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# Chemo- and Stereoselective Reduction of β-Keto-α-oximino Nitriles by Using Baker's Yeast

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The baker's yeast mediated reduction of β-keto-α-oximino nitriles **3** at 20 °C gave β-hydroxy-α-oximino nitriles **4** in high yields with high enantiomeric purity [enantiomeric excess (*ee*) values >99 %]. At room temperature, the same reaction afforded the product in a slightly lower yield. The β-hydroxy-α-oximino nitriles **4** were obtained as single stereoisomers according to chiral GC–MS analyses and the $^{1}H$ and $^{19}F$ NMR spectra of the corresponding Mosher esters. The absolute stereochemistry of alcohol **4a** was determined by hydrolysis of its oximino nitrile group followed by conversion into its corresponding α-hydroxy ester. The β-hydroxy-α-oximino nitrile products were further submitted to oxime- and nitrile-selective transformations. This chemo- and stereoselective reduction can be used to generate important chiral building blocks.

## Introduction

Microbial transformations by using fungi and bacteria have been known for thousands of years, ever since the fermentation of yeast was carried out to brew alcohol. In particular, *Saccharomyces cerevisiae*, also known as baker's yeast, has been widely applied to biocatalytic processes.[1] Such processes have been used to produce chiral compounds for employment as important building blocks in the chemical and pharmaceutical industries.[2] Although enantiomerically pure compounds can be extracted from available natural sources, biocatalytic syntheses of structurally divergent chiral building blocks have the advantage of scalability. Relative to conventional chemical syntheses, biocatalytic syntheses are less hazardous to the health of humans and the environment. Furthermore, biocatalysts such as enzymes or whole cell systems have been used to generate new chirality in a broad range of transformations, including reduction,[3] ligation,[4] and oxidation[5] reactions as well as many others.[6] Recently, the scope of biocatalysis has been expanded to the generation of chemically unfavorable synthetic structures.[7] Compared to purified enzymes, enzymes in whole cell biocatalytic systems are inherently more stable, as they are retained in their natural surroundings.[8] In addition, whole cell systems can regenerate various cofactors such as nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide phosphate (NADPH), which are required for enzymatic reduction.[9]

β-Hydroxy nitriles are versatile building blocks in many chemical syntheses and especially in the preparation of natural products and pharmaceutically important scaffolds.[10] Chiral β-hydroxy nitriles have been generated from asymmetric aldol-type reactions with acetonitrile, the β-boration of α,β-unsaturated nitriles followed by an oxidation reaction, borane reductions, and the hydrogenation of β-keto nitriles with an organometallic catalyst.[11] In addition, an asymmetric synthesis of β-hydroxy nitriles has been developed by using chemo-enzymatic transformations with isolated enzymes or microorganisms. For example, the enantioselective synthesis of a β-hydroxy nitrile was achieved by lipase-catalyzed dynamic kinetic resolution of the corresponding racemate with a maximum 50% conversion.[12] The asymmetric reductions of β-keto nitriles by using whole cell biocatalytic systems such as baker's yeast (*S. cerevisiae*) and *Curvularia lunata* have been hampered by low isolated yields and competing α-alkylation reactions.[13] The amount of ethylated byproduct could be reduced by lowering the reaction temperature or using methanol as a cosolvent.[14]

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Byproducts in the reduction of β-keto nitriles can also be avoided by using isolated carbonyl reductase from various strains of yeast combined with an NADPH cofactor and/or a D-glucose dehydrogenase (GDH) cofactor regeneration system.[10,15] In particular, each enantiomer can be selectively synthesized by selecting an appropriate baker's yeast reductase that offers high stereospecificity.

We designed β-keto-α-oximino nitriles as the substrate for a baker's yeast-mediated reduction (see Figure 1). This strategy largely eliminates the α-ethylated byproducts, and therefore the β-hydroxy nitriles can be practically used as chiral building blocks. It has been hypothesized that an optically pure β-hydroxy-α-oximino nitrile could be used as an intermediate in syntheses of chemically and pharmaceutically important building blocks through appropriate conversions of the α-oximino nitrile unit.[16]

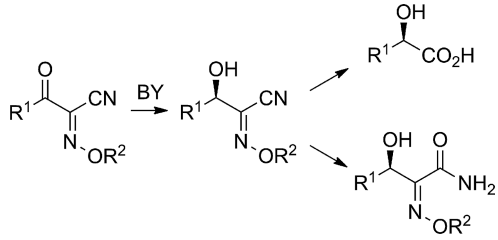
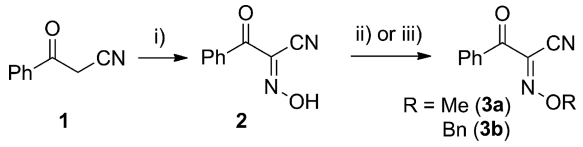



Figure 1. Baker's yeast (BY)-mediated reduction and subsequent conversion of β-keto-α-oximino nitrile.

