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Facile Synthesis of Enantiopure Sugar Alcohols Enabled by Asymmetric Hydrogenation via Dynamic Kinetic Resolution

Jiang Wang,[a],[c] Pan-Lin Shao,*[b],[c] Xin Lin,[b] Baode Ma,[b],[c] Jialin Wen,[c],[d] and Xumu Zhang*[c]

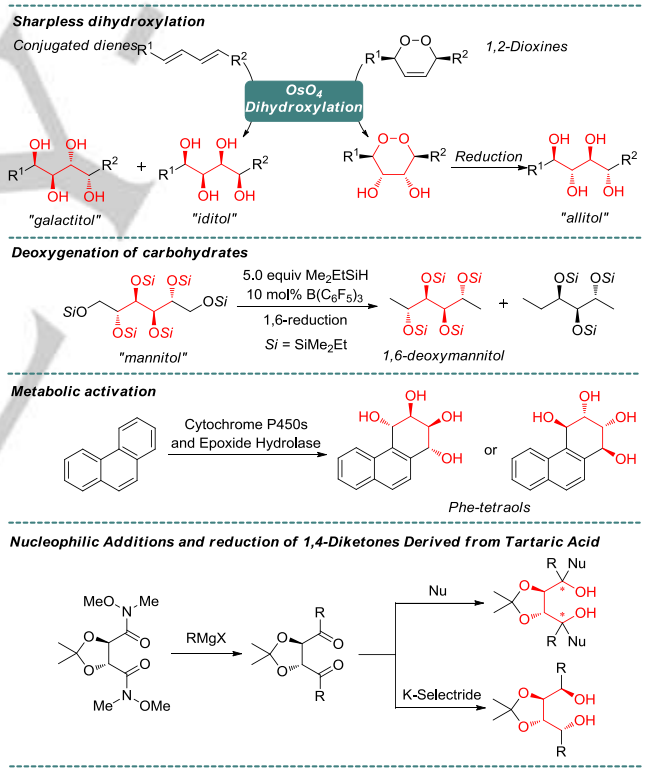
Dedicated to Professor Henry N. C. Wong on the occasion of his 70th birthday

Abstract: *Presented herein is an unprecedented Ir/f-amphox-catalyzed asymmetric hydrogenation of racemic 2,3-syn-dihydroxy-1,4-diones via dynamic kinetic resolution to produce (1R,2R,3R,4R)-tetraols. This protocol constitutes an efficient and straightforward approach to accessing sugar alcohols bearing four contiguous stereocenters. The strategy exhibits various advantages over existing methods, including excellent yields (up to 98%), exceptional stereoselectivities (up to 99:1 dr, 99.9% ee), operational simplicity and substrate generality. Moreover, the nature of the reaction was revealed as a stepwise transformation by in situ FTIR spectroscopy and isolation of intermediates.*

Carbohydrates or sugars constitute a broad range of polyhydroxylated organic compounds which are abundant in nature and implicated in a number of biological processes.[1] Up until recently, sugars were essentially only obtained from natural sources, such densely oxidized scaffolds remain valuable for applications in many disciplines such as medicinal chemistry, material science or synthetic chemistry.[2] As such, sugar alcohols, with the potential to act as sugar mimics and oxygen-functionalized chiral synthons,[3] are becoming increasingly popular as investigation targets for creating drugs and functional materials.[4] The development of straightforward synthetic methods to construct such moieties is significantly rewarding.

Generally, sugar alcohols possess several relevant points of diversity: stereogenic diversity (configuration of hydroxyl groups), substituent diversity, and length diversity of the hydroxyl chain. However, the polyhydroxylated structure always presents poor solubility in organic solvents, thermal instability, and limited scope for functionalization. Thus, sugar alcohols are relatively inaccessible, prohibiting their use in further synthesis, and denying the comprehensive assessment of structure activity relationships necessary for pharmaceutical design.[5] Herein, we report our achievement on the synthesis of 1,2,3,4-tetraols.

