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Asymmetric synthesis of α-chiral ketones by the reduction of enones with baker's yeast

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Abstract—Baker's yeast-mediated asymmetric reduction of α,β-unsaturated ketones (enones) having a pyridyl ring affords the corresponding optically active α-substituted ketones (α-chiral ketones) with excellent stereoselectivity. The position of the heteroatom, as well as the bulk of the α-substituent, plays an important role in governing the stereoselectivity in the reduction of a carbon–carbon double bond.

1. Introduction

Optically active α-substituted ketones are versatile building blocks for the synthesis of natural products, especially in pheromone synthesis.[1–6] A number of methods for the synthesis of α-chiral ketones have been reported, e.g. stereoselective α-alkylation[7–16] and enantioselective protonation of enolates and enols.[17] Although it has been generally accepted that enzymatic transformation is another candidate to obtain chiral compounds, little is known about stereoselective α-chiral ketone synthesis, e.g. via hydrolysis of enol esters[18–20] and the reduction of enones.[21–24] The enantioselective protonation of enol esters[25] and enol ethers[26] using a catalytic antibody has also been reported. In most cases so far reported, however, the stereoselectivity of the reactions are unsatisfactory.

Recently, we revealed a relationship between the structure of enones and the stereoselectivity in the reduction of α,β-disubstituted enones with baker's yeast or enzyme purified from baker's yeast, and reported the stereoselective synthesis of α-chiral ketones.[27–29] Elongation of the α-substituent, from a methyl group to an ethyl group, improves the stereoselectivity drastically. The site of a substituent on the β-phenyl ring is also a crucial factor for the stereodiscrimination of the enzymatic reduction. The reduction of enones having no substituent or a *para*-substituent on the β-phenyl ring affords the corresponding saturated (*S*)-ketones with moderate stereoselectivity, whereas introduction of a *meta*-substituent drastically improves the stereoselectivity, regardless of its type. Steric factors also play a crucial role in the stereoselective reduction.

We became interested in revealing the other factors such as specific interactions (e.g. electrostatic or hydrogen bonding) which affect stereodiscrimination in the reaction. Introduction of a heterocyclic group as the β-substituent is the most suitable means of evaluating of the effect of such interactions on the stereoselectivity. Thus, we herein describe the stereoselectivity in the reduction of enones having a heterocyclic substituent.

2. Results and discussions

Microbial reactions are usually carried out in aqueous media. The poor solubility of hydrophobic substrates causes problems for the progress of the reactions. Since the introduction of a pyridine ring as a substituent much improves the solubility of the substrate in aqueous medium, the pyridyl enone is favorable for the reaction. Recently, we found that the site of a substituent plays a crucial role in the stereoselectivity for various β-aryl enones.[27,28] We expected that the position of the nitrogen and the presence of an N–O moiety in the pyridine ring is also a crucial factor for stereoselectivity in the reduction of a carbon–carbon double bond as in the case which we reported previously.[27,28] At first, a series of pyridyl and pyridyl-*N*-oxide enones **1a**–**f**, which have the nitrogen atom at various positions in the ring, were synthesized and subjected to baker's yeast reduction. The results are summarized in Table 1.

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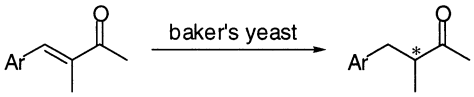
Table 1. Asymmetric reduction of enones with baker's yeast



1a-f **2a-f**

Entry	Ar	Reaction time (h)	Yield (%)	E.e. (%)	Config.
a	2-Py	4	59	65	*S*
b	3-Py	9	76	>95	*S*
c	4-Py	6	72	77	*S*
d	*N*-O-2-Py	16	69	71	*R*
e	*N*-O-3-Py	20	87	>95	*S*
f	*N*-O-4-Py	22	64	72	*S*