## Results and Discussion

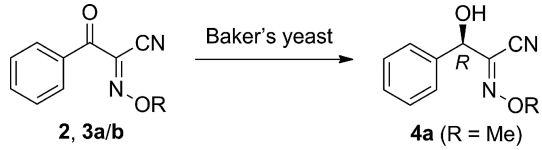
A series of β-keto-α-oximino nitriles **3** were prepared by the nitrosylation of β-keto nitrile **1** and subsequent *O*-alkylation of the resulting α-hydroxyimino-β-keto nitrile **2** in high yields (see Scheme 1).[17]




Scheme 1. The synthetic route for the preparation of compounds **3a** and **3b**. Reagents and conditions: (i) $NaNO_2/H_2O$, AcOH, 75%; (ii) $Me_2SO_4$, $K_2CO_3$, acetone, 91%; (iii) BnBr, $K_2CO_3$, acetone, 94%.

We evaluated the reactivity of α-hydroxyimino-β-keto nitrile **2** and 2-oximino-3-oxo-3-phenylpropionitriles **3a** and **3b** with different strains of baker's yeast under a variety of reaction conditions. Only commercially available baker's yeasts were used. Table 1 shows that oxime **2** and benzyloxime **3b** were not reduced to the alcohol under these conditions. β-Keto-α-methyloximino nitrile **3a** afforded alcohol **4a** in 66% yield after isolation by a keto-selective reduction using Sigma type II yeast at room temperature (23–28 °C) fr 36 h (see Table 1, Entry 2).

Table 1. The reduction of β-keto-α-oximino nitriles with baker's yeast.



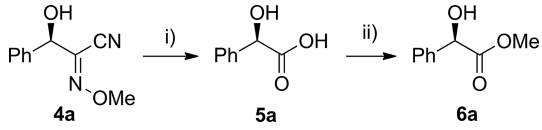

| Entry | | R | Yeast type | Temp. [°C] | Time [h] | % Yield **4a**[a] | % *ee*[b] |
|---|---|---|---|---|---|---|---|
| 1 | **2** | H | Sigma II | r.t. | – | NR | – |
| 2 | **3a** | $CH_3$ | Sigma II | r.t. | 36 | 66 | >99 |
| 3 | **3a** | $CH_3$ | Sigma II | 20 | 16 | 74 | >99 |
| 4 | **3a** | $CH_3$ | IMBY[c] | 20 | 24 | 61 | >99 |
| 5 | **3a** | $CH_3$ | Sigma I | r.t. | 31 | 51 | >99 |
| 6 | **3a** | $CH_3$ | Sigma I | 20 | 39 | 73 | >99 |
| 7 | **3a** | $CH_3$ | Oriental | 20 | 39 | 36 | >99 |
| 8 | **3b** | Bn | Sigma II | r.t. | – | NR | – |

[a] Reactions were performed on a 0.4 mmol scale with baker's yeast (2 g), saccharose (3 g), ethanol (1.5 mL), and tap water (60 mL). Isolated yields are provided (NR = no reaction). [b] Enantiomeric excess (*ee*) values were determined by GC analysis on a Supelco-DEX 225 chiral column (20 mm, 0.25 mm ID, 0.25 μM film) at 170 °C under isothermal conditions. Optical rotation: $[a]_D^{23} = +1.53$ ($c = 1.0$, $CHCl_3$). [c] Sigma type II yeast was immobilized on montmorillonite K10.[18] IMBY: immobilized baker's yeast.

The oxime unit was not reduced in these reactions, which indicates that baker's yeast chemoselectively reduces the ketone moiety of the β-keto-α-methyloximino nitrile.[19] The yield of β-hydroxy-α-methyloximino nitrile **4a** improved to 74% (see Table 1, Entry 3) by using Sigma type II baker's yeast at 20 °C. The immobilization of Sigma type II baker's yeast on montmorillonite K10[18] did not increase the yield of **4a** (see Table 1, Entry 4). Thus, the reaction was influenced primarily by the type of baker's yeast that was employed, with Sigma type II yeast providing the highest yields. The effect of the reaction temperature was also evaluated. The reduction of **3a** with baker's yeast was performed at room temperature and 20 °C, to yield product **4a** in isolated yields of 51 and 73% (see Table 1, Entries 5 and 6), respectively. Thus, decreasing the reaction temperature resulted in a significant improvement in isolated yield. Interestingly, the reduction of **3** with Oriental baker's yeast at 20 °C gave product **4a** in a low yield of 36% (see Table 1, Entry 7). Product **4a** was obtained with >99% enantiomeric purity, which was determined by the chiral GC–MS analysis of **4a** relative to the corresponding racemate obtained by the $NaBH_4$ reduction of **3a**. Compound **4a** was obtained as a single isomer according to the $^1H$ and $^{19}F$ NMR analysis of the corresponding Mosher ester. In the baker's yeast reduction, the enantiomeric purity of **4a** was not affected by the type of baker's yeast or the reaction temperature. The absolute stereochemistry of alcohol **4a** was determined by converting it into mandelic acid methyl ester **6a**, which was performed by the acidic hydrolysis of the oximino nitrile moiety to give acid **5a** followed by esterification to give the ester in 50% yield over the two steps (see Scheme 2). The absolute configuration of the chiral center of mandelic acid methyl ester **6a** {$[a]_D^{24} = -166$ ($c$ =

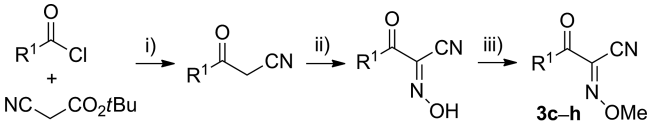
  

1.0, MeOH)} was confirmed as *R* by comparing experimental data with reported optical rotation data {$[\alpha]_D^{20}$ = –144 (*c* = 1.0, MeOH)}.[20]




Scheme 2. The synthesis of methyl mandelate **6a**. Reagents and conditions: (i) HCl (6 N), reflux, 2 h, 80% (for **5a**); (ii) Amberlyst-15, $CH_3OH$, room temp., 21 h, 63% (for **6a**); $[\alpha]_D^{24}$ = –166 (*c* = 1.0, MeOH); ref.[20] $[\alpha]_D^{20}$ = –144 (*c* = 1.0, MeOH).

