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Enantioselective bioreduction of (*E*)-1-phenyl-1,2-alkanedione 2-(*O*-methyloxime)

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Abstract

The baker's yeast reduction of (*E*)-1-phenyl-1,2-alkanedione 2-(*O*-methyloxime), PhC(O)C(NOMe)R (R = Me, Et, *n*-Pr, *n*-Bu), gave the corresponding optically active alcohols $PhCH_2OHC(NOMe)R$ in 88–99% enantiomeric excess and 48–75% chemical yield. The *R* configuration was proposed for these alcohols based on circular dichroism analysis. Only the phenylglyoxal *O*-methylaldoxime (R = H) gave poor enantiomeric excess (65%) and chemical yield (14%). These compounds are potential chiral building blocks for the stereoselective synthesis of norephedrine analogs.

1. Introduction

The stereoselective synthesis of enantiomerically pure 1,2-aminoalcohols is important due to their utilisation as chemotherapeutic drugs, chiral auxiliaries and chiral building blocks in organic synthesis.[1,2] Ephedrine, which is extracted from various species of Ephedra, acts on the sympathetic nervous system. In addition, the analogs of the natural (–)-(1*R*,2*S*)-ephedrine and (+)-(1*S*,2*S*)-pseudoephedrine are an important class of bioactive compounds. The enantioselective synthesis of norephedrine or norpseudoephedrine has been performed by organolithium addition to aldehyde dimethylhydrazones,[3] Friedel–Crafts reaction of L-amino acid chloride,[4] by reductions of esters of natural amino acid blocked in the form of cyanoenamine,[5] by a chiral intermediate of chloramphenicol synthesis,[6] reaction of benzaldehyde and acetyl–CoA promoted by brewer's yeast,[7] from optically active cyanohydrins,[8,9] asymmetric α-amination of ketone enolates by homochiral α-chloro-α-nitroso reagents[10] and baker's yeast reduction of α-azidopropiophenone.[11]

Recently, the reduction of (*E*)-1-phenyl-1,2-propanedione 2-(*O*-methyloxime) by baker's yeast (*Saccharomyces cerevisiae*) was used as a key step in the enantioselective synthesis of (–)-(1*R*,2*S*)-norephedrine and (–)-(1*R*,2*R*)-norpseudoephedrine.[12] In this work, we apply this methodology with phenylglyoxal *O*-methylaldoxime, **2a**, and several (*E*)-1-phenyl-1,2-alkanedione 2-(*O*-methyloxime),

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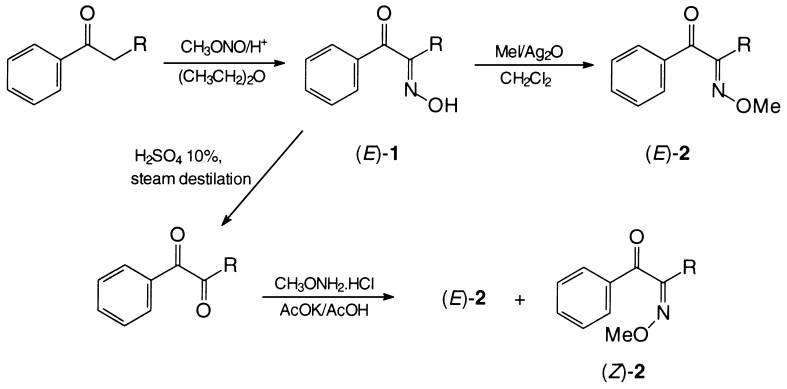
PhC(O)C(NOMe)R, **2c** (R = Et), **2d** (R = *n*-Pr) and **2e** (R = *n*-Bu) in the preparation of chiral building blocks for the synthesis of norephedrine analogs. Comments are made on the influence of the size of alkyl moiety in the baker's yeast reduction of (*E*)-1-phenyl-1,2-alkanedione 2-(*O*-methyloxime).

