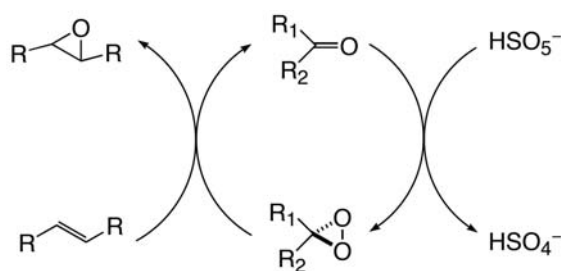# 1,2:4,5-双-O-异丙叉-D-erythro-2,3-己二酮2,6-吡喃糖（Shi不对称环氧化催化剂）的合成

环双氧烷类化合物是有多种用途的氧化试剂，在不对称合成，特别是不对称环氧化反应中给出了很好的结果。环双氧烷可以用过硫酸氢钾与酮原位生成。(Scheme 1).[2]理论上只需催化量的酮，所以有可能用手性酮进行催化的不对称环氧化反应。[3,4]自从Curci于1984年报道了首例手性环双氧烷对烯烃的不对称环氧化反应，[3a]这一领域受到广泛关注并取得了极大进展。

Scheme 1

这个实验中果糖衍生的酮具有如下特征：（1）手性中心靠近反应中心，所以催化剂的立体化学特性可以有效地传递给反应物。（2）稠环或季碳与羰基相连减少了手性中心异构化的可能。（3）*C2*-或准*C2*对称元素阻挡烯烃一个面靠近环双氧烷反应，所以受到立体控制。（4）连接吸电子取代基活化了羰基。这种酮对各种反式二取代烯和三取代烯都显示了很高的对映选择性。[4]此酮催化剂可用很廉价的**D**-果糖很容易地合成：先用丙酮反应得到缩酮[1e,h]，再氧化剩余的羟基得到酮。

一、反应式
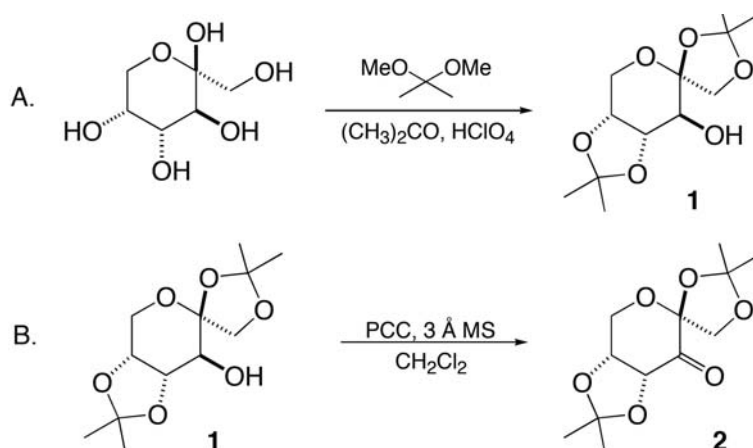
二、操作流程

A. 1,2:4,5-双-O-异丙叉-β-D-吡喃果糖（1）

D-果糖(0.9 g, 5 mmol)，2,2-二甲氧基丙烷(0.4 mL, 3.1 mmol)和15 mL丙酮加入一个50 mL圆底烧瓶，配一个带特氟龙涂层的搅拌磁子。烧瓶在冰浴中冷却15 min，然后一次加入0.2 mL 70%高氯酸(Note 1)。所得悬浮物在0 °C下(Note 2)搅拌6小时。然后加0.25 mL浓氨水将酸中和，再保持于25 °C下旋转蒸发除去溶剂，得到白色固体。将固体溶在10 mL二氯甲烷中，并用饱和氯化钠溶液洗涤(3 mL×2)，加无水Na$_2$SO$_4$干燥，过滤，再旋转蒸发(25 °C)浓缩，直

到体积减小到约2 mL (Note 3)。加入5 mL沸腾的石油醚(Note 4)，然后烧瓶自然冷却到室温，可看到产物晶体析出。继续冷却到-25 °C放4 小时可以结晶出第二批晶体。抽滤分出固体，用冷却到-25 °C的石油醚仔细洗涤(1 mL×3)，得到0.6 g(46%)目标化合物很好的白色针状晶体。

