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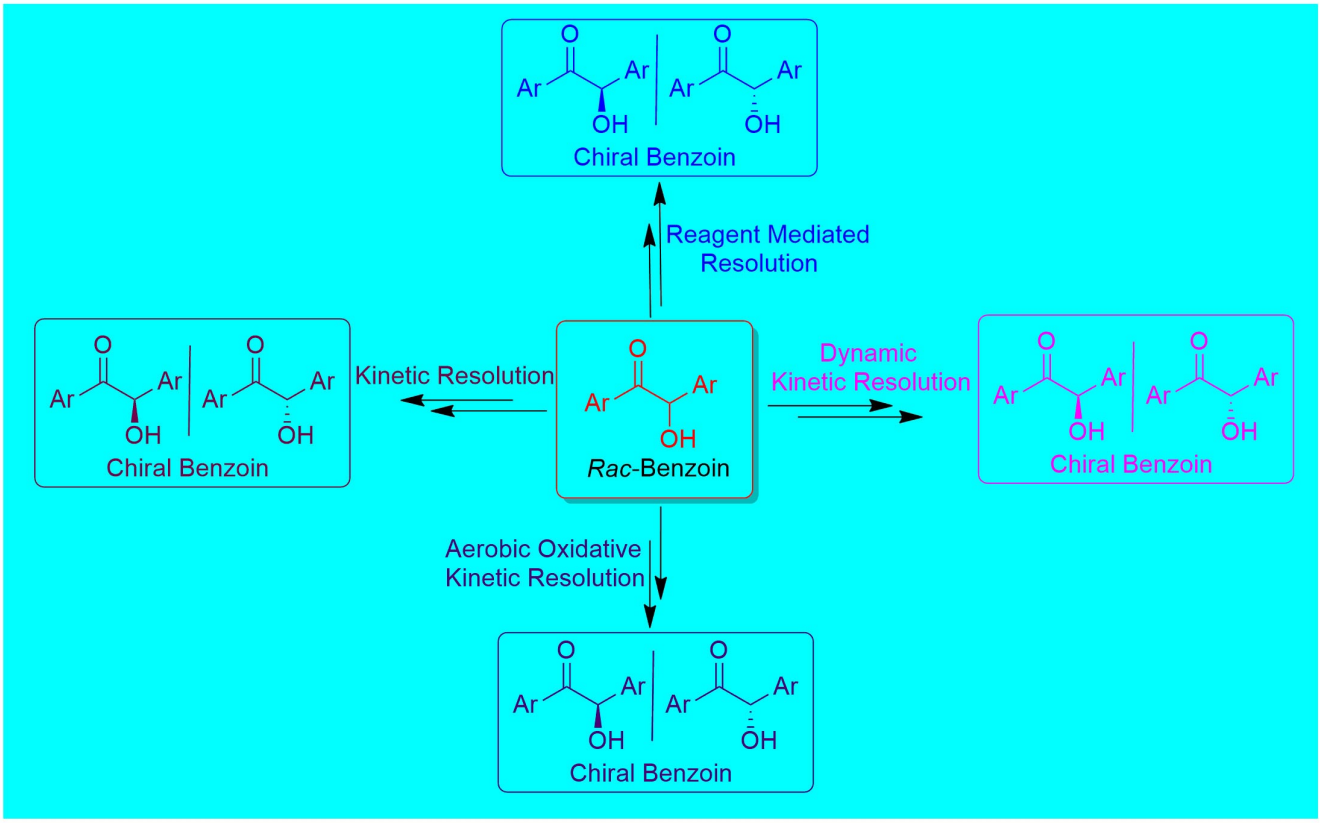
Deracemization of Benzoin and its Derivatives *via* Kinetic, Dynamic Kinetic, Aerobic Oxidative Kinetic, and Reagent-mediated resolution

Raveendra Babu Kothapalli,[a] Bheemreddy Anusha,[b] Marri Naveen Kumar,[c] P. Sundar Singh,[a] S. Ramakrishna,[d] and Ummareddy Venkata Subba Reddy*[c]



The production of enantiomerically pure compounds remains a vital and valuable objective in modern organic chemistry due to their broad applications in fields such as biosensing, optics, electronics, photonics, catalysis, nanotechnology, and drug or DNA delivery. Optically pure α-hydroxy ketones, in particular, are key structural components in many drugs and natural products with significant biological activity. Among these, benzoin type α-hydroxy ketones, which possess two adjacent functional groups, a carbonyl and a hydroxy group, are especially important. These functional groups can be easily transformed into the significant organic compounds such as 1,2 amino alcohols and 1,2 diols etc, which are important intermediates for synthesis of high profile biological active natural products. Deracemization of racemic compounds remains one of the most effective strategies for producing optically pure compounds, despite recent advances in asymmetric synthesis. Due to the importance of chiral benzoins, numerous studies have focused on their asymmetric synthesis. At the same time, many research groups have developed various methods for resolving racemic benzoins, including kinetic resolution, dynamic kinetic resolution, metal-catalyzed aerobic oxidative kinetic resolution, and reagent-mediated resolution. In this context, we aim to provide a comprehensive review of the various resolution methods applied specifically to racemic benzoins. To the best of our knowledge, no comprehensive review on the resolution of racemic benzoins has been published to date.

1. Introduction

The synthesis of enantiomerically pure compounds, is still a crucial and valuable task in contemporary organic chemistry because of their potential applications in a variety of fields, including biosensing, optics, electronics, photonics, catalysis, nanotechnology, and drug or DNA delivery.[1–4] The majority of biomolecules existing in living organisms are chiral and consist of only one of the two possible enantiomeric forms. As a result, molecular interactions of a racemic substrate with these chiral biomolecules will always be different for one enantiomer than the other. This plays a particularly important role not only in the pharmaceutical industry and medicinal chemistry but also in other industrial sectors such as the food, and flavour and fragrance industries. As a result, it is crucial for those industries to produce many of their products (e.g. drugs, food additives, vitamins) as single enantiomer.

Optically pure α-hydroxy ketones are important structural units for many drugs and natural products, such as the antidepressant bupropion and its metabolites[5] a component of indinavir[6] (inhibitor of HIV protease), some antitumoral antibiotics such as olivomycin A and chromomycin A3,[7] or some inhibitors of amyloid-β protein production, useful in the treatment of Alzheimer's disease.[8] Benzoins (1,2 diaryl-2-hydroxyethanone structures) are particularly useful as urease inhibitors[9] or as building blocks for the synthesis of different heterocycles.[10] Moreover, α-hydroxy ketones are of particular value as fine chemicals because of their utility as building blocks for the production of larger molecules. Benzoin type α -hydroxy ketones are important classes of intermediates in synthesis of vital organic functional groups such as 1,2 amino alcohols, 1,2 diols and so forth due to their bi functional structural aspect. Benzoins (1,2 diaryl-2-hydroxyethanone structures) have two adjacent functional groups i.e. carbonyl group and hydroxy group which can be easily convert into any other required organic functional groups and it also has two aryl groups which can also easily alter. Owing to this structural feature's benzoin emerge as a simple and very useful template in organic synthesis (Figure 1).

Because of the importance of benzoins in chemical industry, medicinal chemistry as an intermediate for synthesis of high profile biological active natural products and for synthesis of many vital organic functional groups, increasing interest towards these molecules and its derivatives. There were many research groups have been reported the various methods for synthesis of chiral benzoin.

Synthesis of chiral α-hydroxyketones can be classified into two broad categories: i.e. asymmetrization of prochiral compounds and optical resolution of racemic compounds. Under asymmetrization of prochiral approach, 1,2 α-hydroxy ketones are generally obtained through benzoin condensation.

One of the most traditional C–C bond forming reactions in organic chemistry, which uses a nonchiral catalyst such as cyanide,[11] thiamine[12] and triazolium salts in a biomimetic manner.[13] Chiral benzoins can also be obtained enzymatically by the enantioselective benzoin or acyloin condensation catalyzed by thiamine diphosphate-dependent enzymes[14] pyruvate decarboxylase (PDC),[15] benzoylformate decarboxylase (BFD),[16] and benzaldehyde lyase (BAL).[17] Also, there are many bio-catalytical methods for the synthesis of enantiomerically

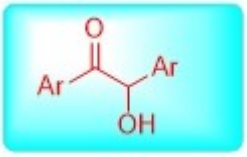


Figure 1. Benzoin: Simple and multifunctional molecule.

[a] *R. Babu Kothapalli, P. S. Singh*
Department of Chemistry, SCIM Govt. College, Tanuku, West Godavari (Dist.), Andhra Pradesh-5534211, India

[b] *B. Anusha*
Department of Chemistry, Silver Jubilee Govt. Degree College, Cluster University, Kurnool, Andhra Pradesh-518002, India

[c] *M. Naveen Kumar, U. Venkata Subba Reddy*
Department of Chemistry, STSN Government Degree College, Kadiri, Sri Sathya Sai (Dist.), Andhra Pradesh-515591, India
E-mail: ummareddyvsr@gmail.com

[d] *S. Ramakrishna*
Department of Chemistry, Govt. Degree College for Men, Srikakulam, Andhra Pradesh-532001India

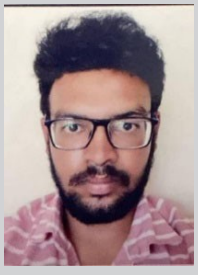
pure benzoins as the enantioselective reduction of α-diketones.[18]

Deracemization of racemic compounds is still the most important strategy for producing optically pure compounds despite many recent advances in asymmetric synthesis. The first person being able to separate a racemic mixture into the two enantiomers was Louis Pasteur, who as early as in 1849 physically separated tartaric acid crystals of opposite handedness. Ever since, the separation of a racemate into its two enantiomers commonly known as resolution has been the most prominent way to separate two enantiomers in numerous applications.

Owing to the importance of chiral benzoin, although there were many reports on the asymmetric synthesis of chiral benzoins, many research groups are also developing the various methods for resolution of racemic benzoin's includes convenient kinetic resolution, dynamic kinetic resolution, metal catalysed aerobic oxidative kinetic resolution, reagent mediated resolution etc. To the best of our knowledge still now there is no comprehensive review reported on resolution of racemic benzoin's even though there were some reviews disclosed the resolution of secondary alcohols.[19] Even though Antonio Mezzetti recently published a short review in 2020 on catalytic strategies to enantiopure benzoin's, it primarily highlights the catalytic approaches developed thus far for synthesizing enantiomerically pure benzoin's, including references to only two reports on the resolution of benzoins.[20] Given the significance of benzoin as a chiral intermediate in organic

Dr. Raveendra Babu Kothapalli was born in 1984 in Andhra Pradesh, India. He earned his MSc from the University of Hyderabad in 2007 and later pursued his Ph.D. under Prof. R. Balamurugan at the same university. In 2011, he joined at Government Degree College Rajahmundry as an Assistant Professor. Currently, he serves as an Associate Professor of Chemistry at SCIM Government College (A) in Tanuku, West Godavari, Andhra Pradesh. His research focuses on the synthesis of organic molecules and their conversion into nanomaterials to investigate their optoelectronic properties. His research work received funding from DST-SERB, India (Grant number: SUR/2022/003623).

Dr. Bheemreddy Anusha was born in Ananthpur, Andhra Pradesh, in 1986. She obtained her B.Sc. degree from S.K. University, Ananthpur, in 2007 and her M.Sc. from Osmania University, Telangana, in 2009. She received her Ph.D. in 2014 from Sri Venkateswara University, Tirupati, A.P. In 2011, she began her career as an Assistant Professor of Chemistry at government degree colleges in Andhra Pradesh and is currently serving associate professor at Silver Jubilee Government College, Cluster University, Kurnool. Her research interests include asymmetric catalysis and the total synthesis of natural products.



Marri Naveen Kumar hails from Telangana, India. Graduated his Bachelor's from Kakatiya University and Master's in chemistry from the University of Hyderabad. later worked as a project assistant on an IoE project under Prof. Periasamy Mariappan, investigating organic electrochemical cells. Currently working as a DST-SERB project associate under the supervision of Dr. U.V. Subba Reddy, exploring synthesis of bioactive natural products using gold catalysis.

P. Sundar Singh was born in 2001 in Andhra Pradesh, India. He received his M.Sc. Degree in 2023 from Acharya Nagarjuna University and he worked few months in Mana Pharma Pvt ltd, Hyderabad as a trainee chemist. At present he is working as Project assistant in DST SERB project with Dr. K. Raveendra babu, SCIM Government College(A) Tanuku, West godavar, Andhra Pradesh, India. His area of research is Synthesis of Organic Nanostructures.

Dr. S. Ramakrishna received his M.Sc. in Chemistry from the University of Hyderabad in 2009 and his Ph.D. from Osmania University in 2015. With over 12 years of teaching experience at both undergraduate and postgraduate levels, he has published nine research papers in reputable international journals. His research interests encompass the synthesis of visible light-driven photocatalysts, the removal of heavy metals from drinking water, and the isolation of secondary metabolites from natural resins. He is also a member of the Royal Society of Chemistry (RSC).

Dr. Ummareddy Venkata Subba Reddy was born in 1983 in Andhra Pradesh, India. He completed his Bachelor's degree at S.K. University, Ananthpur (Silver Jubilee Government College, Kurnool) in 2004, followed by a Master's degree in Chemistry from the University of Hyderabad in 2006. He earned his Ph.D. from Jawaharlal Nehru Technological University, Hyderabad, in 2014. Following that, he worked as a Postdoctoral Fellow at the Muroran Institute of Technology in Japan, collaborating with Prof. Hiroto Nakano on asymmetric catalysis for three years (2015 to 2018). He is currently an Assistant Professor of Chemistry at STSN Government Degree College in Kadiri, A.P. Dr. Reddy has published over 26 scientific papers in reputed international journals. His research focuses on asymmetric catalysis, C–H activation, and total synthesis of natural products. Recently, his research received funding from DST-SERB, India (Grant number: SRG/2023/000972).

transformations and bioactive molecules, this review focuses exclusively on methods for resolving racemic benzoin and its derivatives. These include kinetic resolution, dynamic kinetic resolution, metal-catalyzed aerobic oxidative kinetic resolution, and reagent-mediated resolution. We strongly believe that this review would be very helpful to the various research groups in investigating the methods for deracemization of benzoin's and their utility.

2. Enzyme Kinetic Resolution

Kinetic resolution is one of the most common methods to access enantiomerically enriched compounds.[21] It is defined as a process in which one of the enantiomers of a racemic mixture is transformed into the corresponding product faster than the other one (Scheme 1). These kinetic resolutions can not only be carried out in small scale laboratory experiments, but also in large scale industrial processes. The limitation of such types of 'classic' kinetic resolutions (KR), however, is that both enantiomers can only be obtained in a maximum theoretical yield of 50%. In a kinetic resolution, starting materials do not racemize. Only one enantiomer is transformed to product (maximum 50% yield). Recently, many research groups reported the kinetic resolution of benzoin.

In 2000, Williams and colleagues[22] reported the lipase TL®-mediated kinetic resolution of racemic benzoin **1** using vinyl acetate as an acyl donor. This process yielded optically pure (*R*)-benzoin (*R*)-**1** in 48% yield with 92% enantiomeric excess (*ee*), alongside (*S*)-benzoin-O-acetate (*S*)-**2** in 46% yield with 99% *ee*. Subsequently, (*S*)-benzoin-O-acetate (*S*)-**2** was hydrolyzed without epimerization using K_2CO_3 in methanol-water at 0 °C, yielding (*S*)-benzoin (*S*)-**1** in 91% yield and 96% *ee*. Initially, various commercially available lipases such as PPL, Amano I®, Amano PS®, Amano II®, Lipase MY®, UL®, TL®, SC®, AL®, OF®, and QL® were screened for the kinetic resolution of benzoin with vinyl acetate in THF at room temperature. Lipase TL® proved to be the most effective among these lipases. Notably, similar results were obtained using recovered Lipase TL®. Furthermore, they successfully converted (*R*)-benzoin (*R*)-**1** to optically pure (1*R*,2*S*)-2-amino-1,2 diphenylethanol **3** *via* the corresponding oxime while maintaining the optical purity of (*R*)-**1** (Scheme 2).

