Check for updates

ChemCatChem

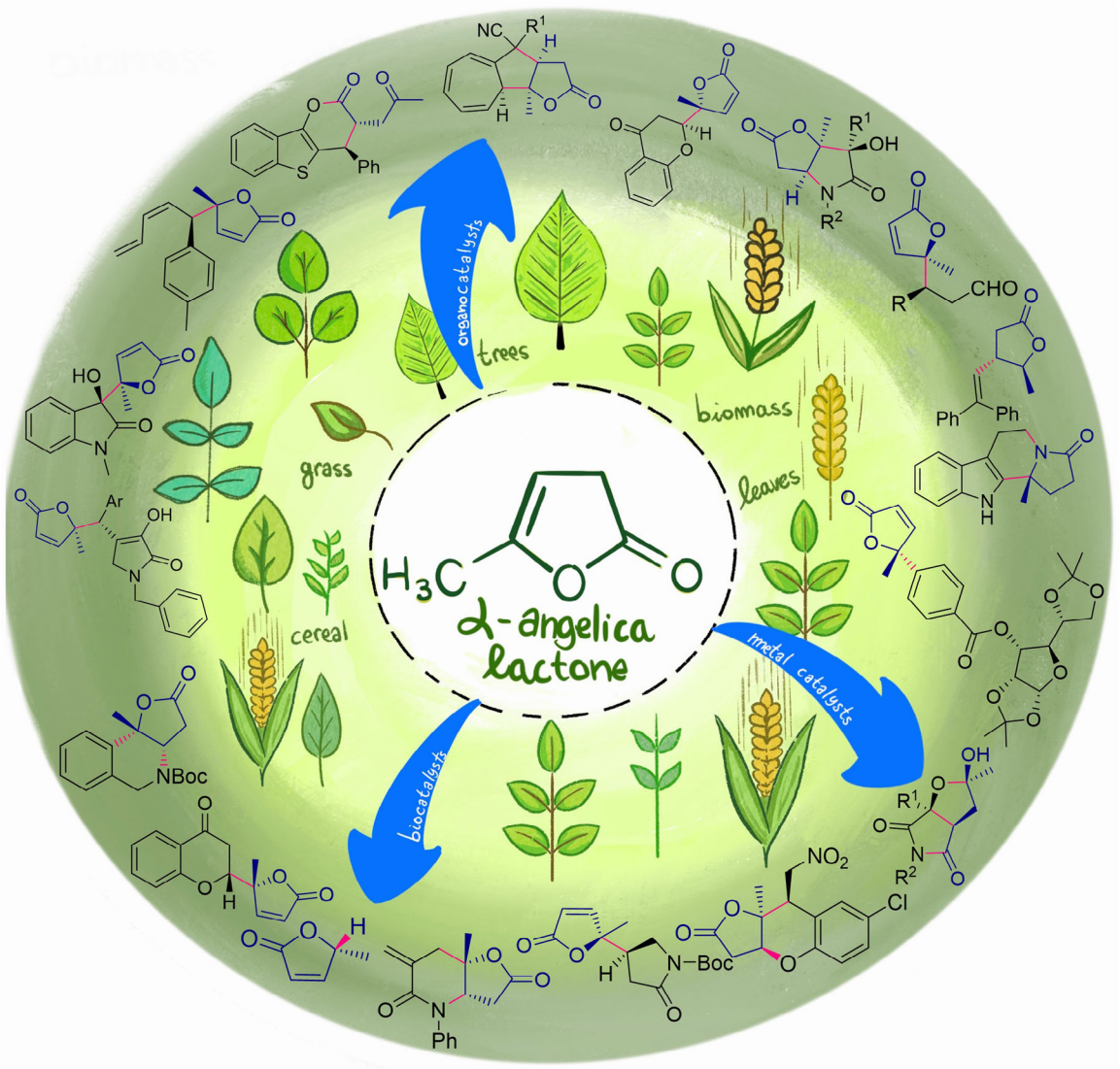
Review
doi.org/10.1002/cctc.202500060

Chemistry Europe
European Chemical Societies Publishing

www.chemcatchem.org

Organo-, Metal-, and Enzyme-Mediated Stereoselective Transformations of α-Angelica Lactone

Amina Moutayakine,[a] Sara Meninno,*[a] and Alessandra Lattanzi*[a]



© 2025 The Author(s). ChemCatChem published by Wiley-VCH GmbH

α-Angelica lactone is a five-membered heterocycle belonging to the rich family of butenolides, a key motif, present in a great variety of bioactive and natural products. Moreover, it is a small compound attainable from the platform molecule levulinic acid, which in turn is readily accessible from lignocellulosic biomass. These important features contributed to arousing interest in α-angelica lactone over the last years. Beyond its upgrading to added value products, such as γ-valerolactone, polymers, and biofuels, α-angelica lactone has been identified as a building block in natural product synthesis and a useful reagent in asymmetric catalysis. In this minireview, we provide an overview of diastereo- and enantioselective organo-, metal-, and enzymatic approaches reported from 2020 up to 2024, where this heterocycle has been used as the starting material. α-Angelica lactone proved to be a versatile scaffold in stereoselective vinylogous 1,4- and 1,2-addition, cycloaddition, isomerization, γ-arylation, and reduction reactions.

1. Introduction

γ-Butenolides are amongst the most interesting five-membered heterocycles, often occurring as enantioenriched framework embedded in natural product structures, endowed with several bioactivities.[1] These can be exemplified by Lambertellol A, a potent antifungal compound produced by mycoparasite *Lambertella* sp. 1346,[2] Asteriscunolide D, which showed a significant anticancer activity toward different cell lines,[3] Avenolide, a hormone involved in the control of *Streptomyces* antibiotic production,[4] (+)-Strigol, a terpenoid phytohormone involved in the regulation of seed germination in plants,[5] and Kallolide A, a member of the pseudopteranes, endowed with anti-inflammatory activity (Figure 1).[6]

As a consequence of γ-butenolides widespread presence in natural products, synthetic efforts have been devoted to approaching molecules containing this motif, assigning absolute configuration of the stereocenters, with a view to assessing the corresponding bioactivities.[7] Moreover, besides total syntheses of γ-butenolide-based natural products, we assisted to a great interest in developing asymmetric catalytic methodologies for the construction of new γ-butenolide architectures or the elaboration of γ-butenolide molecular platforms to achieve diversely functionalized γ-butyrolactones as potential new bioactive products and also functionalized ring-opened intermediates. Specifically, γ-butyrolactones are recognized as a highly important motif present in bioactive compounds, pharmaceuticals, and food chemistry and serve as building blocks for further elaborations.[8]

From a synthetic point of view, β,γ-unsaturated butenolides, alternatively named as deconjugated butyrolactones, are the most versatile compounds, thanks to their mild α-acidicity,[7] and they are suitable for regioselective installation of new stereocenters at α- or γ-positions when using electrophiles.[9] After easy carbon—carbon double bond isomerization, less explored reactivity with nucleophiles at the β-position has been demonstrated.[10] Finally, when using reagents bearing both electrophilic and nucleophilic groups, the construction of complex polycyclic derivatives in cascade processes can be attained (Figure 2).[11]

The synthetic potential of β,γ-unsaturated butenolides has more recently directed at leveraging readily available α-angelica lactone,[12] a flavor present in different natural sources and belonging to the family of angelica lactones, which feature different isomeric forms, according to the position of the carbon—carbon double bond (α-, β-, and γ-angelica lactone). Additionally, α-angelica lactone can be conveniently obtained from lignocellulosic biomass after elaboration of the platform molecule levulinic acid.[13] This allows its employment as a renewable feedstock either to prepare value-added compounds such as γ-valerolactone, biofuels, and fragrances and to develop catalytic asymmetric approaches useful for the construction of bioactive molecules, drugs and functionalized building blocks.[7]

Excellent reviews on the employment of deconjugated butyrolactones in asymmetric synthesis and industrial applications have been previously reported.[7,12] This minireview is meant to highlight the significant advances reported from 2020 up to 2024 in stereoselective reactions employing α-angelica lactone as the starting material. After a first section focused on purely diastereoselective protocols, the manuscript has been subdivided according to organo-, metal-, and bio-catalytic tools applied for the diastereo- and enantioselective synthesis of functionalized derivatives.

2. Diastereoselective Reactions

A straightforward transformation of α-angelica lactone concerns the direct generation of a dienolate/dienol species under mild conditions and its capture by electrophiles at γ-position, leading to the installation of a quaternary stereocenter (Scheme 1). Mostly amine-based catalysts and metal systems were demonstrated to promote asymmetric vinylogous addition with a great number of Michael acceptors, imines, and aldehydes and activated carbonyl compounds.[14]

In this context, a challenging transformation has been illustrated by the Shenvi group using stoichiometric amounts of LDA to promote the reaction of two butenolides with opposite electronic features, with α-angelica lactone as the electron-rich dienolate species, under kinetic conditions (Scheme 2).[15]

[a] Dr. A. Moutayakine, Prof.Dr. S. Meninno, Prof.Dr. A. Lattanzi
Department of Chemistry and Biology, University of Salerno, Via Giovanni Paolo II 132, Fisciano 84084, Italy
E-mail: smeninno@unisa.it
lattanzi@unisa.it

© 2025 The Author(s). ChemCatChem published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

18673899, 2025, 10, Downloaded from https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/cctc.202500060 by Universita Di Salerno, Wiley Online Library on [04/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

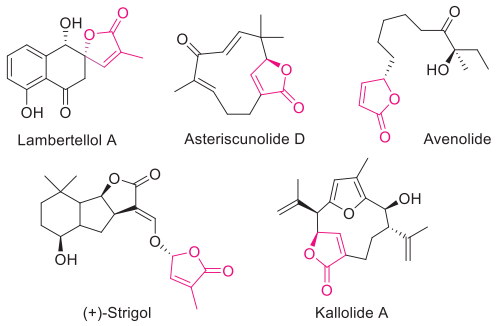


Figure 1. Bioactive natural products bearing a γ-butenolide framework.

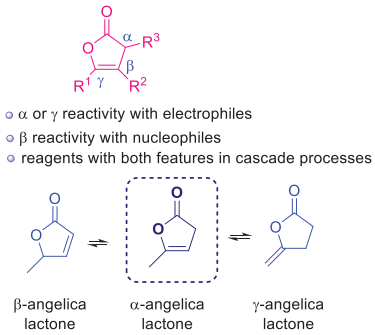
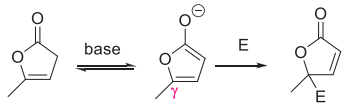
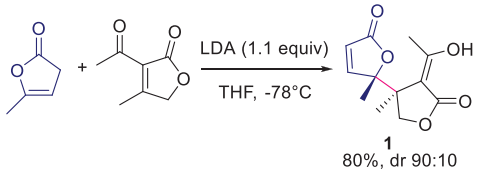


Figure 2. General reactivity of β,γ-unsaturated butenolides and α-angelica lactone isomeric forms.



Scheme 1. Base-catalyzed reactivity of α-angelica lactone at γ-position.



Scheme 2. LDA-promoted diastereoselective heterodimerization of α-angelica lactone with an electrophilic butenolide under kinetic conditions.

Remarkably, a new carbon—carbon bond, connecting two quaternary stereocenters, has been rapidly installed, leading to the racemic butenolide heterodimer **1** in high yield and diastereoselectivity. This challenging reaction has been successfully extended to differently substituted butenolide acceptors and nucleophilic counterparts, although the reaction proved to be particularly sensitive to electronic and steric features of both partners. A detailed mechanistic study, additionally aided by DFT calculations, showed that species aggregation, as well as



Amina Moutayakine received her MSc in Chemistry from the University Hassan II (Morocco), specializing in organic synthesis and medicinal chemistry. In 2023, she obtained her PhD at both the University of Evora (Portugal) and the University of La Laguna (Spain), working under the joint supervision of Prof. Anthony Burke (Evora) and Prof. José M. Padrón (Tenerife). Currently, she is working as a postdoctoral fellow at the University of Salerno (Italy) under the guidance of Prof. Sara Meninno and Prof. Alessandra Lattanzi. Her current project aims to develop pharmaceutically active heterocycles through asymmetric synthesis.



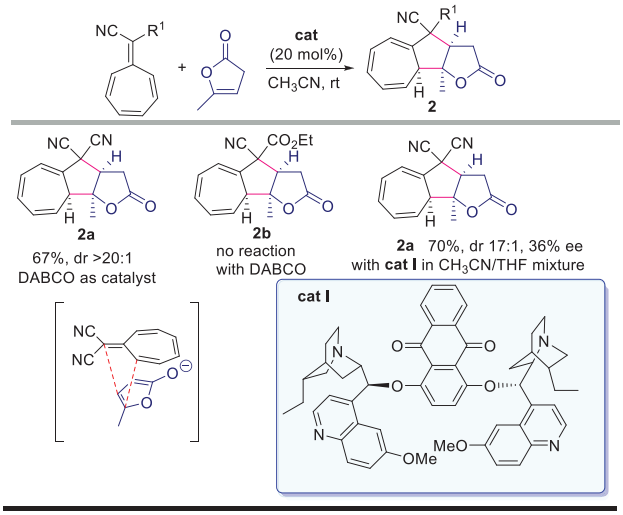
Sara Meninno received her M.S. degree (2011) and Ph.D. degree (2015) from the University of Salerno, under the supervision of Prof. Lattanzi. She did post-doctoral research at the University of Salerno from 2015 to 2018. In 2018, the Accademia Nazionale dei Lincei awarded her a Royal Society of Chemistry fellowship to spend in the UK. She joined Prof. Rios's group at Southampton University. In 2019, she returned to the University of Salerno as a research fellow, and since late 2024, she has been appointed as an associate professor of organic chemistry. Her research interests include the design of green stereoselective organocatalyzed protocols to synthesize functionalized intermediates and bioactive heterocyclic compounds, starting from readily available building blocks, including biomass-derived molecules.



Alessandra Lattanzi graduated and earned her PhD from Sapienza University of Rome in 1997. She has been a visiting scientist in the groups of Prof. V. K. Aggarwal (Sheffield, 1999–2000) and Dr. N. E. Leadbeater (London, 2001). She is full professor of organic chemistry at the University of Salerno. In 2024, she was the recipient of the research award in the Development of Synthetic Methodologies from the Italian Chemical Society. She has been interested in asymmetric metal-catalyzed oxidations and description of molecular chirality through algebraic approaches. Her main interests include asymmetric organocatalysis with a focus on one-pot and environment friendly synthesis of heterocyclic and bioactive compounds.