B. 1,2:4,5-双-O-异丙叉-D-erythro-2,3-己二酮-2,6-吡喃糖 (2)

一个配有梭形磁搅拌子的25 mL圆底烧瓶中加7 mL CH$_2$Cl$_2$，上步产物(0.52 g, 2.0 mmol)和新粉碎的3 Å分子筛0.75 g。氯铬酸吡啶(1.05 g, 5.0 mmol)在10 min内分批加入，所得混合物在室温下搅拌15小时(Note 5)。剧烈搅拌下慢慢加入10 mL乙醚，溶液经2g 硅藻土层抽滤。反应瓶中残留的固体用刮勺转移到硅藻土层上，并用2-3mL乙醚洗涤。得到的雾状棕色滤液在室温下旋转蒸发浓缩后给出棕色固体。将固体与2 mL 1:1乙醚:石油醚混合，用刮勺将固体研碎。混合物倒在用3 g 200-400 目硅胶装填的色谱柱上，液体自然吸附在硅胶上(Note 7)。烧瓶中残留的物料继续用1:1乙醚:石油醚洗涤并转移到硅胶柱上。反复如此操作，直到所有物料均加载到硅胶柱上。产物酮用20-30 mL 1:1乙醚:石油醚洗脱，洗脱液旋转蒸发浓缩后可得到白色固体粗品产物。将这些固体溶解在2 ml沸腾的石油醚中。待溶液冷却到室温，目标产物酮开始结晶。烧瓶在-25 °C冷却2小时。所得固体抽滤收集，用石油醚洗涤(1 mL×3)，干燥后可以得到0.44-0.45 g (86-88%)白色固体。

三、 注意事项

1、70%与有机物的反应可能会出现着火甚至爆炸，无水HClO$_4$是威力很大的爆炸物。操作这种化合物一定要小心。

2、悬浊液在1-2小时后会变成清澈的无色溶液。目标化合物是反应的动力学产物，会很容易异构化为2,3:4,5-di-O-异丙叉-β-D-吡喃果糖（热力学产物）。反应时间控制对减少热力学产物的生成是很重要的。

3、溶剂体积稍改变一点对重结晶一步的产率没有太大影响。

4、白色晶体产物在加石油醚5分钟后就开始沉淀出来。

5、反应过程中混合物颜色从橙棕色变为深褐色，这是Cr(VI)被还原到Cr(III)的表现。

6、乙醚慢加是得到高产率的关键。加乙醚只是将少量还原态的铬盐沉淀出来。过滤主要是除掉分子筛和搅拌过程中吸附上去的铬盐。

7、若不把所有棕色固体加载到硅胶柱上会降低酮的产率（固体中含有一些酮）。

缩酮反应中其他酸，例如H$_2$SO$_4$也可以用。[1c,f,i]尽管这个实验中用PCC来氧化，其它氧化剂如PDC-Ac$_2$O,[1f] DMSO-Ac$_2$O,[1a,b,d] DMSO-DCC,[1e] DMSO-(COCl)$_2$,[1g] RuCl$_3$-NaIO$_4$,[1h] Ru-TBHP,[1j]等也行。这个催化剂的对映体可用L-果糖按相同方式制备出来，而L-果糖可用易得的L-山梨糖制备出来。显然，对映体催化剂在环氧化反应中对映选择性是相同的。

