A Multigram, Catalytic and Enantioselective Synthesis of Optically Active 4-Methyl-2-cyclohexen-1-one: a Useful Chiral Building Block

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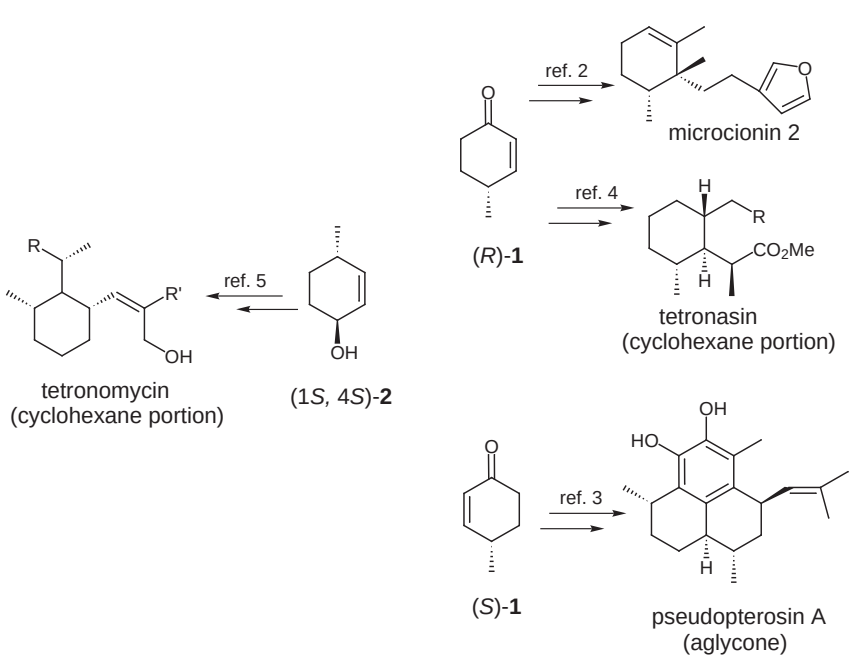
Abstract: The first catalytic asymmetric synthesis of both (*R*)-(+)- and (*S*)-(−)-4-methyl-2-cyclohexen-1-one and a new and improved synthesis of both enantiomers of (1*S*,4*S*)-(−) and (1*R*,4*R*)-(+)-4-methyl-2-cyclohexen-1-ol was developed on a multigram scale. The key step of this approach is the asymmetric catalyzed addition of Me_2Zn (S_N2'-pathway) to racemic 1,3-cyclohexadiene monoepoxide. This step has been optimized as for as enantio- and regioselectivities, and work-up procedures. The striking ligand accelerated catalysis exhibited by the chiral copper complex of the 2,2'-binaphthyl-based phosphoramidite, herein reported, permitted a very low catalyst loading (0.6 mol%).

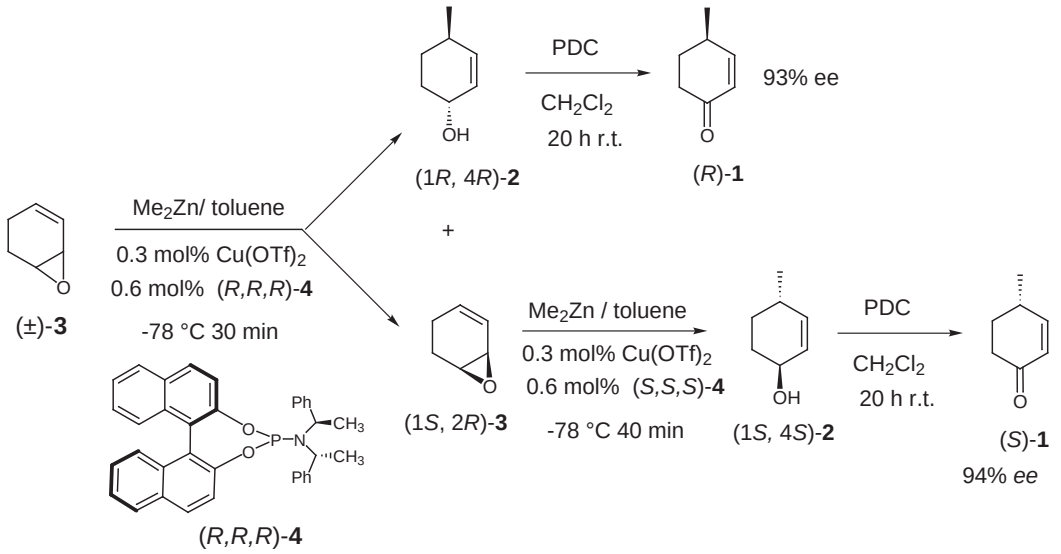
Key words: enantiomer resolution, scale-up, catalysis, organozinc reagent, copper