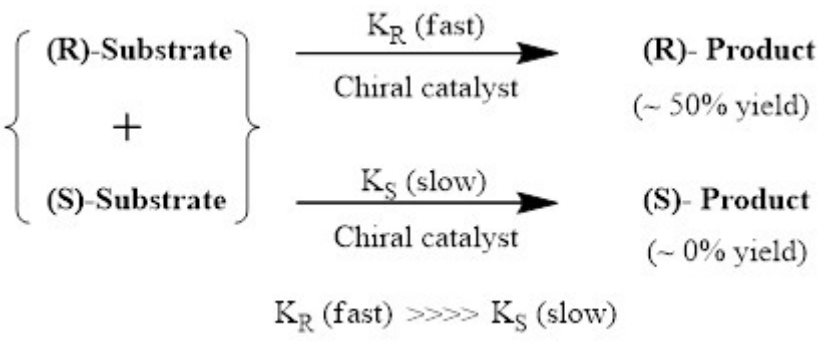
In 2001, the same group reported the Lipase TL-mediated kinetic resolution of benzoin **1** using the same procedure as previously described (Scheme 3).[23] They further converted both enantiomers of benzoin, (*S*)-**1** and (*R*)-**1**, into [^{15}N]-(1*R*,2*S*)- and (1*S*,2*R*)-2-amino-1,2-diphenylethanol **3a** and **3b**, respectively (Scheme 4).[23] Additionally, they demonstrated that [^{15}N]-(1*R*,2*S*)- and (1*S*,2*R*)-2-amino-1,2-diphenylethanol **3a** and **3b** could be transformed into [2,3-^{13}C2,^{15}N]-(5*S*,6*R*)-4-CBz-5,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one **4** a useful template for the synthesis of ^{15}N, ^{13}C-multiply labelled optically active α-amino acids **8** *via* lactone **6** (Scheme 5).[23]

Subsequently, in 2001, Muller *et al.*[24] reported the enzymatic kinetic resolution of benzoin **1** through C–C bond cleavage and formation reactions. This process utilized a thiamine diphosphate (ThDP)-dependent enzyme, benzaldehyde lyase (BAL, EC 4.1.2.38), derived from Pseudomonas fluorescens Biovar I. BAL was effective in the presence of acetaldehyde, with 20% DMSO (v/v) or 15% polyethylene glycol (PEG 400) (v/v) as co-solvents. In this method, when racemic benzoin **1** reacted with BAL and acetaldehyde, only the (*R*)-enantiomer was transformed into (*R*)-2-hydroxy-1-phenylpropanone [(*R*)-2-HPP] (*R*)-**9**, achieving 49% yield with 99% *ee*, while (*S*)-benzoin (*S*)-**1** remained unreacted and was recovered in 49% yield with >99% *ee*. The products were easily separated *via* column chromatography (Scheme 6).

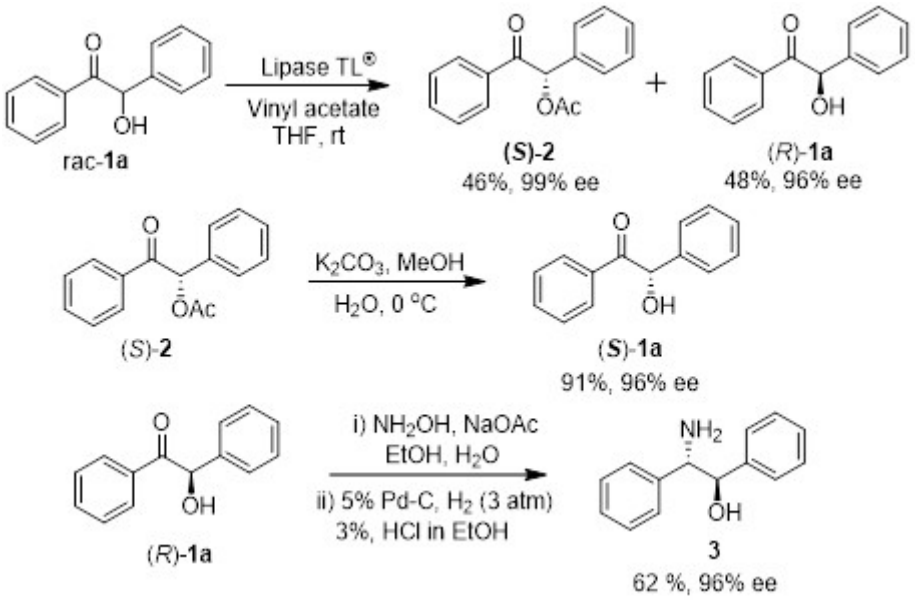
Mechanistic studies revealed that BAL catalyzed C–C bond cleavage and formation exclusively for the (*R*)-benzoin **1** enantiomer, leaving (*S*)-benzoin **1** untouched. This reaction can be scaled up for large-scale synthesis. Moreover, the authors demonstrated the synthesis of enantiopure α-hydroxy ketones in high yield and *ee*, starting from simple and readily available aromatic aldehydes, racemic benzoins, and aliphatic aldehydes.

3. Dynamic Kinetic Resolution

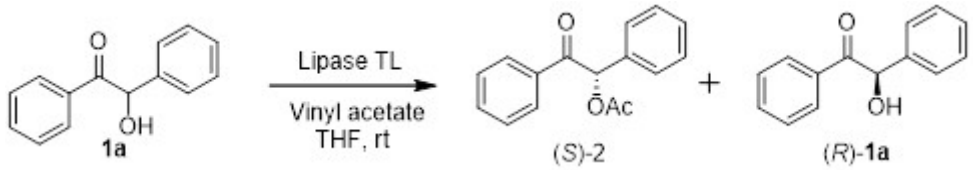
Though, kinetic resolution is a popular method for differentiating two enantiomers in a racemic mixture that react at different rates with a chiral catalyst or reagent, the biggest drawback of kinetic resolution is that the yield of one pure enantiomer is limited to a maximum of 50%. To overcome this drawback, different strategies have been attempted such as the sequential implementation of a KR cycle, a further racemization



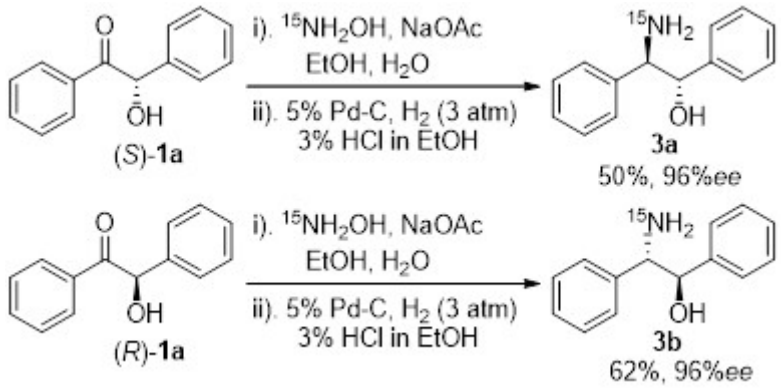
Scheme 1. Mechanism of kinetic resolution of racemic mixture.



Scheme 2. Lipase TL® enzyme mediated kinetic resolution of benzoin.



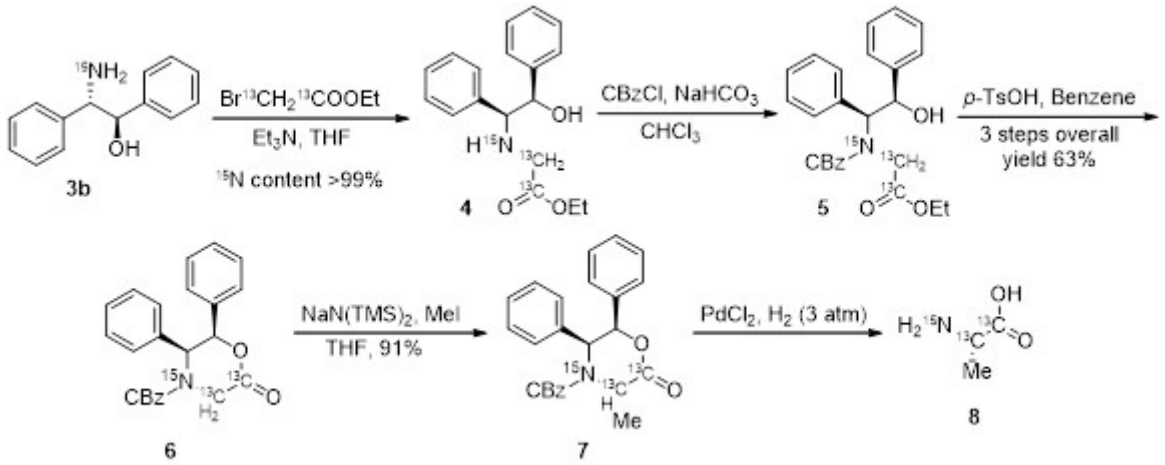
Scheme 3. Lipase TL enzyme mediated kinetic resolution of benzoin.



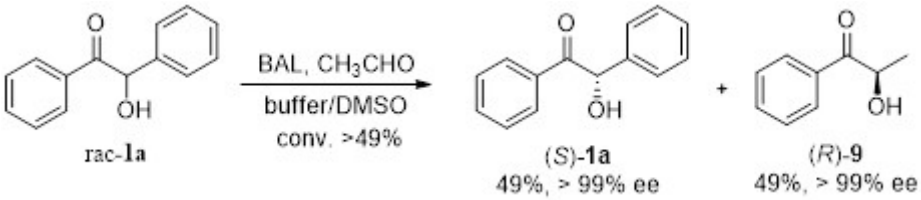
Scheme 4. Synthesis of isotopic labelled (1*S*,2*R*)-2-amino-1,2-diphenylethanol **3 a** and (1*R*,2*S*)-2-amino-1,2-diphenylethanol **3 b.**

of the remnant substrate, and a second KR[25] or the in situ Mitsunobu stereo-inversion of the unreacted enantiomer.[26] Nevertheless, the combination of a KR with the in-situ racemization of the unreacted enantiomer in a one-pot dynamic kinetic resolution (DKR) has received great attention during the last years, because through this methodology optically active products can be obtained with a theoretical 100% conversion (Scheme 7).

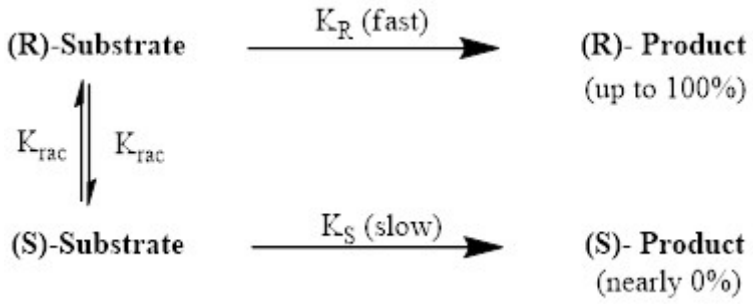
Dynamic kinetic resolution utilizes a center of a particular molecule that can be easily epimerized so that the (*R*) and (*S*) enantiomers can interconvert throughout the reaction process. At this point the catalyst can selectively lower the transition state energy of a single enantiomer, leading to almost 100% yield of one reaction pathway over the other. If a catalyst is able to increase $\Delta\Delta G‡$ to a sufficient degree, then one pathway will dominate over the other, leading to a single (100% yield) chiral product (Figure 2). There have been abundant uses of DKR in the literature for the resolution of benzoin's and their application to the synthesis of natural products.



Scheme 5. Synthesis of [2,3–$^{13}C_2$, ^{15}N]- (L)-alanine **8.**



Scheme 6. BAL mediated kinetic resolution of benzoin **1.**



Scheme 7. The general concept of Dynamic Kinetic Resolution.

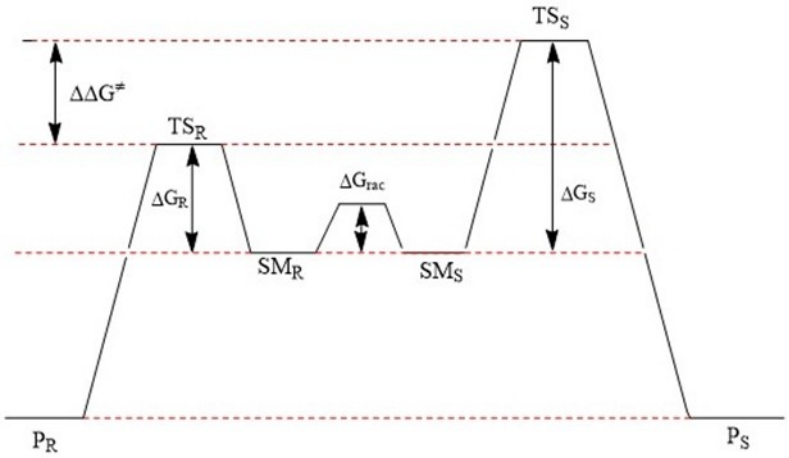
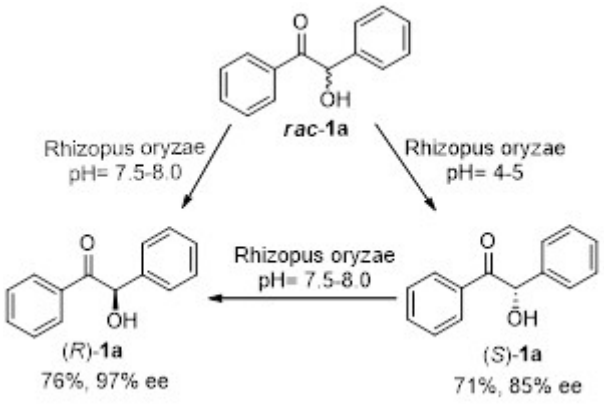


Figure 2. Energy profile concept of Dynamic Kinetic Resolution.

In 2002, Demir *et al.*[27] reported, for the first time, an enzymatic (fungal) dynamic kinetic resolution (deracemization) of racemic benzoin **1a**, catalyzed by the enzyme Rhizopus oryzae (ATCC 9363). By conducting the reaction at different pH levels, they obtained both enantiomers with high enantiomeric excess (*ee*). When the reaction of racemic benzoin **1a** was carried out with Rhizopus oryzae (ATCC 9363) at a pH range of 7.5–8.0 (basic medium), they isolated benzoin (*R*)-**1** in 76% yield with 97% *ee*. In contrast, performing the reaction at a pH of 4–5 (acidic medium) produced benzoin (*S*)-**1** in 71% yield with 85% *ee* (Scheme 8). As a control experiment, when benzoin (*S*)-**1** was used as a substrate with Rhizopus oryzae (ATCC 9363) at a pH of 7.5–8.0, it was converted into (*R*)-benzoin **1** with a 74% yield and 97% *ee*. However, no conversion was observed when (*R*)-benzoin **1** was used as a substrate under the same conditions, and the starting material (*R*)-benzoin **1** was recovered in 77% yield. The authors suggested that the pH dependency might be due to changes in the enzyme, or the fungal strain could contain multiple enzymes that are active at different pH levels. Although the complete mechanism for the enantiomeric conversion was unclear, they proposed a plausible pathway involving the formation of an ene diol intermediate **10** (Scheme 9).

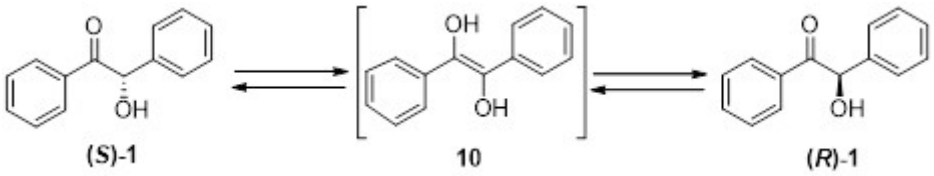
Later, in 2011, the same group i.e. Demir and co-workers[28] reported the synthesis of enantiopure benzoin from racemic benzoin acetate using Rhizopus oryzae (CBS111718). This strain contains various enzymes, including lipase, alcohol dehydrogenase (ADH), catalase, and racemase. Initially, the lipase catalyzes the enantioselective hydrolysis of benzoin acetate rac-**2** into benzoin (*R*)-**1a** and benzoin (*S*)-**1a**. Subsequently, racemase can convert benzoin (*R*)-**1a** to benzoin (*S*)-**1a**, while ADH catalase in the enzyme system can convert benzoin (*S*)-**1a** back to benzoin (*R*)-**1a**. The study found that Rhizopus oryzae performs three transformations: hydrolysis, racemization, and oxidation followed by asymmetric reduction. To optimize the process, both ultrasonic and mechanical homogenization were employed as pre-treatment steps to release enzymes and ensure a homogeneous reaction medium. Ultrasonic homogenization yielded better results in terms of product yield and enantiomeric excess compared to mechanical homogenization. The best outcome 100% conversion with 96% *ee* was achieved at pH 6 with an ultrasound frequency of 20 kHz. The (*S*)-**1a** enantiomer was consistently obtained at all pH levels. During the reaction, the formation of benzyl **11a** was observed in HPLC analysis, leading the researchers to propose that the conversion of benzoin (*R*)-**1a** to benzoin (*S*)-**1a** and vice versa was catalyzed by ADH catalase within the Rhizopus oryzae enzyme system (Scheme 10).[28]



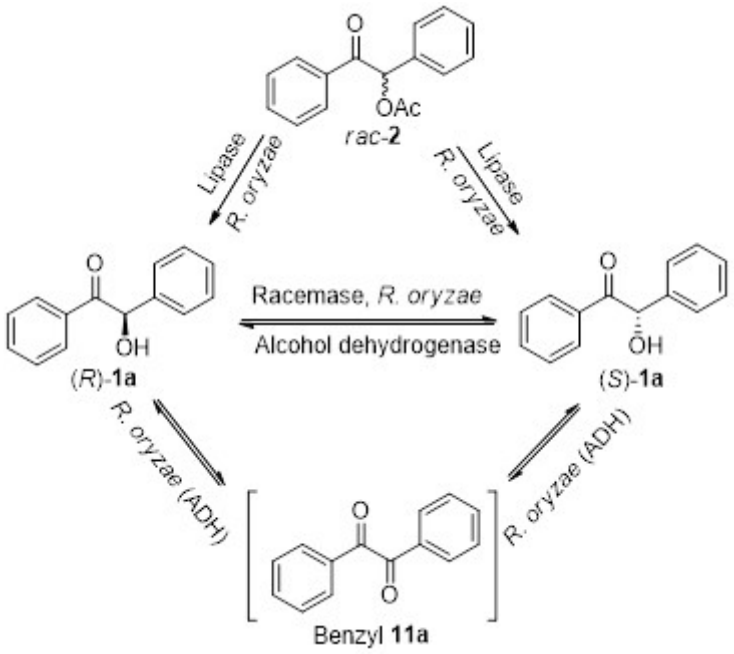
Scheme 8. *Rhizopus oryzae*mediated dynamic kinetic resolution (deracemization) of (*rac*)-benzoin **1**.

