RSC Advances

REVIEW

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Cite this: *RSC Adv.*, 2025, **15**, 11863

Green and sustainable synthesis of chiral alcohols: the role of *Daucus carota* as a biocatalyst in organic chemistry

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Chiral alcohols are essential intermediates in pharmaceuticals, agrochemicals, and advanced materials. Conventional asymmetric reduction of ketones relies on costly metal catalysts with significant environmental impact. Biocatalysis, particularly whole-cell systems, offers a sustainable alternative, providing high regio- and stereoselectivity under mild conditions. *Daucus carota* (carrot) roots serve as a promising biocatalyst due to their broad substrate compatibility and natural cofactor recycling ability, reducing reliance on toxic reagents and energy-intensive processes, making them both environmentally sustainable and economically viable. This review highlights the potential of *D. carota* for chiral alcohol synthesis while addressing challenges such as long reaction times, high biocatalyst requirements, and substrate limitations. Ongoing research focuses on optimizing reaction conditions, testing different carrot varieties, and incorporating additives to enhance efficiency and expand applicability.

Received 7th February 2025
Accepted 9th April 2025

DOI: 10.1039/d5ra00901d

rsc.li/rsc-advances

1 Introduction

Chiral alcohols[1] are key intermediates in synthesizing chiral auxiliaries, pharmaceuticals, agrochemicals, and advanced materials like liquid crystals.[2] Chiral alcohols can be synthesized from ketones through asymmetric reduction, which can be achieved using various methods. Conventional approaches include catalysis with metal hydrides and chiral ligands,[3,4] chiral chromatography for separation,[5] or the use of chiral metal complexes for asymmetric reduction of prochiral compounds.[6] However, these traditional methods have considerable disadvantages, such as operational complexities, unwanted byproducts, high costs, and environmental hazards.[7]

The shift towards a bio-based economy has amplified interest in biocatalysis, making green chemistry increasingly significant. Biocatalytic reactions are highly efficient and carried out under very mild conditions, often solvent-free or carried out using water only. These conditions simplify purification and result in high regio- and stereoselectivity. These advantages highlight that biocatalysis is considered a greener alternative to traditional chemical methods, providing a more environmentally sustainable approach to organic synthesis.[8–10]

Baker's yeast (BY) is a widely used biocatalyst for the stereoselective reduction of ketones and ketoesters to chiral secondary alcohols.[11] Baker's yeast is useful in chiral reductions, but it has certain limitations. It leads to the generation of a mixture of enantiomers, making it challenging to get the required enantiopure product. Reductions in Baker's yeast are enzyme-dependent, requiring costly cofactors like NADH or NADPH, which necessitate the regeneration of oxidized cofactors to maintain the enzyme activity.[12]

Plant tissues have gained attention due to their inherent stereoselectivity, mild reaction conditions, and cost-effectiveness. Compared to microbial biocatalysts such as baker's yeast, plant-based biocatalysts offer simpler handling and lower operational costs, making them attractive for large-scale applications. *D. carota* (carrot) has been extensively studied for its ability to catalyze the enantioselective reduction of prochiral ketones, attributed to its rich enzymatic content, particularly alcohol dehydrogenases (ADHs).[13,14] Compared to other plant sources such as potato (*Solanum tuberosum*), apple (*Malus pumila*), and radish (*Raphanus sativus*), *D. carota* demonstrates superior enantioselectivity and broader functional group tolerance, making it an efficient catalyst for bioreduction applications.[15] This study explores the efficiency, stereoselectivity, and substrate specificity of *D. carota*, shedding light on its potential as a sustainable biocatalyst for producing enantiopure alcohols. The discussion encompasses its advantages over conventional chemical methods, its application in organic synthesis, and strategies to overcome existing challenges to enhance its industrial viability.

In the enantioselective bioreduction of prochiral ketones, oxidoreductases such as alcohol dehydrogenase (ADH)[16,17] play a key role in the transfer of hydride ions from NADH to the carbonyl group. Many plants were used in screening ADH activity, including celeriac (*Apium graveolens*), horseradish (*Armoracia lapathifolia*),[18] and arracacha roots (*Arracacia*

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xanthorrhiza).[19] Among them, *D. carota* (carrot) roots have shown a broad substrate scope and the highest enantioselectivity, making them particularly effective for biocatalytic processes.[20] Biocatalysis in synthesizing chiral secondary alcohols can be accomplished using either isolated enzymes or whole-cell microorganisms and plants.[21]

Whole-cell biocatalysts,[22] especially those using *D. carota*, offer distinct advantages over isolated enzymes. In whole cells, the enzyme and its necessary cofactors are naturally encapsulated within a microenvironment, that can perform biocatalytic action without the addition of costly external cofactors like NADH or NADPH.[23] This makes whole plant cells an economically attractive option because these are economical, biodegradable, and can under mild conditions.[24] Besides this, the use of comminuted (finely chopped) plant material for the preparation of active systems is quite simple. In addition to finely chopping *D. carota* (carrot) roots to increase surface area for biocatalytic applications, several alternative preparation techniques can enhance efficiency. Selecting specific carrot varieties, such as purple carrots, has been shown to improve biocatalytic performance in enantioselective reductions.[25] The addition of surfactants like Tween® 20 can enhance enzyme accessibility and substrate solubility, leading to increased reaction rates.[26] Biphasic systems, which improve substrate availability and product extraction, offer another effective approach to boost productivity in carrot-catalyzed reductions.[27] By optimizing these techniques, the effectiveness of carrot-based biocatalyst systems can be improved for various bioreduction applications. *D. carota* roots as a whole-cell biocatalyst offer a cost-effective, environment friendly, and efficient pathway for synthesizing enantiopure chiral secondary alcohols.[24,28]

2 Stereospecificity in reduction *via D. carota*

Highlighting sustainability, *D. carota* is one of the efficient biocatalysts for the enantioselective reduction of ketones, yielding corresponding chiral alcohols. Even though it has many enzymes, polyphenols, and carotenoids, the main enzymes responsible for bringing about these enantioselective reductions in prochiral ketones are the carbonyl reductases and dehydrogenases.[29] The reducing ability of dehydrogenase[30] primarily depends upon cofactors such as NADH or NADPH with which it binds. These cofactors, along with dehydrogenase, provide hydride ions (H^-) to the carbonyl group, facilitating its reduction. The stereochemistry of the resulting alcohol depends on which face (*Re* or *Si*) of the nicotinamide ring approaches the carbonyl group. In *D. carota*, dehydrogenase donates hydride ions to the *Re* face of ketones, consistent with Prelog's rule, leading to the alcohol with the *S* configuration[31] (Fig. 1).

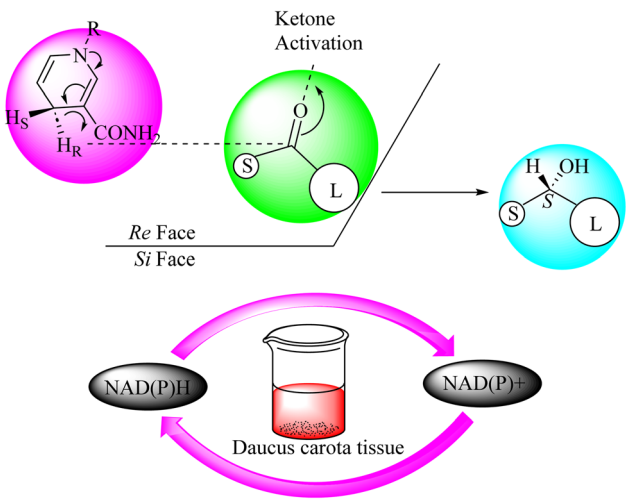


Fig. 1 *D. carota* mediated asymmetric reduction.

3 *D. carota* as a biocatalyst in organic synthesis

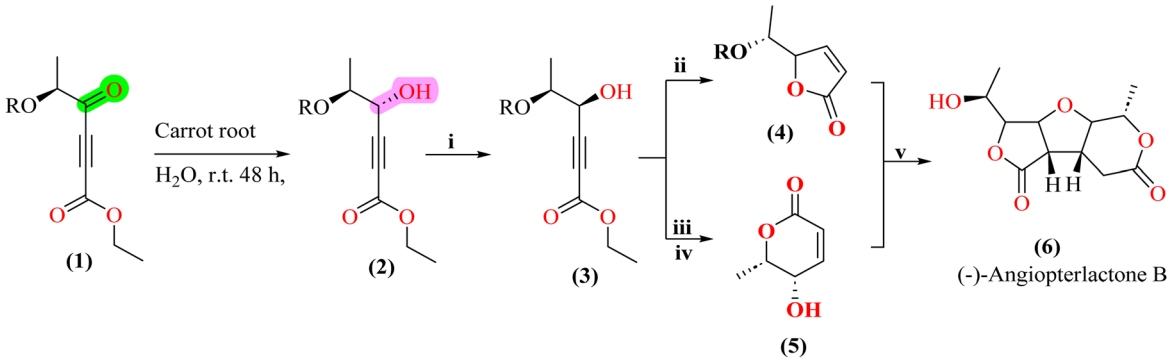
D. carota (carrot) has emerged as a very important biocatalyst in organic synthesis as a natural reducing agent with a lot of enzymes like reductases and dehydrogenases for the reduction of carbonyl compounds to optically active chiral alcohols.[32]

3.1 Reduction of ketones in the total synthesis of natural products

Bioreduction of ketones to chiral alcohols is an important method of natural product synthesis in biocatalysis. It offers high enantioselectivity, efficiency, and environment-friendly conditions.[33] Chiral alcohols are the key intermediate or active functional groups of the bioactive molecule in natural product synthesis. It adds special selectivity to the synthesis of these compounds.[34] Supporting this idea, Navnath B. Khomane[35] and colleagues demonstrated the significant role of carrot roots in natural product synthesis, particularly in the enantioselective reduction of ketones. In their work, they utilized carrot roots as a natural hydrogen source to achieve the bioreduction of a propargylic ketone (**1**), a key intermediate in synthesizing the natural product angiopterlactone B (**6**). This biocatalytic process successfully generated a stereocenter with high enantioselectivity, yielding the alcohol (**2**) in the *R* configuration[36] (Scheme 1).