In the endeavour of natural product total synthesis and the development of efficient routes to new pharmaceuticals, there is a constant need for small chiral non-racemic molecules as starting material. In the course of our studies on the catalytic enantioselective addition of dialkyl zinc reagents to vinyl oxiranes,[1] we realized the potential of our approach for a possible large-scale synthesis of cyclohexene-based enantio-enriched building blocks. Optically pure (*R*)-(+)- and (*S*)-(−)-4-methyl-2-cyclohexen-1-one (**1**) are synthetically useful building blocks for the preparation of a vast array of natural products including (−)-microcionin 2,[2] pseudopterosin A,[3] tetronasin[4] (Scheme 1).

Also enantio-enriched (88% ee) (1*S*, 4*S*)-4-methyl-2-cyclohexenol (**2**) has recently been used as a key building block for the synthesis of the homochiral cyclohexane portion of tetronomycin.[5] Several synthetic preparations of optically active **1** have been reported, all of which employed a "chiral pool approach" from (*R*)-(+)-pulegone[2,6] or (*S*)-(+)-carvone[7] or conventional racemate resolution methods.[8] These procedures are often long and tedious and the overall yields obtained are generally quite low. Hiroi et al. reported the asymmetric synthesis of optically active 4-substituted-2-cyclohexenones by the use of stoichiometric chiral organoselenium compounds, but only with a modest 26% ee.[9] We hypothesized that a straightforward synthesis of both enantiomers of **1** and **2** on a multigram scale could be simply performed by means of our catalytic kinetic resolution (CKR) procedure.



Scheme 1



Scheme 2

We herein report the first catalytic enantioselective approach to optically active **1** by means of a very simple and efficient procedure. The key step of our procedure is the asymmetric addition of Me_2Zn to racemic 1,3-cyclohexadiene monoepoxide (**3**)[10] catalyzed by the chiral copper complex of Binol-derived phosphoramidite (*R*,*R*,*R*)-**4** (Scheme 2). The striking ligand accelerated catalysis[11] exhibited by copper complexes of phosphoramidites[12] permitted a very low catalyst loading (< 1 mol%), and a careful screening of the most suitable chiral ligand permitted an optimization of the key step of our approach for a multigram-scale reaction. The regio- and enantioselectivity of the catalyzed addition of Me_2Zn to 1,3-cyclohexadiene monoepoxide (**3**) was dependent on the extent of conversion of the racemic starting material.[13]

We found a satisfactory compromise between yield and selectivity (both regio- and enantioselectivity) stopping the reaction at 46% conversion (calculated by GC analysis with an internal standard). After filtration of the reaction mixture, in order to remove all inorganic substances, the organic solution was distilled under reduced pressure (100 mmHg) to afford a toluene solution containing the unreacted epoxide (1*S*,2*R*)-**3** (Scheme 2). The crude residue was subsequently distilled (1.5 mmHg) to afford (1*R*,4*R*)-**2** (41% yield, 89% yield based on the reacted epoxide) with a S_N2'/S_N2 regioselectivity of 96:4 and 93% ee (values calculated by chiral GC and ^1H NMR analysis on the distillate). A smooth PDC oxidation[14] of (1*R*,4*R*)-**2** afforded the desired compound (*R*)-**1** with 93% ee and 85% yield (75% overall for two steps). It should be mentioned that the chiral ligand (*R*,*R*,*R*)-**4** was recovered pure in approximately 40% yield in the distillation residue after simple filtration over a pad of silica gel, and re-used for another reaction without any loss of catalytic activity.