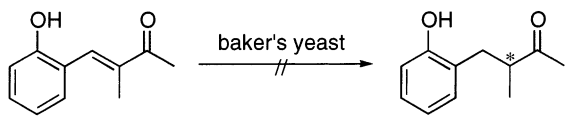
Although enones have two functional groups which are susceptible to the reduction, i.e. a carbon–carbon double bond and a carbonyl group, baker's yeast catalyzes the reduction of the carbon–carbon double bond chemoselectively. The enones having a 2- or 4-pyridyl ring afford chiral ketones in a moderate selectivity, whereas the enones **1b** and **1e** having a 3-pyridyl ring are reduced with excellent stereoselectivity giving a single enantiomer. In most cases investigated, (*S*)-ketones are the predominant products, but the enone **1d** having a 2-pyridyl-*N*-oxide ring affords the (*R*)-ketone with moderate selectivity. These results show that both enantiomers can be obtained by a slight modification of the substrate. It is conceivable that the opposite stereoselectivity arises from the electronegativity of the oxygen atom at the *ortho*-position. To support this consideration, enone **1g** having an *ortho*-hydroxyl group was prepared and subjected to baker's yeast reduction. The attempted reaction did not proceed at all (Scheme 1). Since a heteroatom in the *meta*-position of the heterocycle, **1b** or **1e**, improved the stereoselectivity, the position of the heteroatom plays an important role for the stereoselectivity in the reduction of a carbon–carbon double bond. Therefore, the stereoselectivity should be induced by specific interactions between a substrate and the enzyme, e.g. electrostatic or hydrogen bonding.

Next, to investigate the effect of an α-substituent group on baker's yeast reduction, the enones **1h–m** having an elongated alkyl chain at the α-position from a methyl group to an ethyl group were synthesized. These enones were subjected to baker's yeast reduction. The results are summarized in Table 2, where all enones afforded the (*S*)-ketones. The reduction proceeded stereospecifically regardless of the position of the nitrogen in the pyridyl ring. We have already found that the baker's yeast reduction of the carbon–carbon double bond in the enones proceeds with 100% formal *anti*-addition of hydrogens and low stereoselectivity stems from random positioning of the substrate in the active site of the enzyme.[28,29] Furthermore, we have also found that a hydride from coenzyme is introduced to the β-position of an enone and a proton from water or an amino acid residue is introduced to the α-position.[28] According to this suggestion, the positioning of the substrate is fixed in the pocket of the enzyme, in a better manner, since the steric bulk of the ethyl group is larger than that of the methyl group. Only the enone in a optimum position in the pocket of the enzyme can be reduced selectively.

The absolute configurations of the products were determined as follows. The specific rotations of (+)-(*S*)-1-(2-pyridyl)-2-propanol and (−)-(*R*)-1-(2-pyridyl)-2-propanol have been reported.[30,31] 2-Pyridyl ketone **2a** can be converted into 1-(2-pyridyl)-2-propanol without racemization (Scheme 2). The absolute configuration of 2-pyridyl ketone **2a** was then determined as *S* by comparison of the optical rotation with an authentic sample of the enantiopure alcohol.

The chlorodinitrophenylhydrazone derivatives of chiral ketones **2b–c** and **2h–j** were prepared and their absolute configurations were determined by X-ray crystallographic analysis using the anomalous dispersion effect of a chlorine atom.[32] The absolute configurations of the chiral ketones **2b–c** and **2h–j** were also determined to be *S*.

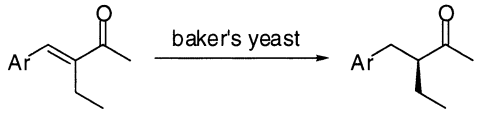
The chiral pyridyl ketones **2a–c** and **2h–j** can be oxidized to the corresponding pyridyl-*N*-oxide ketones **2d–f** and **2k–m** without racemization. The absolute configurations of **2d–f** and **2k–m** were determined by comparison of the optical rotations between the pyridyl-*N*-oxide ketones obtained by baker's yeast reduction and those oxidized of **2a–c** and **2h–j**. The results are shown in Tables 1 and 2.



1g **2g**

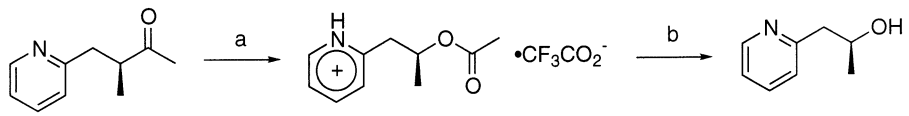
Scheme 1.

