})_2O$	>99	α-L-**8d** (15:1)
5	**7e**, Bz_2O	70	α-L-**8e** (1:1)
6	**7f**, Piv_2O	<10	
7[c]	**7d**	92[d]	α-L-**8d** (15:1)

[a]Conditions: $CDCl_3$, L-**2c** (1.0 equiv), **6** (5 mol %) **7** (2.0 equiv), *i*-Pr_2NEt (2.0 equiv), Na_2SO_4, rt, unless noted otherwise. [b]The conversion of **2c** and dr of **8** were determined by ^1H NMR of the crude product using CH_2Br_2 as the internal standard. [c]The reaction was carried out in $CHCl_3$. [d]Isolated yield of **8d**.

Table 2. Screening of Mixed Anhydride for DKDA[a]



entry	acid **10**	conversion[b] (%)	product (dr)[b]
1	AcOH	85	α-D-**8b** (13:1)
2	$EtCO_2H$	>99	α-D-**8c** (18:1)
3	$i\text{-PrCO}_2H$	>99	α-D-**8d** (9:1)
4	$PhCO_2H$	<10	
5	Ph_2CHCO_2H	>99	α-D-**8f** (14:1)
6	$PhCH_2CO_2H$	>99	α-D-**8g** (>20:1)
7[c]	$PhCH_2CO_2H$	80	α-D-**8g** (16:1)
8[d]	$PhCH_2CO_2H$	>99	α-D-**8g** (>20:1)
9[d]	$PhCH_2CO_2H$	76[e]	α-D-**8g** (>20:1)

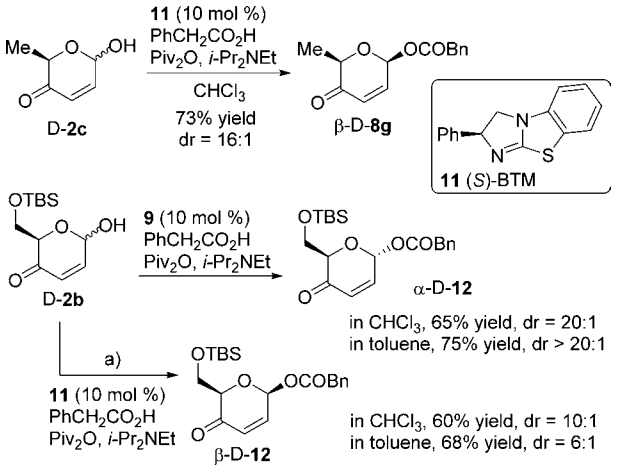
[a]Conditions: D-**2c** (1.0 equiv), **9** (10 mol %), Piv_2O (1.3 equiv), **10** (1.3 equiv), *i*-Pr_2NEt (2.5 equiv), Et_2O, rt, unless noted otherwise. [b]The conversion of **2c** and dr of **8** were determined by ^1H NMR of crude product using CH_2Br_2 as the internal standard. [c]The reaction was carried out in CH_2Cl_2. [d]The reaction was carried out in $CHCl_3$. [e]Isolated yield of **8g**.

DOI: 10.1021/acs.orglett.5b02641
Org. Lett. 2015, 17, 5272−5275

D-**2c** using catalyst **9** as shown in Table 2. The diastereoselectivity for product **8b** was improved from 8:1 (entry 2, Table 1) to 13:1 (entry 1, Table 2) under these new conditions. We quickly found that simple phenylacetic acid yielded α-isomer **8g** exclusively (entry 6). The reaction also worked well in $CHCl_3$ (entries 8 and 9), and it became the choice of solvent since the catalyst is more soluble in $CHCl_3$ than ether.

