Enantioselective Synthesis of Both Enantiomers of Various Propargylic Alcohols by Use of Two Oxidoreductases

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The oxidoreductases *Lactobacillus brevis* alcohol dehydrogenase (LBADH) and *Candida parapsilosis* carbonyl reductase (CPCR) are suitable catalysts for the reduction of ketones to afford enantiopure *sec.* alcohols. A broad variety of alkynones (**1**, **3**, and **5**) are accepted as substrates and the corresponding propargylic alcohols (**2**, **4**, and **6**) are obtained in good yield and excellent enantiomeric excess. By changing the steric demand of the substituents the *ee* values can be adjusted and even the configurations of the products can be altered.

Introduction

Chiral, non-racemic propargylic alcohols are important intermediates in the synthesis of a variety of natural products including alkaloids, pheromones, prostaglandins, steroids, antibiotics, vitamins, and sesquiterpenes.[1] Asymmetric reduction of α,β-acetylenic ketones is a straightforward approach to this class of compounds.

A number of chemical reducing reagents that provide chiral propargylic alcohols in good yields have been developed.[2] Nevertheless, none of these reagents affords all propargylic alcohols with high optical purity and most of them are limited either to hindered or to unhindered alkynones. Furthermore, with the use of hydrolytic enzymes such as lipases, only a few of these alcohols could be obtained in enantiomeric excesses of greater than 99%[3] and, to our surprise, only a small number of α,β-acetylenic ketones were reduced by isolated oxidoreductases at all.[4] Very recently, chloroperoxidase-catalysed propargylic hydroxylation has been reported, affording propargylic alcohols with *ee* values of 83−95%.[5]

However, as alcohol dehydrogenases can react both stereoselectively and chemoselectively under very mild conditions, they should provide good access to enantiopure propargylic alcohols. We therefore performed an enzyme screening in order to identify suitable biocatalysts. Since other commercially available alcohol dehydrogenases showed only moderate activities in reducing differentially substituted alkynones, we also tested two oxidoreductases isolated at the Institute of Enzyme Technology of the Heinrich Heine University, Düsseldorf. For the first time, a detailed alkynone screening was performed to detect compounds susceptible to enzymatic reduction. In this paper we report our results using NADP-dependent *Lactobacillus brevis* alcohol dehydrogenase (LBADH), which is easily available in the form of a crude cell extract (recLBADH) from a recombinant *E. coli* strain, and NAD-dependent *Candida parapsilosis* carbonyl reductase (CPCR).[6,7] Both enzymes catalyse the reduction of various acetylenic carbonyls with high enantioselectivities and efficiencies. Since these two biocatalysts possess complementary stereoselectivities, they enable both enantiomers of the desired products to be synthesised.

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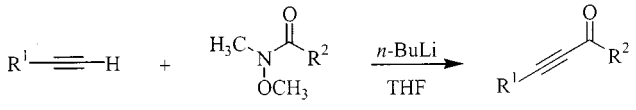
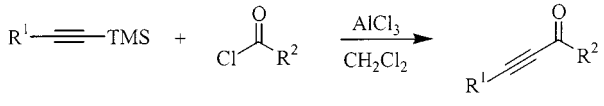
Results and Discussion

Two different strategies were used for the synthesis of the substrates, depending on the availabilities of the starting material. Reagents with a terminal acetylene group were deprotonated with *n*BuLi and the keto functionality was introduced by coupling with *Weinreb* amides (Scheme 1, Method A).[8] Alternatively, syntheses starting from (trimethylsilyl)acetylene derivatives introduced the carbonyl moiety by treatment with acid chloride in the presence of aluminium chloride (Scheme 1, Method B).[9]

Method A



Method B



Scheme 1. Syntheses of alkynones

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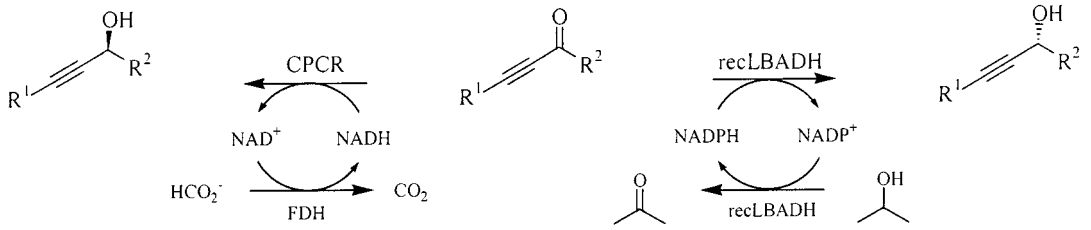


Scheme 2. Enzymatic reductions with cofactor-regeneration

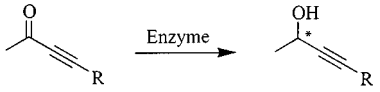
The enzyme activities on these substrates were determined in a UV assay, relative to ethyl 5-oxohexanoate as standard. In order to enable the absolute configurations of the propargylic alcohols to be determined, all reactions were scaled up by reducing 10 μmol to 1 mmol of each ketone in a batch (not optimised conditions). Cofactors were applied in catalytic amounts and regenerated using 2-propanol as co-substrate for NADP(H) and formate dehydrogenase (FDH)/formate system for NAD(H) (Scheme 2).[10] Determination of enantiomeric excesses was accomplished by HPLC or GC on chiral stationary phases. Racemic alcohols were prepared by reduction of the corresponding ketones using $NaBH_4$. Absolute configurations were determined either by comparison of the retention times with those of commercially available enantiomerically pure alcohols or by comparison of the optical rotation values with literature data.

We started our studies with methyl-alkynones **1a−i**, each bearing an aromatic unit attached to the triple bond. Most published methods fail to reduce these carbonyls to the corresponding propargylic alcohols with an enantiomeric excess higher than 99%.[2] With 4-phenyl-3-butyn-2-one (**1a**) as substrate, both recLBADH and CPCR afforded high yields of the enantiopure alcohols (*R*)- and (*S*)-**2a**, respectively (Table 1). Even though electron-rich (compound **1b**) and electron-poor aromatic units with diverse steric hindrance characteristics (compounds **1c−e**) were all tested, no decreases in enzyme activity or enantioselectivity were found. Moreover, the bulky bromo substituent could be present in any of the *ortho*-, *meta*-, or *para*-positions (compounds **1e−g**), resulting in enantiopure alcohols (**2e−g**). Additionally, heteroaromatic compounds **1h−i** were reduced to give the enantiopure alcohols **2h−i**.

