

Pd-Catalyzed Asymmetric Intermolecular Hydroalkoxylation of Allene: An Entry to Cyclic Acetals with Activating Group-Free and Flexible Anomeric Control

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S Supporting Information

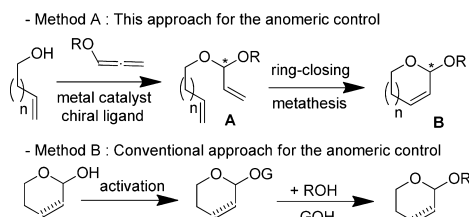
ABSTRACT: A ligand-directed metal-catalyzed asymmetric intermolecular hydroalkoxylation of alkoxyallene is reported. Combined with ring-closing-metathesis, this reaction offers a new atom-efficient synthetic method toward various cyclic acetals with elaborate anomeric control. Synthetic utility of the reaction was demonstrated by the atom-efficient and stereodivergent access to various mono- and disaccharides.

Asymmetric formation of carbon–oxygen bond represents one of the most fundamental transformations in synthetic organic chemistry. Metal-catalyzed addition of alcohols to allenes (hydroalkoxylation) is considered as a most powerful method, due to the excellent chemical efficiency and the rich functional groups installed in the product.¹ In most cases, the scope has been discussed within the realm of oxacycle synthesis which exploits intramolecular reaction.² However, the more challenging intermolecular asymmetric hydroalkoxylation of allene, to our best knowledge, still remains unknown. In this context, we envisioned that the chiral ligand-directed addition of olefinic alcohol to alkoxyallene would generate enantioenriched acyclic mixed acetal **A** (Method A, Scheme 1). The

on the nature of the pre-existing substituents. The proposed method is distinguished from the conventional ones in that the activating groups are not needed. In addition, the diversity can be easily pursued with regard to the ring size and the anomeric configuration of the cyclic acetal. Thus, this strategy offers a highly flexible and chemically efficient approach toward cyclic acetals, and can open up new possibilities for the structurally and stereochemically divergent synthesis of mono- and oligosaccharides.⁶ For the efficient flexible anomeric control, the stereoinduction in the hydroalkoxylation step should be independent of the pre-existing substituents in the alcohol moiety. Upon the basis of our own experience in the hydroamination⁷ and related studies,⁸ we envisioned that the metal-catalyzed hydroalkoxylation invoking π -allyl intermediates would be highly suitable for this transformation.

Unlike various carbon- and nitrogen nucleophiles, however, unactivated aliphatic alcohols are known as a poor nucleophile in asymmetric π -allyl chemistry.^{9–12} In fact, this concern was justified in our initial optimization (Table 1). As shown in entry 1, the reaction of enantioenriched alcohol **1** with *n*-pentoxyallene **3** (10 equiv) in the presence of chiral Trost ligand **2** (6.25 mol %) and Pd(OAc)₂ (5 mol %) in CH₂Cl₂ showed no conversion (entry 1). Quite interestingly, the reaction employing sterically bulkier cyclohexyloxyallene **4** slowly proceeded to give a mixture of acyclic acetal **5a** and **5b** in notable 67% yield after 4 days.¹³ The subsequent RCM proceeded smoothly to give cyclic acetals **6a** and **6b** in 97% yield with 10:1 ratio (65% yield over two steps).¹⁴ Upon the basis of the ¹H NMR analysis, the absolute configuration of the anomeric carbon in **6a** center was tentatively assigned to be (*S*) (entry 2, for the rigorous determination of the anomeric configuration, see below). Encouraged by this preliminary result, we continued the optimization process. Concentration of the solution (entry 3) as well as employing Pd₂(dba)₃ as the precatalyst increased the yield (entry 4), even though the reactions were still very slow. After extensive studies to speed up the reaction, we discovered a remarkable solvent effect. For example, the use of polar DMF almost stopped the reaction (entry 5), while using nonpolar toluene dramatically reduced the reaction time without harming the selectivity (entry 6). In the latter case, the hydroalkoxylation reaction was completed within 4 h to give **5a** as the exclusive diastereomer in 90% yield

