

**Catalytic Asymmetric Diels–Alder Reaction of β,β -Disubstituted Enals:
Synthesis of (–)-(Z)- β -Santalol**



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**Catalytic Asymmetric Diels–Alder Reaction of β,β -Disubstituted Enals:
Synthesis of (–)-(Z)- β -Santalol**

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Abstract

The Diels–Alder reaction remains a cornerstone of organic synthesis, enabling efficient construction of complex chiral frameworks. However, the enantioselective Diels–Alder reaction of β,β -disubstituted enals has long presented a formidable challenge due to the low dienophilicity and steric congestion of these substrates. In this work, we presenting the first general catalytic system for Diels–Alder reactions of this substrate class using strong imidodiphosphorimidate Brønsted acids. The optimized catalytic system displayed excellent robustness, reproducibility, and scalability, allowing for natural extension of this methodology to the concise total synthesis of (–)-(Z)- β -santalol, a key constituent of sandalwood oil. The synthetic route relies purely on bulk chemicals and delivers the target compound with excellent enantioselectivity in just five steps. Comprehensive mechanistic studies revealed the underlying principles responsible for the observed reactivity, and a complex cation exchange process between the imidodiphosphorimidates and molecular sieves.

Kurzzusammenfassung

Die Diels-Alder-Reaktion ist nach wie vor ein Eckpfeiler der organischen Synthese, da sie die effiziente Konstruktion komplexer chiraler Gerüste ermöglicht. Die enantioselective Diels-Alder-Reaktion von β,β -disubstituierten Enalen stellte jedoch aufgrund der geringen Dienophilie und sterischen Hinderung dieser Substrate lange Zeit eine große Herausforderung dar. In dieser Arbeit stellen wir das erste allgemeine katalytische System für Diels-Alder-Reaktionen dieser Substratklasse unter Verwendung starker Imidodiphosphorimidat-Brønsted-Säuren vor. Das optimierte katalytische System zeigte eine ausgezeichnete Robustheit, Reproduzierbarkeit und Skalierbarkeit, was eine natürliche Erweiterung dieser Methodik auf die prägnante Totalsynthese von (–)-(Z)- β -Santalol, einem Hauptbestandteil von Sandelholzöl, ermöglichte. Der Syntheseweg basiert ausschließlich auf Massenchemikalien und liefert die Zielverbindung mit ausgezeichneter Enantioselectivität in nur fünf Schritten. Umfassende mechanistische Studien enthüllten die zugrunde liegenden Prinzipien, die für die beobachtete Reaktivität verantwortlich sind, sowie einen komplexen Kationenaustauschprozess zwischen den Imidodiphosphorimidaten und Molekularsieben.

List of Abbreviations

Ac	acyl
ACDC	asymmetric counteranion-directed catalysis
Ar	aryl
atm	standard atmosphere
BBA	Brønsted acid-assisted Brønsted acid
BINOL	1,1'-bi-2-naphthol
BLA	Brønsted acid-assisted Lewis acid
Bn	benzyl
BSTFA	<i>N,O</i> -bis(trimethylsilyl)trifluoroacetamide
Bz	benzoyl
COD	1,5-cyclooctadiene
CPA	chiral phosphoric acid
CpH	cyclopentadiene
Cp*	1,2,3,4,5-pentamethylcyclopentadienyl
DA	Diels-Alder reaction
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIBAL	diisobutylaluminium hydride
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
DMPU	<i>N,N'</i> -dimethylpropyleneurea
DSI	disulfonimide
EDG	electron donating group
EDS	energy-dispersive X-ray spectroscopy
e.e.	enantiomeric excess
EI	electron impact ionization
e.r.	enantiomeric ratio
Et	ethyl
equiv.	equivalent

ESI	electrospray ionization
EWG	electron withdrawing group
FAU	faujasite
GC	gas chromatography
h	hour
Hal	halogen
HMDS	hexamethyldisilazide or hexamethyldisilazane
HMPA	hexamethylphosphoric triamide
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons reaction
<i>i</i> -Bu	<i>iso</i> -butyl
IDP	imidodiphosphate
IDPi	imidodiphosphorimidate
<i>i</i> IDP	iminoimidodiphosphate
<i>i</i> -Pr	<i>iso</i> -propyl
JINGLE	1,1'-binaphthyl-2,2'-bis(sulfuryl)imides
KIE	kinetic isotope effect
KTMP	potassium-2,2,6,6-tetramethylpiperidide
LAH	lithium aluminium hydride
LBA	Lewis acid-assisted Brønsted acid
LICKOR	Lochmann-Schlosser superbasic system
LLA	Lewis acid-assisted Lewis acid
LTA	Linde Type A
LUMO	lowest unoccupied molecular orbital
<i>m</i> -CPBA	<i>meta</i> -chloroperoxybenzoic acid
MO	molecular orbital
mol%	mole percent
Ms	methanesulfonyl
MS	molecular sieves

MTBE	methyl <i>tert</i> -butyl ether
NLE	non-linear effects
NMR	nuclear magnetic resonance
OAc	acetate
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
Py	pyridine
RaNi	Raney nickel
SBU	secondary building unit
TADDOL	$\alpha,\alpha,\alpha',\alpha'$ -tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol
<i>t</i> -Bu	<i>tert</i> -butyl
TBHP	<i>tert</i> -butyl hydroperoxide
TEA	triethylamine
Tf	trifluoromethylsulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
t_R	retention time
TRIP	3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate
Ts	toluenesulfonyl
TS	transition state

1. Introduction

For billions of years, evolution has refined the ability of living systems to create new matter. The biosynthetic pathways characterized by extraordinary efficiency and selectivity, have perfected transformation of the simplest building blocks into the vast array of complex organic compounds needed for survival, growth, and adaptation of the whole organism.

For centuries, it was believed that such transformations required a mysterious “vital force.” This notion was overturned in 1828, when Friedrich Wöhler serendipitously synthesized urea from inorganic materials.¹ His discovery not only demonstrated that human ingenuity could create organic compounds without invoking the “vital force”² but even further — that such artificial pathways can be in some aspects more efficient than ones employed by living organisms: Wöhler’s synthesis of urea converted ammonia to urea in a single step while the same transformation in nature’s urea cycle requires five enzymatic steps.³

Since their emergence, organic synthesis and chemical industry have undergone continuous evolution, leading to the development of novel types of matter, not found in nature. These advances not only enabled survival under conditions previously deemed insurmountable but also significantly improved the overall quality of human life.^{4,5} Among the most important tools in the repertoire of organic synthesis is undoubtedly the Diels–Alder reaction.^{6,7} By simultaneously forming two new σ -bonds at the expense of two π -bonds within a cyclic product and incorporating all atoms of the reactants, this transformation efficiently generates a high degree of molecular complexity. The discovery of the Diels–Alder reaction not only granted access to an immense variety of new compounds but also provided concise and alternative synthetic routes to numerous natural products. Its synthetic utility was further enhanced through the advent of catalysis. Catalytic strategies broadened the reaction’s scope and, more importantly, opened the door to asymmetric synthesis, enabling the selective formation of a single stereoisomer in compounds bearing stereogenic centers.

The significance of asymmetric synthesis becomes particularly evident when considering the profoundly different biological effects that enantiomers of a single compound can produce in living systems. By ensuring stereochemical control and producing exclusively active isomers, asymmetric synthesis provides an economic and environmental advantage. Within the generally recognized categories of catalysts—transition-metal catalysis, enzymatic catalysis, and organocatalysis—the latter has recently emerged as especially attractive. Organocatalysts rely on naturally abundant elements, thereby eliminating the risk of metal

contamination and some of the economic constraints, while simultaneously offering a broad range of structural tunability and, consequently, excellent control over stereoselectivity.

The following chapters will first provide an overview of the development of asymmetric organocatalysis and asymmetric Diels–Alder reactions of enals as powerful and versatile synthetic tools, outlining both recent methodological advances and the key limitations that remain. The next section will address the challenges and strategies associated with the enantioselective total synthesis of (–)-(Z)- β -santalol — a highly valuable odorant and compelling synthetic target for the implementation of an enantioselective catalytic Diels–Alder reaction.

2. Background

2.1. Catalysis—An Essential Part of Organic Chemistry and Industry

2.1.1. The Fundamental Principles of Catalysis

Catalysis in the form of enzymatic reactions is integral part of cellular life, and neither its spread nor evolution would have been possible without catalysis. The importance of catalysis has been recognized by humankind since antiquity, long before the discovery of enzymes, most notably in the form of fermentation of starchy or sugary materials. Over time, the phenomenon of catalysis—and the deliberate technological use of accelerated chemical processes—expanded beyond natural transformations to artificial processes, becoming a central driving force in human progress.

The first formal recognition of chemical catalysis is often attributed to Jöns Jacob Berzelius, who in 1835 observed commonalities among several reactions⁸ and introduced the term *catalysis*, derived from the Greek words *kata* (“down”) and *lysis* (“to split” or “break”). Nearly fifty years later, Wilhelm Ostwald refined the concept by defining catalysis as “*the acceleration of a slow-running chemical reaction via the presence of a foreign substance.*”⁹ For his pioneering contributions to the field, Ostwald was awarded the Nobel Prize in Chemistry in 1909.

The fundamental principle underlying catalysis is the reduction of the activation energy barrier (Gibbs free energy of activation, $\Delta G^\ddagger$) by providing an alternative mechanistic pathway, while the overall Gibbs free energy change (ΔG) of the reaction remains unaltered (Figure 1A). In most cases, this is achieved through the formation of lower-energy intermediates upon interaction between the catalyst and the reactants (Figure 1B, cat.–A–B). Importantly, the catalyst is not consumed in the process and is regenerated at the end of the catalytic cycle. Because ΔG remains unchanged, catalysis has no effect on the equilibrium constant or the thermodynamics of the reaction; rather, it is a kinetic phenomenon.

Since catalysts can direct reactions along specific pathways, catalytic processes often exhibit enhanced selectivity. Such selectivity may manifest not only as site selectivity, favoring one reactive site over another when multiple are available, but also as stereoselectivity when the catalyst possesses an element of chirality.

In the latter case, the catalyst must provide an additional kinetic advantage ($\Delta\Delta G^\ddagger$) that

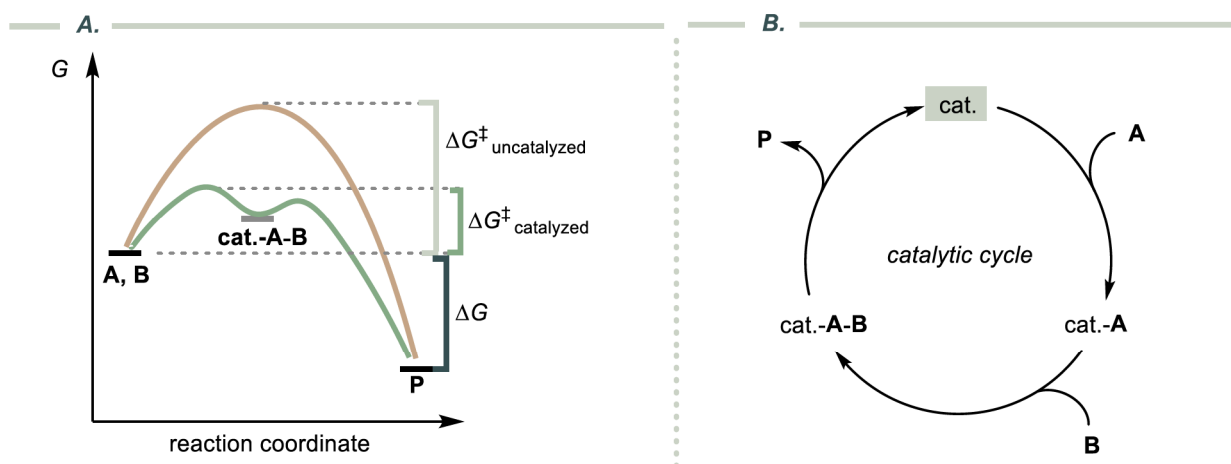


Figure 1. A. Energy diagram of a catalytic process; B. Catalytic cycle. A, B = reactants, P = product, cat. = catalyst.

distinguishes between two stereoisomeric pathways, which otherwise reside at the same Gibbs free energy level (Figure 2A). This is accomplished through the formation of diastereomeric complexes (or transition states) between the catalyst and the reactants, which do differ in energy. The resulting energy difference accounts for enantioselectivity and is referred to as external asymmetric induction. Among various strategies for asymmetric synthesis, external asymmetric induction is the most desirable because the chiral catalyst responsible for stereocontrol is regenerated in each catalytic cycle. This feature renders the process more economically favorable compared to approaches based on the chiral pool or chiral auxiliaries (Figure 2B).

The first enantioselective catalytic reaction is commonly attributed to Wilhelm Marckwald, who in 1904 reported the brucine-catalyzed (natural alkaloid) decarboxylation of 2-ethyl-2-methylmalonic acid¹⁰, showcasing one of the first organocatalytic enantioselective reactions as well.

In general, effective enantioselective catalysts must possess two fundamental properties: the ability to create a chiral environment, and the capacity for reversible interactions with substrates, both of which allow broad opportunities for catalyst development. Today, the field of enantioselective catalysis rests on three major pillars: transition-metal catalysis, enzymatic catalysis, and organocatalysis.¹¹ Transition-metal catalysis dominated enantioselective catalysis for decades, largely due to rapid advances in understanding the Lewis acid properties of metal complexes and the ease of modulating their stereochemical environment through ligand variation.¹² The recent development of the directed evolution methods and protein engineering allowed enzymatic catalysis to emerge into a powerful synthetic methodology, however many limitations still remain, namely limited reactivity range, high production costs and stability.

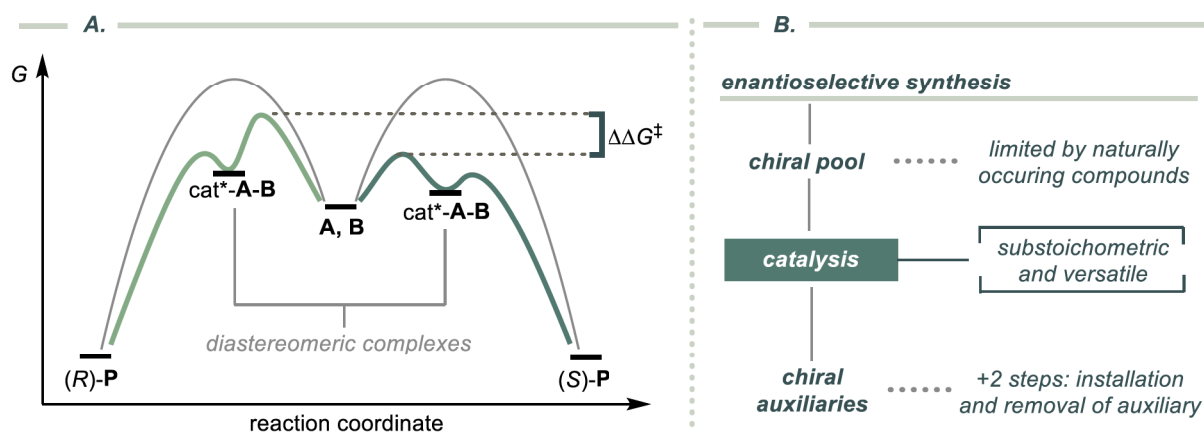


Figure 2. A. Energy diagram of an enantioselective catalytic process; B. Enantioselective synthesis strategies.

In contrast, organocatalysis imposes far fewer constraints on molecular design or transformation scope. Compared to transition-metal catalysis, organocatalysis also offers lower synthetic cost, reduced toxic waste, simplified handling, and greater robustness under ambient conditions.¹³ Despite these advantages (and despite its rather early discovery) organocatalysis remained represented mostly by isolated examples until its resurgence in the early 21st century.

2.1.2. Asymmetric Brønsted Acid Organocatalysis

The first applications of small organic molecules as catalysts can be traced back to 1912, when Bredig¹⁴ reported the use of cinchona alkaloids for the asymmetric addition of hydrogen cyanide to aldehydes, obtaining the corresponding products with low (<60:40 e.r.) enantioselectivities. In 1960, Pracejus¹⁵ achieved promising enantioselectivities (up to 87:13 e.r.) in the addition of methanol to ketene catalyzed by cinchona alkaloids. The discovery of the Hajos–Parrish–Eder–Sauer–Wiechert reaction in 1971¹⁶ and 1974¹⁷ — proline (**2.1**)-catalyzed intramolecular aldol reaction of triketones forming optically pure bicyclic ketones — not only showcased that small organic molecules can provide high levels of enantiocontrol but also found broad application in the synthesis of steroids and other natural products.^{18,19}

True recognition of organocatalysis as a vast field with great potential, however, did not emerge until nearly three decades later, when List and MacMillan independently reported its application to two fundamental transformations: the aldol and the Diels–Alder reactions. In 2000, List et al. demonstrated proline (**2.1**)-catalyzed intermolecular aldol reaction which delivered products in good to excellent yields and enantioselectivities, proceeding via enamine intermediate.²⁰ In the same year, MacMillan et al. described the first organocatalytic Diels–Alder reaction of enals, utilizing an iminium ion activation mode mediated by a chiral imidazolidinone catalyst **2.2**.²¹ At that time, MacMillan also coined the term “organocatalysis”.

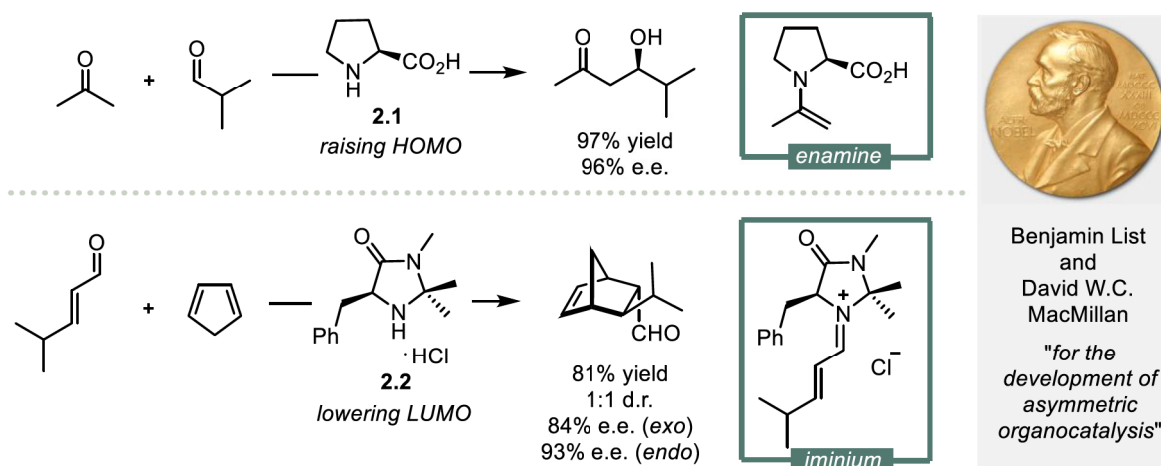


Figure 3. Seminal reports by List and MacMillan.

These two seminal reports not only brought the field to the attention of the broader scientific community but were ultimately recognized with the Nobel Prize in 2021 (Figure 3). Collectively, they exemplify the two foundational covalent activation modes in organocatalysis: enamine and iminium ion catalysis. In both cases, the catalyst functions as a Lewis base to form covalent intermediates, but the activation principles differ: enamine catalysis raises the highest occupied molecular orbital (HOMO) of the nucleophilic partner,²² whereas iminium catalysis lowers the lowest unoccupied molecular orbital (LUMO) of the electrophile, in a manner analogous to Lewis acid activation of dienophiles in the Diels–Alder reaction (see Chapter 2.2).

With the rapid expansion of the field, many new catalyst classes, activation modes, and strategies have been reported, making comprehensive classification increasingly complex. One broadly applied framework relies on acid/base properties (Figure 4).

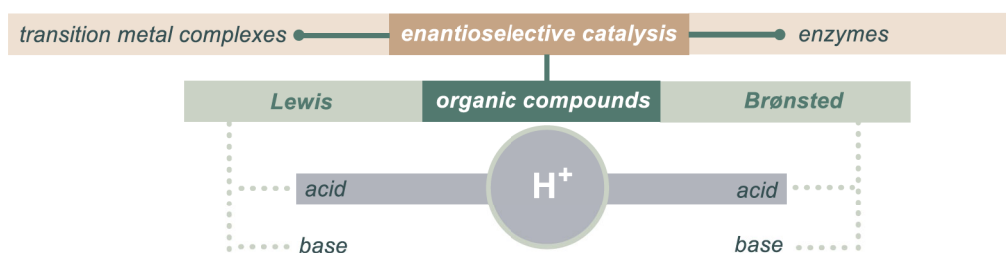


Figure 4. Categories of enantioselective catalysts.

Although less mechanistically precise for certain catalyst types,²³ it highlights one of the most powerful strategies to emerge in recent years: Brønsted acid catalysis.²⁴ By definition, Brønsted acids donate a proton, allowing for an exceptionally broad range of catalyst scaffolds. The proton itself, the smallest positively charged particle, can act as a Lewis acid as well due to its vacant orbital and ability to accept an electron pair. The protonation as an activation mode

thus lowers the LUMO of electrophilic species and leads to build-up of a (partial) positive charge, ultimately resulting in the formation of more reactive species. Brønsted acid catalysis is fundamentally limited only by the ability of the catalyst to protonate the substrate — its acid strength. Continuous advances in the catalyst design have progressively expanded this capability, establishing Brønsted acid catalysis as one of the most versatile and broadly applicable strategies in the modern asymmetric synthesis.

Depending on the pK_a difference between the substrate and the acid, electrophilic activation may occur via full proton transfer (protonation) or through hydrogen bonding, which can be considered the two extremes of one continuum (Figure 5A).²⁵ In the case of protonation, complete proton transfer generates an ion pair between the protonated substrate and the conjugate base of the acid. Since protons are intrinsically achiral the role of enantioinduction solely relies on the anion. This principle of induction of enantioselectivity through the formation of ion pair between a cationic intermediate and a chiral counteranion provided by the catalyst is known as asymmetric counteranion-directed catalysis (ACDC) and represents an important strategy in enantioselective catalysis and especially in Brønsted acid-mediated reactions (Figure 5B).²⁶ Despite the fact that the strict definition of an ion pair implies that the only attractive forces in action are Coulombic in nature, in reality many intermediate cases are possible, which is analogous to the previously discussed spectrum of electrophilic activation with Brønsted acids. For example, hydrogen bonding can be viewed as ion pairing between a “donor bond” and an “acceptor atom” dipoles.

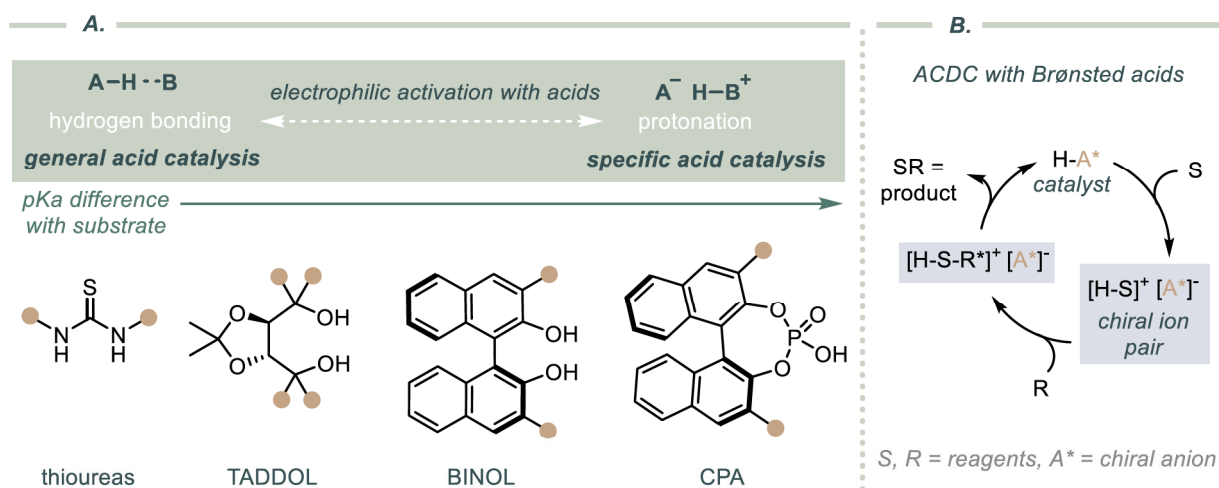


Figure 5. A. Continuum of electrophilic activation by Brønsted acids, TADDOL = $\alpha, \alpha', \alpha', \alpha'$ -tetraaryl-1,3-dioxolan-4,5-dimethanol; BINOL = 1,1'-bi-2-naphthol; CPA = chiral phosphoric acid; B. ACDC catalytic cycle.

Despite the ambiguities regarding the precise nature of attractive forces within ion pairs and the absence of definitive methods for their characterization, this concept has proven

extremely useful in enantioselective transformations. Its potential becomes particularly evident when combined with one of the most versatile catalytic species—the proton, embodied in Brønsted acids.

The first pioneering examples of enantioselective Brønsted acid-catalyzed reactions were independently reported by Akiyama²⁷ and Terada²⁸ in 2004, who demonstrated the use of BINOL-derived chiral phosphoric acids (it was later established, however, that the true catalytic species were often the corresponding phosphoric acid salts; subsequent studies showed that both the acids and their salts can function as catalysts²⁹) in Mannich-type transformations. The BINOL framework employed in the CPAs synthesis provided a multifaceted yet readily available chiral platform for the catalyst design. It allowed systematic modifications of the steric and electronic properties (e.g., at the 3,3'- and 6,6'-positions) as well as tuning of the acidity. These design features paved the way for major advances in enantioselective Brønsted acid organocatalysis. Among first such developments, the introduction of the highly sterically hindered 3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (TRIP), reported by Hoffmann and List in 2005,³⁰ represented a milestone. TRIP remains one of the most widely applied catalysts in the field.

Although a vast number of successful applications of CPAs³¹ was reported, two major challenges have emerged as research advanced toward more ambitious transformations. First, the relatively open catalytic site often fails to provide sufficient steric confinement for small substrates. Second, the acidity range of CPAs' ($pK_a \approx 13.0$ in MeCN) limits their ability to activate less Brønsted-basic substrates.^{32,33} Progress toward overcoming these limitations was initiated by List and co-workers in 2009 with the development of stronger Brønsted acids based on a disulfonimide functionality (DSIs, $pK_a \approx 8.5$ in MeCN) (Figure 6).³⁴ Shortly thereafter, Berkessel introduced 1,1'-binaphthyl-2,2'-bis(sulfuryl)imides (JINGLES, $pK_a \approx 5.2$ in MeCN) in 2010.^{32,35,36} Both catalyst classes were able to promote reactions of substantially less basic substrates: ketones and aldehydes. However, the fine stereocontrol in such highly reactive systems was challenging.

An elegant solution to this stereoselectivity challenge was again provided by the List group, who proposed the design of dimeric BINOL-derived backbone to create a more confined chiral environment around the catalytically active site.

The first realization of this approach was represented by imidodiphosphates³⁷ (IDPs), which exhibited a moderate pK_a (≈ 11.0 in MeCN) but demonstrated the viability of the dimeric

frameworks in reactions with small, unbiased substrates.

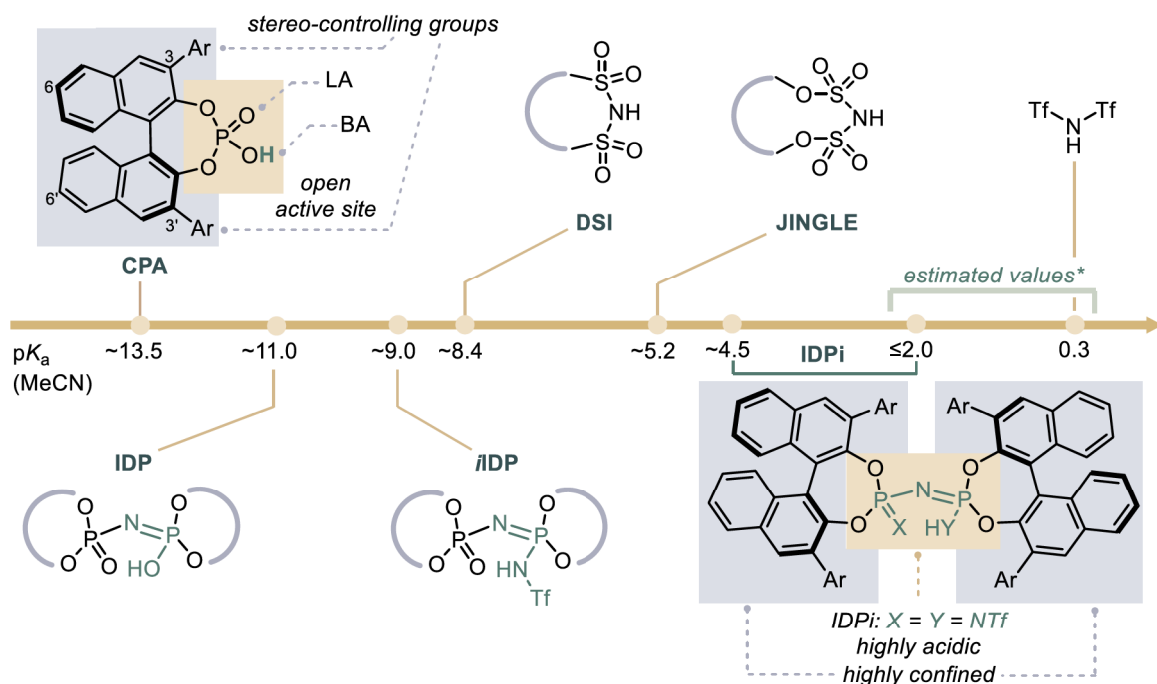


Figure 6. pK_a values of the selected Brønsted acids. LA = Lewis acidic site, BA = Brønsted acidic site. *From the available measurements in DCE.