The effects of different substitution patterns were also investigated with regard to this baker's yeast-mediated stereoselective reduction reaction. β-Keto-α-methyloximino nitriles that contained either a substituted aromatic (i.e., **3c**–**3g**) or a cyclohexyl (i.e., **3h**) group at the β-position were prepared from the appropriate β-keto nitriles by using the same method for the preparation of **3a** (see Scheme 3).

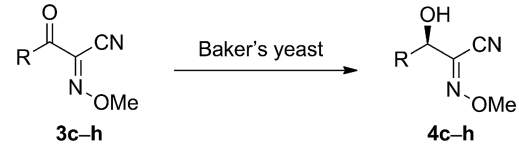



$R^1$ = 2-$ClC_6H_4$, 4-$ClC_6H_4$, 2,4-$Cl_2C_6H_3$, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, cyclohexyl

Scheme 3. The synthesis of β-keto-α-oximino nitriles **3c**–**3h**. Reagents and conditions: (i) NaH/toluene, *p*-toluenesulfonic acid (TsOH), room temp., overnight; (ii) $NaNO_2/H_2O$, AcOH, r.t., 30 min; (iii) $Me_2SO_4$, r.t.

The reduction of β-keto nitriles **3c**–**3g** was performed with three different types of baker's yeasts under the previously optimized conditions. As shown in Table 2, most of the substrates, with the exception of **3f**, were reduced to the alcohol products (i.e., **4c**–**4e**, **4g**, and **4h**) in high yields. β-Keto nitrile **3f**, which contained an electron-donating group at the *para* position of the aromatic group, gave relatively low yields of the product. In contrast, β-cyclohexyl-substituted keto nitrile **3h** was reduced to alcohol **4h** in 95% yield. As discussed above, the type of baker's yeast was important. The reduction of **3c** and **3h** by using Sigma type II baker's yeast resulted in high yields. For the reduction of compounds **3d**–**3g**, Sigma type I baker's yeast gave the highest yields. Interestingly, the Oriental-type baker's yeast gave low yields in general. All of the products **4c**–**4h** were obtained as a single isomer according to chiral GC–MS analysis and the $^1H$ and $^{19}F$ NMR spectra of the corresponding Mosher esters (see Supporting Information). The optical rotation data of products **4c**–**4g**, which have substituted aromatic rings, are reported in the Table 2. The absolute stereochemistry of aliphatic alcohol **4h** was also confirmed as the *R* configuration. This was determined by converting **4h** into

Table 2. Reduction of β-keto-α-oximino nitriles with baker's yeast.

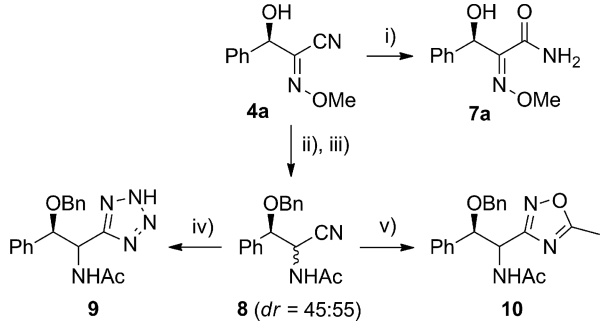



| | R | Yeast type | Time [d] | $[\alpha]_D^{23}$ | % Yield[a] | % *ee*[b] |
|---|---|---|---|---|---|---|
| **3c** | 2-$ClC_6H_4$ | Sigma I | 3 | – | 39 | – |
| **3c** | 2-$ClC_6H_4$ | Sigma II | 3 | –14.79 | 62 | >99 |
| **3c** | 2-$ClC_6H_4$ | Oriental | 3 | – | 43 | – |
| **3d** | 4-$ClC_6H_4$ | Sigma I | 6 | +18.62 | 71 | >99 |
| **3d** | 4-$ClC_6H_4$ | Sigma II | 4 | – | 37 | – |
| **3d** | 4-$ClC_6H_4$ | Oriental | 5 | – | 35 | – |
| **3e** | 2,4-$Cl_2C_6H_3$ | Sigma I | 3 | – | 58 | – |
| **3e** | 2,4-$Cl_2C_6H_3$ | Sigma II | 5 | +2.45 | 54 | >99 |
| **3e** | 2,4-$Cl_2C_6H_3$ | Oriental | 4.5 | – | 40 | – |
| **3f** | 4-$MeOC_6H_4$ | Sigma I | 5.5 | –2.38 | 22 | >99 |
| **3f** | 4-$MeOC_6H_4$ | Sigma II | 5.5 | – | 6 | – |
| **3f** | 4-$MeOC_6H_4$ | Oriental | 4 | – | 13 | – |
| **3g** | 3-$MeOC_6H_4$ | Sigma I | 3 | +18.89 | 84 | >99 |
| **3g** | 3-$MeOC_6H_4$ | Sigma II | 3 | – | 66 | – |
| **3g** | 3-$MeOC_6H_4$ | Oriental | 4 | – | 50 | – |
| **3h** | cyclohexyl | Sigma I | 2 | – | 76 | – |
| **3h** | cyclohexyl | Sigma II | 2 | –4.97 | 95 | >99 |
| **3h** | cyclohexyl | Oriental | 3 | – | 24 | – |