Talampanel (**12**) is an active antagonist (oral) of the AMPA (alpha amino-3-hydroxy-5-methyl-4-isoxazole propionate) glutamate receptor, whose overstimulation leads to excess Ca^{2+} influx, resulting in cell damage and death.[37] It has been implicated in several neurological disorders, such as cerebral ischemia, epilepsy, ALS, and Parkinson's disease, and therefore, Talampanel (**12**) looks promising as a drug candidate. Anderson and coworkers[38] used an environmentally safe synthesis for preparing optically pure Talampanel (**12**), but it had limitations due to microbiological constraints and toxicity issues affecting solution concentration. Addressing these challenges, Alvaro *et al.* reported the reduction of 3,4-methylenedioxy phenylacetone (**8**), a key intermediate in Talampanel (**12**) synthesis, using carrot bits in water as a green alternative[39] (Scheme 2).

Many chiral amino aryl ethanols are recognized as valuable synthetic precursors for pharmaceutically important molecules.



Reagents and Conditions; i) PPh_3, DIAD, PNBA, THF, 0 °C, rt, 6 h, then K_2CO_3, MeOH, rt, 2 h,; ii) H_2, Lindlar catalyst, MeOH, rt, 10 min; iii) Ac_2O, DMAP, NEt_3, DCM, 0 °C, rt, 2 h then Zn(Cu/Ag), TMSCI, CH_3OH:H_2O (1:1), rt, 18 h; iv) PPTS, benzene, reflux, 1 h then K_2CO_3, MeOH, rt; v) NaH, Dry THF, rt, 2 h.

Scheme 1 Stereoselective synthesis of (−)-angiopterlactone B.

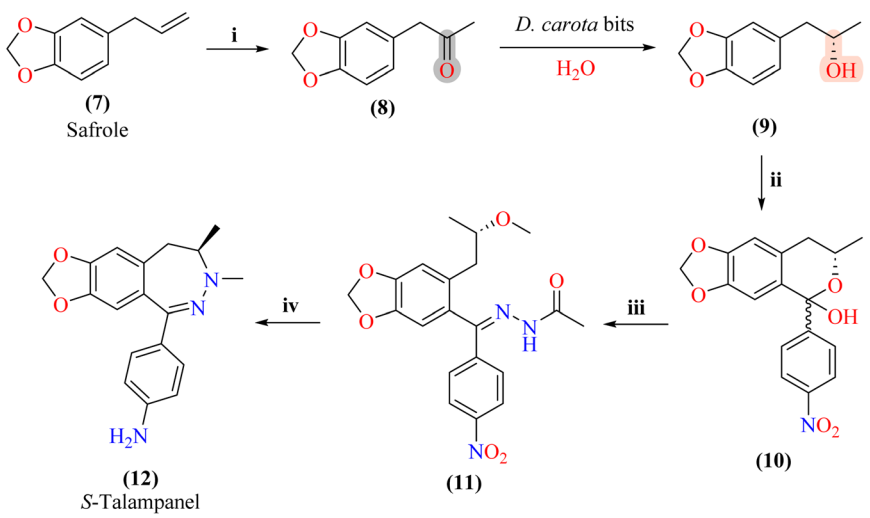
For example, (*R*)-Denopamine (**19**) contains a chiral hydroxyl group that acts as a selective β1-adrenergic receptor agonist for treating congestive heart failure.[40] Similarly, the naturally occurring bioactive molecules (*R*)-Tembamide (**18a**), and (*R*)-Angeline (**18b**) have demonstrated significant hypoglycemic activity.[41] While optically active (*R*)-Tembamide, (*R*)-Angeline, and (*R*)-Denopamine have been synthesized through various methods.[42] These approaches often involve laborious chemical or biological procedures, expensive reagents, and multi-step processes that result in low yields. Overall, J. S. Yadav *et al.* reported an efficient synthesis of (*R*)-chiral azido alcohols (**14**) key intermediates for these molecules, from α-azido aryl ketones (**13**) using *D. carota* root in an aqueous medium[43] (Scheme 3).

3.2 Bioreduction of ketones *via D. carota*

Considering the environmental sustainability, chiral alcohols have been synthesized *via* enantioselective reduction of ketones using biocatalysts. Additionally, several applications of chiral alcohols in pharmaceuticals, agrochemicals, and materials science make this procedure more effective.[44]

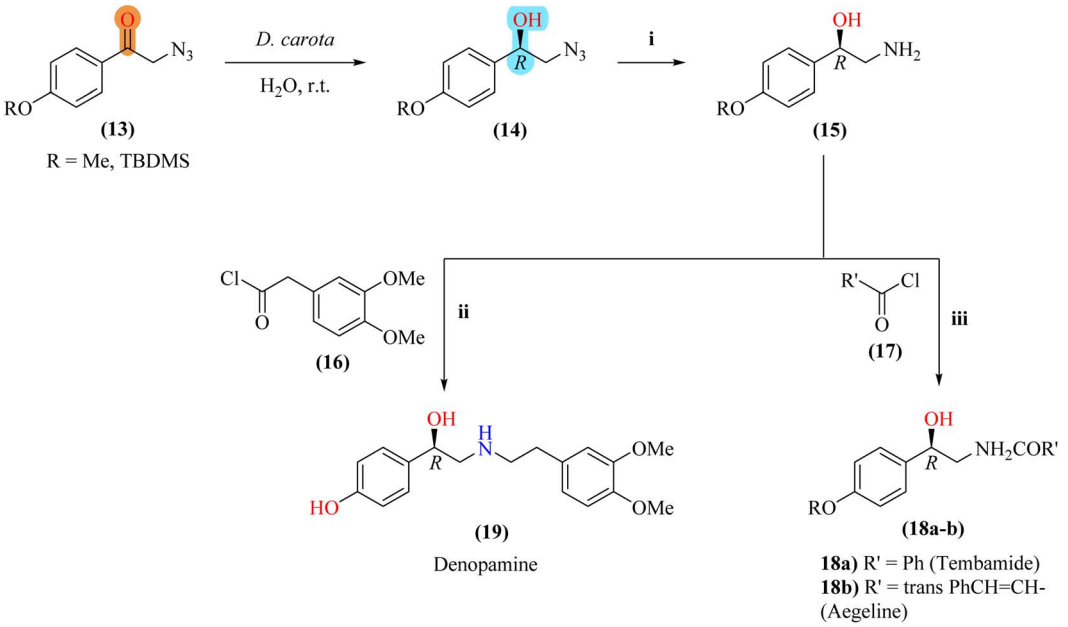
3.2.1 Enantioselective reduction of acetophenones catalyzed by *D. carota*. Chiral alcohols[45] can be synthesized using different methods like asymmetric reduction of prochiral ketones or by hydrolyzing racemic esters enantioselectively. The enzymes of plant cells, as in the case of microorganisms, possess the ability to catalyze reactions with high regio- and stereospecificity. Due to the importance of enantiomerically pure 1-phenyl ethyl alcohols as chiral auxiliaries and synthons, Wanda *et al.* carried out the reduction of ketones (**20a–c**) to optically active alcohols through biotransformation using comminuted *D. carota* root tissues[18] (Scheme 4).

(*S*)-(−)-1-(4-Chlorophenyl) ethanol[46] (**24**) is an important intermediate in synthesizing antitumor drugs that are used to treat hyperproliferative conditions such as melanoma, prostate



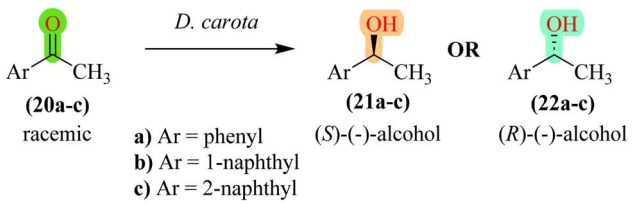
Reagents and conditions; i) *p*-benzoquinone, $PdCl_2$, MeOH/H_2O; ii) *p*-$NO_2C_6H_4CHO$, PTSA, microwave–150W, 110 °C then DDQ, H_2O/CH_2Cl_2; iii) 1) H_2NNHAc, Microwave–200W, 114 °C then CH_3SO_2Cl, Et_3N, CH_2Cl_2; iv) Cs_2CO_3, DMF, Microwave– 150 W, 70 °C then 2) Steel wool, EtOH/vinegar, Sonication.