© 2025 The Author(s). ChemCatChem published by Wiley-VCH GmbH

18673899, 2025, 10, Downloaded from https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/cctc.202500060 by Universita Di Salerno, Wiley Online Library on [04/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License



Scheme 3. Diastereoselective [8 + 2]-cycloaddition of α-angelica lactone with 8,8-dicyanoheptafulvene.

the electronic complementarities between the reacting butenolides, are key to the success of the reaction. Interestingly, the new chemical space, offered by the sterically congested butenolides motif, enabled the identification of promising inhibitors of the cyclic GMP–AMP synthase/stimulator of interferon genes pathway.[16]

In 2022, Albrecht and coauthors reported an uncommon cyclization using heptafulvenes as higherenes, which, thanks to the presence of conjugated double bonds, can serve to build up complex cyclic compounds with useful bioactivities.[17] After a screening of different common bases and solvents, 20 mol% of DABCO was found to be the most effective for the [8 + 2]-cycloaddition of 8,8-dicyanoheptafulvene with α-angelica lactone in acetonitrile as the solvent (Scheme 3).

The tricyclic product **2a** was isolated in 67% yield and essentially as a single diastereoisomer, whose relative configuration was confirmed by single-crystal X-ray analysis. When an ester group replaced the cyano moiety in the heptafulvene, the reaction did not give product **2b**. Attempts to develop an asymmetric version of this process, using common organocatalysts derived from Cinchona alkaloids, proved to be unfruitful. However, when using the dimeric Cinchona alkaloid catalyst **I**, product **2a** was obtained with 70% yield, high diastereoselectivity, and 36% ee.

Mechanistically, the authors proposed a model where the dienolate acts as higherenophile in the cycloaddition, in agreement with the stereochemical result.

In 2023, Kang and coworkers reported a switchable cascade cyclization to obtain either γ-lactone-fused γ-lactams **3** or succinimide-fused hemiketals **4**,[18] present as frameworks in biologically active and natural compounds (Scheme 4).[19] Interestingly, according to the nature of the base and reaction conditions, readily available α-ketoamides and α-angelica lactone underwent chemodivergent cascade pathways, involving: i) aldol/aza-Michael reactions to γ-lactone-fused γ-lactams **3**, or ii) aldol/imidation/hemiketalization to succinimide-fused hemiketals **4**. A variety of differently substituted heterocycles **3**, bearing three stereocenters, have been obtained in generally good yield and high diastereoselectivity when 20 mol% of the strong tetramethyl guanidine (TMG) was used in dioxane as the solvent (Scheme 4). The chemodivergent pathway to succinimide-fused hemiketals **4** required fine optimization of the reaction conditions with the use of 20 mol% of NaOAc in DMF. The heterocycles **4** were isolated in modest to good yield and complete diastereoselectivity. The relative configuration of the three stereocenters for heterocycles **3** and **4** was assigned by X-ray crystallographic analysis. Both cascade processes could be successfully scaled up to 5 mmol of the starting α-ketoamide.

Solvation effects and the nature of the base greatly influenced the α- or γ-selectivity of the α-angelica lactone enolate in the aldol reaction with α-ketoamide (Scheme 5). After deprotonation of α-angelica lactone, γ-selective aldol reaction affords, after proton transfer, intermediate **A**. The latter then undergoes an intramolecular aza-Michael reaction to form intermediate **B**, which, after protonation, would lead to heterocycle **3**.

In the other catalytic cycle, reaction conditions favor an α-selective aldol reaction to afford, after proton transfer, intermediate **C**, suitably positioned to be engaged in the intramolecular imidation, and giving compound **D**. Then, ketalization would complete the cascade sequence to product **4**.

In 2023, Baidya and coworkers illustrated a highly diastereoselective Michael reaction of α-angelica lactone with cyclic α-amide enones **5**, catalyzed by commercially available quinidine (Scheme 6).[20] A small library of butyrolactone–butyrolactam hybrid molecules **6** has been efficiently obtained with complete γ-selectivity and diastereoselectivity. The relative configuration of the stereocenters was assessed by single-crystal X-ray analysis. Unfortunately, the reaction afforded racemic compounds.

α-Amide enones **5** served as a useful masked γ-butyrolactam unit to couple with the nucleophilic reactivity of α-angelica lactone. Important heterocyclic frameworks, of potential use in drug candidates and bioactive complex derivatives synthesis, are easily accessible.

3. Organocatalytic Asymmetric Reactions

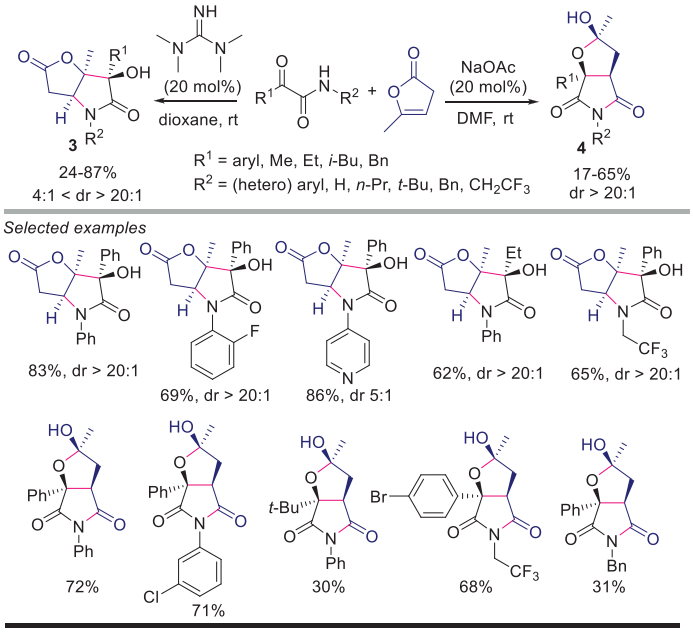
Organocatalysis, alongside metal catalysis, has proven to be an effective strategy for efficiently employing butenolides as pronucleophiles in vinylogous transformations, such as Michael additions, aldol reactions, Mannich reactions, and allylic alkylations of deconjugated butenolides. Leveraging their ability to enolize under basic conditions, deconjugated butenolides have been reacted with numerous electrophilic species.[21]

In this paragraph, the transformations of α-angelica lactone are illustrated based on the class of organocatalyst used, including bifunctional thioureas, catalysts containing a diaminomethylenemalonitrile residue, squaramides, phase-transfer catalysts, phosphines, and chiral phosphoric acids. Finally, an example of synergistic catalysis is discussed, where the Jørgensen–Hayashi prolinol catalyst is combined with a transition metal.

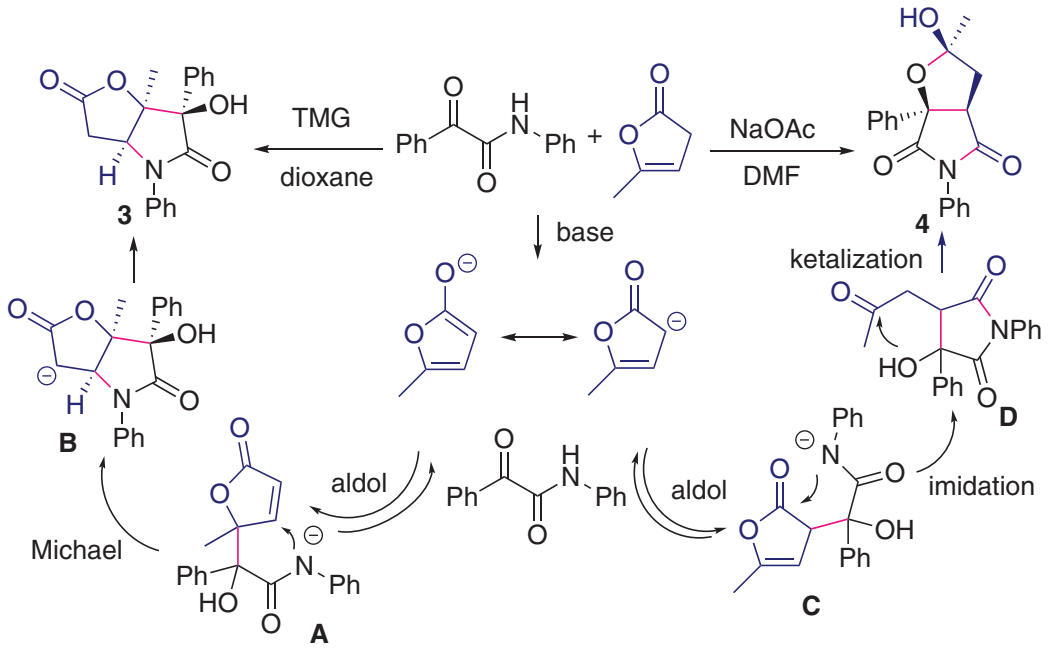
The first vinylogous Michael addition of α-angelica lactone dates back to 2010, as reported by Chen and coworkers, and

© 2025 The Author(s). ChemCatChem published by Wiley-VCH GmbH

18673899, 2025, 10, Downloaded from https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/cctc.202500060 by Universita Di Salerno, Wiley Online Library on [04/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License



Scheme 4. Diastereoselective and chemodivergent base-catalyzed cascade reactions to γ-lactone-fused γ-lactams and succinimide-fused hemiketals.



Scheme 5. Catalytic pathways for the cascade reactions to γ-lactone-fused γ-lactams and succinimide-fused hemiketals.

consisted of an allylic alkylation of several deconjugated butenolides in the presence of Morita–Baylis–Hillman (MBH) carbonate, which proceeded under the catalysis of dimeric Cinchona alkaloid $(DHQD)_2PYR$, leading to a wide variety of bicyclic lactams bearing quaternary and tertiary stereocenters in modest yields, but exceptional enantio- and diastereoselectivity.[22]

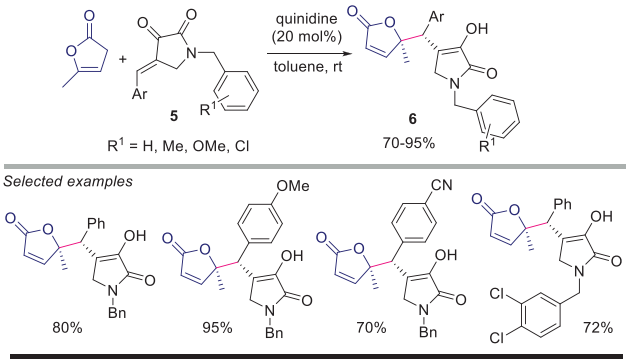
This innovative work inspired the widespread use of α-angelica lactone and butenolide derivatives as fundamental building blocks for the construction of optically active architectures via organocatalyzed methodologies, making this approach increasingly recognized within the field of asymmetric catalysis. This strategy holds significant potential for advancing research and developing chiral intermediates for various applications.

Thiourea-based catalysts have gained increasing popularity in asymmetric synthesis due to their ability to activate a wide range of substrates through hydrogen bonding interactions.[23]

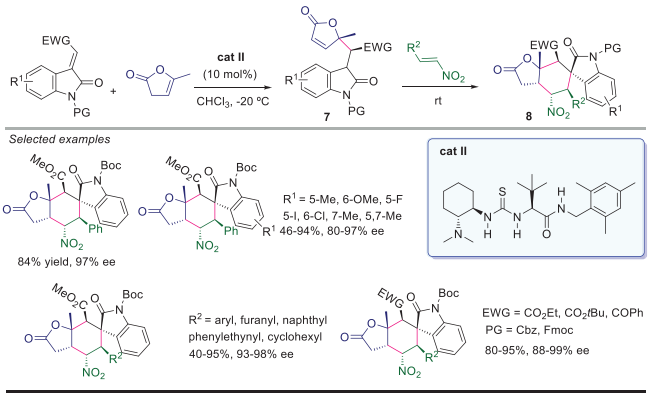
In 2022, You and coworkers reported an unprecedented multicomponent synthesis of cyclohexane-fused α-angelica lactone derivatives **8** containing a spiro-oxindole unit, known for its potent medicinal properties (Scheme 7).[24] This synthesis proceeds through an asymmetric formal [2 + 2 + 2] annulation involving α-angelica lactone/butenolides and two

© 2025 The Author(s). ChemCatChem published by Wiley-VCH GmbH

18673899, 2025, 10, Downloaded from https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/cctc.202500060 by Universita Di Salerno, Wiley Online Library on [04/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License



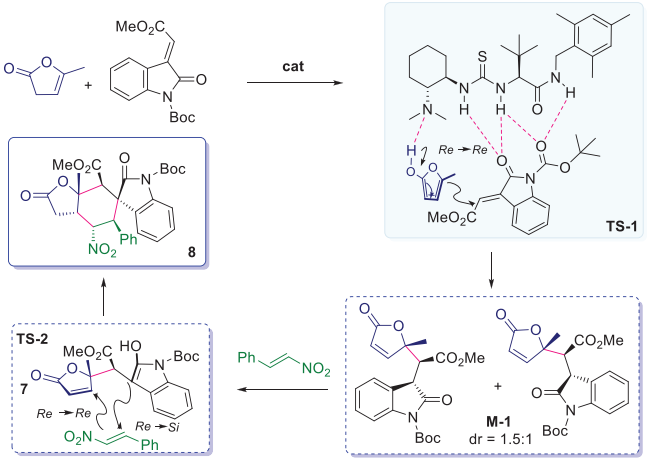
Scheme 6. Highly diastereoselective quinidine-catalyzed vinilogous Michael reaction of α-angelica lactone to butyrolactone–butyrolactam hybrids.