[a] Reactions were carried out on a 0.4 mmol scale with baker's yeast (2 g), saccharose (3 g), ethanol (1.5 mL), and tap water (60 mL) at 20 °C. Isolated yields are provided. [b] The *ee* values were determined by chiral GC–MS analysis and the $^1H$ and $^{19}F$ NMR spectra of the corresponding Mosher esters.

α-hydroxy ester **6h** {$[\alpha]_D^{24}$ = –0.26 (*c* = 1.0, $CHCl_3$)} and then comparing the experimental optical rotation data with that reported for its enantiomer.[21]

In addition to the conversion of optically active β-hydroxy-α-methyloximino nitriles into β-hydroxy acetic acid derivatives, nitrile- and oxime-selective conversions of methyloximino nitrile product **4a** were performed as shown in the Scheme 4. Product **4a** was converted into carboxamide **7a** in a 91% yield by using a nitrile-selective hydrolysis. After *O*-benzyl protection, the oxime of **4a** was selectively re-




Scheme 4. The chemoselective transformation of **4a**. Reagents and conditions: (i) 30% NaOH, reflux, 7 d, 91%; (ii) BnBr, $Ag_2O$, $CH_2Cl_2$, room temp., 48 h, 96%; (iii) Zn, AcOH/$Ac_2O$, r.t., 27 h, 70%; (iv) $NaN_3$, $ZnBr_2$, $H_2O$/*i*PrOH, reflux, 48 h, 92%; (v) $NH_2OH{\cdot}HCl$, $K_2CO_3$, EtOH, reflux, 8 h; NaH, EtOAc, tetrahydrofuran (THF), reflux, 1 h, 50%.

duced to an amine by a zinc-mediated reduction. A subsequent acetylation reaction gave cyanoacetamide **8**, albeit with low diastereoselectivity. The nitrile group of **8** was further converted into tetrazole **9** and oxadiazole **10** heterocycles.

## Conclusions

In summary, the baker's yeast mediated asymmetric reduction of β-keto-α-methoxyimino nitriles was successfully achieved in high yields and with high enantioselectivities. Sigma type II baker's yeast afforded the products in the highest yields. The β-keto-α-methyloximino nitriles that contained a substituted aromatic (i.e., **3c**–**3g**) or cyclohexyl (i.e., **3h**) group at the β-position were reduced in this baker's yeast mediated reaction to give the corresponding β-hydroxy-α-oximino nitrile. The products were exclusively obtained as single stereoisomers, the configurations of which were confirmed as *R* by their conversion into the corresponding β-hydroxy carboxylic acid derivatives. As shown in Scheme 4, methyloximino nitrile **4a** can be further transformed by using an oxime-selective reduction and a nitrile-selective conversion. Additional procedures to convert the functionality of compounds **4** are needed to develop useful chiral building blocks. This new baker's yeast mediated reduction of β-keto-α-oximino nitriles that is described herein is an effective chemo- and stereoselective reaction. In addition, the method makes use of a whole cell system, which is an environmentally benign means to prepare β-hydroxy-α-oximino nitriles with high stereoselectivity.

## Experimental Section

**2-Hydroxyimino-3-oxo-3-phenylpropionitrile (2):** To a solution of benzoylacetonitrile (5.0 g, 34.4 mmol) in acetic acid (10 mL) was added dropwise a solution of sodium nitrite (2.49 g, 36.1 mmol) in water (5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 30 min. Upon completion, the reaction mixture was poured into brine (50 mL), and the resulting solution was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine and dried with $Na_2SO_4$. The solvent was removed under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (hexane/EtOAc, 4:1) to afford compound **2** (3.60 g, 60%). MS (70 eV): *m*/*z* (%) = 174 $[M]^+$, 131, 105 (100), 77, 51. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.28–8.00 (m, 5 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 185.39, 134.77, 134.46, 133.47, 130.89, 128.83, 108.68 ppm. IR (KBr): $\tilde{\nu}$ = 3300 (OH), 2362 (O=C–C=N), 1646 (C=O) $cm^{-1}$.