Scheme 2 Carrot-mediated synthesis of *S*-Talampanel.



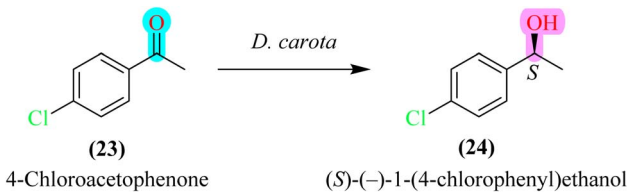
Reagents and conditions; i) Pd/C, H_2, MeOH, r.t; ii) 1) 50% aq. $NaOH/CH_2Cl_2$, Toluene, 5-10 °C then BH_3.THF/A KF/MeOH, 0 °C; iii) 50% aq. $NaOH/CH_2Cl_2$, Toluene, 5-10 °C.

Scheme 3 Stereoselective synthesis of (*R*)-denopamine, (*R*)-Tembamide, and (*R*)-Angeline.



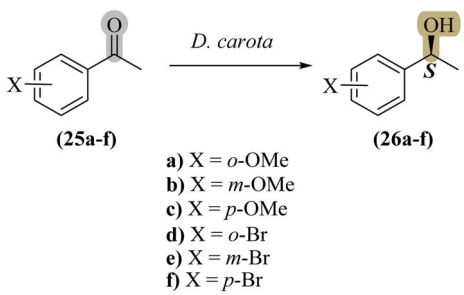
Scheme 4 Enantioselective reduction.

cancer, and breast cancer. It is also employed in the production of the antihistamine Clemastine. The compound (**24**) was synthesized using *D. carota* cells in a biphasic system with water and organic solvents like isooctane, acetonitrile, or 1,4-dioxane, which acted as exogenous reducing agents. However, the reduction rate was slower compared to when only water was used under similar conditions. The process was slow due to shifts in the lipophilic–hydrophilic balance and changes in the conformation of the globular enzyme involved in the reaction. Which affects both the activity and the enantioselectivity of the reduction process[47] (Scheme 5).

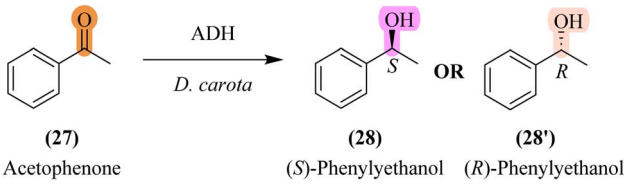


Scheme 5 Bio-reduction of 4-chloroacetophenone.

Asymmetric synthesis of chiral alcohols has been widely adopted as a method by pharmaceutical, agrochemical, flavor, and pigment industries. Over the past 25 years, numerous methods for the asymmetric reduction of carbonyl groups have been developed, with biochemical approaches using higher plants gaining significant popularity.[48] Six acetophenone derivatives (**25a–c**), including *ortho*-, *meta*-, and *para*-methoxy acetophenone, as well as *ortho*-, *meta*-, and *para*-bromoacetophenone, were utilized as substrates in biotransformation processes using comminuted *D. carota* roots. As Nakamura and Matsuda[49] conducted similar studies, bromine-substituted acetophenone derivatives undergo reduction three times faster than methoxy derivatives. The highest enantiomeric excess was observed in *meta*-methoxy and *ortho*-bromo derivatives. The enantioselectivity and reduction efficiency depend primarily on the substituent's position. This enzymatic reaction (Scheme 6) predominantly followed a stereoselective pathway, resulting in the formation of (*S*)-alcohols (**26a–f**).[50]



Scheme 6 Enantioselective reduction of methoxy- and bromo-acetophenones.

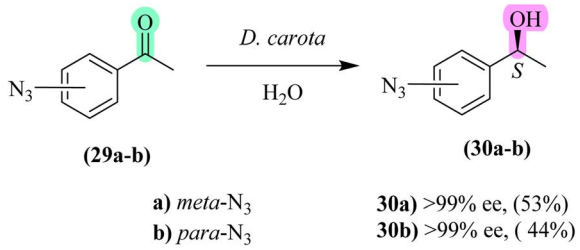


Scheme 7 Asymmetric reduction of ketones using freeze-dried carrots.

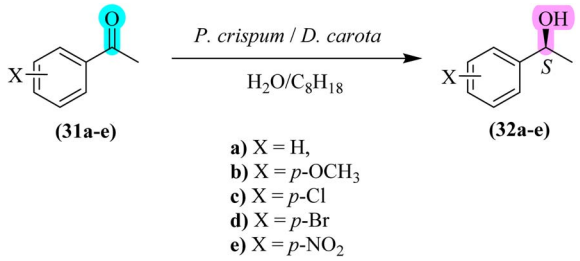
The asymmetric reduction of ketones is of great biological importance because the chiral carbinol obtained from this reaction is a valuable precursor for synthesizing numerous bioactive compounds. This study explored the bioreduction of acetophenone (ACP) (**27**) to produce enantiomerically pure (*S*)-1-phenylethanol (**28**) and (*R*)-1-phenylethanol (**28′**) using freeze-dried carrots as a natural source of alcohol dehydrogenases (ADHs)[51] (Scheme 7).

De Oliveira, C. D. S. *et al.*[52] illustrated the bioreduction of azido acetophenones (**29a–b**) by employing *D. carota* roots as a biocatalyst, producing the corresponding chiral alcohols (**30a–b**) with *S*-configurations in good to excellent yield and excellent enantiomeric excess (Scheme 8).

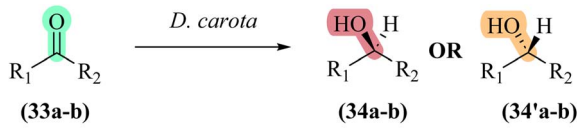
A study explored how substituents on acetophenones (**31a–e**) would affect the rate and direction of bioreduction undertaken using cells of *D. carota* and *Petroselinum crispum*. The findings indicated that both the nature of the substituents and the choice of solvents significantly affect reaction rates and product yields. Electron-withdrawing groups like -Br and -NO_2 increased the reaction rate and product yields, while the electron-donating group –OCH_3 reduced them. Furthermore, reductions in isooctane showed significantly lower rates and yields compared to those in water[53] (Scheme 9).



Scheme 8 Bioreduction of azido acetophenones.



Scheme 9 Bioreduction of substituted acetophenones.



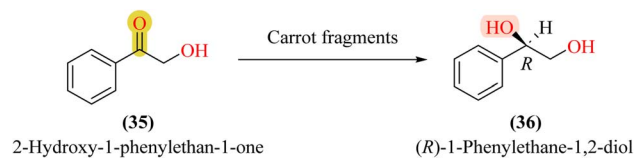
a) R_1 = Ph, R_2 = CH_3
b) R_1 = Ph, R_2 = CH_3N_3

Scheme 10 Efficient enantioselective reduction of ketones with *D. carota* root.

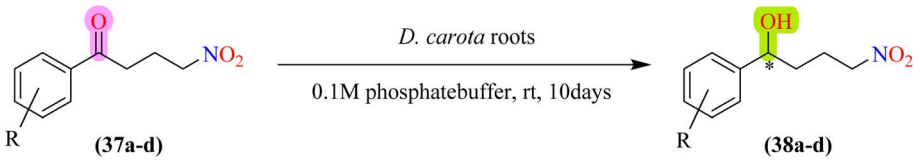
In recent years, asymmetric synthesis of chiral synthons has garnered significant attention due to their growing demand as precursors in drug and agrochemical development. While various chemical and biocatalytic reductions have been reported, challenges persist in achieving enantioselectivity. However, product recovery can be complex, and enzyme activity often requires costly cofactors (NADH, NADPH) with regeneration steps. In view of this consideration, the reduction of various prochiral ketones[54] (**33**), such as cyclic ketones, acetophenones, β-ketoesters, azido ketones, and aliphatic ketones, was carried out using *D. carota* root, resulting in chiral intermediates for the synthesis of chiral drugs and agrochemicals[12] (Scheme 10).

Chiral aryl vicinal diols[55] with specific functional groups serve as the intermediates for synthesizing agrochemicals, pharmaceuticals, and pheromones. The biocatalytic reduction of carbonyl compounds into enantiopure secondary alcohols offers a highly chemo-, regio-, stereoselective, and non-toxic method for establishing chirality. In support of this, the asymmetric reduction of prochiral α-hydroxy aromatic ketones[56] (**35**) was achieved using carrot (*D. carota*) cells, resulting in chiral aryl vicinal diols predominantly in the (*R*)-configuration. The reaction, carried out with small pieces of fresh carrot roots in phosphate buffer or distilled water, produced (*R*)-aryl vicinal diols (**36**) with good yields and excellent enantiomeric excess (ee) (Scheme 11).