Table 2. Asymmetric reduction of enones with baker's yeast



1h-m **2h-m**

Entry	Ar	Reaction time (h)	Yield (%)	E.e. (%)	Config.
h	2-Py	14	72	>99	*S*
i	3-Py	5.5	81	>98	*S*
j	4-Py	12	82	>99	*S*
k	*N*-O-2-Py	26	93	>99	*S*
l	*N*-O-3-Py	23	92	96	*S*
m	*N*-O-4-Py	16	54	>99	*S*



2a

Scheme 2. (a) Baeyer–Villiger reaction: H_2O_2, $(CF_3CO)_2O$, CH_2Cl_2, rt, overnight, 75%; (b) $LiAlH_4$, Et_2O, rt, overnight, 56%.

3. Conclusions

Baker's yeast chemoselectively reduced the carbon–carbon double bond of the enones having a pyridyl ring or their derivatives to afford the corresponding chiral ketones. The reductions proceeded with excellent stereoselectivity for suitable substrates. The major enantiomers of yeast reduction products have (*S*)-configuration except for 2-pyridyl-*N*-oxide ketone **2d**.

The reduction of a series of pyridyl enones with baker's yeast has revealed the crucial factors on the stereoselectivity. With respect to the β-substituent, the selectivity was induced by a specific interaction, e.g. an electrostatic or a hydrogen bonding interaction, as well as the steric factors mentioned above. For an α-substituent, steric factors are overridingly important. This information should help to clarify the reaction mechanism of baker's yeast reduction.

4. Experimental

4.1. Instruments

NMR spectra were recorded on a Varian VXR-200 spectrometer or a JEOL AL-300 spectrometer in $CDCl_3$ solutions with tetramethylsilane (TMS) as an internal reference. Infra-red spectra were collected on a JASCO FT/IR-5300 spectrometer. Melting points were recorded using a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP-181 digital polarimeter. Elemental analyses were performed with a Yanaco MT-5 Elemental Analyzer. Gas chromatograms were recorded on a Shimadzu GC-14B gas chromatograph equipped with a capillary chiral column, CP-Cycrodex B 236M (Chrompack, 0.25 mm×25 m). Liquid chromatograms were recorded on an IRICA Liquid Chromatograph Σ871 equipped with Chiralpak AD (Daical Chemical Industries, Ltd., 0.46 cm×25 cm).

4.2. Materials

Organic reagents and solvents were purchased from Nacalai Tesque, Inc., Wako Pure Chemical Ind., Ltd., Aldrich Chemical Co., Tokyo Kasei Kogyo Co. and Kanto Chemical Co., Inc. Dry baker's yeast was purchased from the Oriental Yeast Co. and stored in a refrigerator. Tetrahydrofuran (THF) and ether were dried over sodium metal and benzophenone and distilled prior to the use.

4.3. General procedure for the preparation of 3-alkyl-4-pyridyl-3-buten-2-one

A slight modification of the reported method was adopted for the synthesis of these compounds.[27,28,33] Pyridinecarboxaldehyde (2.66 g, 25 mmol) and the corresponding 2-alkylketone (50 mmol) were dissolved in acetic acid (35 mL). While stirring, sulfuric acid (7.4 g, 76 mmol) was added to the solution. The solution was stirred at 50°C. After 4 h, water (50 mL) was added to the solution, which was then basified with 20% aqueous sodium hydroxide. The aqueous solution was extracted with ethyl acetate. The combined extracts were washed with brine, dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to obtain 3-alkyl-4-pyridyl-3-buten-2-one. The yields of the isolated products and their spectral and physical data are listed below.

4.3.1. 3-Methyl-4-(2-pyridyl)-3-buten-2-one 1a. This compound was synthesized by the previously reported method[28] in a 53% yield.

4.3.2. 3-Methyl-4-(3-pyridyl)-3-buten-2-one 1b. 75% yield; ^{1}H NMR ($CDCl_3$, TMS) δ 2.06 (3H, d, $J=1.3$ Hz), 2.49 (3H, s), 7.33–7.47 (2H, m), 7.72–7.78 (1H, m), 8.55–8.59 (1H, m), 8.66–8.68 (1H, m); IR (neat) 1669 cm^{-1}. Found: C, 74.44; H, 6.96; N 8.61%. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69%.