In summary, recLBADH and CPCR are excellent catalysts for the reduction of a broad variety of aryl-alkynones, giving access to both enantiomers of the corresponding alcohols in high optical purities.

To demonstrate the applicability of enzymatic reduction of alkynones on preparative scale, we optimised the reaction parameters for the recLBADH-catalysed reduction of **1a**. 4-Phenyl-3-butyn-2-one (**1a**) (2.08 g, 14.4 mmol) in 2-propanol (50 mL) was added steadily by syringe pump over 20 h to a stirred solution of $NADP^+$ (6.0 mg, 0.05 mol %, total turnover number 2000), 2-propanol (50 mL), and recLBADH (250 U) in deionized water (250 mL, 1 mM $MgCl_2$, pH 6.6, HCl) at 22 °C. After this had been stirred for an additional 10 h, the conversion was determined by GCMS and NMR as > 99%. Conventional workup by extraction afforded 1.98 g (94% yield) of (*R*)-**2a** (> 99% *ee*), free of by-products.

Table 1. Screening results of aromatic alkynones (assay conditions were: 2 mM substrate, 0.25 mM NAD(P)H, 1 mM $MgCl_2$, 100 mM TEA/NaOH buffer, pH = 6.5)



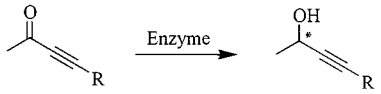
1 2

alcohol	R	recLBADH[a][b] % activity (% conv.)	% *ee*	CPCR[a][b] % activity (% conv.)	% *ee*
2a	C_6H_5	142 (>99)	> 99	41 (80)	> 99
2b	4-MeO-C_6H_4	108 (70)	> 99	89 (30)	> 99
2c	4-F-C_6H_4	138 (100)	> 99	128 (60)	> 99
2d	4-Cl-C_6H_4	114 (85)	> 99	71 (100)	> 99
2e	4-Br-C_6H_4	107 (85)	> 99	51 (20)	> 99
2f	3-Br-C_6H_4	117 (75)	> 99	150 (55)	> 99
2g	2-Br-C_6H_4	132 (70)	> 99	110 (20)	> 99
2h	2-pyridinyl	85 (100)	> 99	94 (40)	> 99
2i	(3-methyl)-2-thienyl	nd[c] (100)	> 99	nd[c] (60)	> 99

[a] Enzyme activity was determined by the decrease in the NAD(P)H extinction at 340 nm relative to 5-oxohexanoic acid ethyl ester. − [b] All alcohols produced by I) recLBADH have the (*R*) configuration, II) CPCR have the (*S*) configuration. Absolute configuration of **2a** + (*R*)-**2b** was determined by comparison of the optical rotations with literature data, **2c−i** by comparison with **2a** + (*R*)-**2b** and with regard to mechanistic aspects of recLBADH/CPCR catalysis.[6,7] − [c] Not determined because of strong UV absorption of the ketone at 340 nm.

Next we focused on the synthesis of (*R*)- and (*S*)-3-butyn-2-ol (**4a**), which are important intermediates in, for example, the synthesis of 5-lipoxygenase inhibitors.[11] The methyl and ethynyl residue of 3-butyn-2-one (**3a**) have similar steric demands,[12] making it difficult for reducing reagents to distinguish between the two enantiotopic faces of the substrate. Thus all methods to date for the reduction of **3a** have failed to afford the enantiopure alcohol **4a**. The best results so far with regard to the enantioselective reduction of **3a** have been obtained with TBADH [*ee* = 86%; (*S*)].[13] Several multistep procedures have been developed to overcome this problem.[11,14] As expected, enzymatic reduction of **3a** with recLBADH and CPCR only produced unsatisfactory results, of 60% and 49% *ee*, respectively

Table 2. Screening results of silyl-alkynones (assay conditions were: 5 mM substrate, 0.25 mM NAD(P)H, 1 mM $MgCl_2$, 100 mM TEA/NaOH buffer, pH = 6,5)

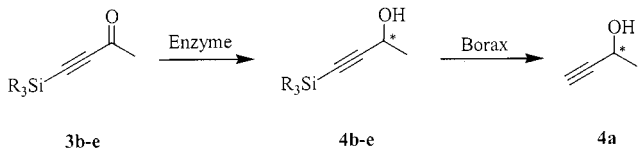


3 4

alcohol	R =	recLBADH[a][b] % activity (% conv.)	% *ee*	CPCR[a][b] % activity (% conv.)	% *ee*
4a	H	66 (100)	60	52 (100)	49
4b	$SiMe_3$	46 (100)	> 99	48 (100)	57
4c	$SiEt_3$	27 (90)	> 99	33 (65)	91.5
4d	$SiMe_2tBu$	34 (40)	> 99	41 (40)	98.5
4e	$SiMe_2Ph$	38 (60)	> 99	44 (80)	> 99

[a] Enzyme activity was determined by the decrease in the NAD(P)H extinction at 340 nm relative to 5-oxohexanoic acid ethyl ester. – [b] All alcohols produced by I) recLBADH have the (*R*) configuration, II) CPCR have the (*S*) configuration, determined after desilylation by comparison of the retention times with those of commercially available (*S*)-3-butyn-2-ol.

(Table 2). The findings outlined above (Table 1) indicate that a bulky substituent at the alkyne moiety results in a higher selectivity in the reduction. We therefore required a functional group that could easily be attached to and removed from the alkyne unit. Silyl groups appeared to be suitable, since they not only fulfil these requirements[15] but their size can also be varied. Furthermore, Bradshaw et al. have reported that *Lactobacillus kefir*-ADH, an enzyme highly homologous to LBADH,[6] affords (*R*)-4-trimethylsilyl-3-butyn-2-ol [(*R*)-**4b**] with an *ee* of 94% in 25% yield.[4b] In our investigations, ketone **3b** was reduced by recLBADH with 100% conversion (Table 2). The enantiomeric excess and absolute configuration of the product were determined by desilylation with borax, converting alcohol (*R*)-**4b** into (*R*)-3-butyn-2-ol [(*R*)-**4a**]. The steric size of the TMS group in the substrate was sufficient to produce optically pure alcohol (*R*)-**4a**. CPCR, however, failed to afford propargylic alcohol with an *ee* higher than 99% even when substrate **3d**, bearing a bulky *tert*-butyldimethylsilyl group, was used. The synthesis of enantiomerically pure (*S*)-3-butyn-2-ol [(*S*)-**4a**] was finally achieved by introduction of a silyl group with an aromatic substituent into the substrate (compound **3e**). In conclusion, we have found an easy access to both enantiomers of **4a** in high optical purity simply by introduction of appropriate silyl derivatives and subsequent removal of the *ee*-enhancing group (Scheme 3).