Inspired by the remarkable selectivity demonstrated in reducing acetophenones and other ketones using *D. carota* (carrot) roots, Dina *et al.* extended this approach to reduce γ-nitroketones. Their goal was to find a more accessible and cost-effective alternative to the traditionally used baker's yeast, which often lacks enantioselectivity. By utilizing *D. carota* roots in an aqueous medium, a series of aromatic γ-nitroketones (**37a–d**) was successfully reduced to their corresponding (*S*)-alcohols, achieving enantiomeric excesses (ee) between 73% and 100%. This biocatalytic method not only enhanced the scope of enantiopure γ-nitroalcohols but also provided valuable



Scheme 11 Asymmetric reduction of α-hydroxy aromatic ketones.



a) R = H, **b)** R = *o*-Br,
c) R = *o*-OMe, **d)** R = *m*-OMe,

Scheme 12 Reduction of γ-nitro ketones using *D. carota* roots.

intermediates for the synthesis of complex natural products, offering a green and sustainable alternative in asymmetric organic synthesis[57] (Scheme 12).

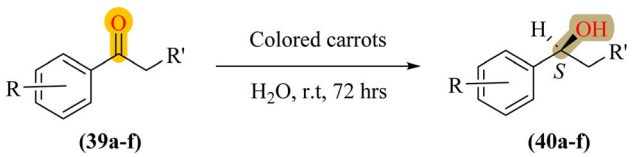
In organic synthesis, chiral alcohols serve as building blocks for producing chiral auxiliaries, natural products, and pharmaceuticals. A green method for obtaining chiral alcohols is the biocatalytic asymmetric reduction of ketones,[58] where carrot root pieces have been successfully employed. This reaction typically occurs under mild conditions, using water as a solvent at room temperature, and offers a simpler workup compared to other biocatalytic systems. A comparative study of the biocatalytic properties of purple, yellow, and orange carrots against substituted acetophenones (**39a–f**) revealed that purple carrots, an ancient variety, exhibited superior reducing activity[25] (Scheme 13).

D. carota exhibits effective ketoreductase activity, cost efficiency, and ease of availability, making it a reliable and user-friendly biocatalyst for enantioselective ketone reductions. However, its long reaction time, high biocatalyst demand, and low substrate concentration pose challenges for large-scale applications. To minimize the disadvantages of bioreduction, Tween® 20 was used as a surfactant to enhance the enantioselective reduction of acetophenone derivatives (**41a–e**) catalyzed by *D. carota*. Tween® 20 significantly improved conversion and enantiomeric excess (ee) in the reduction of acetophenones by enhancing substrate solubility in water. Additionally, it influenced the enantiomeric ratio and enzyme activity.[26] (Scheme 14).

In bioreduction processes, the surfactant Tween 20® enhances the solubility of hydrophobic organic substrates, which could improve the conversion rate of the reaction. By increasing solubility, the substrate disperses more uniformly throughout the reaction medium making it more accessible to the enzyme's active sites. This dispersion minimizes the formation of substrate aggregates that can limit enzyme–substrate interactions and facilitates the catalytic process. Enzymes can operate under optimal conditions, leading to faster and more complete substrate conversion. Studies have shown that this improved substrate availability directly correlates with increased reaction rates and overall process efficiency.[26]

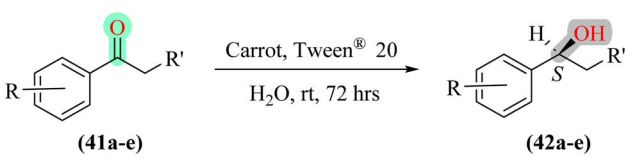
Besides that, the alternative substances to Tween 20® can be used to enhance reaction efficiency and minimize the amount of biocatalyst required. Non-ionic surfactants like Triton X-100® and Tween 80® show similar benefits by improving substrate solubility and enzyme accessibility.[59] Poloxamer 188, commonly used for protein stabilization, can also be used. Cyclodextrins, which are cyclic oligosaccharides are alternatives for enhancing solubility and enzyme stability in biocatalytic systems. The selection of an appropriate surfactant depends on factors such as enzyme compatibility, cost-effectiveness, and its impact on overall reaction performance.[60]

3.2.2 Reductions of alkyl–aryl ketone catalyzed by *Daucus carota*. The chirality transfer from an optically active catalyst to a prochiral reagent is one of the most intriguing and challenging transformations in the field of chemistry. Biocatalysts, with their homochiral nature, excel at providing chirality, as demonstrated by the well-known Baker's yeast[61] (BY) reduction of ketones. The common carrot (*D. carota*) has emerged as a reliable alternative for reducing aryl and aliphatic ketones. The continuous demand for optically pure building blocks, essential in developing selective drugs and materials with defined properties, underscores the importance of such biocatalytic processes. Particularly, heterocyclic compounds,



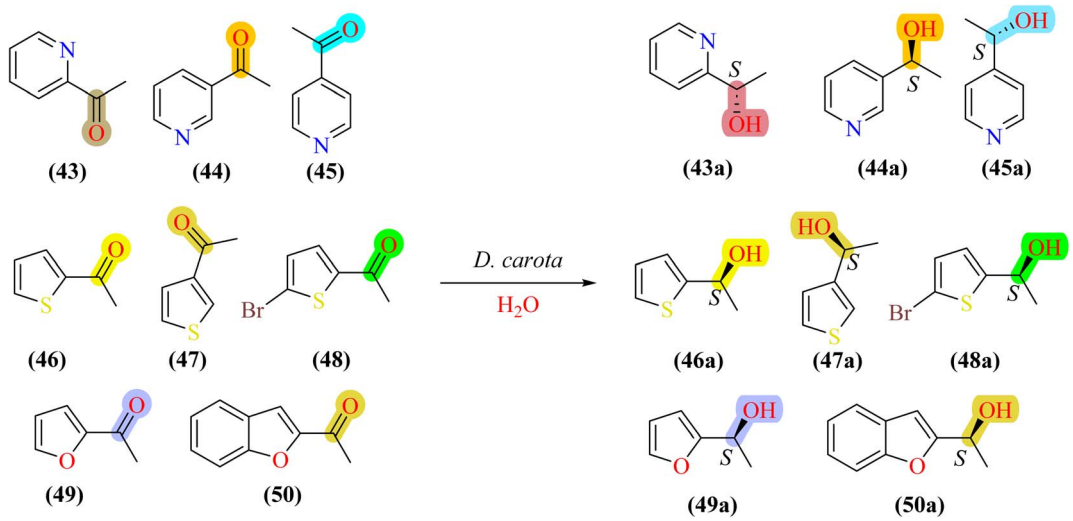
a) R = H, R' = H
b) R = 4-OMe, R' = Br
c) R = H, R' = Br
d) R = 2-Br, R' = H
e) R = 3-Br, R' = H
f) R = 4-Br, R' = H

Scheme 13 Enantioselective reduction of acetophenones.



a) R = 4-Br, R' = CH_3
b) R = H, R' = Br
c) R = 2-Br, R' = CH_3
d) R = 3-Br, R' = CH_3
e) R = 2-NH_2, R' = CH_3

Scheme 14 Enhanced bioreduction of acetophenones.



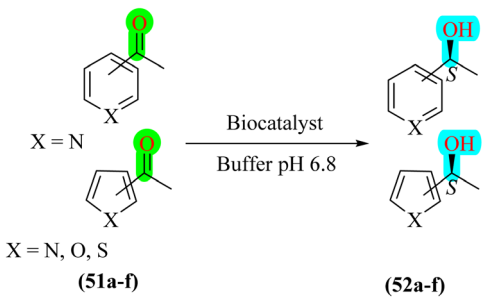
Scheme 15 Enzymatic synthesis of chiral heteroaryl alcohols.

frequently present in bioactive molecules, benefit from this approach. The reduction of methyl heteroaryl ketones (**43–50**) using *D. carota* roots in water has been reported as a green method for producing a small library of optically enriched alcohols (**43a–50a**), offering a sustainable route to enantiopure building blocks[62] (Scheme 15).

Nitrogen, oxygen, or sulfur in the rings of heterocyclic aromatic compounds[63] provide key structural elements in a large number of natural and synthetic biologically active products. Heterocycles like acetyl-pyridines are known as aromatic components in perfumes, foods, and smoking suppressants.[64] Chiral heteroaryl alcohols serve as crucial intermediates in synthesizing biologically active molecules and also as chiral ligands or auxiliaries in asymmetric addition reactions. Asymmetric reduction of heteroaryl methyl ketones is a straightforward approach, though many chemical and biological methods face limitations such as long incubation times, low substrate loading, and poor yields. In this study, the bioreduction of substituted heteroaryl ketones (**51a–f**) using *D. carota* was explored, with the dehydrogenase enzymes in *D. carota* selectively reducing these ketones to chiral secondary alcohols (**52a–f**) in good yields and high enantioselectivity[65] (Scheme 16).