Inspired by Yagupolskii's work³⁸ on the strong acidifying effect of the =NSO₂CF₃ substituent, replacement of a single oxygen atom in the IDP scaffold afforded the more acidic iminoimidodiphosphates (*i*IDPs, pK_a ≈ 9.0).³⁹ Further optimization culminated in the development of the highly confined and strongly acidic imidodiphosphorimidates organocatalysts⁴⁰ (IDPis, pK_a 4.5 to ≤2.0 in MeCN). These Brønsted acids represented a major breakthrough, opening new horizons for both reactivity and stereoselectivity. Importantly, they enabled transformations that were previously inaccessible under Brønsted acid catalysis, including the activation of simple olefins^{41,42} and several challenging Diels-Alder reactions with enal dienophiles, which will be discussed in detail in the next section.

2.2. Diels-Alder Reactions with Enals

2.2.1. Fundamental Principles of Reactivity in Diels-Alder Reaction

Almost a century ago, during the 1920s at the University of Kiel, Otto Diels and his student Kurt Alder began investigating the reactions of diencs. One particular transformation drew their special attention: formation of cyclic structures when dienes are reacted with compounds containing a double bond and a conjugated carbonyl group. Although isolated

examples of this type of reactivity had been reported earlier^{43,44} it wasn't identified as a common reactivity pattern up to this point. Their systematic investigations culminated in a pioneering publication in 1928,⁴⁵ which not only summarized but also advanced the understanding of this transformation. For this landmark discovery, Diels and Alder were awarded the Nobel Prize in Chemistry in 1950 (Figure 7). Since then, this area of organic chemistry has developed dynamically, with continuous efforts expanding the reaction's scope, demonstrating its utility in the synthesis of complex natural products, and establishing new strategies for chemo- and stereocontrol.

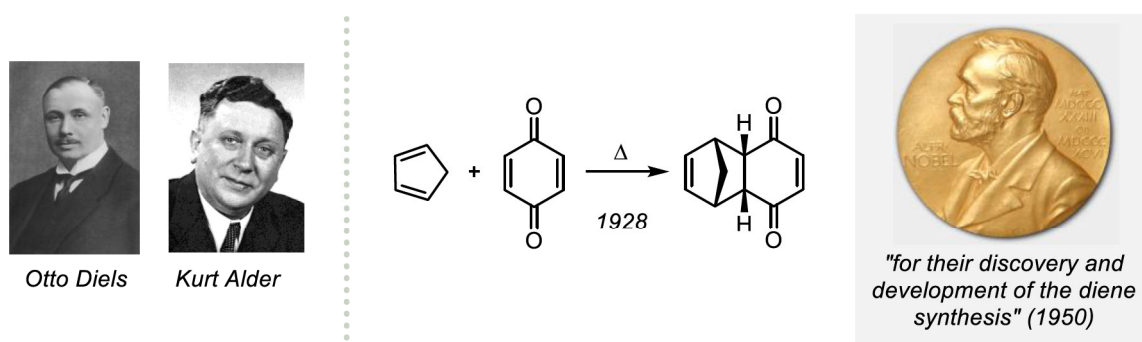


Figure 7. The discovery of the Diels-Alder reaction.

At the core of every Diels–Alder reaction lies the same fundamental interaction: the overlap between the HOMO of the diene and the LUMO of the dienophile.* Prototypically, the reaction is classified as a pericyclic process in which all bond-forming and bond-breaking events occur concertedly through a cyclic transition state, without the involvement of highly reactive intermediates. As such, the reaction is primarily governed by orbital interactions. The thermodynamic driving force of the transformation is the replacement of two relatively less stable π -bonds with two energetically more favorable σ -bonds, resulting in a negative change in enthalpy.⁴⁶ At the same time, the reaction is accompanied by a decrease in entropy, since two separate molecules combine to form one, thereby reducing the overall disorder of the system. Consequently, many Diels–Alder reactions are spontaneous and favorable at ambient temperatures, but can become reversible at elevated temperatures, giving rise to the retro-Diels–Alder reaction.

According to the Woodward–Hoffmann rules, the Diels-Alder reaction can be described as thermally allowed $[\pi 4_s + \pi 2_s]$ cycloaddition. The cyclic transition state is established through

*In the case of the normal electron-demand Diels–Alder reaction. The opposite frontier orbital alignment—interaction of the LUMO of the diene with the HOMO of the dienophile—defines an inverse electron-demand Diels–Alder reaction, which lies beyond the scope of the present discussion.

in-phase suprafacial overlap between the HOMO of the diene and the LUMO of the dienophile. In this interaction, the diene contributes its four electrons from the Ψ_2 molecular orbital, while the dienophile provides its unoccupied π^* orbital. (Figure 8).⁴⁷

Application of the frontier molecular orbital theory, developed by K. Fukui,⁴⁸ to the Diels-Alder reaction is especially helpful for the understanding reactivity trends. The HOMO–LUMO energy gap is a key factor in determining the feasibility of a Diels–Alder reaction. A smaller energy gap enhances stabilization of the newly formed molecular orbitals, allowing electrons to populate lower-energy states and thereby facilitating the reaction. This gap can be modulated by introducing substituents that bias the electron density of either the diene or the dienophile. Electron-donating groups (EDGs) on the diene raise the energy of its HOMO, whereas electron-withdrawing groups (EWGs) on the dienophile lower the energy of its LUMO. Both effects contribute to reducing the HOMO–LUMO gap, thus increasing the relative reaction rate.

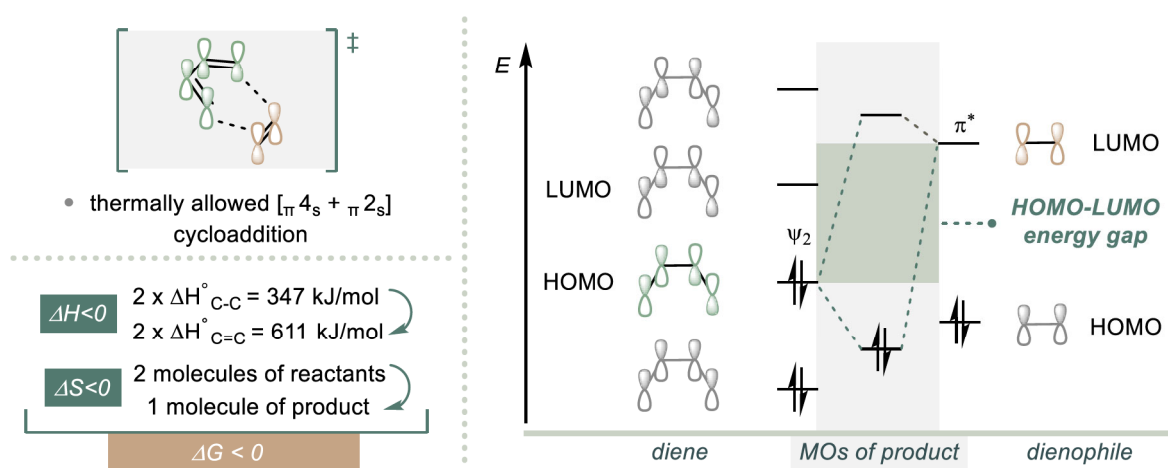


Figure 8. Woodward–Hoffmann, thermodynamic and frontier molecular orbitals description of the Diels-Alder reaction.

Beyond reactivity, substituent effects also play a critical role in governing regio- and stereoselectivity. For example, in the case of mono-terminally substituted diene and dienophile, the introduction of a conjugated EDG substituent at the terminus of the diene perturbs its HOMO, leading to a larger orbital coefficient at the C-4 position. Conversely, the presence of an EWG in the dienophile increases the orbital coefficient at the β -position of its LUMO (Figure 9A). This effect can be enhanced by coordination with Lewis acids, which further increase polarization of the dienophile.⁴⁹ A larger orbital coefficient indicates that an orbital is more localized on a specific atom; for example, in the case of the HOMO, the atom with the largest coefficient exhibits the highest nucleophilicity. The resulting asymmetry in orbital distribution

dictates the preferred orientation of the reactants in the transition state: the most favorable arrangement is the one in which orbitals with the largest coefficients overlap.⁵⁰ Maximization of orbital interactions provides a reliable predictor of experimental outcomes, often offering clearer explanations than the less rigorous, though still commonly applied, *ortho-para rule* (Figure 9B).

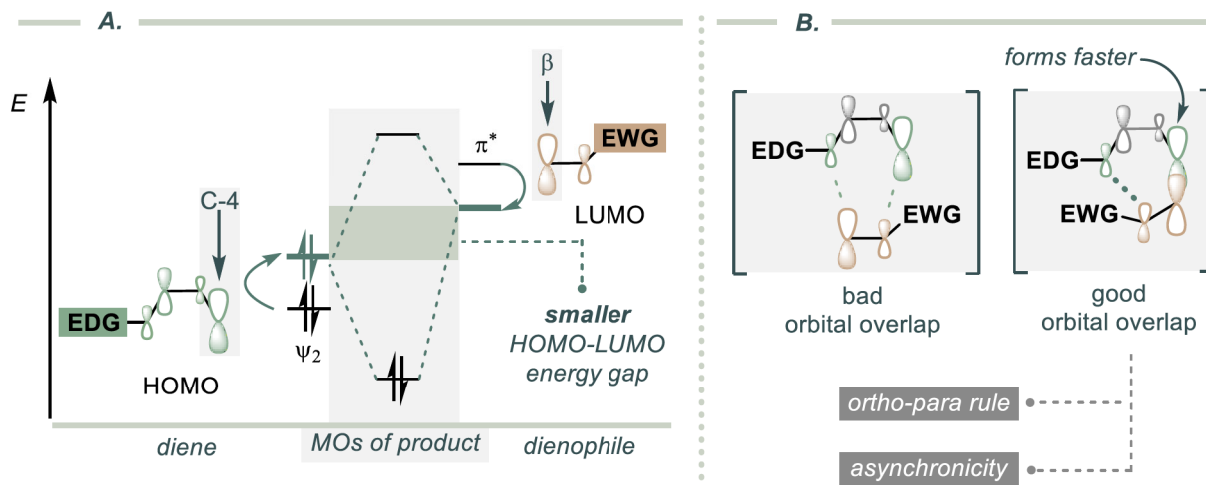


Figure 9. A. Substituents effects on HOMO-LUMO interactions. B. Regioselectivity in Diel–Alder reaction.

Stronger orbital interactions between orbitals with larger coefficients give rise to another important feature of the Diels–Alder reaction involving substituted reactants: asynchronicity. In such cases, the bond between atoms with the largest orbital coefficients, providing better overlap, begins to form more rapidly than the other, resulting in a temporal separation of bond formation, while the overall transition state remains concerted (Figure 9B). The concept of asynchronicity provided a resolution to the long-standing dichotomy between stepwise and concerted mechanisms, originally discussed by Woodward in an attempt to rationalize experimental observations. Although a stepwise mechanism could account for the enhanced reactivity of substituted reactants and the observed regioselectivity, it failed to explain the remarkable stereoselectivity characteristic of Diels–Alder reactions⁵¹:

“The reaction is especially facilitated when the partners to the union are, respectively laden with groups of opposite electrical character. It is easy to comprehend such influences on the basis of the two-step mechanism. By contrast, the one-step mechanism seems ill-adapted to the rationalization of substitutive effects. Similarly, directive effects are much more clearly explicable in terms of the two-step mechanism.”

“By contrast, the two-step mechanism, in the form in which it has been discussed

previously, seems quite incapable of accommodating the stereochemical observations.”

- Woodward, 1959

As a concerted suprafacial cycloaddition, the Diels–Alder reaction preserves the stereochemical information of both the diene and the dienophile, rendering the process stereospecific. The simultaneous formation of two new σ -bonds creates up to at least four potential stereocenters and thus allows for multiple stereochemical outcomes. Depending on the relative orientation of the reactants as they approach the transition state, the substituents in the product may adopt either an *endo* or *exo* configuration. When the EWG of the dienophile is oriented beneath the π -system of the diene, the transition state favors formation of the *endo* product; in the opposite arrangement, the *exo* product is obtained. The *endo* transition state is typically preferred due to stabilizing secondary orbital interactions between the HOMO of the diene and the LUMO of the dienophile. And thus, the resulting *endo* products generally form more rapidly (kinetic products), although they are often less stable than their *exo* counterparts (thermodynamic products) because of the steric factors (Figure 10).

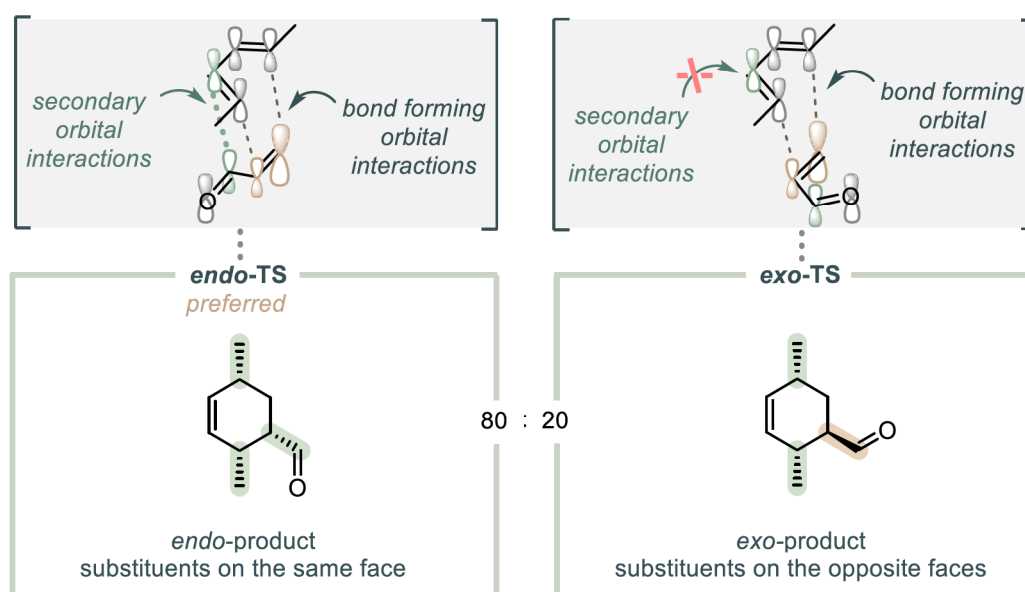


Figure 10. Origins of diastereoselectivity and *endo*-rule in the Diels–Alder reaction. TS = transition state.

Because of its favorable thermodynamics, pericyclic nature, and pronounced orbital control, the Diels–Alder reaction often displays a high degree of both regio- and stereocontrol, especially with substituted polarized reactants. Importantly, these parameters can be further optimized through Lewis acid catalysis. Because dienophiles typically bear an EWG with Lewis basic character, they can readily coordinate to Lewis acids. This coordination amplifies the

electron-withdrawing effect of the substituent, further lowering the energy of the dienophile's LUMO, resulting in increased reactivity and selectivity.

2.2.2. β,β -Disubstituted Enals as Dienophiles

As discussed in the previous chapter, the reactivity of dienophiles depends on the relative energies of the diene HOMO and the dienophile LUMO, and can be modulated through the introduction of EWG or via Lewis acid catalysis. In this context, enals (conjugated α,β -unsaturated aldehydes) represent particularly promising dienophiles. Indeed, when compared to other mono-activated dienophiles, enals display relatively high reactivity (benchmarked against acrylonitrile, Figure 11).⁵² However, a closer inspection reveals that the substitution pattern at the enal double bond[†] exerts a dramatic influence on the reactivity. Acrolein, having the least number of substituents, is the most reactive, whereas each additional substituent progressively diminishes reactivity, culminating in almost unreactive trisubstituted enals.

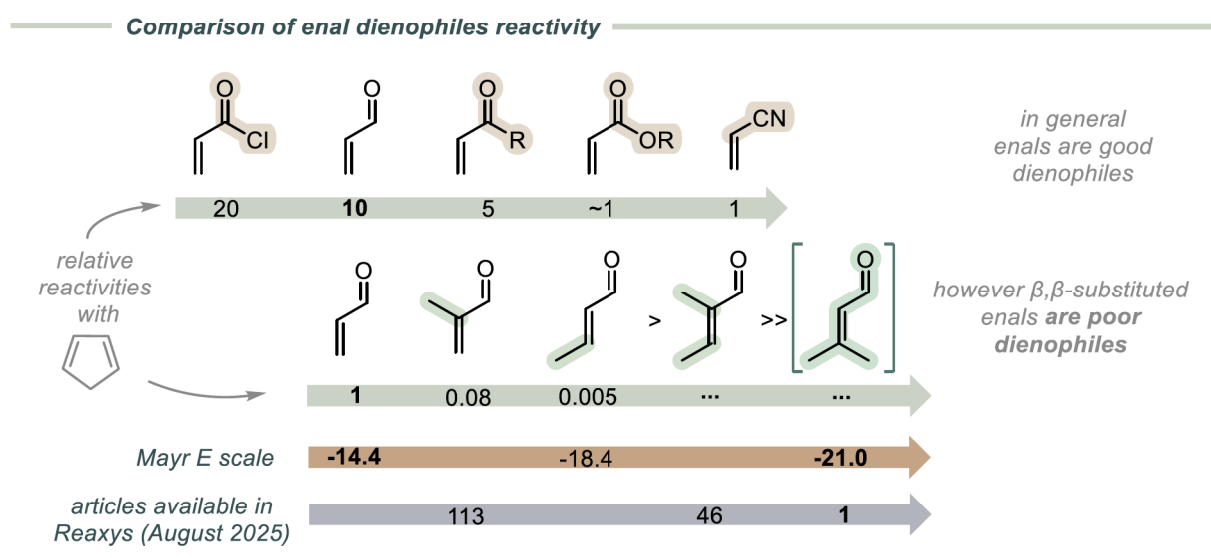


Figure 11. Comparison of carbonyl dienophiles electrophilicity and reactivity towards cyclopentadiene.

Although the electrophilicity–nucleophilicity framework is not typically applied to cycloaddition reactions, its general principles can help to rationalize the relative reactivity of dienes and dienophiles. Typical Diels–Alder reactions involve some degree of manipulation with electronic properties of the diene and dienophiles, namely increasing nucleophilic

[†] In this work, we define substitution patterns and the corresponding substituted enals relative to the parent enal acrolein, which is considered the unsubstituted reference compound (accordingly, the aldehyde group is excluded from the count of substituents).

character of the diene by introduction of an EDG (increasing energy of HOMO) and electrophilic character of the dienophile by introduction of an EWG (lowering LUMO).⁵³ The observed decrease in reactivity of substituted enals can thus be tied to a reduction in their electrophilicity, which is quantifiable via the Mayr electrophilicity (E) scale. For example, introduction of a β -methyl substituent to acrolein results in the reduction of the E parameter of approximately four units on the Mayr scale. Introduction of the second β -methyl substituent brings it down by an additional three units.

The same trend is reflected in the number of reported transformations for different substitution patterns as well, which similarly decreases with increasing substitution (Figure 11). Two principal factors are responsible for these phenomena: steric and electronic.^{54–56} The steric hindrance arising from substitution, generates repulsion between the reactants during approach to the transition state and slows the reaction. In terms of electronic factors in dienophiles, neutral or electron-donating groups raise their LUMO energy.[‡] The impact is especially pronounced for β -position substitution, as the largest orbital coefficient in the dienophile LUMO resides at the β -carbon. Thus, the presence of neutral or EDG at this position makes key orbital overlap less efficient both through steric (more pronounced with neutral) and electronic influence (more pronounced with EDG). Consequently, the presence of two non-EWG substituents at this position results in sluggish dienophile reactivity.

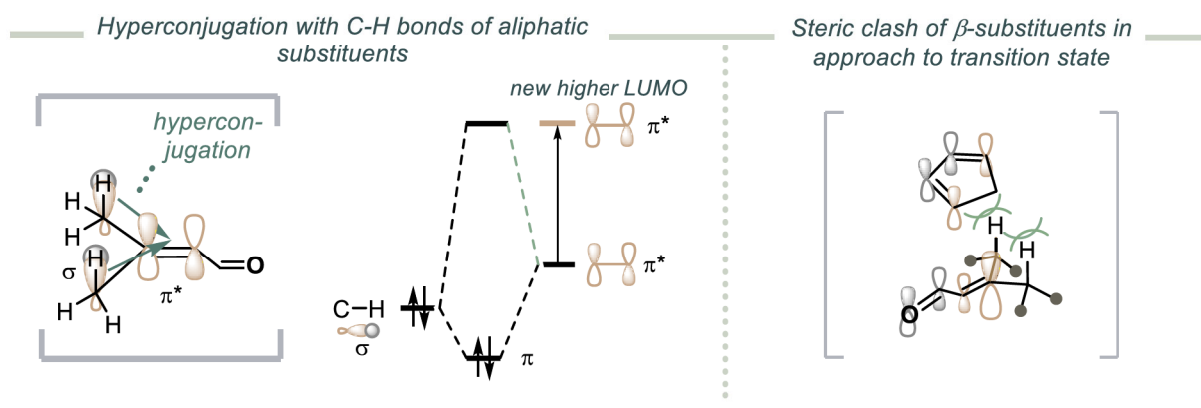


Figure 12. Hyperconjugation and steric effects in β,β -disubstituted enals.

In case of aliphatic β -substituents hyperconjugation, electron donation from C–H σ -bonds into the π^* orbital of the enal, raises LUMO of the dienophile and distorts its shape leading to worse orbital overlap with a diene (Figure 12).

[‡] EWGs at the β -position are excluded from the discussion since the resulting doubly activated alkenes are excellent dienophiles, and the corresponding Diels–Alder reactions are well established in the literature.

Beyond these fundamental considerations, the practical use of enals as dienophiles is complicated by their chemical lability. As aldehydes, they are more prone to decomposition than analogous enones or conjugated esters. Enals readily undergo polymerization upon exposure to light, acids, or bases, making acid catalysis particularly challenging for these substrates.⁵⁷ Additionally, enals can serve as competent Michael acceptors and are prone to self-condensation⁵⁸ leading to competing side reactions.

Despite these challenges, Diels–Alder reactions of β,β -disubstituted enals are of considerable synthetic value, as they enable the construction of complex cyclic frameworks bearing quaternary carbon stereocenters.

2.2.3. Enantioselective Catalysis in Diels–Alder Reactions with Enals

As mentioned earlier, enals are generally considered good dienophiles. Indeed, already in the earliest reports on the Diels–Alder reaction, acrolein was successfully employed as a dienophile. However, a useful degree of regio- and stereocontrol was not achieved until the introduction of Lewis acid catalysis, which enabled the reaction to proceed under milder conditions while simultaneously introducing enantioinduction. Historically, the development of catalysis for the Diels–Alder reaction of enals closely parallels the broader evolution of enantioselective catalysis.

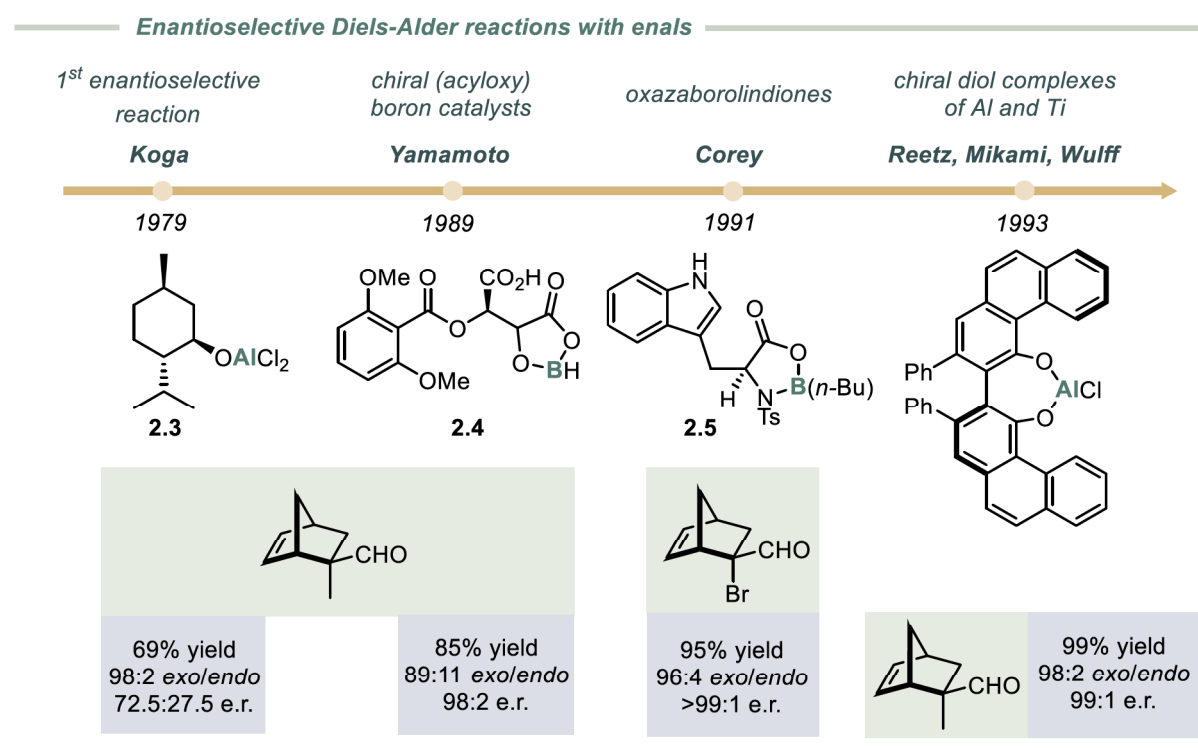


Figure 13. Pioneering works in enantioselective catalytic Diels–Alder reactions of enals.

The first asymmetric catalytic Diels–Alder reaction is typically attributed to the work of Koga et al.,⁵⁹ who reported the successful use of menthoxyaluminium dichloride **2.3** in the reaction between methacrolein and cyclopentadiene, affording the corresponding cycloadduct with 72.5:27.5 e.r. This general strategy—combining Al- and Ti-based Lewis acids (e.g., EtAlCl₂, Al(*i*-Bu)₂Cl, TiCl₂(*Oi*-Pr)₂) with chiral alcohols,⁶⁰ particularly diols and their derivatives, to generate chiral Lewis acid complexes—was further advanced by Reetz,⁶¹ Mikami⁶² and Wulff⁶³ (Figure 13).

Another highly effective catalyst class is based on chiral boron complexes. Early pioneering work came from Yamamoto,⁶⁴ who developed an acyloxyboron catalyst **2.4** derived from tartaric acid, and Corey, who introduced an (*S*)-tryptophan-derived chiral oxazaborolindione **2.5**.⁶⁵ Chiral boron complexes proved to be extremely efficient and selective in catalyzing Diels–Alder reactions.

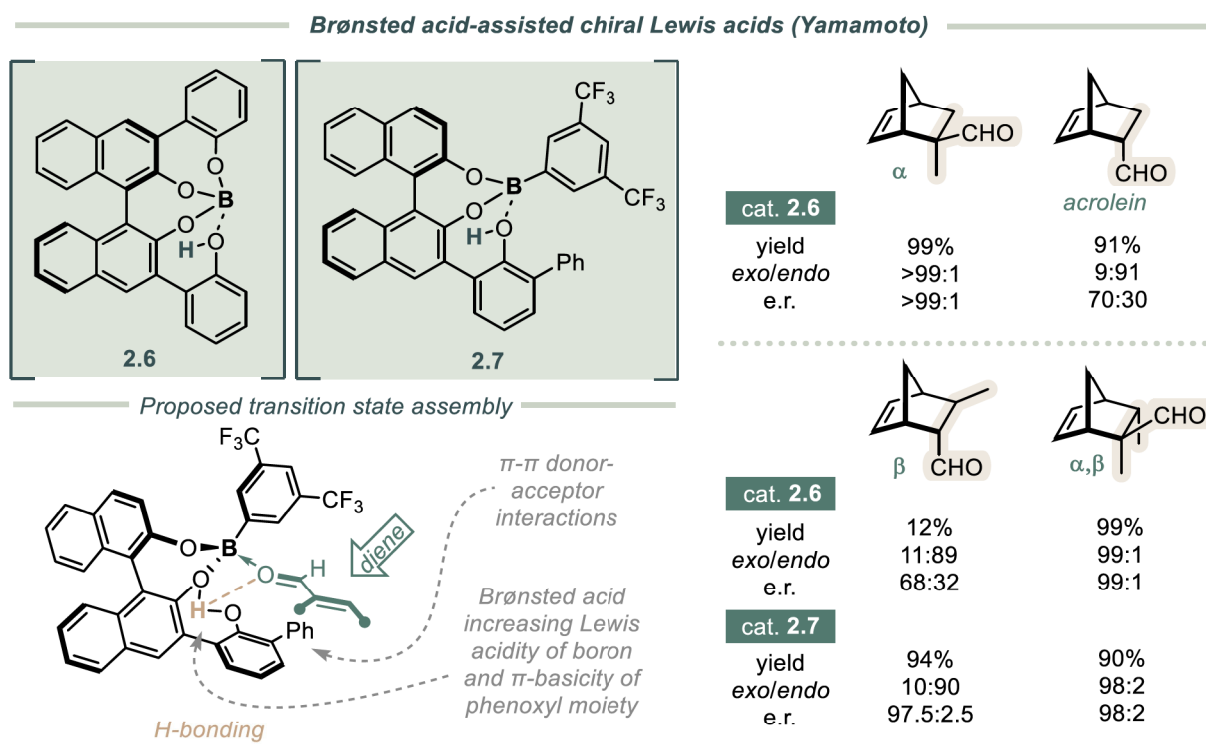


Figure 14. BLA catalysis in Diels–Alder reactions with enals. The α and β descriptors denote substitution pattern in the enal dienophile.