果糖衍生出的酮催化反式二苯乙烯的不对称环氧化

—(*R,R*)-*trans*-环氧化二苯乙烯
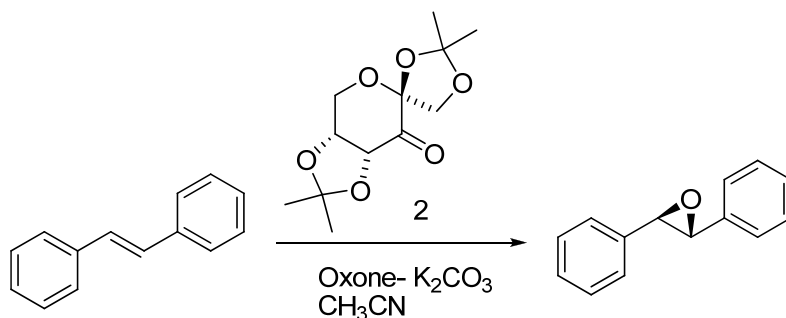
一、操作流程

0.181 g反式二苯乙烯(1 mmol)溶于15 mL乙腈(Note 1)。接着加入10 mL 缓冲溶液(0.05 M Na$_2$B$_4$O$_7$·10H$_2$O 溶于4×10^{-4} M Na$_2$(EDTA)水溶液中制成), 0.015 g四丁基硫酸氢铵 (0.04 mmol)和0.0774 g Shi酮催化剂(0.3 mmol)。反应混合物用冰浴冷却。1.0 g Oxone (1.6 mmol)溶于6.5 mL Na$_2$(EDTA) (4×10^{-4} M)配成的溶液和0.93 g K$_2$CO$_3$(6.74 mmol)溶于6.5 mL水配成的溶液分别用滴液漏斗滴加，90分钟加完(Note 2)。滴加完成后，反应混合物在0 ℃ (Note 3)下继续搅拌0.5- 1 h。反应体系中加10 mL石油醚和10 mL水。混合物用石油醚萃取(3×10 mL)，盐水洗涤，无水Na$_2$SO$_4$干燥，过滤，浓缩(Note 4)，并用制备薄层色谱法纯化(Note 5)。

二、注意事项

1、所有环氧化反应用玻璃仪器必须仔细洗涤干净，除掉微量金属，因为金属会催化Oxone分解。洗涤剂洗过后大量水洗，然后用丙酮洗涤。

2、反应混合物中Oxone的浓度和反应体系的pH是决定环氧化反应效率的重要参数。向反应混合物中滴加Oxone 和K$_2$CO$_3$溶液的速度在1.5小时内一定要保持平稳一致。

3、随着反应进行，有机相与水相逐渐分开。在滴加的前10-20分钟，盐会沉淀出来。一定要剧烈搅拌才能将两相混合，不过，要避免反应混合物过多喷洒出来，这样才能提高转化率。

4、环氧化产物容易挥发。浓缩过程中要小心减少其流失。

5、硅胶板在点样前用含有1%三乙胺的石油醚跑一遍以中和其酸性。

SYNTHESIS OF

1,2:4,5-Di-O-isopropylidene-D-erythro-2,3-hexodiulo-2,6-pyra nose. A HIGHLY ENANTIOSELECTIVE KETONE CATALYST FOR EPOXIDATION

Dioxiranes are remarkably versatile oxidizing agents which show encouraging potential for asymmetric synthesis, particularly asymmetric epoxidation. Dioxiranes can be generated in situ from Oxone ($KHSO_5$) and ketones (Scheme 1).[2] In principle, only a catalytic amount of ketone is required, so with a chiral ketone there exists the opportunity for catalytic asymmetric epoxidation.[3,4] Since the first asymmetric epoxidation of olefins with a chiral dioxirane reported by Curci in 1984,[3a] this area has received intensive interest and significant progress has been made.[3,4]

The fructose-derived ketone described herein is a member of a class of ketones designed to contain the following general features: (1) The stereogenic centers are close to the reacting center, resulting in efficient transfer of stereochemistry between substrate and catalyst. (2) The presence of fused ring(s) or a quaternary center α to the carbonyl group minimizes epimerization of the stereogenic centers. (3) Approach of an olefin to the reacting dioxirane can be controlled by sterically blocking one face or using a C2- or pseudo-C2-symmetric element. (4) Electron-withdrawing (by induction) substitutents are introduced to activate the carbonyl. This ketone gives very high enantioselectivities for a variety of transdisubstituted and trisubstituted olefins.[4] The ketone catalyst can be readily synthesized from very inexpensive D-fructose by ketalization with acetone[1e,h] and subsequent oxidation of the remaining alcohol to the ketone. Other acids such as H_2SO_4 can also be used for ketalization.[1c,f,i] Although the present procedure uses PCC for the oxidation, many other oxidants such as PDC-Ac$_2$O,[1f] DMSO-Ac$_2$O,[1a,b,d] DMSO-DCC,[1e] DMSO-(COCl$_2$),[1g] RuCl$_3$-NaIO$_4$,[1h] Ru-TBHP,[1j] etc. are also effective. The enantiomer of catalyst **1**(**ent-1**) can be prepared in the same fashion from L-fructose, which in turn can be prepared from readily available L-sorbose.[5,4c] As expected, the enantiomeric catalyst shows the same enantioselectivity in epoxidation reactions.
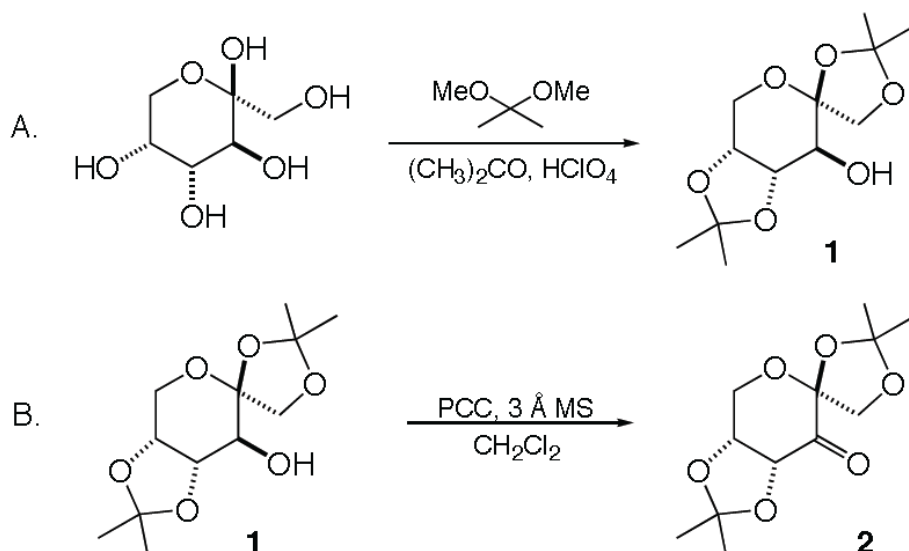
1. Procedure

