A highly enantioselective synthesis of the odorant, 3-hydroxy-4-phenyl-butan-2-one

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An efficient and highly enantioselective synthesis of 3-hydroxy-4-phenylbutan-2-one was developed involving the asymmetric epoxidation of an enone and hydrogenolysis of an α,β-epoxyketone. 1-Phenyl-3-buten-2-one was epoxidised with *t*-butyl hydroperoxide using a chiral La-BINOL-Ph_3P=O complex as the catalyst to give (*3S,4R*)- or (*3R,4S*)-3,4-epoxy-4-phenylbutan-2-one in ~90% yield and 97% ee. The resultant optically active epoxyketone was reduced in the presence of Pd/C (5 mol%) and H_2 (3 bar) in THF at room temperature to produce (*S*)- or (*R*)-3-hydroxy-4-phenylbutan-2-one in ~80% yield with more than 90% enantiomeric excess.

Keywords: 3-hydroxy-4-phenylbutan-2-one, 3,4-epoxy-4-phenylbutan-2-one, asymmetric epoxidation, hydrogenolysis

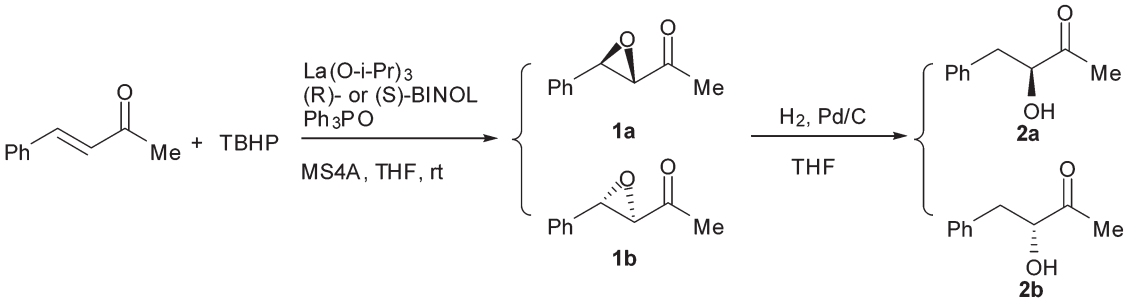
The investigation of chiral odorants has recently recieved attention due to its academic significance and important social and economic implications. The organoleptic properties of more stereoisomers of chiral flavour and fragrance compounds have been examined[1] and some chiral odorants have even entered the market in enantiomerically enriched forms. The availability of chiral samples in high enantiomeric excess (ee) is crucial to the investigation of the sensory properties of stereoisomers. The technique of asymmetric synthesis is a very efficient approaches to produce enantiomerically enriched odorants.

3-Hydroxy-4-phenyl-2-butanone is a flavour compound with a pleasant, mild, warm and creamy sweet aroma, which occurs naturally in honey,[2,3], wine,[4] sherry,[5] apple cider[6] and wisteria flower[7]. It has been identified as one of important biomarkers for thyme honey.[8–10] As one of the important volatile constituents related to the characteristic odour of wisteria flowers, it occurs predominantly in the *R* configuration with ~83.3% ee[7]. Enantiomerically enriched 3-hydroxy-4-phenylbutan-2-one has been prepared in several different ways. Awano *et al.* used Sharpless' kinetic resolution of (±)-1-phenyl-3-buten-2-ol followed by protection of the hydroxyl group, reduction of the epoxide, oxidation of hydroxyl group formed from the reduction and deprotection of hydroxyl group to produce (*S*)- and (*R*)-3-hydroxy-4-phenylbutan-2-one with 85.2% ee and 90.4% ee respectively.[7] Fleming *et al.* reported the Sharpless' asymmetric dihydroxylation (Sharpless AD) of the benzyl substituted allene to give 3-hydroxy-4-phenylbutan-2-one in 30% yield with 77% ee.[11] Enzymatic resolution of acyloins and their esters were investigated to produce optically active 3-hydroxy-4-phenyl-2-butanone and its butyrate in >90% ee.[12,13] In our previous work, we obtained enantiomerically enriched 3-hydroxy-4-phenylbutan-2-one ((*R*)-, 80% ee; (*S*)-, 62% ee) by Shi's asymmetric epoxidation (Shi's AE) or Sharpless AD of silyl enol ether. The different odour quality and intensity of the two enantiomers have been observed by gas chromatography-olfactory analysis.[14] In order to obtain more detailed sensory data of the two enantiomers, such as odour threshold and promote the possible application of enantiomerically enriched products, a practical and highly enantioselective method of preparing optically active 3-hydroxy-4-phenylbutan-2-one is still needed. Here we report the preparation of 3-hydroxy-4-phenylbutan-2-one with high enantioselectivity by a two-step route, including asymmetric epoxidation of 1-phenyl-3-buten-2-one and hydrogenolysis (Scheme 1).