2. Results and discussion

The appropriate alkyl phenyl ketones were nitrosated by Slater's method[13] to give the (*E*)-1-phenyl-1,2-alkanedione 2-oximes that were methylated by a modified Buehler's method[14] (Scheme 1). While the nitrosation of alkyl phenyl ketones gave the (*E*)-1-phenyl-1,2-alkanedione 2-oxime, a mixture of *Z*- and *E*-isomers was obtained by reaction of the appropriate 1-phenyl-1,2-alkanedione with methoxylamine hydrochloride. The evidence for the *E*-isomer is based on the ^{13}C NMR spectrum comparison of a mixture of *Z*- and *E*-isomers and a sample of a pure *E*-isomer.[15] The observed upfield shift (see Table 1) due to the steric compression between the methyl carbon *syn* to the OH or OMe groups (as well as for the methylene carbon has previously been described for the ketone oximes).[16,17] Downfield shifts of 3.6–3.7 ppm were observed for the C1 signals of the *E*-isomers **2b–e**.



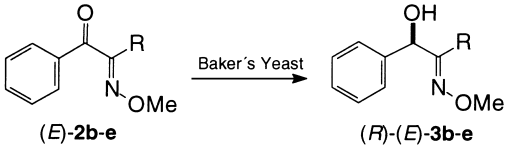
Scheme 1.

Table 1
^{13}C NMR chemical shifts for C1, C2 and C3 of (*Z*)- and (*E*)-1-phenyl-1,2-alkanedione2-(*O*-methyloxime)

PhC(O)C(NOMe)R	C1 (δ)	C2 (δ)	C3 (δ)
(E)-2b,[a] R = Me	191.2	155.3	10.7
(Z)-2b,[a] R = Me	194.8	154.6	17.0
(E)-2c, R = Et	191.5	160.0	18.2
(Z)-2c, R = Et	195.1	159.0	25.1
(E)-2d, R = n-Pr	191.6	159.0	26.5
(Z)-2d, R = n-Pr	195.3	158.3	33.7
(E)-2e, R = n-Bu	192.0	159.6	28.7
(Z)-2e, R = n-Bu	195.7	158.2	31.5

a) From ref. 12

The ketone function of phenylglyoxal *O*-methylaldoxime **2a** and (*E*)-1-phenyl-1,2-alkanedione 2-(*O*-methyloxime) **2b–e** was reduced by baker's yeast yielding the corresponding optically active alcohols **3a–e** (Scheme 2). The optimised reaction times, presented in Table 2, were determined by gas chromatography analysis of samples that were withdrawn from the reaction mixture at appropriate intervals. The reactivities of **2a–e** decrease with the increase of the size of alkyl moiety.



(*E*)-**2b-e** (*R*)-(*E*)-**3b-e**

b) R = Me **d**) R = *n*-Pr
c) R = Et **e**) R = *n*-Bu

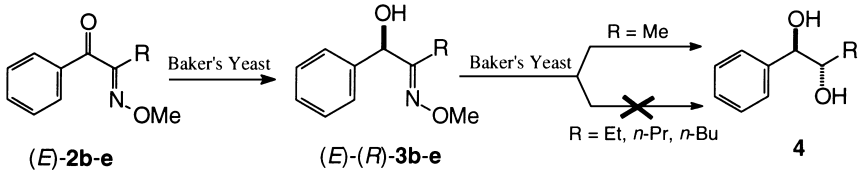
Scheme 2.

Table 2
Baker's yeast reduction of (*E*)-1-phenyl-1,2-alkanedione 2-(*O*-methyloxime)

PhC(O)C(NOMe)R	Reaction time (h)	Yield (%)[a]	$[\alpha]_D^{20}$	ee[b] (%)
(*E*)-**2a** (R = H)	6	14	+3.8[c]	65
(*E*)-**2b** (R = Me)	24	75	-115[d]	88-97[e]
(*E*)-**2c** (R = Et)	48	73	-105[d]	92
(*E*)-**2d** (R = *n*-Pr)	72	52	-137[d]	98
(*E*)-**2e** (R = *n*-Bu)	72	48	-144[d]	>99

a) isolated chemical yield; b) chiral GC (β-cyclodextrin); c) c = 4.5 $CHCl_3$; d) c = 1.3 $CHCl_3$;
e) *R* configuration.[12]