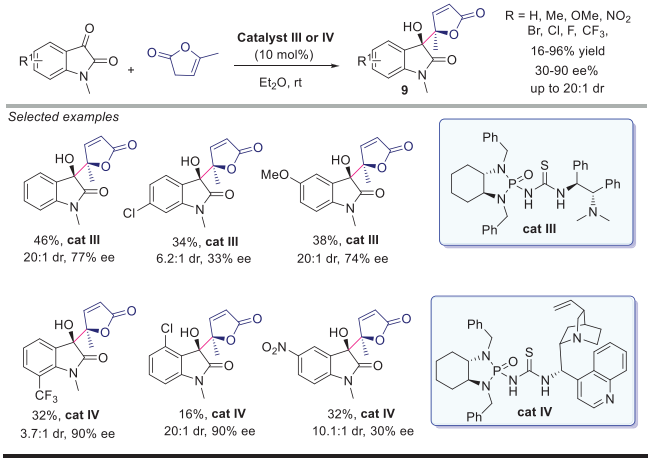
Scheme 7. Enantioselective annulation of α-angelica lactone, methylene indolinones, and nitroalkenes.

Michael acceptors: methylene indoline and nitroalkene. Several organocatalysts were found suitable for this one-pot process. Notably, a bifunctional *L-tert*-leucine-derived thiourea catalyst was identified as particularly effective, outperforming commonly used thioureas screened in the process. This catalyst exhibited enhanced stereocontrol due to its capability to activate the Michael acceptor and donor simultaneously by forming multiple hydrogen bonds. The strategy accommodates a variety of indoline and nitroalkenes, producing a diverse array of complex architectures that feature six contiguous stereocenters, achieved in excellent yields and enantioselectivity. Substrates bearing electron-withdrawing groups adjacent to the alkene, on the indoline motif, considerably enhanced the electrophilicity of the Michael acceptor, thereby facilitating the dual Michael addition.

The authors proposed a mechanistic pathway initiated by a vinylogous Michael addition of α-angelica lactone to methylene indolinones, driven by hydrogen bonding interactions provided by the L-*tert*-Leucine-derived thiourea catalyst (Scheme 8). The Michael addition proceeded through a *Re* → *Re* transition state **(TS-1)** to afford intermediate **(M-1)** as a diastereomeric mixture (1.5:1 dr, determined by ^{1}H NMR) arising from the oxindole ring unit. Under stereoselective induction of the catalyst, the **(M-1)** intermediate undergoes enolization upon the addition of the nitroalkene, triggering a double cascade Michael addition that



Scheme 8. Suggested mechanism for the amino thiourea **II** catalyzed addition of α-angelica lactone, methylene indolinones, and nitroalkenes.



Scheme 9. *N*-Diaminophosphoryl catalyzed vinylogous aldol reaction of isatins and α-angelica lactone.

occurs by *Re* → *Si* and *Re* → *Re* fashion **(TS-2),** respectively, to give the desired product **8** as a single diastereoisomer.

In a recent study, Pansare and coworkers documented the use of enantiomerically enriched *N*-diaminophosphorylaminothiourea catalyst in an asymmetric vinylogous coupling of α-angelica lactone with *N*-methylisatine derivatives,[25] leading to 3-hydroxy-2-oxindole derivatives **9**, an important structural feature omnipresent in countless natural compounds and medicinally relevant units (Scheme 9).[26] Under optimized conditions, a diverse array of 3-hydroxy-2-oxindoles **9** was successfully attained. The thiourea motif was anticipated to activate the isatin motif through hydrogen bonding with the acidic *N*—H functionalities of the thiourea. Simultaneously, the tertiary amine was expected to trigger the generation of the furanone-derived enolate via deprotonation. The incorporation of a chiral cyclic phosphoramide, bearing *N*-benzyl functionality, contributed tremendously to the stereocontrol of this approach, as it is believed to promote greater stabilization of the isatin, thereby controlling its orientation. This finding was conclusively validated by substituting the cyclohexanediamine-derived phosphoramide with

© 2025 The Author(s). ChemCatChem published by Wiley-VCH GmbH

18673899, 2025, 10, Downloaded from https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/cctc.202500060 by Universita Di Salerno, Wiley Online Library on [04/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

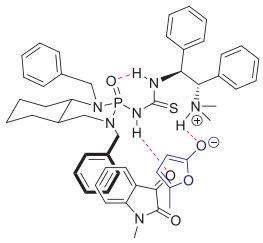
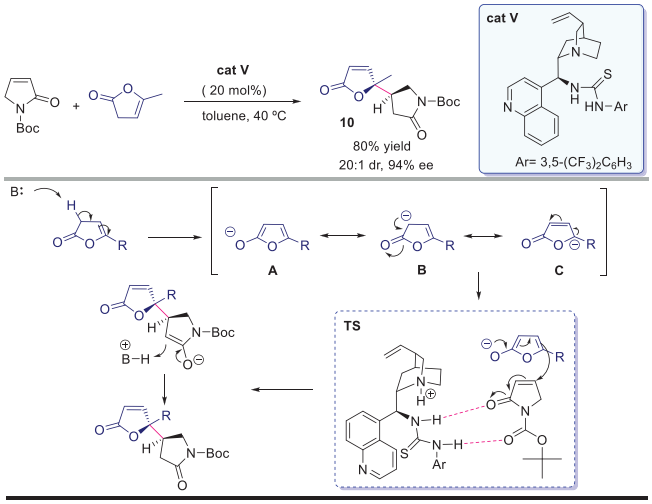


Figure 3. Plausible transition state of the *N*-diaminophosphoryl aminothiourea catalyzed vinylogous aldol reaction.



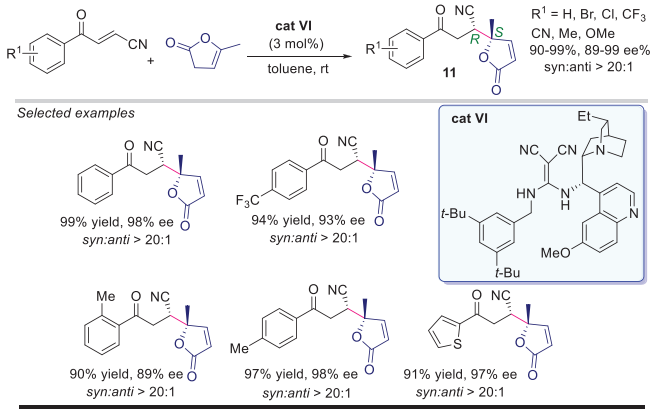
Scheme 10. Cinchonidine-thiourea catalyzed Michael addition of α-angelica lactone to α,β-unsaturated-γ-lactam.

a 1,2-diphenylethanediamine phosphoramide, which significantly undermined the enantioselectivity. Catalysts **III** and **IV** performed the best among an extensive set of thiourea-based catalysts screened in the process.

The low yields, observed in certain instances, were ascribed to side reactions involving nucleophilic addition at the carbonyl group of the furanone, occurring prior to protonation of the aldolate units. The plausible transition state responsible for the high enantiocontrol can be explained as follows: i) The *N*-diamino phosphoryl amino thiourea forms internal hydrogen bonds involving the phosphoryl oxygen atom and the first *N*-H group. ii) The carbonyl group of *N*-methyl isatin forms a second H-bond with the free *N*-H of the thiourea group, whilst the α-lactone enolate establishes an additional H-bond with the ammonium group (Figure 3). The latter is in situ generated via deprotonation of α-angelica lactone by the tertiary amine. The orientation of the isatin and the lactone would be controlled by the chirality of the 1,2-diphenylethanediamine moiety, which favors the *Si–Si* exposition of the two units.

Albrecht and coauthors reported an efficient organocatalytic asymmetric Michael addition of α-angelica lactone/γ-butenolides to α,β-unsaturated-γ-lactam, leading to a promising hybrid scaffold **10**, in a highly diastereoselective and enantioselective manner (Scheme 10).[27]

The process efficiency derives from the concomitant activation of both partners provided by bifunctional Cinchona



Scheme 11. Vinylogous conjugate addition of α-angelica lactone to benzoyl acrylonitriles catalyzed by a hydroquinine-derived DMM catalyst.

alkaloids organocatalyst. The Brønsted base deprotonates the lactone, while the H-bonding donor group activates the α,β-unsaturated-γ-lactam. The reaction exhibited remarkable versatility and structural tolerance toward a wide range of alkyl and aryl-substituted butenolide precursors with diverse substitution patterns.

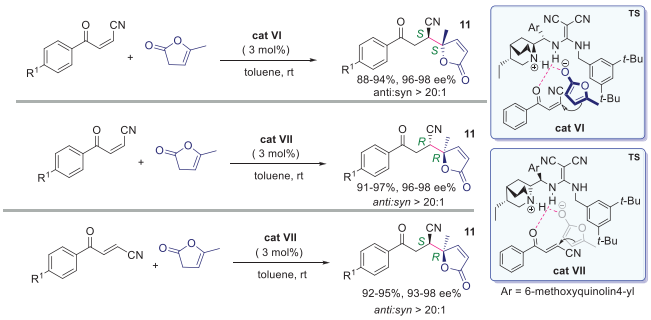
The mechanistic scenario suggested would involve deprotonation of the lactone at the α-position by the catalyst to yield the corresponding dienolate intermediate, described by the mesomeric forms (**A**–**C**), then engagement in ion-pairing with the protonated catalyst (Scheme 10). Simultaneously, the α,β-unsaturated-γ-lactam is activated through H-bonding interactions with the catalyst, which would promote the nucleophilic attack of the dienolate at β-position of the γ-lactam. Finally, the target molecule **10** is generated upon protonation of the Michael adduct.

Bifunctional organocatalysts, incorporating the diaminomethylenemalonitrile (DMM) residue, have proven to be highly effective in a variety of enantioselective transformations. One of the most compelling attributes of these catalysts is their weakly acidic proton, which effectively interacts with the oxygen atom of various Michael acceptors, thereby playing a crucial role in activating multiple substrates simultaneously, leading to significantly enhanced stereo control in the process. The catalytic activity of these compounds can be increased by integrating a chiral cyclic secondary or tertiary amine into the DMM framework, offering even greater potential in several transformations.[28] Recent studies have also emphasized the significant potential of these fragments in promoting the enantioselective carbon-phosphorus (C—P) bond formation, showcasing the versatility of these catalytic systems.[29]

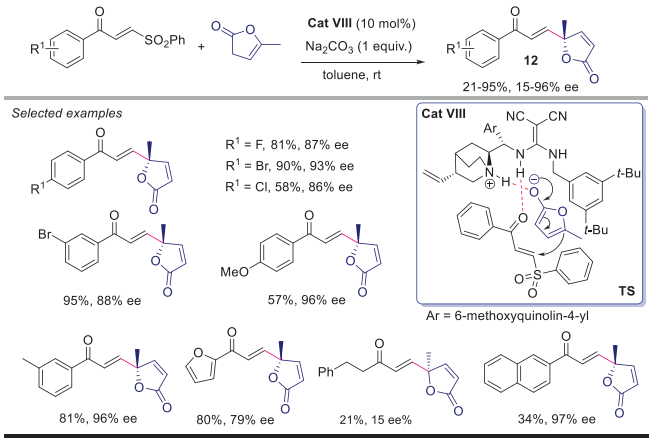
Miura's group has conclusively demonstrated the effectiveness of DMM catalysts, featuring Cinchona alkaloid motifs, in driving the asymmetric vinylogous addition of α-angelica lactone to a range of Michael acceptors. In 2021, they established a highly enantioselective strategy for the construction of a range of γ,γ-disubstituted γ-butenolides **11**, starting from α-angelica lactone building core and benzoyl acrylonitrile derivatives (Scheme 11).[30] This process operates under mild conditions and employs a low catalytic amount (3 mol%) of a hydroquinine-

© 2025 The Author(s). ChemCatChem published by Wiley-VCH GmbH

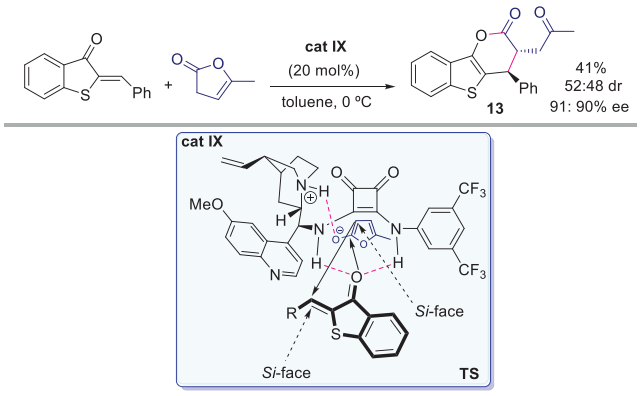
18673899, 2025, 10, Downloaded from https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/cctc.202500060 by Universita Di Salerno, Wiley Online Library on [04/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License



Scheme 12. Stereodivergent synthesis of γ,γ-disubstituted γ-butenolides via DMM-catalyzed addition of α-angelica lactone to (E)- and (*Z*)-benzoyl acrylonitriles.



Scheme 13. DMM-catalyzed asymmetric conjugate addition of α-angelica lactone to β-phenylsulfonylenones.



Scheme 14. Chiral squaramide-catalyzed asymmetric [4 + 2] cycloaddition of α-angelica lactone to 1-thioaurone.

derived DMM catalyst **VI**. The present approach was found to be applicable to a wide array of benzoyl acrylonitriles exhibiting diverse stereoelectronic properties, including thiophene and furan acrylonitrile precursors. γ-Butenolides, bearing ethyl and benzyl groups, were efficiently transformed under these conditions. The high yields and enantioselectivity achieved stem from the presence of the quinuclidine motif, where the tertiary amine plays a key role in trapping the proton from α-angelica lactone, giving access to the reactive furanolate, which then undertakes a nucleophilic attack on the electron-poor, simultaneously H-bonding activated, benzoyl acrylonitrile.

Extension of the methodology was reported in 2022, demonstrating the catalytic utility of this class of organocatalysts in constructing acyclic frameworks **11**, bearing vicinal tertiary and quaternary stereocenters (Scheme 12).[31] In particular, the stereodivergent approach allows the preparation of all four stereoisomers of compound **11**, with high diastereo- and enantioselectivities, through the four possible combinations of (*E*)- or (*Z*)-benzoyl acrylonitriles in the presence of the two pseudo-enantiomeric DMM catalysts **VI** or **VII**.

Mechanistically, the authors proposed two major steps: i) The formation of the reactive furanolate by proton abstraction from enolized form of the α-angelica lactone, which is ion-paired by the ammonium of the quinuclidine moiety of the organocatalyst **VI** or **VII**. ii) The establishment of a second hydrogen bond, between the oxygen atom of the (*E*) or (*Z*)-benzoyl acrylonitrile and the weakly acidic proton on the DMM catalyst, governing the approach of the nucleophilic furanolate.