Results and discussion

Asymmetric epoxidation of α,β-enones could be achieved by many different methodologies such as asymmetric ligand-metal catalysis,[15,16] asymmetric phase transfer catalysis,[17] and asymmetric organocatalysis.[18] Among them, the method developed by Inanaga *et al.* is very practical due to the commercial availability of the required reagents and its high enantioselectivity.[15] In this work, asymmetric epoxidation of 1-phenyl-3-buten-2-one was performed following Inanaga's protocol with chiral La-BINOL-Ph_3P=O complex as the catalyst and *t*-butyl hydroperoxide as the oxidant. Optically active 3,4-epoxy-4-phenylbutan-2-ones (**1a** and **1b**) were obtained in ~90% yield and 97% ee.

Torii *et al.* reported the hydrogenolysis of α,β-epoxykentone and ester to give aldols in Pd(0)/HCOOH/Et_3N and H_2/Pd/C reduction media. However, 3,4-epoxy-4-phenylbutan-2-one was cleaved selectively at the benzylic position to give the acyloin under the condition of hydrogenolysis.[19] The hydrogenolysis of the optically active 3,4-epoxy-4-phenylbutan-2-ones was carried out by two different methods. One used the Pd/C (5 mol%), HCOOH (2 equiv.), and Et_3N (2 equiv.) in refluxing THF. Unfortunately, the ee values of the products were not



Scheme 1 Enantioselective synthesis of 3-hydroxy-4-phenylbutan-2-one.

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reproducible. This might be due to the racemisation of the acyloins under acidic conditions. The other was carried out in the presence of Pd/C (5 mol%) and H_2 (3 bar) in THF at room temperature. (*S*)- and (*R*)-3-Hydroxy-4-phenylbutan-2-one (**2a** and **2b**) were obtained in ~80% yield with more than 90% ee.

In summary, optically active 3-hydroxy-4-phenylbutan-2-ones were produced with high ee values by the asymmetric epoxidation of 1-phenyl-3-buten-2-one using chiral La-BINOL complex as the catalyst and *t*-BuOOH as the oxidant followed the hydrogenolysis in the presence of Pd/C and H_2. Compared with the previously reported methods, this route is more practical, efficient and enantioselective.

Experimental

4-Phenyl-3-buten-2-one and triphenylphosphine oxide were purchased from Beijing Bailingwei Science and Technology Company. (*R*)- and (*S*)-1,1′-bi-2-naphthol (BINOL), t-butyl hydroperoxide (TBHP, ~5.5 M soulution in decane), and La(O-i-Pr)$_3$ were purchased from Sigma-Aldrich Chemical Co., and the other compounds were purchased from the Beijing Huaxue Shiji Company.

The NMR spectra were obtained on a Bruker AV300 MHz NMR in $CDCl_3$ and chemical shifts were referenced to residual protons in $CDCl_3$. Enantiomeric excesses were determined by high-performance liquid chromatography (HPLC) with an Agilent 1200 HPLC using a Chiralcel OD chiral column (0.46 cm diameter × 15 cm). Optical rotations were measured on an Autopol IV digital automatic polarimeter. Absolute configuration of the products was determined by comparing their retention times or specific rotations with the literature data.