In 2006, Alcantara *et al.*[29] reported both the kinetic resolution (KR) and dynamic kinetic resolution (DKR) of benzoin's **1** using Lipase TL and a combination of Lipase TL with a ruthenium catalyst (Shvo's catalyst **13**), respectively. Since efficient kinetic resolution is essential for a successful DKR, they first optimized the reaction conditions for the resolution of benzoin rac-**1a** catalyzed by Lipase TL in THF solvent under various conditions. Their experiments revealed that using vinyl butyrate as the acyl donor at 50 °C provided the best yield and enantiomeric excess (*ee*) in a short reaction time. Under similar conditions, they obtained various symmetrical chiral benzoin's (*R*)-**1** and (*S*)-**12** with moderate yields and high *ee* values (Scheme 11). In this kinetic resolution, a maximum of 50% enantiomer (*S*)-**12** was acylated, while 50% enantiomer (*R*)-**1** remained unreacted. The product configuration was confirmed by comparing it with reported optical rotations and HPLC data.[30] In the same study, the authors also described the dynamic kinetic resolution (DKR) of racemic benzoin **1** using the Lipase TL-Shvo's catalyst **13** combination. This method couple's enzymatic kinetic resolution with an in-situ ruthenium-based racemization process. The ruthenium catalyst oxidizes benzoin (*R*)-**1** into diketone **11**, which can be reduced back to benzoin **1**. In this DKR process, acylated products (*S*)-**12a–b** and **12e** were obtained, achieving yields of up to 90% with more than 99% *ee* (Scheme 12).

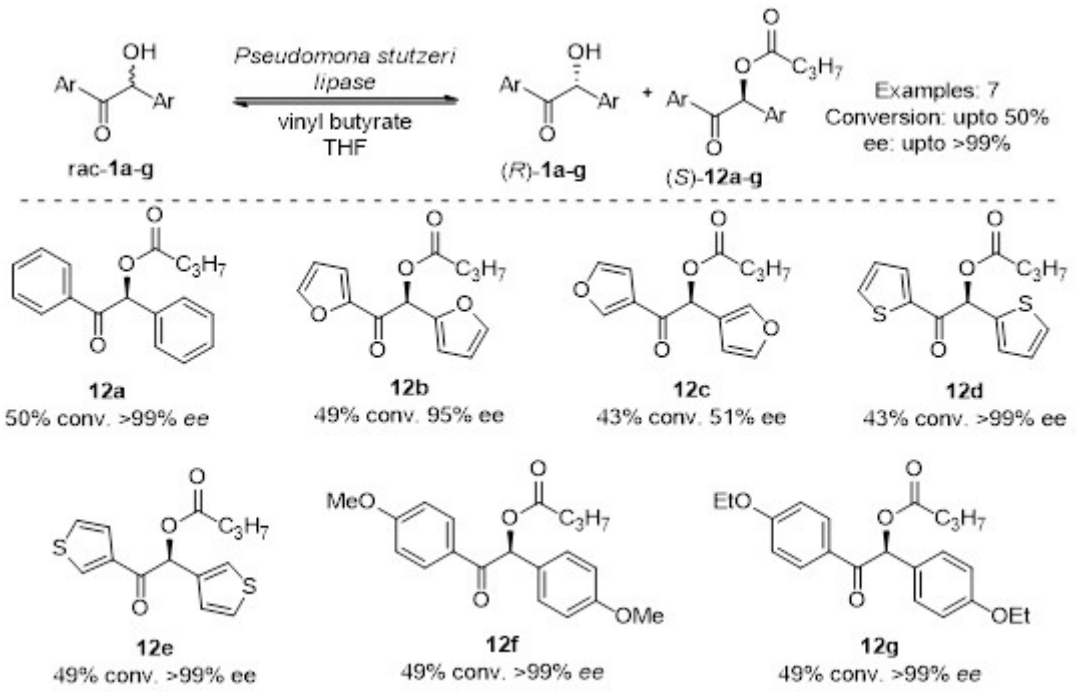
In 2008, the same research group reported an enhanced dynamic kinetic resolution of benzoin using immobilized Pseudomonas stutzeri lipase as a catalyst.[31] They explored three entrapment methods: sol-gel, static emulsion silicone, and silicone elastomer spheres and determined that silicone sphere entrapment was the most effective, significantly activating the



Scheme 9. Deracemization of benzoin *via* ene-diol.



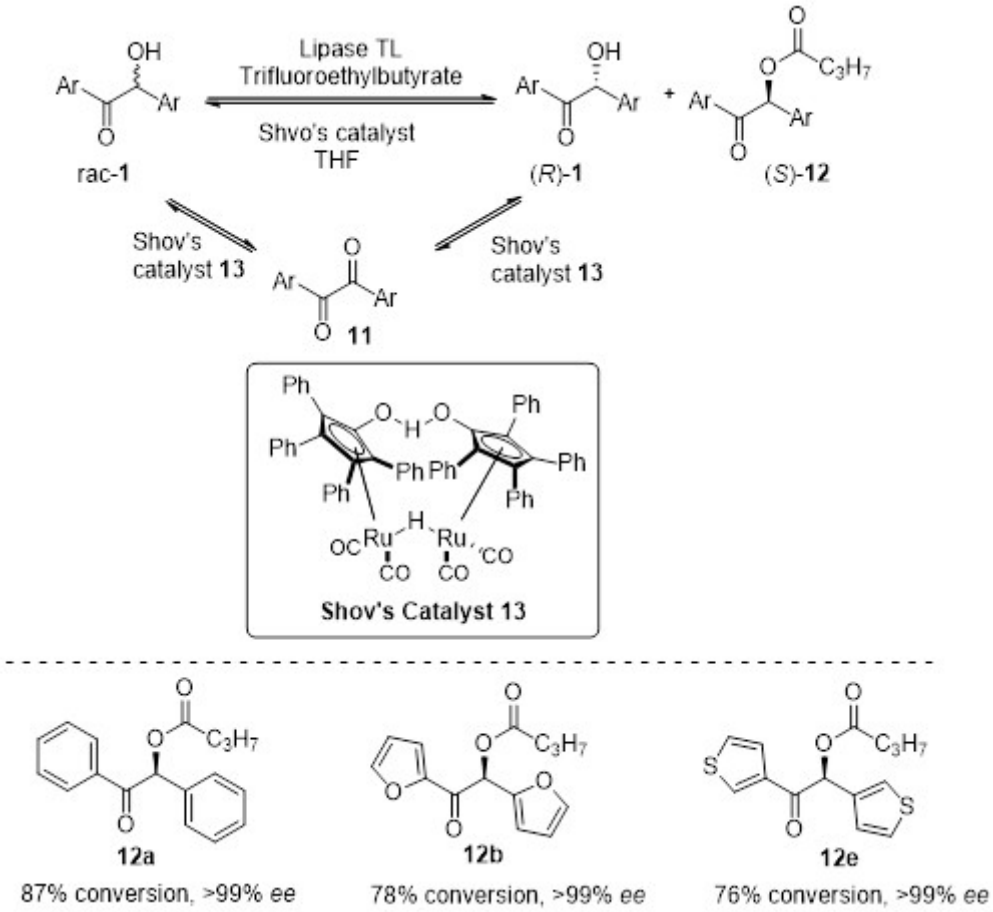
Scheme 10. Enantioselective hydrolysis of benzoin acetate and deracemization of benzoin using *Rhizopus oryzae*.



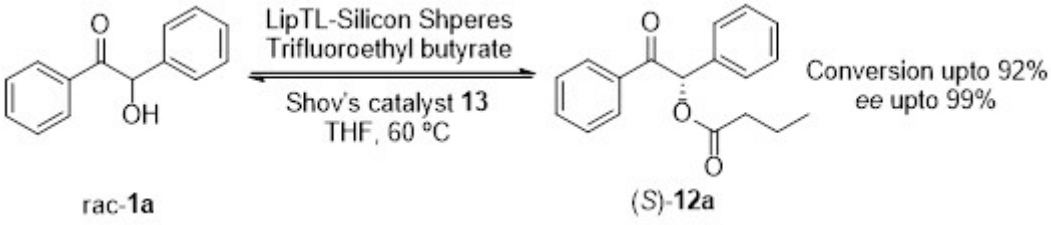
Scheme 11. *Ps. stutzeri Lipase*- catalyzed kinetic resolution of symmetrical benzoin.

lipase. The highest conversion of benzoin **1** (up to 92% conversion) to acylated benzoin product (*S*)-**12a** (up to 99% *ee*) was achieved using silicone sphere-immobilized lipase-Shvo's catalyst **13** at 60 °C over 20 hours. Remarkably, the recycled spheres maintained their activity through at least four uses without a notable loss (Scheme 13).

In 2011, the same research group reported the chemoenzymatic dynamic kinetic resolution (DKR) of unsymmetrical benzoin's using Lipase TL in combination with Shvo's catalyst **13**.[32] The racemic unsymmetrical benzoin's were successfully converted into acylated benzoin's with high enantiomeric excess. This study focused on the substrate specificity of Lipase TL[33,34] which demonstrated a higher preference for stereo-



Scheme 12. One-pot DKR of symmetrical benzoins by Lipase-Shov's metal combo catalyst.



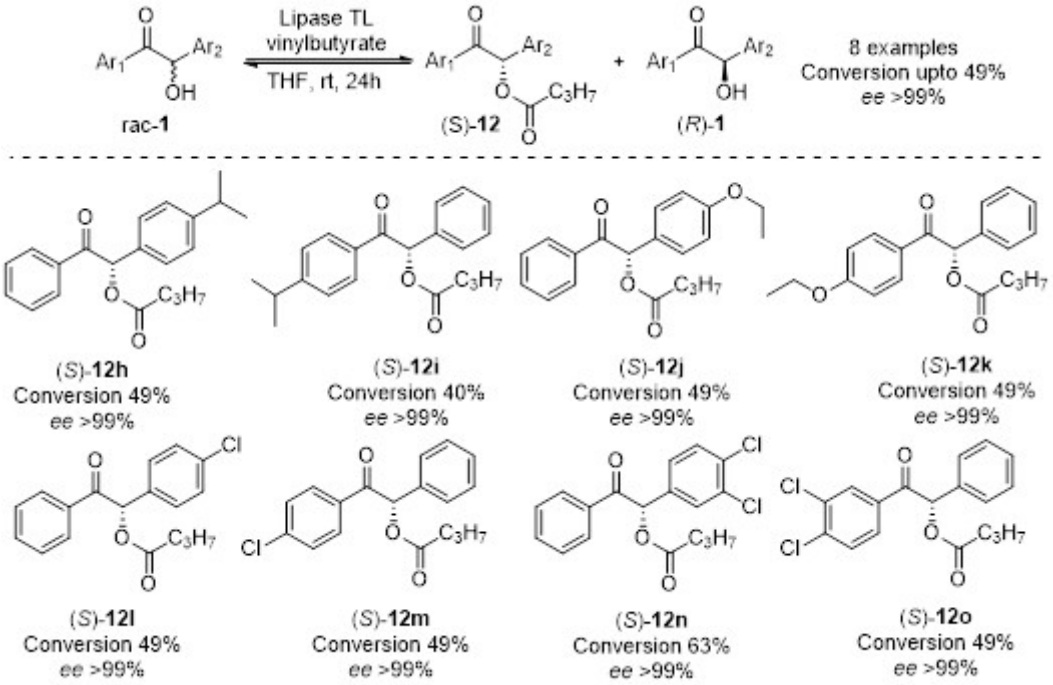
Scheme 13. DKR of benzoin **1** with entrapped lipase.

selective transesterification of benzoin's without substituents on the aromatic ring of the benzoyl moiety (Ar1 in rac-**1**). Lipase TL efficiently accommodated the benzoyl moiety in a medium-sized pocket, while the substituted aromatic ring near the hydroxyl group fit into a larger pocket. Substrates with bulky substituents on the benzoyl moiety showed lower conversion rates.

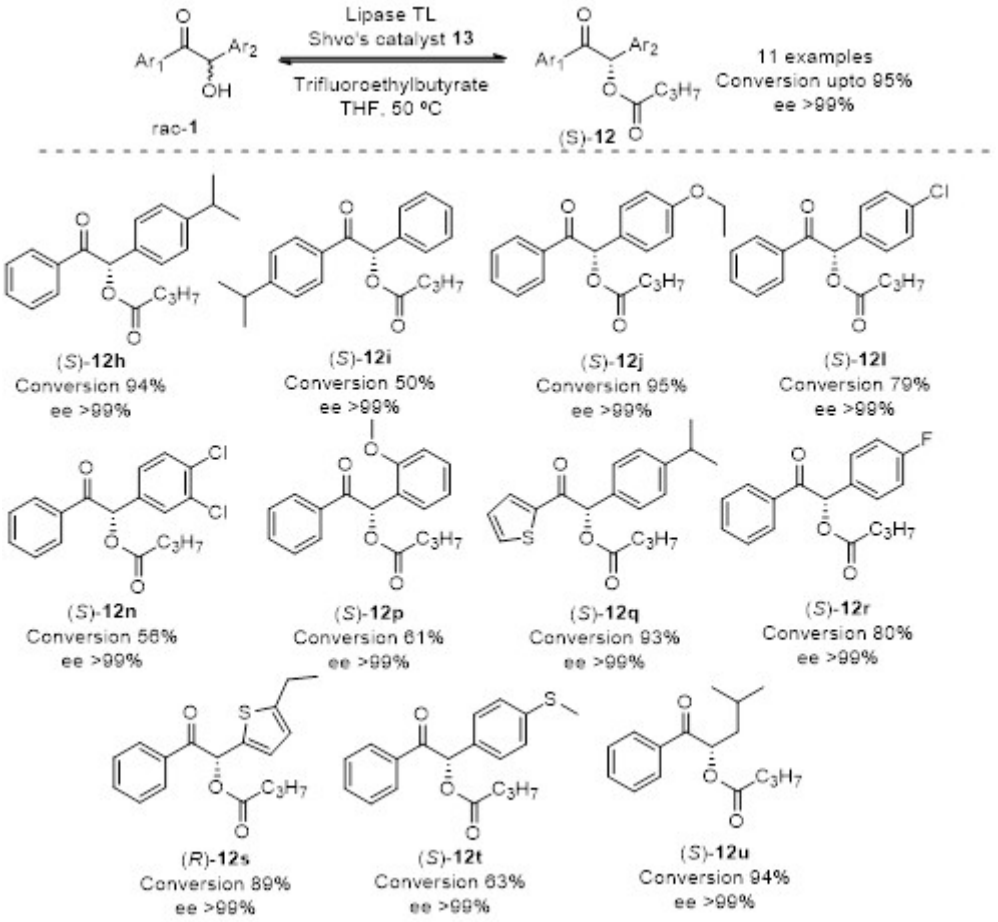
Initially, they carried out the kinetic resolution of benzoin's **1** using Lipase TL and vinyl butyrate as the acyl donor in THF at room temperature for 24 hours, achieving up to 49% conversion with 99% enantiomeric excess (*ee*) for the resolution products (*R*)- and (*S*)-**12** (Scheme 14).

Dynamic kinetic resolution was used to achieve complete conversion. Initially, *rac*-**1** underwent kinetic resolution, reaching ~30% conversion in 1 hour at 50 °C. The mixture was then filtered and concentrated. Fresh lipase, Shvo's catalyst **13**, and trifluoroethyl butyrate were added for dynamic kinetic resolution, completing the reaction in 24 hours at 50 °C to produce (*S*)-**12** with up to 95% yield and > 99% ee (Scheme 15).

The group later achieved the dynamic kinetic resolution (DKR) of benzoin using a chemoenzymatic method with the greener solvent 2-MeTHF.[35] This single-step DKR replaced their previous three-step process.[32] They examined how solvent, acyl donor, and substrate concentrations affected the lipase-catalyzed resolution using lipase fromPseudomonas stutzeri. They found that 2-MeTHF enhanced both the sustainability and catalytic activity compared to THF. Additionally, at least three equivalents of acyl donor were required for maximum con-



Scheme 14. Kinetic resolution of unsymmetrical benzoins using lipase TL.