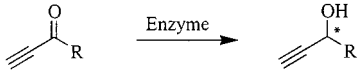


3b-e 4b-e 4a

Scheme 3. Synthesis of enantiopure 3-butyn-2-ol (**4a**)

We then tested recLBADH and CPCR with the *n*-alkyl ethynyl ketones **5a–c** (Table 3) as most other reducing reagents do not yield enantiopure products with these homologues of 3-butyn-2-one (**3a**).[2] Interestingly, the preferred stereochemistry of the resulting propargylic alcohol for both oxidoreductases tested depends on the size of the alkyl unit, an observation similarly reported by Phillips et al. for SADH from *Thermoanaerobacter ethanolicus*.[4e] In the case of recLBADH, reversal of the enantioselectivity of the reduction occurs when 1-pentyn-3-one (**5a**) is used as a substrate. Higher homologues such as 1-hexyn-3-one (**5b**) and 1-octyn-3-one (**5c**) are even reduced with complete enantioselectivity. Surprisingly, the enzymatic activity increases strongly for these substrates bearing longer alkyl chains. Because of the high instability of these compounds in amine buffer[4e] ($t_{1/2} \approx 6-12$ h) use of large amounts of enzyme to reduce the total reaction time would be reasonable under these conditions. However, we found that ketones with a terminal triple bond, and also the corresponding alcohols, are stable in phosphate buffer, and so propargylic alcohol (*S*)-**6b** (*ee* > 99%) could easily be obtained in gram-scale amounts. The terminal alkyne unit can be converted into larger aliphatic groups, thus giving access to enantiopure secondary alcohols bearing two bulky residues. This strategy avoids the difficult enantioselective reduction of the corresponding internal ketones and has been employed previously, for example in the synthesis of leukotriene B_3 derivatives.[16] On the other hand, CPCR is not able to yield an *ee* higher than 76% for the *n*-alkyl ethynyl ketones **5a–c**. Nevertheless, the enantioselectivity of the CPCR-catalysed reduction also changes with elongation of the alkyl chain. Thus, 1-octyn-3-one (**5c**) is converted into (*R*)-**6c** in 62% *ee*. At a certain chain length, both oxidoreductases probably recognise the alkyl unit as the larger substituent of the ketone, resulting in a reversal of the preferred absolute configuration of the product alcohols.

Table 3. Screening results of *n*-alkyl-alkynones (assay conditions were: 5 mM substrate, 0.25 mM NAD(P)H, 1 mM $MgCl_2$, 100 mM TEA/NaOH buffer, pH = 6.5)



5 6

alcohol	R =	recLBADH[a] % activity (% conv.)	% *ee* (configuration)	CPCR[a] % activity (% conv.)	% *ee* (configuration)
4a	CH_3	66 (100)	60 (*R*)[b]	52 (100)	49 (*S*)[b]
6a	C_2H_5	41 (90)	34 (*S*)[c]	34 (90)	67 (*S*)[d]
6b	C_3H_7	28 (100)	> 99 (*S*)[c]	13 (65)	76 (*S*)[d]
6c	C_5H_{11}	85 (100)	> 99 (*S*)[b]	vs[e] (<5)	62 (*R*)[b]

[a] Enzyme activity was determined by the decrease in the NAD(P)H extinction at 340 nm relative to 5-oxohexanoic acid ethyl ester. – [b] Determined by comparison of the retention times with those of commercially available (*S*)-alcohols. – [c] Determined by comparison of the optical rotations with literature data. – [d] Determined by comparison of the retention times with retention times of (*S*)-**6a** and (*S*)-**6b** obtained by recLBADH. – [e] Very slow.

In conclusion, it has been shown that a broad variety of differently substituted acetylenic ketones can be reduced enantioselectively by the oxidoreductases recLBADH and CPCR. Most propargylic alcohols were obtained with *ee* values higher than 99%, making this method superior to chemical reduction techniques. In the majority of cases, the alcohols can be obtained in either enantiomeric form, since these oxidoreductases exhibit complementary enantioselectivities. The substrate spectrum includes aromatic alkynones as well as a number of aliphatic derivatives. By varying the size of the substituents, the enantiomeric excess can be tuned, and even a reversal in enantioselectivity be achieved. Last but not least, the enzymatic reductions can easily be scaled up, making this method highly attractive in ecological and economical terms.

Experimental Section

General Methods: All solvents were used in p.a. quality and dried by standard methods if necessary. Chemicals were purchased from Aldrich, Lancaster, TCI and Fluka. CPCR, recLBADH and FDH (from *Candida boidinii*) were isolated at the Institute of Enzyme Technology, University of Düsseldorf, and can be purchased from Juelich Fine Chemicals. − TLC: silica gel 60 F_{254} (Merck). Flash column chromatography: silica gel 60 (40−63 μm, Merck). − NMR spectra (^{1}H: 300 MHz, ^{13}C: 75.5 MHz) were recorded with an AMX 300 (Bruker Physik AG). Chemical shifts are reported in ppm relative to C*H*Cl_3 (δ^1H: 7.27) and *C*DCl_3 (δ^{13}C: 77.23) as internal standard. − GC: Chrompack CP9002 using a FS-Cyclodex-β-I/P (50 m × 320 μm; CS GmbH) and a Lipodex E column (25 m × 250 μm; Macherey−Nagel). HPLC: Hewlett−Packard Series 1100 using a Chiralcel OB and Chiralpak AD column (each 250 × 4 mm, equipped with a precolumn, 80 × 4 mm; Daicel Chem. Ind.) at 20 °C, 0.5 mL/min. − GCMS: HP 6890 series GC system fitted with a HP 5973 mass selective detector (EI, 70 eV) and a HP-5MS column (30 m × 250 μm), [T_{GC}(injector) = 250 °C, time programme (oven): $T_{0\,min}$ = 60 °C, $T_{3\,min}$ = 60 °C, $T_{14\,min}$ = 280 °C (20°/min), $T_{19\,min}$ = 280 °C]. − Optical rotation: polarimeter 241 (Perkin−Elmer). − IR spectra: Avatar 360 FT-IR (Nicolet). − Syringe pump: Hamilton Microlab 500 series. − Melting points were measured with a Büchi B-540 heating unit. − 4-Phenyl-3-butyn-2-one (**1a**) and 4-trimethylsilyl-3-butyn-2-one (**3b**) were purchased from Aldrich, 3-butyn-2-one (**3a**) from Lancaster. 1-Pentyn-3-one (**5a**)[17] and 1-octyn-3-one (**5c**)[18] were synthesised according to literature procedures.

