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An Improved Synthesis of a Ketone Catalyst for Asymmetric Epoxidation of Olefins

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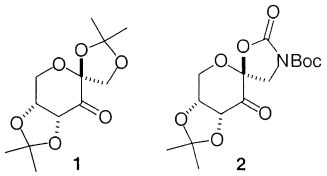
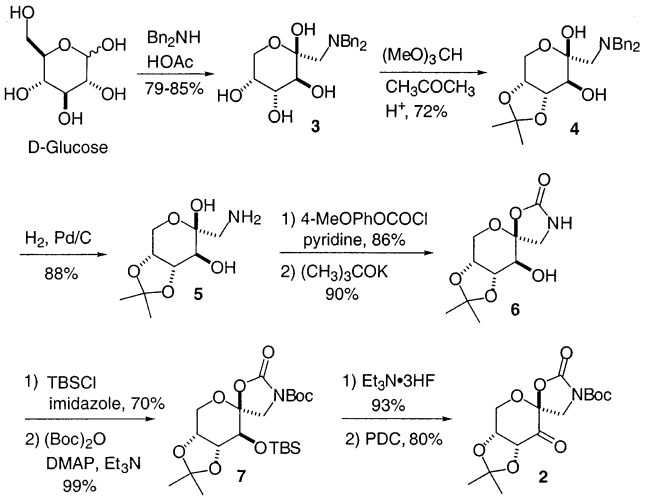
Abstract: An efficient synthesis of a ketone catalyst for asymmetric epoxidation of olefins from D-glucose in six steps is described.

Dioxiranes generated *in situ* from chiral ketones have been shown to be highly enantioselective for the asymmetric epoxidation of olefins.[1−3] Previously, we reported that fructose-derived ketone **1** is an effective epoxidation catalyst and gives high ee's for a variety of *trans*- and trisubstituted olefins (Scheme 1).[4] Recently, we reported that ketone **2**, a nitrogen analogue of **1**, provides encouragingly high ee's for the epoxidation of *cis*-olefins and styrenes.[5] The drawback of our original synthesis of ketone **2** is that it requires nine steps and some expensive reagents (Scheme 2), which makes this ketone catalyst less convenient. Considering that this ketone catalyst can potentially be useful, efforts have been made to improve its synthesis.

SCHEME 1



SCHEME 2. Original Synthesis of Ketone 2



The original and improved syntheses of ketone **2** are outlined in Schemes 2 and 3 respectively. All steps have been improved except for the preparation of 1-dibenzylamino-1-deoxy-D-fructose (**3**) via the Amadori rearrangement. For the ketalization of compound **3**, it was found that the reaction gave cleaner products if quenched before all the starting material was consumed. Compound **4** can then be obtained in 80−87% yield by a simple filtration through a short column of silica gel. For the hydrogenation of compound **4**, the original procedure is sensitive to the purity of the starting material, and the hydrogenation product, amino alcohol **5**, seems to be unstable. Both the reaction and the purification of products need to be carried out carefully. In our subsequent studies, it was found that the hydrogenation could be facilitated by addition of acetic acid, and the resulting product could be used for the next step without further purification.

The initial attempt to directly form the oxazolidinone (**5** to **6**) using $COCl_2-Et_3N$ was unsuccessful.[6] In the

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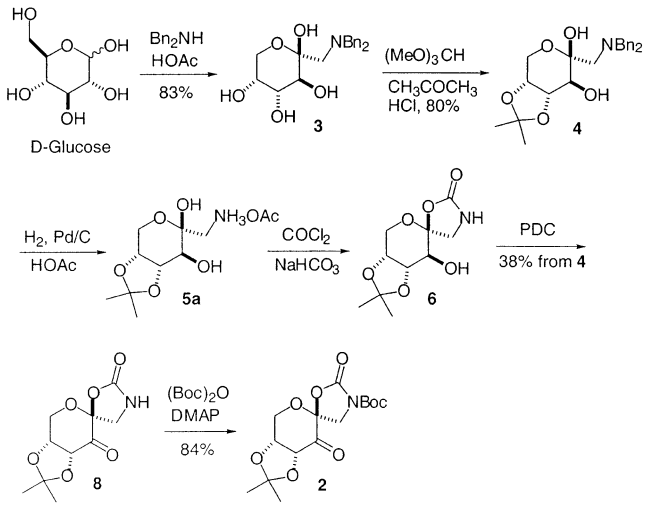
SCHEME 3. Improved Synthesis of Ketone 2



original procedure, the oxazolidinone was therefore prepared by a two-step process using expensive 4-methoxyphenyl chloroformate (Scheme 2). In our subsequent studies, it was found the choice of the base is very important for the formation of the desired oxazolidinone when $COCl_2$ is used. Among the bases tested, $NaHCO_3$ was found to be the best.[7] Treatment of amino alcohol **5a** with $COCl_2$−$NaHCO_3$ led to a one-step formation of oxazolidinone **6** in good yield (Scheme 3).