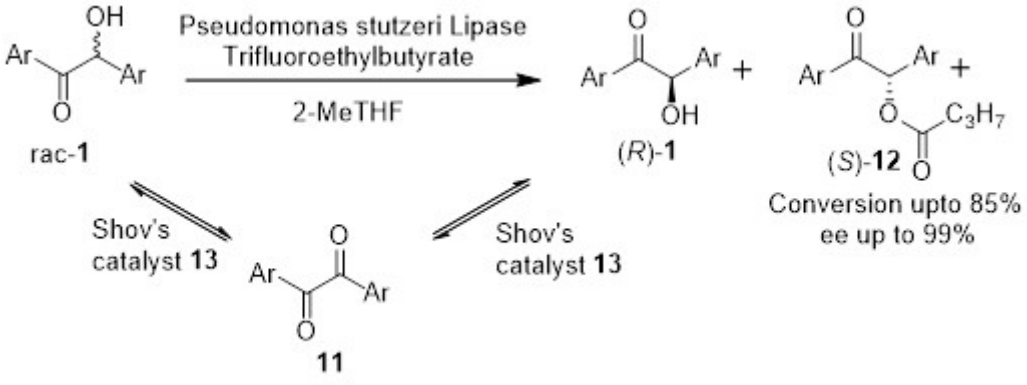
Scheme 15. DKR of unsymmetrical benzoins using lipase TL-Shov's catalyst.

version, and increasing substrate concentration did not significantly delay reaching 50% conversion. After optimizing the conditions for the kinetic resolution, they combined these conditions with Shvo's catalyst **13** to carry out the dynamic kinetic resolution. This single step process used lipase from Pseudomonas stutzeri, Shvo's catalyst **13**, vinyl butyrate as the acyl donor, and 2-MeTHF as the solvent at 55 °C afforded the desired chiral acylated benzoin (*S*)-**12**, with a maximum conversion of 85% and an enantiomeric excess of over 99% (Scheme 16).

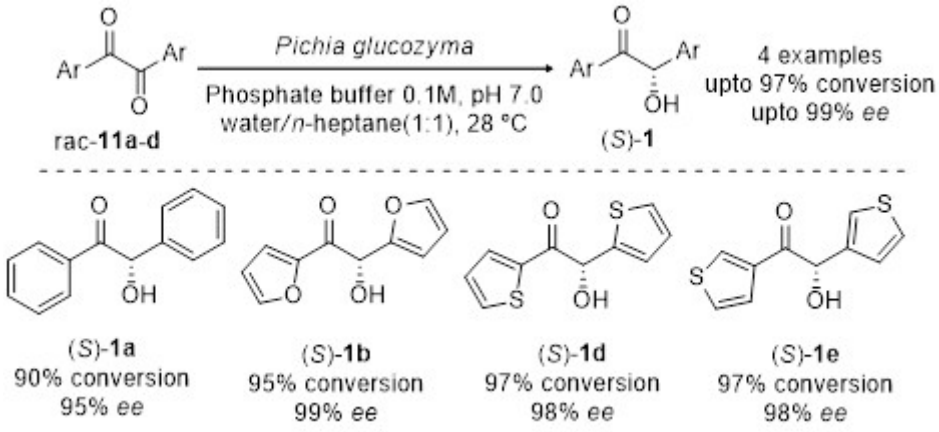
Later, in 2012, Alcantara and colleagues[36] reported two biocatalytic methods for producing (*S*)-benzoin. The first method involved the enantioselective bio-reduction of benzil **11** to (*S*)-benzoin **1**, while the second method focused on the dynamic-kinetic resolution (deracemization) of racemic benzoin. Their first study demonstrated that the enantioselective reduction of various benzils **11** using whole untreated cells of Pichia glucozyma in a phosphate buffer and n-heptane system produced the (*S*)- benzoin **1** with over 90% conversion and 99% enantiomeric excess (*ee*) after 48 hours (Scheme 17). Their second study demonstrated that the dynamic kinetic resolution (deracemization) of different benzoin's **1**, catalyzed by whole cells of Pichia glucozyma in a phosphate buffer and a biphasic water/isooctane (1:1) solvent system, resulted in the corresponding benzoins (*S*)-**1** with excellent enantiomeric excess (Scheme 18).

In 2015, the same group reported the dynamic kinetic resolution (DKR) of benzoin using lipase TL fromPseudomonas stutzeri, immobilized on epoxy-activated poly(GMA-co-HDDMA).[37] The immobilized lipase, used in the green solvent 2-MeTHF, enabled recoverable and reusable catalytic activity for both KR and DKR, achieving high enantioselectivity and yield. Previously, lipase TL had been immobilized by physical adsorption on hydrophobic supports[38] or entrapment in silica spheres.[39] However, in this study, lipase TL was covalently immobilized onto the poly (GMA-co-HDDMA) polymer. The authors evaluated two different supports i.e. commercial Eupergit **C** and poly (GMA-co-HDDMA) and found that the porous poly (GMA-co-HDDMA) copolymer exhibited superior activity. This copolymer was synthesized via solution polymerization and characterized through Porosity Volume Distribution (PVD) analysis, FT-IR, thermal analysis, and scanning electron microscopy (SEM).[40] By using a 1:100 ratio of enzyme to polymer, 100% binding of the enzyme to the poly (GMA-co-HDDMA) was achieved.

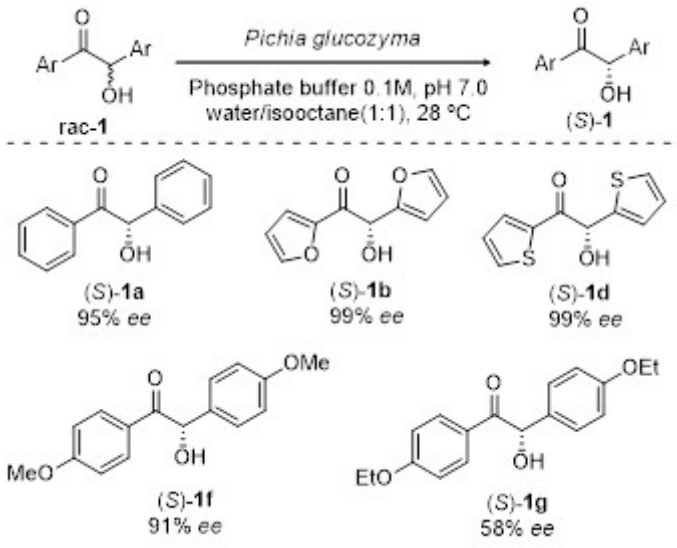
The kinetic resolution of various benzoin's **1** was carried out using TL-PGcH-2 (2 mg of lipase TL immobilized on poly (GMA-co-HDDMA)), with vinyl butyrate as the acyl donor, producing



Scheme 16. DKR process of benzoins (1,2-diaryl-2-hydroxyethanones) catalysed by lipase from Pseudomonas stutzeri and Shvois catalyst.



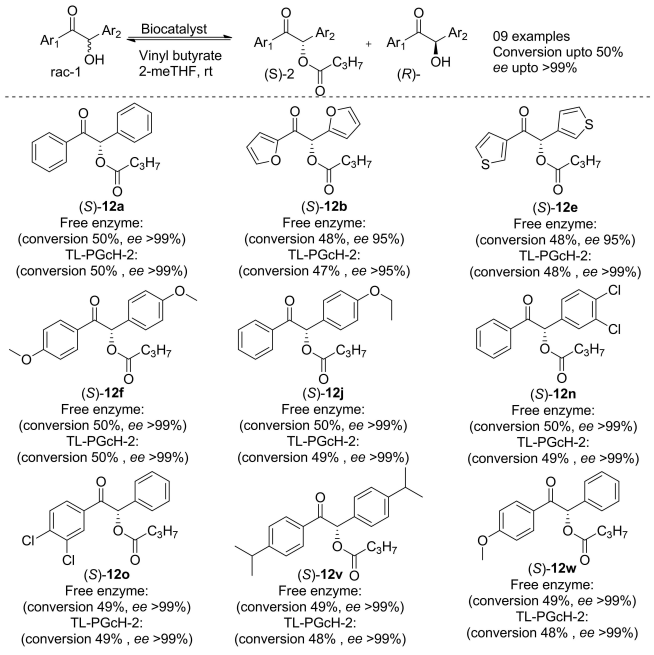
Scheme 17. Reduction of different benzoins catalyzed by whole cells from *P.glucozyma* in a biphasic solvent system.



Scheme 18. Deracemization of benzoins catalyzed by whole cells from *P.glucozyma* in a biphasic solvent system.

acylated benzoin's (*S*)-**12** with up to 50% yield and >99% enantiomeric excess (*ee*) (Scheme 19).

TL-PGcH-2 was reusable for up to 15 cycles in the green solvent 2-MeTHF. Additionally, TL-PGcH-2, combined with Shov's catalyst **13** in a one-pot DKR of benzoin using trifluoroethyl butyrate as the acyl donor, resulted in acylated benzoin's (*S*)-**12** with excellent yields (up to 95%) and enantioselectivity (up to 99% *ee*) at 50 °C in 2-MeTHF (Scheme 20).



Scheme 19. Kinetic Resolution of different benzoins by free Lipase TL and TL-PGcH-2

They further demonstrated that the TL-PGcH-2 catalyst could be reused for at least six catalytic cycles without loss of activity (Table 1). They also compared the catalytic efficiency of free lipase TL and immobilized lipase TL (TL-PGcH-2), finding that while both systems achieved the desired product with similar conversion rates and enantioselectivity, the immobilized lipase TL (TL-PGcH-2) demonstrated greater durability. It retained its catalytic activity for up to six cycles, whereas the free enzyme did not maintain its activity over multiple uses.

In 2014, Martin-Matute and colleagues[41] reported a one-pot dynamic kinetic resolution of aromatic α-hydroxy ketones using ruthenium catalysts **14**–**17**, phosphine ligands **18**–**25**, lipase TL, and vinyl butyrate as an acyl donor in THF at room temperature.

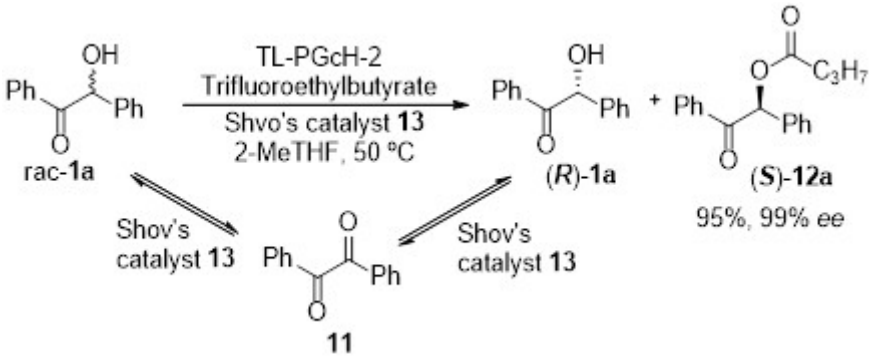
The optimal combination of $[Ru(p\text{-cymene})Cl_2]_2$ **17**, 1,4-bis(diphenylphosphino)butane **25**, lipase TL, vinyl butyrate, and *t*-BuOK yielded chiral benzoin derivatives (*S*)-**12** with up to 93% yield and 99% ee in a single step, eliminating the need for sequential addition of lipase TL (Scheme 21).

The authors further assessed the protocol's efficiency by transforming the products into valuable intermediates, successfully converting the α-hydroxy ketones into amino alcohols **26**, 1,2 diols **27**, and diol derivatives **28** with high diastereo and enantioselectivity, which are crucial for the total synthesis of biologically active natural products (Scheme 22).

In 2014, Ansorge Schumacher *et al.*[42] reported a chemo-enzymatic dynamic kinetic resolution to selectively produce (*S*)-benzoin. They employed the racemic mixture (rac)-**1**, combining heterogeneous chemo-enzymatic dynamic kinetic resolution with Acc-Lip TL as the enzyme catalyst, Zr/Al-TUD-1 as the metal catalyst, and vinyl butyrate as the acyl donor in 2-MeTHF as the solvent. In this process, Acc-Lip TL selectively acylated benzoin (*S*)-**12a**, while benzoin (*R*)-**1** was racemized by Zr-TUD-1. This continuous reaction resulted in the formation of acylated benzoin (*S*)-**12a** with high chemical yield (up to 98%) and excellent enantiomeric excess (up to 99% *ee*) (Scheme 23). The

Table 1. Repetitive DKR of benzoin with trifluroethyl butyrate as a acyl donor.

Cycle	Catalyst	Conversion (%)	*ee*
1	Commercial LipTL, THF, 50 °C	92	99
	Commercial LipTL, 2-MeTHF, 50 °C	85	99
	LipTL-SS, THF, 60 °C	87	99
	TL-PGcH-2, 2-MeTHF	95	99
2	LipTL-SS, THF, 60 °C	81	99
	TL-PGcH-2, 2-MeTHF	90	99
3	LipTL-SS, THF, 60 °C	80	99
	TL-PGcH-2, 2-MeTHF	87	99
4	LipTL-SS, THF, 60 °C	78	99
	TL-PGcH-2, 2-MeTHF	82	99
5	TL-PGcH-2, 2-MeTHF	80	99
6	TL-PGcH-2, 2-MeTHF	74	99



Scheme 20. DKR of benzoin with TL-PGcH-2.

enzyme catalyst Acc-Lip TL was prepared by immobilizing lipase TL onto the porous polypropylene resin Accurel MP1001. The racemization catalysts Zr-TUD-1 and Al-TUD-1 were synthesized by combining Zr or Al into TUD-1. Both catalysts showed excellent racemization within 20 hours at 50 °C, with the racemization rate increasing as the temperature rose. It was also observed that Al-TUD-1 exhibited strong transesterification activity at all temperatures, while Zr-TUD-1 showed this activity only at higher temperatures. Additionally, they showed that Acc-Lip TL was reusable for up to five cycles. The practicality of this method was further demonstrated through dynamic kinetic resolution on a semi-preparative scale.

The same group further investigated the effect of water on the dynamic kinetic resolution of rac-**1** in a chemo-enzymatic cascade reaction.[43] They observed that the catalytic performance of both the enzyme catalyst Acc-Lip TL and the chemo-catalyst Zr-TUD-1 was improved in anhydrous solvents. Among the solvents tested, the catalytic activity was highest in cyclopentyl methyl ether (CPME) compared to 2-MeTHF, toluene, and 1,3 dioxalane. Additionally, the enzyme catalyst's performance was tested in deep eutectic solvents, where it was found to be lower than in CPME, 2-MeTHF, toluene, and 1,3 dioxane.

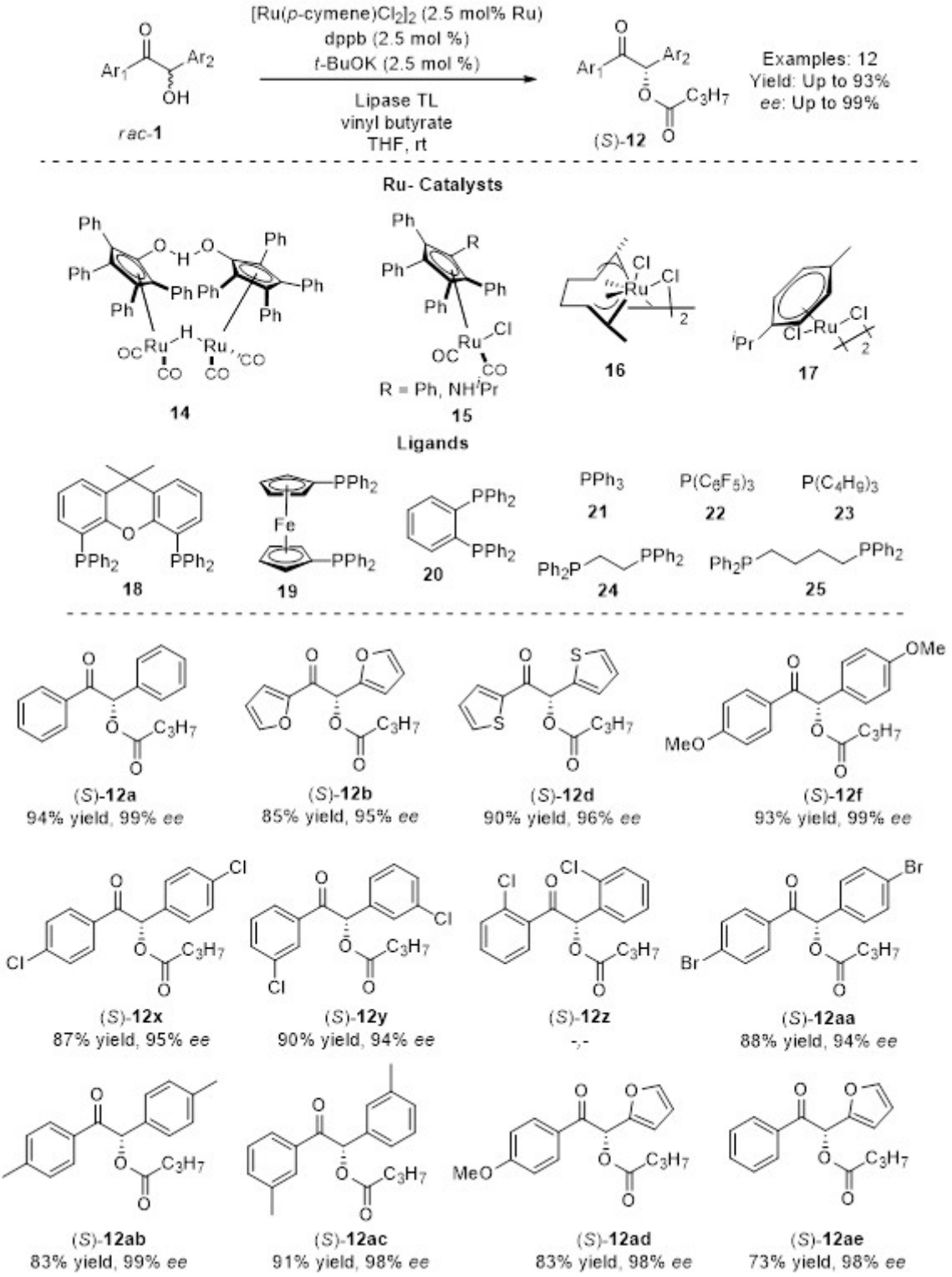
The same group later reported the chemo-enzymatic dynamic kinetic resolution (DKR) of both symmetric and non-symmetric α-hydroxy ketones.[44] In this study, they demonstrated DKR for compounds such as 2,2′ furoin **1 b**, 2-hydroxy-1-phenylpropan-1-one (HPP) rac-**9** and phenylacetyl carbinol (PAC) **30**. Initially, kinetic resolution using immobilized lipase TL (Acc-Lip TL) in dry cyclopentyl methyl ether (CPME) produced good results for benzoin, 2,2′ furoin **1 b**, and PAC **30**, while the kinetic resolution of HPP rac-**9** was successful with CalBiP in dry CPME. Dynamic kinetic resolution was achieved by coupling the kinetic resolution using Acc-Lip TL and CalBiP with the heterogeneous chemo-catalyst Zr-TUD-1 in CPME as an anhydrous solvent, in a one-pot process. This approach led to the formation of the corresponding butyrated chiral benzoins **12 b**, **29**, and **31** with high yields and excellent enantioselectivities (Scheme 24). This chemo-enzymatic system was reusable for up to six DKR cycles without any loss in yield or enantioselectivity. Additionally, the synthesis of (*S*)-phenylacetyl carbinol (PAC) butyrate via chemo-enzymatic DKR was demonstrated on a preparative scale. The utilization ratios of enzyme and metal catalysts were provided in grams per liter (g/L). (Scheme 24).