1,2,3,4-tetraols (C4 sugar alcohol), with four contiguous stereogenic oxidized carbons, have been considered “privileged scaffolds”, are commonly found in pharmaceuticals, agrochemicals, commodity chemicals and organic materials. Traditional synthesis to assemble 1,2,3,4-tetraol frameworks is dominated by the iterative Sharpless dihydroxylation of conjugated dienes,[6] sequential dihydroxylation of 1,2-dioxines and reduction,[7] deoxygenation of carbohydrates[8], metabolic activation,[9] and nucleophilic addition or reduction of 1,4-diketones derived from tartaric acid (Scheme 1).[10] Nevertheless, these methods are often painstaking, laborious, and time-consuming multistep processes, making the preparations typically inefficient and uneconomical.



Scheme 1. Representative strategies for 1,2,3,4-tetraol synthesis.

We sought to develop catalytic methods to construct 1,2,3,4-tetraols from non-carbohydrate starting materials, employing asymmetric hydrogenation, particularly *via* dynamic kinetic resolution (DKR) manner (Scheme 2). Over the past three decades, asymmetric hydrogenation has undergone tremendous development, evolving from pioneering examples into robust tools for modern organic synthesis.[11] These methods lay solid foundations in the context of asymmetric hydrogenation of prochiral (functional) ketones. Moreover, various stereoselective hydrogenation of racemic α-substituted (alkyl, aryl, amino, amido *et al.*) ketones were accomplished with DKR processes in the past few years, and the corresponding (functional) alcohols were

[a] J. Wang
School of Chemical Biology and Biotechnology, Peking University Shenzhen Graduate School, University Town, Nanshan District, Shenzhen, 518055, China.
[b] X. Lin, Prof. Dr. P.-L. Shao and Prof. Dr. B. Ma
College of Innovation and Entrepreneurship, Southern University of Science and Technology, 1088 Xueyuan Road, Shenzhen, 518055, China.
E-mail: shaopl@sustech.edu.cn.
[c] J. Wang, Prof. Dr. P.-L. Shao, Prof. Dr. B. Ma, Prof. Dr. J. Wen and Prof. Dr. X. Zhang
Guangdong Provincial Key Laboratory of Catalysis, Department of Chemistry, Southern University of Science and Technology, 1088 Xueyuan Road, Shenzhen, 518055, China.
E-mail: zhangxm@sustech.edu.cn.
[d] Prof. Dr. J. Wen
Academy for Advanced Interdisciplinary Studies, Southern University of Science and Technology, 1088 Xueyuan Road, Shenzhen, 518055, China.
Supporting information and the ORCID identification number(s) for the author(s) for this article can be found under http://www.angewandte.org

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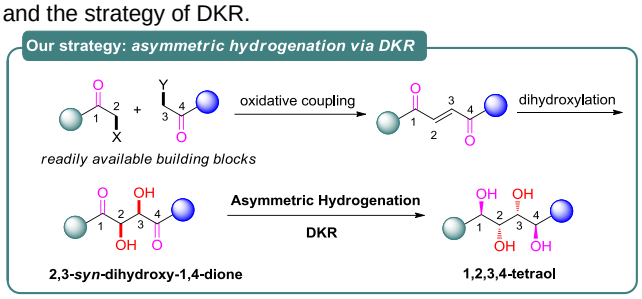
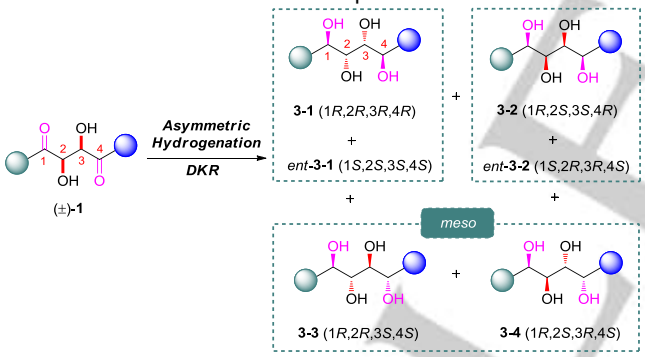
efficiently produced.[12] However, to the best of our knowledge, the asymmetric hydrogenation of *α*-hydroxyketones *via* DKR, and specifically, the synthesis of polyols have been systematically neglected. Hereby, we envisioned that a facile synthetic route to 1,2,3,4-tetraols from cheap building blocks such as acetophenones might be realized with asymmetric hydrogenation and the strategy of DKR.



Scheme 2. Our strategy for 1,2,3,4-tetraol synthesis.