The quinoxaline nucleus served as a vital scaffold in the synthesis of pharmacophores with a wide range of pharmacological activities, including anti-bacterial,[66,67] anti-viral,[68,69] anti-HIV,[70] anti-malarial,[71,72] anti-cancer,[73] anti-tubercular,[74] and anti-leishmanial[75] properties, along with potential applications in neurological disorders. Exploiting the biotransformation capabilities of *D. carota*, which contain alcohol dehydrogenase enzymes that selectively reduce keto compounds, quinoxaline ketones (**53a–d**) were effectively transformed into chiral alcohols. This reduction, in alignment with green chemistry principles, utilized alginate-immobilized *D. carota* homogenate beads as a biocatalyst. The resulting chiral alcohols (**54a–d**), characterized through X-ray crystallography, exclusively exhibited the *R*-configuration in high yields and exceptional enantioselectivity (98%)[76] (Scheme 17).

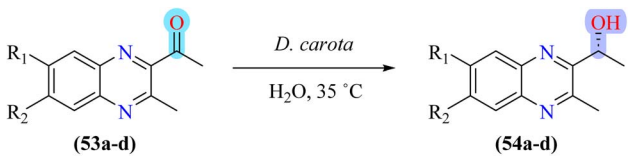
Biotransformation proposes a greener and more viable choice to conventional chemical processes in organic synthesis. One of the earliest examples is the reduction of ketones and ketoesters to alcohol using baker's yeast. Later, it was found that various plants could also reduce prochiral compounds with



a) 2-acetyl pyridine
b) 3-acetyl pyridine
c) 4-acetyl pyridine
d) 2-acetyl pyrrol
e) 2-acetyl thiophene
f) 2-acetyl furan

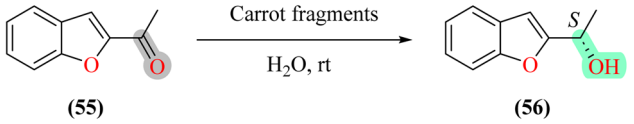
a) 2-(hydroxy acetyl) pyridine
b) 3-(hydroxy acetyl) pyridine
c) 4-(hydroxy acetyl)pyridine
d) 2-(hydroxy acetyl) pyrrol
e) 2-(hydroxy acetyl) thiophene
f) 2-(hydroxy acetyl) furan

Scheme 16 Asymmetric reduction of various substituted heteroaryl ketones.



a) R_1 = H, R_2 = H
b) R_1 = Cl, R_2 = NO_2
c) R_1 = F, R_2 = Cl
d) R_1 = CH_3, R_2 = CH_3

Scheme 17 Synthesis of novel chiral quinoxaline alcohols.



(55) (56)

Scheme 18 Reduction of benzofuran-2-yl methyl ketone with carrot.

different degrees of enantioselectivity, with *D. carota* (carrot) roots consistently yielding superior results. Utilizing the biological importance of the benzofuran moiety, *D. carota* roots were used to reduce benzofuran-2-yl-methyl ketone (**55**) to its chiral alcohol (**56**) in aqueous medium, highlighting the efficiency of plant-based biocatalysts in enantioselective synthesis[27] (Scheme 18).

Plant-based biocatalysts offer a sustainable and environmentally friendly alternative to conventional chemical catalysts. These biocatalysts have advantages such as high selectivity, broad substrate acceptance, and operation under mild conditions.[77,78] Their ability to catalyze reactions with chemo-, regio-, and stereoselectivity makes them important in pharmaceutical and chemical synthesis, reducing the need for protection and deprotection steps.[79] The renewable aspect of these biocatalysts fits perfectly with the principles of green chemistry, helping to reduce toxic waste and energy use. Plant-based biocatalysis faces challenges like limited availability, lower stability, and issues with large-scale production, which makes it tough to be widely used in industry.[80] Plant-derived enzymes need to be extracted and purified from their natural sources, which can result in variations in both enzyme activity and yield. Substrate and product inhibition can hinder the efficiency of reactions, necessitating further optimization strategies. Despite these challenges, recent advancements in enzyme engineering and immobilization techniques show promise for improving the industrial use of plant-based biocatalysts, positioning them as a strong contender for sustainable chemical processes.[81]

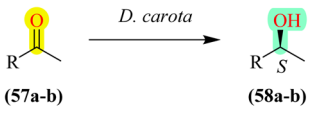
Plant-derived components, like hemicellulose and lignin, hinder enzymatic bioreduction by creating structural and chemical barriers that restrict enzyme accessibility, stability, and activity. Hemicellulose wraps around cellulose microfibrils, further limiting the enzymes' ability to do their job.[82] On the other hand, lignin, which is a complex polyphenolic polymer, adds mechanical strength and hydrophobic properties, making it harder for enzymes to penetrate. It has aromatic rings and hydroxyl groups that interact with enzymes, creating hydrophobic interactions and hydrogen bonds. Unfortunately, this can cause enzymes to become deactivated and bind in ways that aren't productive. As a result, it is often required to use higher amounts of enzymes to achieve effective bioreduction.[83] When lignin breaks down, it releases phenolic compounds like vanillin and syringaldehyde, as well as furfural and hydroxymethylfurfural (HMF) from the breakdown of hemicellulose. These compounds can hinder enzyme activity by messing with the active sites and interfering with reactions that depend on NADH and NADPH.[84] Acidic degradation products, such as acetic acid, can change the microenvironments of enzymes, leading to denaturation or a decrease in their activity.

On the other hand, oligosaccharides derived from hemicellulose boost ionic strength, which can interfere with the interactions between enzymes and their substrates.[85] To mitigate these challenges, many strategies can be employed, including pretreatment methods (acid, alkaline, oxidative, or enzymatic) to remove lignin and hemicellulose[86] and supplementing cofactors like NADH to counteract redox imbalances.[87] Implementing these approaches can enhance enzyme efficiency and improve the overall bioreduction process.

3.2.3 Reductions of alkyl ketone catalyzed by *D. carota*. Enantiomerically pure secondary aliphatic alcohols, such as (2*S*)-(+)-heptan-2-ol and (2*S*)-(+)-octan-2-ol, serve as key intermediates in drug synthesis and are widely used in the agrochemical and perfume industries. These optically pure alcohols were obtained *via* the bio-reduction of their respective ketones, heptan-2-one (**57a**), and octan-2-one (**57b**), catalyzed by *D. carota* cells in water at room temperature over 144 hours. The process yielded (2*S*)-(+)-heptan-2-ol (**58a**) with a 67% yield and 90% enantiomeric excess (ee), and (2*S*)-(+)-octan-2-ol (**58b**) with a 50% yield and 87% ee[88] (Scheme 19).

3.2.4 Reductions of cyclic alkyl ketone catalyzed by *D. carota*. Chiral heterocyclic alcohols serve as the key building blocks for various bioactive compounds, including sulopenem,[89] thiarabine,[90] and ibrutinib.[91] The asymmetric synthesis of these compounds through non-enzymatic methods is usually considered to demonstrate low selectivity, making enzymatic methods more promising for achieving high enantioselectivity. Naira V. M. and Alvaro T. O. reported a bioreduction of 5-membered heterocyclic ketones (**59a–d**) using carrots, a green and economical biocatalyst[92] (Scheme 20).

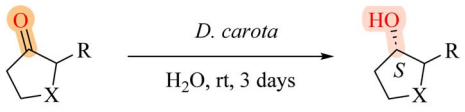
Five- and six-membered nitrogen-containing heterocyclic compounds with a quaternary stereogenic center at C3, in either (*R*)- or (*S*)-configuration, are crucial as building blocks for numerous bioactive scaffolds. Notably, they are used in the synthesis of compounds like Capromorelin,[93] an orally active



(57a-b) (58a-b)

a) R = C_5H_{11}
b) R = C_6H_{13}

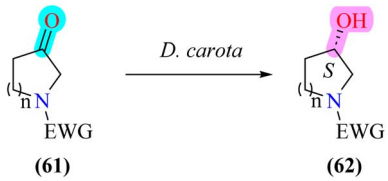
Scheme 19 Bio-reduction of heptane-2-one and octan-2-one.



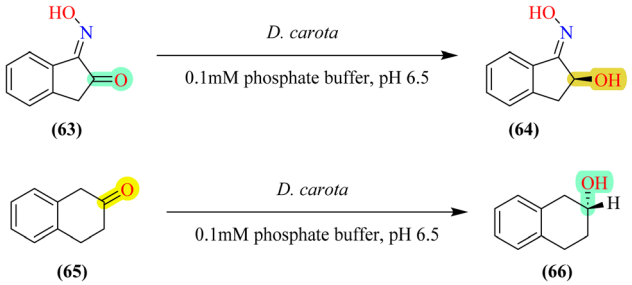
(59a-d) (60a-d)

a) X = S, R = H
b) X = O, R = CH_3
c) X = N, R = H
d) X = O, R = H

Scheme 20 Enantioselective synthesis of 5-member heterocyclic secondary alcohols.



Scheme 21 Reduction of cyclic amino ketones.