In 2021, Sakamoto *et al.*[45] reported a highly enantioselective synthesis of *p*-anisoin **1 f** through dynamic kinetic resolution *via* benzoin condensation of prochiral *p*-anisaldehyde **32** using achiral NHC catalysts **33**–**35**. Using this approach, the authors successfully synthesized chiral *p*-anisoin **1 f** as a single enantiomer with 99% enantioselectivity. The process involved condensing prochiral *p*-anisaldehyde **32** with achiral NHC catalysts **33**–**35**, followed by dynamic kinetic resolution via Viedma ripening in a single step. Deracemization occurred through dynamic crystallization, where one enantiomer preferentially crystallized while the other racemized in solution to maintain balance, resulting in single-enantiomer crystals. Adding catalytic amounts of (*D*)- or (*L*)-valine directed the outcome: (*L*)-valine produced (*R*)-**1f**, and (*D*)-valine yielded (*S*)-**1f**, both with high enantioselectivity (Scheme 25).

4. Aerobic Oxidative Kinetic Resolution

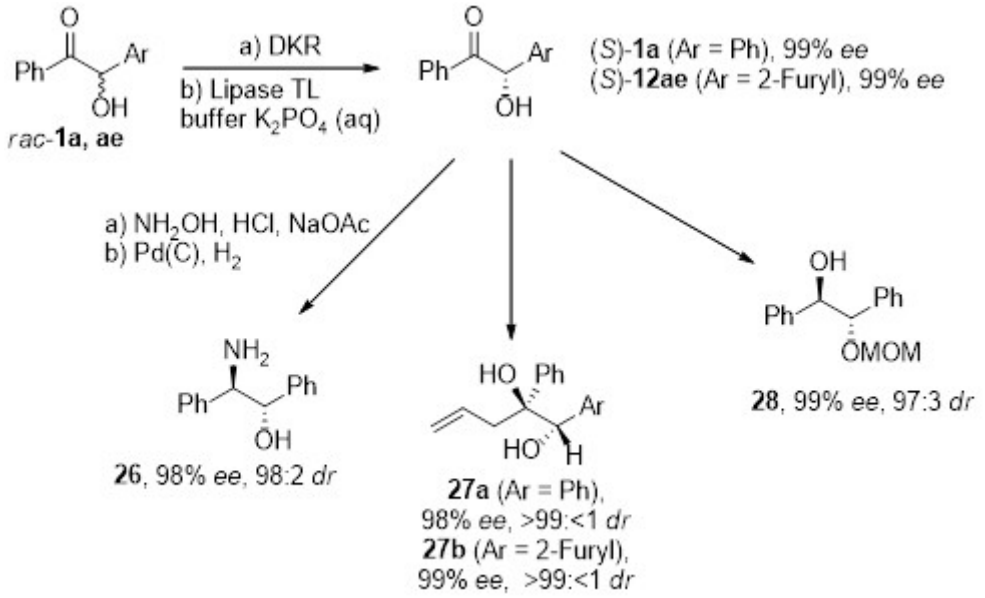
The oxidation of alcohols to carbonyl compounds using air as the terminal oxidant is highly desirable. Over the past few years, the transition metal catalyzed aerobic oxidative kinetic resolution of racemic alcohols has received much attention as a synthetic method for the preparation of optically active alcohols. Recently, a few research groups have reported the oxidative kinetic resolution of racemic alcohols using transition metal catalysts such as Pd,[46] Ru,[47] V,[48] Ir,[49] and Mn,[50] which have considerably widened the scope of this field. Since most of these catalysts are made of precious metals, there is still a need for new catalysts that are economical and available. The enantioselective aerobic oxidation kinetic resolution of benzoin's can be effectively utilized for resolving racemic benzoin's.

In 2009, Sekar *et al.*[51] reported the aerobic oxidative kinetic resolution (AOKR) of racemic benzoin's **1** using an in situ-prepared Galactose Oxidase (GO) model, consisting of the Cu {(R)-BINAM}$_2$][OTf]$_2$ complex, formed from Cu(OTf)$_2$ and (*R*)-BINAM **36**, with 5 mol% TEMPO, under stoichiometric molecular oxygen (O_2) in toluene at 60 °C. Initially, when (*rac*)-benzoin **1** was subjected to AOKR using 5 mol% (*R*)-BINAM, 5 mol%

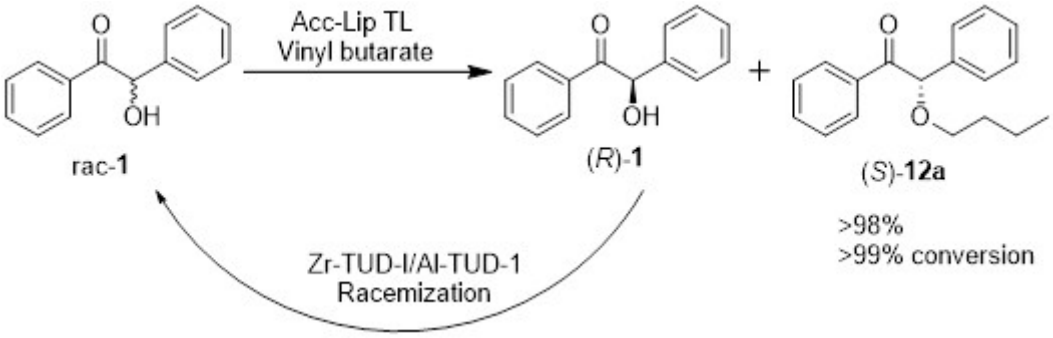


Scheme 21. One-pot dynamic kinetic resolution of benzoin's using Ru-complex in combination with Lipase TL.

$Cu(OTf)_2$, and 5 mol% TEMPO under stoichiometric O_2, the reaction produced 84% oxidized benzil **11** and 15% benzoin (*R*)-**1** with 90% enantiomeric excess (*ee*). Increasing the ratio to 2:1 (i.e., 10 mol% (*R*)-BINAM and 5 mol% $Cu(OTf)_2$ while keeping 5 mol% TEMPO under stoichiometric O_2 improved the yield of chiral benzoin (*R*)-**1** to 33% with enantiomeric excess to 92%. This method was verified on various benzoin's **1**, yielding the corresponding chiral benzoin's (*R*)-**1** with excellent enantioselectivity, up to 37%. In this process, the *S* enantiomer of the racemic benzoin was oxidized to benzil more quickly, leaving



Scheme 22. α-Hydroxyl ketones as synthetic intermediates.



Scheme 23. Chemo-enzymatic DKR of benzoin by Acc-Lip TL and Zr-TUD-1.

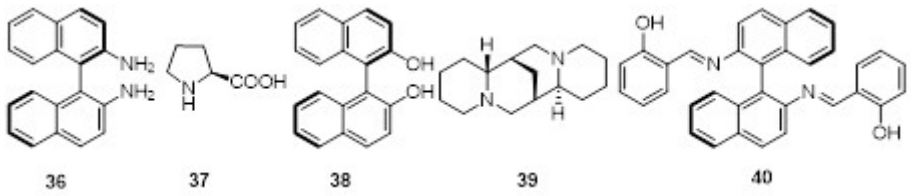
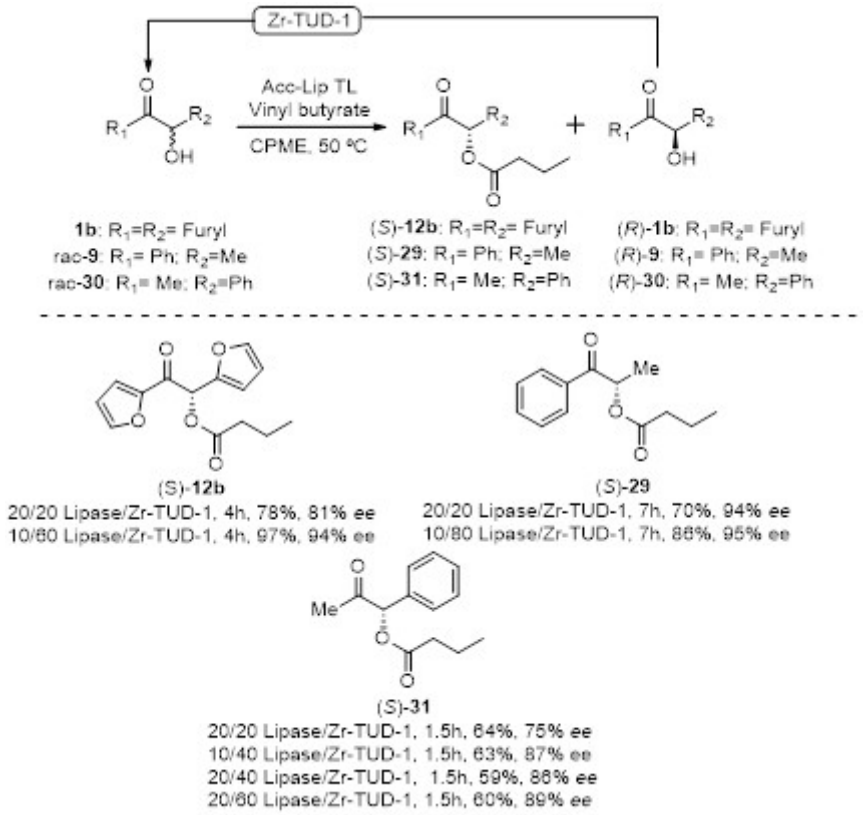


Figure 3. Various chiral ligands examined for OKR.

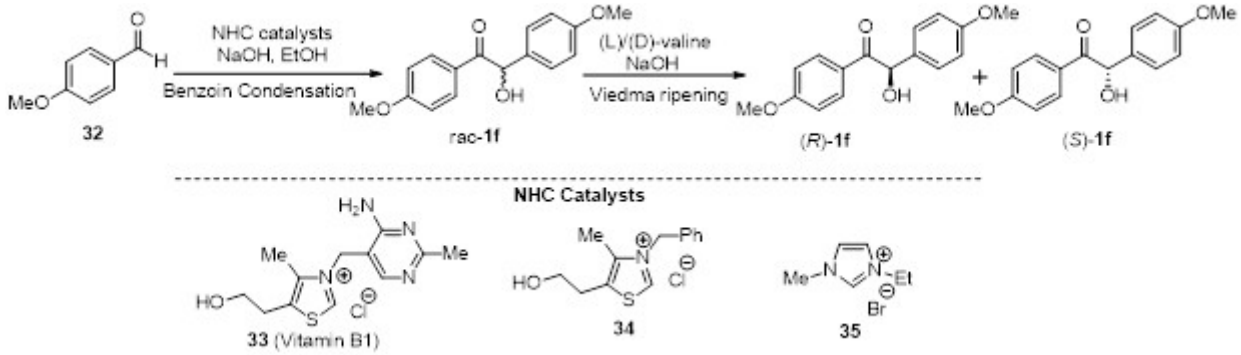
the slower-reacting *R* enantiomer in a highly enantiomerically enriched form. They also found that electron-withdrawing groups at the para position increased reactivity, while electron-donating groups at the para and meta positions decreased the reactivity of the benzoin's **1** (Scheme 26).

In 2009, Sekar et al.[52] reported an efficient method for the asymmetric aerobic oxidation of benzoin's using a chiral cobalt complex with molecular oxygen as the stoichiometric oxidant. Initially, they explored the oxidative kinetic resolution of racemic 4-methoxy benzoin 1f using various chiral ligands (Figure 3), including (R)-BINAP 36, (L)-proline 37, (R)-BINOL 38, (−)-sparteine 39, and Schiff base 40, in combination with cobalt catalysts such as Co(OAc)2, Co(NO3)2, and CoCl2. From this screening, they identified Co(OAc)2 combined with Schiff base 40 as the most effective, yielding the desired chiral benzoin (S)-1 with 57% conversion and 91% enantiomeric excess (ee) (Table 2).

The authors further investigated the influence of solvents on the reaction, using racemic 4-methoxy benzoin **1f** as a model substrate. Employing the optimal catalytic system, $Co(OAc)_2$ and Schiff base **40** (5 mol%) with TEMPO (5 mol%), they found that $CHCl_3$ provided the best results for oxidative



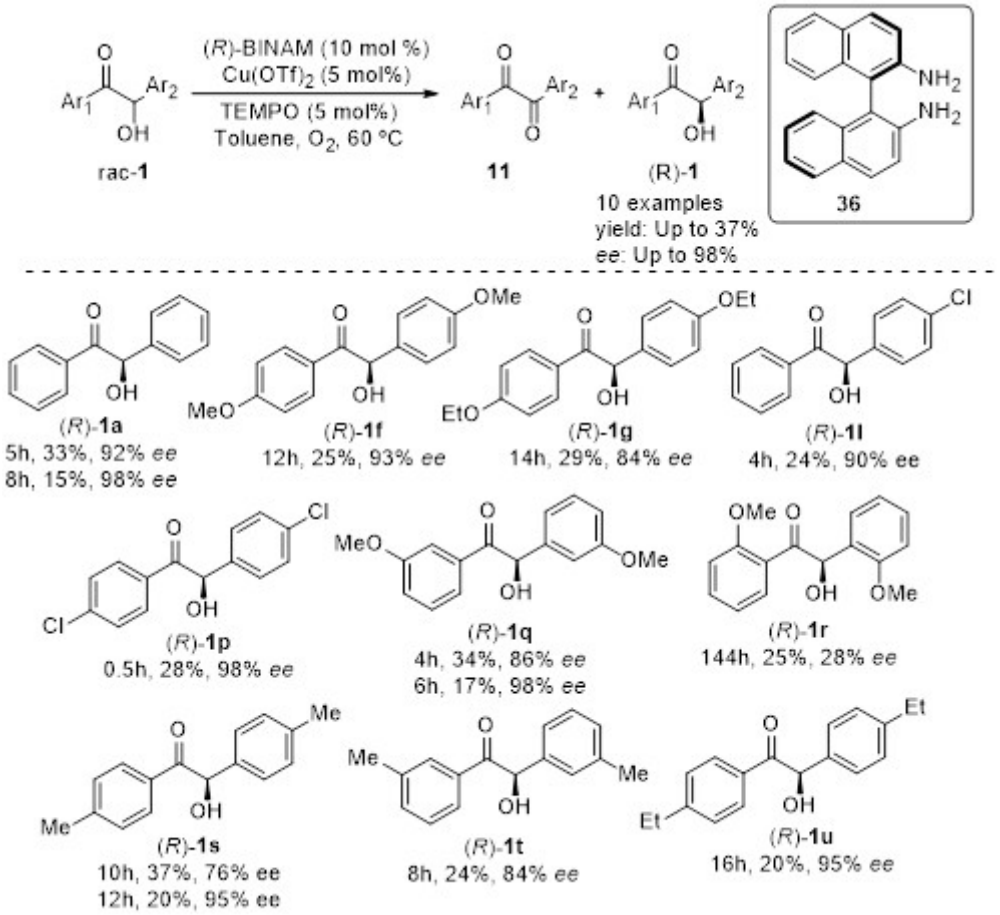
Scheme 24. Chemo-enzymatic DKR of symmetric and non-symmetric α-hydroxy ketones.