With these new conditions in hand, we examined the acylation of substrate D-**2c** using catalyst **11**; the more challenging mismatched scenario (Scheme 3). Product β-D-**8g** was prepared in high yield and diastereoselectivity. We were also pleased to find that both α- and β-isomeric products **12** could be prepared in high diastereoselectivity using catalyst **9** or **11**, though the reaction was much slower for the mismatched case in $CHCl_3$. Faster reaction and higher yield were observed in toluene for products α-D-**12** and β-D-**12**. Both enantiomers of substrates **2b** were prepared highly enantioselectively (98% ee) according to our previous protocols.[17] All diastereoisomers of **8** and **12** could be easily separated by SiO_2 column chromatography, and the yield refers to the isolated yield of a single isomer. All of these isomers are basic chiral building blocks for the synthesis of various oligosaccharides via Pd-catalyzed glycosidation.[4,15]

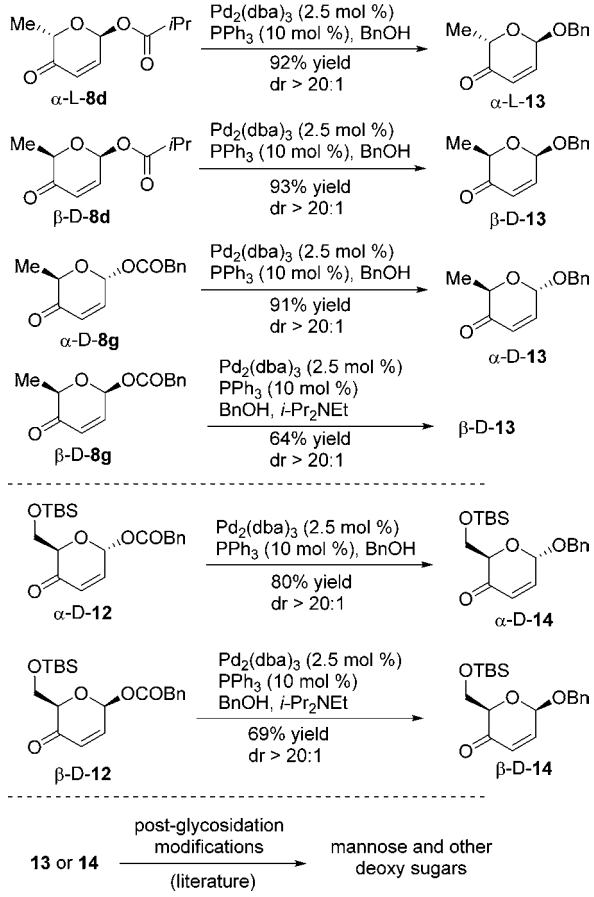
Scheme 3. Catalyst-Directed DKDA of Different Lactols



Following O'Doherty's conditions,[16] glycosides **13** and **14** were prepared efficiently and stereospecifically from the corresponding esters via Pd–π-allyl intermediates (Scheme 4). All of the ester substrates (**8d**, **8g**, and **12**) employed here are single stereoisomers (drs >20:1). The standard conditions worked well for most substrates, including α-L-**8d**, β-D-**8d**, α-D-**8g**, and α-D-**12**. However, the dr of the product dropped to 6:1 for *cis*-substrate β-D-**8g**. The addition of organic base significantly improved the dr. Similarly, the addition of base is required for the preparation of β-D-**14**. Various postglycosidation modification methods have been developed by O'Doherty and co-workers for the conversion of products in Scheme 4 to diverse range of mono- and oligomeric saccharides.[4,15]

In summary, the combination of chiral organocatalyst-directed DKDA and Pd-catalyzed glycosidation allows the complete stereochemical control of the anomeric center and paves the way for highly stereoselective *de novo* synthesis of many natural and non-natural carbohydrates.

Scheme 4. Pd-Catalyzed Stereospecific Glycosidation



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02641.

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

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the University of Wisconsin—Madison for funding. C.L. thanks Guangzhou Medical University for financial support of her visiting scholarship.

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DOI: 10.1021/acs.orglett.5b02641
Org. Lett. 2015, 17, 5272–5275