4.3.3. 3-Methyl-4-(4-pyridyl)-3-buten-2-one 1c. 48% yield; ^{1}H NMR ($CDCl_3$, TMS) δ 2.04 (3H, d, $J=1.4$ Hz), 2.48 (3H, s), 7.25–7.29 (2H, m),7.40 (1H, br), 8.65–8.69 (2H, m); IR (neat) 1671 cm^{-1}. Found: C, 74.36; H, 6.96; N 8.53%. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69%.

4.3.4. 3-Ethyl-4-(2-pyridyl)-3-buten-2-one 1h. 71% yield; ^{1}H NMR ($CDCl_3$, TMS) δ 1.09 (3H, t, $J=7.5$ Hz), 2.48 (3H, s), 2.76 (2H, q, $J=7.5$ Hz), 7.18–7.30 (1H, m), 7.38–7.46 (2H, m), 7.68–7.79 (1H, m), 8.66–8.73 (1H, m); IR (neat) 1668 cm^{-1}. Found: C, 75.44; H, 7.50; N 8.00%. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99%.

4.3.5. 3-Ethyl-4-(3-pyridyl)-3-buten-2-one 1i. 65% yield; mp 49.0–51.8°C; ^{1}H NMR ($CDCl_3$, TMS) δ 1.11 (3H, t, $J=7.4$ Hz), 2.47 (3H, s), 2.51 (2H, q, $J=7.4$ Hz), 7.31–7.41 (2H, m), 7.67–7.76 (1H, m), 8.55–8.68 (2H, m); IR (neat) 1656 cm^{-1}. Found: C, 75.25; H, 7.52; N 7.85%. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99%.

4.3.6. 3-Ethyl-4-(4-pyridyl)-3-buten-2-one 1j. 77% yield; ^{1}H NMR ($CDCl_3$, TMS) δ 1.09 (3H, t, $J=7.5$ Hz), 2.47 (3H, s), 2.48 (2H, q, $J=7.5$ Hz), 7.23–7.28 (2H, m), 7.35 (1H, br), 8.64–8.69 (2H, m); IR (neat) 1673 cm^{-1}. Found: C, 75.57; H, 7.59; N 7.94%. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99%.

4.4. General procedure for the preparation of 3-alkyl-4-pyridyl-3-buten-2-one *N*-oxide

A mixture of the corresponding enone (5 mmol) and 3-chloroperbenzoic acid (5 mmol) in chloroform (4 mL) was stirred for 3 h at room temperature. The solution was passed through a column of aluminum oxide (basic) and eluted with chloroform then methanol/chloroform (1/3). After removal of the solvent, the residue was purified by recrystallization. The solvent for recrystallization, the yield of the isolated products, and their spectral and physical data are listed below.

4.4.1. 3-Methyl-4-(2-pyridyl)-3-buten-2-one *N*-oxide 1d. Recrystallized from dichloromethane/ethyl acetate. 73% yield; mp 76.5–77.1°C; ^{1}H NMR ($CDCl_3$, TMS) δ 2.04 (3H, d, $J=1.5$ Hz), 2.54 (3H, s), 7.27–7.50 (3H, m), 7.77–7.81 (1H, m), 8.31–8.35 (1H, m); IR (KBr) 1671 cm^{-1}. Found: C, 67.69; H, 6.37; N 7.90%. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90%.

4.4.2. 3-Methyl-4-(3-pyridyl)-3-buten-2-one *N*-oxide 1e. Recrystallized from dichloromethane/ethyl acetate. 77% yield; mp 113.3–115.2°C; ^{1}H NMR ($CDCl_3$, TMS) δ 2.05 (3H, d, $J=1.4$ Hz), 2.47 (3H, s), 7.23–7.39 (4H, m), 8.15–8.28 (1H, m); IR (KBr) 1661 cm^{-1}. Found: C, 67.68; H, 6.14; N 7.79%. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90%.

4.4.3. 3-Methyl-4-(4-pyridyl)-3-buten-2-one *N*-oxide 1f. Recrystallized from dichloromethane/ethyl acetate. 71% yield; mp 125.5–125.9°C; ^{1}H NMR ($CDCl_3$, TMS) δ 2.09 (3H, d, $J=1.4$ Hz), 2.47 (3H, s), 7.27–7.37 (3H, m), 8.20–8.26 (2H, m); IR (KBr) 1665 cm^{-1}. Found: C, 67.50; H, 6.22; N 7.83%. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90%.