Scheme 1. Basic Concept



subsequent RCM (ring-closing-metathesis) reaction^{3,4} would give the cyclic acetal **B**. This unprecedented pathway proposes a unique way to control the anomeric information on the cyclic acetals, which is of crucial importance in delineating the structure and function of structurally complex oligosaccharides and glycoconjugates.⁵ In conventional approaches for the anomeric control, synthesis of the oxacyclic framework precedes formation of the anomeric center (Method B, Scheme 1). This method generally requires stoichiometric amount of activating groups and extensive protective group strategies. Moreover, controlling the anomeric configuration relies heavily

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Table 1. Optimization^a

entry	allene (eq)	method ^b	solvent	conc. (M)	time (h)	yield ^{c,d} (%)	ratio ^e (6a:6b)
1	3 (10)	A	CH ₂ Cl ₂	0.05	96	No Rxn	-
2	4 (10)	A	CH ₂ Cl ₂	0.05	96	65	10:1
3	4 (10)	A	CH ₂ Cl ₂	0.5	96	86	10:1
4	4 (10)	B	CH ₂ Cl ₂	0.5	96	92	10:1
5	4 (10)	B	DMF	0.5	96	10	2.4:1
6	4 (10)	B	Toluene	0.5	4	90	>20:1
7	4 (2)	B	Toluene	0.5	4	93	>20:1
8	4 (1.2)	B	Toluene	0.5	6	82	>20:1
9 ^f	4 (2)	B	Toluene	0.5	4	95	1:15

^aFor more detailed information on the optimization, see the SI. ^bMethod A: Pd(OAc)₂ (5 mol %) and ligand 2 (6.25 mol %) were used. Method B: Pd₂(dba)₃ (2.5 mol %) and ligand 2 (5 mol %) were used. ^cCombined yield for two steps. ^dIn all cases, the RCM reaction proceeded in >95% yield. ^eDetermined by the integration of ¹H NMR spectrum. ^fligand (S,S)-2 was used.

(over two steps). Notably, reducing the amount of alkoxyallene 4 to 2 equiv under this condition still showed full conversion within 4 h (entry 7). Further reduction of allene 4 to 1.2 equiv gave the product 6a in 82% yield (entry 8). As we expected, the use of enantiomeric ligand (S,S)-2 had no adverse effect in the yield and selectivity to give the diastereomeric acyclic acetal 5b, which could be uneventfully transformed into cyclic acetal 6b by RCM (entry 9).¹⁵ This result corroborates our hypothesis that the stereoselectivity in the hydroalkoxylation step is controlled by the chiral information on the ligand.

With the optimized conditions (entries 7 and 9 in Table 1) in hand, we explored an array of substrates for the two-step synthesis of diverse anomerically well-defined cyclic acetals (Table 2). As shown in entries 1 and 2, the substrate 7 possessing benzyloxy group at the neighboring carbon gave diastereomeric cyclic acetal products (8a and 8b) in good yield with high selectivity (entries 1 and 2). In addition, the scope of the reaction was successfully extended to the synthesis of various 7-membered cyclic acetals (entries 3–6). In some cases, higher loading of Pd₂(dba)₃ catalyst (3.5 mol %) was required for the complete conversion in the hydroalkoxylation step (entries 3–4 and 6). Nevertheless, the subsequent RCM reaction using 5 mol % Grubbs catalyst proceeded consistently to give the cyclic acetal products (10 and 12) in good yield with no decrease in the diastereoselectivity. Then, we examined substrates 13 and 15 possessing additional alkoxy substituent at the allylic position to see if the current method can be used for the synthesis of cyclohexyl glycoside forms of 2,3,6-trideoxysugars such as amictose and rhodinoses. As described in entries 7 and 8, employing the two-step protocol with 3.5 mol % Pd₂(dba)₃ and the subsequent RCM converted the alcohol 13¹⁶ into the dehydrogenated forms of amictose glycosides 14a and 14b in good yield and stereoselectivity. It should be noted that

