Efficient Synthesis of (*R*)-4-((Trimethylsilyl)oxy)-2-cyclopentenone by Enantioselective Catalytic Epoxide Ring Opening

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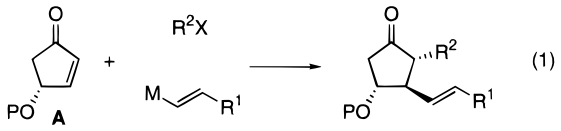
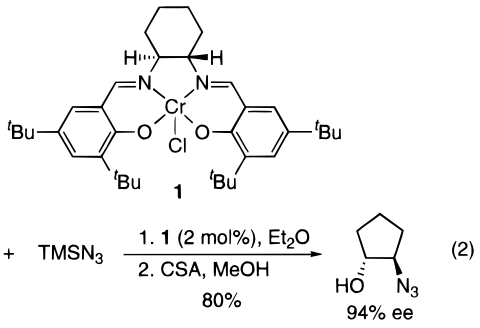
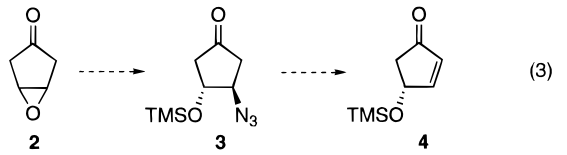
As a result of their interesting structures and their remarkable biological activity, the prostaglandins have attracted the attention of synthetic chemists for decades.[1] The so-called three-component coupling method pioneered by Noyori has emerged as one of the most general and useful synthetic routes to these compounds.[2,3] This approach involves a diastereoselective conjugate addition/enolate alkylation sequence effected on *O*-protected (*R*)-4-hydroxy-2-cyclopentenone, **A** (eq 1). Accordingly, the development of practical routes to the requisite core structure **A** in optically active form is recognized as an important synthetic goal.[4]



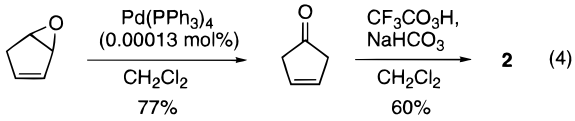
We reported recently that (salen)CrCl complex **1** is an effective catalyst for the enantioselective ring opening of meso epoxides with trimethylsilyl azide ($TMSN_3$).[5] For example, treatment of cyclopentene oxide with $TMSN_3$ (1.05 equiv) and 2 mol % (*S*,*S*)-**1** in Et_2O, followed by desilylation with camphorsulfonic acid (CSA), leads to the generation of (1*R*,2*R*)-1-azido-2-hydroxycyclopentane in 80% isolated yield and 94% enantiomeric excess (ee) (eq 2). We reasoned that application of this methodology to



the ring opening of epoxide **2** could lead to an efficient synthesis of (*R*)-4-((trimethylsilyl)oxy)-2-cyclopentenone as shown in eq 3. Ring opening of epoxide **2** would afford the azido silyl ether **3**, and selective elimination of the azide would then provide the desired enone **4**. The reduction of this plan to a practical form is outlined below.

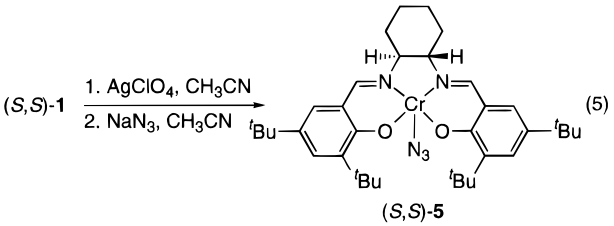


The requisite epoxide **2** for the enantioselective ring-opening reaction was prepared according to the method of Noyori (eq 4).[6] Thus, 3-cyclopentenone was synthe-



sized via the Pd(0)-catalyzed rearrangement of 3,4-epoxycyclopentene, a reaction remarkable both for the efficiency of catalysis and the ease of the experimental procedure. Epoxidation of 3-cyclopentenone was effected with trifluoroperacetic acid to afford 3,4-epoxycyclopentanone (**2**) in 60% isolated yield after distillation. We found that treatment of trifluoroacetic anhydride with hydrogen peroxide·urea addition compound provided a useful alternative to the literature method for the preparation of trifluoroperacetic acid.[7] Overall, this two-step sequence provided multigram quantities of epoxide **2** in pure form with no chromatographic purification necessary.

The asymmetric ring opening of epoxide **2** was effected using the (salen)CrN_3 complex (*S*,*S*)-**5**. Complex **5** catalyzes the ring opening of epoxides by $TMSN_3$ with virtually the same enantioselectivity as the chloride complex **1**; preliminary mechanistic studies indicate that **1** is in fact a precatalyst and that **5** is the active catalyst.[5] A distinct synthetic advantage to using catalyst **5** in catalytic ring-opening reactions is that the chloride addition side product observed using catalyst **1** is avoided. A one-pot synthesis of azide complex (*S*,*S*)-**5** is outlined in eq 5. Thus, treatment of complex **1** with $AgClO_4$ in



CH_3CN, filtration to remove the AgCl, and treatment of the filtrate with NaN_3 permitted the isolation of **5** in ≥90% yield.