A. *1,2:4,5-Di-O-isopropylidene-β-D-fructopyranose* (1).

D-Fructose (0.9 g, 5 mmol) and 2,2-dimethoxypropane (0.4 mL, 3.1 mmol) are added to 15 mL of acetone in a 50 mL, round-bottomed flask equipped with a Teflon-coated magnetic stir bar. The flask is cooled in an ice bath for 15 min, then 0.2 mL of 70% perchloric acid (Note 1) is added in one portion. The resulting suspension is stirred for 6 h at 0 °C (Note 2). Concentrated ammonium hydroxide (0.25 mL) is then added to neutralize the acid and the solvent is removed by rotary evaporation at 25 °C to give a white solid. This solid is dissolved in 10 mL of dichloromethane (CH$_2$Cl$_2$) and washed with two 3-mL portions of saturated sodium chloride solution, dried over sodium sulfate (Na$_2$SO$_4$), filtered, and concentrated by rotary evaporation (25 °C) until the total volume is about 2 mL (Note 3). Boiling hexane (5 mL) is then added (Note 4) and the flask is allowed to cool to room temperature, during which time the bulk of the product crystallizes out of solution. Additional product crystallizes upon cooling to -25 °C for 4 h. Isolation of the solid by vacuum filtration and careful washing with three 1-mL portions of cold (-25 °C) hexane gives 0.6 g (46%) of the title alcohol as fine white needles.

### B. *1,2:4,5-Di-O-isopropylidene-D-erythro-2,3-hexodiulo-2,6-pyranose*

(2).

A 25-mL, round-bottomed flask equipped with a egg-shaped Teflon-coated magnetic stir bar is charged with 7 mL of CH$_2$Cl$_2$, the alcohol prepared in Step A (0.52 g, 2.0 mmol), and 0.75 g of freshly powdered 3 Å molecular sieves. Pyridinium chlorochromate (1.05 g, 5.0 mmol) is added portionwise over 10 min and the resulting mixture is stirred at room temperature for 15 h (Note 5). Ether (10 mL) is added slowly with vigorous stirring and the solution is filtered under vacuum through a pad of 2 g of Celite (Note 6). The solids remaining in the reaction flask are transferred to the Celite pad by scraping with a spatula and washing with three 2-3-mL portions of ether. The resulting cloudy brown filtrate is concentrated by rotary evaporation at room temperature to give a brown solid. To this solid is added 2 mL of 1:1 ether:hexane and the solids are scraped with a

spatula. The mixture is then poured onto 3 g of Whatman 60 Å (230-400 mesh) silica gel packed in a chromatography column and the liquid is adsorbed onto the silica gel by gravity (Note 7). The material remaining in the flask is further washed with 1:1 ether:hexane and transferred onto the silica gel; this process is repeated until all the material has been loaded onto the silica gel. The ketone is eluted using 20-30 mL of 1:1 ether:hexane and the eluent is concentrated by rotary evaporation to afford the crude ketone as a white solid. This material is dissolved in 2 mL of boiling hexane. Upon cooling the solution to room temperature, the ketone begins to crystallize. The flask is then cooled to -25 °C for 2 h. The resulting solids are collected by filtration, washed with three 1-mL portions of cold (-25 °C) hexane, and dried to afford 0.44-0.45 g (86-88%) of the ketone as a white solid.