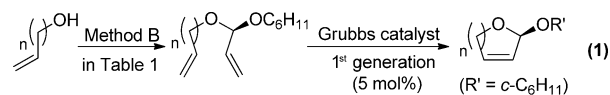
Table 2. Scope of the Alcohol^{a,b}

Entry	S.M.	Method ^c	Time	yield ^d	Product ^e (ratio)
1	7: (n = 1, R = CH ₂ OBn)	A	6 h	87	8a / 8b (>25:1)
2	7: (n = 1, R = CH ₂ OBn)	B	6 h	84	(1:20)
3	9: (n = 2, R = CH ₃)	C	14 h	93	10a / 10b (>25:1)
4	9: (n = 2, R = CH ₃)	D	15 h	82	(<1:25)
5	11: (n = 2, R = CH ₂ OBn)	A	11 h	97	12a / 12b (>25:1)
6	11: (n = 2, R = CH ₂ OBn)	D	28 h	91	(<1:25)
7 ^f	13: (R = MEM)	C	16 h	88	14a / 14b (18:1)
8 ^f	13: (R = MEM)	D	18 h	93	(<1:25)
9 ^g	15: (R = MEM)	C	16 h	71	16a / 16b (11:1)
10 ^g	15: (R = MEM)	D	14 h	83	(1:13)

^aTypical procedure: (i) first step, a mixture of Pd₂(dba)₃, ligand 2, Et₃N (1.5 equiv), alkoxyallene 4 (2 equiv), and the starting material (1 equiv) was reacted in toluene (0.5 M) at 40 °C. (ii) Second step: a mixture of acyclic acetal and 1st generation Grubbs catalyst (5 mol %) was reacted at rt. ^bR' = *c*-C₆H₁₁. ^cMethod A: Pd (2.5 mol %)/(R,R)-2 (5 mol %). Method B: Pd (2.5 mol %)/(S,S)-2 (5 mol %). Method C: Pd (3.5 mol %)/(R,R)-2 (7 mol %). Method D: Pd (3.5 mol %)/(S,S)-2 (7 mol %). ^dCombined yield for two steps. ^eDetermined by the integration of ¹H NMR spectrum after the RCM reaction. ^f0.10 equiv of Et₃N was used. ^g4 equiv of allene was used.

both anomeric configurations could be accessed with comparable chemical efficiency.¹⁷ Additionally, the reaction was successfully expanded to the stereodivergent synthesis of dehydrogenated rhodinoses glycosides 16a and 16b, which proceeded from the alcohol 15 in good yield with >10:1 stereoselectivity (entries 9 and 10). In these cases, complete conversion in the hydroalkoxylation required the use of 4 equiv of alkoxyallene 4.

Next, we investigated achiral olefinic alcohols 17–19 to rigorously determine the enantioselectivity of the ligand-directed hydroalkoxylation reaction. As shown in eq 1, 5- to 7-membered

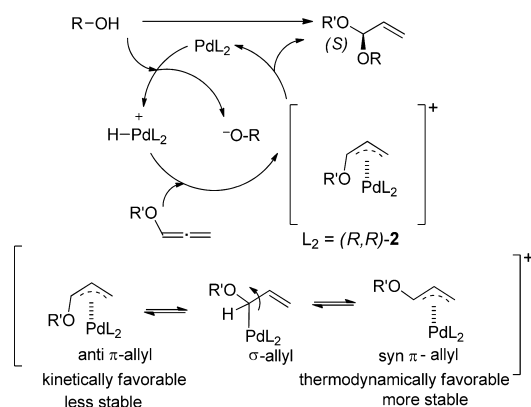


17: n = 1	20: n = 1 (87 %)	23: n = 1 (94 %, 99% ee)
18: n = 2	21: n = 2 (99 %)	24: n = 2 (96 %, 94% ee)
19: n = 3	22: n = 3 (99 %)	25: n = 3 (91 %, 91% ee)