Submission of epoxide **2** to the previously described ring-opening conditions[5] with azide catalyst (*S*,*S*)-**5** produced azido silyl ether **3** which was invariably contaminated with ∼10% of 4-((trimethylsilyl)oxy)-2-cyclopen-

(1) (a) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley: New York, 1989; pp 249−309. (b) Mitra, A. *The Synthesis of Prostaglandins*; Wiley: New York, 1977. (c) Bindra, J. S.; Bindra, R. *Prostaglandin Synthesis*; Academic Press: New York, 1977. (d) Collins, P. W.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533−1564.

(2) (a) Noyori, R.; Suzuki, M. *Chemtracts:-Org. Chem.* **1990**, *3*, 173−197. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; pp 298−322.

(3) For examples of recent applications of the three-component coupling approach, see: (a) Sato, T.; Shima, H.; Otera, J. *J. Org. Chem.* **1995**, *60*, 3936−3937. (b) Lipshutz, B. H.; Wood, M. R. *J. Am. Chem. Soc.* **1994**, *116*, 11689−11702.

(4) See: Paquette, L. A.; Earle, M. J.; Smith, G. F. *Org. Synth.* **1995**, *73*, 36 and references therein.

(5) Martínez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897−5898.

(6) Suzuki, M.; Oda, Y.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 1623−1625.

(7) Noyori's procedure for preparation of trifluoroperacetic acid specifies the use of 90% H_2O_2.

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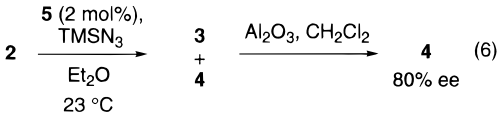
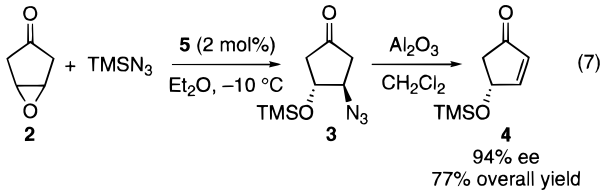
tenone (**4**) (eq 6). Treatment of this mixture with basic



alumina induced selective elimination of the azide to cleanly provide the desired enone (*R*)-**4**. However, HPLC analysis of this material ((*R*,*R*) Whelk-O, 97:3 hexane:2-propanol, 1.0 mL/min) revealed an overall enantioselectivity of only 80%.

Reasoning that the enone side product **4** obtained in the epoxide ring-opening reaction might be due to nonenantioselective β-elimination from **2** followed by silylation of the resulting alcohol with $TMSN_3$,[8] we examined several reaction parameters with the goal of suppressing this pathway and thus enhancing the enantioselectivity in the ultimate generation of **4**. When the ring-opening



reaction was run at −10 °C for 22 h and then warmed slowly to 10 °C over 3 h, **3** was obtained in ∼90% yield, with only ∼2% contamination by enone **4** as judged by ^{1}H NMR analysis of the crude product mixture. Basic alumina-promoted azide elimination followed by distillation under reduced pressure then provided the desired enone **4** in 94% ee and 77% overall yield from epoxide **2**. These data support the notion that the significantly lower ee at higher temperatures is, at least in part, due to nonenantioselective β-elimination of the epoxide.

The present method provides the useful chiral building block **4** in 94% ee and in four steps from cyclopentadiene. As such, this asymmetric catalytic method represents an attractive alternative to existing enzyme-based procedures.

Experimental Section

Complex (*S*,*S*)-5. A 200 mL round bottom flask fitted with a dropping funnel was charged with 2.18 g (10.5 mmol) of $AgClO_4$ and 30 mL of CH_3CN. The dropping funnel was charged with a solution of 6.76 g (10.0 mmol) of (salen)CrCl complex (*S*,*S*)-**1**[5] in 20 mL of CH_3CN. This solution was added over 5 min to the $AgClO_4$ solution. A precipitate began forming almost immediately. The heterogeneous brown mixture was stirred 16 h and then filtered through a pad of Celite with two 25 mL CH_3CN washes. The filtrate was concentrated to a volume of ∼30 mL. Solid NaN_3 (1.30 g, 20.0 mmol) was added, and the brown solution was stirred for 24 h during which time the mixture became heterogeneous. The reaction mixture was diluted with *tert*-butyl methyl ether (300 mL) and washed with H_2O (3 × 300 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated to give 5.92 g (90%) of **5** as a brown powder. This material was used for the asymmetric ring opening of epoxides as described below.