Scheme 22 Asymmetric bio-reduction of indanone and tetralone.

small molecule that mimics ghrelin, acting as a potent and selective GHS-R agonist to stimulate appetite and GH secretion, as well as in the synthesis of isonitramine[94] and sibirine.[95] In support of this, Romain L. *et al.* reported the efficient reduction of six-membered N-containing β-ketoesters and five-membered amino ketones (**61**) to their corresponding chiral alcohols (**62**) using *D. carota* (carrots), achieving excellent yields and high enantiomeric excess (ee)[96] (Scheme 21).

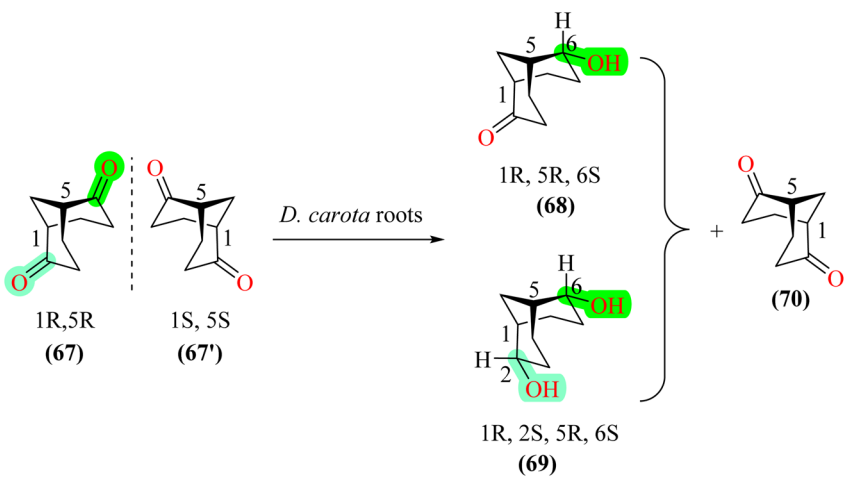
Non-racemic chiral alcohols have been obtained through the asymmetric reduction of prochiral ketones using a variety of chemical and biological methods. However, achieving high yields and enantiomeric excess remains challenging due to the reliance on costly chiral reagents. To tackle this issue, the asymmetric bio-reduction of indanone (**63**) and tetralone (**65**) was carried out using *D. carota* (carrot) roots, yielding the corresponding enantiomerically pure (*S*)-alcohols[97] (Scheme 22).

The bicyclo [3.3.1] nonane[98,99] framework is very abundant in natural products, serving as an excellent scaffold for the synthesis of many bioactive compounds. Notably, the transformation of the bicyclo [3.3.1] nonane system into the bicyclo [5.3.1] undecane ring system represents a crucial step in taxoid synthesis.[100] Bicyclo [3.3.1] nonane-2,6-dione (**67–67′**) was utilized in the synthesis of chiral compounds and the determination of their chiroptical properties. That was quite significant because most bioactive natural products with this moiety show optical activity.[101–103] A stereoselective reduction of the racemic diketone was carried out using plant enzymes. The unreacted (+)-enantiomer was extracted from the reaction mixture with an organic solvent, while the (−)-enantiomer underwent enzymatic reduction, yielding 6-hydroxybicyclo [3.3.1]nonane-2-one (**68**) as the reaction product[99] (Scheme 23).

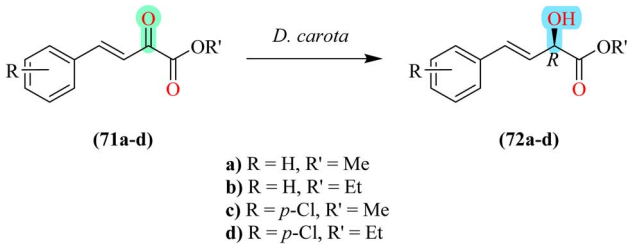
3.3 Chemoselective reductions

Chiral-hydroxy carboxylic acids and their esters are used as a valuable precursor for the synthesis of many bioactive compounds.[104–107] Multifunctional chiral-hydroxy carboxylic acid esters, *e.g.* chiral-hydroxy-but-3-enoic carboxylic acid esters are of great importance due to their ability to form new chiral centers and undergo stereoselective transformations of the adjacent alkene influenced by C-2 hydroxyl group. Both biocatalytic as well as chemical methods have been employed for the synthesis of optically pure-hydroxy-but-3-enoic carboxylic acid esters. In particular, asymmetric reduction of 4-aryl-oxo-but-3-enoic carboxylic acid esters (**71a–d**) was achieved using *D. carota* tissue culture cells, yielding 4-aryl-hydroxy-but-3-enoic carboxylic acid esters (**72a–d**) in high enantiomeric excess and conversion[108] (Scheme 24).

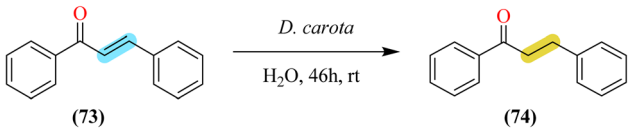
Dihydrochalcones, found in numerous biologically active natural products such as nothofagin, trilobatin, phlorizin, and glycyphyllin,[109] play a significant role in various applications. They are particularly used as food additives due to their remarkable sweetness. Notably, trilobatin (TLB), a natural



Scheme 23 Reduction of racemic bicyclo [3.3.1] nonane-2,6-dione.



Scheme 24 Stereoselective reduction of 4-aryl-2-oxo but-3-enoic carboxylic esters.

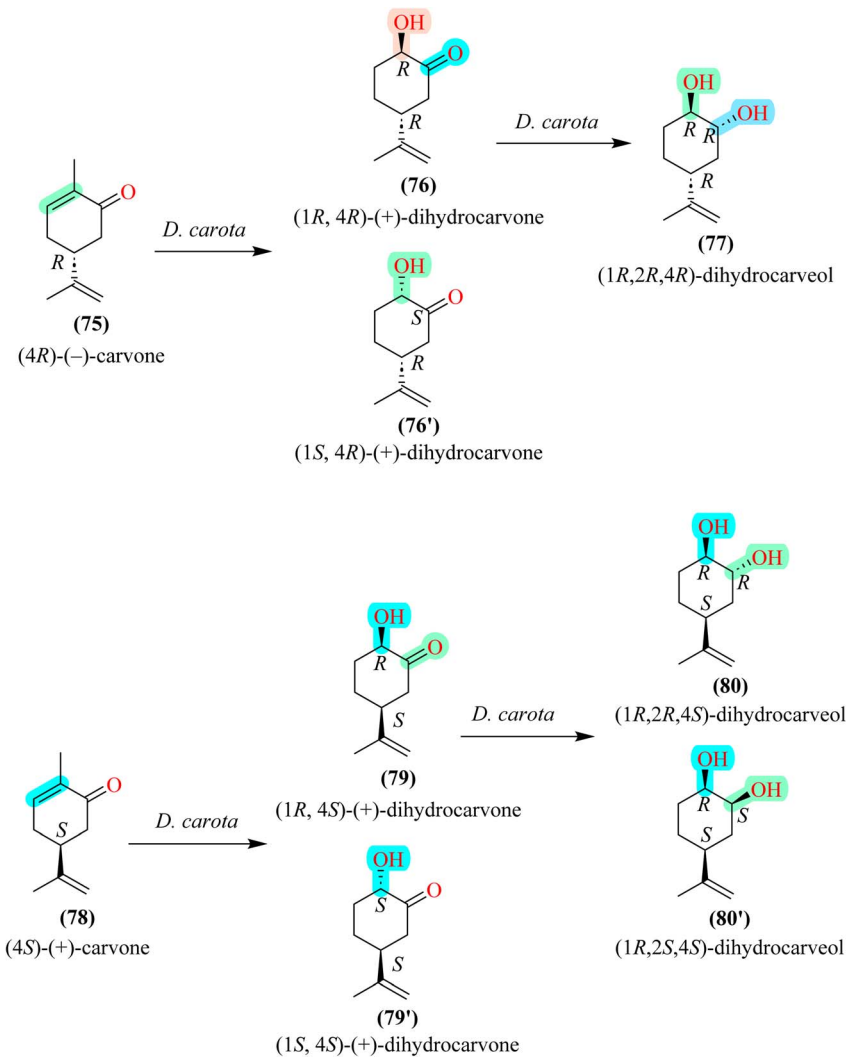


Scheme 25 Chemoselective reduction of conjugated double bonds.

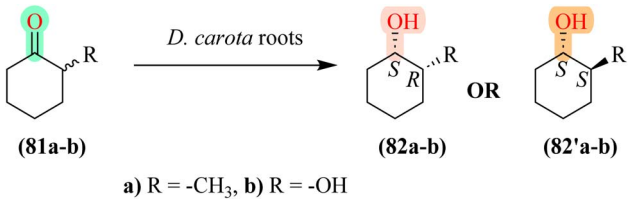
dihydrochalcone, demonstrates excellent anti-type 2 diabetic activity.[110] As a result of growing recognition of dihydrochalcone's health benefits, an increased interest in the synthesis of dihydrochalcone derivatives has been observed. Given the significance of biocatalysis in organic synthesis, the biocatalytic reduction of conjugated olefins (**73**) to dihydrochalcones (**74**) using *D. carota* roots under mild conditions has been reported. This reaction demonstrates high selectivity, favoring 1,4-reduction over 1,2-reduction in chalcones, a preference attributed to the involvement of ene-reductase enzymes[111] (Scheme 25).