The further advancement in the catalytic performance of these systems came with the incorporation of additional Lewis or Brønsted-acidic sites into the catalyst structure. Yamamoto's group first introduced the concept of Brønsted acid-assisted Lewis acid (BLA)⁶⁶ catalysis, designing BINOL-derived ligands functionalized with phenolic groups (**2.6** and **2.7**,

Figure 14). These additional Brønsted acidic sites provided intermolecular hydrogen-bonding interactions that stabilized the transition state. The high levels of enantioinduction observed were attributed to the combination of hydrogen bonding and attractive π – π donor–acceptor interactions within the transition-state assembly period. Mechanistic studies further confirmed the crucial role of the Brønsted acidic sites: replacing a triol-based ligand in **2.7** with a methoxyphenyl-substituted analogue led to a ninefold decrease in yield and a twofold reduction in enantioselectivity. The developed catalytic system was successfully applied to a variety of carbonyl compounds, including structurally diverse enals.⁶⁷ Despite their impressive performance, these catalytic systems suffer from practical limitations. The catalysts must generally be prepared in situ from the corresponding chiral alcohol and boronic acid (or its ester) and are highly sensitive to the water content in the reaction mixture. Catalyst recovery and immobilization also remain problematic.

A logical extension of this concept is the design of Lewis acid-assisted Lewis acid (LLA) catalysts. This area is mostly represented by catalysts based on aluminum and titanium Lewis acids often forming polynuclear complexes.⁶⁸ One of the peculiar examples of application of this strategy was reported in 2011 by Ishihara and co-workers,⁶⁹ who developed a conformationally flexible chiral supramolecular catalyst **2.8** based on phosphorinanyl BINOL derivatives, boronic acid, and boranes. In this system, two bulky tris(pentafluorophenyl)borane moieties coordinate to phosphoryl (P=O) groups, generating a deep chiral cavity and increasing the Lewis acidity of the active boron center (Figure 15). This complex exhibited both high Lewis acidity and a sterically sterically confined chiral pocket, resulting in unusual *endo*-selectivities with α -substituted enals alongside excellent enantioselectivities across a broad substrate scope.

Later, in 2016 Ishihara's group pursued an alternative strategy, employing CN–borane coordination bonds to establish a chiral environment while attenuating the Lewis acidity of the active center of **2.9** (Figure 15). The resulting catalysts were tested in Diels–Alder reactions of various enals and generally provided good yields and diastereoselectivities across different substitution patterns. However, enantioselectivities were inconsistent and often unsatisfactory, highlighting the continuing challenge of fine-tuning these systems.⁷⁰

Remaining Lewis acid-assisted Brønsted acid catalysis (LBA) can be described as “unique proton”⁷¹ and found the most successful application in enantioselective protonations and isomerizations. Brønsted acid-assisted Brønsted acid catalysis (BBA), mostly represented by TADDOL-type catalysts, was reported to be useful in Diels–Alder reactions, albeit only with

highly activated dienes and dienophiles since the main mode of activation with such catalysts is the hydrogen bonding.⁶⁸

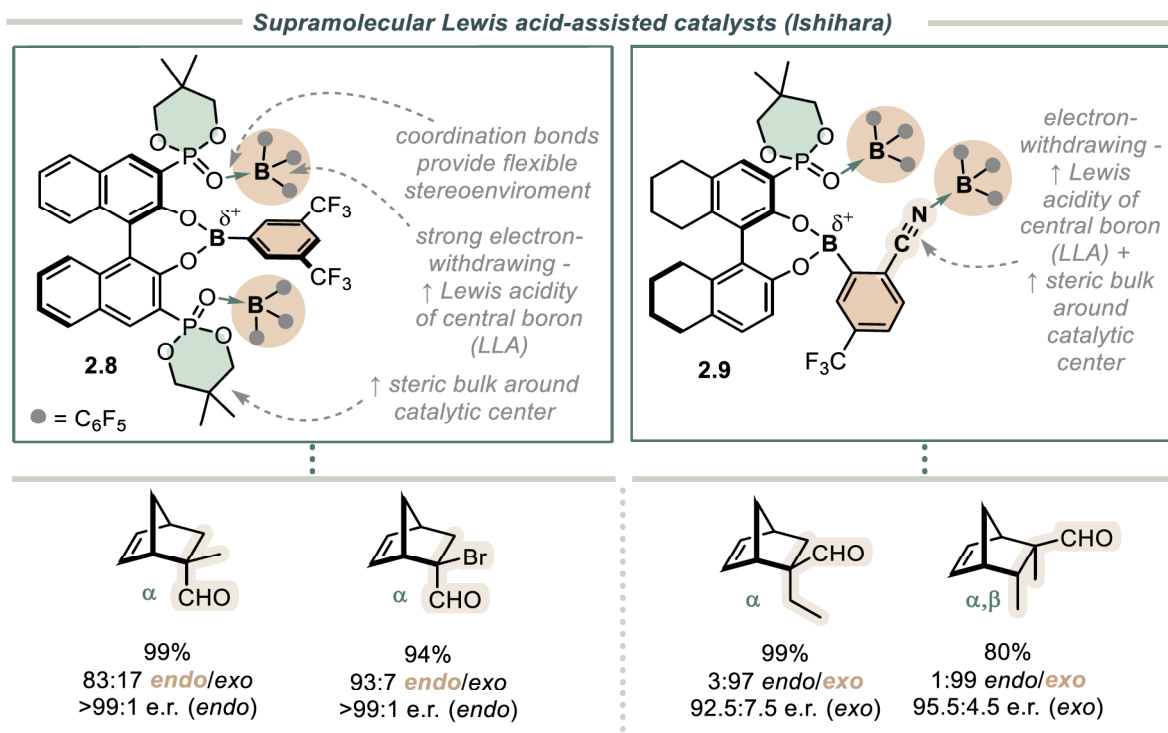


Figure 15. LLA supramolecular catalysts in Diels-Alder reactions of enals.

In 2002, Corey and co-workers made a significant contribution to the field of Brønsted acid-assisted boron complexes. Building on their earlier work on oxazaborolidines, they developed a new class of catalysts that incorporated activation by strong Brønsted acids, specifically triflic acid or triflimide.⁷² The resulting protonated species **2.10** (Figure 16) were proposed to exhibit acidities comparable to the parent Brønsted acids, as evidenced by the fact that only very strong acids were able to achieve protonation and by the ability of these complexes to catalyze reactions of previously inaccessible substrates. The protonated oxazaborolidines **2.10** (especially EWG-substituted, so-called “2nd generation”) displayed superior Lewis acid properties, efficiently catalyzing Diels–Alder reactions of various α,β -unsaturated aldehydes, ketones, and esters with high yields.^{73–75} The high degree of stereocontrol was attributed to effective shielding of one enal face by three aryl substituents in the transition state, in combination with aldehydic C–H $\cdots$ O hydrogen bonding as an additional organizing element.

The Lewis acidity of protonated oxazaborolidines could be further enhanced by coordination with bis-coordinating Lewis acids such as TiCl_4 or SnCl_4 . Coordination of these

species separates the triflimide anion formed upon protonation, generating a complex, highly delocalized non-coordinating counteranion (**2.11**, Figure 16). This prevents formation of “ *α hydrogen-bonded complex or ... a contact ion pair*” between the oxazaborolidine and the counteranion, thereby maximizing Lewis acidity. Remarkably, it is the only catalytic system reported to catalyze the Diels–Alder reaction with β,β -disubstituted enal (3-methyl-2-butenal), albeit with moderate stereoselectivity.⁷⁶

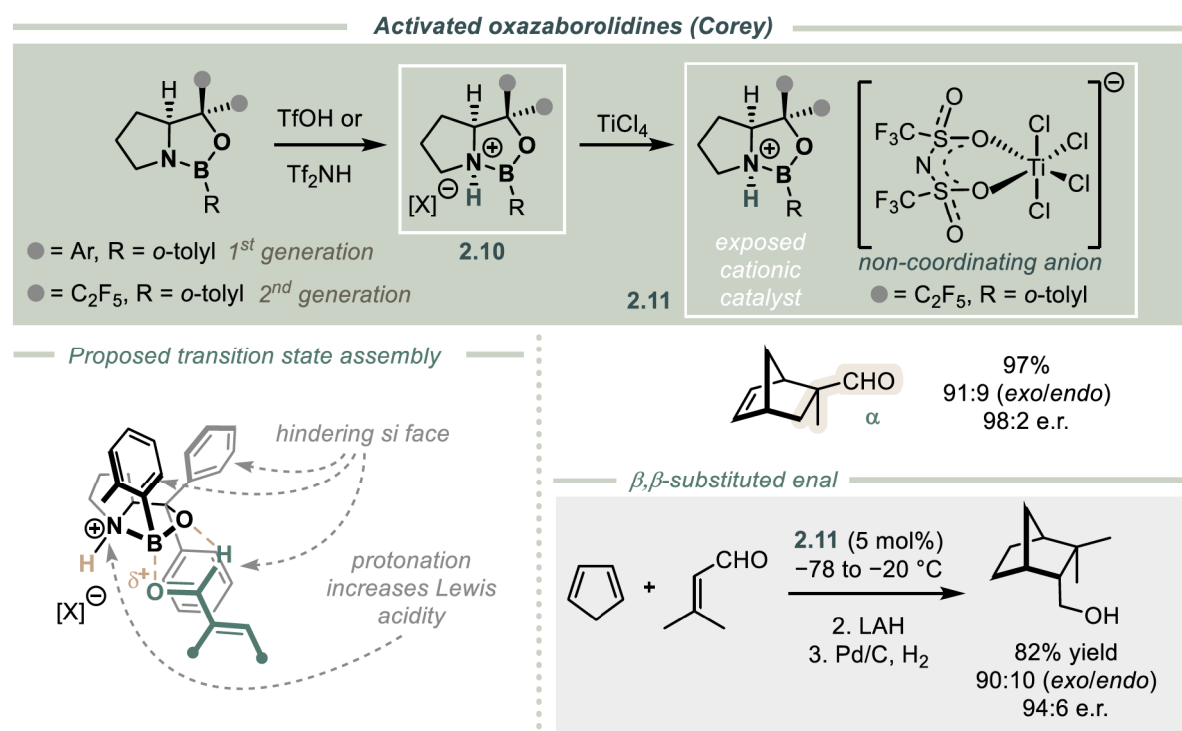


Figure 16. Chiral oxazaborolidines and the first example of enantioselective Diels–Alder reaction with β,β -disubstituted enal. LAH = lithium aluminium hydride.

Concurrently, significant progress was made in the development of transition-metal catalysis, with a broad range of complexes derived from transition and rare-earth metals being identified as highly effective catalysts for the Diels–Alder reaction.⁷⁷ However, these systems generally required dienes and/or dienophiles bearing additional nitrogen or oxygen-containing substituents, and often failed to provide stereoselectivities superior to those obtained with boron-based catalysts. Combined with their air- and moisture-sensitivity, these drawbacks made them less practical than boron complexes or emerging organocatalytic approaches.

By contrast, the newly developing field of organocatalysis—particularly iminium catalysis—appeared to be an excellent match for the Diels–Alder reaction of enals.⁷⁸ The pioneering work of MacMillan, discussed in Chapter 3.1.2, successfully applied imidazolidinone catalysts **2.2** to reactions of β -substituted enals and acrolein. However,

iminium catalysis also presented limitations: α -substituted enals proved unsuitable due to the steric hindrance obstructing formation of the iminium intermediate,^{79,80} and reactions with electronically unbiased substrates generally delivered products with unsatisfactory diastereoselectivity (close to 1:1) (Figure 17). Nevertheless, imidazolidinone catalysts **2.2** found broad synthetic application, especially in immobilized forms.^{81,82}

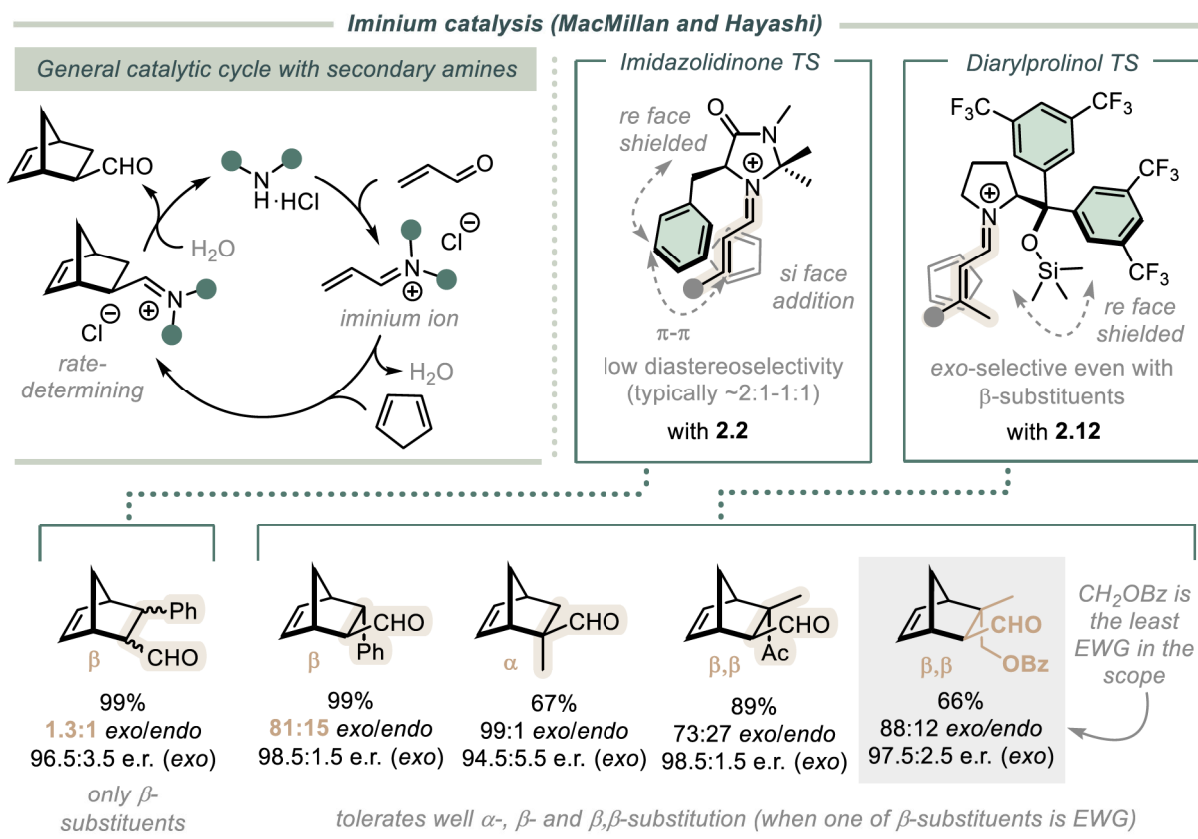


Figure 17. Imidazolidinone and diarylprolinol catalysts in Diels-Alder reactions.

A parallel line of research was pursued by Hayashi, who developed (simultaneously but independently with Jørgensen's group⁸³) diarylprolinol-derived catalysts **2.12** in combination with Brønsted acids.

Initially, these catalysts were employed in stereoselective ene reaction⁸⁴ between cyclopentadiene and enals, but were later adapted to the Diels-Alder reaction.⁸⁵ Remarkably, a simple change of the acid additive shifted the reactivity mode: *para*-nitrophenol favored the ene reaction, while trifluoroacetic acid promoted the Diels-Alder cycloaddition. Further optimization revealed that perchloric acid salts were also effective, particularly in aqueous media.⁸⁶ Systematic screening ultimately identified conditions compatible with α -, β -, and even certain β, β -substituted enals.⁸⁷ This is another example of organocatalytic Diels-Alder reactions involving β, β -disubstituted enals, although this part of the substrate scope was limited to enals

bearing at least one β -substituent with some degree of electron-withdrawing character. The authors stated that “...almost no reaction took place with dienophiles possessing an aromatic and aliphatic groups at the β -position, such as 3-phenyl-2-butenal, 3-(*p*-bromophenyl)-2-butenal, and 3-methyl-5-phenylpent-2-enal. This would be because LUMO of these dienophiles is not low enough to react with diene”.

An additional distinguishing feature of diarylprolinol catalysts **2.12** is their tendency to promote *exo*-selective cycloadditions, even with β -substituted enals that typically favor *endo*-products. The generally high stereoselectivities observed can be rationalized by examining the transition state: bulky aryl and trimethylsilyl ether (OTMS) groups effectively shield the *re*-face of the enal, enforcing preferential attack from the opposite side (Figure 17).⁸⁸

Further developments in the field can be attributed to the works of Ogilvie⁸⁹ and Lee⁹⁰, who reported the design of chiral hydrazide catalysts. These catalysts possessed enhanced nucleophilicity due to the presence of a neighboring nitrogen atom at the catalytic center, an effect often referred to as the α -effect.⁹¹ As a result, iminium ion formation was significantly accelerated, leading to more efficient catalytic performance. The developed platform provided typically good to excellent enantioselectivities, although diastereoselectivities remained modest.

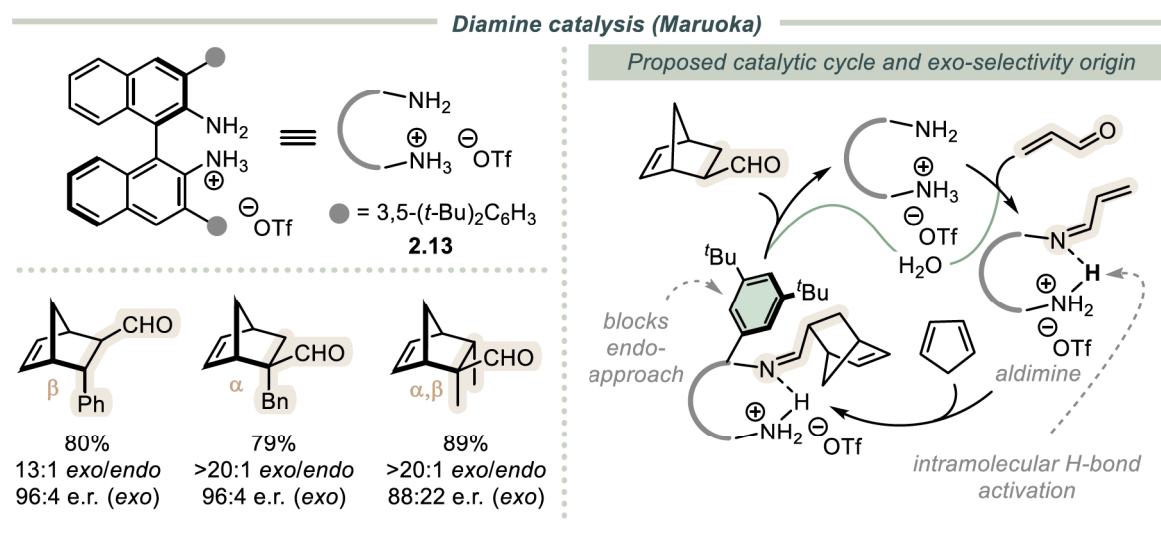


Figure 18. Diamine salt catalysts reported by Maruoka.

Another important class of highly *exo*-selective organocatalysts was introduced by Maruoka and coworkers. The developed binaphthyl-based diamines **2.13** (Figure 18) were found to efficiently catalyze the Diels–Alder reactions of a wide range of enals, including α -, β -, and α,β -substituted derivatives, in the presence of Brønsted acid additives.^{92,93} Under mild

conditions with 20 mol% catalyst loading, these catalysts consistently delivered Diels–Alder adducts with >20:1 *exo/endo* ratios and excellent enantioselectivities. In contrast to the previously discussed iminium-based systems, these reactions are believed to proceed via imine intermediates formed upon reaction with one of the amino groups of the catalyst, and activated through intramolecular hydrogen bonding from the adjacent amino group. As with all secondary amine-catalyzed reactions, the presence of an equimolar Brønsted acid was essential to facilitate both imine formation and subsequent hydrolysis.

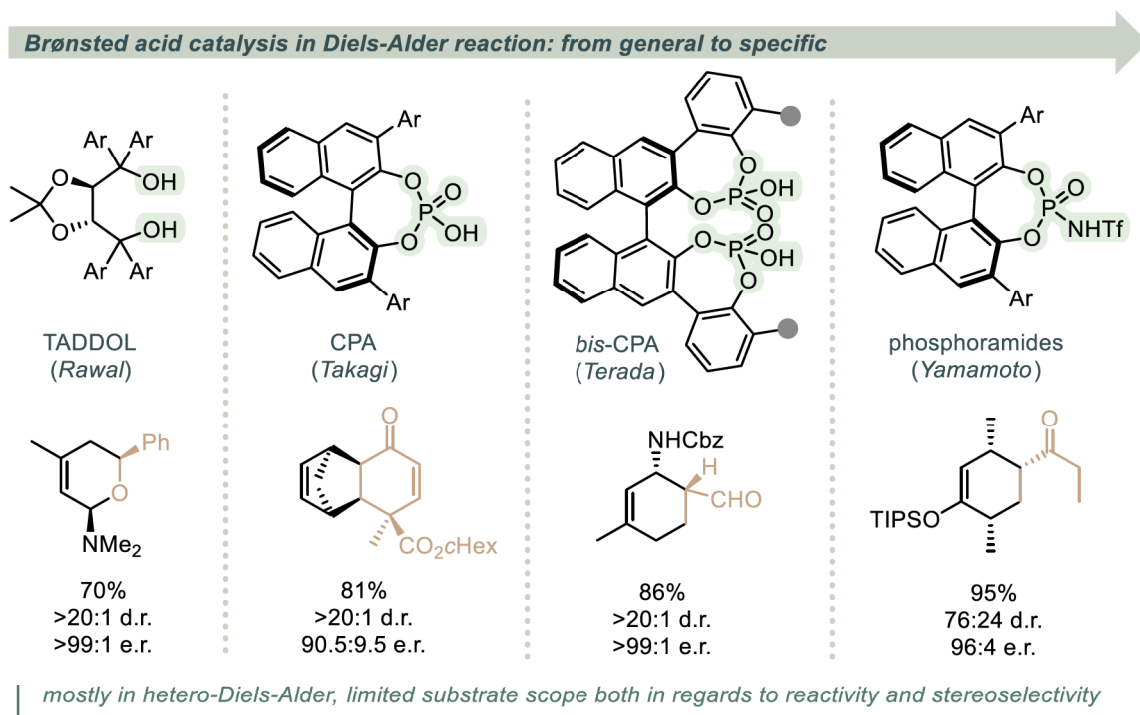


Figure 19. Pioneering works in Brønsted acid catalyzed Diels–Alder reactions.

Brønsted acids and hydrogen bonding, in fact, have always played an important role in the catalytic systems discussed so far. Protonation, or more generally, acid catalysis, represents an effective strategy for activating the π -basic carbonyl groups of enal dienophiles. The first reports of Diels–Alder reactions catalyzed directly by Brønsted acids came from Göbel⁹⁴ and Rawal,⁹⁵ who employed amidinium ions and TADDOL derivatives, respectively (Figure 19). Both studies relied on either activated dienes (e.g., Danishefsky-type) or activated dienophiles (e.g., imines or endiones). The first reports utilizing CPAs came from groups of Akiyama⁹⁶ and Gong⁹⁷ in 2006, both targeting hetero-Diels–Alder reactions of significantly Brønsted-basic imine dienophiles.⁹⁸ In 2016, Takagi reported one of the rare all-carbon Diels–Alder reactions catalyzed by CPAs,⁹⁹ although enantioselectivities were suboptimal. To expand the scope toward less reactive substrates such as unactivated enals and enones, stronger Brønsted acids were required.¹⁰⁰

One logical approach was pursued by Terada, who introduced a second phosphoric acid group into the catalyst framework,¹⁰¹ thereby forming chiral bisphosphoric acids which demonstrated increased catalytic activity and stereoselectivity compared to monophosphoric acids. Yamamoto's group designed *N*-triflyl phosphoramidate derivatives of CPAs,¹⁰² a considerably stronger Brønsted acids. This catalyst enabled Diels–Alder reactions of electron-rich dienes with ethyl vinyl ketone, delivering the products with high enantioselectivities, whereas the parent CPA was completely inactive. These findings established that sufficiently strong chiral Brønsted acids could indeed function as effective catalysts for Diels–Alder reactions (Figure 19).

Before such strong acids became widely available, alternative strategies were explored. One such approach was silylium-ACDC reported by List group, which generated highly active Lewis acids from binaphthyl-allyl-tetrasulfones. This system enabled the enantioselective Diels–Alder reactions of unsaturated esters with unactivated dienes, producing the desired products in excellent yields and stereoselectivities.¹⁰³ However, the inability to recover the silylating reagent remained a significant drawback. Another strategy, employed by Ishihara, involved LBA catalysis: a combination of CPA and BBr₃ sufficiently enhanced the Brønsted acidity to activate challenging α -aryl- β -substituted enals. The resulting products were obtained with excellent enantioselectivity and notable *exo*-preference.¹⁰⁴

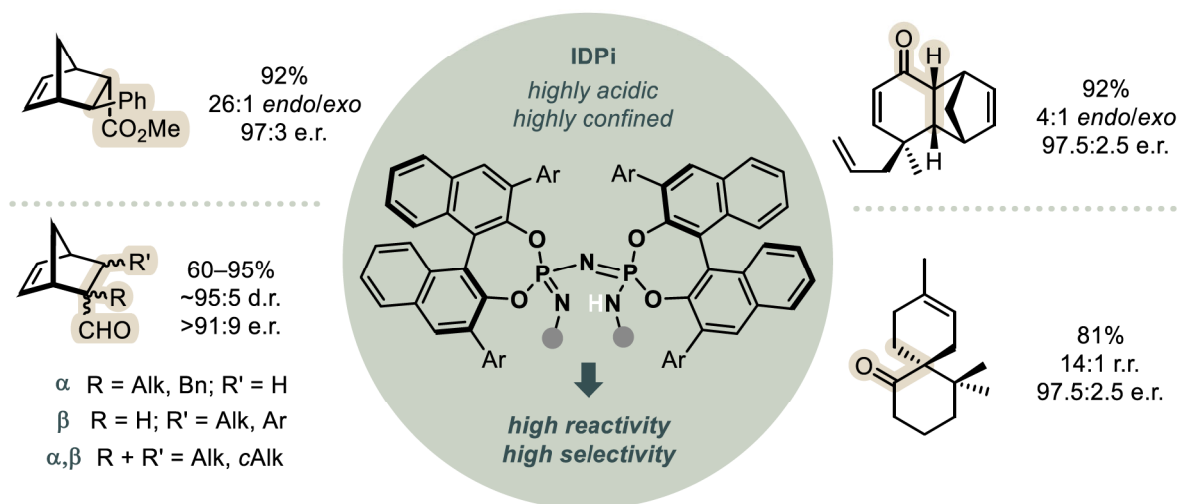


Figure 20. IDPi-catalyzed Diels–Alder reactions.

Finally, the introduction of highly acidic and sterically confined IDPi catalysts by List and co-workers represented a major advance, showing that purely Brønsted acid catalysis is capable of promoting Diels–Alder reactions of synthetically valuable, non-engineered substrates. These catalysts not only proved effective in activating enals but were also broadly

compatible with different substitution patterns, including α -, β -, and α,β -substituted derivatives. The reactions typically proceeded in good to excellent yields, with excellent enantioselectivities and unprecedented generality and consistency.¹⁰⁵

The synthetic power of IDPi catalysis was further showcased in the Diels–Alder reaction between electronically unbiased cyclohexadienones and cyclopentadiene, which simultaneously established up to five stereocenters with high stereocontrol,¹⁰⁶ as well as in spirocyclizing Diels–Alder reactions of *exo*-enones¹⁰⁷ (Figure 20).