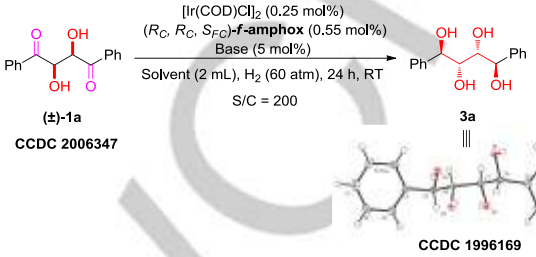
For an asymmetric hydrogenation strategy to reach its full potential, the transformation with high levels of chemo-, regio- and stereo-selectivities must be identified and developed. As a benchmark for testing our strategy, we hypothesized that if the enantioselective hydrogenation of racemic 2,3-*syn*-dihydroxy-1,4-diones (±)-**1**[13] via DKR could be performed, chiral 1,2,3,4-tetraols (**3**) with four contiguous stereocenters would be obtained with high stereochemical purity in a single reaction (Scheme 3). Taken symmetry into consideration, the absolute configuration of C1 should be kept the same with C4, and similarly, the absolute configuration of C2 should be the same with C3. Therefore, no *meso*-isomers **3-3** and **3-4** should be generate. In fact, the rationale was consistent with our experimental results.



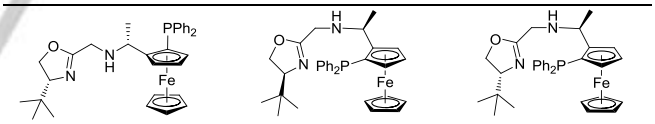
Scheme 3. Concept of catalytic asymmetric hydrogenation of 2,3-*syn*-dihydroxy-1,4-diones.

Our recent effort has accumulated in the use of Ir/*f*-amphox-catalyzed asymmetric hydrogenation system to synthesize secondary (functionalized) alcohols.[14] We were drawn to this particular catalyst, due to its inherent advantages and the major contributions it has already made with superb activities and excellent enantioselectivities (up to 1,000,000 TON). As shown in Table 1, our study commenced with assaying the asymmetric hydrogenation and investigation the feasibility of DKR using the racemic *syn*-2,3-dihydroxy-1,4-diphenyl-1,4-butanedione (±)-**1a** (CCDC **2006347**, see SI for details)[15] as the model substrate, and Ir/(*Rc*, *Rc*, *SFC*)-*f*-amphox as the catalyst. A survey of solvents identified THF as the most suitable media (entries 1-7), affording predominantly the desired 1,2,3,4-tetraol **3a** with excellent enantioselectivity (>99.9% ee) and diastereoselectivity (>99:1 dr) in quantative yield (entry 7). Interestingly, using (*Rc*, *Sc*, *RFC*)-*f*-amphox as ligand, we did obtain the product enriched in the opposite enantiomer in full conversion though with moderate enantioselectivity (entry 8). Several bases were screened to evaluate their ability to promote the hydrogenation (entries 9-14), however the level of efficiency and selectivities were far from satisfactory. Lowering the H_2 pressure (30 atm) led to a dramatic negative impact on the conversion (entry 12).

Table 1. Screening of reaction conditions.[a]



Entry	Solvent	Base	Conversion (%)[b]	ee (%)[c]
1	MeOH	Cs_2CO_3	72	79
2	EtOH	Cs_2CO_3	77	87
3	^{i}PrOH	Cs_2CO_3	83	99.4
4	DCM	Cs_2CO_3	70	>99.9
5	EA	Cs_2CO_3	85	91
6	Toluene	Cs_2CO_3	87	86
7	THF	Cs_2CO_3	>99	>99.9
8[d]	THF	Cs_2CO_3	>99	-57
9	THF	Na_2CO_3	13	71
10	THF	K_2CO_3	64	99
11	THF	NaOH	78	79
12	THF	KOH	73	99
13	THF	^{t}BuONa	<5	--
14	THF	^{t}BuOK	22	88
15[e]	THF	Cs_2CO_3	70	>99.9



[a] Reaction conditions: (±)-**1a** (0.20 mmol), $[Ir(COD)Cl]_2$ (0.0005 mmol), (*Rc*, *Rc*, *SFC*)-*f*-amphox (0.0011 mmol), Cs_2CO_3 (0.01 mmol), solvent (2 mL), H_2 (60 atm), RT, 24 h. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC analysis, and racemic samples for the standard of chiral HPLC spectra were prepared using the mixture of 0.25 mol % (*Rc*, *Rc*, *SFC*)-*f*-amphox and 0.25 mol % (*Sc*, *Sc*, *RFC*)-*f*-amphox as ligands. [d] (*Rc*, *Sc*, *RFC*)-*f*-amphox (0.0011 mmol) instead of (*Rc*, *Rc*, *SFC*)-*f*-amphox. [e] H_2 pressure = 30 atm.