cyclic acetals 23–25 were accessed in high yields and enantioselectivity by using the two-step protocol shown in Table 1, via the corresponding acyclic acetal intermediates 20–22 (For the determination of the ee and absolute configuration of compounds 23–25, see the Supporting Information (SI)). The yield and enantioselectivity of the cyclic acetals did not vary significantly. Thus, this result firmly establishes the generality of the asymmetric hydroalkoxylation reaction.

From a mechanistic viewpoint, the current result is particularly noteworthy because unactivated aliphatic alcohols have been considered as a poor nucleophile in asymmetric π -allyl chemistry. As depicted in Scheme 2, the initially formed Pd–H

Scheme 2. Mechanism

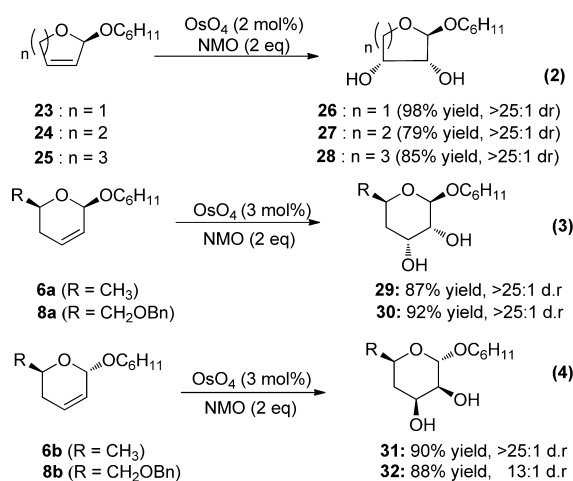


species will generate kinetically favored *anti* π -allyl complex associated with alkoxide counteranion.^{7,8} High level of enantioselectivity for (*S*)-configuration with the use of (*R,R*)-**2** ligand can be reasonably explained by the fast outer-sphere addition of the alkoxide anion to the *anti* π -allyl complex relative to the π - σ - π equilibration process. Key observations presented in the optimization are consistent with this hypothesis. For example, using nonpolar solvent toluene may render a tighter ion pair between kinetic π -allyl complex and the alkoxide anion, thus fastening the attack of the alkoxide ion.¹⁸ Particularly noteworthy is the size effect of the alkoxy moiety in the allene species. Higher yield and selectivity with bulkier alkoxyallene **4** seems apparently confusing because increasing the size of alkoxy moiety should shift the π - σ - π equilibrium toward the more stable *syn* π -allyl complex. However, we point out that the bulky alkoxy moiety may kinetically slow the equilibration process because the σ -allyl intermediate should be more sterically congested than the π -allyl complexes.