Conclusion and Outlook

The developments reviewed above underscore the remarkable potential of Brønsted acids as catalysts for Diels–Alder reactions. In comparison to traditional boron- or metal-based Lewis acids, Brønsted acids offer higher operational robustness, simpler handling and new reactivity prospects. Amine-based catalysts, while operationally convenient and attractive from the economical point of view, are intrinsically biased toward *exo*-selectivity and appear to be insufficient for activating β,β -substituted enals. The advent of IDPis as highly acidic and confined catalysts has markedly expanded the accessible substrate scope and stereocontrol. Nevertheless, the efficient enantioselective catalytic Diels–Alder reaction of β,β -disubstituted enals remain a formidable challenge and an important direction for future research.

2.3. β -Santalol: Application and Synthesis

2.3.1. Availability and Properties of (–)-(Z)- β -santalol

(–)-(Z)- β -Santalol is the principal odor vector of sandalwood oil, exhibiting the characteristic warm and rich, woody scent with creamy undertones. The traditional production of sandalwood oil is labor-intensive: steam distillation of the heartwood of *Santalum album* trees, which must be at least 30 years old, yields only about 5–7% of the oil. Two major constituents have been identified in sandalwood oil, namely α - and β -santalols, with (–)-(Z)- β -santalol **2.15** being the most important despite comprising only ~20% of the oil by weight. Biosynthetically, (–)-(Z)- β -santalol is formed from the common terpene precursor (2*E*,6*E*)-farnesyl diphosphate through the action of the promiscuous santalene/bergamotene synthase (SaSSy),¹⁰⁸ which also produces α -santalene, *epi*- β -santalene, and *exo*- α -bergamotene (Figure 21).¹⁰⁹ The first cyclization yields a bisabolyl cation, which undergoes a second intramolecular

2. Background

cyclization to generate the bicyclic core. The resulting carbocation then undergoes a Wagner–Meerwein-type rearrangement involving a 1,2-alkyl shift, producing an *exo*-double bond and yielding β -santalene **2.16**. Hydroxylation of **2.16** is subsequently catalyzed by cytochrome P450 monooxygenases, including members of the CYP76F and CYP736A families,¹¹⁰ to furnish (–)-(Z)- β -santalol (Figure 21).

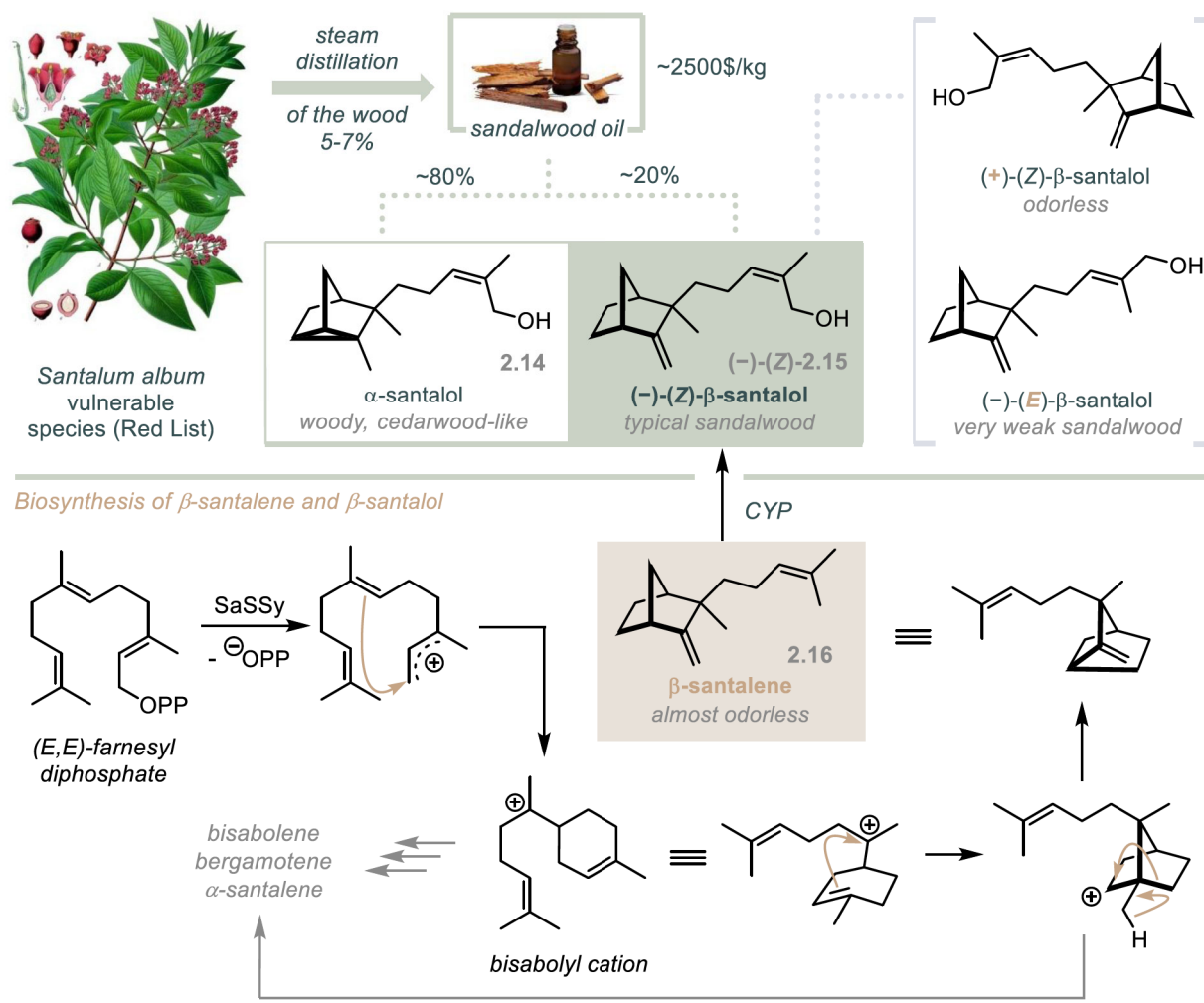


Figure 21. Main constituents of sandalwood oil, stereochemistry of β -santalols and (–)-(Z)- β -santalol biosynthesis.

The unique scent of sandalwood has long been highly valued both in perfumery and in broader cultural context, leading to high demand for sandalwood and overexploitation of *Santalum album* species in India. Today, harvesting of sandalwood is heavily restricted and regulated by the Indian government. This scarcity, coupled with sustained commercial demand, has motivated an extensive search for synthetic routes to **2.15** since the late 1970s. But even before the commercial pressures emerged, sandalwood constituents attracted the attention of organic chemists: the chemical structure of **2.15** was first elucidated by Ruzicka in 1935,

although its complete stereochemical assignment was not achieved until the 1990s. As is the case with many fragrance compounds, the stereochemistry plays a decisive role in olfactory properties of β -santalol: (+)- β -santalol is odorless, while the (–)-(*E*)-isomer exhibits only a weak sandalwood scent.

2.3.2. Sandalwood Odorants

While academic research was primarily devoted to elucidating the properties and developing synthetic approaches to **2.15** — a challenge that will be addressed in the following chapter — industrial research focused on identifying more sustainable and economically viable synthetic substitutes of characteristic sandalwood scent.¹¹¹

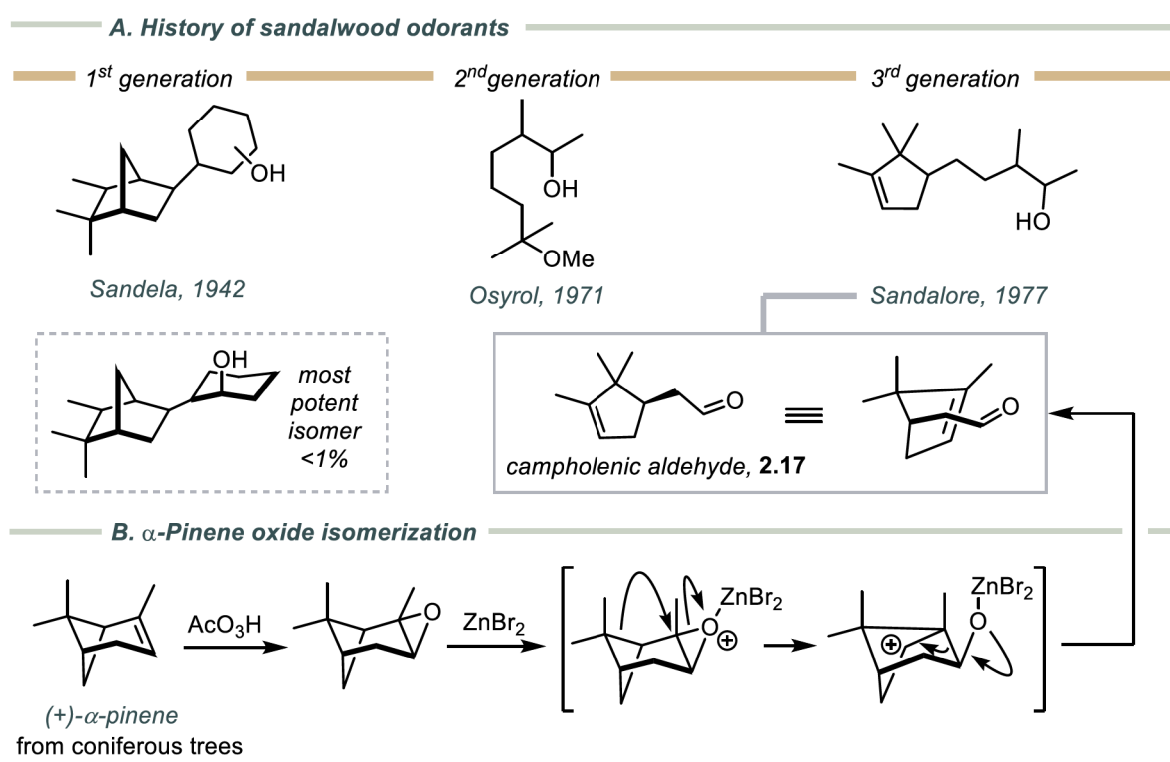


Figure 22. A. History and main families of sandalwood odorants. B. α -Pinene oxide isomerization.

The first sandalwood odorants were discovered serendipitously. In 1964, Erman and co-workers at Procter & Gamble reported that Lewis-acid-promoted condensation of camphene with phenols¹¹² afforded a mixture of alcohols exhibiting characteristic sandalwood scent, and was later marketed under the trade name Sandela (the first patents for this process were filed in 1942 by I.G. Farbenindustrie,¹¹³ however the exact composition was unknown) (Figure 22A). Later, Demole carried out the detailed studies on the properties of the compounds constituting the mixture and established that only the isomers bearing an axial hydroxyl group at the C-3 position of the cyclohexane ring contributed to the sandalwood note.¹¹⁴ Around the same time,

Bush Boake Allen Ltd. (now IFF) introduced Osyrol, obtained via methanolysis of dihydromyrcene followed by epoxidation and reduction.¹¹⁵ These discoveries initiated systematic structure–odor relationship studies^{116–118} and ultimately led to early formulations of “santalol rules”.¹¹⁹ Yet, despite the widening range of candidate structures and accumulated empirical knowledge, the targeted design of sandalwood odorants and development of the reliable predictive models have remained difficult.

A major breakthrough came with the next generation of sandalwood odorants derived from campholenic aldehyde **2.17**, a readily available chiral building block obtainable in both enantiomeric forms from (+)- or (–)- α -pinene via stereospecific epoxidation and Lewis-acid-induced rearrangement (Figure 22B). Aldol condensation of campholenic aldehyde with simple ketones, optionally followed by hydrogenation, afforded a diverse family of highly potent sandalwood odorants.

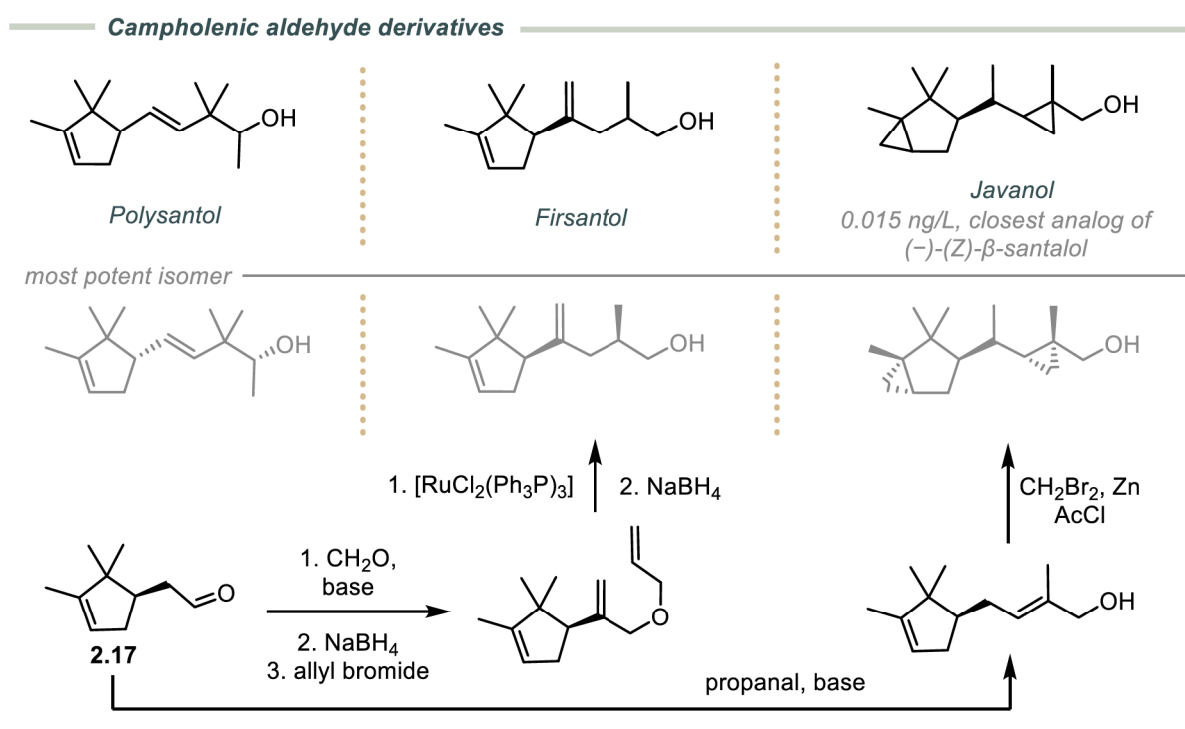


Figure 23. Representative modern sandalwood odorants of campholenic aldehyde family.

The first commercial representative, Sandalore, was introduced by Givaudan¹²⁰ and was soon followed by a series of structurally related analogs. Among them the more conformationally constrained Polysantol¹²¹ and Firsantol¹²² (DSM–Firmenich) found the most commercial success (Figure 23). Although these compounds were generally obtained as mixtures of stereoisomers, extensive olfactory profiling revealed that the desirable odor characteristics are often associated with only one stereoisomer, underscoring the importance of

stereoselective synthetic approaches.

The most potent and by far the closest (–)-(Z)- β -santalol scent surrogate identified to date is Givaudan’s Javanol¹²³, which possesses an exceptionally low odor threshold of 0.015 ng/L. Its industrial synthesis notably employs a Simmons–Smith cyclopropanation, one of the rare large-scale applications of this reaction.

Although remarkable progress has been made in the field of the sandalwood odorants, (–)-(Z)- β -santalol itself remains the olfactory benchmark.¹²⁴ In addition to its unique olfactory profile, (–)-(Z)- β -santalol was found to exhibit biologically relevant antimicrobial, antitumor, and anti-inflammatory properties.¹²⁵ Taken together, these factors strongly motivate further development of the concise, scalable, and stereoselective synthetic routes to this natural product and its analogs.

2.3.3. Overview of Synthetic Approaches towards β -Santalol

The total synthesis of (–)-(Z)- β -santalol **2.15** has long been a subject of considerable interest, driven by both the complex structure and odorant properties. As a retrosynthetic target **2.15** presents two major challenges that have shaped synthetic efforts over the decades:

- the enantioselective construction of the bicyclo[2.2.1]heptane core bearing a sterically demanding quaternary stereocenter and an exocyclic double bond, and
- the installation of the (Z)-allylic alcohol side chain.

Most reported strategies have approached these challenges separately, disconnecting the bicyclic framework from the allylic side chain. This is logical: the bicyclo[2.2.1]heptane moiety can be efficiently assembled via a Diels–Alder cycloaddition, while the (Z)-allylic alcohol generally requires several synthetic transformations or independent synthesis altogether.

The earliest synthetic routes were racemic. In 1979, Hoffmann¹²⁶ reported the use of a Diels–Alder reaction with an α,β -substituted enals bearing a leaving group (Cl or acetate (OAc)) **2.18**, available from the BASF industrial synthesis of vitamin A, to directly install the *exo*-double bond. The resulting intermediate was then elaborated to a common aldehyde **2.19** (Figure 24). The installation of the allylic alcohol side chain was accomplished via an aldol condensation reaction followed by reduction, which predominantly furnished the less desirable *E*-isomer of **2.15**.

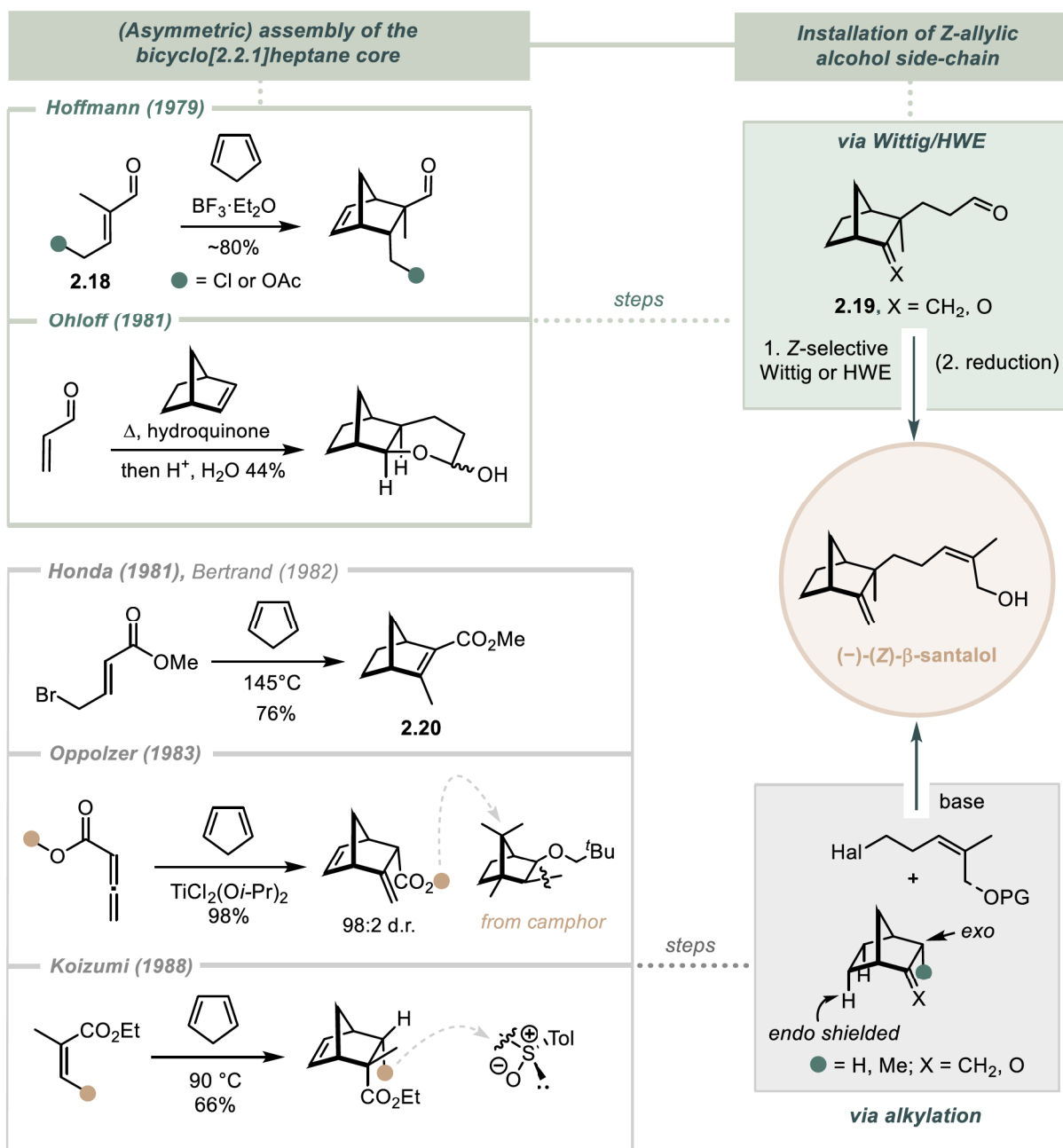


Figure 24. Achiral and chiral auxiliaries-based synthetic routes to β-santalol. HWE = Horner-Wadsworth-Emmons reaction.

Shortly after, in 1981, Ohloff¹²⁷ described a hetero-Diels–Alder reaction between acrolein and norbornene. In this case, introduction of the methyl substituent in the bicyclic scaffold was performed by alkylation, leading to the formation of an undesired *epi*-isomer of **2.19**. The following Wittig reaction¹²⁸ in Corey’s modification successfully introduced the (Z)-allylic alcohol moiety delivering racemic *epi*-(Z)-**2.15**.

Alternative Diels–Alder intermediates were later reported by Honda,¹²⁹ who employed γ-bromo-crotonate, and Bertrand,^{130,131} who used methyl 2-butynoate as dienophiles in Diels–Alder reaction with cyclopentadiene both yielding same bicyclic unsaturated ester **2.20**. In these

2. Background

derivatives, and citral **2.21-CHO** as dienophiles for the key Diels-Alder reaction step, however the yields of the corresponding products remained unsatisfactory. Interestingly, the reaction with citral **2.21-CHO** failed completely due to polymerization of the starting material under the harsh reaction conditions.

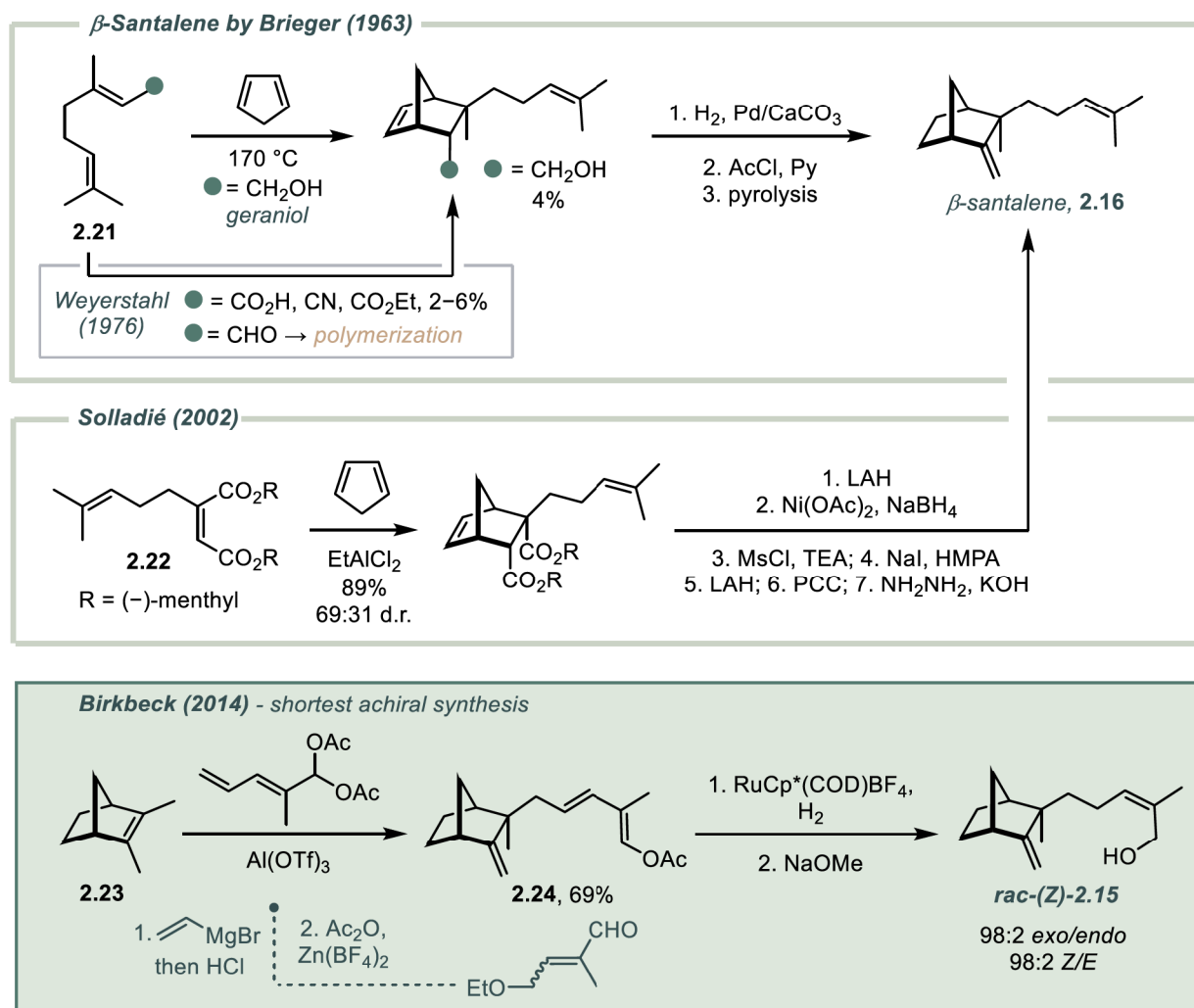


Figure 25. Examples of more efficient assembly of *β*-santalol's carbon skeleton.

Other disconnections were explored as well. In 2002, Solladié reported the use of a substituted maleate **2.22**, enabling the incorporation of two chiral auxiliaries and improved dienophile reactivity.¹⁴⁰ However, the cycloadduct was obtained with only moderate diastereoselectivity, and the need for further multistep functional group manipulations diminished the efficiency of the route. The most industrially promising synthesis of this category was later reported by Birkbeck,¹⁴¹ who employed the Scriabine reaction between santene **2.23** and dienyl acetate. This approach furnished the desired intermediate **2.24** with excellent 98:2 *exo/endo* selectivity. Subsequent Ru-catalyzed *cis*-selective 1,4-hydrogenation¹⁴² and deprotection provided racemic (*Z*)-*β*-santalol (98:2 *Z/E*) in just three steps (five including

preparation of the dienyl acetate).

The application of enantioselective catalytic Diels–Alder reactions to the total synthesis of β -santalol began to emerge in 2009. Fehr and co-workers reported the construction of the target bicyclo[2.2.1]heptane core from cyclopentadiene and crotonaldehyde using a Hayashi's prolinol-based catalytic system **2.12** (Figure 26).¹⁴³ As discussed previously, this system delivers cycloadducts of α -substituted enals with a pronounced *exo* preference. In this case, the reaction delivered the product in 96:4 *exo/endo* ratio and with excellent enantioselectivity (97.5:2.5 e.r.). Subsequent steps furnished intermediate alcohol **2.25**, which in the presence of $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{BF}_4$ underwent a key cyclization–fragmentation cascade to give common aldehyde **2.19**, the immediate precursor for the *Z*-selective (97:3 *Z/E*) Corey's modification of the Wittig reaction. Recognizing, however, that the Wittig approach is often impractical on industrial scale, the authors also reported an alternative route: conversion of **2.19** to the dienol acetate **2.24**, followed by *cis*-selective 1,4-hydrogenation, which delivered (–)-(Z)- β -santalol with excellent 98:2 *Z/E* selectivity as well.¹⁴⁴

Another application of enantioselective catalytic Diels–Alder reactions in the synthesis of (–)-(Z)- β -santalol was described by Chapuis and co-workers.^{145,146} In this case, Corey's oxazaborolidine catalyst **2.10** promoted the reaction of the α,β -disubstituted enal **2.18** with cyclopentadiene (the same starting materials as originally employed by Hoffmann), affording the cycloadduct in 86% yield with 95:5 *exo/endo* selectivity and 96.5:3.5 e.r. The subsequent transformations led to the propargylic alcohol intermediate **2.26** analogous to Fehr's route. The alcohol **2.26** then undergoes the Meyer–Schuster rearrangement catalyzed by organosilyl vanadate complex $[\text{V}_2\text{O}_6\text{SiPh}_2]_n$,¹⁴⁷ providing the key aldehyde **2.19** for the final Wittig reaction. Both Fehr's and Chapuis' syntheses are considered industrially relevant and have been patented.