The ease of preparation of both enantiomers of the chiral ligand **4** makes further CKR of enantiomerically enriched epoxide **3** an attractive option (i.e., so-called "double CKR").[15] The toluene solution containing enantio-enriched epoxide (1*S*,2*R*)-**3**, recovered in the kinetic resolution protocol, was directly used in "double CKR" by treatment with Me_2Zn in the presence of catalytic amounts of enantiomeric chiral ligand (*S*,*S*,*S*)-**4**. Under these circumstances, the (1*S*,2*R*)-**3** enantiomer, in which the starting material is enriched, is now the faster-reacting enantiomer and consequently the opposite (1*S*,4*S*)-**2** S_N2' adduct with 94% ee was obtained (50% yield) with complete (>98%) regioselectivity (see Scheme 2 and experimental section). Subsequent PDC oxidation gave (*S*)-**1** with 94% ee (85% yield). As expected, a direct synthesis of (1*S*,4*S*)-**2** was also accomplished with the catalyzed addition reaction of Me_2Zn to racemic **3** by the use of a copper complex of ligand (*S*,*S*,*S*)-**4** (0.6 mol%) as the chiral catalyst in a multigram-scale reaction. In this case, the reaction was stopped at 42% conversion after 15 minutes of reaction time at −78 °C. Usual work-up afforded (1*S*,4*S*)-(−)-**2** (36% yield, 86% yield based on the reacted epoxide) with a slight increase in both enantio- and regioselectivity (94% ee and S_N2'/S_N2 = 97:3).

In summary, the present work describes the first catalytic asymmetric synthesis of both (*R*)-(+)- and (*S*)-(−)-4-methyl-2-cyclohexen-1-one (**1**) and a new and improved synthesis of both enantiomers of 4-methyl-2-cyclohexenol (**2**). Compared with other multistep syntheses of **1**, our two-step procedure is simple and starts from commercially cheap and readily available reagents. An attractive feature of this approach is represented by the simple work-up procedures based on filtration and distillation, which qualifies the procedure for further scale-up. As a large number of dialkylzinc reagents are available by standard methods,[16] it is reasonable to assume that other optically active 4-alkyl-2-cyclohexenones (and 4-alkyl-2-cyclohexenols) can be synthesized by this procedure, allowing a novel,

easy and practical multigram-scale synthesis of this interesting class of compounds by the use of minimal amounts of Binol-derived phosphoramidites.

All reactions were conducted in flame-dried glassware with magnetic stirring under an Ar atm. Toluene was distilled from sodium/benzophenone ketyl and stored under Ar. Me_2Zn (2.0 M solution in toluene) and 1,3-cyclohexadiene were purchased from Aldrich. Enantiomeric excesses were determined on a Perkin−Elmer 8420 apparatus (FI detector) using a Chrompak fused silica 50 m × 0.25 mm column coated with CP-Cyclodextrin-B-236-M-19. In all cases, the injector and detector temperature was 250 °C and a 0.9 mL/min He flow was employed. Conversions were determined on a HP-5890 instrument equipped with a HP-5 capillary column (30 m X 0.25 mm). For other experimental details, see ref. 1b.

(1*R*,4*R*)-(+)-4-Methyl-2-cyclohexen-1-ol (2); Typical Procedure for the Enantioselective Conjugate Addition Reaction of Me_2Zn to (±)-3

A solution of $Cu(OTf)_2$ (54.3 mg, 0.15 mmol) and (*R*,*R*,*R*)-**4** (0.160 g, 0.3 mmol) in anhyd toluene (30 mL) was stirred for 40 min. The colorless solution was cooled to −78 °C and (±)-**3** (4.80 g, 50 mmol) in anhyd toluene (5 mL) and isopropylbenzene (1.80 g as the internal standard) were added. Then a solution of Me_2Zn in toluene (2.0 M, 11.4 mL) was added dropwise to the cooled (−78 °C) reaction mixture over a period of 7 min. The reaction was monitored by GC and quenched with H_2O (15 mL) after 30 min (46% conversion). The slight yellow suspension obtained was vigorously stirred for 1 h at r.t. The precipitate was filtered through a glass sintered Buchner washing with the minimal amount of CH_2Cl_2 (3 × 8 mL). The organic layer was separated and the dried ($MgSO_4$). The organic phase was distilled with a Vigreux column under reduced pressure (100 mmHg), thus obtaining a toluene solution (total volume 35 mL) containing the enantio-enriched unreacted epoxide (1*S*,2*R*)-**3**. The remaining liquid was distilled at 1.5 mmHg (43−45 °C) to give (1*R*,4*R*)-**2** (2.296 g, 41%), as a colorless liquid (contaminated with 4% regioisomeric alcohol). The enantiomeric excess (93%) was determined by chiral GC, isothermal 104 °C: t_R18.91 (−); t_R 19.75 (+).