On the basis of their previous work, Miura and coauthors demonstrated the versatility of DMM-derived catalyst **VIII** in a different approach, using β-phenyl sulfonylenones as Michael acceptors, to deliver γ-alkenyl γ-butenolides **12** (Scheme 13).[32]

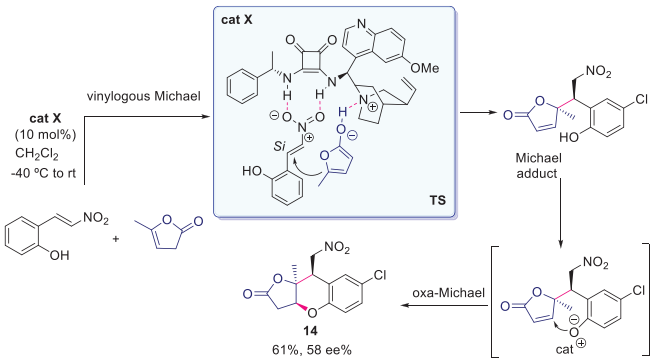
The distinguishing feature of this procedure relies on the use of Na_2CO_3 to prevent racemization. The elimination of the sulfonyl group is the key feature of the process, leading to the formal alkenylation of α-angelica lactone.[33] The reaction was found applicable to a vast library of differently substituted β-arylsulfonylenones, giving access to the target compounds **12** in high yield and enantioselectivity (up to 97% ee). Electronic factors did not affect the reaction outcome, as several sulfonylenones with electron-withdrawing and donating substituents on the phenyl ring reacted smoothly under the optimized reaction conditions.

Chiral squaramide motifs have been widely applied in asymmetric synthesis as powerful and multifunctional organocatalysts capable of promoting numerous transformations with high stereoselectivity.[34] The effectiveness of the squaramide-based catalysts has been attributed to the strong H-bonding donor ability of the *N*H groups, in close proximity to the two carbonyls. Moreover, the delocalization of the nitrogen lone pair over the cyclobutenedione framework enhances the aromaticity of the four-membered ring system. This, in turn, increases the thermodynamic stability of the catalyst and improves its binding ability with various substrates through $\pi-\pi$ stacking interactions. In 2022, Zhou and coworkers introduced a novel synthetic route to produce optically active six-membered heterocyclic compounds **13** through a chiral squaramide-catalyzed asymmetric addition of α-angelica lactone/γ-butenolides to 1-thioaurones (Scheme 14).[35]

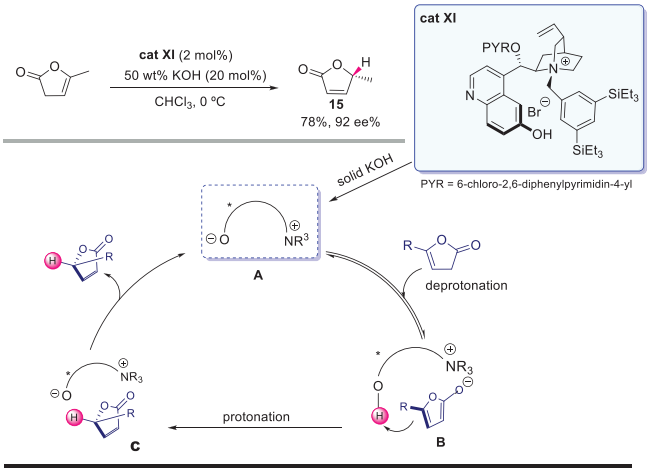
The reaction proceeded smoothly under mild reaction conditions in the presence of a quinine-derived squaramide catalyst **IX**, which was found to be crucial for ensuring the diastereo- and enantioselectivity of the process. The authors hypothesized that the transformation would occur through an inverse

© 2025 The Author(s). ChemCatChem published by Wiley-VCH GmbH

18673899, 2025, 10, Downloaded from https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/cctc.202500060 by Universita Di Salerno, Wiley Online Library on [04/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License



Scheme 15. Synthesis of chiral tricyclic chroman-butyrolactones from α-angelica lactone and (*E*)-2-(2-nitrovinyl)phenol catalyzed by squaramide **X**.



Scheme 16. Betaine-catalyzed asymmetric isomerization of α-angelica lactone through proton-transfer catalysis.

electron-demand (IED) [4 + 2] cycloaddition of the nucleophilic butenolide in the presence of the electron-poor oxa-dienes (1-thioaurones, azlactones). The aromaticity arising from these conjugated systems exhibits electrophilic dipole-like properties, making it prone to a nucleophilic addition by the dienophile (γ-butenolide). α-Angelica lactone reacted with 1-thioaurone, under standard conditions, delivering the corresponding bicyclic motif in modest yield, 52:48 dr ratio, but with high enantioselectivity for both diastereoisomers. Aryl/heteroaryl γ-butenolides were also employed as precursors in the present approach, providing a successful access to a rich library of indole-fused δ-lactones/benzothiophene-fused δ-lactones. The synthetic utility of this procedure was further explored by employing 1-azaaurones and azlactones as coupling partners, without any noticeable loss of the diastereo- and enantiocontrol.

The transition state proposed by the authors illustrates the dual role of the catalyst in the activation of both the diene and dienophile. The formation of dual *N*Hs hydrogen bonds from the squaramide would be responsible for activating and directing the 1-thioaurone, whereas the tertiary quinuclidine amine is responsible for the enolization of α-angelica lactone. The chiral induction provided by the bifunctional catalyst triggers the *Si-Si* attack of the furanolate on the 1-thioaurone, giving rise to the formation of two stereocenters. Finally, an intramolecular transesterification occurs, yielding the bicyclic product.

In another example, Huang and coworkers disclosed an innovative strategy to access chiral tricyclic chroman-butyrolactones through vinylogous Michael/oxa-Michael intramolecular cyclization of (*E*)-2-(2-nitrovinyl)phenol with α-angelica lactone as coupling partner (Scheme 15).[36]

The synthetic approach, designed to exploit the reactivity of γ-aryl butenolides at γ- and β-positions, exhibited high efficiency, leading to diversified chroman-butyrolactones in good to high diastereo- and enantioselectivity (up to 86% ee). The control of enantioselectivity was maximized working at −40 °C. The γ-selectivity in the enantiodifferentiating addition of the furanolate unit was driven by the tertiary amine group in the chiral squaramide **X**, promoting the dienolate formation, which then attacks with γ-selectivity the *Si*-face of the active hydroxynitrostyrene. The Michael adduct subsequently undergoes β-selective intramolecular cyclization, upon a room temperature increase, to give the final product **14**. Several deconjugated γ-aryl butenolides were found suitable substrates, including α-angelica lactone, which unfortunately furnished the corresponding chroman-fused lactone **14** with 61% yield and 58% ee.

Asymmetric organocatalytic isomerization of β,γ-unsaturated butenolides opens up new possibilities for the synthesis of optically active scaffolds. However, despite the reliability of this approach, only two documented examples of such transformation exist to date. Previous research undertook the catalytic asymmetric isomerization of β,γ-unsaturated butenolides, using either a bifunctional Cinchona alkaloid catalyst[37] or a chiral copper catalyst.[38]

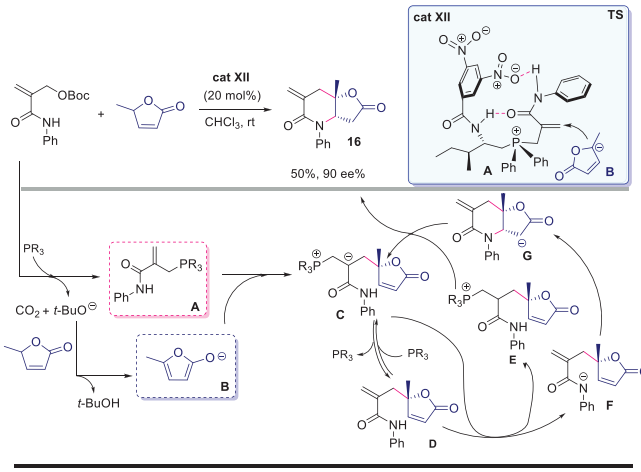
In 2023, Deng and coworkers explored the synthesis of these chiral cores through an unprecedented strategy, involving proton-transfer catalysis, provided by a novel betaine-based catalyst, generated from **XI** (Scheme 16).[39]

The reactivity and enantioselectivity of this process were found to be highly dependent on the substitution pattern of *N*-aryl methyl portion in the betaine-based catalyst. Higher catalytic performance was observed when triethyl silyl units were introduced in the structure. The isomerization of the α-angelica lactone and other unsaturated butenolides could be efficiently accomplished with a 0.2–2 mol% loading of the newly developed betaine catalyst, 50 wt% KOH (20 mol%) in $CHCl_3$ at temperatures ranging from −10 to 0 °C. A broad library of chiral unsaturated butenolides was isolated in good to excellent yield (36%–90%) and enantioselectivity (up to 97 ee%). The mechanistic proposal envisioned the formation of the active chiral betaine specie **A,** under the action of solid KOH, which deprotonates α-angelica lactone to deliver ionic pair **B**. Then, the dienolate intermediate undergoes an enantioselective protonation to give (*R*)-β-angelica lactone **15** in 92% ee.

Nucleophilic phosphine catalysis stands out as a significant tool for producing highly useful intermediates and products in organic synthesis. This method unlocks an impressive array of transformative possibilities by facilitating a straightforward addition of alkene-based compounds to diverse allylation partners such as alkenes, allenes, alkynes, and MBH carbonates. An essen-

© 2025 The Author(s). ChemCatChem published by Wiley-VCH GmbH

18673899, 2025, 10, Downloaded from https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/cctc.202500060 by Universita Di Salerno, Wiley Online Library on [04/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

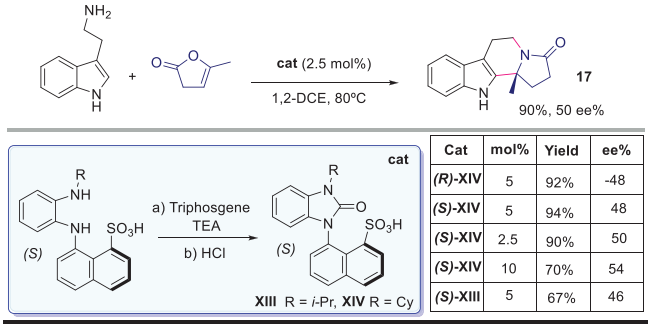


Scheme 17. Chiral phosphine-catalyzed annulation of amide MBH carbonates with α-angelica lactone.

tial step in this process involves the formation of a Horner's type zwitterionic adduct, achieved by reacting a tertiary phosphine unit with activated carbon–carbon multiple bonds in an olefin coupling partner.[40]

Recently, Guo and coworkers documented a highly enantioselective synthesis of bicyclic δ-lactam γ-butyrolactone backbone **16**, through chiral phosphine-catalyzed annulation of amide-based MBH carbonates with α-angelica lactone/γ-butenolides (Scheme 17).[41]

A large substrate scope was achieved in the presence of 20 mol% of the phosphine catalyst **XII**. It should be mentioned that the in situ generated phosphorus intermediates, obtained through the nucleophilic addition of the phosphine to the activated MBH carbonate, were found to be essential in this transformation. Interestingly, the reaction of α-angelica lactone proceeded smoothly under standard conditions, delivering the corresponding bicyclic product **16** in 50% yield, almost complete diastereoselectivity (dr $>$ 20:1), and 90% ee. Other alkyl-substituted butenolides were reacted, albeit delivering reduced yields, compared to their aryl/heteroaryl substituted γ-butenolide counterparts, which were transformed more efficiently in terms of conversion and enantioselectivity. Based on control experiments and related studies on phosphine-catalyzed allylation of MBH carbonates,[42] a mechanism, reported in Scheme 17, was proposed. Formation of the intermediate **A** through the nucleophilic attack of the phosphine species to the electron-poor MBH carbonate, along with the simultaneous release of CO_2 and *tert*-butoxyoxide anion, occurs. The latter would deprotonate α-angelica lactone to generate the active furanolate **B** that subsequently undergoes γ-carbon addition to **A** through *Si*-face affording ylide **C**. Then, a phosphine-promoted allylation reaction occurs to give intermediate **D**, which upon ylide **C**-mediated deprotonation leads to key species **E** and **F**. Finally, intermediate **F** undergoes an intramolecular conjugate addition to give intermediate **G**, finally protonated by **E** to the desired bicyclic δ-lactam γ-butyrolactone, along with the regeneration of ylide **C**.



Cat	mol%	Yield	ee%
(R)-XIV	5	92%	-48
(S)-XIV	5	94%	48
(S)-XIV	2.5	90%	50
(S)-XIV	10	70%	54
(S)-XIII	5	67%	46

Scheme 18. Pictet–Spengler reaction of tryptamine with α-angelica lactone catalyzed by axially chiral sulfonic acids.

Chiral Brønsted acid catalysis has opened a new frontier in asymmetric synthesis. The range of stereoselective transformations catalyzed by chiral Brønsted acids is continuously increasing over time. The extensive tunability, stable chirality, and commercial availability of these catalysts contributed to their integration in the field as a fundamental tool to promote countless enantioselective reactions with high efficiency.[43] The use of chiral Brønsted acids was pioneered by Akiyama[44] and Terada,[45] who independently highlighted the applicability of chiral phosphoric acids (CPA) derived from 1,1′-binaphthyl-2,2′-diol BINOLs in asymmetric Mannich-type reactions. The popularity of CPA derivatives arises from their strong binding ability with various basic motifs, which occurs through H-bonding or ion-pairing interactions. Despite their common use, these derivatives exhibit a certain range of acidity,[46] which indisputably restricts their effectiveness when employing weakly basic components. Therefore, developing CPA catalysts with enhanced acidity holds promise to significantly broaden their range of applications in asymmetric transformations.

