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Catalytic enantioselective epoxidation with arabinose-derived uloses containing tunable steric sensors

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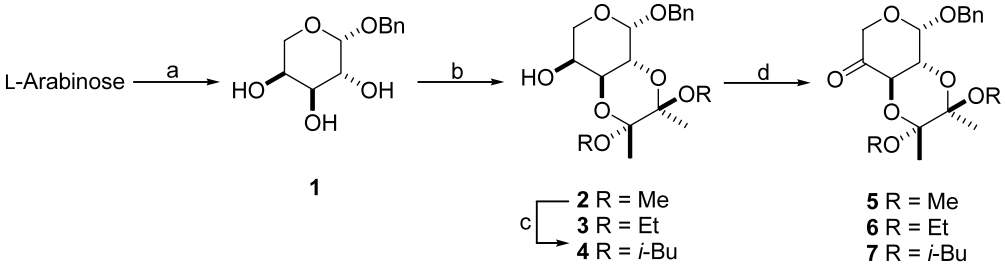
Abstract—Readily available arabinose-derived 4-uloses, containing a tunable butane-2,3-diacetal as the steric sensor, displayed increasing enantioselectivity (up to 93% ee) with the size of the acetal alkyl group in catalytic asymmetric epoxidation of *trans*-disubstituted and trisubstituted alkenes.

Recently, chiral dioxiranes, generated in situ from chiral ketones and Oxone®, have become promising reagents for asymmetric epoxidation of unfunctionalised alkenes.[1] D-Fructose-derived 1,2:4,5-di-*O*-isopropylidene-3-ulose, reported by Shi, was the most impressive and had demonstrated excellent enantioselectivity towards *trans*-disubstituted and trisubstituted alkenes.[2] However, this 3-ulose underwent decomposition under the reaction conditions and had to be used in high loading, thus rendering the reaction non-catalytic. The preparation of a more robust D-fructose-derived catalyst containing a fused oxazolidinone has recently been improved to a six-step synthesis.[3] Unfortunately, L-fructose is not commercially available and its scarcity diminishes its attractiveness as the enantiocomplement since a short and facile preparation of L-fructose remains elusive.[2] Consequently, there is room for the discovery of easily accessible ulose catalysts in catalytic enantioselective epoxidation. Our long-term interest[4] in the application of carbohydrates in asymmetric synthesis has prompted us to search for an efficient ulose catalyst to induce chirality with high ee in asymmetric epoxidation. D- and L-Arabinose are both commercially available in large quantities and therefore are the first choice for our investigation. We recently described our studies on enantioselective epoxidation of alkenes catalyzed by uloses derived from D-glucose[5] as well as by 2-uloses and 3-uloses derived from L-arabinose.[6] Now, we report our results on asymmetric epoxidation of *trans*-disubstituted and trisubstituted alkenes, using Oxone® as oxidant, catalyzed by readily available arabinose-derived 4-uloses containing tunable steric sensors that control the enantioselectivity of the epoxidation.



Scheme 1. *Reagents and conditions:* (a) BnOH, AcCl (0.6 equiv.), rt, 5 days, 87%; (b) 2,2,3,3-tetramethoxybutane (1.2 equiv.), $CH(OMe)_3$ (4 equiv.), (±)-CSA (0.1 equiv.), reflux, 12 h, 76% for **2**; 2,2,3,3-tetraethoxybutane (1.2 equiv.), $CH(OEt)_3$ (4 equiv.), (±)-CSA (0.1 equiv.), reflux, 12 h, 50% for **3**; (c) 2-methyl-1-propanol (4 equiv.), *p*-TsOH, PhH, Dean & Stark trap, reflux, 12 h, 85%; (d) PDC (1.5 equiv.), 3 Å MS, CH_2Cl_2, rt, 12 h, 90% for **5**, 85% for **6**, 95% for **7**.