We identified the following protocol as optimal: hydrogenation of (±)-**1a** with Ir/(*Rc*, *Rc*, *SFC*)-*f*-amphox (0.5 mol%) in the presence of H_2 (60 atm) and Cs_2CO_3 (5 mol%) in THF at room temperature for 24 h. The relative and absolute configurations of **3a** were determined to be "*anti*−*syn*−*anti*" and (1*R*,2*R*,3*R*,4*R*) by single crystal X-ray crystallographic analysis (CCDC **1996169**, see SI for details).[15] The configurations of other 1,2,3,4-tetraols **3** and **4** in Table 2 were assigned by analogy.

Under the optimal conditions, the effect of substitution of 2,3-*syn*-dihydroxy-1,4-diones (±)-**1** on the reactivity and stereoselectivity was investigated (Table 2). Gratifyingly, with

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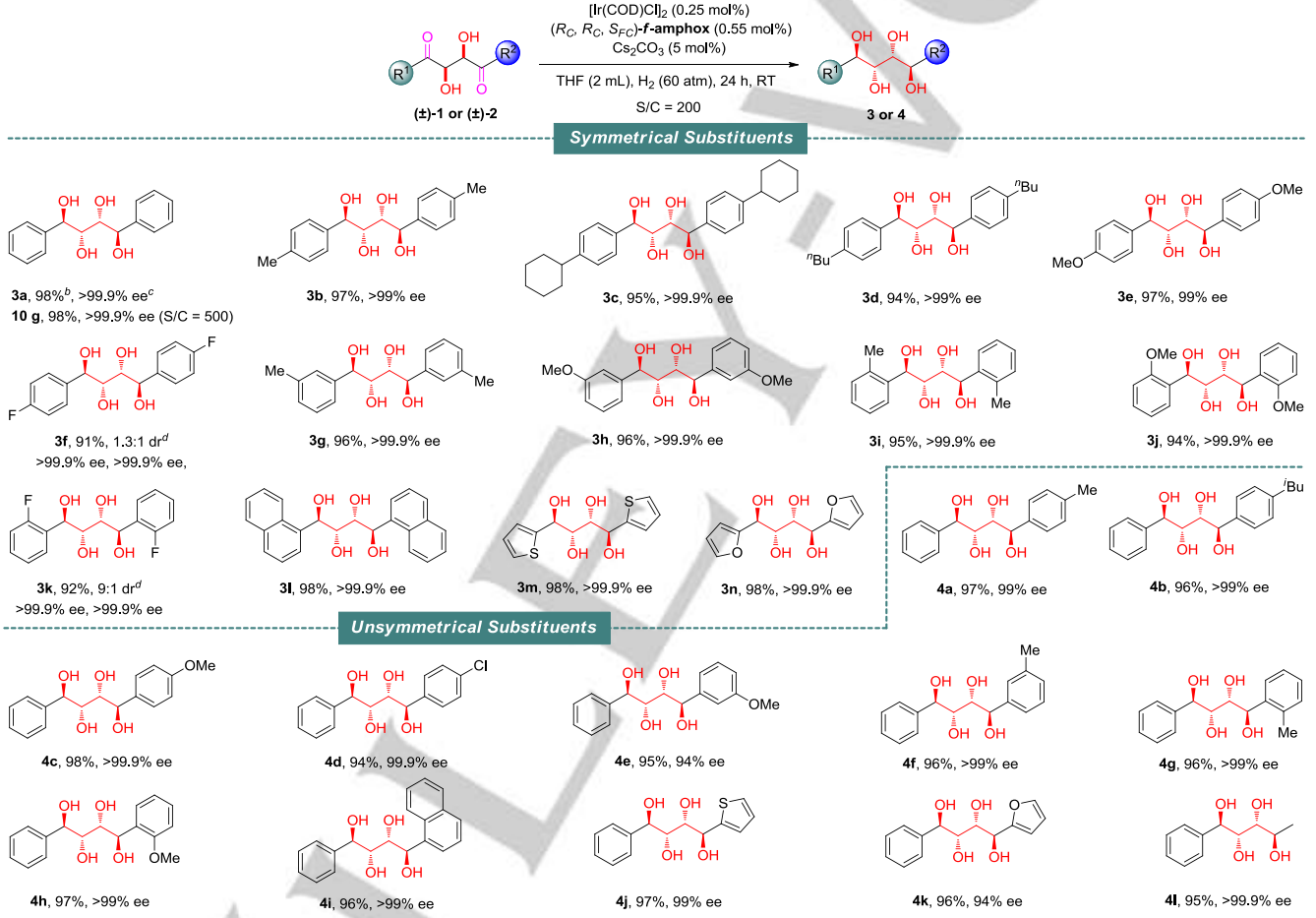
respect to the substrates bearing symmetrical substituents (±)-**1** ($R^1 = R^2$) or unsymmetrical substituents (±)-**2** ($R^1 \neq R^2$), Ir/(*Rc*, *Rc*, S_{FC})-*f*-amphox system could act as the highly efficient catalyst in the asymmetric hydrogenation *via* DKR sequence, furnishing the *anti*−*syn*−*anti*-tetraols **3 or 4** in uniformly almost quantitative yields with exclusive enantioselectivities, respectively. Different substitution patterns on the aryl ring (*para*, *meta* and *ortho*) were all well tolerated, and the electronic properties of these substituents does not show notable influence. Moreover and notably, in almost all cases perfect diastereoselectivities were obtained for the 1,2,3,4-tetraols (>99:1 dr) except **3f** (1.3:1 dr) and **3k** (9:1 dr), which bear F atom at the *para* or *ortho* position of the phenyl groups, respectively. To our delight, when the R^2 group of **3i** was an aliphatic substituent (Me), the reaction also showed perfect enantioselectivity (>99.9% ee) and diastereoselectivity (>99:1 dr). Such a facile transformation with excellent stereocontrol represents an important and straightforward approach, which would constitute significant interests, not only because chiral 1,2,3,4-tetraols are a privileged substructure in various bioactive molecules, but also because it could rapidly increase molecular diversity and complexity, thereby facilitating streamlined synthesis of polyhydroxylated organic compounds.