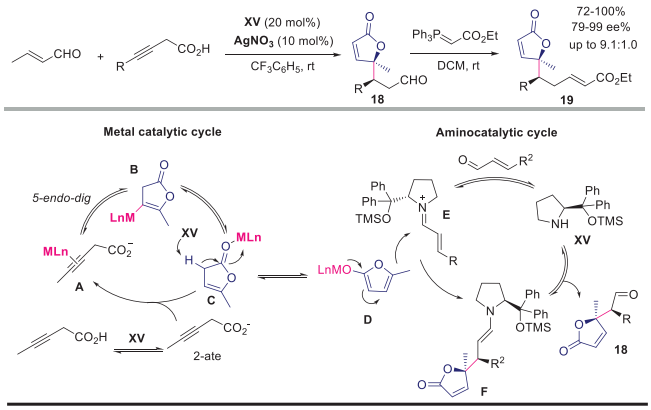
Recently, Cankař and coworkers proposed a practical approach to a library of chiral benzoimidazolyl naphthalene sulfonic acids, including compounds **XIII** and **XIV**, with high structural variability through the cyclization of *peri*-substituted 8-aminonaphthalene sulfonic acid with different coupling partners, including triphosgene (Scheme 18).[47]

The versatility of this precursor allowed for the development of axially chiral sulfonic acids containing a benzimidazole portion. This design enabled tuning of the basicity, resulting in a range of catalysts with different acid dissociation constants. It is noteworthy that substitution at the benzimidazole nitrogen led to a drastic decrease in *p*Ka and, therefore, contributed to a significant enhancement of the catalytic activity of these compounds. The restricted rotation around the C—N bond determines the axial chirality, and the atropoisomers of benzoimidazolyl naphthalene sulfonic acids were isolated through diastereomeric salt formation. Promising synthetic utility of the benzoimidazolyl naphthalene sulfonic acids was demonstrated as organocatalysts for the preparation of a tetracyclic scaffold **17**, via the Pictet–Spengler reaction of tryptamine with α-angelica lactone. The reaction proceeded in high yield and up to 50% ee (Scheme 18).

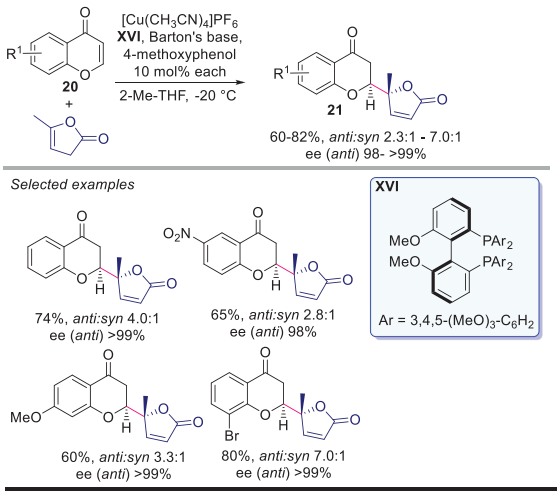
The integration of transition metal (TM) catalysis with aminocatalysis has emerged as a promising strategy for address-

© 2025 The Author(s). ChemCatChem published by Wiley-VCH GmbH

18673899, 2025, 10, Downloaded from https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/cctc.202500060 by Universita Di Salerno, Wiley Online Library on [04/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License



Scheme 19. Chiral amine/Lewis acid co-catalyzed synthesis of γ,γ-disubstituted butenolides through in situ formation of α-angelica lactone.



Scheme 20. *Anti*-Selective vinylogous addition of α-angelica lactone to chromones.

ing complex enantioselective transformations effectively.[48] This cooperative approach could unlock transformative possibilities that are unattainable with either a metal catalyst or an organocatalyst on their own.

Inspired by this concept, Wang and coworkers. targeted the synthesis of chiral γ,γ-disubstituted butenolides **19** utilizing cooperative catalysis provided by TMS-ether diphenyl prolinol **XV** and $AgNO_3$ or Ph_3PAuCl (Scheme 19).[49] The key aspect of this approach represents the co-catalyzed cascade approach, which proceeds through the in situ formation of α-angelica lactone starting from alkynoic acids and enal precursors, which would subsequently undergo amine-catalyzed conjugate addition, ultimately leading to the desired γ,γ-disubstituted butenolides structure **18**, then amenable to olefination to give products **19**.

While the Lewis acid-catalyzed synthesis of γ,γ-disubstituted butenolides from alkynoic acids is well-documented,[50] the aforementioned method offers a distinctive alternative by featuring the in situ formation of the α-angelica lactone, which eliminates the need for time-consuming isolation and purification steps. Lewis acid and the amino catalyst **XV** work synergistically, leading to a significant enhancement in the efficiency of the Michael cascade addition. The enantioselectivity of this process remained unaffected by the electronic properties and steric hindrance of the α,β-unsaturated aldehyde precursors. In contrast, both diastereoselectivity and yields were influenced to some extent. In general, aromatic α,β-unsaturated aldehydes, bearing electron-withdrawing groups, displayed higher yields compared to those with electron-donating groups. Switching to $Ph_3PAuCl/AgOTf$ as Lewis acid system was necessary in the case of aliphatic enals, which failed to proceed under standard conditions with $AgNO_3$. Based on mechanistic studies, the authors proposed a catalytic cycle that involves deprotonation of alkynoic acids by the amine catalyst **XV** to the active 2-ate species, which then undergoes a metal-catalyzed intramolecular *5-endo-dig* cyclization in the presence of Ag(I) or Au(I) catalyst, generating intermediate **C**. Cooperative catalysis of the amine base and Lewis acid enables the conversion of intermediate **C** into the reactive LA-oxy furan **D**. Subsequently, in situ formed iminium ion **E** undergoes a nucleophilic attack by species **D** with *Si*-face selectivity, releasing the product **18** and the amine catalyst **XV**.

4. Metal-Catalyzed Asymmetric Reactions

Alongside organocatalysis, metal catalysis paved the way for the development of significant enantioselective transformations of non-conjugated butenolides, including α-angelica lactone, to access enantioenriched γ-lactones, as well as other heterocycles and acyclic compounds.[7a]

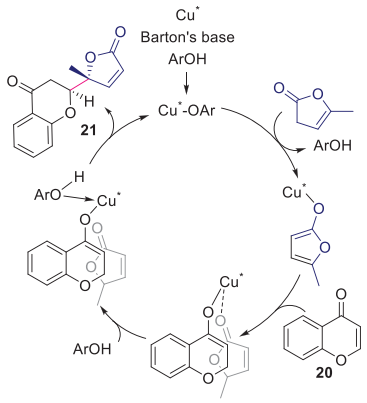
In 2020, Watanabe and Shibasaki developed an asymmetric catalytic protocol for the vinylogous addition of β,γ-butenolides to chromones **20**, using a chiral cationic copper (I) catalyst (Scheme 20).[51]

The catalyst was in situ generated from $[Cu(CH_3—CN)_4]PF_6$ in the presence of a Brønsted base and a biphep-type-biphenyl-based chiral ligand **XVI**. The methodology enables the synthesis of natural product-like antiadducts **21**. It complements the dinuclear zinc-ProPhenol-catalyzed approach, previously described by Trost, which predominantly gave access to *syn*-products, less abundant in nature.[52] Careful selection and fine-tuning of aryl substituents on the phosphorus atom of the chiral ligand **XVI**, along with the appropriate phenolic additive in the presence of Barton's base, were found to be essential for improving both the conversion and the *anti*-diastereoselectivity. 4-Methoxyphenol was chosen as the optimal additive to reach high conversion, a satisfactory level of diastereoselectivity and excellent enantioselectivity. The effect of the coordinative additive consists of improving catalyst turnover from the Cu^I-alkoxide (Scheme 21).

The catalyst **XVI**/Cu^I-alkoxide, generated from **XVI**/Cu^I/Barton's base/phenolic additive, deprotonates the butenolide, thus forming a Cu^I-dienolate intermediate. Cu^I-dienolate interacts with chromone **20** through a cyclic transition state, which brings to the *anti*-stereoisomer of the product **21** upon coordination of the phenol with Cu^I-cation, followed by protonation and regeneration of the catalyst.

© 2025 The Author(s). ChemCatChem published by Wiley-VCH GmbH

18673899, 2025, 10, Downloaded from https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/cctc.202500060 by Universita Di Salerno, Wiley Online Library on [04/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License



Scheme 21. Proposed catalytic cycle of the copper-mediated vinylogous addition of α-angelica lactone to chromones.

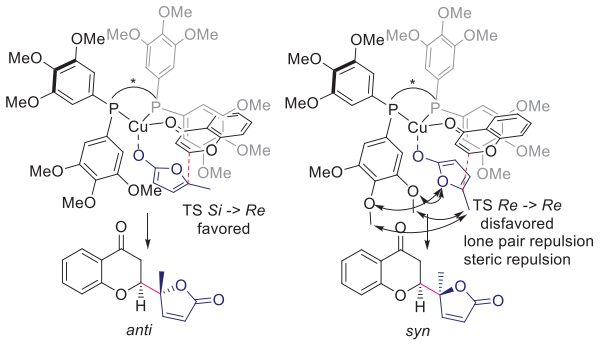
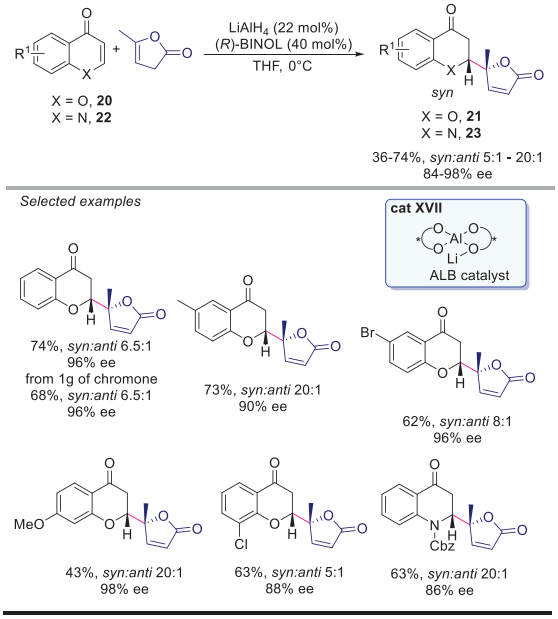


Figure 4. Rationalization of the observed *anti*-diastereoselectivity.

Steric and electronic properties of the substituents on the chiral ligand were optimized to enhance and rationalize the inversion of diastereoselectivity toward the *anti*-diastereomer. In the prior system, *syn*-adduct formation was intrinsically favored, due to minimized electrostatic repulsion between the heterocyclic oxygen atoms in the transition state. The optimal chiral ligand for inverting diastereoselection was identified as (*R*)-3,4,5-(MeO)$_3$-MeOBIPHEP **XVI**. The explanation lies in the electrostatic repulsion between the ligand bearing the methoxy groups and the oxygen atoms of the butenolide, which destabilizes the *Re–Re* transition state, while favoring the *Si–Re* transition state, ultimately leading to the *anti*-stereoisomer (Figure 4).

By using this protocol, differently substituted chromones at different positions reacted with α-angelica lactone, affording the corresponding adducts in excellent enantioselectivity (98%–99% ee) for the *anti*-stereoisomer, good to high yields, and modest to good diastereoselectivity (from 2.3:1 to 7:1 dr). Moreover, the methodology can be performed on a gram scale, obtaining the *anti*-diastereomer of the product in 72% yield and unmodified level of stereoselectivity.

More recently, the same group found that an Al-Li-BINOL (ALB) complex, **XVII**, readily prepared by mixing $LiAlH_4$ and BINOL, is a suitable catalyst to promote the *syn*-selective asymmetric vinylogous addition of α-angelica lactone to chromones **20**.[53] The optimized protocol afforded the *syn*-adducts with a satisfactory level of diastereoselectivity, from 5:1 to 20:1, and



Scheme 22. *Syn*-Selective vinylogous addition of α-angelica lactone to chromones.

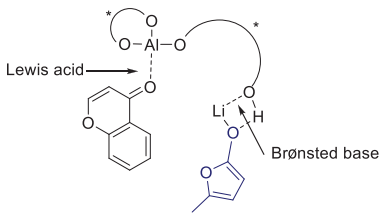


Figure 5. Bifunctionality of ALB catalyst.

enantioselectivity ranging from 84% to 98% ee, improving in some cases previous results achieved by the Trost's system[52] (Scheme 22). Moreover, the procedure was demonstrated to be applicable to 4-quinolone derivatives **22**, affording a different class of α-angelica lactone-containing heterocycles **23**. The scale-up of the reaction enables the gram-scale synthesis of the chromone-lactone framework, making it ideal for use as a building block in the synthesis of natural products. Computational studies were conducted to rationalize the *syn*-diastereoselectivity and the role of the catalyst (Figure 5).

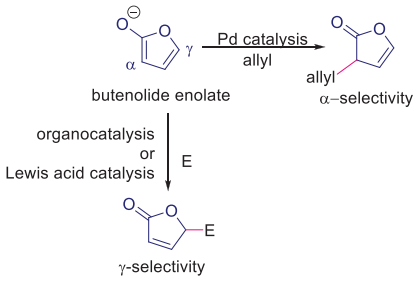
The butenolide is deprotonated by the lithium aryloxide Brønsted base, forming the enolate. This then reacts with the chromone electrophile, activated by the aluminum Lewis acid. Thus, the ALB acts as a bifunctional catalyst. Moreover, H-bonding interactions between the lithium enolate and naphthol portion drive facial selectivity toward a *syn*-forming transition state.