In the original synthesis, the *N*-Boc group was introduced after the alcohol was protected with TBSCl (Scheme 2). Protection and deprotection add two steps to the synthesis, and the desilylation of **7** with $Et_3N{\cdot}3HF$ takes about 4 days to complete. Efforts were then made to introduce the Boc group onto the oxazolidinone of ketone **8** directly (Scheme 3), thus avoiding the protection and deprotection steps. After much experimentation, it has been found that the Boc group can be added in high yield by treatment of ketone **8** with $(Boc)_2O$ in the presence of a catalytic amount of DMAP (Scheme 3).

In summary, we report an improved synthesis of a ketone catalyst for asymmetric epoxidation of olefins. The ketone can be prepared from D-glucose as starting material in six steps without extensive chromatography purification.

Experimental Section

To a suspension of D-glucose (59.8 g, 332.0 mmol) and Bn_2-NH (64.0 mL, 332.0 mmol) in absolute ethanol (350 mL) was added HOAc (57.0 mL, 995.7 mmol). Upon refluxing for 3 h,[8] the reaction mixture was cooled to 0 °C and filtered with suction. The resulting filter cake was washed thoroughly with ethanol to white and dried under vacuum to give 1-dibenzylamino-1-deoxy-D-fructose (**3**) as a white solid (98.4 g, 83%).[9]

To a suspension of 1-dibenzylamino-1-deoxy-D-fructose (**3**) (26.93 g, 75.0 mmol) and trimethylorthoformate (35.0 mL, 320.0 mmol) in acetone (700 mL) at 0 °C under N_2 was added concentrated hydrochloric acid (9.0 mL, 108.0 mmol). Upon vigorous stirring at 0 °C for about 1.5 h,[10] the reaction mixture was quenched with NH_4OH (12 mL), filtered through a pad of silica gel with suction to remove NH_4Cl, and washed with additional acetone. The resulting solution was concentrated to about 50 mL, diluted with hexanes−EtOAc (3:2, 400 mL), and allowed to stand in the freezer for about 3 h to precipitate most of the unreacted starting material. The mixture was then filtered through a second pad of silica gel with suction to remove the remaining starting material dissolved in the solution, and the pad was washed with hexanes−EtOAc (3:2, 200 mL). The filtrate was concentrated and dried under vacuum overnight to give compound **4** as a pale yellow oil (24.0 g, 80%).[5c]

A solution of the above oil (26.0 g, ca. 65.0 mmol) in absolute ethanol (450 mL) was degassed and purged with N_2 three times. After AcOH (4.3 g, 72.0 mmol) and 10% Pd/C (4.3 g) were added, the reaction mixture was degassed and filled with H_2 three times. Upon stirring at room temperature under H_2 to completion as judged by TLC (about 4.5 h),[11] the reaction mixture was filtered through a short pad of Celite to remove the catalyst. The filtrate was then concentrated at room temperature and dried under vacuum to give compound **5a** as a brown solid (17.5 g, crude yield 96%), which was used directly in the next step without further purification (the product must be dried under vacuum to remove any remaining EtOH, which will otherwise consume phosgene in the next step).

To a suspension of the above compound (17.4 g, 62.0 mmol) and $NaHCO_3$ (30.0 g, 360.0 mmol) in CH_2Cl_2 (300 mL) was added dropwise a solution of 20% phosgene in toluene (46.2 mL, 87.0 mmol) at 0 °C under N_2 with vigorous stirring over 30 min.[12,13] The reaction mixture was stirred at room temperature to completion as judged by TLC (about 6 h).[14] After the flask was opened to air, MeOH (100 mL) was added dropwise at room temperature with vigorous stirring over 30 min.[15] After an additional 30 min stirring, the mixture was flushed through a short column of silica gel and washed with additional methanol until the brown liquid no longer came off the column (it is important not to wash with too much methanol in order to prevent excess salts from passing through the silica gel). The resulting solution was concentrated and dried under vacuum to give the crude alcohol **6** as a light brown solid (16.4 g) (the product must be dried under vacuum to remove any remaining MeOH, which will otherwise consume PDC in the next step).[5c]

To a solution of the above alcohol (16.4 g, ca. 62.0 mmol) in dry CH_2Cl_2 (300 mL) were added 3 Å MS (unactivated) (56 g), PDC (35.0 g, 93.0 mmol), and acetic acid (5 drops). Upon stirring at room temperature to completion as judged by TLC (about 5

(6) Et_3N is believed to react with $COCl_2$ to form an ammonium salt which further decomposes due to the poor reactivity of the primary amine of **5** with $COCl_2$. For a leading review on amine dealkylations with acyl chlorides, see: Cooley, J. H.; Evain, E. J. *Synthesis* **1989**, 1.

(7) Other bases such as 2,6-lutidine, Na_2CO_3, and K_2CO_3 worked as well. In the case of Na_2CO_3 and K_2CO_3, more phosgene was required due to the more rapid decomposition of phosgene by these bases.

(8) The reaction mixture became orange and viscous, so it is very important that stirring continue at all times. Also, to prevent decomposition, the bath temperature should not exceed 90 °C.