4.4.4. 3-Ethyl-4-(2-pyridyl)-3-buten-2-one *N*-oxide 1k. Recrystallized from ethyl acetate. 59% yield; mp 99.1–99.9°C; ^{1}H NMR ($CDCl_3$, TMS) δ 1.11 (3H, t, $J=7.5$ Hz), 2.49 (2H, q, $J=7.5$ Hz), 2.52 (3H, s), 7.24–7.33 (3H, m), 7.72 (1H, br), 8.29–8.34 (1H, m); IR (KBr) 1660 cm^{-1}. Found: C, 68.95; H, 6.88; N, 7.16%. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32%.

4.4.5. 3-Ethyl-4-(3-pyridyl)-3-buten-2-one *N*-oxide 1l. Recrystallized from ethyl acetate. 58% yield; mp 119.0–120.2°C; ^{1}H NMR ($CDCl_3$, TMS) δ 1.09 (3H, t, $J=7.5$ Hz), 2.46 (3H, s), 2.48 (2H, q, $J=7.5$ Hz), 7.18–7.39 (3H, m), 8.15–8.26 (2H, m); IR (KBr) 1663 cm^{-1}. Found: C, 69.00; H, 6.84; N, 7.21%. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32%.

4.4.6. 3-Ethyl-4-(4-pyridyl)-3-buten-2-one *N*-oxide 1m. Recrystallized from ethyl acetate. 79% yield; mp 117.0–117.8°C; ^{1}H NMR ($CDCl_3$, TMS) δ 1.12 (3H, t, $J=7.5$ Hz), 2.45 (3H, s), 2.54 (2H, q, $J=7.5$ Hz), 7.22–7.37 (3H, m), 8.19–8.26 (2H, m); IR (KBr) 1651 cm^{-1}. Found: C, 68.82; H, 6.84; N, 7.19%. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32%.

4.5. 3-Bromo-2-butanone

A slight modification of the reported method was adopted for the synthesis of this compound.[34] Reaction of 2-butanone (40.0 g, 55.5 mmol) with bromine (30.7 g, 192 mmol) gave 3-bromo-2-butanone quantitatively.

4.6. (1-Methyl-2-oxopropyl)triphenylphosphonium bromide

3-Bromo-2-butanone (4.53 g, 30 mmol) and triphenylphosphine (8.66 g, 33 mmol) in benzene (40 mL) were heated under reflux for 8 h. After cooling, the resulting white precipitate was collected via suction filtration to obtain (1-methyl-2-oxopropyl)triphenylphosphonium bromide as a white solid (8.48 g, 71%). ^{1}H NMR ($CDCl_3$, TMS) δ 1.70 (3H, dd, $J=7.4$, 18.4 Hz), 2.63 (3H, d, $J=1.6$ Hz), 5.89 (1H, d, $J=12.0$ Hz), 7.34–8.05 (15H, m).

4.7. 4-(2-Hydroxyphenyl)-3-methyl-3-buten-2-one 1g

In a three-necked flask, (1-methyl-2-oxopropyl)triphenylphosphonium bromide (4.69 g, 11.3 mmol) in dry THF (100 mL) was cooled at 0°C under an argon atmosphere. While stirring, a solution of butyllithium in hexane (1.5 M, 18 mL, 27 mmol) was added to the mixture, the color of the solution changed to dark red. After 1 h, a solution of salicylaldehyde (1.38 g, 11.3 mmol) in dry THF (5 mL) was added to the solution, and the temperature was raised to room temperature. The solution was neutralized with aqueous saturated ammonium chloride and the aqueous solution was extracted with ethyl acetate. The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Removal of the solvent gave the crude product. The residue was chromatographed on silica gel and eluted with hexane/ethyl acetate (4/1) to obtain the mixture of 4-(2-hydroxyphenyl)-3-methyl-3-buten-2-one and 1-(2-hydroxyphenyl)-1-buten-3-pentanone. The mixture was recrystallized from ether to afford 4-(2-hydroxyphenyl)-3-methyl-3-buten-2-one (0.84 g, 42%). Mp 124.6–126.0°C, ^{1}H NMR ($CDCl_3$, TMS) δ 1.99 (3H, d, $J=1.4$ Hz), 2.49 (3H, s), 5.68 (1H, s), 6.87–7.01 (2H, m), 7.21–7.32 (2H, m), 7.69 (1H, br); IR (KBr) 1637 cm^{-1}. Found: C, 74.81; H, 6.93%. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86%.