3.4 Reduction of diastereomeric ketones

Carvone is a well-known example of an odoriferous compound where the two enantiomers exhibit distinct scents.[112] The (4*R*)-(−)-carvone, characterized by a minty fragrance, is a key component of the essential oils of *Mentha viridis* and *Mentha spicata*, alongside dihydrocarveol and *cis*-dihydrocarvones.[113] In contrast, the (4*S*)-(+)-carvone has a caraway scent found in the



Scheme 26 Reduction reactions of (4*S*)-(+)-carvone and (4*R*)-(−)-carvone.



Scheme 27 Preparative synthesis of chiral alcohols.

essential oils of *Carum carvi* L. and *Anethum graveolens* L. As a fragrant compound, carvone is widely used in the production of cosmetics, toothpaste, and chewing gum.[114] Beyond its aromatic properties, carvone has also displayed notable biological activities, including anticancer and free radical scavenging effects,[115] and showed potential as an inhibitor of acetylcholinesterase (AChE).[116] Enzymatic reductions involve the transfer of reducing cofactors, with the enzyme distinguishing between substituents around the carbonyl group, resulting in enantioselectivity when the products are chiral. In the biotransformation of both enantiomers (Scheme 26) of carvone by enzymatic systems from selected plants (*D. carota*), dihydrocarvones were obtained.[117]

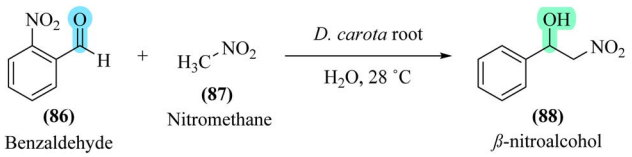
Significant focus has been placed on enantioselective syntheses of enantiomerically pure compounds or chiral synthons, which are increasingly sought after for the advancement of modern pharmaceuticals and agrochemicals.[118] The low cost, ready availability of the biocatalyst, and simplicity of the reaction conditions make biotransformation highly promising for large-scale production of valuable chiral alcohols.[119] The enzymatic reduction of *trans*-2-methylcyclohexanone (**81a–b**) using fresh carrot root as a biocatalyst proceeded in a completely diastereoselective manner, yielding an equal 1 : 1 mixture of enantiomerically pure 1*S*, 2*R*- and 1*S*, 2*S*-2-methylcyclohexanol (**82′a–b**). In contrast, the reaction performed on racemic 2-hydroxy cyclohexanone produced a 1 : 2 mixture of 1*S*, 2*R* (**82a–b**) and 1*S*, 2*S*-1,2-cyclohexane diol[32] (Scheme 27).

Enol acetate (**83**) underwent hydrolysis with *D. carota* cells in water, yielding a substituted ketone (**84a**). Subsequent asymmetric protonation under identical conditions produced cyclohexanone (**84b**) in 89% yield with 45% ee, favoring the (*S*)-enantiomer. A diastereospecific reduction of the enantioenriched cyclohexanone (**84b**) selectively targeted the *Re*-face, affording cyclohexanol (**85**) with 75% yield and 100% ee after 24 hours at room temperature, highlighting the efficiency of this domino process[20] (Scheme 28).

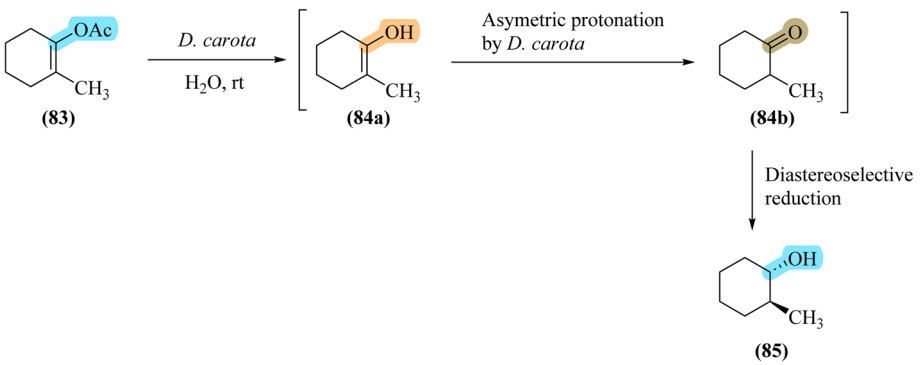
3.5 Miscellaneous

The Henry reaction was first reported in 1895, involves the reaction of aldehydes with nitroalkanes to produce β-nitro alcohols, and has garnered significant interest in medicinal chemistry due to its applications in synthesizing pharmaceutical agents, natural product precursors, and other bioactive compounds. However, using conventional bases in this reaction often leads to unwanted side products along-with the desired β-nitro alcohols. While metal and organocatalysts have been introduced to overcome this issue, their toxicity and high costs remain challenges. To address these concerns, a greener approach was developed using *D. carota* root enzymes, which efficiently catalyzed the Henry reaction of 2-nitrobenzaldehyde (**86**) and nitromethane (**87**), yielding β-nitro alcohol (**88**) in 93% yield under mild conditions (phosphate buffer, pH 7, 28 °C, 8 hours)[120] (Scheme 29).

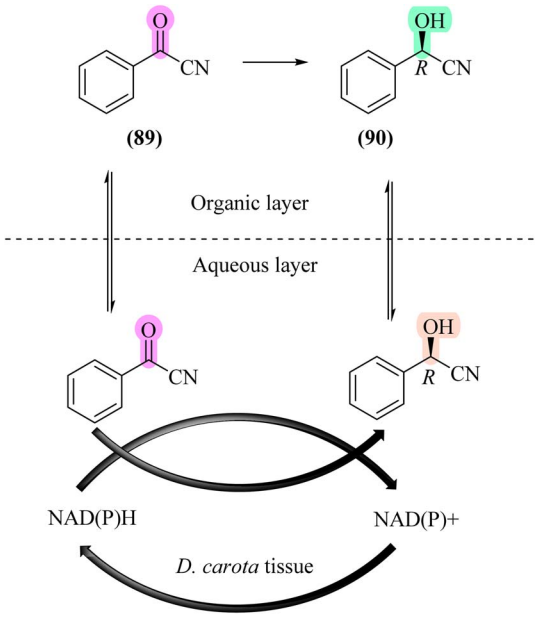
Biotransformation processes using plant tissues are typically conducted in aqueous media, but their effectiveness is limited due to the low solubility of pure substrates in water, making scale-up to bioreactors unfeasible. To address this, Schewe *et al.* suggested the use of biphasic systems, which offer several advantages, including improved substrate solubility, easier product removal, overcoming unfavorable equilibria, and suppression of side reactions. Enantiomerically pure cyanohydrins (**90**), important intermediates in organic synthesis, were produced using *D. carota* as a biocatalyst in a biphasic system using dibutyl phthalate as a co-solvent due to its hydrophobic nature, thermal stability, resistance to photooxidation, and



Scheme 29 *D. Carota* meditated on Henry's reaction.



Scheme 28 *D. carota* mediated hydrolysis of enol acetate.

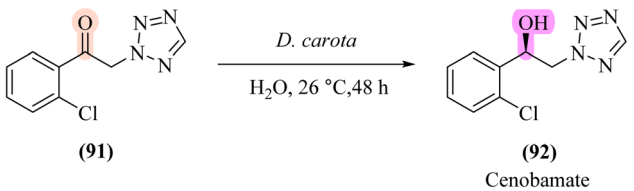


Scheme 30 Biotransformation using a biphasic system.

cost-effectiveness. Under optimized conditions, the bio-reduction productivity of alcohol increased from 0.58 to 1.36 g L^{-1} (ref. 121) (Scheme 30).

Cenobamate (**92**) is a recently introduced medication for treating partial-onset seizures in adults. While the enantioselective synthesis of β-heteroaryl amino alcohols has been achieved through Ru-catalyzed asymmetric hydrogenation, many of these methods rely on costly and environmentally harmful chiral reagents, which limits their large-scale application. A more sustainable and efficient approach for producing cenobamate has been developed, utilizing a bio-reduction of β-ketotetrazole (**91**) with whole *D. carota* plant cells, yielding 70% and >99% enantiomeric excess (ee). The corresponding β-hydroxytetrazole (**92**) was isolated with a 60% yield and >98% ee. This is the first report of a biocatalytic reduction of β-ketotetrazole (**91**) using plant enzymes from *D. carota* root cells, that shows outstanding enantioselectivity (Scheme 31).[122]

Wen-JuBai *et al.* has systematically explored the scope of carrot-mediated reduction of Keto-derived nitrogen-heteroaromatics. The five- and six-membered nitrogen-containing heteroaromatic compounds most commonly found in FDA-approved small-molecule drugs were chosen for evaluation. A methyl group was used as a substitute for more complex ketone substituents, as outlined in the basic substrate scope.



Scheme 31 Enantioselective synthesis of β-heteroaryl alcohols.