$[\alpha]_D^{23}$ = +146° (*c* 2.6, $CHCl_3$).

^{1}H NMR: δ = 5.56−5.68 (m, 2H), 4.12−4.27 (m, 1H), 1.19−2.29 (m, 5H), 0.94 (d, 3H, *J* = 7.0 Hz).

^{13}C NMR: δ = 135.96, 129.69, 66.83, 31.86, 30.27, 28.97, 21.23.

Anal. Calcd. for $C_7H_{12}O$: C, 74.96; H, 10.78. Found : C, 74.80; H, 10.85.

(*1S,4S*)-(−)-4-Methyl-2-cyclohexen-1-ol (2)

Following the typical procedure, the reaction of (±)-**3** (6.0 g, 62.5 mmol) and Me_2Zn (14.0 mL) in the presence of $Cu(OTf)_2$ (67.9 mg, 0.187 mmol) and (*S*,*S*,*S*)-**4** (0.20 g, 0.375 mmol) was quenched with H_2O (16 mL) after 15 min reaction time at −78 °C (42% conversion). Fractional distillation afforded (1*S*,4*S*)-**2** (2.53 g, 36%) as a colorless liquid (contaminated with 3% regioisomeric alcohol). The enantiomeric excess (94%) was determined as described above.

"Double CKR" Method

A solution of $Cu(OTf)_2$ (16.7 mg, 0.046 mmol) and (*S*,*S*,*S*)-**4** (50 mg, 0.093 mmol) in anhyd toluene (7 mL) was stirred for 40 min. The colorless solution was cooled to −78 °C and a solution of the epoxide (1*S*,2*R*)-**3** (19 mL deriving from the fractional distillation, approx. 7.7 mmol) and isopropylbenzene (0.30 g as the internal standard) were added. Then a solution of Me_2Zn in toluene (2.0 M, 3.1 mL) was added dropwise to the cooled (−78 °C) reaction mixture over a period of 5 min. The reaction was monitored by GC and quenched with H_2O (6 mL) at approx. 63% conversion (reaction time 40 min). Extraction with Et_2O and evaporation of the dried ($MgSO_4$) organic phase gave a crude product, which was purified by chromatography (SiO_2, hexanes/EtOAc, 85:15) to afford pure (1*S*,4*S*)-**2** (0.40 g, approx. 46% yield). The enantiomeric excess (94%) was determined by chiral GC as described above.

(4*R*)-4-Methyl-2-cyclohexenone (1); Typical Procedure for the PDC Oxidation of Allylic Alcohol 2

To a solution of (1*R*,4*R*)-**2** (2.18 g, 19.5 mmol) in anhyd CH_2Cl_2 (26 mL) was added in two portions PDC (11.0 g, 29 mmol) at 0 °C and the mixture obtained was stirred at r.t. After 20 h, the reaction mixture was diluted with of hexanes/Et_2O(20 mL, 75:25 mixture) and directly filtered through a short pad of SiO_2. Flash chromatography (hexanes with 15% EtOAc) afforded pure (*R*)-**1** (1.823 g, 85%) as a liquid. The enantiomeric excess (≥93% ee, not complete baseline separation) was determined by chiral GC, isothermal 90 °C, t_R 26.00 (−), t_R 26.28 (+).

$[\alpha]_D^{23}$ = +110° (*c* 1.4, EtOH) {Lit.[8] $[\alpha]_D^{23}$ = +117° (*c* 0.0372, EtOH)}.

^{1}H NMR: δ = 6.72−6.69 (m, 1H), 5.89 (dd, 1H, *J* = 10.1, 2.3 Hz), 1.65−2.55 (m, 5H), 1.11 (d, 3H, *J* = 7.3 Hz).

^{13}C NMR: δ = 199.60, 156.14, 128.55, 36.77, 31.01, 30.79, 20.10.

Anal. Calcd. for $C_7H_{10}O$: C, 76.33; H, 9.15. Found : C, 76.30; H, 9.10.

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