While the *O*-methyloximes **3c–e** were stable in the bioreduction medium, **3a** and **3b** undergo subsequent reactions. For example, the *O*-methyloxime **3b** was converted into (–)-(1*R*,2*S*)-1-phenyl-1,2-propanediol, **4** (R = Me), after 120 h[12] (Scheme 3). It is reasonable to suppose that the transformation of **3** into **4** should involve two steps: a hydrolysis of the *O*-methyloxime function giving a ketone followed by the stereoselective reduction of this ketone giving the optically active diol.[18] The diol **4** (R = Me) is generally obtained when 1-phenyl-1,2-propanedione is subjected to baker's yeast reduction without pH control.[19,20] These two steps seem to be mediated by baker's yeast. The hydrolysis of the *O*-methyloxime function is a critical step and seems to be dependent on the size of the R group (Scheme 3). In addition, we were unable to perform the chemical deoximation of **3b**[12] using the available methodologies for oximes.[21–24]



(*E*)-**2b-e** (*E*)-(*R*)-**3b-e** **4**

Scheme 3.

The configuration of *O*-methyloxime **3b** was determined as *R* by diastereoselective reduction of **3b** using $LiAlH_4$ to obtain the (–)-(1*R*,2*S*)-norephedrine with ee >82% and (–)-(1*R*,2*R*)-norpseudoephedrine with 93% ee, respectively, in a 4:1 ratio.[12] The circular dichroism (CD) spectra of *O*-methyloximes **3b–e** show a large and positive Cotton effect (CE) at $\lambda = 221$–224 nm and also a positive CE of ^1L_b determined by vibronic borrowing[25,26] from benzene transitions at wavelengths 240–270 nm (Fig. 1). Due to the similarity of CE spectra we can assume that the *O*-methyloximes **3c–e** have the same configuration as **3b**, i.e. *R* configuration. Applying the empirical sector rule,[27] which correlate the sign of the ^1L_b CEs and the absolute configuration of a chiral centre contiguous to the benzene ring, we can state that the sequences for summation of contributions[27] to the ^1L_b CEs are –C(=NOMe)R > –OH as shown in Fig. 2.

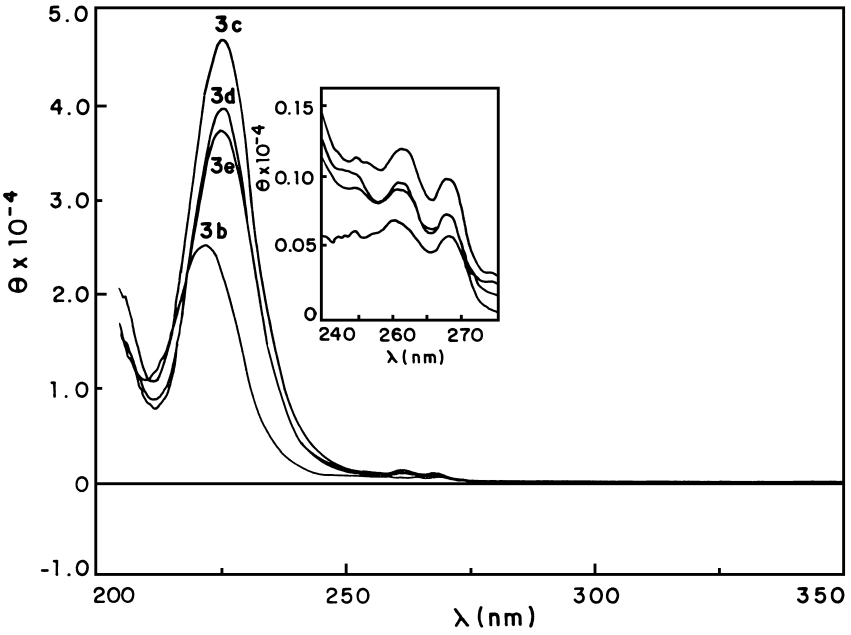


Figure 1. CD spectra of **3b–e** obtained by baker's yeast reduction of (*E*)-**2b–e**