Wang and Gong reported a novel chiral phosphoramidite-palladium catalyst for the regio- and stereoselective γ-allylation of α-angelica lactone and related butenolides through C—H activation of 1,4-dienes **24** (Scheme 23).[54]

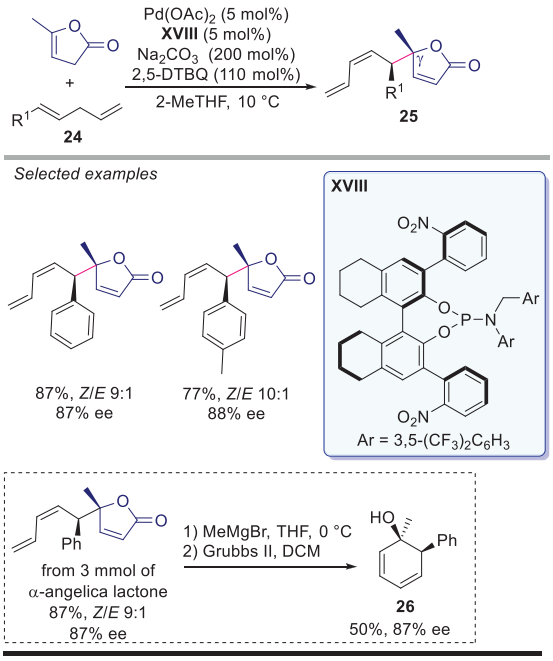
Pd-catalyzed allylation of butenolides generally favors α-regioselectivity, whereas organocatalysis and Lewis acid catalysis

© 2025 The Author(s). ChemCatChem published by Wiley-VCH GmbH

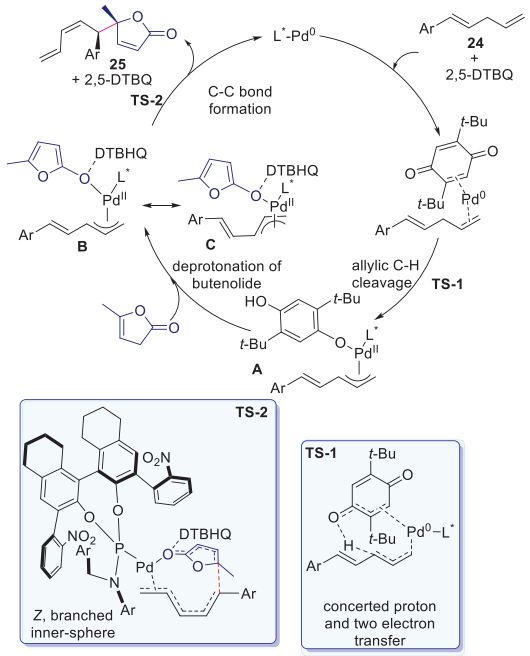
18673899, 2025, 10, Downloaded from https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/cctc.202500060 by Universita Di Salerno, Wiley Online Library on [04/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License



Scheme 23. γ-Selective allylic C—H alkylation of 1,4-pentadienes with α-angelica lactone.



Scheme 24. Catalytic transformation of butenolide enolate.



Scheme 25. *Syn*-Selective vinylogous addition of α-angelica lactone to chromones.

have been used to achieve the asymmetric functionalization of butenolide enolates with γ-selectivity (Scheme 24).[54]

The novel phosphoramidite ligand **XVIII**, featuring three chiral axes and functionalized with 2-nitrophenyl groups at the 3,3′-positions of the H_8-binaphthyl moiety, has been demonstrated to effectively induce the palladium catalyst to promote the γ-regioselective asymmetric C—H alkylation of 1,4-pentadienes **24** and α-angelica lactone. The reaction, performed with $Pd(OAc)_2$, ligand **XVIII**, 2,5-di*tert*-butyl hydroquinone (2,5-DTBQ), and Na_2CO_3 in 2-MeTHF at 10 °C, yields γ,γ-disubstituted butenolides **25** bearing a *Z*-dienyl moiety via a *Z*-branched inner-sphere transition state (vide infra). The products were isolated in moderate to good yield, high levels of regioselectivity, *Z*/*E* diastereoselectivity and enantioselectivity. The scale-up of the reaction to 3 mmol of α-angelica lactone afforded the enantioenriched chiral butenolide with comparable results. The latter was transformed into 1,3-cyclohexadiene **26** with good overall yield and maintained enantioselectivity (Scheme 24).

The mechanism illustrated in Scheme 25 was proposed to explain the observed regio- and stereoselectivity.

A 16-electron palladium(0) species is generated through the coordination of the palladium(0) catalyst, 1,4-diene **24**, and 2,5-DTBQ. Allylic C—H cleavage occurs via a concerted proton and two-electron transfer mechanism (**TS-1**), forming a π—allyl—Pd species **A**. This species deprotonates α-angelica lactone, yielding intermediate **B**, where the diene adopts a *s-trans* geometry. Intermediate **B** readily isomerizes to the less stable intermediate **C**, featuring a *s-cis*-diene, and the subsequent C—C bond formation preferentially occurs through **TS-2**, due to more favorable geometric requirements of butenolide. This pathway promotes the formation of the *Z*-dienyl product, whereas the *E*-dienyl product is kinetically disfavored.

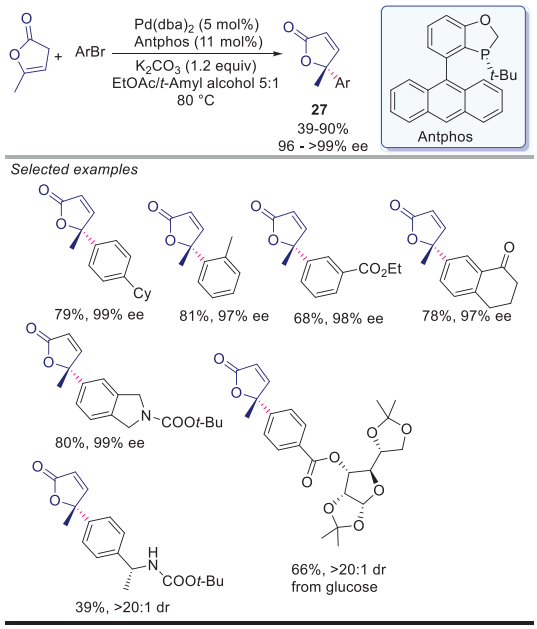
Yang and Zhang developed the enantioselective palladium-catalyzed γ-arylation of α-angelica lactone with aryl bromides (Scheme 26).[55]

A diverse array of functional groups on aryl bromide is generally accepted, affording γ-arylated butenolides **27**, bearing a quaternary stereocenter, in high yields, excellent regioselectivity, and enantioselectivity, even in the presence of reactive functionalities including ketone, ester, cyanide, nitro, and protected amines. In addition, aryl bromides derived from amino acids, menthol, and glucose led to the products in high yield and diastereoselectivity. On the contrary, aryl chlorides, iodides, and triflates were found to be unsuitable substrates. The utility of the protocol was demonstrated in the synthesis of enantioenriched tricyclic tetrahydroindolines **30** and tetrahydroisoquinolinones **31** starting directly from α-angelica lactone and Boc-protected 2-bromoaniline **28** and 2-bromobenzylamine **29** (Scheme 27a).

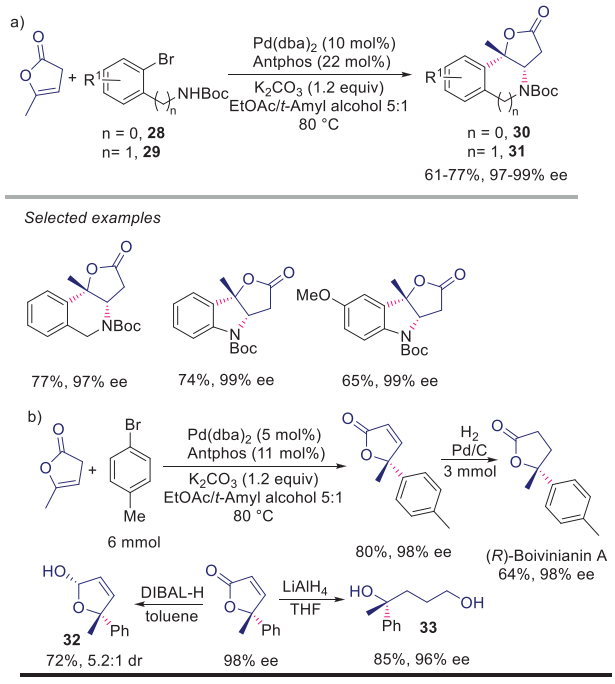
Moreover, the process was performed on a gram scale without losing efficiency in terms of yield and enantioselectivity, and the γ-arylated butenolide was readily transformed into natural product (*R*)-(+)-boivinianin, 1,4-diol **33**, or compound **32** upon

© 2025 The Author(s). ChemCatChem published by Wiley-VCH GmbH

18673899, 2025, 10, Downloaded from https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/cctc.202500060 by Universita Di Salerno, Wiley Online Library on [04/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License



Scheme 26. Enantioselective γ-arylation of α-angelica lactone with aryl bromides catalyzed by palladium.

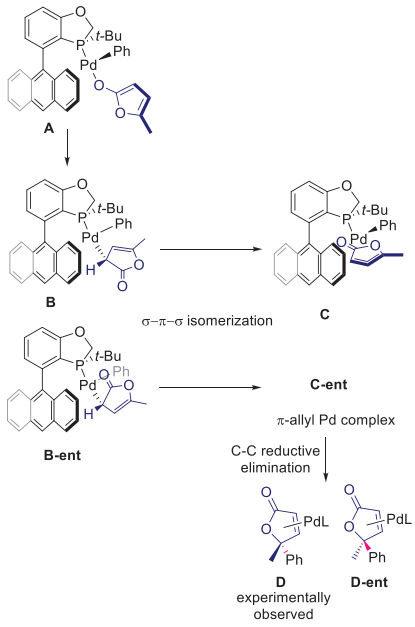


Scheme 27. Transformation of α-angelica lactone into (a) enantioenriched tricyclic tetrahydroindolines and tetrahydroisoquinolinones and into (b) natural product (*R*)-Boivinianin A.

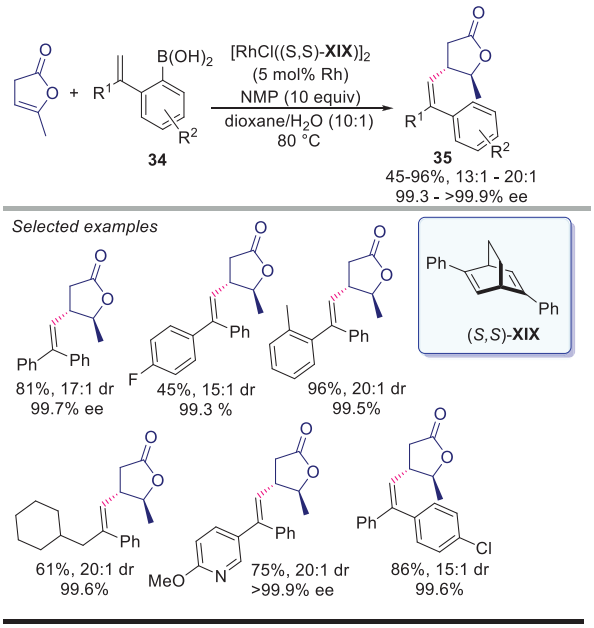
reduction with H_2 and Pd/C, $LiAlH_4$, or DIBAL-H, respectively (Scheme 27b).

DFT calculations supported the experimental findings, identifying the most energetically favorable pathway (Scheme 28).

Oxidative addition of aryl bromide on Pd-complex and transmetalation produces Pd/O-enolate complex A, which easily isomerizes into Pd/C_α-enolate complex B. Then, α–π isomerization generates a more stable π—allyl Pd complex C. Subsequently, the



Scheme 28. Energetically favored C—C reductive elimination pathway affording (*R*)-γ-arylated butenolides.



Scheme 29. Diastereo- and enantioselective β-alkenylation of α-angelica lactone via dynamic kinetic resolution catalyzed by rhodium.

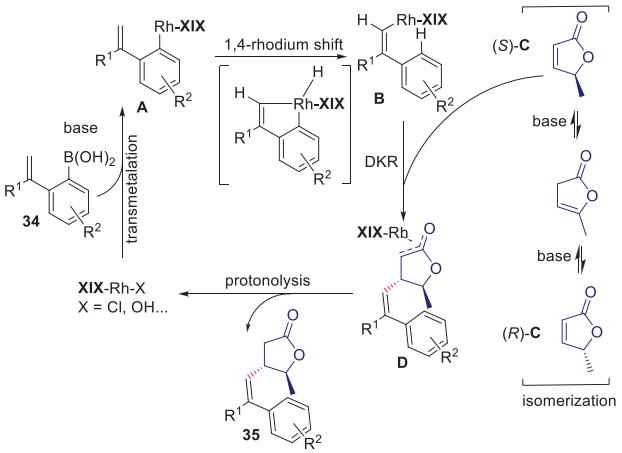
C—C reductive elimination of the allyl—Pd intermediate **C** yields the γ-arylation product **D**. The transition state leading to the experimentally observed (*R*)-enantiomer is more stable than the one leading to the opposite enantiomer.

Moreover, DFT calculations confirmed that the transition state of the γ-arylation is energetically favored over that of α-arylation, thereby explaining the observed γ-regioselectivity.

Huang developed the first protocol for the diastereo- and enantioselective alkenylation at the β-position of α-angelica lactone (Scheme 29).[56]

© 2025 The Author(s). ChemCatChem published by Wiley-VCH GmbH

18673899, 2025, 10, Downloaded from https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/cctc.202500060 by Universita Di Salerno, Wiley Online Library on [04/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License



Scheme 30. Proposed mechanism for the alkenylation of α-angelica lactone via rhodium-catalyzed dynamic kinetic resolution.

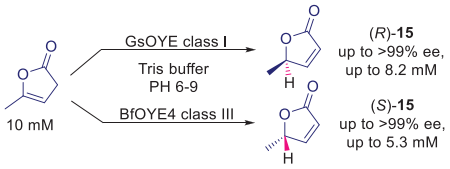
The nucleophilic β-regioselective functionalization of α-angelica lactone has been rarely explored in the past. Furthermore, a stereoselective methodology for alkenylation at any position has been lacking.

In this work, rhodium catalysis in combination with chiral diene ligand **XIX** enabled the synthesis of differently functionalized chiral butyrolactones **35** in enantiomerically pure form (>99% ee in all cases), high diastereoselectivity (13:1–20:1) and good to high yields (45%–96%) through an efficient process of dynamic kinetic resolution. Substitution on the aromatic rings at position 1 of the 2-(1-arylvinyl)aryl boronic acids **34** is well tolerated, regardless of the position or electronic properties of the substituents as well as naphthyl and pyridinyl rings. A bulky alkyl substituent, such as a cyclohexanylmethyl group, can be introduced at R^1 position of the (*o*-vinyl)aryl boronic acid **34**, whereas smaller alkyl groups result in poorer outcomes in terms of conversion and selectivity.