In parallel with the developments in chemical synthesis, extensive efforts have also been devoted to the biotechnological production of (–)-(Z)- β -santalol.^{124,148} Most strategies yield β -santalenes or complex mixtures resembling sandalwood oil composition, owing to the inherent promiscuity of the natural enzymes and the challenge of efficiently combining santalene cyclization with subsequent oxidation. Two processes have nevertheless proven to be industrially relevant: Firmenich's route, which affords sandalwood oil-like mixtures of products,¹⁴⁹ and Isobionics' method, which produces mixture of santalenes and related terpenes.¹⁵⁰

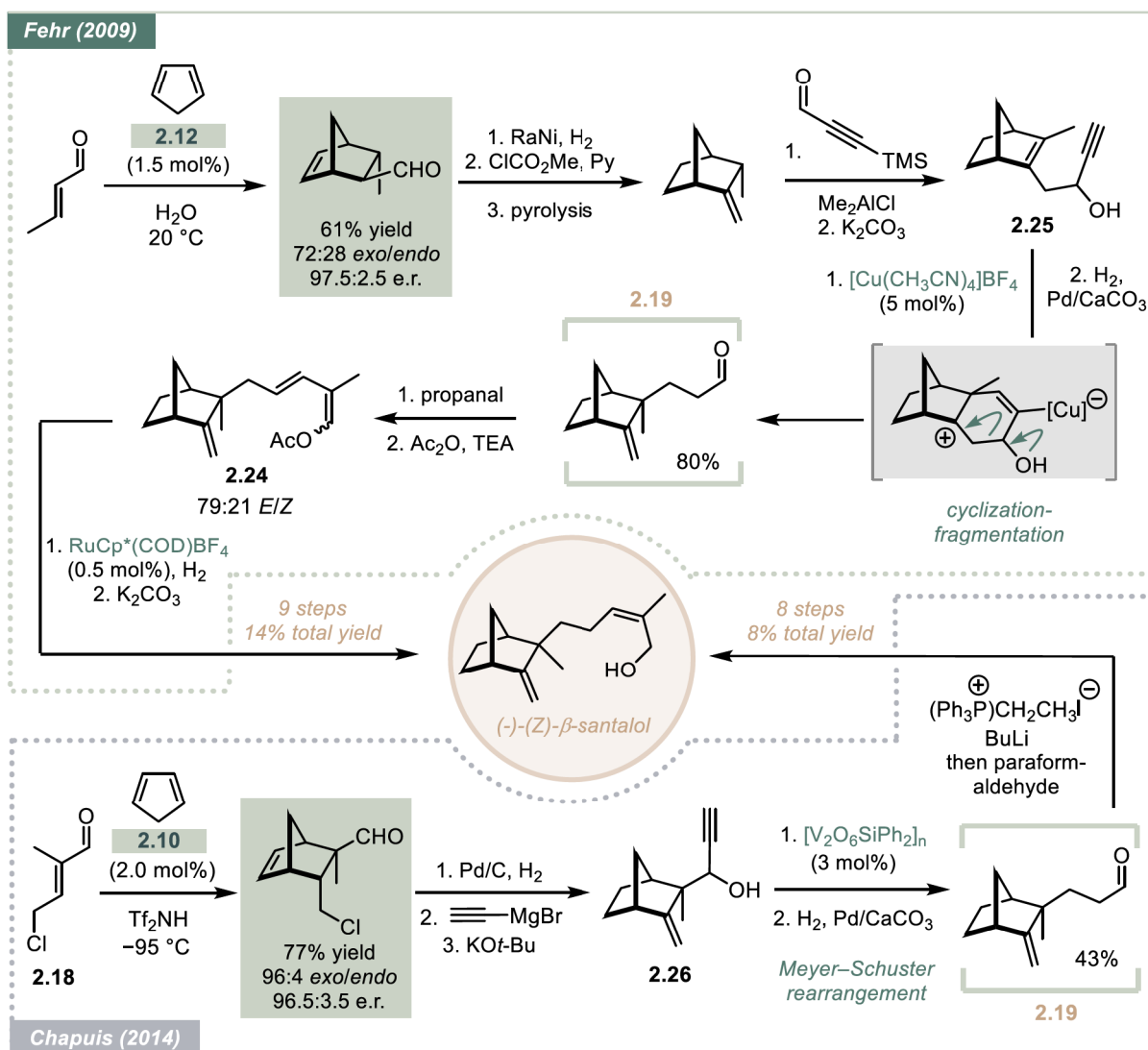


Figure 26. Industrially feasible enantioselective approaches towards **(-)-(Z)-β-santalol**.

Conclusion and Outlook

Despite the long history and substantial progress toward enantioselective, scalable syntheses of **(-)-(Z)-β-santalol**, significant challenges remain. The main among them are poor redox efficiency, the reliance on protecting groups (e.g., Ac , TMS), dependence on costly or waste-generating stoichiometric reagents (organometallics, Wittig reagents), and the heavy use of metal-based catalysts, making synthetic efficiency vulnerable to fluctuations in metal prices. These limitations highlight the pressing need for new, more sustainable and robust approaches.

3. Objectives

As demonstrated in the preceding chapters, the Diels–Alder reaction, despite its long history, remarkable versatility, and immense progress in terms of synthetic utility, continues to face certain challenges. Among these, β,β -disubstituted enal dienophiles stand out as a particularly persistent problem. Substitution at the β -position markedly diminishes their reactivity through a combination of steric and electronic effects. Furthermore, many of those substrates are intrinsically labile and prone to undesired side reactions, including polymerization and self-condensation, which further complicate their direct application. Consequently, β,β -substituted enals remain an underdeveloped class of dienophiles, despite their considerable synthetic value — particularly as key building blocks for constructing quaternary stereocenters within complex frameworks accessible through the Diels–Alder reaction.

While metal- and boron-based Lewis acids and amine-based catalysts have historically dominated the field of enantioselective Diels–Alder reactions, their performance remains constrained: Lewis acids often suffer from poor substrate generality, sensitivity to the reaction conditions and operational difficulties, whereas amine-based organocatalysts, although operationally simple and highly effective with many substrates, preferentially afford *exo*-products and lack the catalytic activity required to engage sterically and electronically demanding β,β -substituted enals.

Recent advances in Brønsted acid catalysis suggest a compelling solution. Confined chiral Brønsted acids, particularly the IDPi family, uniquely integrate several important properties:

- high acidity, enabling significant lowering of the dienophile LUMO;
- a highly confined, chiral pocket that enforces precise stereocontrol;
- robustness and versatility, with demonstrated compatibility across diverse substrate classes including all other substituted enals; and
- operational simplicity, as metal-free, recoverable and recyclable catalysts.

Taken together, these features provide a strong rationale to explore IDPi catalysts as the long-sought solution to the activation of β,β -disubstituted enals in the Diels–Alder reaction.

The successful development of such a catalytic system would have dual significance. On the fundamental level, it would constitute a major advance in asymmetric catalysis, resolving one of the persistent limitations of the Diels–Alder reaction and extending its scope

to some of the most sterically and electronically challenging dienophiles. On the applied level, it would directly enable efficient synthetic access to high-value natural product targets. In particular, the enantioselective Diels–Alder reaction of cyclopentadiene with geranial offers a streamlined disconnection toward (–)-(Z)- β -santalol. Such a transformation would allow to introduce *all carbon atoms and stereocenters* of the β -santalol skeleton in a single step from readily available bulk chemicals. The establishing and optimization of this synthetic route would therefore provide a more concise and sustainable alternative to the existing enantioselective syntheses of (–)-(Z)- β -santalol (Figure 27).

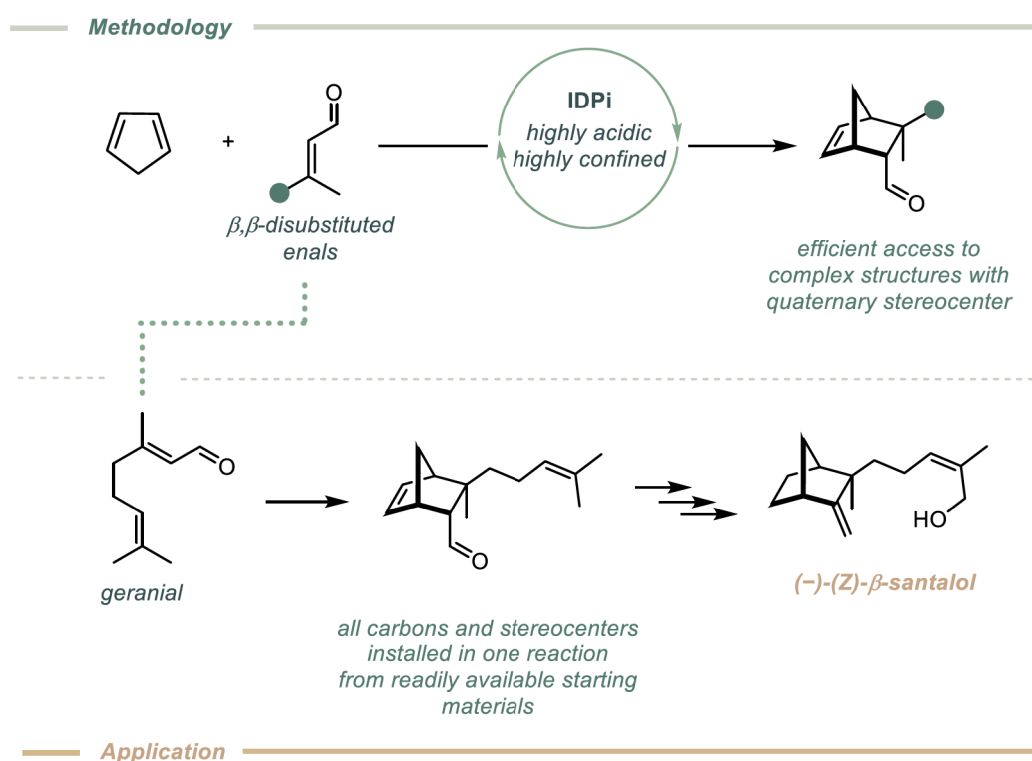


Figure 27. Synthetic aims of this work.

Through this work, we aim to demonstrate not only the academic value of extending Brønsted acid catalysis to previously inaccessible substrates, but also the practical utility of such advances in addressing real-world synthetic challenges.

4. Discussion

The body of research described in this dissertation is divided into two principal parts. The first part is devoted to the development of an enantioselective Diels–Alder reaction of unactivated β,β -substituted enals: optimization of the reaction conditions, the systematic exploration of substrate scope, and the execution of mechanistic studies designed to elucidate the underlying principles governing reactivity and stereocontrol. The second part illustrates the synthetic utility of the developed methodology through its application to the enantioselective total synthesis of (–)-(Z)- β -santalol.

4.1. Asymmetric Organocatalytic Diels–Alder Reaction with β,β -Disubstituted Enals

4.1.1. Reaction Design and Optimization

The following studies were performed in collaboration with Dr. Santanu Ghosh.

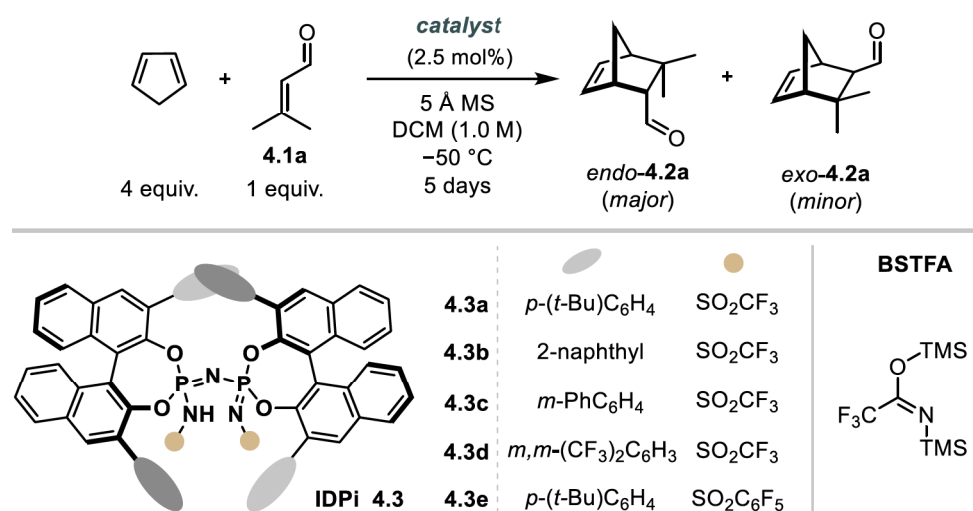
We initiated our studies by investigating the Diels–Alder reaction between the simplest commercially available β,β -substituted enal, 3-methylbut-2-enal **4.1a**, and cyclopentadiene. Cyclopentadiene was selected as the diene for two main reasons: first, its increased reactivity arising from the locked *s-cis* conformation, which is advantageous considering low reactivity of β,β -substituted enals; and second, because this diene directly furnishes the characteristic bicyclo[2.2.1]heptane core of (–)-(Z)- β -santalol **2.15**. Based on the previously reported Diels–Alder reactions of enals,¹⁰⁵ for the initial screening of Brønsted acid catalysts the following set of conditions was chosen: dichloromethane (DCM) as solvent, the reaction temperature was set at –50 °C—higher than the typical –78 °C to –100 °C range used for less hindered substrates—to compensate for the diminished reactivity of β,β -substituted enals and as a standard additive known to be beneficial in Diels–Alder transformations, 5 Å molecular sieves (MS) were included.¹⁵¹

To establish a reactivity baseline, the reaction was first tested with a strong Brønsted acid, bis(trifluoromethane)sulfonimide (HNTf₂) (Table 1, entry 1), which predictably yielded a complex mixture of products, including polymeric compounds. This result highlighted the lability of the starting materials in acidic conditions and the need for more selective catalytic systems. We therefore proceeded to evaluate IDPi catalysts **4.3**, readily available in our lab and offering a balance between sufficient acidity to activate β,β -substituted enals and the stereocontrol provided by their confined catalytic sites, superior to those of the related

monomeric DSI or CPA derivatives.

To our satisfaction, a relatively simple IDPi catalyst bearing *p*-(*t*-Bu) C_6H_4 substituents at the 3,3'-positions of the BINOL framework and internal triflyl groups **4.3a** afforded the desired cycloadduct **4.2a** with promising diastereoselectivity favoring the desired *endo*-isomer (80:20 *endo/exo*) and high enantioselectivity, albeit in low yield (26%). Other common 3,3'-hydrocarbon-substituted IDPi catalysts (entries 3–4) failed to improve either yield or stereoselectivity. Switching to a more acidic CF_3 -substituted IDPi **4.3d** resulted in a significant loss of stereocontrol (entry 5). Seeking to improve both yield and robustness, we next examined a related, slightly less acidic¹⁵² and more sterically encumbered catalyst featuring a C_6F_5 -substituted “core” **4.3e**, which indeed provided an improved yield (34%) while maintaining high stereoselectivity (entry 6).

Table 1. Initial screening of reaction conditions and catalysts.



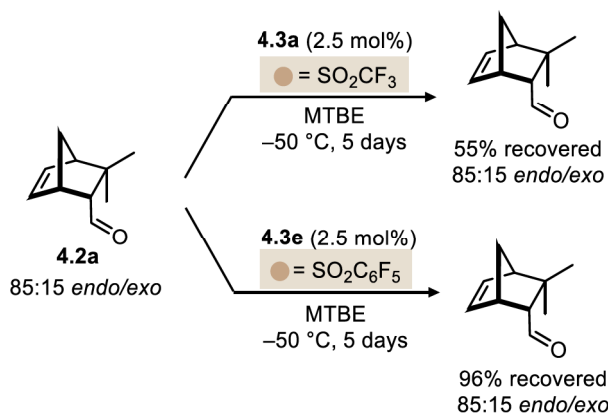
entry	catalyst	additive	conversion, %	yield, %	<i>endo/exo</i>	e.r. (<i>endo</i>)
1	HNTf ₂ *	-	full	4	-	-
2	4.3a	-	96	26	80:20	91:9
3	4.3b	-	82	17	82:18	76:24
4	4.3c	-	89	15	71:29	88:12
5	4.3d	-	full	32	63:37	60:40
6	4.3e	-	98	34	85:15	93:7
7	4.3e	BSTFA (0.5 equiv.)	75	14	85:15	90:10

*15 mol%; conversions, yields and *endo/exo* ratios were determined using NMR (nuclear magnetic resonance spectroscopy) in crude sample with CH_2Br_2 as internal standard; enantiomeric ratios (e.r.) determined by chiral gas chromatography (GC)

Given that Lewis acids are effective catalysts in Diels–Alder reactions, we also

attempted to perform the reaction under Lewis acidic conditions using catalyst **4.3e** in the presence of *N,O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA), generating silylium IDPi Lewis acid in situ. However, no significant improvement in yield or selectivity was observed (entry 7).

Suspecting that the product being an aldehyde may be prone to decomposition in the presence of the more acidic catalyst **4.3a** we conducted a control experiment. The isolated product **4.2a** was subjected to the reaction conditions with catalysts **4.3a** and **4.3e** in the presence of internal standard. After 5 days recovered yields were determined and confirmed our hypothesis: only 55% of the product remained in the case of catalyst **4.3a**, while with the catalyst **4.3e** only minor loss was observed (Scheme 2).

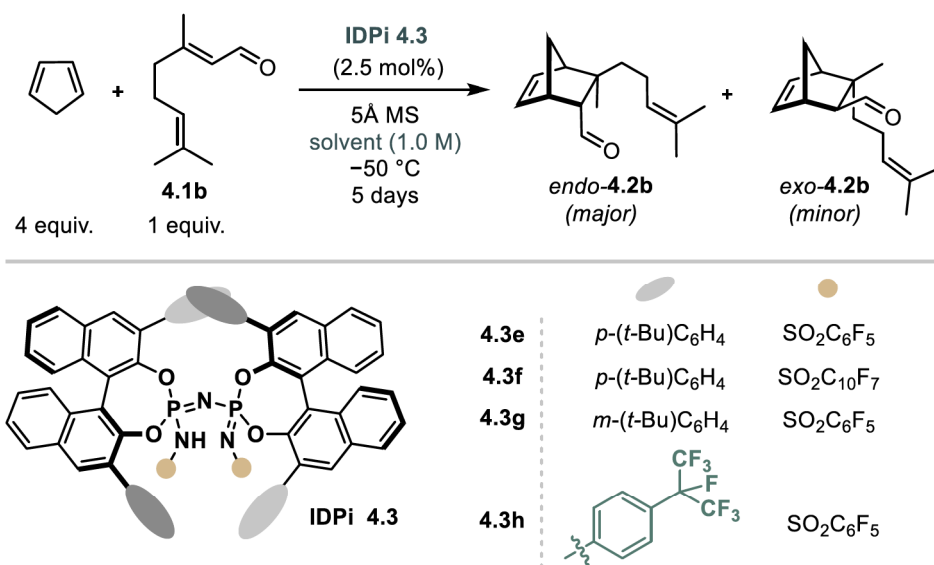


Scheme 2. Decomposition of the Diels-Alder product **4.2a** in the reaction conditions. MTBE = methyl *tert*-butyl ether.

Encouraged by these initial results with the model substrate **4.1a**, we next evaluated the system's performance with a more valuable and challenging substrate, geranial **4.1b**. Gratifyingly, the corresponding Diels-Alder adduct was obtained with similarly promising stereoselectivity (80:20 *endo/exo*, 98:2 e.r. (*endo*)) albeit in low yield (12%) (Table 2, entry 1).

We then sought to optimize other key reaction parameters. Among the solvents tested, chloroform afforded both improved yield and higher enantioselectivity, whereas hydrocarbon solvents proved unsuitable (Table 2, entries 2–4). Interestingly, the reaction could also successfully proceed in neat conditions (1.0 M cyclopentadiene (CpH), entry 5), though with reduced efficiency compared to CHCl₃. Switching to ether solvents—diethyl ether (Et₂O) and methyl *tert*-butyl ether (MTBE)—further enhanced yields and provided excellent enantioselectivities (entries 6–7).

Building on these promising results, we pursued additional catalyst optimization.

Table 2. Initial solvent screening and continuation of the catalyst screening with geranial **4.1b**.

entry	catalyst	solvent	conversion, %	yield, %	<i>endo/exo</i>	e.r. (<i>endo</i>)
1	4.3e	DCM	78	12	80:20	92:8
2		CHCl ₃	89	27	89:11	95:5
3		toluene	33	0	-	-
4		cyclohexane	37	3	-	-
5		CpH (neat)	82	19	88:12	96:4
6		Et ₂ O	75	33	85:15	94:6
7		MTBE	full	41	88:12	99:1
8	4.3f	MTBE	47	1	-	-
9	4.3g	MTBE	82	18	90:10	98:2
10	4.3h	MTBE	98	37	94:6	98:2

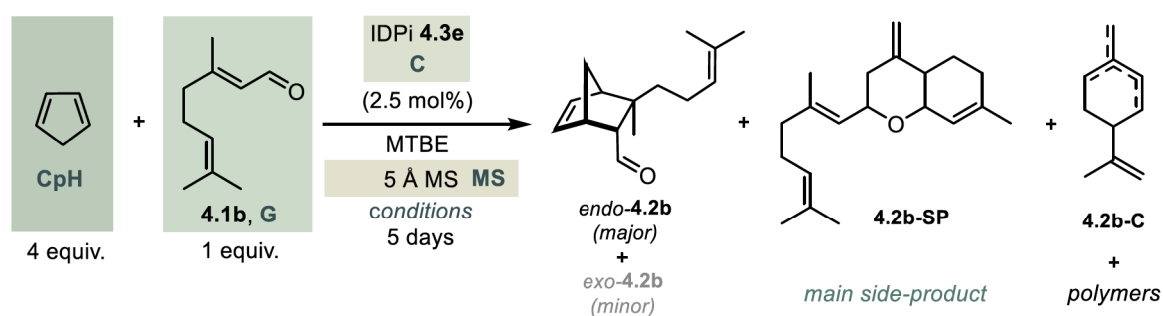
conversions, yields and *endo/exo* ratios were determined in crude NMR using CH₂Br₂ as internal standard; e.r. determined by chiral GC.

Two key design elements were considered: the presence of bulky *tert*-butyl or similar aliphatic groups in 3,3'-positions and the use of a C₆F₅ (or related) aromatic inner ("core") substituent. Extending the aromatic framework of the "core" substituent to C₁₀F₇ (Table 2, entry 8) **4.3f** or repositioning the *tert*-butyl group to the *meta*-position **4.3g** — closer to the catalytic pocket (entry 9) — did not lead to notable improvements. However, reasoning that introduction of EWGs on the periphery of the active site might enhance Lewis acidity and increase the catalyst's activating power, we explored a fluorinated analog of the *tert*-butyl substituent. Indeed, the corresponding catalyst with a C₆F₅ inner substituents **4.3h** afforded a slightly improved yield and better diastereoselectivity, likely due to the increased steric demand introduced by fluorine atoms combined with the higher acidity of **4.3h** compared to the other

catalysts, and thus more efficient activation of the enal (entry 10).

Taking into account the easy accessibility of catalyst **4.3e** and its superior performance in terms of yield and enantioselectivity, it was selected as the most suitable catalyst for this transformation.

Table 3. Conditions optimization.



entry	concentration, M	addition of the reagents	temperature, °C	conversion, %	yield, %	endo/exo	e.r. (endo)
1	1.0	MS→C→G→CpH**	−50	full	41	88:12	99:1
2		MS→C→CpH→G (G via syringe pump over 3 days)***		76	20	85:15	-
3		MS→C→CpH→G		98	50	89:11	99:1
4		MS→G→CpH→C		55	14	-	-
5		C→G→CpH→MS		71	21	82:18	-
6	0.5	MS→C→CpH→G		88	14	91:9	-
7	1.0			98	50	89:11	99:1
8	1.5			full	53	88:12	-
9	2.4*			56	10	-	-
10	1.7			full	56	89:11	99:1
11			−30	full	38	80:20	93:7
12			−40	full	59	88:12	99:1
13			−60	95	45	91:9	99:1
14			−70	77	24	91:9	99:1

MS = 5 Å MS, C = **4.3e**, G = **4.1b**, CpH = cyclopentadiene; *no proper stirring; **standard order of addition; **after the addition was complete (3 days), the reaction was left for additional 3 days; conversions and yields were determined in crude NMR using CH₂Br₂ as internal standard; e.r. determined by chiral GC

To gain insight into the factors limiting the yield, we carried out a larger-scale experiment in an attempt to isolate and characterize the side products. The reaction was found to be accompanied by the formation of polymeric byproducts as well as cyclization products¹⁵³

(detected by mass spectrometry) such as **4.2b-C**. The major side product was identified as a condensation adduct of two geranial molecules **4.2b-SP** (Table 3), confirmed by the high-resolution mass spectrometry (HRMS) and NMR spectroscopy.

Several strategies were tested to suppress the formation of these side products, including lowering the reaction concentration, slow addition of **4.1b** using a syringe pump, and varying the order of reagent addition. Slow addition of **4.1b** (Table 3, entry 2) led to a significant reduction of the yield of the desired product, while the overall substrate conversion remained disproportionately high, indicating that competitive side processes were still predominant. In contrast, altering the order of addition provided a modest improvement in yield when geranial **4.1b** was added last (50% vs 41% for the standard sequence) to the reaction mixture (entry 3), likely because the highly acidic IDPi catalyst did not encounter the aldehyde substrate in the absence of the reactive diene. Other addition sequences did not result in improved yields.

Concentration screening revealed that optimal reactivity was achieved at relatively high concentration (1.7 M, Table 3, entry 10), whereas dilution significantly slowed the reaction rate (entry 6). Similarly, lowering the reaction temperature reduced the conversion (entry 14), while temperatures above $-40\text{ }^{\circ}\text{C}$ promoted side reactions, leading to the decreased yields of the target product (entry 11). The optimal temperature range was found to be between $-40\text{ }^{\circ}\text{C}$ and $-50\text{ }^{\circ}\text{C}$. Extending the reaction time did not result in any improvement in yield. It was also found that maintaining an inert atmosphere throughout the reaction was not necessary — yields and stereoselectivities remained essentially unchanged whether the reaction was conducted under a continuous argon flow or left as it is after the initial argon flush.

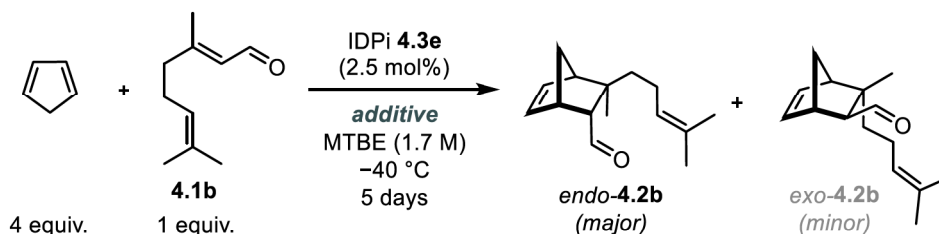
From a practical standpoint, we sought to further optimize the reaction conditions, particularly by examining the role of 5 Å MS, which had been routinely included as additives. Surprisingly, no product formation was observed when the reaction was performed in the absence of MS. Likewise, performing the reaction in the presence of 1.0 equiv. of BSTFA, which should efficiently scavenge trace water¹⁵⁴, also failed to deliver product **4.2b** (Table 4). Thus, our first objective was to determine the minimal effective loading of MS. Loadings as low as 250 mg/mmol of enal substrate were found sufficient for full reaction conversion, with no apparent upper limit, except for the practical issue of insufficient stirring.

We next examined other common laboratory desiccants, such as Na_2SO_4 , MgSO_4 , CaCl_2 , CaSO_4 , and Drierite™ (activated by drying at $100\text{ }^{\circ}\text{C}$ for 2 days and ground to fine powder before use). In most cases, these additives failed to promote the product formation.

4. Discussion

Interestingly, DrieriteTM, which consists of CaSO₄ and 2% w/w CoCl₂ as an indicator, was the only desiccant to deliver a measurable amount of the desired product, whereas pure CaSO₄ on its own was inactive.

Table 4. Additives screening.



additive*	none	BSTFA**	5 Å MS (100/mmol)	5 Å MS (250/mmol)	5 Å MS (400/mmol)	5 Å MS*** (500/mmol)
conversion, %	29	25	61	93	full	full
yield, %	3	0	13	51	59	50
<i>endo/exo</i>	-	-	88:12	89:11	88:12	88:12
e.r. (<i>endo</i>)	-	-	98:2	99:1	99:1	99:1
additive	Na ₂ SO ₄	MgSO ₄	CaCl ₂	Drierite TM	Al ₂ O ₃ (var.)	SiO ₂ (var.)
conversion, %	18	39	31	86	~25	~27
yield, %	0	2	2	17	~1	~1
<i>endo/exo</i>	-	-	-	85:15	-	-
e.r. (<i>endo</i>)	-	-	-	98:2	-	-
additive	K10	Zeolite Y (H)	Zeolite Y (Na)	13X MS	3 Å MS	4 Å MS
conversion, %	14	26	32	19	22	39
yield, %	0	0	0	0	4	15
<i>endo/exo</i>	-	-	-	-	-	85:15
e.r. (<i>endo</i>)	-	-	-	-	-	98:2

*300 mg/mmol (of **4.1b**), unless otherwise noted; **1.5 equiv.; ***proper stirring was not possible; conversions, yields and *endo/exo* ratios were determined in crude NMR using CH₂Br₂ as internal standard; e.r. determined by chiral GC

Various forms of Al₂O₃ (activated Brockmann I, basic/neutral/acidic, and mesoporous MSU-X type) and SiO₂ (powder with 0.040–0.063 mm and 0.063–0.200 mm particle sizes, fumed silica, and mesostructured MCM-41) were tested as well. However, the addition of these materials didn't promote the formation of the desired cycloadduct.