Scheme 25. One-pot asymmetric synthesis of *p*-anision by benzoin condensation dynamic crystallization ion.

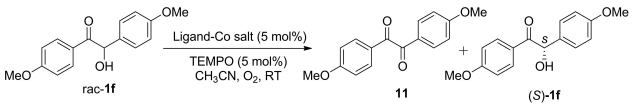
kinetic resolution, achieving 56% conversion and >99% *ee* at room temperature (Table 3). Under these optimized conditions, various racemic benzoins were oxidized, with the corresponding (*R*)-isomers being converted to benzils, while the (*S*)-enantiomers were recovered in highly enantiomerically enriched form (Scheme 27). The reaction was shown to tolerate benzoin derivatives with electron-donating groups at para and meta positions, as well as electron withdrawing substituents at para positions.

The same group later reported an efficient, cost-effective, and environmentally friendly method for the asymmetric oxidative kinetic resolution of benzoin's, catalyzed by a chiral iron complex using molecular oxygen as the stoichiometric oxidant.[53] They investigated the catalytic activity of various iron salts, including $Fe(OAc)_2$, $FeCl_3$, $Fe(acac)_3$, and $Fe(NO_3)_3 \cdot 9H_2O$, along with chiral ligands such as (*R*)-BINAM **36**, (*R*)-BINOL **38**, a derivative of (*R*)-BINAM **41**, salen ligand **42**, and a sterically hindered salen ligand **43** (Figure 4). Among these, they found that a combination of 10 mol% $Fe(OAc)_2$ and 10 mol% ligand **43** at 60 °C resulted in the highest selectivity, yielding chiral benzoin (*R*)-**1** with up to 91% enantiomeric excess (*ee*) and 70% conversion (Table 4). However, when the reaction temperature was lowered from 60 °C, the selectivity decreased. The reaction conditions were shown to tolerate both electron-donating and electron-withdrawing substituents at the para and meta positions, yielding products with excellent enantio-



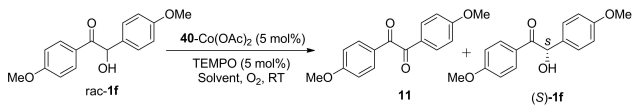
Scheme 26. Cu{(*R*)–BINAM}$_2$][OTf]$_2$-catalyzed AOKR of (*rac*)-benzoin's.

Table 2. OKR of (*rac*)-benzoin using cobalt catalysts with chiral ligands **47**–**51**.



Entry	Ligand	Co-salt	Time	Conversion (%)	(*S*)-43 (% of *ee*)
1	**36**	$Co(OAc)_2$	7 d	44	4
2	**37**	$Co(OAc)_2$	7 d	-	-
3	**38**	$Co(OAc)_2$	4 d	49	0
4	**39**	$Co(OAc)_2$	4 d	56	0
5	**40**	**$Co(OAc)_2$**	**5 h**	**57**	**91**
6	**40**	$Co(OAc)_2$	4.5 h	50	52
7	**40**	$Co(NO_3)_2$	7 d	-	–
8	**40**	$CoCl_2$	6 d	46	44
9	–	–	7 d	–	–

Table 3. Effect of solvents in the optimization of OKR of (*rac*)-benzoin.



Entry	Solvent	Time	Conversion (%)	(*S*)-1 (% of *ee*)
1	CH_3CN	5h	57	91
2	Benzene	5.5 d	24	8
3	THF	17h	50	77
4	Dioxane	66h	41	48
5	CH_3NO_2	66h	40	43
6	EtOAc	13h	54	90
7	CH_2Cl_2	21h	49	80
8	**$CHCl_3$**	**40h**	**56**	**99.5**
9	DMF	17h	45	30
10	DMSO	12h	45	30

meric excess (up to 90–98% *ee*). Under the optimized conditions, the (*S*)-enantiomer of the racemic benzoin mixture was selectively oxidized to benzil, while the slower-reacting (*R*)-enantiomer was recovered in a highly enantiomerically enriched form. This method was applied to various benzoin's, producing the corresponding (*R*)-enantiomers with excellent enantiomeric excess (Scheme 28).

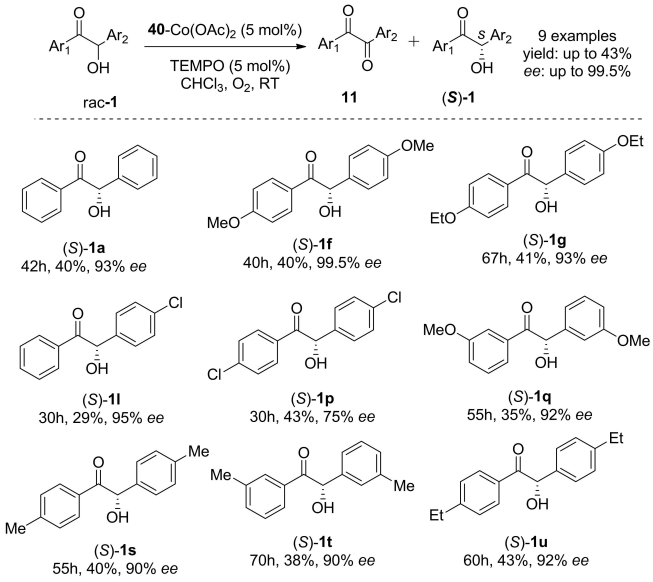


Table 4. Effect of ligands, Fe salts and solvents for OKR of (*rac*)-benzoin.

Entry	Ligand	Fe salt	Solvent	Time	Con. (%)	(*R*)-43 (% of *ee*)
1	**36**	$Fe(OAc)_2$	PhMe	31 h	63.0	9
2	**38**	$Fe(OAc)_2$	PhMe	24 h	74.0	0
3	**41**	$Fe(OAc)_2$	PhMe	8 d	30.0	18
4	**42**	$Fe(OAc)_2$	PhMe	4 d	50.0	34
5	**43**	$Fe(OAc)_2$	PhMe	3 d	68.0	87
6	**43**	$FeCl_3$	PhMe	25 h	69.0	10
7	**43**	$Fe(acac)_3$	PhMe	30 h	86.0	23
8	**43**	$Fe(NO_3)_3.9H_2O$	PhMe	3 d	60.0	7
9	**43**	$Fe(OAc)_2$	EtOAc	8 d	52.5	26
10	**43**	$Fe(OAc)_2$	$CHCl_3$	8 d	47.8	5
11	**43**	$Fe(OAc)_2$	THF	33 h	85.7	4
12	**43**	**$Fe(OAc)_2$**	**hexane**	**21 h**	**70.0**	**91**

Scheme 27. Chiral cobalt-catalyzed OKR of (*rac*)-benzoin's using O_2.

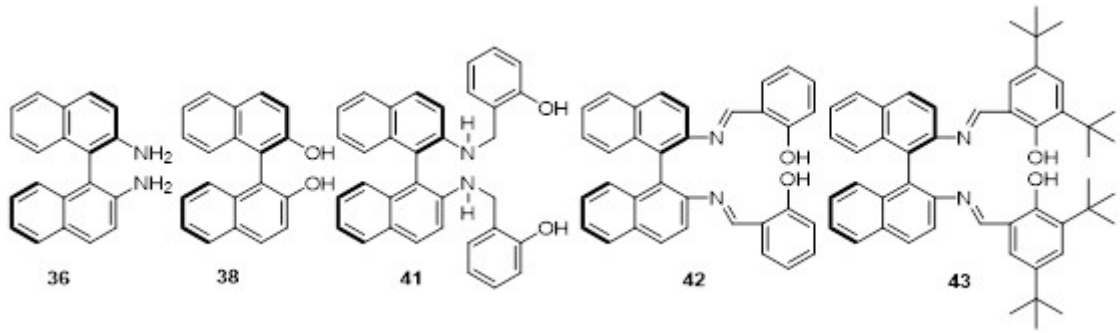
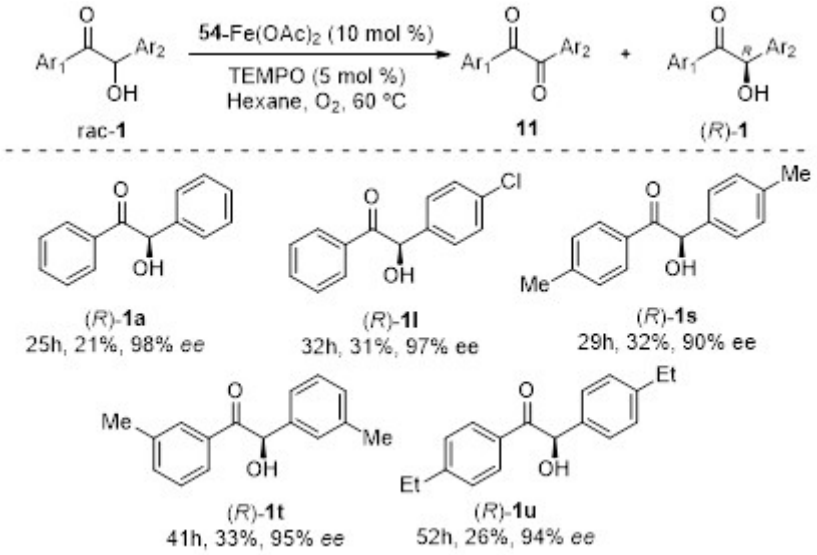


Figure 4. Ligands tested for OKR of (*rac*)-benzoin's.



Scheme 28. Chiral iron complex-catalyzed OKR of (*rac*)-benzoins using O_2.

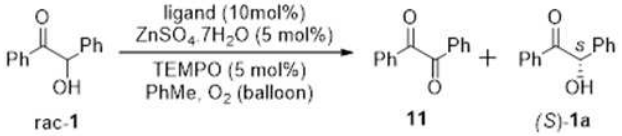
The same group later extended their work by reporting the oxidative kinetic resolution of α-hydroxy ketones using a chiral zinc complex as a catalyst, with molecular oxygen as the stoichiometric oxidant.[54] Initially, they attempted the oxidative kinetic resolution of benzoin **1** using $ZnSO_4 \cdot 7H_2O$ in combination with various chiral ligands, such as (*R*)-BINAM **36**, (*R*)-BINAM- derived imine **42**, sterically hindered salen ligand **43**, (*R*)-BINAM-derived prolinamide **44**, (*R*)-BINAM-derived imidazole **45**, quinine ligand **46**, and other quinine-based ligands **47**–**50** (Figure 5). They found that quinine ligand **46** provided superior reactivity and selectivity in producing chiral benzoin (*S*)-**1 a** compared to the other ligands (Table 5).

The oxidative kinetic resolution of benzoin **1** was optimized using quinine ligand **46** and various zinc salts and solvents. The best results were achieved with $ZnSO_4 \cdot 7H_2O$ (5 mol%) and quinine ligand **46** (10 mol%) in toluene at 60 °C, yielding chiral benzoin (*S*)-**1a** with high enantiomeric excess (Table 6). The protocol effectively resolved racemic benzoin's **1** with electron-donating or withdrawing groups at para, meta, and ortho positions (Scheme 29). Under these conditions, the (*R*)-enantiomer was selectively oxidized to benzils, leaving the (*S*)-enantiomer highly enriched.

In 2011, Chen *et al.*[55] reported the enantioselective aerobic oxidation of α-hydroxy ketones, catalyzed by various chiral oxidovanadium (V) methoxides **51**–**52** (Figure 6). They successfully carried out the asymmetric aerobic oxidation of α-hydroxy ketones with alkyl, aryl, and heteroaryl substituents, particularly focusing on substrates containing a 2-pyrrolyl group, using these chiral oxidovanadium (V) methoxides as catalysts. Initially, benzoin rac-**1 a** was used as a test substrate for the asymmetric aerobic oxidation with oxidovanadium(V) methoxide catalyst **51 g**, which the authors had previously identified as the best catalyst for the asymmetric aerobic oxidation of α-hydroxy phosphates.[56] This reaction produced chiral benzoin (*R*)-**1 a** with 41 % enantiomeric excess (ee). They then applied this protocol to various substituted benzoins **53 a**–**h** using catalyst **51 g**, achieving excellent results in terms of enantioselectivity, with values reaching up to > 99 % ee. The highest enantiomeric excess (up to 99 % ee) was observed in the corresponding products **54 c** & **54 d**,

when the phenyl group attached to the ketone was replaced with alkyl groups, as in substrates **53 c** and **53 d**, probably due to the stronger coordination of these substrates to the catalyst. In contrast, enantioselectivity dropped to 40 %

Table 5. Effect of ligands on oxidative kinetic resolution of (±)-benzoin.



Entry	Ligand	T (°C)	Time	Conversion (%)	(*S*)-1a (% of *ee*)
1	36 (5 mol%)	90	9 d	54	8
2	42 (5 mol%)	90	6 d	67	12
3	43 (5 mol%)	90	6 d	64	43
4	44 (10 mol%)	90	7 d	61	18
5	45 (10 mol%)	90	8 d	59	0
6	46 (10 mol%)	90	8 h	68	46
7	46 (10 mol%)	60	20 h	60	55
8	46 (10 mol%)	rt	10 d	20	0
9	47 (10 mol%)	60	21 h	65	6
10	48 (5 mol%)	60	29 h	67	0
11	49 (10 mol%)	60	11 h	69	28
12	50 (5 mol%)	60	5 d	63	4

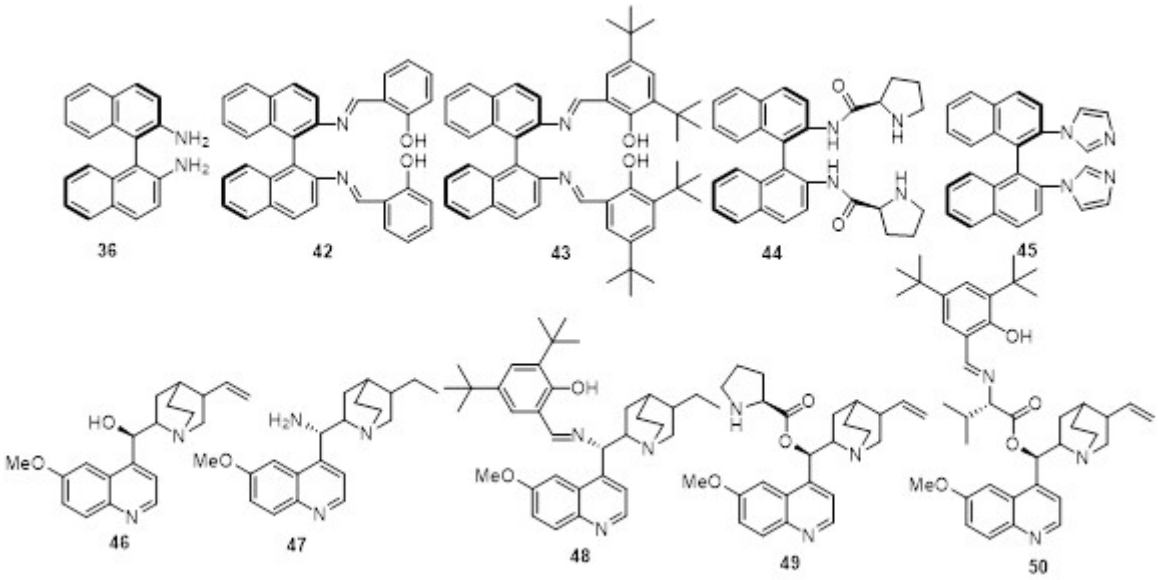
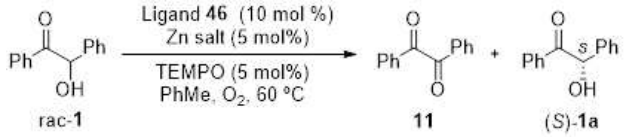


Figure 5. Ligands screened for the oxidative kinetic resolution of (±)-benzoin's.

Table 6. Effect of zinc salts and solvents on the oxidative kinetic resolution of (±)-benzoin.