4.8. General procedure for baker's yeast reduction of enones

The substrate (0.5 mmol) in tap water (20 mL) was stirred vigorously at 35°C and dry baker's yeast (5.0 g) was added. The reaction was monitored by gas chromatography analysis. After an appropriate reaction time, acetone (20 mL) was added and the yeast was removed by suction filtration. After evaporation of the acetone under reduced pressure, the residue was extracted with dichloromethane. The combined extracts were dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to obtain the corresponding ketones. The enantiomeric excess (e.e.) of each chiral ketone was determined by GLC except for **2c**. The e.e. of **2c** was determined by HPLC. The yields of the isolated products, their e.e. and spectral and physical data are listed below.

4.8.1. 3-Methyl-3-(2-pyridyl)-2-butanone 2a. 59% yield; 65% e.e. (*S*)-enantiomer; $[\alpha]_D^{30}$ +6.5 (*c* 1.77, EtOH, 49% e.e.). Spectroscopic data agreed with the previous report.[28]

4.8.2. 3-Methyl-3-(3-pyridyl)-2-butanone 2b. 76% yield; >95% e.e. (*S*)-enantiomer; ^{1}H NMR ($CDCl_3$, TMS) δ 1.13 (3H, d, $J=7.0$ Hz), 2.13 (3H, s), 2.57 (1H, dd, $J=7.1$, 13.4 Hz), 2.83 (1H, sextet, $J=7.1$ Hz), 3.02 (1H, dd, $J=6.9$, 13.3 Hz), 7.17–7.25 (1H, m), 7.45–7.53 (1H, m), 8.42–8.48 (2H, m); IR (neat) 1712 cm^{-1}; $[\alpha]_D^{24}$ +2.3 (*c* 0.61, EtOH, 14% e.e.). Found: C, 73.47; H, 8.11; N, 8.34%. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58%.

4.8.3. 3-Methyl-3-(4-pyridyl)-2-butanone 2c. 72% yield; 77% e.e. (*S*)-enantiomer; ^{1}H NMR ($CDCl_3$, TMS) δ 1.13 (3H, d, $J=7.0$ Hz), 2.13 (3H, s), 2.55 (1H, dd, $J=7.1$, 13.1 Hz), 2.85 (1H, sextet, $J=6.9$ Hz), 3.02 (1H, dd, $J=7.0$, 13.2 Hz), 7.07–7.11 (2H, m), 8.48–8.52 (2H, m); IR (neat) 1713 cm^{-1}; $[\alpha]_D^{26}$ +2.04 (*c* 1.56, EtOH). Found: C, 73.58; H, 8.01; N, 8.41%. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58%.

4.8.4. 3-(2-Pyridylmethyl)-2-pentanone 2h. 72% yield; >99% e.e. (*S*)-enantiomer; ^{1}H NMR ($CDCl_3$, TMS) δ 0.92 (3H, t, $J=7.4$ Hz), 1.40–1.81 (2H, m), 2.11 (3H, s), 2.78–2.95 (1H, m), 3.04–3.19 (2H, m), 7.07–7.15 (2H, m), 7.52–7.63 (1H, m), 8.49–8.54 (1H, m); IR (neat) 1711 cm^{-1}; $[\alpha]_D^{24}$ +13.0 (*c* 2.05, EtOH). Found: C, 74.43; H, 8.58; N, 7.85%. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90%.

4.8.5. 3-(3-Pyridylmethyl)-2-pentanone 2i. 81% yield; 96% e.e. (*S*)-enantiomer; ^{1}H NMR ($CDCl_3$, TMS) δ 0.92 (3H, t, $J=7.3$ Hz), 1.45–1.80 (2H, m), 2.06 (3H, s), 2.61–3.02 (3H, m), 7.19–7.30 (1H. m), 7.40–7.48 (1H, m), 8.43–8.56 (2H, m); IR (neat) 1711 cm^{-1}; $[\alpha]_D^{23}$ +11.1 (*c* 5.39, EtOH). Found: C, 74.36; H, 8.61; N, 7.75%. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90%.