Of particular note, the method can be readily scaled up to a preparative scale (10 g) without erosion of the yield and enantioselectivity. Moreover and interestingly, the product can be obtained by simply filtering the precipitates formed from the reaction. So the scaling up was straightforward and demonstrated the practicability of this methodology.

Table 2. Substrate scope.[a]



[a] Unless otherwise indicated, the reactions were carried out with (±)-**1** or (±)-**2** (0.20 mmol), $[Ir(COD)Cl]_2$ (0.0005 mmol), (R_C, R_C, S_{FC})-*f*-amphox (0.0011 mmol), Cs_2CO_3 (0.01 mmol), THF (2 mL), H_2 (60 atm), RT, 24 h; [b] Determined after chromatographic purification; [c] Determined by HPLC analysis; [d] Determined by ^{1}H NMR analysis of crude reaction mixture.

In an effort to better understand the mechanism of the system, the kinetics of the reaction were monitored by *in situ* FTIR spectroscopy. The intensity of carbonyl peak at ~1695 cm^{-1} decaded over the course of reaction time. It suggested neither a first order or a zeroth order kinetics and a noticeable change of slope was found when the curve droped to half (marked with red dotted line). We made the assumption that the reaction from (±)-**1a** to **3a** is stepwise since the intensity of carbonyl is in proportional to the number of carbonyls. The formation of mono-reduced species **5** was supposed to be much faster than the further hydrogenation to double-reduced tetraol **3a** ($k_1 > k_2$). The stimulated concentration of species in the reaction mixture was depicted in Scheme 4 (see SI for details).