2. Notes

1. Reaction of 70% perchloric acid with organic materials can lead to fires and explosions, and anhydrous $HClO_4$ is potentially explosive. Care should be taken in handling this compound.
2. The suspension turns into a clear, colorless solution after 1-2 h. The title compound is the kinetic product of the reaction, and can readily isomerize to 2,3:4,5-di-O-isopropylidene-**β**-D-fructopyranose (the thermodynamic product). Control of the reaction time is important to minimize the formation of the thermodynamic product.
3. The solvent volume can vary slightly without much effect on the yield of the recrystallization step.
4. The white, crystalline product begins to precipitate in the first 5 min after the addition of hexane.
5. The mixture turns from orange-brown to a dark brown color during the course of the reaction, indicating the reduction of Cr(VI) to Cr(III).
6. Slow addition of ether is necessary for a high yield. The addition of ether leads to the precipitation of only a small amount of the reduced chromium. This filtration mainly removes the molecular sieves and chromium species adsorbed during stirring.
7. The yield of the ketone will be reduced if all the brown solids are not loaded onto the column (these solids contain some of the ketone).

ASYMMETRIC EPOXIDATION OF *trans*-STILBENE USING A D-FRUCTOSEDERIVED KETONE: (*R,R*)-*trans*- STILBENE OXIDE
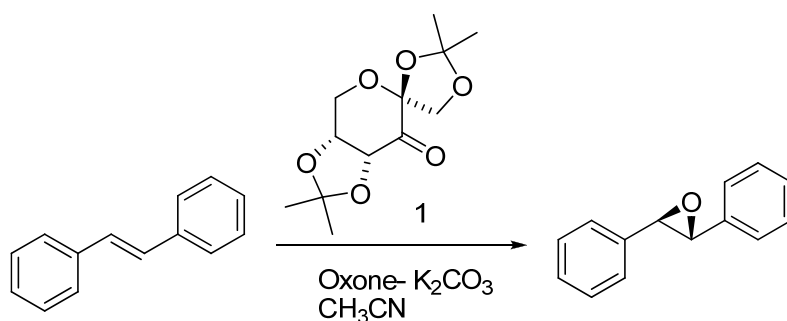
1. Procedure

trans-Stilbene (0.181 g, 1 mmol) was dissolved in 15 mL acetonitrile, (Note 1). Subsequently were added buffer (10 mL, 0.05 M solution of $Na_2B_4O_7 \cdot 10H_2O$ in 4×10^{-4} M aqueous $Na_2(EDTA)$), tetrabutylammonium hydrogen sulfate (0.015 g, 0.04 mmol), and ketone 1 (0.0774 g, 0.3 mmol). The reaction mixture was cooled with an ice bath. A solution of Oxone (1.0 g, 1.6 mmol) in aqueous $Na_2(EDTA)$ (4×10^{-4} M, 6.5 mL) and a solution of K_2CO_3 (0.93 g, 6.74 mmol) in water (6.5 mL) were added dropwise separately over a period of 90 min (via addition funnels) (Note 2). After completion of the addition, the reaction mixture was stirred for another 0.5- 1 h at 0 °C (Note 3). At this point, the reaction was added pentane (10 mL) and water (10 mL). The mixture was extracted with pentane (3×10 mL), washed with brine, dried over Na_2SO_4, filtered, concentrated (Note 4), and purified by preparatory thin layer chromatography (Note 5).

2. Notes

1. All glassware used for the epoxidation reaction is carefully washed to remove trace metals, which may catalyze the decomposition of Oxone. The checkers used Alconox, followed by water, and then acetone.
2. The concentration of Oxone in the reaction mixture and the reaction pH are very important factors in determining the epoxidation efficiency. Both the Oxone and K_2CO_3 solutions must be added to the reaction mixture in a steady, uniform manner over 1.5 h.
3. As the reaction progresses, the organic and aqueous phases separate. Salts precipitate during the first 10-20 min of addition. Vigorous stirring is required to sufficiently mix the two phases; however, excessive splashing of the reaction mixture must be avoided in order to maximize conversion.
4. The epoxide product is volatile. Care should be taken to minimize the loss of the epoxide during concentration.

5. The silica gel is buffered by running the plate with hexane containing 1% triethylamine before the sample is spotted.

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Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 7819; (h) Tu, Y.; Wang, Z.-X.; Frohn, M.; He, M.; Yu, H.; Tang, Y.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 8475; (i) Wang, Z.-X.; Cao, G.-A.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7646; (j) Warren, J. D.; Shi, Y. *J.Org. Chem.* **1999**, *64*, 7675; (k) Shu, L.; Shi, Y. *Tetrahedron Lett.* **1999**, *40*, 8721.

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