4.8.6. 3-(4-Pyridylmethyl)-2-pentanone 2j. 82% yield; >99% e.e. (*S*)-enantiomer; ^{1}H NMR ($CDCl_3$, TMS) δ 0.92 (3H, t, $J=7.4$ Hz), 1.45–1.80 (2H, m), 2.06 (3H, s), 2.61–2.98 (3H, m), 7.06–7.10 (2H, m), 8.48–8.51 (2H, m); IR (neat) 1711 cm^{-1}; $[\alpha]_D^{23}$ +4.21 (*c* 2.44, EtOH). Found: C, 74.26; H, 8.56; N, 7.89%. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90%.

4.8.7. 3-Methyl-3-(2-pyridyl)-2-butanone *N*-oxide 2d. 69% yield; 71% e.e. (*R*)-enantiomer; ^{1}H NMR ($CDCl_3$, TMS) δ 1.18 (3H, d, $J=7.1$ Hz), 2.16 (3H, s), 2.85 (1H, dd, $J=6.1$, 13.1 Hz), 3.19–3.48 (2H, m), 7.11–7.32 (3H, m), 8.20–8.26 (1H, m); IR (neat) 1710 cm^{-1}; $[\alpha]_D^{24}$ −4.5 (*c* 1.68, EtOH); HRMS *m*/*z* found: 179.0945; calcd for $C_{10}H_{13}NO_2$: 179.0946.

4.8.8. 3-Methyl-3-(3-pyridyl)-2-butanone *N*-oxide 2e. 87% yield; >95% e.e. (*S*)-enantiomer; ^{1}H NMR ($CDCl_3$, TMS) δ 1.13 (3H, d, $J=7.0$ Hz), 2.13 (3H, s), 2.57 (1H, dd, $J=7.0$, 13.5 Hz), 2.83 (1H, sextet, $J=7.0$ Hz), 3.02 (1H, dd, $J=7.0$, 13.5 Hz), 7.08–7.18 (2H, m), 7.47–7.55 (1H, m), 8.42–8.51 (1H, m); IR (neat) 1708 cm^{-1}; $[\alpha]_D^{24}$ −16.2 (*c* 1.29, EtOH); HRMS *m*/*z* found: 179.0940; calcd for $C_{10}H_{13}NO_2$: 179.0946.

4.8.9. 3-Methyl-3-(4-pyridyl)-2-butanone *N*-oxide 2f. 64% yield; 72% e.e. (*S*)-enantiomer; ^{1}H NMR ($CDCl_3$, TMS) δ 1.17 (3H, d, $J=7.0$ Hz), 2.14 (3H, s), 2.56 (1H, dd, $J=6.4$, 13.4 Hz), 2.82 (1H, sextet, $J=6.9$ Hz), 3.01 (1H, dd, $J=7.6$, 13.4 Hz), 7.08–7.12 (2H, m), 8.11–8.15 (2H, m); IR (neat) 1709 cm^{-1}; $[\alpha]_D^{24}$ −2.2 (*c* 1.92, EtOH); HRMS *m*/*z* found: 179.0938; calcd for $C_{10}H_{13}NO_2$: 179.0946.

4.8.10. 3-(2-Pyridylmethyl)-2-pentanone *N*-oxide 2k. 93% yield; >99% e.e. (*S*)-enantiomer; ^{1}H NMR ($CDCl_3$, TMS) δ 0.95 (3H, t, $J=7.5$ Hz), 1.50–1.86 (2H, m),

2.11 (3H, s), 2.93–3.19 (2H, m), 3.24–3.37 (1H, m), 7.15–7.31 (3H, m), 8.21–8.26 (1H, m); IR (neat) 1708 cm^{-1}; $[\alpha]_D^{23}$ +25.8 (*c* 5.00, EtOH); HRMS *m*/*z* found: 193.1113; calcd for $C_{11}H_{15}NO_2$: 193.1103.