Actually, we have experimentally revealed the nature of this stepwise transformation from (±)-**1a** to **3a**. As shown in Scheme 5a, when the reaction was quenched at 30 min, the mono-reduced product triol **5** was isolated in 27% yield with 4:1 dr[16] and >99.9% ee (major), and the double-reduced product tetraol **3a** was trace. Meanwhile, the kinetic resolution of (±)-**1a** was also observed. When the reaction was quenched at 1 h (Scheme 5b), the triol **5**

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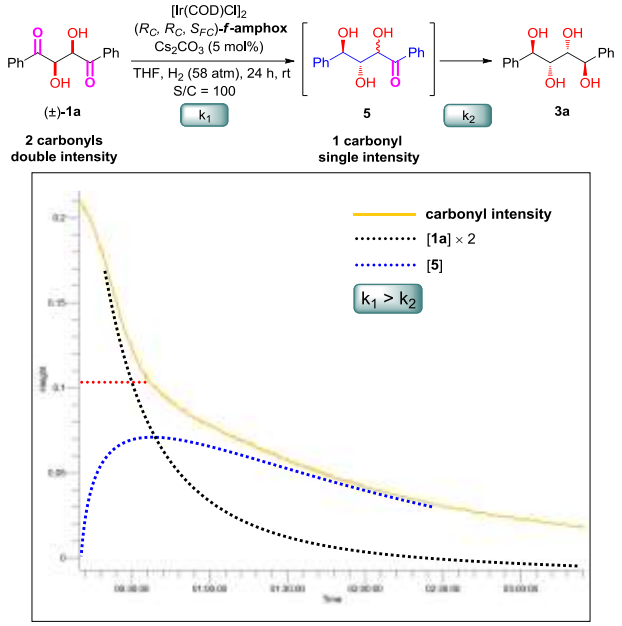
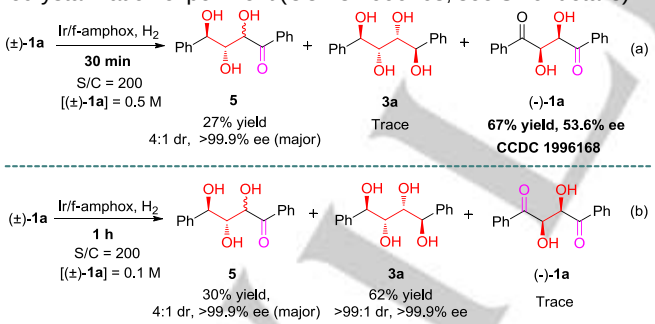


Scheme 4. React kinetics obtained with FTIR demonstrating a stepwise pathway. An approximation was made that the intensity of carbonyl peak is in proportational to the numbers of carbonyls, regardless of different species.

was isolated in 30% yield with 4:1 dr[16] and >99.9% ee (major), and tetraol **3a** was isolated in 62% yield with >99:1 dr and >99.9% ee. Only a trace amount of **1a** was detected.

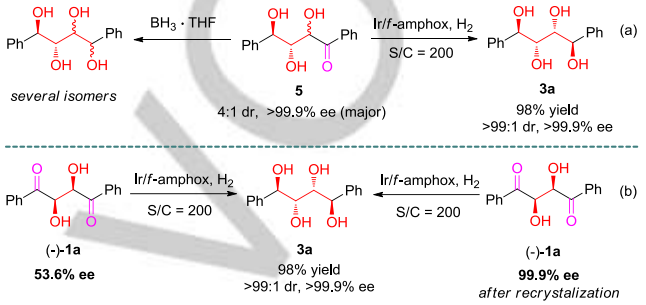
More interestingly, 67% of the diol with 53.6% ee was recovered after 30 min (Scheme 5a). This means that the enantiomeric ratio ((-)-**1a** : (+)-**1a**) is 76.8 : 23.2. This suggest that initially only (+)-**1a** is converted and the racemization of (-)-**1a** starts once (+)-**1a** have been largely consumed (see SI for details). The hydrogenation only occurs, highly selectively, on the carbonyl flanked by the carbon atom with the correct configuration. The absolute configuration of (-)-**1a** was unambiguously determined to be (2*R*,3*R*) by single crystal X-ray crystallographic analysis after recrystallization experiment (CCDC **1996168**, see SI for details).[15]



Scheme 5. Isolation of intermediate.