Synthesis of (3S,4R)- or (3R,4S)-3,4-epoxy-4-phenylbutan-2-one (**1a** or **1b**)

A solution of (*R*)- or (*S*)-BINOL (174 mg, 0.6 mmol) and triphenylphosphine oxide (507 mg, 1.8 mmol) in THF (40 mL) was added to a mixture of La(O-i-Pr)$_3$ (195 mg, 0.6 mmol) and activated MS 4A (300 mg). The mixture was stirred for 1 h at room temperature under nitrogen. After the addition of TBHP (0.8 mL, 5.5M, 4.5 mmol), the mixture was then stirred for 30 min and then a solution of 4-phenyl-3-buten-2-one (447 mg, 3 mmol) in THF (10 mL) was added. The whole mixture was stirred for 30 min at room temperature to complete the reaction. Silica gel was added and the insoluble materials were filtered through Celite. After concentration of the filtrate, the residue was subjected to column chromatography on silica gel (ethyl acetate-petroleum ether 1:30) to give the epoxy ketone **1a** or **1b**. (*3S,4R*)-3,4-Epoxy-4-phenylbutan-2-one **1a** (442 mg, 91% yield), colourless oil, $[\alpha]_D^{20}$ = +99.5° [c = 1.088, $CHCl_3$ (97.1% ee)]; (*3R,4S*)-3,4-epoxy-4-phenylbutan-2-one **1b** (428 mg, 88% yield), colourless oil, $[\alpha]_D^{20}$ = –99.8° [c = 1.059, $CHCl_3$ (97.3% ee)]. HPLC (Chiralcel OD, 2-propanol-hexane 10:90, 1 mL min^{-1}): t_R ((*3S,4R*)-) 13.8 min; t_R ((*3R,4S*)-) 12.6 min. ^{1}H NMR δ 2.19 (s, 3H, Me), 3.49 (d, *J* = 1.8 Hz, 1H, H-3), 4.00 (d, *J* = 1.8 Hz, 1H, H-4), 7.26 (m, 2H, ArH), 7.36 (m, 3H, ArH). ^{13}C NMR δ 203.9, 134.8, 128.7, 128.4, 125.5, 63.2, 57.4, 24.5. GC/MS (EI) *m/z* (%) 162 (25, M$^+$), 120 (40), 91 (100), 77 (16), 43 (51).

Synthesis of (S)- or (R)-3-hydroxy-4- phenylbutan-2-one (**2a** or **2b**)

The solution of (*3S,4R*)- or (*3R,4S*)-3,4-epoxy-4-phenylbutan-2-one (**1a** or **1b**) (162 mg, 1 mmol) in THF (15 mL) and a catalytic amount of Pd (10% on charcoal, 50 mg) was added to a 100 mL pressure vessel. The reaction mixture was stirred under H_2 atmosphere (3 bar) for 24 h. The Pd/C catalyst was filtered off and the filtrate was concentrated by rotary evaporation. The residue was subjected to column chromatography on silica gel (ethyl acetate-petroleum ether 1:8) to give the acyloin **2a** or **2b**. (*S*)-3-Hydroxy-4-phenylbutan-2-one **2a** (131 mg, 80% yield), light yellow oil, $[\alpha]_D^{20}$ = +54.2° [c = 1.125, $CHCl_3$ (93.2% ee)]; (*R*)-3-hydroxy-4-phenylbutan-2-one **2b** (133 mg, 81% yield), light yellow oil, $[\alpha]_D^{20}$ = –52.7° [c = 1.091, $CHCl_3$ (90.1% ee)]. HPLC (Chiralcel OD, 2-propanol-hexane 10:90, 1 mL min^{-1}): t_R ((*R*)-) 7.9 min; t_R ((*S*)-) 9.9 min. ^{1}H NMR δ 2.21 (s, 3H, Me), 2.88 (dd, *J* = 14.1, 7.2 Hz, 1H, H-4), 3.14 (dd, J_1 = 14.1, 4.5 Hz, 1H, H-4), 3.38 (d, *J* = 5.4 Hz, 1H, OH), 4.43 (m, 1H, H-3), 7.27(m, 5H, ArH). ^{13}C NMR δ 209.1, 136.4, 129.2, 128.5, 126.9, 77.6, 39.9, 25.8. GC/MS (EI) *m/z* (%) 164 (1, M$^+$), 146 (30), 121 (58), 103 (66), 91 (100), 77 (21).

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