Synthesis of α,β-Acetylenic Ketones

Method A.[8] **− 4-(4-Methoxyphenyl)-3-butyn-2-one (1b):** *n*BuLi (1.9 mL, 3.0 mmol, 1.6 M in hexane) was added at 0 °C to a solution of 1-ethynyl-4-methoxybenzene (396 mg, 3.0 mmol) in dry THF (50 mL). After 15 min the mixture was cooled to −78 °C and *N*-methoxy-*N*-methylacetamide (362 mg, 3.5 mmol) was added dropwise over 3 min. After stirring for 30 min, the solution was heated to room temperature and stirred for an additional 2 h. The mixture was quenched with 2 M HCl, followed by extraction with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. Flash chromatography afforded 429 mg (2.5 mmol, 82% yield) of ketone **1b** as a yellow solid, R_f = 0.12 (isohexane/ethyl acetate, 30:1), m.p. 45−46 °C. − ^{1}H NMR ($CDCl_3$): δ = 2.42 (s, 3 H, CH_3), 3.83 (s, 3 H, OCH_3), 6.88 (d, *J* = 9.0 Hz, 2 H), 7.51 (d, *J* = 9.0 Hz, 2 H, ar-H). − ^{13}C NMR ($CDCl_3$): δ = 32.8 (CH_3), 55.6 (OCH_3), 88.4, 91.7 (C_q), 111.7, 114.5, 135.3, 161.8 (ar-C), 184.9 (CO). − GCMS: R_t = 10.1 min: *m*/*z* (%) = 174 (33) [M^+], 159 (100) [$M^+ - CH_3$], 144 (13) [$M^+ - 2\,CH_3$], 131 (5) [$M^+ - CH_3 - CO$], 116 (8) [$M^+ - 2\,CH_3 - CO$].

4-(4-Fluorophenyl)-3-butyn-2-one (1c): Method A was employed with 1-ethynyl-4-fluorobenzene (360 mg, 3.0 mmol) to yield 355 mg (2.2 mmol, 73% yield) of ketone **1c** as a light yellow oil, R_f = 0.23 (isohexane/ethyl acetate, 30:1). − ^{1}H NMR ($CDCl_3$): δ = 2.42 (s, 3 H, CH_3), 7.05 (m, 2 H), 7.55 (m, 2 H, ar-H). − ^{13}C NMR ($CDCl_3$): δ = 32.8 (CH_3), 88.3, 89.2 (C_q), 115.7, 116.2 (d, *J* = 23.0 Hz), 135.4 (d, *J* = 9.0 Hz), 164.5 (d, *J* = 257 Hz), (ar-C), 184.6 (CO). − GCMS: R_t = 7.8 min: *m*/*z* (%) = 162 (20) [M^+], 147 (100) [$M^+ - CH_3$], 119 (6) [$M^+ - CH_3 - CO$].

4-(4-Chlorophenyl)-3-butyn-2-one (1d): Method A was employed with 1-ethynyl-4-chlorobenzene (408 mg, 3.0 mmol) to yield 370 mg (2.1 mmol, 69% yield) of ketone **1d** as a yellow solid, R_f = 0.28 (isohexane/ethyl acetate, 30:1), m.p. 53−54 °C (ref.:[19] m.p. 54 °C). − ^{1}H NMR ($CDCl_3$): δ = 2.46 (s, 3 H, CH_3), 7.38 (d, *J* = 6.6 Hz, 2 H), 7.51 (d, *J* = 6.6 Hz, 2 H, ar-H). − ^{13}C NMR ($CDCl_3$): δ = 32.9 (CH_3), 89.0, 89.1 (C_q), 118.5, 129.3, 134.4, 137.4 (ar-C), 184.7 (CO). − GCMS: R_t = 9.6 min: *m*/*z* (%) = 178 (19) [M^+], 163 (100) [$M^+ - CH_3$], 135 (5) [$M^+ - CH_3 - CO$], 128 (1) [$M^+ - Cl - CH_3$].

Method B.[9] **− 4-(4-Bromophenyl)-3-butyn-2-one (1e):** $AlCl_3$ (1150 mg, 8.6 mmol) was added at 0 °C with vigorous stirring to a solution of (4-bromophenylethynyl)trimethylsilane (760 mg, 3.0 mmol) and acetyl chloride (224 mg, 2.8 mmol) in dry CH_2Cl_2 (50 mL). After 30 min the suspension was heated to room temperature and stirring was continued for 30 min. The reaction was quenched with excess 2 M HCl and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. Flash chromatography afforded 537 mg (2.4 mmol, 86% yield) of ketone **1e** as a light brown solid, R_f = 0.21 (isohexane/ethyl acetate, 30:1), m.p. 64−65 °C. − ^{1}H NMR ($CDCl_3$): δ = 2.45 (s, 3 H, CH_3), 7.43 (d, *J* = 8.6 Hz, 2 H), 7.53 (d, *J* = 8.6 Hz, 2 H, ar-H). − ^{13}C NMR ($CDCl_3$): δ = 32.9 (CH_3), 89.0, 89.1 (C_q), 118.9, 125.7, 132.2, 134.5 (ar-C), 184.6 (CO). − GCMS: R_t = 9.6 min: *m*/*z* (%) = 222 (22) [M^+], 207 (100) [$M^+ - CH_3$], 179 (2) [$M^+ - CH_3 - CO$], 128 (16) [$M^+ - Br - CH_3$], 100 (14) [$M^+ - Br - CH_3 - CO$].