In the control experiment in the absence of IDPi catalyst **4.3e** no conversion of the starting materials was observed. These peculiar observations raised questions about the actual

function of MS in this reaction. We thus turned our attention to the composition and properties of the MS.

Molecular sieves are porous materials capable of size-specific adsorption, most commonly represented by zeolite-based solids.¹⁵⁵ In standard laboratory practice, their primary purpose is the removal of trace water from solvents, reagents, or reaction mixtures—that is, they function as desiccants. The most common varieties used for this purpose are 4 Å ($\text{Na}_{12}[(\text{AlO}_2)_{12}(\text{SiO}_2)_{12}] \cdot x\text{H}_2\text{O}$) and 5 Å ($\text{Ca}_n/\text{Na}_{12-2n}[(\text{AlO}_2)_{12}(\text{SiO}_2)_{12}] \cdot x\text{H}_2\text{O}$) molecular sieves of the Linde Type A (LTA) zeolite family. However, zeolite frameworks also possess potential Lewis and Brønsted acidic properties in addition to their molecular sieving ability. Zeolites consist of silicon and aluminum atoms linked by oxygen bridges, forming a negatively charged aluminosilicate lattice (Figure 28). This charge is typically compensated by metal cations, the nature of which determines pore size and influences the Lewis acidity of the material.¹⁵⁶ Cation exchange with Brønsted acids is a well-established phenomenon¹⁵⁷ and under forcing conditions can yield proton-exchanged zeolites, which are widely used as solid acid catalysts in industrial cracking and isomerization processes.¹⁵⁸ These multifaceted properties make molecular sieves highly versatile additives¹⁵⁹ and broadly reflected in their importance for many Diels–Alder reactions.^{160,161}

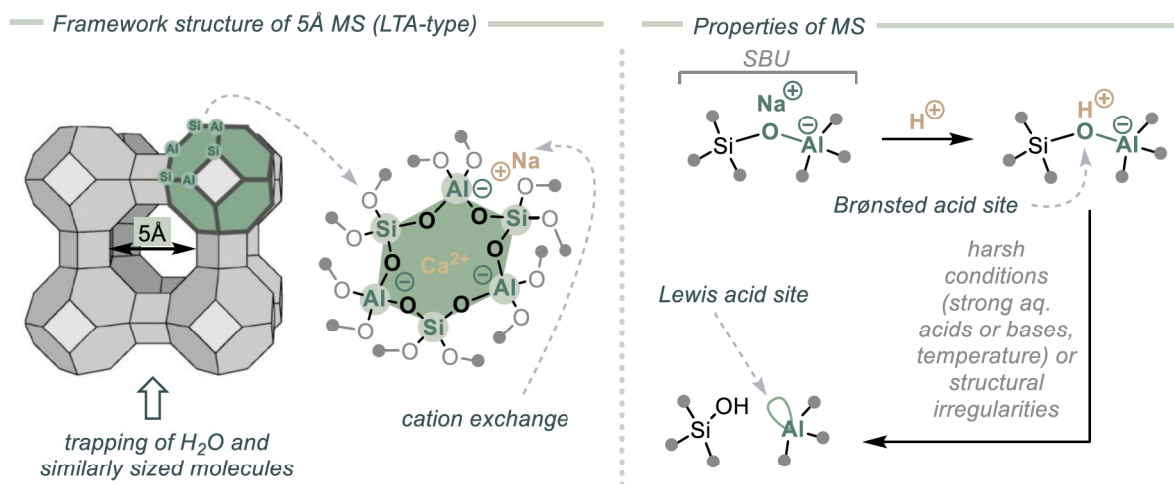


Figure 28. MS structure and properties as zeolite materials. SBU = secondary building units.

To evaluate whether the MS properties arising from the zeolite structure are responsible for the observed reactivity, we screened a series of common zeolites, including zeolite Y in both H- and Na-forms (FAU-type, pore size ≈ 7.4 Å), MS 13X (FAU-type, pore size ≈ 10.0 Å), 3 Å MS (LTA-type, K^+ -exchanged), and 4 Å MS (LTA-type, Na^+ -exchanged). All materials were pre-activated by high-vacuum drying at 120 °C for 2 days hours. In nearly all cases,

10–20% conversion of geranial into polymeric materials was observed, with no detectable formation of the desired cycloadduct — except in the case of 4 Å MS, which delivered 15% yield of **4.2b** (Table 4). Interestingly, despite both 3 Å and 4 Å MS belonging to the same zeolite family and possessing similar water adsorption properties, only 4 Å MS promoted product formation. The only difference lies in the lattice-stabilizing cation: potassium for 3 Å MS (resulting in smaller diameter pores) and sodium for 4 Å MS.

We then turned our attention to non-zeolite aluminosilicate materials such as montmorillonite clay (K10), a hydrated sodium calcium aluminum magnesium silicate hydroxide, $((\text{Na,Ca})_{0.33}(\text{Al,Mg})_2(\text{Si}_4\text{O}_{10})(\text{OH})_2 \cdot n\text{H}_2\text{O})$, which is capable of cation exchange analogous to zeolites and can serve as a solid acid and adsorbent upon dehydration. Notably, montmorillonite K10 has been reported as a solid acid catalyst for the selective conversion of neral in citral mixtures to cyclized and polymeric byproducts, leaving the geranial fraction largely intact.¹⁶² However, it did not promote the desired Diels–Alder reaction in our case.

Although the screening was not fully conclusive, three additives: Drierite™, 4 Å MS, and 5 Å MS, capable of promoting product formation were identified. The latter two, both sodium-based zeolites with slightly different pore sizes, are exceptionally efficient water scavengers, whereas Drierite™, a layered calcium sulfate material containing cobalt, likely operates through a different mechanism. Since the best results were obtained with 5 Å MS, this additive was adopted as standard for the subsequent reactions, typically at a loading of 400 mg/mmol. Further discussion of the mechanistic implications and the role of molecular sieves in this transformation will be presented in Chapter 4.2.

Having established reliable reaction conditions, we next explored the substrate scope of the developed enantioselective Diels–Alder reaction.

4.1.2. Scope of the β,β -Disubstituted Enals

Our investigation of the reaction scope began with the systematic variation of one of the β -substituents of the enal dienophile. The corresponding enals substrates were prepared either by oxidation of the commercially available allylic alcohols or via the HWE reaction between various methylketones and cyanomethylphosphonate followed by reduction of the cyano-group to the aldehyde (the detailed procedures are given in Chapter 7).

As it was previously established during screening and optimization studies, the catalytic system efficiently promotes reaction of the 3-methylbut-2-enal **4.1a** and geranial **4.1b** with

cyclopentadiene, affording the corresponding cycloadducts in good yields and with excellent enantioselectivity (Figure 29). The system was also found to tolerate aliphatic substituents: for instance, the *n*-butyl-substituted enal underwent smooth conversion to the corresponding product **4.2c** with 66% yield and 98:2 e.r. The hydrogenated geranial analog, bearing an elongated branched alkyl chain, reacted efficiently under the same conditions, yielding 68% of the cycloadduct **4.2d** with excellent enantioselectivity.

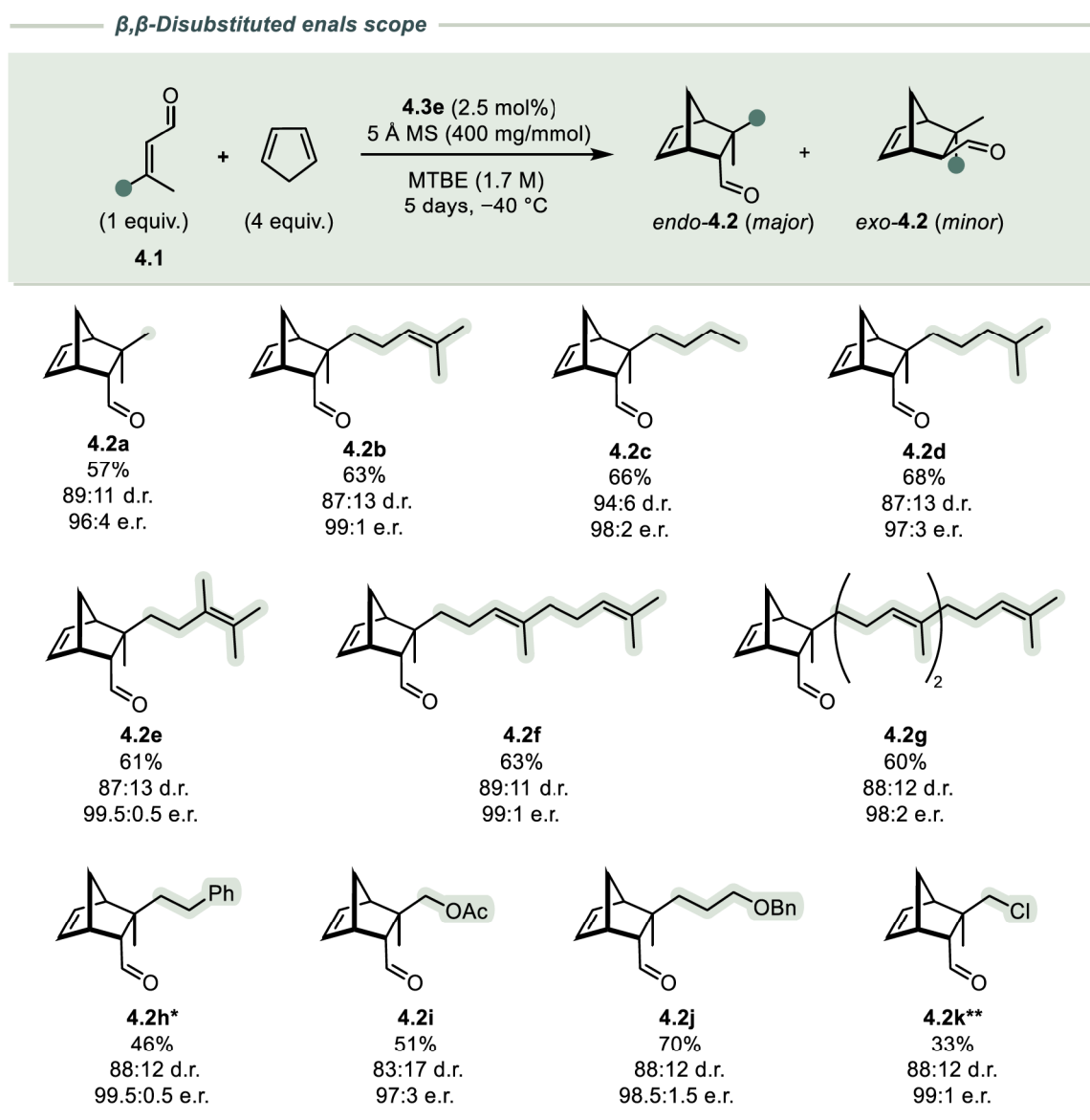


Figure 29. Substrate scope regarding various β,β -disubstituted enals. The reactions performed of 0.2 mmol scale, the reported yields are isolated yields after column chromatography; e.r. determined by chiral GC and refers to the *endo*-**4.2**. *7 days reaction time, **at -60 °C.

Continuing within the terpenoid series, a methyl-substituted geranial analog exhibited similar behavior, affording the product **4.2e** in comparable yield and enantioselectivity to that obtained for the unsubstituted geranial. Larger terpenoid enals such as farnesal (C_{12}) and

geranylgeranial (C₁₆) were likewise well tolerated, delivering the desired products **4.2f** and **4.2g** in good yields and with consistently excellent enantioselectivity. These results collectively demonstrate the robustness of the catalytic system across a range of β -alkyl-substituted substrates, including long-chain and branched analogs.

We next turned our attention to more challenging substrates bearing functionalized β -substituents that introduce potential secondary reactive sites and potentially alter the electronic properties of the enal. The phenyl-substituted enal displayed noticeably reduced reactivity, affording the product **4.2h** in diminished yield even after the prolonged reaction time. Since the phenyl group is separated from the C=C bond of the enal by a two-carbon spacer, its direct electron-withdrawing or conjugative influence on the LUMO of the enal is expected to be minimal. A more plausible explanation for the observed decrease in reactivity could be the occurrence of the unfavorable steric or π - π interactions between the aromatic ring and the framework of the IDPi catalyst in the approach to the transition state, which might hinder productive coordination of the enal substrate.

An acetoxy-substituted enal, one of the most electron-deficient substrates in the series, displayed a slight decrease in yield as well, while maintaining the same high level of enantioselectivity of the product **4.2i**. Remarkably, the benzyloxy-substituted enal provided the highest yield among all tested substrates, delivering the cycloadduct **4.2j** in 70% yield. These examples demonstrate that both polar and nonpolar β -substituents are compatible with our catalytic system.

4-Chloro-3-methylbut-2-enal proved to be the most challenging substrate in the reaction scope. Considerable difficulties were encountered already at the substrate preparation stage: the compound was found to be extremely unstable, rapidly decomposing to a polymeric material even when stored in the dark at $-20\text{ }^{\circ}\text{C}$. Moreover, upon attempted cycloaddition under the standard conditions, intramolecular alkylation of the initially formed cycloadduct occurred, leading to a fused cyclopropane byproduct. This side process could be substantially suppressed by performing the reaction at a lower temperature ($-60\text{ }^{\circ}\text{C}$). When freshly prepared β -chloromethyl enal is used at $-60\text{ }^{\circ}\text{C}$, the desired Diels–Alder cycloadduct can be obtained with excellent enantioselectivity albeit in only 33% yield as a result of the accompanying side reactions.

4.1.3. Limitations of the Reaction Scope

Curious about the broader applicability of the developed catalytic system, we further

explored the Diels–Alder reaction with more structurally diverse β,β -substituted enals. Unfortunately, none of the alkyl substituents with the branching point directly adjacent to the enal double bond were tolerated. For substrates bearing tertiary, secondary, or cycloalkyl β -substituents, only 10–20% background conversion was observed, and no detectable amount of the desired cycloadduct (Figure 30). The most plausible explanation for this behavior is the presence of severe steric repulsion in the approach to the Diels–Alder reaction transition state, which prevents the necessary orbital overlap. A similar issue likely accounts for the failure of the β,β -*n*-propyl-disubstituted substrate, which also did not yield the desired product.

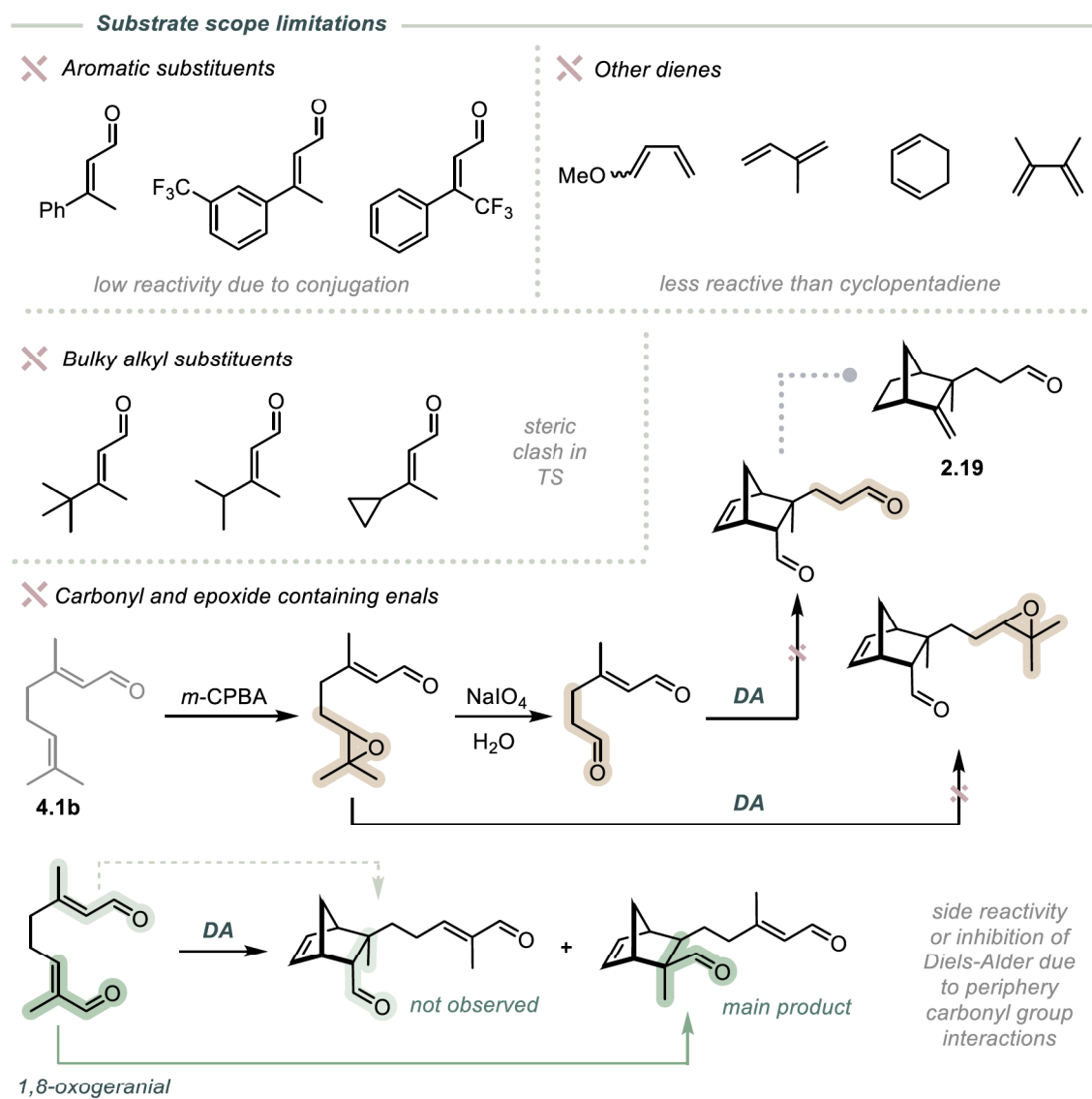


Figure 30. Substrate limitations. DA = Diels–Alder reaction, TS = transition state, *m*-CPBA = *meta*-chloroperoxybenzoic acid.

Aromatic substituents adjacent to the C=C bond were also found to significantly suppress the dienophile reactivity of the enal. The conjugation between the enal π -system and

the aromatic ring delocalizes π -electrons across the extended π -framework, thereby increasing the electron density of the conjugated HOMO and stabilizing the system, which in turn reduces its electrophilicity and reactivity as a dienophile. To the best of our knowledge, such conjugated aryl-substituted enals have not been successfully employed in Diels–Alder reactions with cyclopentadiene to date. Consistent with this, our attempts to use these substrates under the optimized IDPi-catalyzed conditions were unsuccessful. Even aryl-enals bearing the electron-withdrawing substituents, which should theoretically restore some degree of the electrophilic character in the enal, exhibited sluggish reactivity.

We next turned our attention to more complex and reactive substrates, which could potentially provide useful handles for downstream functionalization of the corresponding cycloadducts and are readily derived from geranial or citral. Among these, geranial epoxide gave only trace amounts of the desired cycloadduct and displayed overall moderate conversion, likely due to competing side reactions involving acid-catalyzed epoxide opening and intramolecular cyclization.

To test the selectivity of the developed catalytic system we designed a probe experiment to evaluate its ability to differentiate between β,β -disubstituted and α,β -disubstituted enal moieties within the same molecule. For this purpose, 1,8-oxogeranial was selected—a naturally occurring terpenoid and biosynthetic precursor of several iridoids^{163,164}—containing both disubstituted enal functionalities. The substrate was prepared via SeO₂-mediated allylic oxidation of geraniol acetate, followed by deprotection¹⁶⁵ and final oxidation. Under the optimized catalytic conditions, 1,8-oxogeranial displayed modest overall reactivity, reaching 52% conversion after five days and delivering the cycloadduct corresponding to the addition at β -monosubstituted enal site. This outcome is consistent with the established higher intrinsic reactivity of α,β -disubstituted enal dienophiles compared to their β,β -disubstituted counterparts.

To evaluate the tolerance of the reaction toward additional non-conjugated carbonyl functionalities, we next examined a dicarbonyl substrate derived from oxidative cleavage of geranial epoxide using either NaIO₄.¹⁶⁶ This substrate was of the particular interest because the corresponding cycloadduct would closely resemble the common aldehyde intermediate **2.19** of many (–)-(Z)- β -santalol syntheses, thus potentially enabling combination of the developed Diels–Alder platform with the previously developed highly selective Z-allylic alcohol installation. Unfortunately, no product was obtained even after prolonged reaction time. Approximately 30% of the starting material was consumed, forming a complex mixture of unidentified products, likely due to decomposition or alternative acid-promoted pathways.

Considering these observations and the previous discussion on the low reactivity of β,β -substituted enals as dienophiles, we did not expect significant success with less reactive dienes. Nevertheless, several common and easily accessible dienes, including 1-methoxybutadiene, isoprene, cyclohexadiene, and 2,3-dimethyl-1,3-butadiene — were tested. In all cases, no desired product formation was observed, and the enal substrate remained largely intact.

Accordingly, the effective reactivity window of this methodology is defined by β,β -disubstituted enals featuring a methyl group at the β -position and an alkyl substituent containing at least one $-\text{CH}_2-$ unit as the second β -substituent. The reaction exhibits remarkable robustness with respect to the chain length (from C_5 up to C_{20}) of the alkyl and alkenyl substituents fulfilling the first criteria, delivering the products with consistent yield and high enantioselectivity. In addition, a variety of synthetically useful functional groups can be introduced into the $-\text{CH}_2-$ alkyl substituent including protected alcohols, esters and halogens.

4.2. Mechanistic Investigations

To gain deeper insight into the underlying mechanism and the factors influencing the reaction outcome, several mechanistic experiments were performed. The first part of these studies focused on classical mechanistic probes, including the determination of kinetic isotope effects (KIEs), the investigation of nonlinear effects, ruling out kinetic resolution and product inhibition. The second part of the mechanistic investigation focused on elucidating the role and potential effects of molecular sieves in the reaction.

4.2.1. ^{13}C Kinetic Isotope Effect at Natural Abundance

The KIE experiments provide information about the transition state geometry and the rate-determining step by monitoring the change in reaction rate when an atom participating in bond formation is replaced with its heavier isotope. Given that the Diels–Alder reaction developed in this work affords products in substantial quantities, we attempted to determine the ^{13}C KIE at natural abundance following the approach pioneered by Singleton¹⁶⁷ and later advanced by Kwan¹⁶⁸. This method utilizes quantitative ^{13}C NMR analysis for the determination of the isotopic distribution in the product, identifying the position in which enrichment in the faster-reacting lighter isotope is observed, thereby reflecting faster bond formation with this position in the transition state. It's especially useful for the reactions which result in the breaking of symmetry, which our reaction is, in regards to cyclopentadiene.

As the analysis requires highly pure material, the aldehyde group in the Diels–Alder

product was first reduced to the corresponding alcohol **4.4**, which was then purified by HPLC. In the resulting compound, carbon atoms C3 and C4 were chosen as an internal reference $k(^{12}\text{C})/k(^{13}\text{C}) = 1.000$. The isotopic enrichment was then evaluated at carbons C5 and C6. The obtained results (Figure 31) represent the average of eight independent measurements, showing a substantial KIE of 1.040 ± 0.004 at C6.

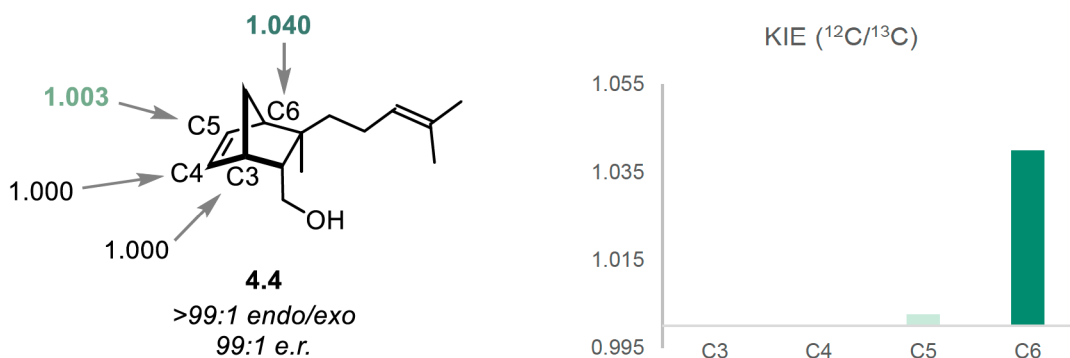


Figure 31. Intramolecular ^{13}C KIE at natural abundance.

This pronounced isotope effect indicates that the reaction proceeds through a highly asynchronous transition state.¹⁶⁹ According to the previous reports, despite high asynchronicity most of the studied Diels-Alder reaction still proceed in a concerted fashion. Thus, Singleton and coworkers demonstrated that across a series of AlCl_3 -catalyzed Diels-Alder reactions of acrolein, methyl vinyl ketone, and ethyl acrylate, similar KIE values were observed, suggesting uniformly asynchronous concerted mechanisms, a finding later corroborated by computational data.¹⁷⁰ Additionally, high asynchronicity of the transition state implies strong polarization of the dienophile,¹⁷¹ reflecting the potency of the employed acid catalyst. We thus conclude that our Diels-Alder reaction proceeds via highly asynchronous concerted transition state, although the stepwise mechanism cannot be completely excluded.

4.2.2. Non-linear Effects and Kinetic Resolution

Nonlinear effects (NLE) describe deviations from a direct proportional relationship between the enantiopurity of a chiral catalyst and the enantioenrichment of the corresponding product in an asymmetric transformation. A variety of phenomena can give rise to such outcome, with the most common being the formation of catalyst aggregates of differing enantiomeric composition that exhibit distinct catalytic activities or solubilities. In some cases, precipitation¹⁷² of one aggregate enantiomer can further enhance the observed nonlinearity. However, nonlinear effects can also arise from other factors. For example, systems involving

kinetic resolution have been reported to display intrinsic negative NLE.¹⁷³ Likewise, physical phenomena, such as phase behavior, can also contribute to nonlinear correlations.¹⁷⁴ Depending on the nature of the underlying cause, the nonlinear behavior may result either in amplification of the product enantiomeric excess ((+)-NLE) or its diminution ((-)-NLE).

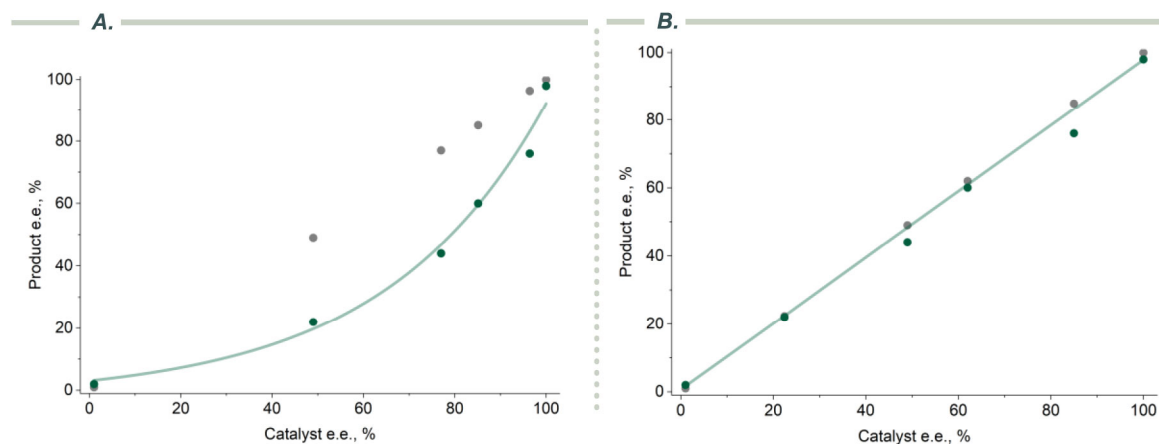


Figure 32. Non-linear effects study. A. In MTBE; B. In DCM.

Given that our Diels–Alder reaction consistently delivered products with high enantioselectivity under heterogeneous conditions (in the presence of solid molecular sieves), we sought to examine whether any of the aforementioned phenomena might influence the observed stereochemical outcome. A standard nonlinear effect study was conducted by evaluating the relationship between the enantiomeric excess of the catalyst and that of the corresponding cycloadduct (Figure 32A). A series of scalemic catalyst mixtures with gradually increasing enantiopurity was prepared gravimetrically, starting from a racemic mixture and progressing in 20% e.e. increments up to enantiopure (*S,S*)-IDPi **4.3e**. Each catalyst mixture was dissolved in MTBE and divided into two portions: one was analyzed by chiral HPLC to verify the actual e.e. values of the catalyst, and the other was used in the Diels–Alder reaction after evaporating the solvent and drying the catalyst in high vacuum for 2 days at 40 °C. The obtained data revealed a slight (–)-NLE, which may indicate the formation of higher-order catalytic species or, alternatively, reflect physical phenomena such as solubility differences that influence the effective concentration of the active catalyst.