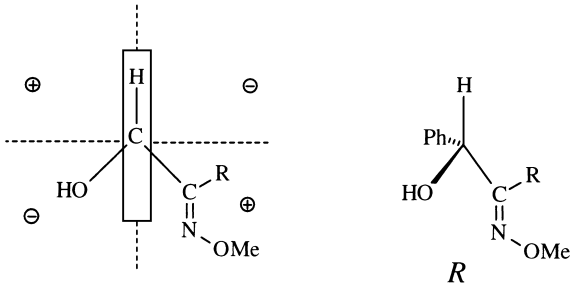


Figure 2. Empirical sector rule (^1L_b transition)[1] for chiral benzylic derivatives with OH and C(=NOMe)R groups

The specific rotation values of *O*-methyloximes **3c–e** are similar ($[\alpha]_D^{20} = -105$ to -144). Only **3a** shows a slightly positive rotation and poor enantiomeric excess (65%). The enantiomeric excesses of the *O*-methyloximes **3b–e** (88–99%) increase and the chemical yields decrease with the size of alkyl moiety.

3. Conclusion

The baker's yeast reduction of the ketone function of (*E*)-1-phenyl-1,2-alkanedione 2-(*O*-methyloxime) affords the corresponding (*E*)–(*R*)-1-hydroxy-1-phenyl-2-alkanone 2-(*O*-methyloxime) with reasonable yields and good enantiomeric excesses. A substrate selectivity, which is influenced by the size of R group, was observed in the reduction of the ketone function and also in the subsequent reaction giving the corresponding diol.

4. Experimental

4.1. General

Melting points were measured on a Microquimica MQAFP-301 apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 1600 FT spectrophotometer. NMR spectra were recorded on a Bruker AC 300P or Varian Gemini 300 spectrometer with $CDCl_3$ as solvent and TMS as an internal standard. CD spectra were recorded on a JASCO J-720 spectropolarimeter. Gas chromatography analyses were performed on a HP 5890 chromatograph, with a HP-5 column (crosslinked 5% Ph Me Silicone, ID 0.53 mm, 30 m length). Enantiomeric excesses were determined by GC analysis using a chiral column [stationary phase: heptakis-(2,6-methyl-3-penthyl)-β-cyclodextrine]. Chromatographical column separations were performed with Silica gel-60. Mass spectra were obtained on a Shimadzu CGMS-QP5000 spectrometer and high-resolution mass spectra were obtained on a Fisons VG Autoespec Varian. Specific rotations were measured on a Carl Zeis Polamat A polarimeter. Commercially available chemicals and solvents were used without further purification. Commercially available dry baker's yeast from N. V. Algist-Bruggeman S. A. was used in this work. The compounds **2b** and **3b** were described previously.[12]

4.2. General procedure for the preparation of (E)-1-phenyl-1,2-alkanedione 2-(O-methyloxime)

The appropriated alkyl phenyl ketone, nitrosated by Slater's method,[12] was methylated by the following modified Buehler's method:[14] Ag_2O (3.2 g, 13.8 mmol) was slowly added with stirring to a solution of (*E*)-1-phenyl-1,2-alkanedione 2-oxime (12.3 mmol) and MeI (8.7 mL, 61.5 mmol) in 15 mL of CH_2Cl_2, and cooled with an ice–water bath. After 0.5 h of reaction, the precipitate was filtered off and washed with CH_2Cl_2. The CH_2Cl_2 was evaporated from the filtrate yielding the corresponding (*E*)-1-phenyl-1,2-alkanedione 2-(*O*-methyloxime).

4.3. General procedure for the preparation of a mixture of (E)- and (Z)-1-phenyl-1,2-alkanedione 2-(O-methyloxime)

The title isomer mixture was obtained following the modified Denmark method.[28] A solution of the appropriate 1-phenyl-1,2-alkanedione (1.5 equiv.) in glacial acetic acid (0.33 M) was treated with potassium acetate (3.0 equiv.) and methoxylamine hydrochloride (3.0 equiv.). This mixture was stirred for 1 h at room temperature, poured into water and the resulting solution was

neutralised with a saturated solution of sodium bicarbonate. The products were extracted with ethyl acetate, dried with magnesium sulphate and the solvent evaporated at reduced pressure.