4-(3-Bromophenyl)-3-butyn-2-one (1f): Method B was employed with (3-bromophenylethynyl)trimethylsilane (760 mg, 3.0 mmol), to yield 556 mg (2.5 mmol, 89% yield) of ketone **1f** as a yellow oil, R_f = 0.28 (isohexane/ethyl acetate, 30:1). − ^{1}H NMR ($CDCl_3$): δ = 2.45 (s, 3 H, CH_3), 7.26 ("t", *J* = 7.8 Hz, 1 H), 7.51 (d, *J* = 7.8 Hz, 1 H), 7.59 (d, *J* = 7.8 Hz, 1 H), 7.71 (s, 1 H, ar-H). − ^{13}C NMR ($CDCl_3$): δ = 32.9 (CH_3), 88.1, 88.9 (C_q), 122.0, 122.6, 130.3, 131.7, 134.0, 135.7 (ar-C), 184.5 (CO). − GCMS: R_t = 9.8 min: *m*/*z* (%) = 222 (22) [M^+], 207 (100) [$M^+ - CH_3$], 128 (24) [$M^+ - Br - CH_3$], 115 (9) [$M^+ - Br - CO$], 100 (14) [$M^+ - Br - CH_3 - CO$].

4-(2-Bromophenyl)-3-butyn-2-one (1g): Method B was employed with (2-bromophenylethynyl)trimethylsilane (760 mg, 3.0 mmol), to yield 400 mg (2.2 mmol, 64% yield) of ketone **1g** as a brown oil, R_f = 0.29 (isohexane/ethyl acetate, 30:1). − ^{1}H NMR ($CDCl_3$): δ = 2.42 (s, 3 H, CH_3), 7.25 (m, 2 H), 7.52 (m, 2 H, ar-H). − ^{13}C NMR ($CDCl_3$): δ = 33.0 (CH_3), 88.5, 91.6 (C_q), 122.5, 127.0, 127.5, 132.0, 132.9, 135.0 (ar-C), 184.6 (CO). − GCMS: R_t = 9.6 min: *m*/*z* (%) = 222 (34) [M^+], 207 (100) [$M^+ - CH_3$], 128 (25) [$M^+ - Br - CH_3$], 115 (11) [$M^+ - Br - CO$], 100 (21) [$M^+ - Br - CH_3 - CO$].

4-(2-Pyridinyl)-3-butyn-2-one (1h): Method A was employed with 2-ethynylpyridine (309 mg, 3.0 mmol), to yield 157 mg (1.1 mmol,

36% yield) of ketone **1h** as a red oil, R_f = 0.32 (isohexane/ethyl acetate, 30:1). − ^{1}H NMR ($CDCl_3$): δ = 2.45 (s, 3 H, CH_3), 7.33 (m, 1 H), 7.55 (d, *J* = 7.8 Hz, 1 H), 7.70 (m, 1 H), 8.62 (d, *J* = 4.3 Hz, 1 H, ar-H). − ^{13}C NMR ($CDCl_3$): δ = 32.9 (CH_3), 86.1, 87.7 (C_q), 124.8, 128.9, 136.6, 140.8, 150.7 (ar-C), 184.5 (CO). − GCMS: R_t = 8.4 min: *m/z* (%) = 145 (23) [M^+], 130 (100) [$M^+ - CH_3$], 102 (3) [$M^+ - CH_3 - CO$], 78 (15).

4-(3-Methyl-2-thienyl)-3-butyn-2-one (1i): Method A was employed with 2-ethynyl-5-methylthiophene[20] (366 mg, 3.0 mmol), to yield 361 mg (2.2 mmol, 73% yield) of ketone **1i** as a yellow oil, R_f = 0.23 (isohexane/ethyl acetate, 30:1). − ^{1}H NMR ($CDCl_3$): δ = 2.41 (s, 3 H, CH_3), 2.51 (s, 3 H, CH_3), 6.74 (d, *J* = 3.8 Hz, 1 H), 7.30 (d, *J* = 3.8 Hz, 1 H, ar-H). − ^{13}C NMR ($CDCl_3$): δ = 15.9 (CH_3), 32.6 (CH_3), 85.6, 93.0 (C_q), 117.3, 126.5, 137.7, 147.7 (ar-C), 184.4 (CO). − GCMS: R_t = 9.0 min: *m/z* (%) = 164 (44) [M^+], 149 (100) [$M^+ - CH_3$], 121 (24) [$M^+ - CH_3 - CO$].

4-(Triethylsilyl)-3-butyn-2-one (3c): Method A was employed with (triethylsilyl)acetylene (420 mg, 3.0 mmol), to yield 377 mg (2.1 mmol, 69% yield) of ketone **3c** as a colourless oil, R_f = 0.34 (isohexane/ethyl acetate, 30:1). − ^{1}H NMR ($CDCl_3$): δ = 0.69 (q, *J* = 7.8 Hz, 6 H, CH_2), 1.20 (t, *J* = 7.8 Hz, 9 H, CH_3), 2.37 (s, 3 H, CH_3). − ^{13}C NMR ($CDCl_3$): δ = 3.9 (CH_2), 7.5 (CH_3), 32.9 (CH_3), 95.9, 103.9 (C_q), 184.6 (CO). − GCMS: R_t = 7.3 min: *m/z* (%) = 182 (1) [M^+], 167 (3) [$M^+ - CH_3$], 153 (100) [$M^+ - CH_2CH_3$], 125 (52) [$M^+ - CH_2CH_3 - CO$].

4-(*tert*-Butyldimethylsilyl)-3-butyn-2-one (3d): Method A was employed with (*tert*-butyldimethylsilyl)acetylene (420 mg, 3.0 mmol), to yield 355 mg (2.0 mmol, 65% yield) of ketone **3d** as a colourless oil, R_f = 0.32 (isohexane/ethyl acetate, 30:1). − ^{1}H NMR ($CDCl_3$): δ = 0.17 (s, 6 H, CH_3), 0.95 (s, 9 H, *t*Bu), 2.33 (s, 3 H, CH_3). − ^{13}C NMR ($CDCl_3$): δ = −4.9 (CH_3), 16.7 (C_q), 26.1 (CH_3), 32.8 (CH_3), 96.4, 103.3 (C_q), 184.5 (CO). − GCMS: R_t = 6.5 min: *m/z* (%) = 182 (5) [M^+], 167 (17) [$M^+ - CH_3$], 125 (100) [$M^+ - 2\,CH_3 - CO$].