4.8.11. 3-(3-Pyridylmethyl)-2-pentanone *N*-oxide 2l. 92% yield; 96% e.e. (*S*)-enantiomer; ^1H NMR ($CDCl_3$, TMS) δ 0.93 (3H, t, $J=7.4$ Hz), 1.48–1.81 (2H, m), 2.10 (3H, s), 2.59 (1H, dd, $J=5.6$, 13.2 Hz), 2.69–2.82 (1H, m), 2.93 (1H, dd, $J=8.2$, 13.2 Hz), 7.09–7.23 (2H, m), 8.08–8.12 (2H, m); IR (neat) 1703 cm^{-1}; $[\alpha]_D^{23}$ −18.4 (*c* 3.02, EtOH); HRMS *m*/*z* found: 193.1109; calcd for $C_{11}H_{15}NO_2$: 193.1103.

4.8.12. 3-(4-Pyridylmethyl)-2-pentanone *N*-oxide 2m. 54% yield; >99% e.e. (*S*)-enantiomer; ^1H NMR ($CDCl_3$, TMS) δ 0.94 (3H, t, $J=7.4$ Hz), 1.47–1.78 (2H, m), 2.08 (3H, s), 2.62 (1H, dd, $J=5.1$, 12.9 Hz), 2.69–2.81 (1H, m), 2.95 (1H, dd, $J=8.4$, 12.9 Hz), 7.06–7.10 (2H, m), 8.10–8.13 (2H, m); IR (neat) 1706 cm^{-1}; $[\alpha]_D^{24}$ −1.1 (*c* 1.63, EtOH); HRMS *m*/*z* found: 193.1104; calcd for $C_{11}H_{15}NO_2$: 193.1103.

4.9. Determination of the absolute configuration

4.9.1. Baeyer–Villiger reaction of 2a[35]. A mixture of trifluoroacetic anhydride (1.0 g, 4.8 mmol), aqueous hydrogen peroxide (35%, 90 μL), and dichloromethane (0.75 mL) was stirred at 0°C. After 30 min, 3-methyl-4-(2-pyridyl)-2-butanone **2a** obtained by baker's yeast reduction (0.23 g, 1.4 mmol) in dichloromethane (1 mL) was added over a period of 5 min and the mixture was stirred at room temperature overnight. Removal of the solvent gave a mixture of Baeyer–Villiger reaction product and pyridinium trifluoroacetate. The residue was chromatographed on silica gel and eluted with methanol/ethyl acetate (1/4–2/3) to obtain 2-(2-acetoxypropyl)pyridinium trifluoroacetate (0.20 g, 49%). ^1H NMR ($CDCl_3$, TMS) δ 1.35 (3H, d, $J=6.3$ Hz), 1.98 (3H, s), 3.31–3.56 (2H, m), 5.21–5.37 (1H, m), 7.02–7.90 (1H, br) 7.58–7.69 (2H, m), 8.10–8.20 (1H, m), 8.85–8.89 (1H, m).

4.9.2. Reduction of 2-(2-acetoxypropyl)pyridinium trifluoroacetate. A suspension of 2-(2-acetoxypropyl)-pyridinium trifluoroacetate (0.2 g, 0.69 mmol) and lithium aluminum hydride (53 mg, 1.4 mmol) in dry ether (5 mL) was stirred at room temperature overnight under an argon atmosphere. To the mixture was added ethyl acetate, water, and 2 M hydrochloric acid to decompose excess lithium aluminum hydride. An insoluble material was removed with suction filtration. The aqueous solution was extracted with dichloromethane. The combined extracts were washed with brine, dried over anhydrous magnesium sulfate and filtered. Removal of the solvent gave crude products. The residue was chromatographed on silica gel and eluted with ethyl acetate to obtain 3-(2-pyridyl)-2-pentanol (53 mg, 56%). 52% e.e. (*S*)-enantiomer; ^1H NMR ($CDCl_3$, TMS) δ 1.28 (3H, d, $J=6.2$ Hz), 2.85–2.89 (2H, m), 4.07–4.33 (1H, m), 7.11–7.18 (2H, m), 7.58–7.67 (1H, m), 8.48–8.53 (1H, m); $[\alpha]_D^{29}$ +17.4 (*c* 1.09, EtOH) (lit.[30] $[\alpha]_D^{25}$ +15.3 (*S*), $[\alpha]_D^{25}$ −17.9 (*R*) (98% EtOH)).

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