Notably, the thiazole-containing drugs often feature two substituents at the C2- and C4-positions of the thiazole ring, hence substrates with similar substitution patterns were tested. After the reduction of thiazoles (**93a**) substituents at the C2- and C4-positions, the alcohols (**93a′**) were obtained in yields of 78–95% with >99 : 1 enantiomeric ratio. However, no reactivity was observed for ketones containing imidazole (**93d**) or indole (**93b**) groups, and only a trace conversion was seen with the tetrazole-containing ketone (**93c**). Following the substitution patterns seen in benzimidazole-containing drugs, both mono- and di-substituted substrates (**93e**) at the most commonly observed positions were tested. These substrates performed well, resulting in alcohols with yields of 73–89% and >99 : 1 enantiomeric ratio (Scheme 32).[123]

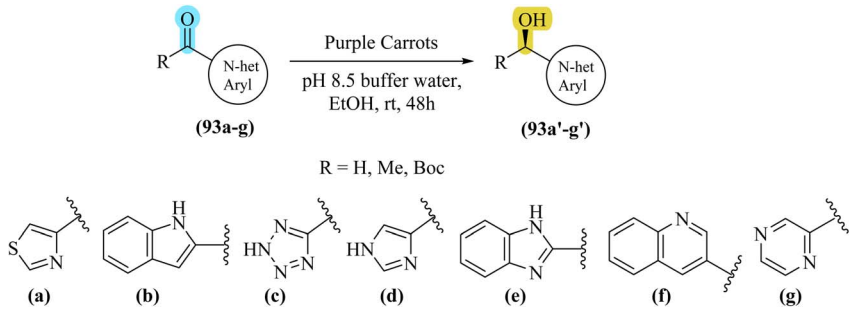
Due to the importance of enantiomerically pure 1-phenyl ethyl alcohols as chiral auxiliaries and synthons, Wanda *et al.* carried out the hydrolysis of esters (**94a–c**) of 1-phenyl ethyl analogs to optically active alcohols through biotransformation using comminuted *D. carota* root tissue (Scheme 33).[18]

The biocatalytic potential of *D. carota* roots has emerged as a powerful tool in the sustainable production of chiral intermediates, which are crucial for synthesizing bioactive compounds. These enzymatic reactions proceed under mild, aqueous conditions, and eliminate the need for toxic reagents, heavy metals, or harsh reaction conditions, marking a significant advancement in green chemistry.

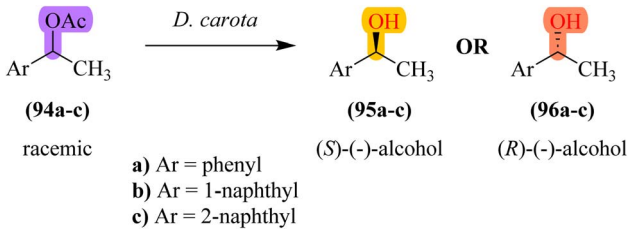
One of the most notable contributions of *D. carota* is its ability to catalyze the asymmetric reduction of prochiral ketones, such as acetophenones, and other related compounds. These reactions result in the production of chiral alcohols with high enantiomeric purity, which are essential for the synthesis of a variety of bioactive molecules. *D. carota* catalyzes the production of (*S*)-alcohols, key intermediates in pharmaceutical and agrochemical synthesis. Carrot roots also play an important role in the synthesis of (*R*)-chiral azido alcohols, essential for bioactive compounds like Tembamide, Angeline, and Denopamine.

The versatility of *D. carota* roots is further demonstrated in their ability to catalyze the reduction of a diverse range of substrates, including heteroaryl and quinoxaline ketones, as well as β-ketoesters and α-hydroxy aromatic ketones. These reactions enable the production of optically pure intermediates for the synthesis of drugs, fragrances, and other bioactive compounds, highlighting the potential of carrot-derived biocatalysts for use in industrial applications. *D. carota* can be effectively used in a biphasic system, in combination with co-solvents such as dibutyl phthalate, to enhance substrate solubility and increase the scalability of reactions like cyanohydrin formation. This approach significantly improves reaction yields and efficiency, demonstrating the scalability of carrot root catalysis for larger-scale industrial applications. The ability to use such systems under mild conditions further emphasizes the eco-friendly nature of this biotransformation, contributing to the growing demand for green and sustainable chemical processes.

D. carota is involved in the reduction of conjugated olefins to dihydrochalcones, using its ene-reductase enzymes. This



Scheme 32 Carrot-mediated reduction of keto-derived nitrogen heteroaromatics.



Scheme 33 Carrot-mediated hydrolysis of esters.

biocatalytic reaction offers a mild, efficient method for producing valuable dihydrochalcone derivatives, which have applications in the food, cosmetic, and pharmaceutical industries. Similarly, the selective reduction of carvone enantiomers by *D. carota* results in dihydrocarvones, which possess distinct biological and aromatic properties, expanding the utility of carrot-derived biocatalysts in the synthesis of fragrance compounds. Moreover, *D. carota* root enzymes contribute to stereoselective reductions with cofactor recycling, ensuring high enantiomeric excess and excellent yields in various green chemistry applications. This characteristic makes carrot-based biocatalysis a promising approach for large-scale industrial processes, offering a sustainable and cost-effective alternative to traditional synthetic methods.

Plant-derived biocatalysts have revealed significant potential in the asymmetric reduction of ketones, yielding optically active alcohols with a high enantiomeric excess (ee). *Cynara scolymus* L., for instance, has been used to asymmetrically reduce various acetophenones, including 4′-haloacetophenones and 4′-nitroacetophenone, achieving (ee) values from 71.4% to 96.5% over a period of 2 to 4 days. *Phoenix dactylifera* L., commonly known as the date palm, has shown a remarkable ability to convert acetophenone derivatives into chiral alcohols. Reaction yields vary from 52.0% to 77.2%, with enantiomeric excess (ee) values ranging from 60.0% to 89.0%. This emphasizes its potential as a biocatalyst for asymmetric reduction. Additionally, *Brassica oleracea* has demonstrated impressive stereoselectivity, achieving over 99% ee in the reduction of benzyl acetoacetate to benzyl (*S*)-(+)-3-hydroxybutyrate, with higher selectivity. *Pastinaca sativa* (parsnip) has been reported to facilitate the reduction of ketones such as benzyl acetoacetate and ethyl 3-oxopentanoate, producing chiral alcohols with substantial enantiomeric excess. These findings underscore the potential of plant-based biocatalysts as sustainable and effective alternatives for stereoselective bioreduction processes.[15,124]

Despite its environmental benefits as a greener alternative, *D. carota* biocatalysis faces limitations in catalytic efficiency due to low turnover numbers and extended reaction times, making it less efficient than ketoreductases (KREDs) and alcohol dehydrogenases (ADHs), which require costly cofactors or toxic reagents. To enhance its industrial viability, optimization strategies such as enzyme immobilization (*e.g.*, alginate/silica beads), genetic engineering (heterologous ADH expression), and reaction engineering (biphasic systems, selective surfactants) can improve stability, conversion rates, and mass transfer. Future research should focus on refining reaction kinetics and cost-effectiveness to establish *D. carota* as a scalable green biocatalyst.

4 Conclusion and future perspectives

D. carota roots serve as sustainable biocatalysts for enantioselective reductions of ketones, esters, and olefins. Unlike traditional chemical methods that can be costly, environmentally damaging, and complicated to operate, biocatalysis with *D. carota* provides a greener alternative. What's really impressive is its ability to catalyze the asymmetric reduction of prochiral ketones, producing enantiopure (*S*)- and (*R*)-chiral alcohols, which are crucial intermediates in the pharmaceutical and agrochemical industries. Moreover, it exhibits broad catalytic potential, efficiently reducing β-ketoesters, heteroaryl ketones, and conjugated olefins, positioning it as a valuable tool in sustainable organic synthesis. The whole-cell systems of *D. carota* naturally have enzymes and cofactors, making bioreduction efficient under mild conditions without needing extra additives. This results in high regio- and stereoselectivity due to enzyme compartmentalization, cofactor recycling, and selective substrate recognition. These benefits underscore *D. carota's* potential to advance green chemistry, aligning perfectly with the vision of a more sustainable and biobased economy.

Future studies should focus on enzyme immobilization (*e.g.*, alginate/silica bead encapsulation), and genetic modifications to enhance substrate range, dehydrogenase activity, and biocatalytic efficiency of *D. carota*, by optimizing reaction conditions such as pH, solvent choice, and temperature. Enzyme

engineering and cofactor regeneration could also play a significant role in improving specificity, making it a more versatile biocatalyst for sustainable organic synthesis. Streamlining purification through *in situ* product removal, minimal pretreatment, and membrane filtration can help reduce complexity, while techniques like selective precipitation and phase-specific separation can boost efficiency and cost-effectiveness. Integrating *D. carota* with continuous flow systems might further improve scalability and process control, making it more suitable for industrial use. Conducting economic and life cycle assessments will be essential to validate its feasibility and reinforce its position as a green and sustainable alternative in organic synthesis.

Data availability

There is no additional data available for this article.

Conflicts of interest

There are no conflicts to declare.

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