4-Dimethylphenylsilyl-3-butyn-2-one (3e): Method A was employed with (dimethylphenylsilyl)acetylene[21] (480 mg, 3.0 mmol), to yield 345 mg (1.7 mmol, 57% yield) of ketone **3e** as a colourless oil, R_f = 0.24 (isohexane/ethyl acetate, 30:1). − ^{1}H NMR ($CDCl_3$): δ = 0.49 (s, 6 H, CH_3), 2.37 (s, 3 H, CH_3), 7.32−7.70 (m, 5 H, ar-H). − ^{13}C NMR ($CDCl_3$): δ = −1.7 (CH_3), 32.6 (CH_3), 96.8, 102.7 (C_q), 128.1, 130.0, 133.7, 134.2 (ar-C), 184.5 (CO). − GCMS: R_t = 8.8 min: *m/z* (%) = 201 (23) [M^+ − H], 187 (100) [$M^+ - CH_3$], 159 (86) [$M^+ - CH_3 - CO$], 145 (58) [$M^+ - 2\,CH_3 - CO$].

3-Hexyn-2-one (5b): Method B was employed with ethynyltrimethylsilane (12.0 g, 122.4 mmol) and butyryl chloride (12.2 g, 114.2 mmol), to yield 4.5 g (46.8 mmol, 41% yield) of ketone **5b** as a colourless oil after distillation (b.p. 63 °C/30 mm). − ^{1}H NMR ($CDCl_3$): δ = 0.94 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.72 ("hex", *J* = 7.4 Hz, 2 H, CH_2), 2.58 (t, *J* = 7.4 Hz, 2 H, CH_2), 3.21 (s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 13.6 (CH_3), 17.5 (CH_2), 47.4 (CH_2), 78.5, 81.6 (C_q), 187.7 (CO). − GCMS (T_0 min. = 40 °C): R_t = 4.4 min: *m/z* (%) = 95 (42) [M^+ − H], 81 (36) [$M^+ - CH_3$], 68 (97) [$M^+ - C_2H_4$], 53 (100) [$M^+ - C_3H_7$].

Enzyme Assays: recLBADH[6] and CPCR[7] assays were performed by combining the following solutions and monitoring at 340 nm ($\varepsilon_{NAD(P)H}$ 6.22 $L \cdot mol^{-1} \cdot cm^{-1}$) and 20 °C: 970 μL solution of ketone in TEA/NaOH buffer (5 mM ketone [2 mM for aromatically substituted alkynones], 100 mM TEA, 1 mM $MgCl_2$) pH 6.5, 20 μL NAD(P)H solution (12.5 mM), and 10 μL enzyme solution. Initial rate data were recorded relative to ethyl 5-oxohexanoate.

RecLBADH-Catalysed Reductions of α,β-Acetylenic Ketones (Preparative Scale). − (*R*)-4-(4-Methoxyphenyl)-3-butyn-2-ol [(*R*)-2b]: Compound **1b** (174 mg, 1 mmol) was stirred at room temperature with $NADP^+$ (50 mg, 60 μmol), 2-propanol (1.5 mL), and recLBADH (50 U) in TEA/NaOH buffer (100 mL, 100 mM TEA, 1 mM $MgCl_2$; pH 6.5). After 16 h the reaction mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. Flash chromatography afforded alcohol **2b** (113 mg, 640 μmol, 64% yield) as a pale yellow solid, R_f = 0.17 (isohexane/ethyl acetate, 10:1), m.p. 44−45 °C. > 99% *ee* as determined by HPLC on Chiralcel OB (isohexane/2-propanol, 85:15), R_t = 29.0 min (*R*). − ^{1}H NMR ($CDCl_3$): δ = 1.55 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.90 (s, 1 H, OH), 3.80 (s, 3 H, OCH_3), 4.75 (q, *J* = 6.5 Hz, 1 H), 6.82 (d, *J* = 7.1 Hz, 2 H), 7.37 (d, *J* = 7.1 Hz, 2 H, ar-H). − ^{13}C NMR ($CDCl_3$): δ = 24.7 (CH_3), 55.5 (OCH_3), 59.1 (CH), 84.1, 89.8 (C_q), 114.1, 114.8, 133.3, 159.8 (ar-C). − GCMS: R_t = 10.3 min: *m/z* (%) = 176 (40) [M^+], 161 (100) [$M^+ - CH_3$], 145 (5) [$M^+ - 2\,CH_3$], 133 (26) [$M^+ - CH_3 - CO$], 118 (14) [$M^+ - 2\,CH_3 - CO$]. − $[\alpha]_D^{22}$ = +39.9 (*c* = 1.4, Et_2O) [ref.[3b]: (*S*)-**2b**: $[\alpha]_D^{25}$ = −35.1 (*c* = 1.0, Et_2O; *ee* = 97%)].

(*S*)-1-Pentyn-3-ol [(*S*)-6a]: Compound **5a** (82 mg, 1 mmol) was stirred at room temperature with $NADP^+$ (50 mg, 60 μmol), 2-propanol (1.5 mL), and recLBADH (50 U) in TEA/NaOH buffer (100 mL, 100 mM TEA, 1 mM $MgCl_2$; pH 6.5). After 16 h the reaction mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. Alcohol **6a** was obtained in 90% conversion as crude product; 34% *ee* as determined by GC on Lipodex E column (*T* = 35 °C), R_t = 30.5 min (*S*) + 32.0 min (*R*). − IR (neat): $\tilde{\nu}$ = 3292 (C≡CH), 2973, 2938, 2881 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 1.01 (t, *J* = 7.4 Hz, 3 H, C5), 1.72 (m, 2 H, C4), 2.45 (s, 1 H, C1), 4.32 (t, *J* = 6.4 Hz, 1 H, C3). − ^{13}C NMR ($CDCl_3$): δ = 9.4 (C5), 30.9 (C4), 63.6 (C3), 72.9 (C1), 84.9 (C2). − $[\alpha]_D^{21}$ = −8.4 (*c* = 0.5, Et_2O) [ref.[22] (*R*)-**6a**: $[\alpha]_D^{22}$ = +34.0 (*c* = 2.2, Et_2O; *ee* > 97%)].