Upon closer inspection of the catalyst samples prepared for HPLC analysis in the reaction solvent (MTBE), we observed slow formation of a fine solid. When the solvent for these samples was switched to DCM, a clear and stable solution was obtained that remained unchanged for several weeks. After remeasuring the samples under these conditions, an almost linear relationship between the enantiopurity of the catalyst and that of the product was restored

(Figure 32B). This observation suggests that the apparent (–)-NLE originates from limited solubility of scalemic catalyst aggregates in MTBE.

As discussed previously, we also sought to determine whether kinetic resolution could contribute to the high enantioselectivities observed. To test this, the enantiomeric excess of the product was monitored at different conversion levels throughout the reaction course. The resulting data (Figure 33) show that the product enantiomeric excess remains constant at all stages of the reaction, thereby ruling out kinetic resolution as a contributing factor to the observed stereochemical outcome.

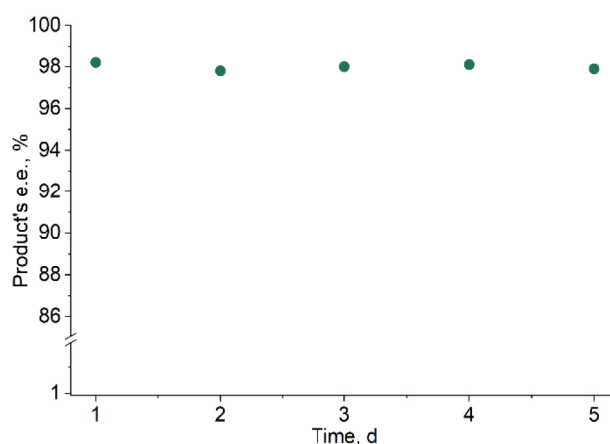


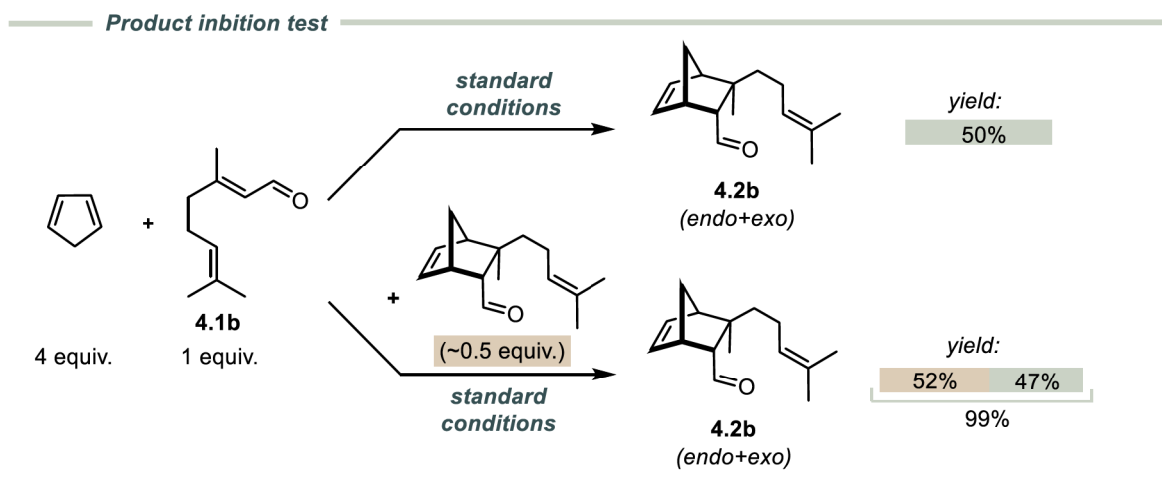
Figure 33. Ruling out kinetic resolution: the dependence of e.e. of the product on the reaction time.

4.2.3. Product Inhibition

Given that the Diels–Alder reaction generally proceeded with high conversion but the isolated yields did not exceed ~70%, we considered whether product accumulation might inhibit the catalyst or if the catalyst could undergo partial decomposition during the course of the reaction.

To assess possible product inhibition, the Diels–Alder reaction was performed in the presence of approximately 0.5 equiv. of the isolated cycloadduct product **4.2b**. The experiment followed the standard reaction screening procedure, with the additional product (6.0 μ L, corresponding to ~0.5 equiv.) introduced immediately after addition of the enal substrate **4.1b**. The exact amount of the added product was quantified by ^1H NMR spectroscopy using an internal standard, and is indicated as yield in the pale-brown box (Scheme 3). A parallel control reaction under standard conditions (without the addition of **4.2b**) served as a benchmark. Only a slightly reduced yield was observed in the reaction containing the added product. This minor decrease is most likely attributable either to the slow decomposition of the product under

reaction conditions (as discussed earlier in Chapter 4.1.1) or to experimental variability during the setup. Overall, these results indicate that the product does not significantly inhibit the catalytic performance of **4.3e**.



Scheme 3. Probing the product inhibition.

4.2.4. Stoichiometric Experiment: Interactions between IDPi and Enals

To gain insight into the activation mode of the β,β -disubstituted enal by the IDPi catalyst, we next attempted to detect interaction between the catalyst and the substrate under stoichiometric conditions using NMR spectroscopy.

For this purpose, a stoichiometric mixture of geranial **4.1b-(E)** (95:5 *E/Z*) and catalyst **4.3e** was prepared by dissolving the compounds in CD_2Cl_2 , followed by addition of 5 Å MS. The mixture was cooled to $-40\text{ }^\circ\text{C}$, and after stirring for 30 min, the mixture was transferred to an NMR tube, allowing the sieves to settle before spectra were recorded at $-40\text{ }^\circ\text{C}$ (Figure 34).

The resulting ^1H NMR spectra revealed only weak activation of the carbonyl group, as evidenced by slight broadening of the **4.1b-(E)** aldehydic signals, while the corresponding trace neral **4.1b-(Z)** signals remained nearly unchanged.

Given that full conversion was typically achieved in the catalytic reaction without quantitative product yield, and that a disproportionate amount of neral-derived cyclization byproducts was detected, we hypothesized that geranial **4.1b-(E)** might undergo acid-catalyzed isomerization to neral **4.1b-(Z)** under reaction conditions (using MTBE as solvent). Indeed, when the reaction progress was monitored by ^{13}C NMR spectroscopy (since ^1H NMR was not feasible due to the presence of MS and MTBE), (Figure 35A) an almost constant concentration of neral **4.1b-(Z)** was observed throughout the first 3 days of the reaction course. This behavior

can be rationalized either by

- complete inertness of neral under these conditions, or
- fast isomerization of geranial to neral, continuously replenishing the neral concentration, before its change due to the consumption in the side reactions can be detected.

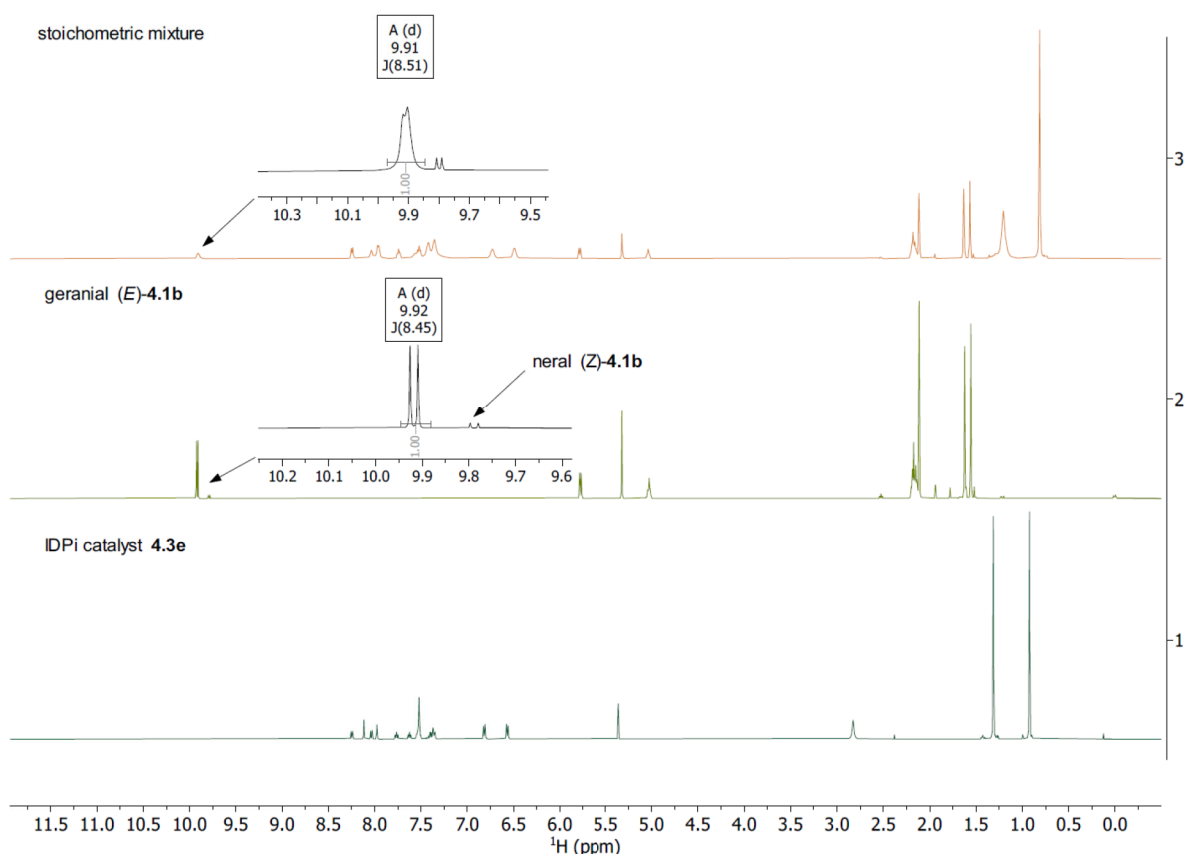


Figure 34. Probing enals activation in the presence of IDPi **4.3e**.

The latter hypothesis is consistent with the experiments using geranial/neral mixtures as substrate (see Chapter 4.3.1), in which full conversion of neral to intramolecular cyclization side products was observed. Therefore, the apparent rapid depletion of **4.1b-(E)** likely arises from the dynamic isomerization to **4.1b-(Z)** under acidic conditions — presumably via a transient Michael addition intermediate with trace alcohol in MTBE, which allows free rotation around the former double bond — followed by its facile intramolecular cyclization to **4.2b-C** and the observed dimerization to **4.2b-SP** (Figure 35B).

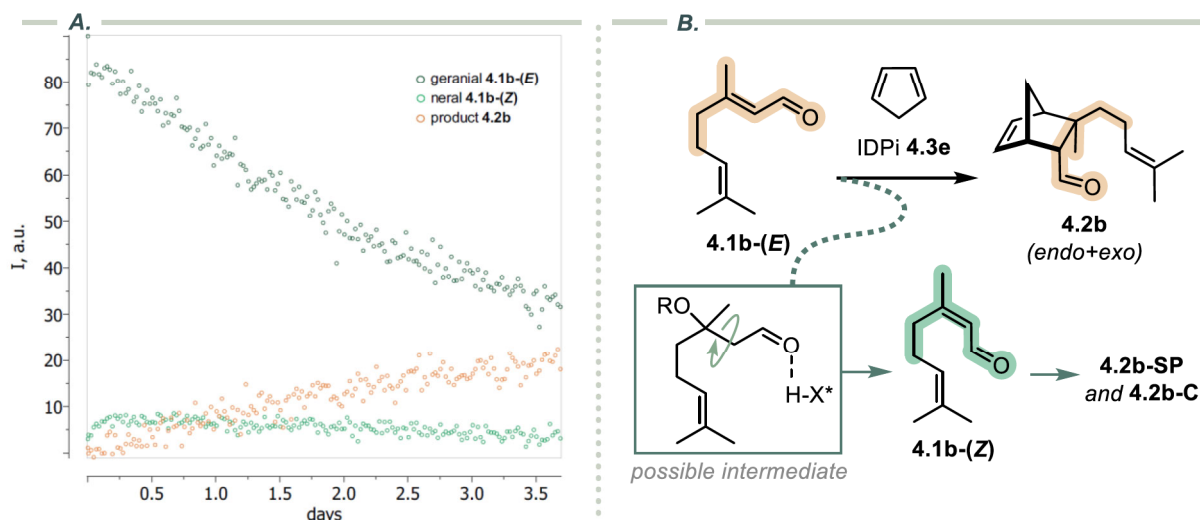


Figure 35. Geranial isomerization. A. ^{13}C NMR monitoring of the Diels-Alder reaction (in the absence of stirring), B. Possible isomerization pathway. X^* = chiral IDPi-anion.

4.2.5. Interactions between IDPi Catalysts and Molecular Sieves

Having established that the reaction does not proceed in the absence of MS, we next turned our attention to understanding their precise influence on the reactivity and potential interactions with the IDPi catalyst.

The ^{31}P NMR spectrum of the catalyst **4.3e** recorded under reaction-like conditions (in MTBE, in the presence of $5\text{ \AA}$ MS) revealed a noteworthy phenomenon: a new phosphorus signal (~ 1.9 ppm) appeared significantly shifted relative to the main IDPi signal (~ -5.54 ppm in MTBE) (Figure 36A, spectrum 2 and 1 correspondingly). The new signal closely resembled those typically observed in IDPi salts obtained after column chromatography (~ -1.1 to 2.5 ppm). When the sample was left for a prolonged time, the new peak gradually reverted back to that of the original IDPi (spectrum 3), which can suggest an exchange between these new species and the IDPi. The possible salt-like nature of the new species is further supported by the fact that addition of the strong bistriflimidic acid led to the complete disappearance of the new signal, leaving only the standard protonated IDPi peak (spectrum 4). Together, these findings indicate that the newly observed species correspond to an IDPi salt that forms reversibly under reaction conditions. The reversibility of this exchange is further in line with almost complete recovery of the IDPi catalyst (97%) after the reaction.

In contrast, when the catalyst was left in the absence of MS, no formation of these species was detected and significant decomposition of **4.3e** was observed. The ^{31}P NMR spectrum showed two distinct doublets arising from desymmetrization of the imidodiphosphorimidate unit (Figure 36B).

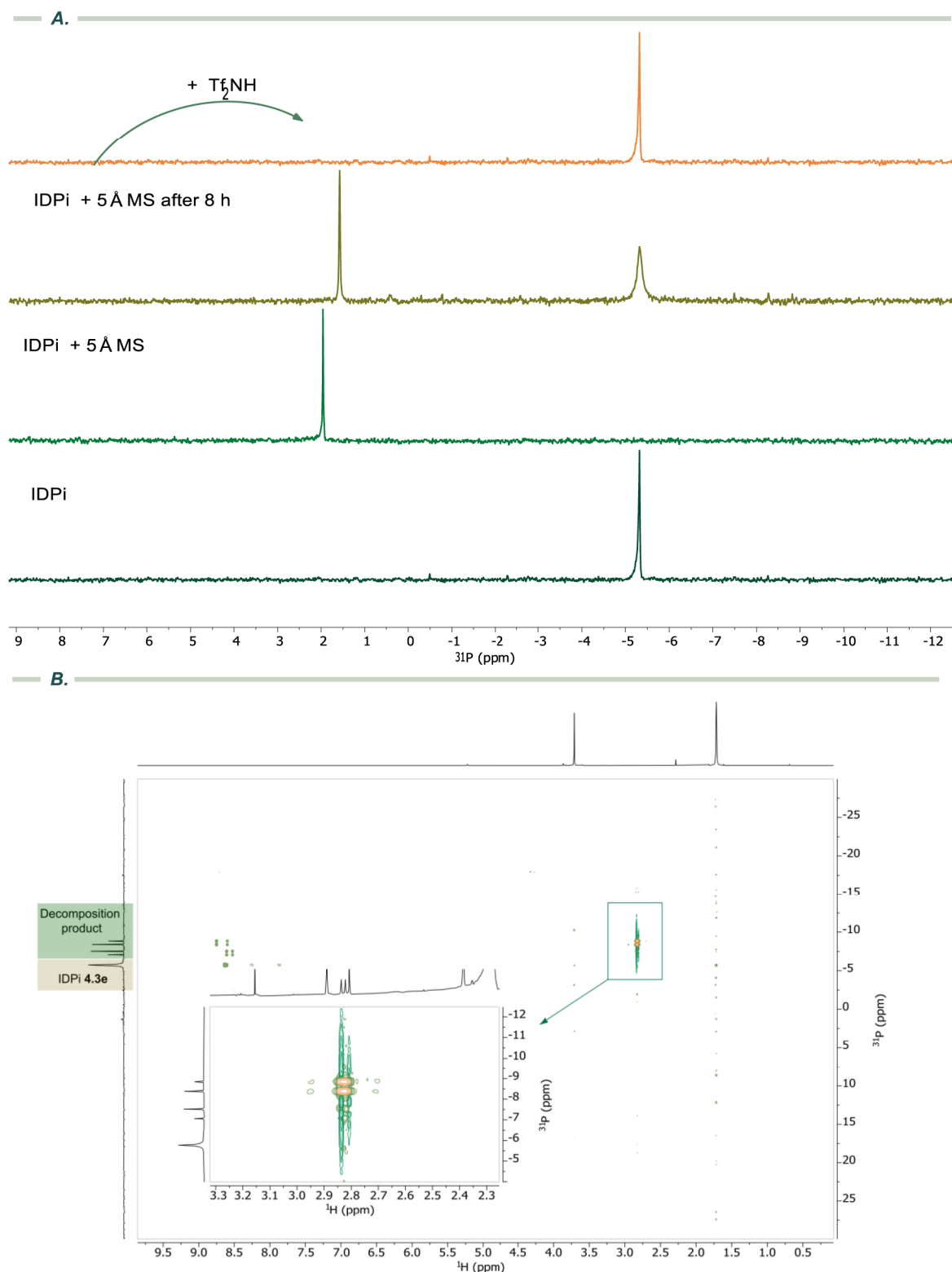


Figure 36. A. Interactions of IDPi **4.3e** with 5 Å MS and bistriflimidic acid B. Decomposition of **4.3e** in MTBE in the absence of MS.

Two plausible decomposition pathways can be considered: hydrolysis to *i*IDP¹⁷⁵, or *N*-/*O*-alkylation of the catalyst core, analogous to methylation previously reported in the presence of methyl esters.¹⁷⁶ ¹H–³¹P correlation spectra (HMBC) revealed a cross-peak between

the phosphorus nucleus of the decomposition product and a proton doublet at 2.83 ppm, suggesting methylation of the catalyst which most likely arises from the protonation of MTBE by the catalyst.

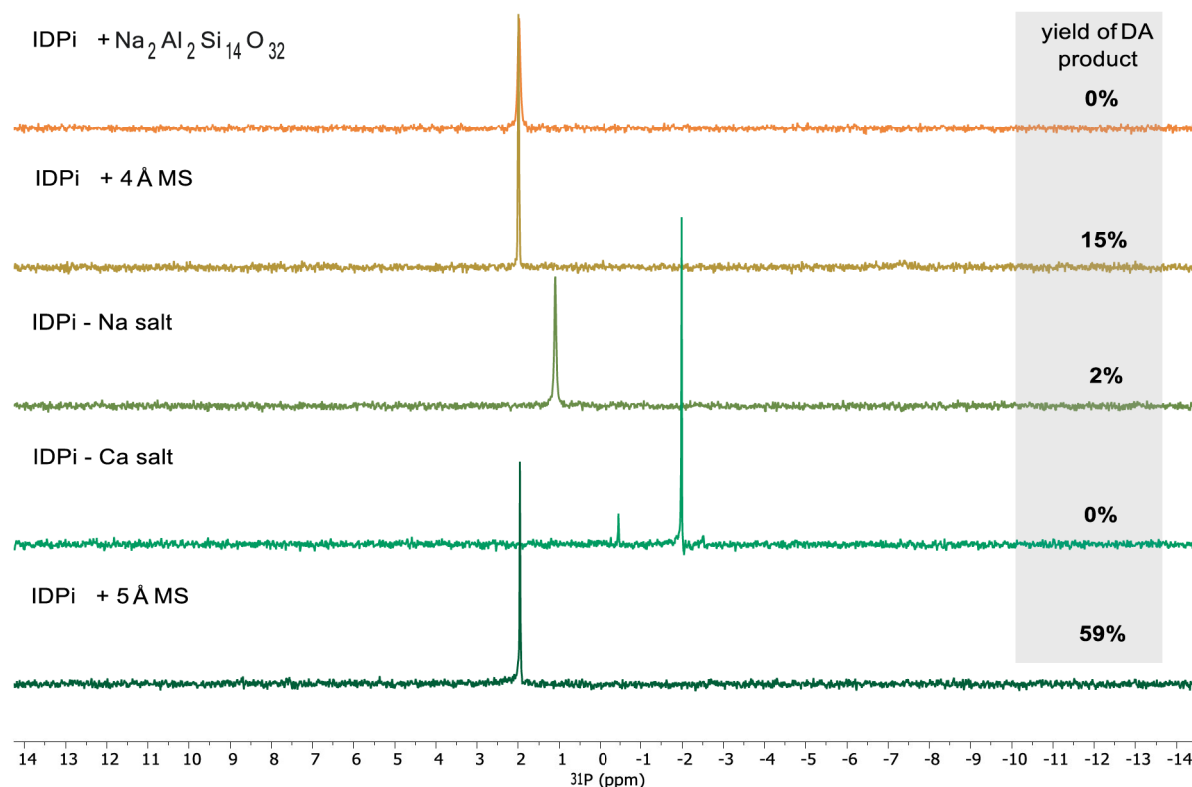


Figure 37. ³¹P NMR spectra and reactivity of IDPi **4.3e** or its derivatives in the presence of different additives.

To further elucidate the nature of the new species, we independently synthesized sodium and calcium IDPi salts via reaction of the acidified IDPi **4.3e** with the corresponding carbonates. The ³¹P NMR spectra of these salts (Figure 37) revealed characteristic chemical shifts: the calcium salt displayed a deshielded signal relative to the parent IDPi, whereas the sodium salt exhibited a shift nearly identical to that of the new species detected in the presence of 5 Å MS. Importantly, neither of the isolated salts was catalytically active under the standard Diels–Alder reaction conditions, both in the presence and absence of the additional portion of 5 Å MS, suggesting that the Brønsted acid form of the catalyst is essential for the catalytic activity. Furthermore, identical ³¹P chemical shifts were observed when 4 Å MS (which also contain Na⁺) or sodium aluminosilicate, a non-zeolite structured analogue of 4 Å MS, were employed. The combination of the IDPi with 4 Å MS afforded the target cycloadduct in 15% yield. However, in the case of sodium aluminosilicate additive which does not exhibit desiccant properties, the Diels–Alder product was not formed, both in the absence and presence of 5 Å MS. Collectively, these results identify the newly observed species as the sodium salt of the

IDPi catalyst **4.3e** and highlight the importance of the molecular sieves' drying properties in maintaining catalyst performance.

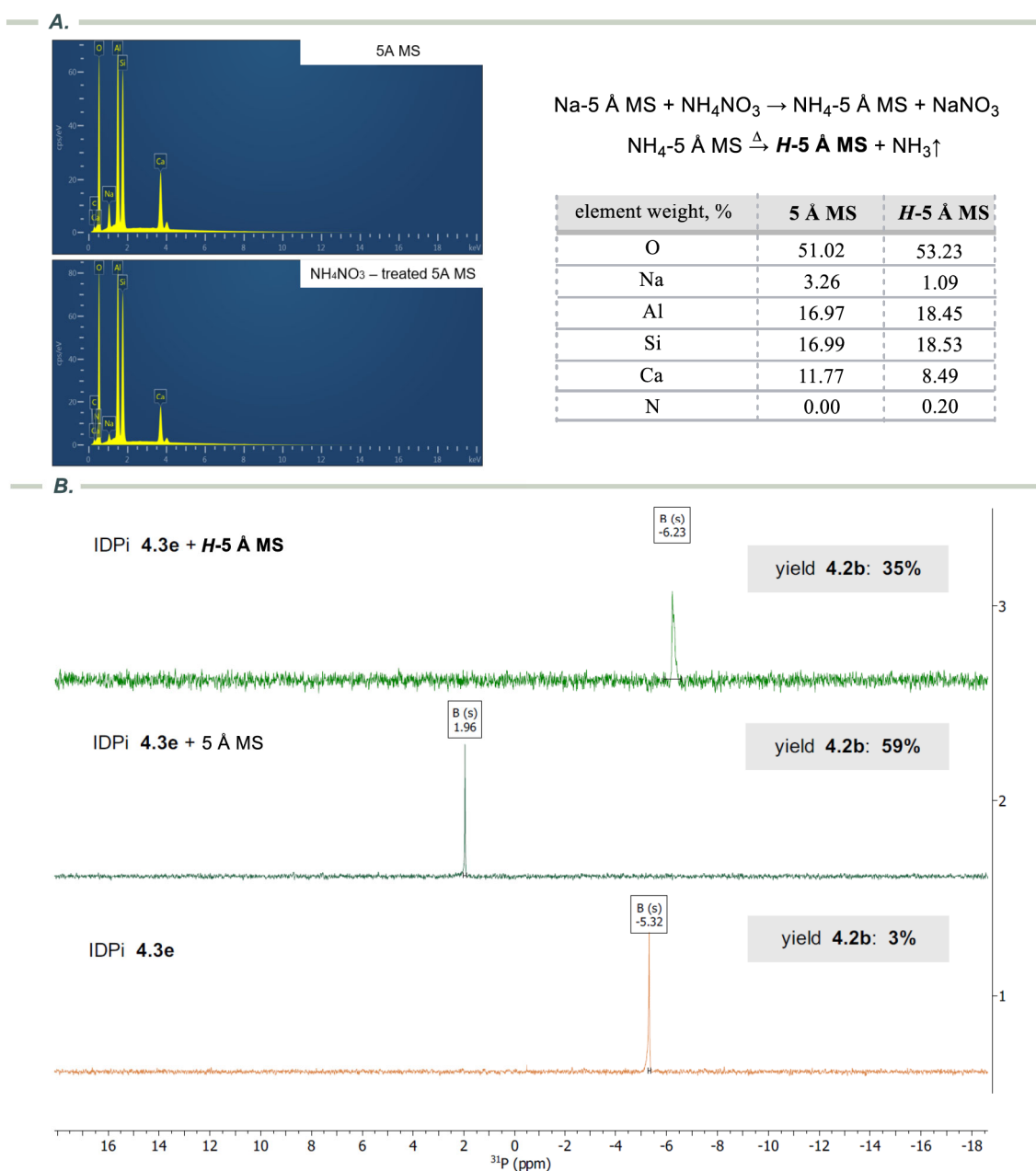


Figure 38. A. Preparation and characterization of H-5 Å MS by EDS and elemental mapping; B. ^{31}P NMR spectra and reactivity of IDPi **4.3e** in the presence of 5 Å MS and H-5 Å MS.

Since the detected sodium IDPi salt was demonstrated to convert back to the protonated IDPi form under reaction conditions, and neither of the pure salts produced Diels–Alder product, we hypothesized that the reaction relies on Brønsted acid catalysis, with MS serving as drying agents and preventing the IDPi catalyst from decomposition.

To test this hypothesis, we prepared molecular sieves depleted of sodium cations by performing ion exchange between 5 Å MS and NH_4NO_3 solution followed by calcination,

according to the method reported by Meng et al.¹⁷⁷ This treatment replaces Na^+ with NH_4^+ , which upon calcination releases NH_3 , leaving behind the H-form (*H*-5 Å MS) of MS. This modified material retains the zeolite crystal structure and, therefore, can function as a molecular sieve but lacks Na^+ , thus preventing formation of the sodium salt of the **4.3e**. The success of the performed MS modification was confirmed by energy-dispersive X-ray spectroscopy (EDS) and elemental mapping (Figure 38A).

The absence of the characteristic sodium IDPi salt signal in the ^{31}P NMR spectrum of the IDPi and *H*-5 Å MS mixture (Figure 38B) further corroborated successful ion exchange in the prepared MS. Even though the formation of the new salt species was not observed in this case, the proton exchange between *H*-5 Å MS and IDPi cannot be fully excluded. Interestingly, the ^{31}P NMR peak of IDPi in the presence of H-substituted MS was slightly shifted upfield (from -5.32 ppm to -6.23 ppm), consistent with the removal of water or solvent molecules from the catalyst cavity. In accordance with our hypothesis, under these conditions product formation was still observed in somewhat reduced yield (35%), but with the preserved enantioselectivity (99:1 e.r.). This result confirms that the Brønsted-acidic protonated form of IDPi **4.3e** plays an essential role in the catalysis of the reaction. At the same time, it underlines that superior desiccant properties of the MS is required for maintaining the catalytic activity, as also evidenced by the unsuccessful outcomes obtained with alternative drying agents.