**2-Methoxyimino-3-oxo-3-phenylpropionitrile (3a):** To a stirred solution of **2** (1.0 g, 5.7 mmol) and dimethyl sulfate (0.82 mL, 1.5 equiv.) in acetone (10 mL) was added $K_2CO_3$ (1.19 g, 1.5 equiv.) portionwise at 0 °C. The reaction mixture was stirred at room temperature for 5 h. The reaction mixture was then filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 7:1) to give compound **3a** (0.98 g, 91%). MS (70 eV): *m*/*z* (%) = 188 $[M]^+$, 129, 105 (100), 77, 51. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.01–7.47 (m, 5 H), 4.33 (s, 3 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 184.04, 134.67, 134.53, 132.23, 130.90, 128.99, 108.37, 66.50 ppm. IR (KBr): $\tilde{\nu}$ = 2362 (O=C–C=N), 1648 (C=O) $cm^{-1}$.

**3-(2-Chlorophenyl)-2-methoxyimino-3-oxopropionitrile (3c):** MS (70 eV): *m*/*z* (%) = 222 $[M]^+$, 187, 139 (100), 111, 75, 51. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.47–7.37 (m, 4 H), 4.24 (s, 3 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 185.62, 135.17, 132.65, 131.87, 130.98, 130.16, 129.86, 126.72, 107.29, 66.33 ppm. IR (KBr): $\tilde{\nu}$ = 2364 (O=C–C=N), 1700 (C=O) $cm^{-1}$.

**3-(4-Chlorophenyl)-2-methoxyimino-3-oxopropionitrile (3d):** MS (70 eV): *m*/*z* (%) = 222 $[M]^+$, 139 (100), 111, 85, 75, 51. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.98–7.46 (m, 4 H), 4.34 (s, 3 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 182.33, 140.94, 132.38, 131.83, 129.78, 128.93, 107.66, 66.13 ppm. IR (KBr): $\tilde{\nu}$ = 2364 (O=C–C=N), 1700 (C=O) $cm^{-1}$.

**3-(2,4-Dichlorophenyl)-2-methoxyimino-3-oxopropionitrile (3e):** MS (70 eV): *m*/*z* (%) = 256 $[M]^+$, 221, 173 (100), 145, 109, 74. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.48–7.36 (m, 3 H), 4.25 (s, 3 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 184.64, 138.46, 133.61, 133.07, 132.45, 130.90, 130.26, 127.24, 107.14, 64.04 ppm. IR (KBr): $\tilde{\nu}$ = 2365 (O=C–C=N), 1702 (C=O) $cm^{-1}$.

**2-Methoxyimino-3-(4-methoxyphenyl)-3-oxopropionitrile (3f):** MS (70 eV): *m*/*z* (%) = 218 $[M]^+$, 187, 159, 135 (100), 107, 92, 77, 64. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.07–6.94 (m, 4 H), 4.33 (s, 3 H), 3.90 (s, 3 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 133.29, 132.29, 132.48, 131.78, 114.98, 114.20, 113.83, 66.02, 55.85 ppm. IR (KBr): $\tilde{\nu}$ = 2360 (O=C–C=N), 1693 (C=O) $cm^{-1}$.

**2-Methoxyimino-3-(3-methoxyphenyl)-3-oxopropionitrile (3g):** MS (70 eV): *m*/*z* (%) = 218 $[M]^+$, 135 (100), 107, 92, 77, 64. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.61–7.17 (m, 4 H), 4.33 (s, 3), 3.86 (s, 3 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 183.26, 159.58, 135.24, 131.79, 129.50, 123.23, 120.70, 114.58, 107.89, 65.97, 55.48 ppm. IR (KBr): $\tilde{\nu}$ = 2359 (O=C–C=N), 1692 (C=O) $cm^{-1}$.

**3-Cyclohexyl-2-methoxyimino-3-oxopropionitrile (3h):** The procedure for the preparation of **3a** was followed by starting from the corresponding oxime, which was obtained by nitrosylation of 3-cyclohexyl-3-oxopropanenitrile, to afford **3h** (69%). MS (70 eV): *m*/*z* (%) = 194 $[M]^+$, 179, 163, 136, 111, 83 (100), 67, 55. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 4.31 (s, 3 H), 1.83–1.20 (m, 10 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 195.71, 131.59, 107.94, 66.37, 45.66, 28.93, 25.99, 25.76 ppm. IR ($CCl_4$): $\tilde{\nu}$ = 2362 (O=C–C=N), 1696 (C=O) $cm^{-1}$.

**Synthesis of 3-Hydroxy-2-methoxyimino-3-phenylpropionitrile (4a):** 2-Methoxyimino-3-oxo-3-phenylpropionitrile (**3a**, 0.4 mmol) was dissolved in ethanol (1.5 mL), and the solution was added to a suspension of baker's yeast (2 g) and saccharose (3 g) in tap water (60 mL) with shaking at 20 °C. The reaction mixture was shaken for the specified time (see Table 1) and then saturated with sodium chloride. The resulting mixture was filtered through Celite, which was rinsed with chloroform. The filtrate was then extracted with chloroform (3×), and the combined organic layers were dried with $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 7:1) to give compound **4a** (55.9 mg, 74%) as an oil. MS (70 eV): *m*/*z* (%) = 190 $[M]^+$, 161, 170 (100), 79, 51. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.46–7.39 (m, 5 H), 5.53 (s, 1 H), 4.10 (s, 3 H), 2.78 (s, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 137.36, 134.28, 129.20, 129.04, 126.27, 108.52, 72.65, 64.08 ppm. HRMS (FAB): calcd. for $C_{10}H_{10}N_2O_2Na^+$ [M + Na]$^+$ 213.0640; found 213.0645. IR ($CCl_4$): $\tilde{\nu}$ = 3742 (OH) $cm^{-1}$.