4.4. (E)-1-Phenyl-1,2-butanedione 2-oxime **1c**

Following Buehler's general procedure, compound **1c** was obtained as an orange oil in 85% yield. IR (film): 3362, 2977, 2877, 1654, 1597, 1449, 877 cm^{-1}; MS (70 eV) *m/z* 177 (M^+, 2%), 160 (5), 105 (100), 77 (57), 51 (29); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.12 (t, 3H), 2.71 (q, 2H), 7.40–7.48 (m, 2H), 7.56–7.62 (m, 1H), 7.86–7.90 (m, 2H), 9.50 (bs, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 10.1, 17.9, 128.8, 130.1, 132.8, 136.5, 160.9, 192.0; HRMS found: *m/z* 177.0794; calcd for $C_{10}H_{11}NO_2$ $[M]^+$: 177.0790.

4.5. (E)-1-Phenyl-1,2-pentanedione 2-oxime **1d**

Following Buehler's general procedure, compound **1d** was obtained as an orange oil in 79% yield. IR (film): 3251, 3038, 2961, 1635, 1576, 1447, 1017, 728, 694 cm^{-1}; MS (70 eV) *m/z* 191 (M^+, 0.8%), 174 (12), 105 (65), 77 (100), 51 (65); ^1H NMR (300 MHz, $CDCl_3$) δ: 0.96 (t, 3H), 1.58 (m, 2H), 2.70 (t, 2H), 7.41–7.45 (m, 2H), 7.53–7.58 (m, 1H), 7.85–7.88 (m, 2H), 8.76 (bs, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.3, 19.3, 26.4, 128.7, 130.7, 133.4, 137.3, 160.8, 192.8; HRMS found: *m/z* 191.0948; calcd for $C_{11}H_{13}NO_2$ $[M]^+$: 191.0946.

4.6. (E)-1-Phenyl-1-2-hexanedione 2-oxime **1e**

Following Buehler's general procedure, compound **1e** was obtained as an orange oil in 72% yield. IR (film): 3349, 2960, 2932, 1708, 1664, 1452, 1281, 1217, 1004, 713 cm^{-1}; MS (70 eV) *m/z* 205 (M^+, 2%), 188 (7), 105 (100), 84 (19), 77 (76), 51 (40), 41 (48); ^1H NMR (300 MHz, $CDCl_3$) δ: 0.91 (t, 3H), 1.33–1.43 (m, 2H), 1.47–1.57 (m, 2H), 2.71 (t, 2H), 7.34–7.48 (m, 2H), 7.53–7.58 (m, 1H), 7.85–7.90 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.8, 23.0, 24.3, 28.0, 128.7, 130.8, 133.4, 137.2, 160.9, 192.8; HRMS found: *m/z* 205.1106; calcd for $C_{12}H_{15}NO_2$ $[M]^+$: 205.1103.

4.7. Phenylglyoxal (O-methylaldoxime) **2a**

Following the general procedure, compound **2a** was obtained as an orange oil in 96% yield from the corresponding oxime. IR (film): 3060, 2941, 1651, 1588, 1446, 1327, 1277, 1038, 1019, 695, 640 cm^{-1}; MS (70 eV) *m/z*: 163 (M^+, 4%), 105 (100), 77 (62), 51 (47); ^1H NMR (300 MHz, $CDCl_3$) δ: 4.09 (s, 3H), 7.36–7.56 (m, 2H), 7.57–7.63 (m, 1H), 7.95 (s, 1H), 8.11–8.30 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 63.7, 128.9, 130.6, 133.9, 136.4, 144.6, 188.9.

4.8. (E)-1-Phenyl-1,2-butanedione 2-(O-methyloxime) **2c**

Following the general procedure, compound **2c** was obtained as an orange oil in 91% yield from the corresponding oxime. IR (film): 2973, 2935, 1661, 1597, 1040, 861, 720 cm^{-1}; MS (70 eV) *m/z*: 191 (M^+, 2%), 160 (22), 105 (100), 77 (52), 51 (33); ^1H NMR (300 MHz, $CDCl_3$, TMS) δ: 1.11 (t, 3H), 2.68 (q, 2H), 4.01 (s, 3H), 7.39–7.46 (m, 2H), 7.51–7.58 (m, 1H), 7.95–7.99 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 10.1, 18.2, 62.3, 128.1, 130.7, 132.8, 136.9, 160.0, 191.5; HRMS found: *m/z* 191.0943; calcd for $C_{11}H_{13}NO_2$ $[M]^+$: 191.0946.