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(10) The byproducts formed in this step could significantly retard the following hydrogenation reaction. Therefore, the reaction needs to be carefully monitored by TLC and be stopped immediately upon byproduct appearing on TLC (regardless of whether any impurity is present, the reaction must not be allowed to stir for longer than 2 h). TLC was carried out by taking a small amount of the reaction mixture and quenching it with NH_4OH. The R_f of the product is about 0.6 in hexane−AcOEt 1:1, and the R_f of the byproduct is about 0.5.

(11) EtOAc is used for TLC. The product stays at the baseline. The starting material and monobenzylamine intermediate can be detected by UV with R_f values of 0.8 and 0.2, respectively. The reaction time for the hydrogenation varies with the activity of the Pd catalyst and stirring. Active catalyst and vigorous stirring usually results in shorter reaction time and better yield. Also, the reaction goes faster if less solvent is used.

(12) Phosgene is very toxic and needs to be handled carefully.

(13) Vigorous stirring is required to facilitate the neutralization of the formed HCl by $NaHCO_3$.

(14) The product R_f is about 0.5 using EtOAc as a solvent, and the starting material stays at the baseline.

(15) MeOH is used to hydrolyze the unreacted phosgene and the corresponding chloroformate of compound **6**. Methanol should be added *very slowly* at the beginning via pipet, and the reaction mixture should be vigorously stirred to avoid the build-up of HCl, which will catalyze the hydrolysis of the dimethyl ketal of compound **6** to give the undesired diol instead.

h),[16] the reaction mixture was filtered through a short column of silica gel and washed with EtOAc−hexane (3:1).[17] The filtrate was concentrated, dried under vacuum,[18] and recrystallized using hexane−CH_2Cl_2 (3:1) to afford ketone **8** as a white solid (6.0 g, 38% overall yield from compound **4**):[5c] IR (film) 3378, 3319, 1759, 1731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 5.48 (brs, 1H), 4.82 (d, J = 5.4 Hz, 1H), 4.64−4.53 (m, 2H), 4.32 (d, J = 10.7 Hz, 1H), 4.23 (d, J = 13.5 Hz, 1H), 3.38 (dd, J = 10.7, 0.6 Hz, 1H), 1.46 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 195.1, 155.9, 111.1, 102.8, 77.6, 75.6, 61.2, 45.4, 27.3, 26.2.

To a solution of the above ketone **8** (2.56 g, 10.5 mmol) and $(Boc)_2O$ (2.75 g, 12.6 mmol) in freshly distilled THF (32 mL) was added DMAP (0.013 g, 0.11 mmol). Upon stirring under N_2 at room temperature to completion as judged by TLC (about 15−20 min),[19,20] the reaction mixture was *immediately* quenched with oxalic acid (0.01 g, 0.11 mmol), *immediately* flushed through a prepacked column of silica gel, and washed with hexanes−EtOAc (dried over K_2CO_3) (1:1, 42 mL). The solution was concentrated, and the residue began to crystallize. Hot hexanes−ether (3:1, 27 mL) was added to the solid, and the resulting suspension was stirred for 10 min (without further heating). The suspension was then filtered with suction and washed with cold hexanes−ether (3:1, 20 mL). Ketone **2** was obtained as a white solid[21] (3.02 g, 84% yield):[5c] IR (film) 3446 (hydrate), 1823, 1756, 1731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 4.79 (d, J = 5.6 Hz, 1H), 4.61 (dd, J = 5.6, 1.8 Hz, 1H), 4.56 (d, J = 11.6 Hz, 1H), 4.51 (dd, J = 13.6, 1.8 Hz, 1H), 4.23 (d, J = 13.6 Hz, 1H), 3.71 (d, J = 11.6 Hz, 1H), 1.53 (s, 9H), 1.45 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 194.7, 148.8, 148.4, 111.3, 98.9, 85.0, 77.4, 75.5, 61.3, 48.5, 28.1, 27.3, 26.1.

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(16) The product in this step is a mixture of the ketone and its hydrate. In EtOAc, the R_f of the ketone is about 0.8, but the hydrate only appears slightly above the starting material at around 0.5. The two can be differentiated by color with *p*-anisaldehyde stain. The hydrate has a reddish tint, while the starting material appears darker.

(17) Excess wash should be avoided to reduce impurities which will affect the following recrystallization.

(18) The hydrate can be converted to the ketone by extensive drying under high vacuum line.

(19) The reaction time and the amount of $(Boc)_2O$ used are critical factors. Too little time leads to a messy mixture of the starting material and product, while too much time results in product decomposition, since ketone **2** seems to be unstable in this reaction mixture. Longer reaction time and excess $(Boc)_2O$ will make the reaction less clean.

(20) The product is a mixture of the ketone and its hydrate. The R_f of the ketone is about 0.6 in hexanes−EtOAc (1: 1). TLC shows that the reaction mixture also contains a small amount of impurity [R_f about 0.8 in hexanes−EtOAc (1:1)]. The impurity is removed during the subsequent treatment with hexanes−ether (3:1).

(21) To simplify the NMR spectrum, the hydrate can be converted to the ketone by heating the compound under vacuum.