**3-(2-Chlorophenyl)-3-hydroxy-2-methoxyiminopropionitrile (4c):** MS (70 eV): *m*/*z* (%) = 224 $[M]^+$, 189 (100), 162, 141, 113, 105, 77, 51. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.73–7.28 (m, 4 H), 5.95 (s, 1 H), 4.11 (s, 3 H), 2.96 (s, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 135.15, 133.17, 132.95, 130.69, 130.21, 128.54, 127.94, 108.93, 69.62, 64.66 ppm. HRMS (FAB): calcd. for $C_{10}H_9ClN_2O_2Na^+$ $[M + Na]^+$ 247.0250; found 247.0251. IR ($CCl_4$): $\tilde{\nu}$ = 3744 (OH) $cm^{-1}$.

**3-(4-Chlorophenyl)-3-hydroxy-2-methoxyiminopropionitrile (4d):** MS (70 eV): *m*/*z* (%) = 224 $[M]^+$, 195, 141 (100), 113, 77, 51. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.40 (s, 4 H), 5.53 (s, 1 H), 4.11 (s, 3 H), 2.88 (s, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 136.18, 135.53, 134.34, 129.63, 128.08, 108.78, 72.03, 64.62 ppm. HRMS (FAB): calcd. for $C_{10}H_9ClN_2O_2Na^+$ $[M + Na]^+$ 247.0250; found 247.0250. IR ($CCl_4$): $\tilde{\nu}$ = 3743 (OH) $cm^{-1}$.

**3-(2,4-Dichlorophenyl)-3-hydroxy-2-methoxyiminopropionitrile (4e):** MS (70 eV): *m*/*z* (%) = 258 $[M]^+$, 231, 223, 196, 175 (100), 147, 111, 75. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.66–7.35 (m, 3 H), 5.89 (s, 1 H), 4.09 (s, 3 H), 2.94 (s, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 135.59, 133.33, 133.11, 132.35, 129.56, 129.07, 127.87, 108.40, 68.77, 64.33 ppm. HRMS (FAB): calcd. for $C_{10}H_8Cl_2N_2O_2Na^+$ $[M + Na]^+$ 280.9855; found 280.9857. IR ($CCl_4$): $\tilde{\nu}$ = 3746 (OH) $cm^{-1}$.

**3-Hydroxy-2-methoxyimino-3-(4-methoxyphenyl)propionitrile (4f):** MS (70 eV): *m*/*z* (%) = 220 $[M]^+$, 191, 137 (100), 109, 94, 77, 66, 51. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.40–6.92 (m, 4 H), 5.48 (s, 1 H), 4.09 (s, 3 H), 3.82 (s, 3 H), 2.69 (s, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 160.68, 134.85, 129.91, 128.13, 114.87, 109.05, 72.78, 64.44, 55.76 ppm. HRMS (FAB): calcd. for $C_{11}H_{12}N_2O_3Na^+$ $[M + Na]^+$ 243.0740; found 243.0745. IR ($CCl_4$): $\tilde{\nu}$ = 3738 $cm^{-1}$.

**3-Hydroxy-2-methoxyimino-3-(3-methoxyphenyl)propionitrile (4g):** MS (70 eV): *m*/*z* (%) = 220 $[M]^+$, 191, 162, 135, 109 (100), 94, 77, 66, 51. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.36–6.90 (m, 4 H), 5.49 (s, 1 H), 4.10 (s, 3 H), 3.83 (s, 3 H), 2.07 (s, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 160.44, 139.39, 134.66, 130.53, 118.90, 115.90, 112.09, 108.97, 72.85, 64.49, 55.76 ppm. HRMS (FAB): calcd. for $C_{11}H_{12}N_2O_3Na^+$ $[M + Na]^+$ 243.0740; found 243.0741. IR ($CCl_4$): $\tilde{\nu}$ = 3738 $cm^{-1}$.

**3-Cyclohexyl-3-hydroxy-2-methoxyiminopropionitrile (4h):** MS (70 eV): *m*/*z* (%) = 195 $[M]^+$, 165, 114, 83 (100), 67, 55. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 4.11 (d, *J* = 9 Hz, 1 H), 4.06 (s, 3 H), 2.84 (s, 1 H), 1.93–1.02 (m, 11 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 134.89, 109.40, 75.20, 64.27, 41.76 28.50, 26.46, 26.01 ppm. HRMS (FAB): calcd. for $C_{10}H_{16}N_2O_2$ $[M]^+$ 196.1212; found 197.1290. IR ($CCl_4$): $\tilde{\nu}$ = 3742 (OH) $cm^{-1}$.