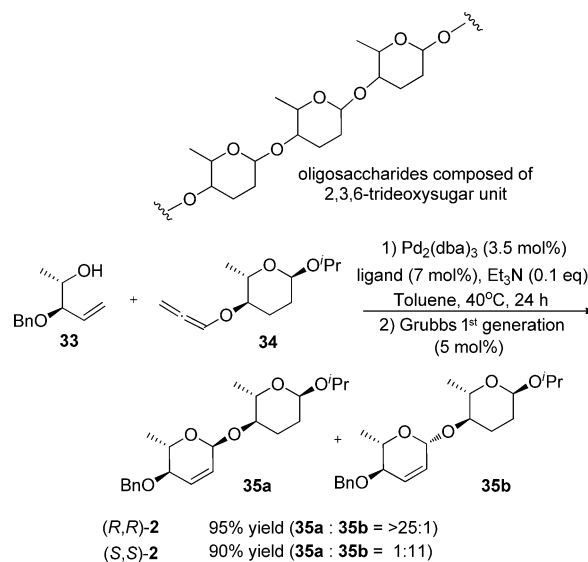
From a synthetic viewpoint, the current method produces highly valuable building blocks that can be potentially used for the synthesis of various monosaccharides. To address this issue, we examined the stereoselective dihydroxylation of various cyclic acetals obtained in this work (Scheme 3). As summarized in eq 2, compounds **23–25** obtained from achiral olefinic alcohols gave the *trans*-dihydroxylated products **26–28** in high yield with excellent (>25:1) stereoselectivity.^{19,20} Furthermore, dihydroxylation of the cyclic pyran acetal compounds **6a** and **8a** showed excellent diastereoselectivity to give cyclohexyl 4,6-dideoxyalloglycoside **29** and 4-deoxyalloglycoside **30** (eq 3). The acetal-directed diastereoselectivity is also demonstrated by the reaction of substrates **6b** and **8b**, which generated the corresponding 4,6-dideoxymannoglycoside **31** and 4-deoxymannoglycoside **32** with high diastereoselectivity.²¹

In addition to the flexible synthesis of monosaccharides presented above, the current method could be expanded for the synthesis of oligosaccharides containing 2,3,6-trideoxysugars, which are found in numerous bioactive natural products²² (Scheme 4). They represent an attractive synthetic challenge, due to the stereochemical diversity of the anomeric configuration as well as the instability of the 2,3,6-trideoxysugar moiety. However, it is well-known that the stereodivergent anomeric

Scheme 3. Stereoselective Dihydroxylation: Monosaccharide Synthesis



Scheme 4. Synthesis of Disaccharides Containing 2,3,6-Tri-deoxysugar



control based upon the conventional (substrate-controlled) reactions is extremely difficult.^{6a,23}

To our delight, the coupling reaction of the easily available alcohol **33**¹⁶ and the deoxysugar-derived alkoxyallene **34**¹⁶ in the presence of ligand (*R,R*)-**2** gave the disaccharide **35a** in 95% yield with >25:1 selectivity (Scheme 4). Switching the ligand to enantiomeric (*S,S*)-**2** gave the diastereomeric disaccharide **35b** again in comparable yield with 11:1 selectivity.²¹ These examples firmly establish the potential utility of the conceptually new chiral ligand-driven stereoinduction in anomerically flexible oligosaccharide synthesis.

In summary, we developed a highly efficient synthesis of cyclic allylic acetal using the Pd-catalyzed asymmetric intermolecular hydroalkoxylation as the key method for the unique anomeric control. The synthetic utility of the proposed method was demonstrated by the anomerically flexible synthesis of various mono- and disaccharides. Currently, we are working on expanding the scope of the proposed reaction in the flexible and chemoselective synthesis of various oligosaccharides. The result of these efforts will be reported in a due course.

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental data and copies of ^1H and ^{13}C spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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- (13) Unlike the acyclic acetals **5a** and **5b**, cyclic acetals **6a** and **6b** could be easily resolved by ^1H NMR. The characteristic anomeric methine hydrogen peak appears at 3.85 ppm (for compound **6a**) and at 4.07 ppm (for compound **6b**).
- (14) The reaction at high temperature (above 50 °C) gave the product in significantly lower selectivity.
- (15) The high selectivity confirms that the RCM step does not harm the selectivity obtained in the hydroalkoxylation step.
- (16) For the detailed procedure for the preparation of **13**, **15**, **33**, and **34**, see the SI.
- (17) The structure of compound **14a** was unambiguously confirmed by an alternative synthesis starting from known the acetyl derivative of *ent*-**14a** (R = Ac) by deacetylation and the subsequent MEM protection (see the SI). For the reference, see: Chen, P.; Lin, L. *Tetrahedron* **2013**, *69*, 10045.
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