The racemization/epimerization of (-)-**1a** (99.9% ee, after recrystalization) was observed in the presence of Cs_2CO_3 (5 mol%) (see SI for details). Strikingly, during the first 30 minutes, a rapid 16.1% conversion of (-)-**1a** into (+)-**1a** (11.6%, racemization) and *meso*-**1a** (4.5%, epimerization) was obtained. Within 60 minutes, the conversion rose to 21.4% (15.5% into (+)-**1a**, 5.9% into *meso*-**1a**). Later on, there was no obvious racemization/epimerization occurred. Within 24 hours, 25.8% conversion of (-)-**1a** into (+)-**1a** (18.6%) and *meso*-**1a** (7.1%) was observed.

In addition, the isolated mono-reduced product triol **5** could be further hydrogenated. However, using BH_3•THF as reducing reagent, the reaction gave a complicated mixture, which might be attributed to the formation of several isomers. To our delight, using Ir/(*Rc*, *Rc, S*$_{FC}$)-*f*-amphox as the catalyst, the reaction could afford the desired 1,2,3,4-tetraol **3a** in 98% yield with >99:1 dr and >99.9% ee by asymmetric hydrogenation *via* DKR (Scheme 6a). Furthermore, the recovered optically active diol (-)-**1a** (53.6% ee or 99.9% ee) could be hydrogenated as expected under the optimal conditions, both furnishing **3a** in 98% yield with >99:1 dr and >99.9% ee (Scheme 6b).



Scheme 6. Hydrogenation of optically active triol **5** and diol (-)-**1a**.

In this report, we have introduced a facile, practical and straightforward synthetic method for the construction of sugar alcohol 1,2,3,4-tetraols using Ir/*f*-amphox-catalyzed asymmetric hydrogenation of 2,3-*syn*-dihydroxy-1,4-diones *via* dynamic kinetic resolution. A variety of optically enriched sugar alcohols bearing four contiguous stereocenters were obtained from non-carbohydrate starting materials. The strategy exhibits various advantages over existing methods, including excellent yields (up to 98%), exceptional stereoselectivities (up to 99:1 dr, 99.9% ee), operational simplicity and substrate generality. Moreover, the nature of the reaction was revealed as a stepwise transformation by *in situ* FTIR spectroscopy and isolation of intermediates.

Acknowledgements

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Keywords: Asymmetric Hydrogenation • 1,2,3,4-Tetraols • Sugar Alcohol• Dynamic Kinetic Resolution

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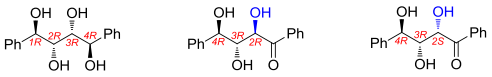
[15] CCDC 2006347 ((±)-**1a**), 1996168 (**(-)-1a**) and 1996169 (**3a**) contain the supplementary crystallographic data for this paper. Selected data is also included in the Supporting Information.

[16] The absolute configurations of C3 and C4 of triol **5** should be kept the same with the C1 and C2 of 1,2,3,4-tetraol **3a**. The diastereomers are *anti-anti*-**5** and *anti-syn*-**5**. The dr of compound **5** is the molar ratio of the two diastereomers (major : minor), and the dr value was determined by ^{1}H NMR analysis of crude reaction mixture. Because the two diastereomers are easy to epimerize at C2 stereocenter, the dr value (4:1) does not mean the real diastereoselectivity, only reflects the molar ratio of the diastereomers at the time of NMR data acquisition.



3a ***anti-anti*-5** ***anti-syn*-5**

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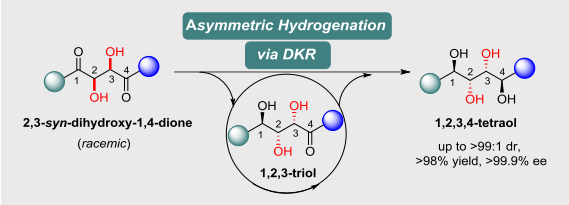

Presented herein is an Ir/*f*-amphox-catalyzed asymmetric hydrogenation of racemic 2,3-*syn*-dihydroxy-1,4-diones *via* dynamic kinetic resolution to produce 1,2,3,4-tetraols. This protocol constitutes an efficient and straightforward approach to accessing chiral sugar alcohols. The nature of the reaction was revealed as a stepwise transformation by *in situ* FTIR spectroscopy and isolation of intermediates.

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Facile Synthesis of Enantiopure Sugar Alcohols Enabled by Asymmetric Hydrogenation via Dynamic Kinetic Resolution