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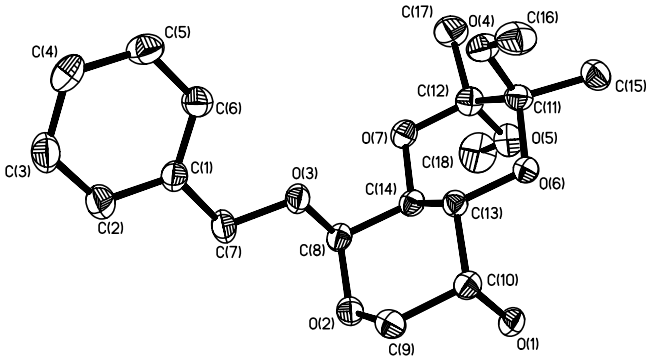


Figure 1. X-Ray structure alcohol **2** (CCDC no. 184258) (ORTEP view).

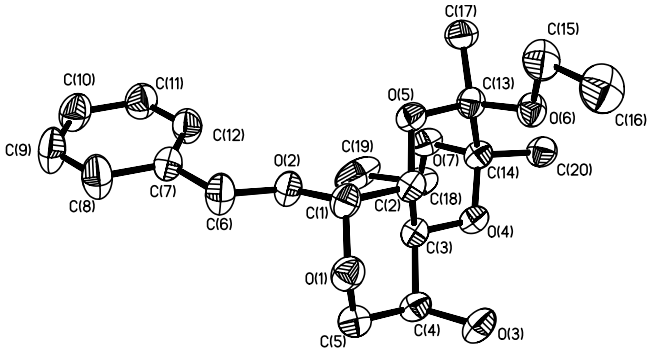
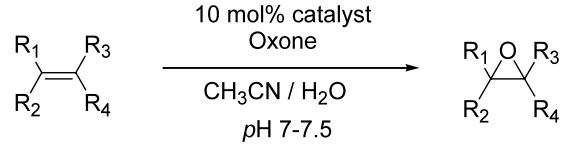


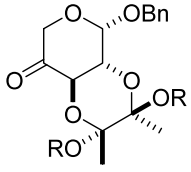
Figure 2. X-Ray structure alcohol **3** (CCDC no. 184257) (ORTEP view).

Uloses **5**–**7** were readily accessible from L-arabinose via a reaction sequence involving Fischer glycosidation, transacetalization, and oxidation (Scheme 1). The known benzyl glycoside **1**,[6] readily obtained from L-arabinose, was converted into dimethyl acetal **2**[6] with 2,2,3,3-tetramethoxybutane in 76% yield. Similar reaction of **1** with 2,2,3,3-tetraethylbutane afforded diethyl acetal **3**.[7] The structures of **2** and **3** were confirmed by X-ray crystallography (Figs. 1 and 2), thereby demonstrating that the benzyl aglycone and the alkoxy groups

Table 1. Asymmetric epoxidation of alkenes using uloses **5**, **6**, **7** as catalysts at room temperature

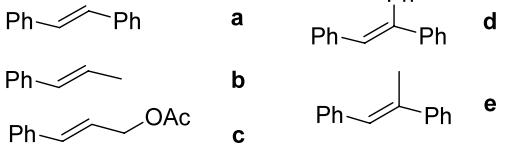


Catalyst:



5 R = Me
6 R = Et
7 R = *i*-Bu

Substrates:



Entry[a]	Catalysts	Substrates	Yield (%)[b]	Ee (%)[c]	Config.[d]
1	**5**	a	89	42	(−)-(*S*,*S*)[8]
2	**6**	a	95	54	(−)-(*S*,*S*)[8]
3	**7**	a	93	65	(−)-(*S*,*S*)[8]
4	**5**	b	82	43	(−)-(*S*,*S*)[9]
5	**6**	b	81	60	(−)-(*S*,*S*)[9]
6	**7**	b	92	68	(−)-(*S*,*S*)[9]
7	**5**	c	90	43	(−)
8	**6**	c	88	56	(−)
9	**7**	c	90	67	(−)
10	**5**	d	97	68	(+)-(*S*)[9]
11	**6**	d	95	78	(+)-(*S*)[9]
12	**7**	d	96	85	(+)-(*S*)[9]
13	**5**	e	80	75	(−)-(*S*,*S*)[9]
14	**6**	e	88	75	(−)-(*S*,*S*)[9]
15	**7**	e	95	83	(−)-(*S*,*S*)[9]

[a] All epoxidations were carried out with substrate (0.1 mmol), ulose catalyst (0.01 mmol), Oxone® (1 mmol) and $NaHCO_3$ (3.1 mmol) in CH_3CN:4×10^{-4} M aqueous EDTA (5:1, v/v) for 2.5 h.