(*S*)-1-Hexyn-3-ol [(*S*)-6b]: Compound **5b** (1.50 g, 15.6 mmol) was stirred at room temperature with $NADP^+$ (115 mg, 138 μmol), 2-propanol (30 mL), and recLBADH (750 U) in phosphate buffer (1000 mL, 50 mM phosphate, 1 mM $MgCl_2$; pH 7). After 16 h the reaction mixture was extracted with Et_2O (3 × 200 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. Distillation afforded **6b** (1.06 g, 10.8 mmol, 69% yield) as a colourless liquid (92 °C/100 mm). > 99% *ee* as determined by GC on FS-Cyclodex-β-I/P column (*T* = 60 °C), R_t = 26.3 min (*S*). − IR (neat): $\tilde{\nu}$ = 3311 (C≡CH), 2965, 2935, 2874 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 0.94 (t, *J* = 7.3 Hz, 3 H, C6), 1.50 (m, 2 H, C5), 1.72 (m, 2 H, C4), 2.48 (s, 1 H, C1), 4.39 (t, *J* = 6.4 Hz, 1 H, C3). − ^{13}C NMR ($CDCl_3$): δ = 13.8 (C6), 18.4 (C5), 39.8 (C4), 62.2 (C3), 72.9 (C1), 85.3 (C2). − GCMS (T_0 min = 40 °C): R_t = 5.7 min: *m/z* (%) = 97 (5) [M^+ − H], 83 (33) [$M^+ - CH_3$], 70 (17) [$M^+ - H_2O$], 55 (100) [$M^+ - CH_3 - CO$]. − $[\alpha]_D^{21}$ = −33.8 (*c* = 1.2, Et_2O) [ref.:[23] $[\alpha]_D^{22}$ = −24.0 (*c* = 2.4, Et_2O; *ee* = 68%)].

(*R*)-4-Phenyl-3-butyn-2-ol [(*R*)-2a]: 4-Phenyl-3-butyn-2-one (**1a**) (2.08 g, 14.4 mmol) in 2-propanol (50 mL) was steadily added by syringe pump over 20 h to a stirred solution of $NADP^+$ (6.0 mg, 7.2 μmol, 0.05 mol %, total turnover number 2000), 2-propanol (50 mL), and recLBADH (250 U) in deionized water (250 mL, 1 mM $MgCl_2$, ph 6.6, HCl) at 22 °C. After this had stirred for an additional 4 h, the conversion was determined by GCMS and NMR as 98%. After a total reaction time of 30 h the conversion was determined as > 99%. Extraction with ethyl acetate afforded (*R*)-**2a** (1.98 g, 13.5 mmol, 94% yield) as a light yellow oil, free of

by-products. > 99% *ee* as determined by HPLC on Chiralcel OB (isohexane/2-propanol, 95:5), R_t = 24.3 min (*R*). − ^{1}H NMR ($CDCl_3$): δ = 1.55 (d, *J* = 6.6 Hz, 3 H, CH_3), 2.13 (s, 1 H, OH), 4.75 (q, *J* = 6.6 Hz, 1 H), 7.31−7.42 (m, 5 H, ar-H). − ^{13}C NMR ($CDCl_3$): δ = 24.3 (CH_3), 58.7 (CH), 83.9, 90.9 (C_q), 122.5, 128.2, 128.3, 131.6 (ar-C). − GCMS: R_t = 8.0 min: *m*/*z* (%) = 146 (50) [M^+], 131 (100) [$M^+ - CH_3$], 103 (61) [$M^+ - CH_3 - CO$], 77 (35) [$C_6H_5^+$]. − $[\alpha]_D^{21}$ = +47.5 (*c* = 1.1, Et_2O) [ref.[3b]: (*S*)-**2a**: $[\alpha]_D^{25}$ = −44.8 (*c* = 1.0, Et_2O; *ee* = 97%)].

CPCR-Catalysed Reductions of α,β-Acetylenic Ketones (Preparative Scale): The carbonyl compound (1 mmol) was stirred at room temperature with NAD^+ (45 mg, 60 μmol), sodium formate (6.8 g), formate dehydrogenase (24 U), and CPCR (6 U) in TEA/NaOH buffer (100 mL, 100 mM TEA; pH 7.0). After 16 h the reaction mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried with Na_2SO_4, concentrated in vacuo, and purified by flash chromatography [isohexane/ethyl acetate (**2a**) or pentane/CH_2Cl_2 (**4b**)].

(*S*)-4-Phenyl-3-butyn-2-ol [(*S*)-2a]: 66% yield; > 99% *ee* as determined by HPLC on a Chiralcel OB (isohexane/2-propanol, 95:5), R_t = 31.9 min (*S*). − ^{1}H NMR, ^{13}C NMR, and GCMS as (*R*)-**2a**. − $[\alpha]_D^{21}$ = −46.8 (*c* = 1.0, Et_2O) [ref.[3b]: $[\alpha]_D^{25}$ = −44.8 (*c* = 1.0, Et_2O; *ee* = 97%)].

(*S*)-4-Trimethylsilyl-3-butyn-2-ol [(*S*)-4b]: 78% yield; 57% *ee* as determined by GC on FS-Cyclodex-β-I/P column (*T* = 35 °C) after desilylation, R_t = 13.9 min (*R*) + 15.5 min (*S*). − ^{1}H NMR ($CDCl_3$): δ = 0.17 (s, 9 H, TMS), 1.45 (d, *J* = 6.6 Hz, 1 H, CH_3), 2.01 (s, 1 H, OH), 4.52 (q, *J* = 6.6 Hz, 1 H, CH). − ^{13}C NMR ($CDCl_3$): δ = 0.0 (TMS), 24.4 (CH_3), 58.9 (CH), 88.6, 107.8 (C_q). − GCMS: R_t = 5.1 min: *m*/*z* (%) = 141 (1) [$M^+ - H$], 127 (14) [$M^+ - CH_3$], 109 (5) [$M^+ - CH_3 - H_2O$], 99 (100) [$M^+ - CH_3 - CO$], 73 (12). − $[\alpha]_D^{21}$ = −15.8 (*c* = 0.75, $CHCl_3$) [ref.[3d]: (*S*)-**4b**: $[\alpha]_D^{25}$ = −25.9 (*c* = 3.1, $CHCl_3$; *ee* > 95%)].

Synthesis of Racemic Alcohols and Separation of the Enantiomers (Analytical Scale): Alkynone (10 μmol) and $NaBH_4$ (0.2 mg, 5 μmol) in EtOH (1 mL) were stirred for 1 h at 0 °C. The reaction was hydrolysed with HCl (1 M, 1 mL), brine (4 mL) was added, and the mixture was extracted with CH_2Cl_2 (1 mL). All alkynones were reduced to the corresponding alcohols with 100% conversion.