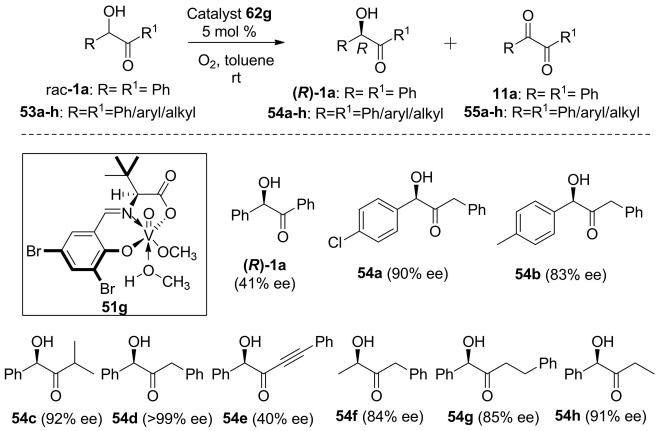


Entry	Zn salt	Solvent	Time	Conversion (%)	(*S*)-1a (% of *ee*)
1	$Zn(OAc)_2.7H_2O$	PhMe	8 h	66	26
2	ZnO	PhMe	14 h	61	28
3	ZnCl2	PhMe	47 h	63	0
4	$Zn(NO_3)_2.6H_2O$	PhMe	3 d	65	0
5	$Zn(OAc)_2.7H_2O$	PhMe	20 h	60	55
6	$Zn(OAc)_2.7H_2O$	Benzene	34 h	67	42
7	$Zn(OAc)_2.7H_2O$	$CHCl_3$	6 d	63	10
8	$Zn(OAc)_2.7H_2O$	CH_3CN	3 d	57	0
9	$Zn(OAc)_2.7H_2O$	DMF	2 d	60	0
10	$Zn(OAc)_2.7H_2O$	EtOH	4 d	56	8
11	$Zn(OAc)_2.7H_2O$	THF	3 d	60	23
12	$Zn(OAc)_2.7H_2O$	Acetone	9 d	61	14

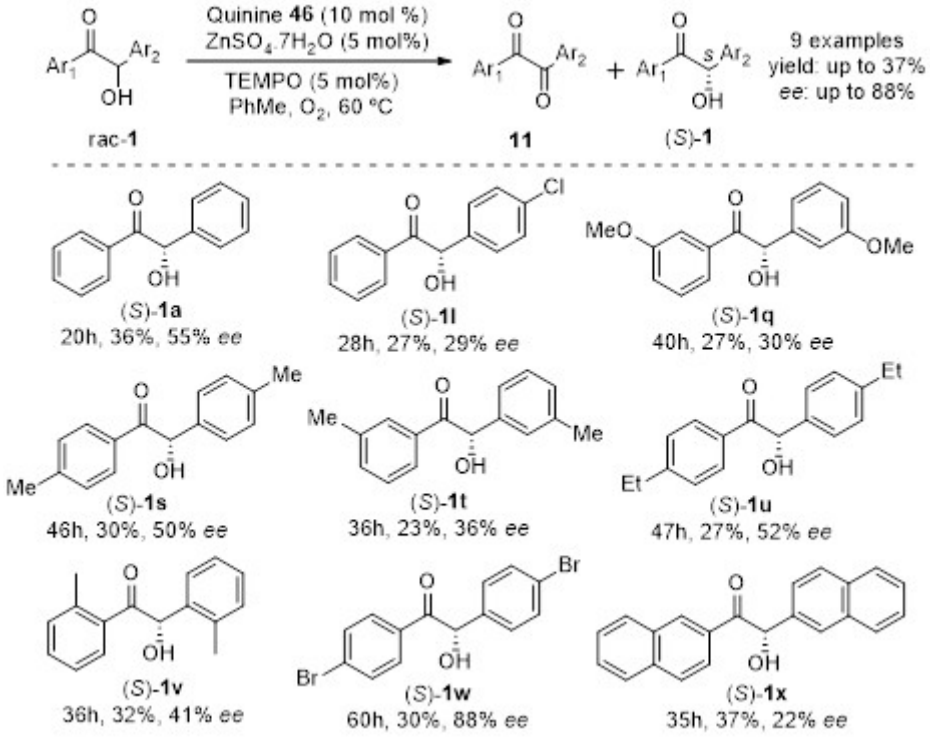
ee in the case of alkynyl ketone **53e**, possibly due to the reduced steric hindrance of the alkynyl group (Scheme 30).

The aerobic kinetic resolution of rac-benzoin **1** was screened using chiral oxidovanadium(V) methoxide catalysts **51d**, **51g**, and **52a** in various solvents. Catalyst **52a** in TBME (5 mol%) proved most effective, yielding (*R*)-**1** with 41–48% yields and up to 98% enantiomeric excess. The method also showed good enantioselectivity (up to 97% ee) for benzoin's with electron-donating or withdrawing groups at the para position of phenyl rings and heteroaryl groups like 2-furanyl, 2-thiophenyl, and 2-pyrrolyl at the R2 position (Scheme 31).

The applicability of this methodology was further demonstrated by applying the aerobic kinetic resolution protocol to benzoin derivatives bearing a 2-pyrrolyl group at the ketone side and aryl, alkyl, or aralkyl groups next to the hydroxyl group, using one of the best catalysts, **52d**. It was observed that ortho-



Scheme 30. Chiral Vanadium complex-catalyzed OKR of (*rac*)-benzoins using O_2.



Scheme 29. Chiral zinc complex-catalyzed OKR of (*rac*)-benzoins using O_2.

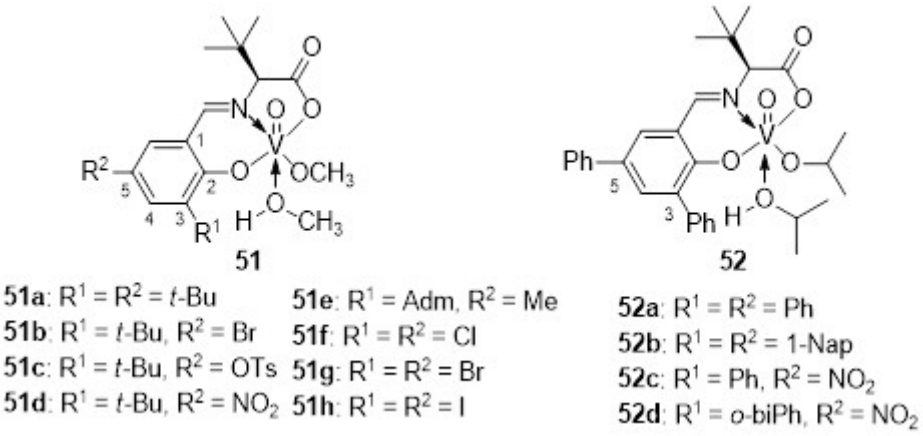
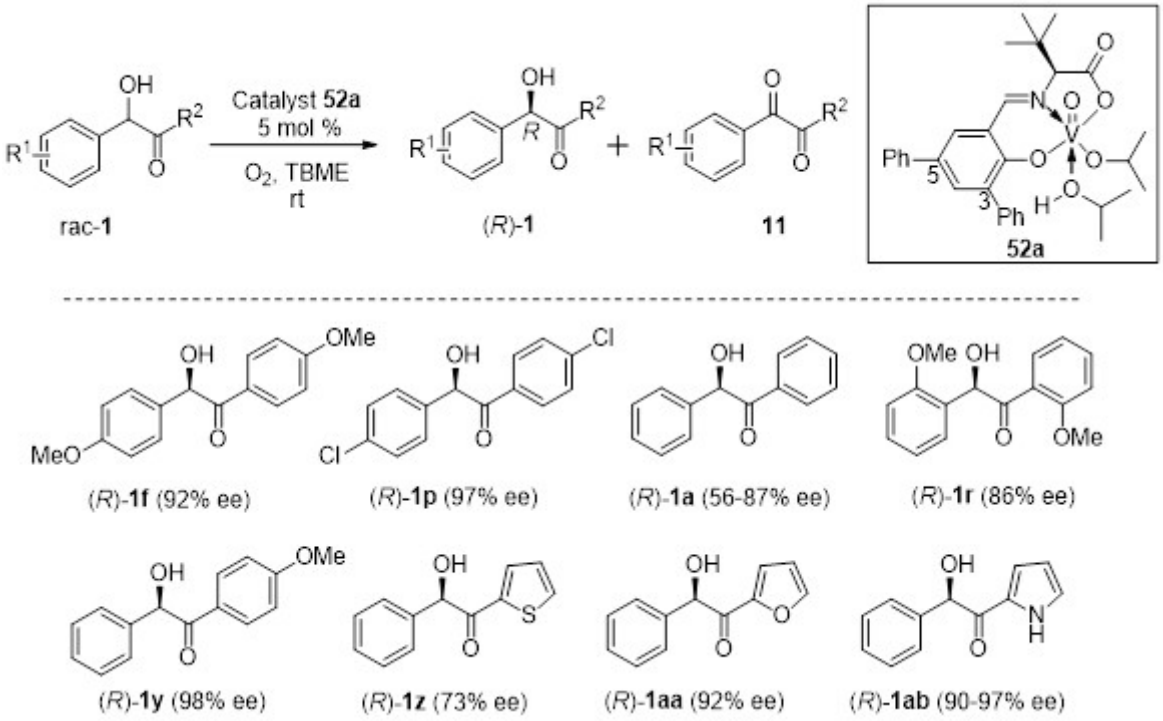


Figure 6. Chiral oxidovanadium(V) methoxides **62** & **63**.

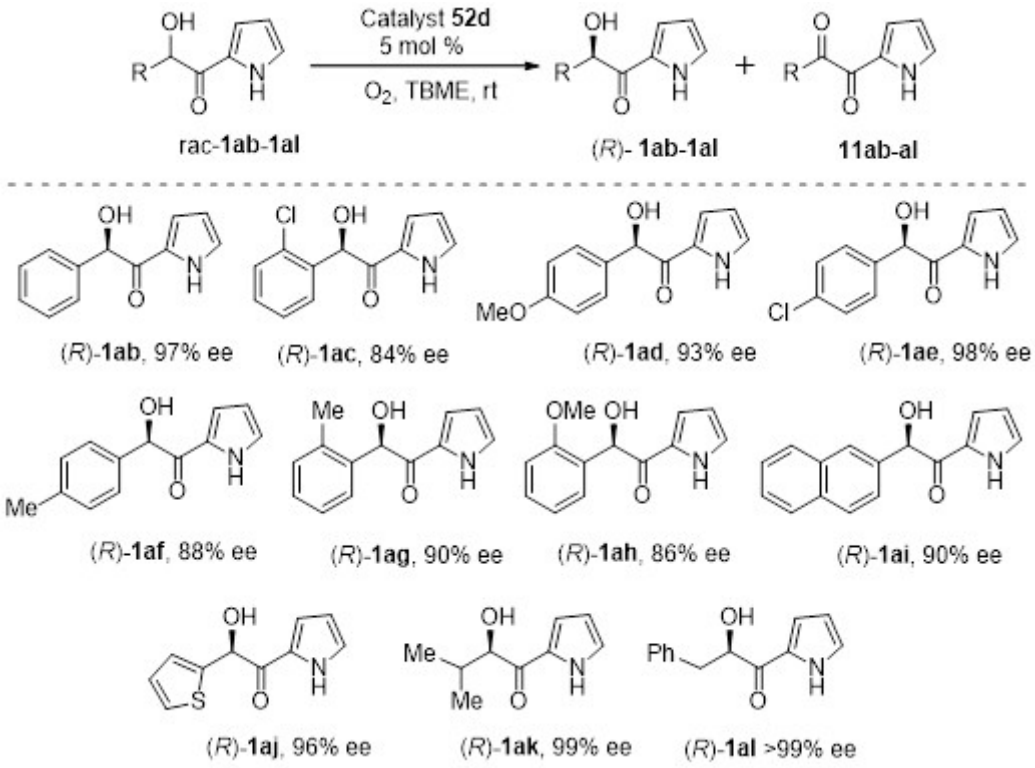


Scheme 31. Chiral Vanadium complex-catalyzed OKR of (*rac*)-benzoins using O_2.

substituted substrates provided the corresponding products with slightly lower enantioselectivity compared to their para-substituted counterparts, likely due to increased steric repulsion between the ortho-substituent and the o-biPh group at C3 of catalyst **52 d**. However, substrates with α-2-naphthyl rac-**1 ai**, and α-(2-thiophenyl) groups rac-**1 aj** also underwent asymmetric aerobic oxidation, yielding products (*R*)-**1 ai** and (*R*)-**1 aj** with excellent enantioselectivities. Interestingly, substrates containing α-alkyl groups rac-**1 ak** and rac-**1 al** also successfully underwent asymmetric aerobic oxidation, producing products (*R*)-**1 ak** and (*R*)-**1 al** with outstanding enantioselectivities (Scheme 32).

5. Reagent Mediated Resolution

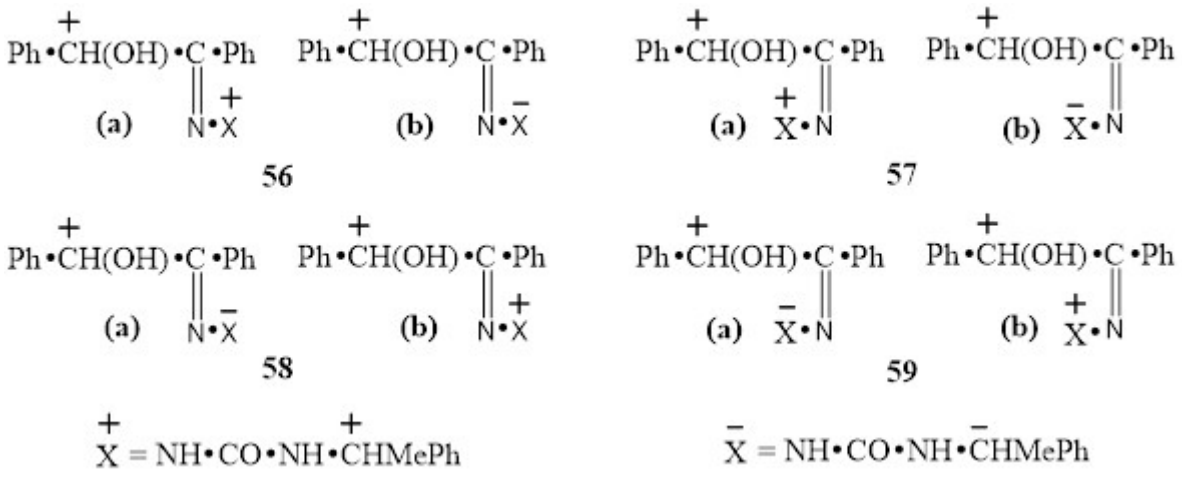
Racemic benzoin's can be resolved by adding chiral reagents, which react with the racemic benzoin's to form a diastereomeric mixture. This mixture can then be easily separated using column chromatography. In 1928, Wilson *et al.*[57] first reported the resolution of racemic benzoin using chiral δ-(α-phenylethyl)semicarbazide hydrochloride (NH_2.NH.CO.NH.CHMePh.HCl). They synthesized chiral semicarbazones δ-(α-phenylethyl)semicarbazones by reacting racemic benzoin with chiral δ-(α-phenylethyl)semicarbazide hydrochloride. Four isomers of (d)-δ-(α-phenylethyl)semicarbazone of (d)-benzoin were obtained, la-



Scheme 32. Chiral Vanadium complex-catalysed OKR of (*rac*)-benzoins using O_2.

beled as **56a**, **57a**, **58b**, and **59b**, by combining racemic benzoin with (d)-δ-(α-phenylethyl)semicarbazide (Scheme 33). When these four isomers were dissolved in pyridine, only one crystallized, while the others remained oily and highly soluble. The crystalline isomer was separated through simple filtration. Further purification by repeated recrystallization in alcohol yielded (d)-δ-(α-phenylethyl)semicarbazone, which was hydrolysed using aqueous oxalic acid to liberate pure (*d*)-benzoin with a melting point of 133–134 °C and specific rotation $[\alpha]^D = +118.3°$. Similarly, (*l*)-benzoin was obtained in pure form by reacting racemic benzoin with (l)-δ-(α-phenylethyl)semicarbazide, with a melting point of 133–134 °C and specific rotation $[\alpha]^D = -118.5°$.

In 1934, Wilson *et al.*[58] reported the resolution of benzoin using (l)-δ-menthylsemicarbazide ($NH_2NHCONHC_{10}H_{19}$). They synthesized (l)-benzoin-(l)-δ-menthylsemicarbazone by reacting chiral (l)-δ-menthylsemicarbazide with racemic benzoin in the presence of glacial acetic acid. The resulting product was purified through recrystallization in absolute alcohol, yielding (l)-benzoin-(l)-δ-menthylsemicarbazone in its pure form. This



Scheme 33. Isomers of - δ-(α-phenylethyl)semicarbazone of racemic- benzoin.