For the purposes of characterization, an analytical sample of **5** was prepared as follows. In a N_2-filled drybox, 1.0 g of **5** prepared as described above was treated with Et_2O (2.0 mL) and $TMSN_3$ (1.0 mL). The initially homogeneous mixture was stirred for 1 h, during which time a precipitate was deposited. The volatiles were removed *in vacuo*, and the resulting brown powder was placed in a fritted funnel and washed with Et_2O (5 × 5 mL). The recovered solid material was dried *in vacuo* to give complex **5** as a brown powder: IR (KBr) 2953, 2907, 2866, 2084, 1620, 1530, 1434, 1391, 1321, 1254, 1169, 837 cm^{-1}. Anal. (H. Kolbe; Ar/V_2O_5) Calcd for $C_{36}H_{52}CrN_5O_2$: C, 67.69; H, 8.20; N, 10.96; Cr, 8.14. Found: C, 67.75; H, 8.16; N, 10.95; Cr, 8.08.

3,4-Epoxycyclopentanone (2). To a cooled (0 °C) suspension of H_2O_2·urea addition compound (9.27 g, 98.5 mmol) in CH_2Cl_2 (100 mL) was added 16.1 mL (23.9 g, 114 mmol) of trifluoroacetic anhydride over 3 min. The mixture was stirred 15 min during which time it became slightly cloudy and biphasic. A 1 L round bottom flask fitted with a dropping funnel was charged with 3-cyclopentenone[6] (6.22 g, 75.8 mmol) and CH_2Cl_2 (160 mL). The solution was cooled to 0 °C, and $NaHCO_3$ (20.7 g, 246 mmol) was added. The biphasic oxidant solution was transferred to the dropping funnel and was added over 5 min to the 3-cyclopentenone solution. The resulting heterogeneous mixture was stirred for 15 min at 0 °C and then for 16 h at 23 °C. The reaction was quenched by the addition of $Na_2S_2O_3$·5 H_2O (20.7 g, 83.4 mmol) and H_2O (300 mL), followed by vigorous stirring for 5 min. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (150 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Distillation of the residue (short path, ∼250 mTorr, bp 46−50 °C) provided 4.43 g (60%) of epoxide **2** as an oil, which was used without further purification.

***(R)*-4-((Trimethylsilyl)oxy)-2-cyclopentenone (4).** To a solution of epoxide **2** (1.30 g, 13.3 mmol) in Et_2O (2.0 mL) was added catalyst **5** (0.173 g, 0.266 mmol). After 5 min, the solution was cooled to −10 °C and $TMSN_3$ (1.86 mL, 1.61 g, 14.0 mmol) was added by syringe. The solution was stirred at −10 °C for 22 h and then allowed to warm to 10 °C over 3 h. The reaction mixture was concentrated, and the residue was filtered through a pad (∼20 mL) of silica gel with 20:80 EtOAc/hexane (200 mL). The filtrate was concentrated to give azido silyl ether **3**, contaminated with ∼2% of **4** as judged by ^{1}H NMR spectroscopy. Data for **3**: ^{1}H NMR ($CDCl_3$) δ 4.30 (m, 1H), 4.05 (m, 1H), 2.74−2.52 (m, 2H), 2.25−2.13 (m, 2H), 0.16 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 211.8, 73.4, 64.9, 45.6, 41.5, −0.2; IR (thin film) 2958, 2105, 1757, 1254, 1134, 1082, 879 cm^{-1}.

The azido silyl ether **3** obtained as described above was dissolved in CH_2Cl_2 (20 mL) and treated with 10 g of basic alumina (Fisher, Brockman activity I). The slurry was stirred for 30 min and then filtered through a pad (∼20 mL) of basic alumina with 150 mL of 95:5 CH_2Cl_2:EtOAc. The filtrate was concentrated, and purification of the residue by distillation (short path, ∼250 mTorr, bp 54−55 °C) provided enone **4** as an oil which was >98% pure as determined by ^{1}H NMR analysis (1.74 g, 77% overall yield from epoxide **2**). Analysis by HPLC ((*R*,*R*) Whelk-O column, 97:3 hexane:2-propanol, 1.0 mL/min, 205 nm) revealed an enantiomeric excess of 94% (t_r(minor) = 10.7 min, t_r(major) = 11.9 min). IR (thin film) 2958, 2900, 1723, 1357, 1253, 1109, 1071, 904, 844 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.46 (dd, 1H, J = 2.2 and 5.7 Hz), 6.20 (dd, 1H, J = 1.2 and 5.7 Hz), 4.96 (m, 1H), 2.71 (dd, 1H, J = 6.0 and 18.2 Hz), 2.25 (dd, 1H, J = 2.2 and 18.2 Hz), 0.18 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 206.3, 163.6, 134.6, 70.4, 44.8, 0.0.

The absolute configuration of **4** was assigned by desilylation of a small sample of **4** (80% ee) to provide (*R*)-4-hydroxy-2-cyclopentenone: $[\alpha]^{23}_D$ +73.7° (*c* 0.700, $CHCl_3$) [lit:[9] $[\alpha]^{22}_D$ +81° (*c* 0.1035, $CHCl_3$)].

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Supporting Information Available: ^{1}H NMR spectrum of **4** (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(8) Separation of **4** from **3**, or analysis of the enantiomeric composition of **4** generated in the epoxide ring-opening reaction, proved impossible because of the extreme propensity of **3** to undergo elimination to generate **4**.

(9) Gill, M.; Rickards, R. W. *Tetrahedron Lett.* **1979**, 1539−1542.