4.9. (E)-1-Phenyl-1,2-pentanedione 2-(O-methyloxime) **2d**

Following the general procedure, compound **2d** was obtained as an orange oil in 93% yield from the corresponding oxime. IR (film): 3058, 2963, 2937, 1660, 1598, 1446, 1043, 714 cm^{-1}; MS (70 eV) *m/z*: 205 (M^+, 2%), 174 (12), 105 (100), 77 (88), 58 (12), 51 (59); ^1H NMR (300 MHz, $CDCl_3$, TMS) δ: 0.96 (t, 3H), 1.57 (m, 2H), 2.67 (m, 2H), 4.00 (s, 3H), 7.39–7.44 (m, 2H), 7.51–7.53 (m, 1H), 7.95–7.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 13.9, 19.2, 26.5, 62.8, 128.0, 130.7, 132.7, 136.9, 159.0, 191.6; HRMS found: *m/z* 205.1103; calcd for $C_{12}H_{15}NO_2$ $[M]^+$: 205.1103.

4.10. (E)-1-Phenyl-1-2-hexanedione 2-(O-methyloxime) **2e**

Following the general procedure, compound **2e** was obtained as an orange oil in 92% yield from the corresponding oxime. IR (film): 3060, 2959, 2936, 1663, 1596, 1451, 1220, 1043, 906, 719 cm^{-1}; MS (70 eV) *m/z*: 219 (M^+, 2%), 188 (20), 105 (100), 77 (71), 51 (33); ^1H NMR (300 MHz, $CDCl_3$, TMS) δ: 0.91 (t, 3H), 1.38 (m, 2H), 1.48 (m, 2H), 2.69 (t, 2H), 4.02 (s, 3H), 7.40–7.45 (m, 2H), 7.50–7.57 (m, 1H), 7.94–7.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 13.9, 23.1, 24.8, 28.7, 63.2, 128.5, 131.1, 133.1, 137.3, 159.6, 192.0; HRMS found: *m/z* 219.1257; calcd for $C_{13}H_{17}NO_2$ $[M]^+$: 219.1259.

4.11. General procedure for the reduction of (E)-1-phenyl-1,2-alkanedione 2-(O-methyloxime) by free baker's yeast

O-Methyloxime (3 mmol) dissolved in 5 mL of ethanol was added with stirring at 30°C to a suspension of 10 g of dry baker's yeast and 30 g of sucrose in 1 L of aqueous solution of 2% KCl. After continuous stirring for the specified time (see Table 2), the reaction mixture was saturated with sodium chloride and the product was extracted with chloroform in a liquid–liquid continuous extractor during 72 h. After solvent evaporation, the residue was subjected to a chromatography column with hexane:ethyl acetate (5:1) as eluent in order to separate the product and the unreacted *O*-methyloxime.

4.12. Yeast immobilisation[29]

Dry baker's yeast (10 g) was added to a suspension of 30 g of Montmorillonite K10 in 1 L of water and then the resultant suspension was gently shaking for 1.5. After vacuum filtration the immobilised baker's yeast (IMBY) was suspended in 1 L of an aqueous solution of 2% KCl.

4.13. General procedure for the reduction of (E)-1-phenyl-1,2-alkanedione 2-(O-methyloxime) by IMBY

Sucrose (30 g) was added to the previous prepared suspension of IMBY. After 30 min of mechanical stirring at 30°C, the *O*-methyloxime (3.0 mmol) dissolved in 5 mL of ethanol was added and the stirring continued for the additional specified time (see Table 2). The IMBY was then filtered off and the filtrate was extracted with ethyl acetate. After solvent evaporation, the residue was subjected to the same procedure described above.