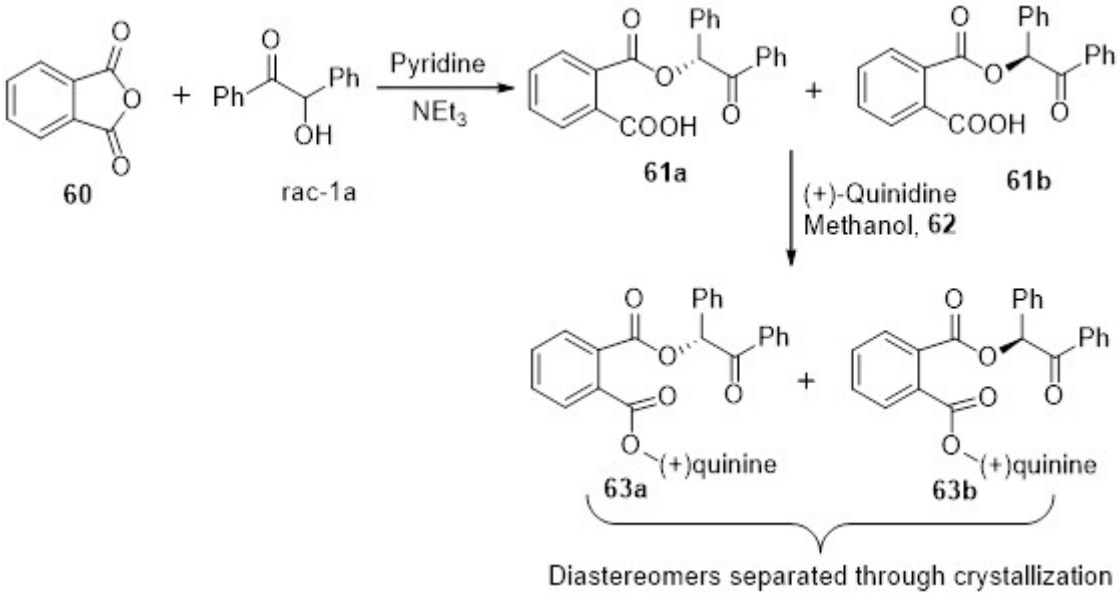
compound was then hydrolyzed using dilute aqueous-alcoholic sulfuric acid, producing pure (l)-benzoin. Due to the lengthy recrystallization process for (l)-benzoin-(l)-δ-menthylsemicarbazone, the authors did not attempt to produce the corresponding (d)-benzoin derivative.

In 1940, the same research group reported the resolution of benzoin using chiral δ-(α-phenylpropyl)semicarbazide NH_2.NH.CO.NH.CHEtPh.[59] They synthesized (d)-benzoin-(d)-δ-(α-phenylpropyl)semicarbazone by reacting (d)-δ-(α-phenylpropyl)semicarbazide hydrochloride with racemic benzoin in pyridine, followed by recrystallization in alcohol. Subsequently, (d)-benzoin-(d)-δ-(α-phenylpropyl)semicarbazone was hydrolyzed in 0.3 N sulfuric acid, yielding pure (d)-benzoin, which was recrystallized in alcohol. The resulting (d)-benzoin had a melting point of 133–134 °C and specific rotation $[\alpha]^D = +118.1°$. Interestingly, (l)-benzoin was isolated from the mother liquor remaining after the removal of (d)-benzoin-(d)-δ-(α-phenylpropyl)semicarbazone. The mother liquor, containing (l)-benzoin-(d)-δ-(α-phenylpropyl)semicarbazone, was hydrolyzed using 5 N hydrochloric acid, extracted with carbon tetrachloride, and recrystallized in alcohol. The obtained (l)-benzoin was nearly optically pure with a melting point of 133–134 °C and specific rotation $[\alpha]^D = -116.6°$. Additionally, pure (l)-benzoin was obtained similarly to (d)-benzoin by reacting racemic benzoin with (l)-δ-(α-phenylpropyl)semicarbazide hydrochloride in pyridine, followed by recrystallization in alcohol.

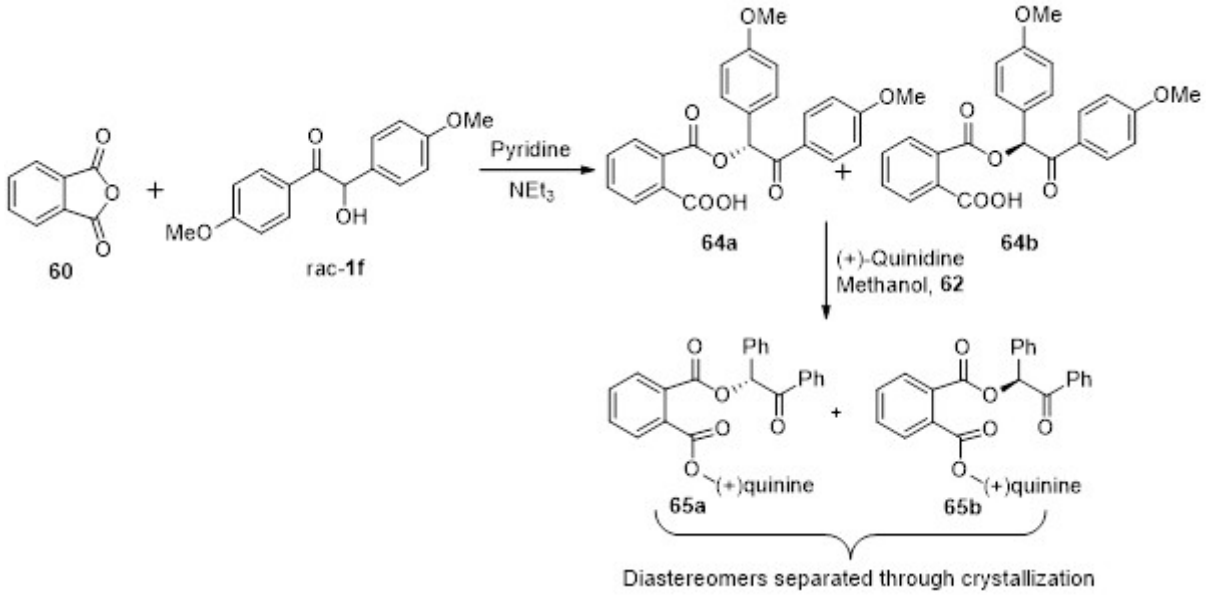
In 1965, Patel et al.[60] reported the resolution of rac-benzoin **1a** by forming diastereomers with (+)-quinidine, which were then separated using a simple crystallization technique. Initially, rac-benzoin **1a** was treated with phthalic anhydride **60** in the presence of pyridine and triethylamine to produce the hydrogen phthalate ester of (+/−)-benzoin **61a,b**. This ester subsequently reacted with (+)-quinidine **62**, yielding a mixture of two diastereomeric salts of hydrogen phthalate (+/−)-benzoin **63a,b**. The diastereomers were then separated through crystallization and filtration. Finally, enantiomerically pure (+)-benzoin was obtained by hydrolyzing the crystalline (+)-quinidine salt of the (+)-hydrogen phthalate diastereomer using 1 N sulfuric acid in ethanol, resulting in a melting point of 132–133 °C and $[\alpha]D = +118.4°$. Similarly, (−)-benzoin was liberated from the (+)-quinidine salt of the (−)-hydrogen phthalate diastereomer, also with a melting point of 132–133 °C and $[\alpha]D = -118.3°$ (Scheme 34).

In 1966,[61] the same group reported the resolution of (+/−)-4-methoxybenzoin rac-**1f** using fractional crystallization of the (+)-quinidine **65** salt of the hydrogen phthalate ester, employing a methodology similar to that used for the resolution of (+/−)-benzoin. The (+)-4-methoxybenzoin derived from the (+)-quinidine salt **65** of the (+)-hydrogen phthalate had a melting point of 102–103 °C and a specific rotation of $[\alpha]5461 = +72°$ (c 1.00 in pyridine). Conversely, the (−)-4-methoxybenzoin obtained from the (−)-hydrogen phthalate of 4-methoxybenzoin also exhibited a melting point of 102–103 °C, with a specific rotation of $[\alpha]5461 = -71.8°$ (c 1.00 in acetone) (Scheme 35).

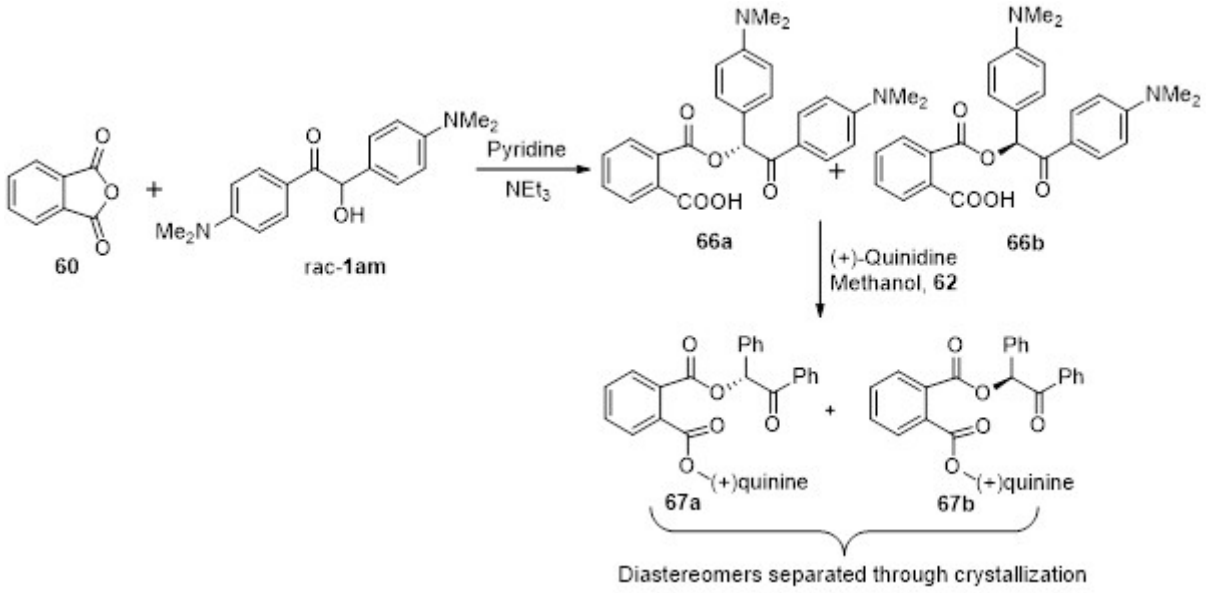
They also reported[62] the resolution of (+/−)-4-dimethylaminobenzoin rac-**1am** by forming diastereomeric salts with (+)-quinidine **62** in methanol, using the (+/−)-hydrogen phthalate of 4-dimethylaminobenzoin. The resulting (+)- and (−)-hydrogen phthalate salts **67a,b** were then hydrolyzed with hot ethanolic sulfuric acid. The (−)-4-dimethylaminobenzoin obtained from the (+)-hydrogen phthalate had a melting point of 165–166 °C and a specific rotation of $[\alpha]5893 = -22.6°$ (c 1.00 in acetone). In contrast, the (+)-4-dimethylaminobenzoin derived from the (−)-hydrogen phthalate also had a melting point of 165–166 °C, with a specific rotation of $[\alpha]5893 = +22.5°$ (c 1.06 in acetone) (Scheme 36).



Scheme 34. Resolution of rac-benzoin *via* quinidine diastereomers.



Scheme 35. Resolution of rac-4-methoxy benzoin *via* quinidine diastereomers.



Scheme 36. Resolution of rac-4-N-dimethyl benzoin *via* quinidine diastereomers.

6. Challenging Issues & Potential Progress

Resolution, while a valuable method and a noteworthy alternative to catalytic asymmetric synthesis for obtaining enantiopure molecules, comes with its own set of limitations. In the case of kinetic resolution, the process typically yields only one enantiomer, with a theoretical maximum yield of 50%. In practice, the yields for benzoin derivatives are often limited to around 45%, and the more reactive enantiomer is usually unrecoverable from the reaction mixture. Dynamic kinetic resolution has emerged as a superior approach, addressing the yield limitations associated with kinetic resolution. This method has successfully produced benzoin derivatives with impressive yields ranging from 60% to 98%. However, it primarily delivers a single enantiomer, which is often not the desired one. Most dynamic kinetic resolution techniques rely extensively on lipase enzymes. These enzymes, while effective, are scarce, costly, and prone to instability when exposed to organic acids and alcohols. Furthermore, their recovery and reuse remain significant challenges in organic synthesis.Aerobic oxidation methods for resolving benzoin derivatives have demonstrated limited success, producing enantiopure products with yields typically ranging from 15% to 45%. Additionally, reagent-mediated resolution methods for benzoin derivatives, once reported

occasionally in earlier research, have received little attention in recent years. Despite these obstacles, a considerable number of studies have explored various resolution strategies for benzoin derivatives, including kinetic, dynamic kinetic, aerobic oxidative kinetic, and reagent-mediated approaches.

7. Conclusions

Benzoins (1,2 diaryl-2-hydroxyethanone structures) feature two adjacent functional groups a carbonyl and a hydroxy group that can easily be converted into vital organic intermediates, such as 1,2 amino alcohols and 1,2 diols. Additionally, the two aryl groups present in benzoins can be readily modified, further enhancing their versatility. Due to these structural characteristics, chiral benzoins play a crucial role in the chemical and pharmaceutical industries, serving as intermediates for the synthesis of biologically active natural products. Moreover, their derivatives are used as catalysts in photopolymerization and serve as anticratering agents in powder coatings. Benzoin has also been reported to exhibit antibacterial and antifungal properties, making it useful in treating skin disorders. Additionally, it serves as a starting material for the synthesis of complexes such as Schiff base compounds, which have significant applications in medicine, biochemistry, and various industries. Given their importance, numerous research groups have developed deracemization protocols to produce chiral benzoins, including methods such as kinetic resolution, dynamic kinetic resolution, metal-catalyzed aerobic oxidative kinetic resolution, and reagent-mediated resolution, alongside existing reports on the asymmetric synthesis of chiral benzoins. In this review, we broadly present the various deracemization methods for obtaining chiral benzoins. As far as we know, no comprehensive review on the resolution of racemic benzoins has been published to date. We strongly believe that our review will be a valuable resource for modern synthetic organic chemists working in the field of asymmetric synthesis, and we anticipate exciting advancements in this area in the near future.

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Author Contributions

Literature survey, original draft preparation, K. Raveendra Babu.; visualization, validation, B.Anusha.; visualization, validation, Marri Naveen kumar.; visualization, validation, P. Sundar Singh.; visualization, validation, S. Ramakrishna.; original draft preparation, super vision, U.V. Subba Reddy.

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Conflict of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Keywords: Benzoin · Kinetic resolution · Dynamic kinetic resolution · Aerobic oxidation kinetic resolution · Reagent mediated resolution · Optically pure α-hydroxy ketones

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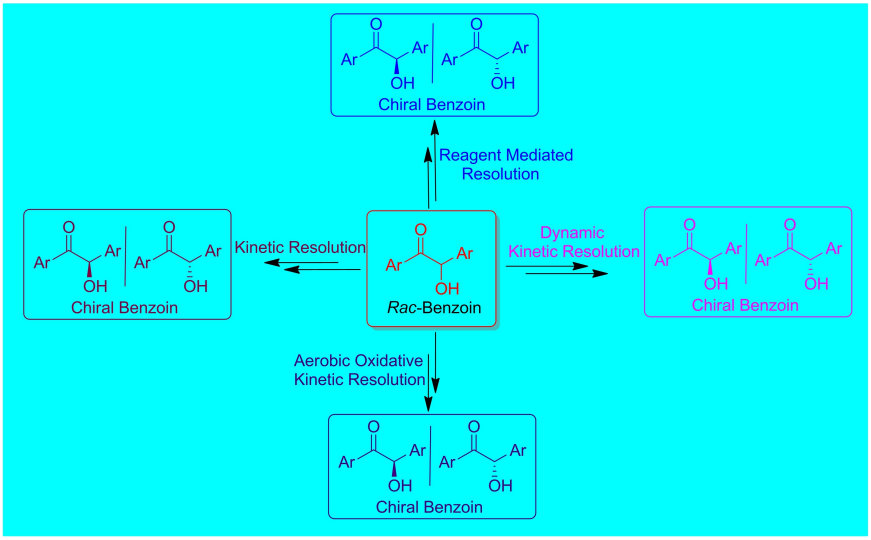

*R. Babu Kothapalli, B. Anusha, M. Naveen Kumar, P. S. Singh, S. Ramakrishna, U. Venkata Subba Reddy**

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Deracemization of Benzoin and its Derivatives *via* Kinetic, Dynamic Kinetic, Aerobic Oxidative Kinetic, and Reagent-mediated resolution

The production of enantiomerically pure compounds remains a vital and valuable objective in modern organic chemistry due to their broad applications in fields such as biosensing, optics, electronics, photonics, catalysis, nanotechnology, and drug or DNA delivery. Optically pure α-hydroxy ketones, in particular, are key structural components in many drugs and natural products with significant biological activity. Among these, benzoin-type α-hydroxy ketones, which possess two adjacent functional groups a carbonyl and a hydroxy group are especially important. These functional groups can be easily transformed into vital organic compounds such as 1,2-amino alcohols and 1,2-diols etc, which are important intermediates for synthesis of high profile biological active natural products. Deracemization of racemic compounds remains one of the most effective strategies for producing optically pure compounds, despite recent advances in asymmetric synthesis. Due to the importance of chiral benzoins, numerous studies have focused on their asymmetric synthesis. At the same time, many research groups have developed various methods for resolving racemic benzoins, including kinetic resolution, dynamic kinetic resolution, metal-catalyzed aerobic oxidative kinetic resolution, and reagent-mediated resolution. In this context, we aim to provide a comprehensive review of the various resolution methods applied specifically to racemic benzoins. To the best of our knowledge, no comprehensive review on the resolution of racemic benzoins has been published to date