The proposed mechanism, supported by deuterium labeling experiments, involves the formation of an aryl-Rh species **A** upon transmetallation of the boronic acid with the rhodium catalyst in the presence of a base (Scheme 30). Then, 1,4-rhodium migration from aryl to vinyl generates the key alkenyl-Rh species **B** in situ. Simultaneously, β,γ-unsaturated butenolide isomerizes to racemic α,β-unsaturated butenolide **C** in the presence of the base. Only the (*S*)-enantiomer of compound **C** reacts with alkenyl-Rh species **B** due to its coordination with the chiral ligand (*S,S*)-**XIX**, affording intermediate **D**, which, after protonolysis, yields product **35** and regenerates the rhodium catalyst.

5. Asymmetric Reactions via Biocatalytic Tools

Recently, Hall and coauthors reported the asymmetric isomerization of α-angelica lactone to the corresponding (*R*)- and (*S*)-β-angelica lactone **15**, by exploiting for the first time, the non-redox hydride-independent stereocomplementary catalysis of two flavoproteins from the old yellow enzyme (OYE) family (Scheme 31).[57]



Scheme 31. Asymmetric isomerization of α-angelica lactone by two stereocomplementary old yellow enzymes via asymmetric proton transfer.

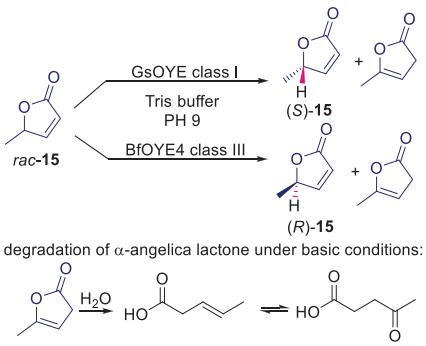
In general, both natural and non-natural activity of flavin-dependent OYEs relies on a redox catalysis mechanism that requires electron transfer to generate the reduced flavin coenzyme necessary to initiate the reaction.[58] Moreover, the native NAD(P)H-dependent reducing activity of flavoproteins from this family requires the presence of an electron-withdrawing group that lowers the electron density of the C—C double bond, enabling its reduction by the hydride attack at the β-position.[59] Only one case has been documented where the isomerization of the non-activated C—C double bond of α-angelica lactone was achieved using an OYE reductase from *Saccharomyces cerevisiae*. In this preliminary case, reported by the Hall group in 2016, the enzyme catalyzes the neutral redox isomerization of the double bond, affording racemic β-angelica lactone **15**.[60] In 2022, the same group devised two stereocomplementary OYEs, derived from algae and fungi, to facilitate the asymmetric isomerization of the C—C double bond in α-angelica lactone.[57] This process successfully produced both enantiomers of β-angelica lactone **15** with high ee values through asymmetric redox-neutral proton transfer catalysis. GsOYE class I from polyextremophilic alga *Galdieria sulphuraria* was stereoselective for (*R*)-**15**, which was obtained with 84% ee at pH 7. The amount of (*R*)-**15** obtained from a solution of 10 mM of α-angelica lactone in Tris-HCl buffer was 6.3 mM at pH 7.5. BfOYE4 class III from *Botryotinia fuckeliana* afforded the (*S*)-enantiomer in 98% ee (4.3 M at pH 7.5).

However, the maximum amount of **15** produced by both enzymes was shown to vary with the pH. Furthermore, a clear pH-dependent stereoselectivity was more pronounced with GsOYE, whereas using BfOYE4, the (*S*)-**15** product was obtained with high ee values even under basic conditions up to pH 9. The decrease in enantioselectivity observed under basic conditions was explained by considering that basic conditions favor a reverse isomerization process, regenerating α-angelica lactone, thus eliminating the stereogenic center and eroding the enantiomeric excess of **15**. Moreover, α-angelica lactone is unstable under basic conditions, leading to degradation products (Scheme 32).

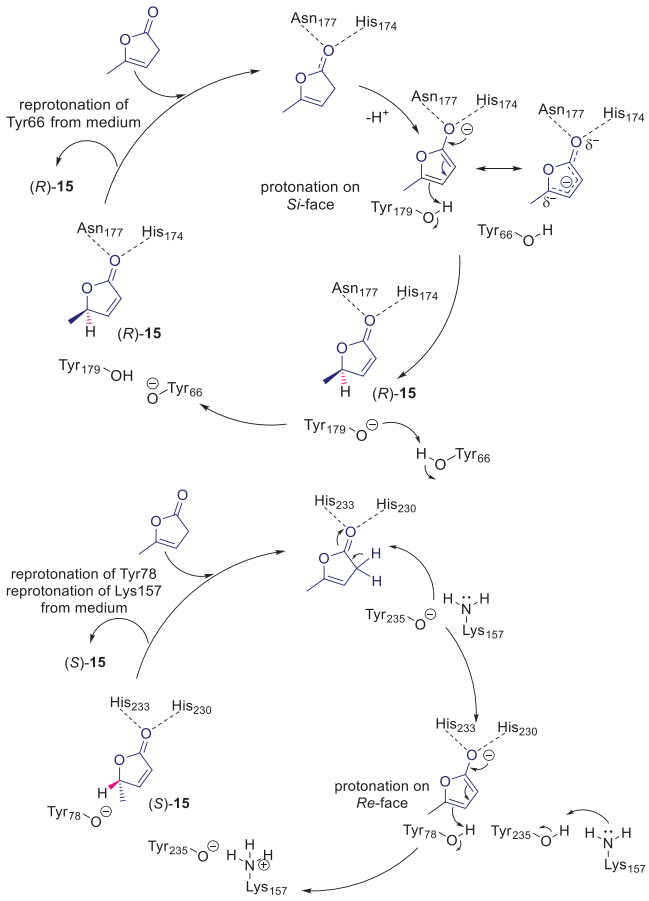
In fact, when treating racemic **15** with GsOYE and BfOYE4 at pH 9 for 5 h, the remaining **15** was isolated with 16% ee (*S*) and 17% ee (*R*), respectively. These data indicate that kinetic resolution through the (*R*)-enantioselective (by GsOYE) and (*S*)-enantioselective (by BfOYE4) reverse isomerization of **15** occurs under basic conditions. The crystal structures of the enzymes, soaking experiments, and site-directed mutagenesis were analyzed to elucidate the mechanism and to identify the amino acids involved and responsible for the stereoselectivity, with evidence suggesting that tyrosine residues play a key role in the Brønsted acid catalysis (Scheme 33).

© 2025 The Author(s). ChemCatChem published by Wiley-VCH GmbH

18673899, 2025, 10, Downloaded from https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/cctc.202500060 by Universita Di Salerno, Wiley Online Library on [04/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

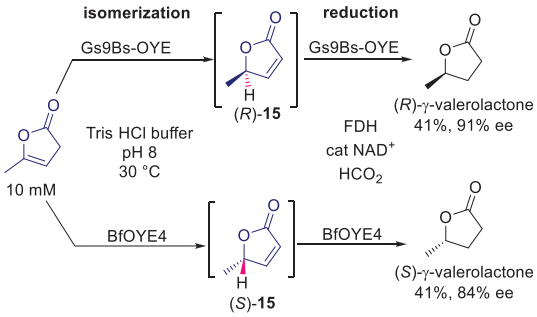


Scheme 32. Reverse isomerization of *rac*-**15** and instability of the produced α-angelica lactone under basic conditions.



Scheme 33. Proposed mechanism for the enantioselective isomerization of α-angelica lactone biocatalyzed by GsOYE and BfOYE4.

In 2023, the same research group exploited the stereoselective isomerization of α-angelica lactone to set up a one-pot process for the stereodivergent formal reduction to (*R*)- and (*S*)-γ-valerolactone (Scheme 34).[61] The one-pot strategy combined the OYEs non-natural activity of catalyzing the redox-neural hydride-free isomerization of α-angelica lactone with the native reductase activity of these flavoproteins. A cascade process has been developed by employing two different OYEs, one stereoselective enzyme with high isomerase activity for the first step and one OYE with high reductase activity (but poor isomerase activity) for the second step. More interestingly, an artificial



Scheme 34. One-pot biocatalytic formal reduction of α-angelica lactone to (*R*)- and (*S*)-γ-valerolactone.

bifunctional enzyme, Gs9Bs-OYE, was prepared by combining GsOYE, with high stereoselective isomerase activity with YqiM showing poor isomerase activity, but good reductase activity. The two enzymatic units were linked by a nine-amino-acid sequence, joining the *N*-terminus of YqiM to the *C*-terminus of GsOYE. The artificial enzyme retains the (*R*)-stereoselectivity of the isolated GsOYE, whereas the reductive activity of GsOYE and YqiM is additive. This system catalyzed the formal reduction of α-angelica lactone into (*R*)-γ-valerolactone, without isolating β-angelica lactone intermediate **15** in cascade fashion, affording (*R*)-γ-valerolactone with higher ee than the values obtained by using two distinct enzymes in the cascade. An ee value of 91% and a good conversion (41%, 4.1 mM) to (*R*)- γ-valerolactone were achieved using 0.048 mol% of catalyst (4.8 µM, 400 µg/mL) by providing the reducing equivalents for the second step after the isomerization was completed (Scheme 34). A nicotinamide FDH-based recycling system was employed to supply the reducing equivalents (catalytic amounts of NAD+/formate dehydrogenase (FDH) and 2 equivalents of ammonium formate). (*S*)-γ-valerolactone was obtained in up to 84% ee and 41% overall conversion by using BfOYE4, which demonstrated to be a suitable catalyst for promoting both steps.

6. Summary and Outlook

The need to leverage renewable raw materials instead of petroleum-based sources is resulting in increasing efforts of chemists to use platform molecules or their derivatives for the synthesis of commodities and value-added chemicals.[62] In this contribution, we have illustrated applications of biomass-derived α-angelica lactone in asymmetric catalysis, reported in the last 5 years. The number of methodologies developed so far clearly attests to this compound as a valuable building block, mostly for monoselective γ-functionalization of the butenolide scaffold. Cascade processes to complex structures through both γ- and β-functionalizations have also been developed. A variety of polycyclic γ-butyrolactone-containing motifs has been prepared with good to high stereoselectivity, under mild reaction conditions, using readily available bases, organocatalysts, and mostly palladium-based systems. The heterocyclic scaffolds illustrated in this review are useful building blocks, which have the potential for elaboration to new bioactive derivatives and drugs.

© 2025 The Author(s). ChemCatChem published by Wiley-VCH GmbH

18673899, 2025, 10, Downloaded from https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/cctc.202500060 by Universita Di Salerno, Wiley Online Library on [04/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Biocatalyzed isomerization is a feasible process to obtain (*R*)- and (*S*)-β-angelica lactone with high enantioselectivity. Additionally, isomerization followed by reduction of α-angelica lactone provides an alternative one-pot route to highly valuable γ-valerolactone in both enantiomerically enriched forms.

Although different catalytic systems have witnessed the reactivity of α-angelica lactone at the γ-position over the last years, and a first example of enantioselective β-functionalization has been documented, future efforts will still be necessary to develop suitable systems to promote asymmetric catalytic α-functionalization, which remains an unmet goal.

Acknowledgements

The Ministry of University and Research (MUR) is acknowledged for the PRIN 2022 PNRR project, grant number P2022MWY3P, titled "Old but Gold! Identification of molecular platforms for age-associated diseases to promote healthy and active aging". The authors also acknowledge funding by the European Union Next Generation EU, Mission 4 Component 1, CUP D53D23017160001.

Open access publishing facilitated by Universita degli Studi di Salerno, as part of the Wiley - CRUI-CARE agreement.

Conflict of Interests

The authors declare no conflict of interest.

Keywords: Asymmetric synthesis · Biomass resource · Cascade reaction · α-Angelica lactone · γ-Butenolides