[b] Isolated yield.

[c] Enantioselectivity was determined by ^1H NMR analysis of the epoxide products directly with shift reagent $Eu(hfc)_3$.

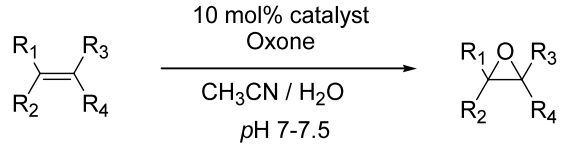
[d] The absolute configurations were determined by comparing the measured optical rotations with the reported ones.

of the acetal occupy axial positions. It is noteworthy that transacetalisation of dimethyl acetal **2** with 2-methyl-1-propanol furnished di-isobutyl acetal **4** in 85% yield. In fact, diethyl acetal **3** could also be obtained from **2** using this transacetalisation protocol. Oxidation of the free alcohol in acetals **2**–**4** with pyridinium dichromate (PDC) gave the respective uloses **5**–**7** in good yields. Uloses **5**–**7** had steric sensors, i.e. the acetal alkyl group, of different sizes that might induce different degree of enantioselectivity in catalytic epoxidation of alkenes.

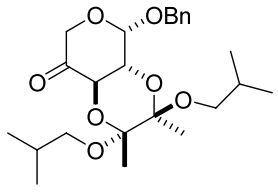
Initially, we prepared only uloses **5** and **6** to test our design of catalyst. On the basis of our previous studies,[5,6] we reasoned that the enantioselectivity should be sensitive to the size of the acetal steric sensor. The epoxidation reactions were carried out at room temperature with 0.1 mmol of substrate (disubstituted alkenes) and 10 mol% of catalyst in aqueous CH_3CN at almost neutral conditions (pH 7–7.5). These uloses **5** and **6** were found to be efficient catalysts with high chemical conversions (82–95% yields) as shown in Table 1 (entries 1, 2, 4, 5, 7, 8). Ulose **6** with a more bulky ethyl acetal group consistently displayed better chiral induction than **5**, although the ees were still moderate (54–60%). Encouraged by these results, we therefore prepared ulose **7** in order to improve the enantioselectivity of the epoxidation. The results of asymmetric epoxidation of *trans*-disubstituted and trisubstituted alkenes with uloses **5**–**7** are shown in Table 1. Indeed, the ee's enhanced with the size of the acetal alkyl group from **5** to **7** as anticipated. Ulose **7** was the most efficient catalyst (90–96% conversions) and displayed good stereochemical communication with the substrate (65–85% ee) (Table 1, entries 3, 6, 9, 12, 15).

Under improved reaction conditions at 0°C, the catalytic and chiral induction properties of **7** were further studied together with additional alkenes and the results are summarized in Table 2. The chemical yields remained high and the enantioselectivity improved significantly (up to 11% ee increase). Simple *trans*-disubstituted alkene without a phenyl substituent displayed the highest ee of 93% (Table 2, entry 5). It is noteworthy that ulose **7** could be recovered in no less than 95% yield after work-up (Table 2, entry 1) and the recovered catalyst **7** was subject to an epoxidation/recovery cycle without loss of catalytic and chiral induction power. Facile formation of other steric sensors via the transacetalisation protocol described in this paper was feasible

Table 2. Asymmetric epoxidation of alkenes using ulose **7** as catalyst at 0°C

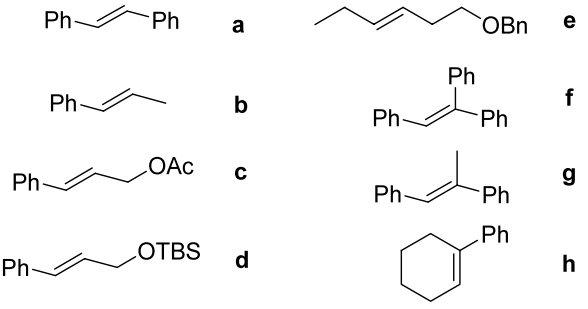


Catalyst:



7

Substrates:



Entry[a]	Substrates	Yield (%)[b]	Ee (%)[c]	Config.[d]
1	a	97	76	(−)-(*S*,*S*)[8]
2	b	89	79	(−)-(*S*,*S*)[9]
3	c	93	77	(−)
4	d	85	75	(−)-(*S*,*S*)[11,12]
5	e	92	93	(−)
6	f	99	90	(+)-(*S*)[9]
7	g	93	87	(−)-(*S*,*S*)[10]
8	h	92	85	(−)-(*S*,*S*)[13,14]

[a] All epoxidations were carried out with substrate (0.1 mmol), ulose catalyst (0.01 mmol), Oxone® (1 mmol) and $NaHCO_3$ (3.1 mmol) in CH_3CN:4×10^{-4} M aqueous EDTA (10:1, v/v) for 12 h.

[b] Isolated yield.

[c] Enantioselectivity was determined by ^1H NMR analysis of the epoxide products directly with shift reagent $Eu(hfc)_3$.

[d] The absolute configurations were determined by comparing the measured optical rotations with the reported ones.

and uloses with various acetals, such as an isopropyl group, a benzyl group, a cyclohexylmethyl, an isopentyl and a neopentyl group, had been readily synthesised. The enantioselectivity displayed by these uloses in catalytic asymmetric epoxidation is under investigation and will be reported in the full paper.

The preponderant formation of the (*S*,*S*)-enantiomer may be rationalised by the spiro[2,3] transition state resulted from a minimum steric interaction between the steric sensor and the alkene substrate, using *trans*-stilbene as an example (Fig. 3). Firstly, attack on the equatorial oxygen in dioxirane should be preferred because the axial approach of the alkene would be hindered by the axial proton of the pyran ring. Secondly, the steric repulsion between the phenyl group and the acetal alkyl group in transition state (**spiro-2**) is absent in (**spiro-1**). We have also prepared the enantiomer of **7** readily from D-arabinose and ent-**7** displayed almost identical conversion yields and ees in the formation of the (*R*,*R*)-enantiomer.

In conclusion, uloses **5**–**7**, easily prepared from L-arabinose, afforded excellent chemical yields (80–99%) of epoxides in catalytic asymmetric epoxidation. The acetal steric sensors exhibited good stereochemical communication towards *trans*-disubstituted and trisubstituted alkenes, and the enantioselectivity increased with the size of the sensor (up to 93% ee). Ulose **7** was shown to be the best catalyst and to display the best chiral induction power (93% ee for a simple *trans*-disubstituted alkene). The excellent catalytic property of **7** was demonstrated by the epoxidation/recovery cycle without loss of activity. It is noteworthy that the benzyl aglycone in ulose **7** is amenable for elaboration into a polymer support and hence opens an avenue for the development of solid-phase catalysis. The research in this direction is underway.

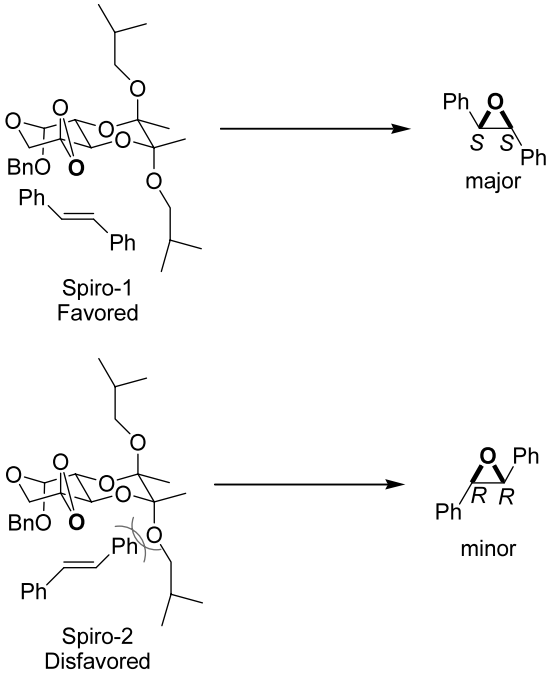


Figure 3. Spiro transition states for *trans*-stilbene epoxidation catalyzed by ulose **7**.

Acknowledgements

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