4-Phenyl-3-butyn-2-ol (2a): Enantiomers were separated by HPLC on a Chiralcel OB column (isohexane/2-propanol, 95:5), R_t = 24.3 min (*R*) + 31.9 min (*S*).

4-(4-Methoxyphenyl)-3-butyn-2-ol (2b): Enantiomers were separated by HPLC on a Chiralcel OB column (isohexane/2-propanol, 85:15), R_t = 29.0 min (*R*) + 38.2 min (*S*).

4-(4-Fluorophenyl)-3-butyn-2-ol (2c): Enantiomers were separated by HPLC on a Chiralpak AD column (isohexane/2-propanol, 99:1), R_t = 45.5 min (*S*) + 47.8 min (*R*). − GCMS: R_t = 8.5 min: *m*/*z* (%) = 164 (33) [M^+], 149 (100) [$M^+ - CH_3$], 121 (43) [$M^+ - CH_3 - CO$], 101 (47) [$M^+ - CH_3 - CO - F$].

4-(4-Chlorophenyl)-3-butyn-2-ol (2d): Enantiomers were separated by HPLC on a Chiralpak AD column (isohexane/2-propanol, 99:1), R_t = 49.4 min (*S*) + 54.4 min (*R*). − GCMS: R_t = 9.8 min: *m*/*z* (%) = 180 (29) [M^+], 165 (100) [$M^+ - CH_3$], 145 (11) [$M^+ - Cl$], 137 (16) [$M^+ - CH_3 - CO$], 102 (14) [$M^+ - CH_3 - CO - Cl$].

4-(4-Bromophenyl)-3-butyn-2-ol (2e): Enantiomers were separated by HPLC on a Chiralpak AD column (isohexane/2-propanol, 99:1), R_t = 54.4 min (*S*) + 60.6 min (*R*). − GCMS: R_t = 10.4 min: *m*/*z* (%) = 224 (33) [M^+], 209 (100) [$M^+ - CH_3$], 181 (22) [$M^+ - CH_3 - CO$], 145 (26) [$M^+ - Br$], 102 (75) [$M^+ - Br - CH_3 - CO$].

4-(3-Bromophenyl)-3-butyn-2-ol (2f): Enantiomers were separated by HPLC on a Chiralcel OB column (isohexane/2-propanol, 98:2), R_t = 63.8 min (*S*) + 69.2 min (*R*). − GCMS: R_t = 10.2 min: *m*/*z* (%) = 224 (16) [M^+], 209 (33) [$M^+ - CH_3$], 181 (17) [$M^+ - CH_3 - CO$], 145 (100) [$M^+ - Br$], 102 (62) [$M^+ - Br - CH_3 - CO$].

4-(2-Bromophenyl)-3-butyn-2-ol (2g): Enantiomers were separated by HPLC on a Chiralcel OB column (isohexane/2-propanol, 95:5), R_t = 26.2 min (*R*) + 35.1 min (*S*). − GCMS: R_t = 10.4 min: *m*/*z* (%) = 224 (27) [M^+], 209 (100) [$M^+ - CH_3$], 181 (19) [$M^+ - CH_3 - CO$], 145 (35) [$M^+ - Br$], 102 (62) [$M^+ - Br - CH_3 - CO$].

4-(2-Pyridinyl)-3-butyn-2-ol (2h): Enantiomers were separated by HPLC on a Chiralcel OB column (isohexane/2-propanol, 98:2), R_t = 61.9 min (*R*) + 68.1 min (*S*). − GCMS: R_t = 9.2 min: *m*/*z* (%) = 147 (8) [M^+], 132 (15) [$M^+ - CH_3$], 104 (100) [$M^+ - CH_3 - CO$], 78 (24).

4-(3-Methyl-2-thienyl)-3-butyn-2-ol (2i): Enantiomers were separated by HPLC on a Chiralcel OB column (isohexane/2-propanol, 95:5), R_t = 33.6 min (*R*) + 38.6 min (*S*). − GCMS: R_t = 8.8 min: *m*/*z* (%) = 166 (44) [M^+], 151 (100) [$M^+ - CH_3$], 134 (10) [$M^+ - S$], 123 (32) [$M^+ - CH_3 - CO$].

3-Butyn-2-ol (4a): Enantiomers were separated by GC on an FS-Cyclodex-β-I/P column (T = 35 °C), R_t = 13.9 min (*R*) + 15.5 min (*S*).

1-Pentyn-3-ol (6a): Enantiomers were separated by GC on a Lipodex E column (*T* = 35 °C), R_t = 30.5 min (*S*) + 32.0 min (*R*).

1-Hexyn-3-ol (6b): Enantiomers were separated by GC on an FS-Cyclodex-β-I/P column (T = 60 °C), R_t = 26.3 min (*S*) + 28.4 min (*R*).

1-Octyn-3-ol (6c). Enantiomers were separated by GC on an FS-Cyclodex-β-I/P column (*T* = 80 °C), R_t = 41.8 min (*S*) + 44.9 min (*R*). − GCMS: R_t = 5.0 min: *m*/*z* (%) = 125 (3) [$M^+ - H$], 111 (3) [$M^+ - CH_3$], 107 (7) [$M^+ - H_2O - H$], 97 (19) [$M^+ - C_2H_5$], 83 (42) [$M^+ - CH_3 - CO$], 55 (100) [C_4H_7].

RecLBADH-Catalysed Reductions of α,β-Acetylenic Ketones (Analytical Scale): In a typical procedure, the carbonyl compound (10 μmol) was shaken at room temperature with $NADP^+$ (0.5 mg, 0.6 μmol), 2-propanol (15 μL), and recLBADH (0.5 U) in TEA/NaOH buffer (1 mL, 100 mM TEA, 1 mM $MgCl_2$; pH 6.5). After 16 h the reaction mixture was extracted with CH_2Cl_2 (200 μL). Analytical data were acquired as described above; conversions and enantiomeric excess are given in Table 1−3.

CPCR-Catalysed Reductions of α,β-Acetylenic Ketones (Analytical Scale): In a typical procedure, the carbonyl compound (10 μmol) was shaken at room temperature with NAD^+ (0.45 mg, 0.6 μmol), sodium formate (68 mg), formate dehydrogenase (2 U), and CPCR (0.5 U) in TEA/NaOH-buffer (1 mL, 100 mM TEA; pH 7.0). After 16 h the reaction mixture was extracted with CH_2Cl_2 (200 μL). Analytical data were acquired as described above; conversions and enantiomeric excess are given in Table 1−3.

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