[1] For selected reviews, see: a) M. Seitz, O. Reiser, *Curr. Opin. Chem. Biol.* **2005**, *9*, 285–292; b) R. R. A. Kitson, A. Millemaggi, R. J. K. Taylor, *Angew. Chem., Int. Ed.* **2009**, *48*, 9426–9451; c) S. Chatterjee, R. Sahoo, S. Nanda, *Org. Biomol. Chem.* **2021**, *19*, 7928-7332.
[2] T. Murakami, Y. Takahashi, E. Fukushi, J. Kawabata, M. Hashimoto, T. Okuno, Y. Harada, *J. Am. Chem. Soc.* **2004**, *126*, 9214–9220.
[3] B. M. Trost, A. C. Burns, M. J. Bartlett, T. Tautz, A. H. Weiss, *J. Am. Chem. Soc.* **2012**, *134*, 1474–1477.
[4] S. Kitani, K. T. Miyamoto, S. Takamatsu, E. Herawati, H. Iguchi, K. Nishitomi, M. Uchida, T. Nagamitsu, S. Omura, H. Ikeda, T. Nihira, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 16410–16415.
[5] E. Villedieu-Percheron, M. Lachia, P. M. J. Jung, C. Screpanti, R. Fonné -Pfister, S. Wendeborn, D. Zurwerra, A. De Mesmaeker, *Chimia* **2014**, *68*, 654–663.
[6] S. A. Look, M. T. Burch, W. Fenical, Q.-T. Zhen, J. Clardy, *J. Org. Chem.* **1985**, *50*, 5741–5746.
[7] For recent reviews, see: a) A. R. Choudhury, S. Mukherjee, *Chem. Soc. Rev.* **2020**, *49*, 6755–6788; b) B. Mao, M. Fañanás-Mastral, B. L. Feringa, *Chem. Rev.* **2017**, *117*, 10502–10566; c) X. Jusseau, L. Chabaud, C. Guillou, *Tetrahedron* **2014**, *70*, 2595–2615; d) L. Zhou, H. Yang, C. Yang, Z. Zhao, Q. Li, *Chin. J. Org. Chem.* **2023**, *43*, 2407–2424.
[8] a) S. K. Sartori, M. A. N. Diaz, G. Diaz-Muñoz, *Tetrahedron* **2021**, *84*, 132001; b) J. Hur, J. Jang, J. Sim, *Int. J. Mol. Sci.* **2021**, *22*, 2769.
[9] For selected examples, see: a) J. A. Griswold, M. A. Horwitz, L. V. Leiva, J. S. Johnson, *J. Org. Chem.* **2017**, *82*, 2276–2280; b) X. Li, M. Lu, Y. Dong, W. Wu, Q. Qian, J. Ye, D. J. Dixon, *Nat. Commun.* **2014**, *5*, 4479–4483; c) Z.-Y. Dai, P.-S. Wang, L.-Z. Gong, *Chem. Commun.* **2021**, *57*, 6748–6751.
[10] a) J. A. Griswold, J. S. Johnson, *ACS Catal.* **2019**, *9*, 11614–11618; b) X. Lu, J. Zhu, Y. Huang, *Org. Lett.* **2022**, *24*, 8816–8820.
[11] R. Lagoutte, C. Besnard, A. Alexakis, *Eur. J. Org. Chem.* **2016**, *2016*, 4372–4381.
[12] C. G. S. Lima, J. L. Monteiro, T. de Melo Lima, M. Weber Paixão, A. G. Corrêa, *ChemSusChem* **2018**, *11*, 25–47.
[13] J. H. Helberger, S. Ulubay, H. Civelekoglu, *Liebigs Ann. Chem.* **1949**, *561*, 215–220.
[14] For selected examples in Michael addition reactions, see: a) A. Quintard, A. Lefranc, A. Alexakis, *Org. Lett.* **2011**, *13*, 1540–1543; b) W. Zhang, D. Tan, R. Lee, G. Tong, W. Chen, B. Qi, K.-W. Huang, C.-H. Tan, Z. Jiang, *Angew. Chem., Int. Ed.* **2012**, *51*, 10069–10073; c) M. S. Manna, S. Mukherjee, *Chem. Eur J.* **2012**, *18*, 15277–15282; d) L. Yin, H. Takada, S. Lin, N. Kumagai, M. Shibasaki, *Angew. Chem., Int. Ed.* **2014**, *53*, 5327–5331. For examples in 1,2-addition reactions, see: e) L. Zhou, L.-L. Lin, J. Ji, M.-S. Xie, X.-H. Liu, X.-M. Feng, *Org. Lett.* **2011**, *13*, 3056–3059; f) Q. Tang, L.-L. Lin, J. Ji, H.-P. Hu, X.-H. Liu, X.-M. Feng, *Chem. Eur J.* **2017**, *23*, 16447–16451; g) J. Ji, L.-L. Lin, Q. Tang, T.-F. Kang, X.-H. Liu, X.-M. Feng, *ACS Catal.* **2017**, *7*, 3763–3767; h) T. Sakai, S. Hirashima, Y. Matsushima, T. Nakano, D. Ishii, Y. Yamashita, K. Nakashima, Y. Koseki, T. Miura, *Org. Lett.* **2019**, *21*, 2606–2609.
[15] B. J. Huffman, S. Chen, J. L. Schwarz, R. E. Plata, E. N. Chin, L. L. Lairson, K. N. Houk, R. A. Shenvi, *Nat. Chem.* **2020**, *12*, 310–318.
[16] L. Sun, J. Wu, F. Du, X. Chen, Z. Chen, *Science* **2013**, *339*, 786–791.
[17] M. Romaniszyn, L. Sieroń, Ł. Albrecht, *J. Org. Chem.* **2022**, *87*, 5296–5302.
[18] Y.-M. Song, C.-F. Wu, J.-H. Zhang, W.-H. Zhang, X. Qin, Y.-X. Yang, G.-W. Kang, J. Jiang, H.-X. Liu, *Chem. Commun.* **2023**, *59*, 3313–3316.
[19] a) A. Barco, N. Baricordi, S. Benetti, C. De Risi, G. P. Pollini, V. Zanirato, *Tetrahedron* **2007**, *63*, 4278–4283; b) L. Li, M.-C. Tang, S. Tang, S. Gao, S. Soliman, L. Hang, W. Xu, T. Ye, K. Watanabe, Y. Tang, *J. Am. Chem. Soc.* **2018**, *140*, 2067–2071; c) K. C. Nicolaou, K. K. Pulukuri, S. Rigol, M. Buchman, A. A. Shah, N. Cen, M. D. McCurry, K. Beabout, Y. Shamoo, *J. Am. Chem. Soc.* **2017**, *139*, 15868–15877.
[20] S. L. Mondal, K. Patra, R. Yadav, M. Baidya, *Synlett* **2023**, *34*, 2465–2470.
[21] R. R. A. Kitson, A. Millemaggi, R. J. K. Taylor, *Angew. Chem., Int. Ed.* **2009**, *48*, 9426–9451.
[22] H.-L. Cui, J.-R. Huang, J. Lei, Z.-F. Wang, S. Chen, L. Wu, Y.-C. Chen, *Org. Lett.* **2010**, *12*, 720–723.
[23] a) I. Smajlagic, M. Guest, R. Durán, B. Herrera, T. Dudding, *J. Org. Chem.* **2019**, *85*, 585–593; b) S. Gandhi, V. Sivadas, B. Baire, *Eur. J. Org. Chem.* **2020**, *2021*, 220–234.
[24] Z.-H. You, S. Zou, Y.-L. Song, X.-Q. Song, *Org. Lett.* **2022**, *24*, 7183–7187.
[25] D. V. Hrishikesh, R. A. Annadate, S. V. Pansare, *ACS Omega* **2023**, *8*, 3190–3197.
[26] C. Wei, X. Yang, S. Shi, L. Bai, D. Hu, R. Song, B. Song, *J. Agric. Food. Chem.* **2022**, *71*, 267–275.
[27] M. Romaniszyn, L. Sieroń, Ł. Albrecht, *Org. Biomol. Chem.* **2020**, *18*, 8633–8637.
[28] a) K. Nakashima, S. Hirashima, M. Kawada, Y. Koseki, , N., Tada, A. Itoh, T. Miura, *Tetrahedron Lett.* **2014**, *55*, 2703–2706; b) S. Hirashima, T. Narushima, M. Kawada, K. Nakashima, K. Hanai, Y. Koseki, T. Miura, *Chem. Pharm. Bull* **2017**, *65*, 1185–1190; c) S. Hirashima, K. Nakashima, Y. Fujino, R. Arai, T. Sakai, M. Kawada, Y. Koseki, M. Murahashi, N. Tada, A. Itoh, T. Miura, *Tetrahedron Lett.* **2014**, *55*, 4619–4622.
[29] R. Arai, S. Hirashima, J. Kondo, K. Nakashima, Y. Koseki, T. Miura, *Org. Lett.* **2018**, *20*, 5569–5572.
[30] D. Ishii, S. Hirashima, K. Nakashima, H. Akutsu, T. Sakai, Y. Matsushima, M. Kawada, T. Miura, *Org. Lett.* **2021**, *23*, 480–485.
[31] D. Ishii, S. Hirashima, H. Akutsu, K. Nakashima, Y. Matsushima, T. Sakai, T. Miura, *Asian J. Org. Chem.* **2022**, *11*, e202200048.
[32] Y. Iino, Y. Matsushima, K. Nakashima, S. Hirashima, T. Miura, *J. Org. Chem.* **2024**, *89*, 11789–11795.
[33] For selected examples concerning sulfonyl group elimination in synthesis employing only enone as an alkenyl donor see: a) S. G. Pyne, D. M. David, Z. Dong, *Tetrahedron Lett.* **1998**, *39*, 8499–8502; b) S. G. Pyne, Z. Dong, *Tetrahedron Lett.* **1999**, *40*, 6131–6134.
[34] a) J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416–14417; b) X. Han, H.-B. Zhou, C. Dong, *Chem. Rec.* **2016**, *16*, 897–907; c) E. A. Popova, Y. A. Pronina, A. V. Davtian, G. D. Nepochatyi, M. L. Petrov, V. M. Boitsov, A. V. Stepakov, *Russ. J. Gen. Chem.* **2022**, *92*, 287–347; d) S. Vera, A. García-Urricelqui, A. Mielgo, M. Oiarbide, *Eur. J. Org. Chem.* **2023**, *26*, e202201254.

© 2025 The Author(s). ChemCatChem published by Wiley-VCH GmbH

18673899, 2025, 10, Downloaded from https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/cctc.202500060 by Universita Di Salerno, Wiley Online Library on [04/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

[35] S.-P. Yuan, P.-H. Dou, Y.-Q. Jia, J.-Q. Zhao, Y. You, Z.-H. Wang, M.-Q. Zhou, W.-C. Yuan, *Chem. Comm.* **2022**, *58*, 553–556.
[36] Y. Zheng, W. Jiang, J. Tan, J. Yan, R. Zhan, H. Huang, *J. Org. Chem* **2021**, *86*, 12821–12830.
[37] Y. Wu, R. P. Singh, L. Deng, *J. Am. Chem. Soc.* **2011**, *133*, 12458–12461.
[38] X. Cheng, T. Li, K. Gutman, L. Zhang, *J. Am. Chem. Soc.* **2021**, *143*, 10876–10881.
[39] Y. Zeng, C. Fei, X. Zhou, J. Luo, L. Deng, *Synlett* **2023**, *34*, 2429–2432.
[40] H. Guo, Y. C. Fan, Y. Wu, O. Kwon, *Chem. Rev.* **2018**, *118*, 10049–10293.
[41] M. Liu, Q. Han, L. Wang, X. Chen, X. Zhang, H. Guo, *Chin. J. Chem.* **2024**, *42*, 3269–3277.
[42] a) C.-W. Cho, M. J. Krische, *Angew. Chem., Int. Ed.* **2004**, *43*, 6689–6691; b) Y.-Q. Jiang, Y.-L. Shi, M. Shi, *J. Am. Chem. Soc.* **2008**, *130*, 7202–7203; c) P. Chen, Z. Yue, J. Zhang, X. Lv, L. Wang, J. Zhang, *Angew. Chem., Int. Ed.* **2016**, *55*, 13316–13320; d) J. Zhang, H.-H. Wu, J. Zhang, *Org. Lett.* **2017**, *19*, 6080–6083.
[43] a) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, *114*, 9047–9153; b) B. Peng, J. Ma, J. Guo, Y. Gong, R. Wang, Y. Zhang, J. Zeng, W.-W. Chen, K. Ding, B. Zhao, *J. Am. Chem. Soc.* **2022**, *144*, 2853–2860; c) X.-L. Liu, M.-L. Gong, X. Yang, P. Tian, Q.-H. Li, *Org. Chem. Front.* **2024**, *11*, 4934–4953.
[44] T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem., Int. Ed.* **2004**, *43*, 1566–1568.
[45] D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357.
[46] a) A. Kütt, I. Leito, I. Kaljurand, L. Sooväli, V. M. Vlasov, L. M. Yagupolskii, I. A. Koppel, *J. Org. Chem.* **2006**, *71*, 2829–2838; b) K. Kaupmees, N. Tolstoluzhsky, S. Raja, M. Rueping, I. Leito, *Angew. Chem., Int. Ed.* **2013**, *52*, 11569–11572.
[47] M. Tomanová, I. Vaňková, D. Toman, A. Přibylka, I. Nemec, P. Cankař, *J. Org. Chem.* **2023**, *88*, 9265–9276.
[48] a) M. Meazza, R. Rios, *Synthesis* **2016**, *48*, 960–973; b) Z. Shao, H. Zhang, *Chem, Soc. Rev.* **2009**, *38*, 2745–2755; c) C. Zhong, X. Shi, *Eur. J. Org. Chem.* **2010**, *2010*, 2999–3925.
[49] C. Yu, P. Ji, Y. Zhang, X. Meng, W. Wang, *Org. Lett.* **2021**, *23*, 7656–7660.
[50] a) S. Li, W. Jia, N. Jiao, *Adv. Synth. Catal.* **2009**, *351*, 569–575; b) D. Gasperini, L. Maggi, S. Dupuy, R. M. P. Veenboer, D. B. Cordes, A. M. Z. Slawin, S. P. Nolan, *Adv. Synth. Catal.*, **2016**, *358*, 3857–3862.
[51] J. Cui, N. Kumagai, T. Watanabe, M. Shibasaki, *Chem. Sci.* **2020**, *11*, 7170–7176.
[52] B. M. Trost, E. Gnanamani, C. A. Kalnmals, C.-I. J. Hung, J. S. Tracy, *J. Am. Chem. Soc.* **2019**, *141*, 1489–1493.
[53] S. Samanta, J. Cui, H. Noda, T. Watanabe, M. Shibasaki, *J. Org. Chem.* **2023**, *88*, 1177–1184.
[54] Z.-Y. Dai, P.-S. Wang, L.-Z. Gong, *Chem. Commun.* **2021**, *57*, 6748–6751.
[55] S. Li, Q. Chen, J. Yang, J. Zhang, *Angew. Chem., Int. Ed.* **2022**, *61*, e202202046.
[56] X. Lu, J. Zhu, Y. Huang, *Org. Lett.* **2022**, *24*, 8816–8820.
[57] M. S. Robescu, L. Cendron, A. Bacchin, K. Wagner, T. Reiter, I. Janicki, K. Merusic, M. Illek, M. Aleotti, E. Bergantino, M. Hall, *ACS Catal.* **2022**, *12*, 7396–7405.
[58] B. A. Sandoval, T. K. Hyster, *Curr. Opin. Chem. Biol.* **2020**, *55*, 45–51.
[59] H. S. Toogood, N. S. Scrutton, *ACS Catal.* **2018**, *8*, 3532–3549.
[60] N. G. Turrini, E. Eger, T. C. Reiter, K. Faber, M. Hall, *ChemSusChem* **2016**, *9*, 3393–3396.
[61] A. Tonoli, K. Wagner, A. Bacchin, T. Reiter, E. Bergantino, M. S. Robescu, M. Hall, *ChemBioChem* **2023**, *24*, e202300146.
[62] a) A. A. Koutinas, A. Vlysidis, D. Pleissner, N. Kopsahelis, I. Lopez Garcia, I. K. Kookos, S. Papanikolaou, T. H. Kwan, C. S. K. Lin, *Chem. Soc. Rev.* **2014**, *43*, 2587–2627; b) E. J. Cho, L. T. P. Trinh, Y. Song, Y. G. Lee, H.-J. Bae, *Bioresour. Technol.* **2020**, *298*, 122386; c) S. Meninno, *Eur. J. Org. Chem.* **2023**, *26*, e202300264.

Manuscript received: January 13, 2025
Revised manuscript received: February 12, 2025
Accepted manuscript online: February 13, 2025
Version of record online: March 5, 2025

© 2025 The Author(s). ChemCatChem published by Wiley-VCH GmbH

18673899, 2025, 10, Downloaded from https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/cctc.202500060 by Universita Di Salerno, Wiley Online Library on [04/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License