**Methyl (*R*)-Mandelate (6a):** A solution of compound **4a** (50 mg, 0.26 mmol) in HCl (6 N solution, 3 mL) was heated at reflux and stirred for 2 h. The reaction mixture was then cooled and extracted with diethyl ether (3× 10 mL). The combined organic fractions were concentrated in vacuo, and the resulting residue was dissolved in a 10% sodium hydrogen carbonate solution. This aqueous solution was washed with diethyl ether (10 mL) and then acidified to pH = 2 by the addition of HCl (1 N solution). This aqueous solution was then extracted with diethyl ether (3× 10 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure to yield mandelic acid **5a** (32 mg, 80%). Amberlyst-15 resin (50 mg) was added to a solution of **5a** in methanol (3 mL). The reaction mixture was stirred at room temperature for 21 h and then filtered through Celite. The filtrate was concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (*n*-hexane/EtOAc, 4:1) to give compound **6a** (22 mg, 63%). MS (70 eV): *m*/*z* (%) = 166 $[M]^+$, 107, 79 (100), 51. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.45–7.34 (m, 4 H), 5.19 (d, *J* = 6 Hz, 1 H), 3.77 (s, 3 H), 3.51 (d, *J* = 6 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 174.50, 138.70, 129.00, 128.90, 127.00, 73.30, 53.40 ppm. HRMS (FAB): calcd. for $C_9H_{10}O_3Na^+$ $[M + Na]^+$ 189.0522; found 189.0524. IR ($CCl_4$): $\tilde{\nu}$ = 3440 (OH), 1740 $cm^{-1}$.

**Methyl (*R*)-2-Cyclohexyl-2-hydroxyacetate (6h):** The title compound was obtained from **4h** by following the procedure for the preparation of **6a**. In this case, flash chromatography on silica gel (hexane/EtOAc, 8:1) afforded **6h** (48%). $[\alpha]_D^{24}$ = –0.26 (*c* = 1.0, $CHCl_3$); for enantiomer, ref.[21] $[\alpha]_D^{20}$ = +0.33 ($CHCl_3$). MS (70 eV): *m*/*z* (%) = 172 $[M]^+$, 113, 83, 67, 55 (100). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 4.03 (d, *J* = 6.3 Hz, 1 H), 3.79 (s, 3 H), 2.63 (d, *J* = 6.0 Hz, 1 H), 1.76–1.10 (m, 11 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 185.70, 76.40, 52.64, 42.56, 28.30, 26.64, 26.30 ppm. HRMS (FAB): calcd. for $C_9H_{16}O_3Na^+$ $[M + Na]^+$ 195.0992; found 195.0995.

**3-Hydroxy-2-(methoxyimino)-3-phenylpropanamide (7a):** A suspension of compound **4a** (49 mg, 0.26 mmol) in 30% NaOH (5 mL) was heated at reflux and stirred for 7 d. The mixture was extracted with ethyl acetate (10 mL), and the organic layer was dried with $MgSO_4$ and concentrated. The residue was purified by chromatography on a silica gel column (*n*-hexane/EtOAc, 2:1) to give compound **7a** (49 mg, 91%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.42–7.23 (m, 5 H), 6.69 (s, 1 H), 6.08 (d, *J* = 11.1 Hz, 1 H), 5.74 (s, 1 H), 5.45 (d, *J* = 11.1 Hz, 1 H), 4.03 (s, 3 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 165.70, 150.62, 140.32, 128.49, 127.71, 125.73, 68.45, 63.63 ppm. Data for *O*-TBS protected **7a** (TBS = *tert*-butyldimethylsilyl): $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.41–7.23 (m, 5 H), 6.88 (s, 1 H), 6.40 (s, 1 H), 5.39 (s, 1 H), 4.08 (s, 3 H), 0.95 (s, 9 H), 0.12 (s, 6 H) ppm.

***O*-Benzyl Protection of 4a:** To a solution of 3-hydroxy-2-methoxyimino-3-phenylpropionitrile (120 mg, 0.63 mmol) and silver oxide (219 mg, 1.5 equiv.) in dichloromethane (6.3 mL), was added benzyl bromide (0.2 mL, 162 mg, 1.5 equiv.) at room temperature. The reaction mixture was stirred at room temperature for 48 h. Upon completion, the reaction mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography on a silica gel column (*n*-hexane/EtOAc, 10:1) to afford *O*-benzyl protected **4a** (170 mg, 96%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.45–7.26 (m, 10 H), 5.19 (s, 1 H), 4.65, 4.61 (ABq, *J* = 11.7 Hz, 2 H), 4.09 (s, 3 H) ppm.

***N*-[2-(Benzyloxy)-1-cyano-2-phenylethyl]acetamide (8):** To a solution of 3-benzyloxy-2-methoxyimino-3-phenylpropionitrile (100 mg, 0.36 mmol) in a mixture of acetic acid/acetic anhydride (1:1, 3.6 mL) was added a solution of activated zinc dust (466.3 mg, 20.0 equiv.) in AcOH/$Ac_2O$ (1:1, 1.4 mL) at room temperature. The reaction mixture was stirred at 40 °C for 27 h. The zinc dust was removed by filtration and washed with dichloromethane. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (*n*-hexane/EtOAc, 3:1) to afford diastereomeric upper (36.1 mg) and lower (36.9 mg) spots of compound **8** (total 70% yield). Data for upper spot of **8**: MS (70 eV): *m*/*z* (%) = 294 $[M]^+$, 197, 105, 91 (100), 77, 65, 51. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.46–7.26 (m, 10 H), 5.91 (d, *J* = 8.7 Hz, 1 H), 5.18 (dd, *J* = 8.7, 3.9 Hz, 1 H), 4.71 (d, *J* = 3.9 Hz, 1 H), 4.64 (d, *J* = 11.4 Hz, 1 H), 4.43 (d, *J* = 11.4 Hz, 1 H), 1.88 (s, 3 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 169.30, 136.60, 135.14, 129.30, 128.89, 128.55, 128.23, 128.09, 127.07, 117.04, 78.70, 71.39, 45.78, 22.54 ppm. HRMS (FAB): calcd. for $C_{18}H_{19}N_2O_2$ $[M + H^+]$ 295.1447; found 295.1446. IR ($CCl_4$): $\tilde{\nu}$ =