4.14. Baker's yeast reduction of phenylglyoxal (O-methylaldoxime) **2a**

Following the general procedure using free baker's yeast, compound **3a** was isolated after 6 h of reaction as an oil in 14% yield. $[\alpha]_D^{20} = +3.8$ (*c* 4.5, $CHCl_3$), 62% ee; IR (film): 3398, 3064, 3031, 2960, 2937, 1686, 1492, 1451, 1034, 700 cm^{-1}; MS (70 eV) *m*/*z*: 149 (0.8), 136 (100), 107 (21), 105 (41), 91 (9), 79 (85), 77 (92), 60 (94), 51 (52); ^1H NMR (300 MHz, $CDCl_3$) δ: 3.87 (s, 3H), 5.31 (d, 1H), 7.32–7.39 (m, 5H), 7.45 (d, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 62.0, 71.8, 126.6, 128.5, 129.0, 140.0, 150.7.

4.15. Baker's yeast reduction of (E)-1-phenyl-1,2-butanedione 2-(O-methyloxime) **2c**

Following the general procedure using IMBY, compound **3c** was isolated after 24 h of reaction as an oil in 73% yield. $[\alpha]_D^{20} = -105$ (*c* 1.3, $CHCl_3$), 92% ee; IR (film): 3410, 3063, 3030, 2974, 2939, 1445, 1188, 1046, 907, 703 cm^{-1}; MS (70 eV) *m*/*z*: 193 (M^+, 2%), 164 (3), 132 (11), 107 (57), 77 (100), 37 (77); ^1H NMR (500 MHz, $CDCl_3$, TMS) δ: 0.82 (t, 3H), 1.97–2.01 (m, 1H), 2.18–2.32 (m, 1H), 3.90 (s, OH), 3.93 (s, 3H), 5.18 (d, 1H), 7.32 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ: 10.4, 19.9, 62.2, 74.6, 127.7, 128.7, 129.0, 140.5, 161.6. HRMS found: *m*/*z* 193.1103; calcd for $C_{11}H_{15}NO_2$ $[M]^+$: 193.1103.

4.16. Baker's yeast reduction of (E)-1-phenyl-1,2-pentanedione 2-(O-methyloxime) **2d**

Following the general procedure using IMBY, compound **3d** was isolated after 72 h of reaction as an oil in 52% yield. $[\alpha]_D^{20} = -137$ (*c* 1.3, $CHCl_3$), 98% ee; IR (film): 3426, 2962, 2933, 1662, 1451, 1046, 907, 703 cm^{-1}; MS (70 eV) *m*/*z*: 207 (M^+, 4%), 178 (13), 146 (31), 107 (100), 77 (67), 51 (36), 41 (55); ^1H NMR (500 MHz, $CDCl_3$, TMS) δ: 0.80 (t, 3H), 1.17–1.41 (m, 2H), 1.68 (s br, OH), 1.83–1.93 (m, 1H), 2.18–2.29 (m, 1H), 3.92 (s, 3H), 5.16 (d, 1H), 7.28–7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ: 14.3, 19.4, 28.6, 62.1, 74.9, 127.4, 128.4, 128.8, 140.4, 160.1; HRMS found: *m*/*z* 207.1258; calcd for $C_{12}H_{17}NO_2$ $[M]^+$: 207.1259.

4.17. Baker's yeast reduction of (E)-1-phenyl-1,2-hexanedione 2-(O-methyloxime) **2e**

Following the general procedure using free baker's yeast, compound **3e** was isolated after 72 h of reaction as an oil in 48% yield. $[\alpha]_D^{20} = -144$ (*c* 1.3, $CHCl_3$), ee >99%; IR (film): 3373, 3063, 2957, 2953, 1682, 1595, 1450, 1254, 1041, 714 cm^{-1}; MS (70 eV) *m*/*z*: 221 (M^+, 3%), 192 (10), 160 (15), 116 (27), 107 (91), 77 (100), 54 (36), 51 (52), 43 (90), 41 (98); ^1H NMR (300 MHz, $CDCl_3$, TMS) δ: 0.79 (t, 3H), 1.15–1.27 (m, 4H), 1.85–1.90 (m, 1H), 2.19–2.28 (m, 1H), 3.91 (s, 3H), 3.98 (d, 1H), 5.16 (d, 1H), 7.29–7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 13.6, 22.9, 26.3, 28.0, 62.0, 74.8, 127.4, 128.4, 128.8, 140.4, 160.4; HRMS found: *m*/*z* 221.1417; calcd for $C_{13}H_{19}NO_2$ $[M]^+$: 221.1416.

Acknowledgements

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