3215 (NH), 1518, 1658 (C=O) $cm^{-1}$. Data for lower spot of **8**: $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.66–7.32 (m, 10 H), 6.19 (d, $J$ = 9.0 Hz, 1 H), 5.07 (dd, $J$ = 9.3, 3.9 Hz, 1 H), 4.72 (d, $J$ = 12.0 Hz, 1 H), 4.54 (d, $J$ = 3.9 Hz, 1 H), 4.29 (d, $J$ = 12.0 Hz, 1 H), 1.93 (s, 3 H) ppm.

***N*-[2-(Benzyloxy)-2-phenyl-1-(2*H*-tetrazol-5-yl)ethyl]acetamide (9):** To a solution of the upper isomer of **8** (36 mg, 0.12 mmol) in water/2-propanol (2:1, 3 mL) were added sodium azide (15.9 mg, 2.0 equiv.) and zinc bromide ($ZnBr_2$, 3.8 mg, 0.5 equiv.) at room temperature. The reaction mixture was heated at reflux and stirred for 48 h. Upon completion, HCl (1 N solution) and ethyl acetate were added, and the resulting mixture was stirred until the solid was entirely dissolved. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2×). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column ($CH_2Cl_2$/MeOH, 30:1–1:1) to give tetrazole **9** (38 mg, 92%). MS (70 eV): *m/z* (%) = 338 $[M]^+$, 197, 99, 91 (100), 77, 65, 51. $^1H$ NMR (300 MHz, $CD_3OD$): $\delta$ = 7.38–6.96 (m, 10 H), 5.54 (d, $J$ = 9.0 Hz, 1 H), 4.72 (d, $J$ = 9.0 Hz, 1 H), 4.43 (d, $J$ = 12.0 Hz, 1 H), 4.18 (d, $J$ = 11.4 Hz, 1 H), 1.71 (s, 3 H) ppm. $^{13}C$ NMR (75 MHz, $CD_3OD$): $\delta$ = 172.53, 157.07, 138.62, 129.91, 129.63, 129.34, 128.99, 128.85, 128.55, 128.23, 82.04, 71.73, 50.76, 22.08 ppm. HRMS (FAB): calcd. for $C_{18}H_{20}N_5O_2$ $[M + H]^+$ 338.1617; found 338.1616. IR (KBr): $\tilde{\nu}$ = 3220 (NH), 1516, 1648 (C=O) $cm^{-1}$.

***N*-[2-(Benzyloxy)-1-(5-methyl-1,2,4-oxadiazol-3-yl)-2-phenylethyl]-acetamide (10):** A suspension of nitrile **8** (90 mg, 0.31 mmol), hydroxylamine hydrochloride (64 mg, 3.0 equiv.), and potassium carbonate (253 mg, 6.0 equiv.) in absolute ethanol (5 mL) was heated at reflux for 8 h. The reaction mixture was cooled to room temperature and filtered, and the filtrate was concentrated under reduced pressure. The resulting amide oxime was dissolved in anhydrous tetrahydrofuran (5 mL) that contained powdered molecular sieves (4 Å, 120 mg), and the mixture was stirred for 30 min. Sodium hydride (60% dispersion in oil, 18.5 mg prewashed with hexane, 1.5 equiv.) was added, and the mixture was heated at 60 °C for 30 min and then was cooled to room temperature. Ethyl acetate (60 mL, 2.0 equiv.) was added, and the reaction mixture was heated at reflux for 1 h and then cooled to room temperature. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give a residue, which was purified by flash chromatography on a silica gel column (*n*-hexane/EtOAc, 4:1) to afford compound **10** (54 mg, 50%). MS (70 eV): *m/z* (%) = 352 $[M]^+$, 197, 112, 91 (100), 77, 65, 51. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.39–7.09 (m, 10 H), 6.41 (d, $J$ = 9.0 Hz, 1 H), 5.40 (dd, $J$ = 9.3, 2.7 Hz, 1 H), 4.97 (d, $J$ = 2.7 Hz, 1 H), 4.59 (d, $J$ = 11.4 Hz, 1 H), 4.22 (d, $J$ = 12.0 Hz, 1 H), 2.52 (s, 3 H), 1.95 (s, 3 H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 176.57, 169.77, 169.30, 137.27, 128.57, 128.41, 128.24, 127.90, 127.83, 126.72, 79.82, 71.11, 52.29, 29.65, 22.92, 12.31 ppm. HRMS (FAB): calcd. for $C_{20}H_{22}N_3O_3$ $[M + H]^+$ 352.1661; found 352.1656. IR ($CCl_4$): $\tilde{\nu}$ = 3227 (NH), 1514, 1650 (C=O) $cm^{-1}$.

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