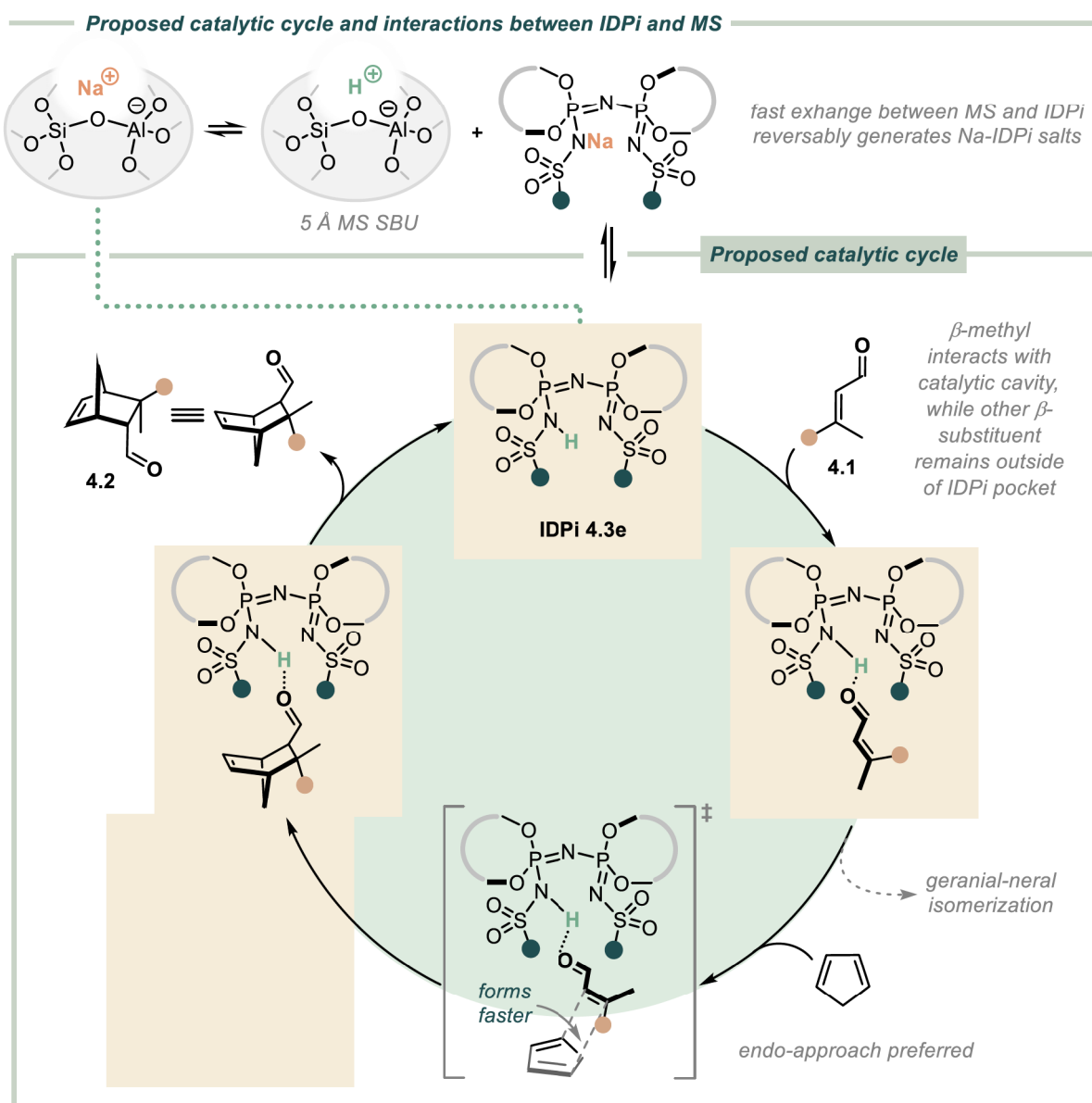
In summary, these studies demonstrate that MS might play a dual role in the IDPi-catalyzed Diels–Alder reaction. Their primary function is to serve as efficient drying agents and preventing hydrolysis of the IDPi. Simultaneously, the sodium ions present in 5 Å MS can engage in the formation of sodium IDPi salts, acting as “reservoir species” that protect the catalyst from alkylation-induced decomposition in MTBE and potentially moderate Brønsted acidity, preventing undesired acid-catalyzed side reactions of enals.

4.2.6. Proposed Catalytic Cycle and Contribution of Molecular Sieves

The following paragraph will summarize our observations and propose a mechanistic framework that rationalizes both the catalytic and off-cycle events observed during the enantioselective Diels–Alder reaction of β,β -disubstituted enals (Scheme 4).

At the initial stage of the reaction procedure, the IDPi catalyst is pre-mixed with molecular sieves in MTBE. In the absence of MS, the catalyst prone to the partial decomposition through hydrolysis by water to *i*IDP and alkylation by MTBE. The latter most likely proceeds through the formation of an ion pair which, upon collapse, leads to *O*- or

N-methylation of the IDPi core and liberates the *tert*-butanol. The latter may subsequently participate in the undesired *E/Z*-isomerization of the enals, and particularly of geranial **4.1b-(E)** to neral **4.1b-(Z)**. The decomposition/alkylation pathways are suppressed in the presence of molecular sieves.



Scheme 4. Proposed catalytic cycle and off-cycle processes. SBU = secondary building unit.

Furthermore, in the presence of MS exchange between the IDPi and Na^+ ions contained in the zeolite lattice leads to the formation of the sodium salt of IDPi, which exists in equilibrium with its protonated (Brønsted acidic) form. A series of control experiments, including the direct use of the isolated sodium salt in the Diels–Alder reaction and reactions performed with H-substituted 5 Å MS, in which the salt formation was not detected, confirmed that this salt is catalytically inactive. The reaction therefore proceeds via Brønsted acid

catalysis. Although the IDPi sodium salt does not appear to be directly involved in the catalytic cycle, it may serve as a dormant reservoir of the active catalyst, preventing deleterious decomposition/alkylation pathways and faster acid-catalyzed side-reactions of enals.

In the subsequent stage of the procedure, the substrates are introduced sequentially: first cyclopentadiene and then the enal, to minimize the contact time between the dienophile and the catalyst in the absence of the reactive diene. The Brønsted acid form of the IDPi is believed to activate the enal by transient protonation or strong hydrogen bonding to the carbonyl oxygen as the most nucleophilic position. The coordination geometry of the enal is proposed to orient the β -methyl substituent toward the chiral pocket of the catalyst while positioning the other β -substituent outside the cavity. The experimentally observed invariance of stereoselectivity with respect to the size of the alkyl β -substituents, together with the strict requirement for one of the β -substituents to be a methyl group, supports this binding model. This arrangement also favors an *endo*-approach of the cyclopentadiene.

The pronounced polarization of the dienophile, arising both from the electron-withdrawing carbonyl group and its activation by Brønsted acid **4.3e**, leads to a highly asynchronous but concerted bond-forming process, reflected in the observation of substantial KIE. Finally, the cycloaddition product is released and the catalyst is liberated, closing the proposed catalytic cycle.

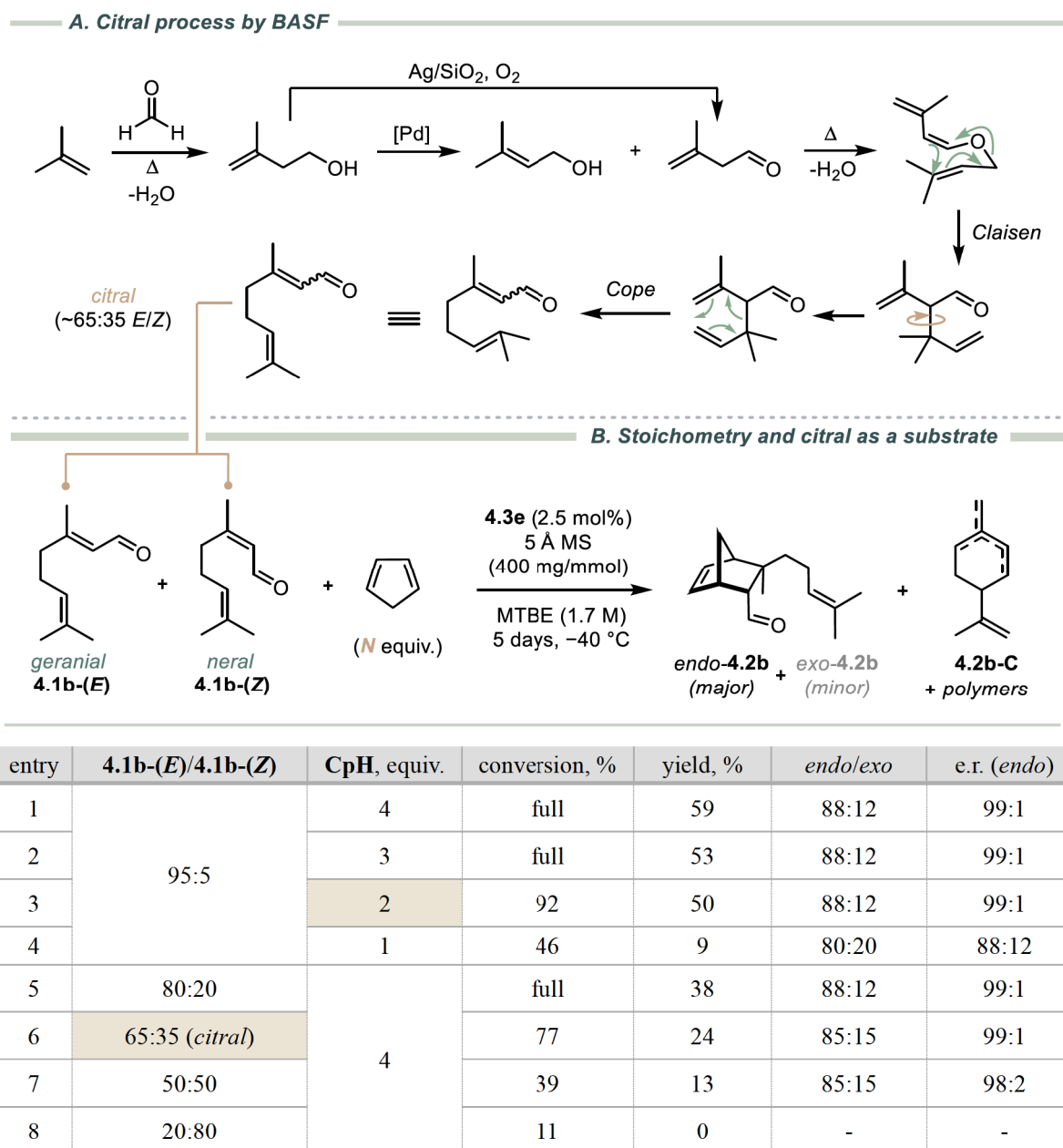
4.3. Total Synthesis of (–)-(Z)- β -Santalol

4.3.1. Upscaling of the Diels-Alder Reaction of Geranial

We next focused on further optimization of the Diels-Alder reaction between geranial **4.1b** and cyclopentadiene with the goal of enhancing its overall efficiency on a larger scale setup.

Previous screening results demonstrated that MTBE serves as the optimal reaction solvent, and that low temperature (–40 °C) is crucial for maintaining both desired reactivity and stereoselectivity. Conveniently, the reaction performs best under highly concentrated conditions (1.7 M), minimizing solvent use. To assess whether the transformation could be carried out under milder conditions, a range of ethereal solvents (cyclopentyl methyl ether, (*t*-Bu)₂O, (*i*-Pr)₂O, THF, 1,4-dioxane, and diglyme) as well as binary mixtures of MTBE and DCM (ratios from 1:5 to 5:1) were evaluated. However, all tested solvents and solvent mixtures provided significantly lower yields or no product formation at all compared to the benchmark reactions

in Et₂O and MTBE.



conversions, yields and *endo/exo* ratios were determined in crude NMR using CH₂Br₂ as internal standard; e.r. determined by chiral GC

Figure 39. A. Citral process; B. Optimization of the reaction stoichiometry and use of citral as a substrate.

We then turned our attention to the reaction stoichiometry. In the initial optimization and substrate scope studies, four equivalents of cyclopentadiene were employed, consistent with a common practice in the Diels–Alder reactions. Although cyclopentadiene is inexpensive, readily available, and easily recoverable, we sought to reduce its loading. Gratifyingly, the reaction proceeded almost identically when only two equivalents of cyclopentadiene were used (Figure 39B, entry 3). Further reducing the ratio to 1:1 (entry 4), however, resulted in a marked decrease in both yield and overall conversion.

While relatively inexpensive, molecular sieves still contribute to the operational cost of the reaction. As discussed previously, the MS loading could be safely decreased from the standard 400 mg/mmol to 250 mg/mmol without a significant reduction in yield or enantioselectivity.

From a practical standpoint, it is worth noting that although geranial **4.1b-(E)** is a bulk chemical, it is not widely available from the common laboratory suppliers due to its thermal instability. It can, however, be readily synthesized from commercially available geraniol, whereas on the industrial scale it is typically obtained by dynamic distillation¹⁷⁸ of citral. Citral itself is an inexpensive bulk material (500 mL/175 € as of October 2025 at Sigma-Aldrich), consisting of two geometric isomers: *cis*-citral (neral, *Z*-isomer, **4.1b-(Z)**) and *trans*-citral (geranial, *E*-isomer, **4.1b-(E)**) in a typical 65:35 *E/Z* ratio. Industrially, citral is produced from isobutene and formaldehyde through an efficient carbonyl-ene/Prins reaction sequence to give isoprenol (3-methyl-3-buten-1-ol), which is subsequently isomerized to prenol or oxidized to isoprenal. Upon heating, these intermediates undergo two consecutive [3,3]-sigmatropic rearrangements (Claisen and Cope), delivering citral (Figure 39A).¹⁷⁹

In our work, we were fortunate to receive pure samples of both geranial **4.1b-(E)** and neral **4.1b-(Z)** directly from BASF. Screening various mixtures of geranial and neral under the optimized reaction conditions revealed that the geranial **4.1b-(E)** component undergoes the desired Diels–Alder cycloaddition without loss in enantioselectivity, albeit with proportionally reduced yield as the fraction of **4.1b-(E)** in the mixture decreases (Figure 39B, entries 5–8). No corresponding Diels–Alder product from **4.1b-(Z)** was detected; instead, neral underwent rapid cyclization followed by decomposition to **4.2b-C**, consistent with previous observations in the presence of IDPi catalysts¹⁵³ and montmorillonite clay or zeolite- β .¹⁶² Despite the lower yield (Figure 39B, entry 6), these results suggest that commercially available citral mixture can be used in place of pure geranial to obtain the target enantiopure intermediate **4.2b**.

With the further tailored conditions in hands, we proceeded with the reaction upscaling. Upscaling reactions were performed in standard flame-dried round-bottom flasks flushed with dry argon after addition of the solid materials. No special measures were taken to sustain inert atmosphere afterwards. Our first attempt was performed with 10.0 mmol of **4.1b-(E)**, 2.5 equivalents of cyclopentadiene, 250 mg/mmol loading of 5 Å MS, and with the decreased catalyst loading of 1.5 mol%. To our delight, these conditions delivered very good yield (71%) of the desired product without loss in enantioselectivity (99:1 e.r.) (Figure 40).

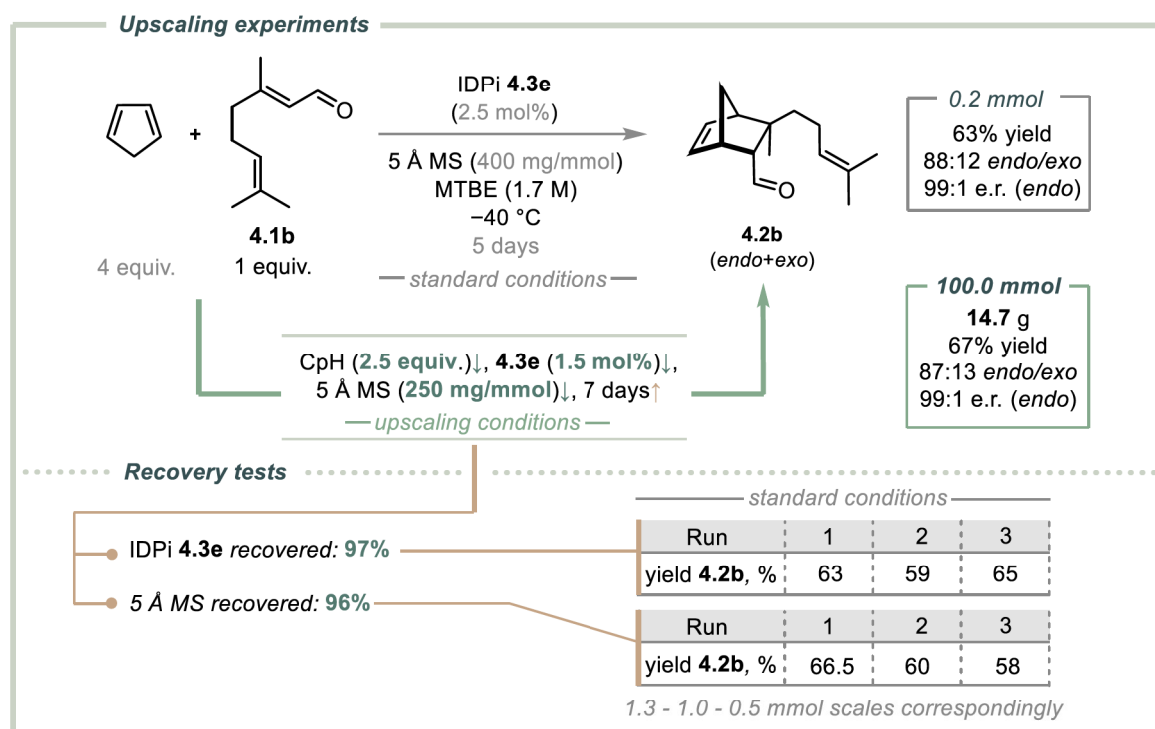


Figure 40. Upscaling of the Diels-Alder reaction and recovery tests for the catalyst and MS.

Without delay we moved on to a bigger scale of 100.0 mmol. In this case however after standard reaction time of five days, the conversion of geranial **4.1b**-(*E*) reached only 75%, so the reaction was left for a prolonged time (seven days). The product **4.2b** was then isolated in 67% yield (14.7 g) with 87:13 *endo/exo* ratio and 99:1 e.r. (*endo*).

This run was also used for the evaluation of recoverability of the catalyst **4.3e** and MS. MS were removed from the reaction mixture by filtration through a fritted glass filter, dried at 100 °C for 2 days in a laboratory oven and then activated at 130 °C for 4 days in high vacuum. The catalyst was recovered from the reaction mixture by column chromatography (as mixed salt), passed through a Dowex column for acidification and dried at 40 °C for 2 days, delivering 97% of recovered IDPi **4.3e**. The recovered materials were then tested on smaller scales (1.3–1.0–0.5 mmol) in the standard screening conditions, using for every consecutive run the material recovered after the previous run. The recovered IDPi **4.3e** demonstrated identical reactivity to the authentic sample across all runs. The use of the recovered MS however resulted in gradual decrease of the consecutive reactions yield (Figure 40). This phenomenon might be attributed to the slow degradation of the zeolite structure of the MS due to the repeated influence of strongly acidic IDPi and solvent, leading to the worsening of the drying properties.

Having a significant amount of the enantiopure intermediate in our hands, we proceeded with investigating further synthetic steps towards (–)-(*Z*)-β-santalol **2.15**.

4.3.2. Total Synthesis of (-)- β -Santalene

Starting from the intermediate **4.2b**, essentially three key transformations should be performed to obtain (-)-(*Z*)- β -santalol: reduction of the bicyclo[2.2.1]heptene core, installation of the exocyclic double bond to furnish (-)- β -santalene **2.16**, and, finally, (*Z*)-selective allylic oxidation of the side chain.

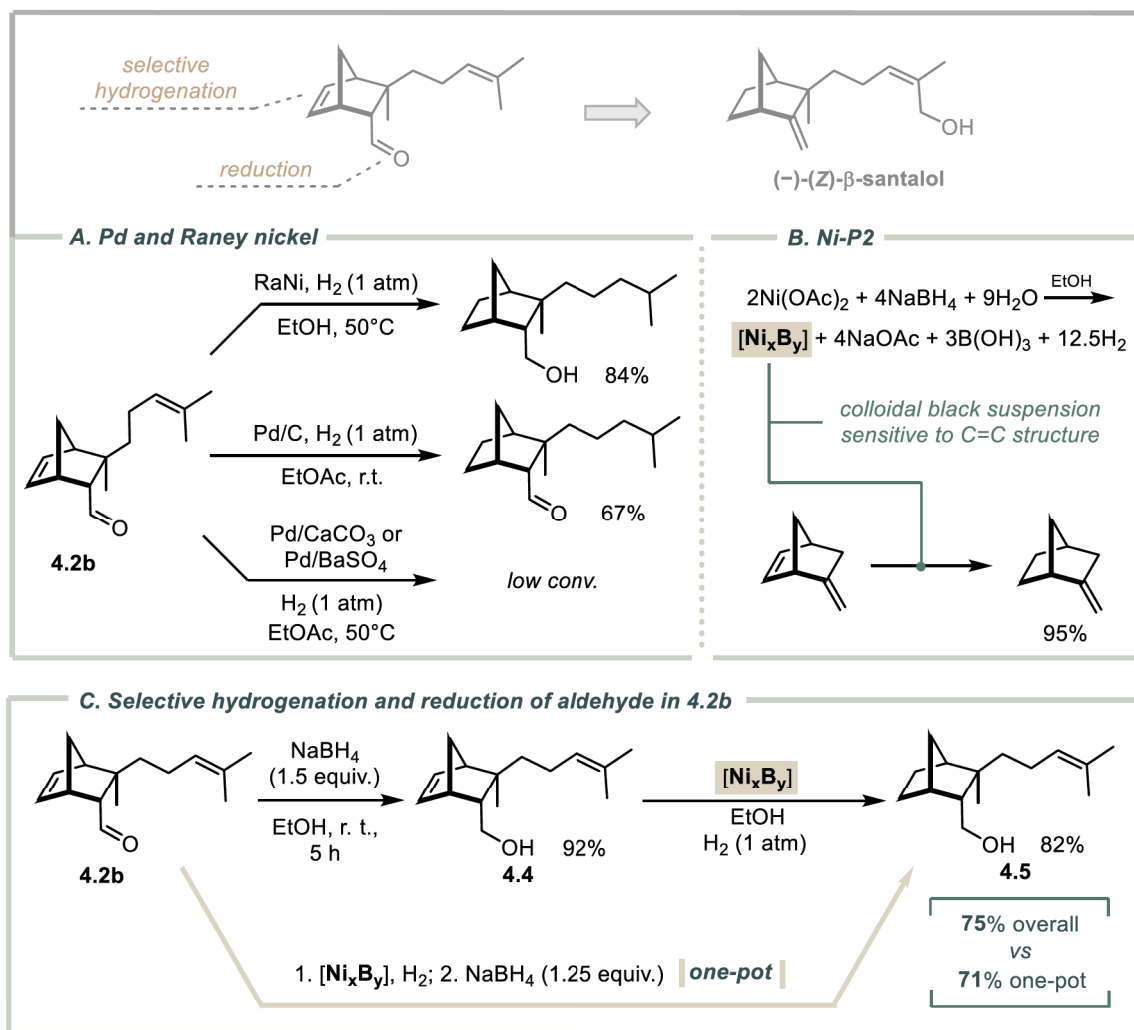


Figure 41. (-)-(*Z*)- β -santalol: selective hydrogenation and reduction. [Ni_xB_y] generated from Ni(OAc)₂·4H₂O (0.2 equiv.), NaBH₄ (0.2 equiv.) and NaOH (0.008 equiv.).

The similar synthetic sequence of reduction/hydrogenation and elimination was employed by Fehr¹⁴³ and Solladié¹⁴⁰ on the related more simple substrates. Inspired by a global reduction approach reported by Fehr using Raney nickel (RaNi), we attempted to identify suitable conditions for our substrate **4.2b**, which would be selective towards the internal bicyclic olefin and aldehyde while preserving the double bond of the side chain. In our hands, Raney nickel delivered the fully hydrogenated alcohol product. Screening of the heterogeneous palladium-based catalysts revealed moderate activity for Pd/C, which led to partial reduction of

the bicyclic double bond while preserving the aldehyde functionality. Other catalysts such as Pd/BaSO₄ and Pd/CaCO₃ proved ineffective under analogous conditions (Figure 41A).

Given the unsatisfactory selectivity of these catalytic hydrogenation routes, we turned our attention to hydride reduction strategies. Reduction of the aldehyde moiety with NaBH₄ proceeded smoothly, affording the corresponding primary alcohol **4.4** in 92% yield after 4 hours.

We now, however, were facing the selective hydrogenation of the endocyclic double bond: a problem which was encountered and addressed by Solladié group using the nickel boride system.¹⁴⁰ We thus turned our attention to this versatile class of hydrogenation catalysts, specifically the Ni-P2 variant first reported by Brown.¹⁸⁰ Nickel borides can be conveniently prepared in situ by reduction of nickel (II) salts (e.g., nickel chloride or acetate) with NaBH₄, forming a fine black colloidal suspension. This material is air-stable and non-pyrophoric, offering practical advantages over Raney nickel. Moreover, nickel boride catalysts are known for their pronounced chemoselectivity, efficiently reducing C=C double bonds while leaving carbonyls and epoxides intact. Depending on the preparation protocol, two forms — Ni-P1 and Ni-P2 — can be obtained, with the latter being notably more selective and more sensitive to steric effects (Figure 41B).^{181–183}

Inspired by the successful application of the Ni-P2 system to a substrate structurally similar to ours, we subjected the alcohol obtained in the previous step to Ni-P2/H₂ hydrogenation conditions. To our satisfaction, the reaction proceeded with the remarkable chemoselectivity toward the desired endocyclic double bond, affording the saturated intermediate **4.5** in 82% yield.

Since both reduction steps in this sequence employ NaBH₄, we were intrigued by the possibility of performing them in a *one-pot* fashion, thereby simplifying the protocol and improving solvent-, time- and energy-efficiency. In our initial attempt, nickel acetate was added directly to the reaction mixture after consumption conversion of the aldehyde, followed by the introduction of hydrogen gas. This approach resulted in a significantly diminished yield of the target alcohol. As discussed previously, nickel boride catalysts are highly sensitive to their mode of preparation, and the uncontrolled residual amount of NaBH₄ in the reaction medium might have compromised catalyst formation and activity. However, switching the reactions order in the one-pot procedure, namely starting with the hydrogenation and following with NaBH₄ reduction, afforded **4.5** in a comparable to the two-step approach yield (71% vs 75%

correspondingly) (Figure 41C).

With the reliable access to alcohol **4.5** secured, our attention turned to exploring efficient elimination strategies to install the exocyclic double bond of (–)- β -santalene **2.16**. The first requirement in this transformation was conversion of the hydroxyl group into a suitable leaving group, followed by elimination to form the alkene. Two possible approaches were considered: E2-type elimination in basic conditions and thermal (pyrolytic) concerted elimination of easily available esters and carbonates. We excluded other commonly employed laboratory methods, such as Grieco¹⁸⁴ or Chugaev elimination¹⁸⁵ due to their limited scalability and poor economic practicality.

Conversion to the mesylate followed by elimination was previously reported by Solladié, though the transformation required harsh conditions and the use of hexamethylphosphoric triamide (HMPA), resulting in modest yields. In contrast, Fehr demonstrated an efficient elimination of the corresponding carbonate on a structurally related substrate. Thus, for our studies we selected several representative leaving groups: mesylate, tosylate, acetate, and carbonate (Figure 42A). All the derivatives were obtained in high yields using the corresponding chlorides and acylchloride reagents and used in the next step without purification.

The true challenge emerged at the elimination stage. The base-induced elimination, expected to proceed via an E2-type mechanism, is severely complicated by the steric hindrance arising from the rigid bicyclic framework of the substrate, particularly the bridgehead hydrogens and bulky side-chain. Moreover, formation of the exocyclic double bond is intrinsically disfavored, further reducing the reaction efficiency. Indeed, a significant portion of the literature addressing similar transformations relies on in situ formation of alkyl iodides as superior leaving groups to facilitate elimination.^{186–188}

We first evaluated direct base-promoted elimination from both mesylate **4.6** and tosylate intermediates using a range of strong bases (Figure 42B). Under the conditions employing potassium *tert*-butoxide (*t*-BuOK), only minimal conversion was observed, while NaH afforded trace amounts of the desired alkene accompanied by a complex reaction mixture. The use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) provided slightly improved results, giving 13% yield of the elimination product after prolonged heating at 80 °C.

Since the basic elimination approach proved to be challenging, we turned our attention to more common procedure for such elimination utilizing DBU and NaI first reported by

Sato,¹⁸⁹ via in situ formation of the intermediate iodide. Gratifyingly, application of these conditions to the mesylate **4.6** delivered the target (–)- β -santalene **2.16** in 67% yield, with the remaining material consisting predominantly of unreacted starting compound.

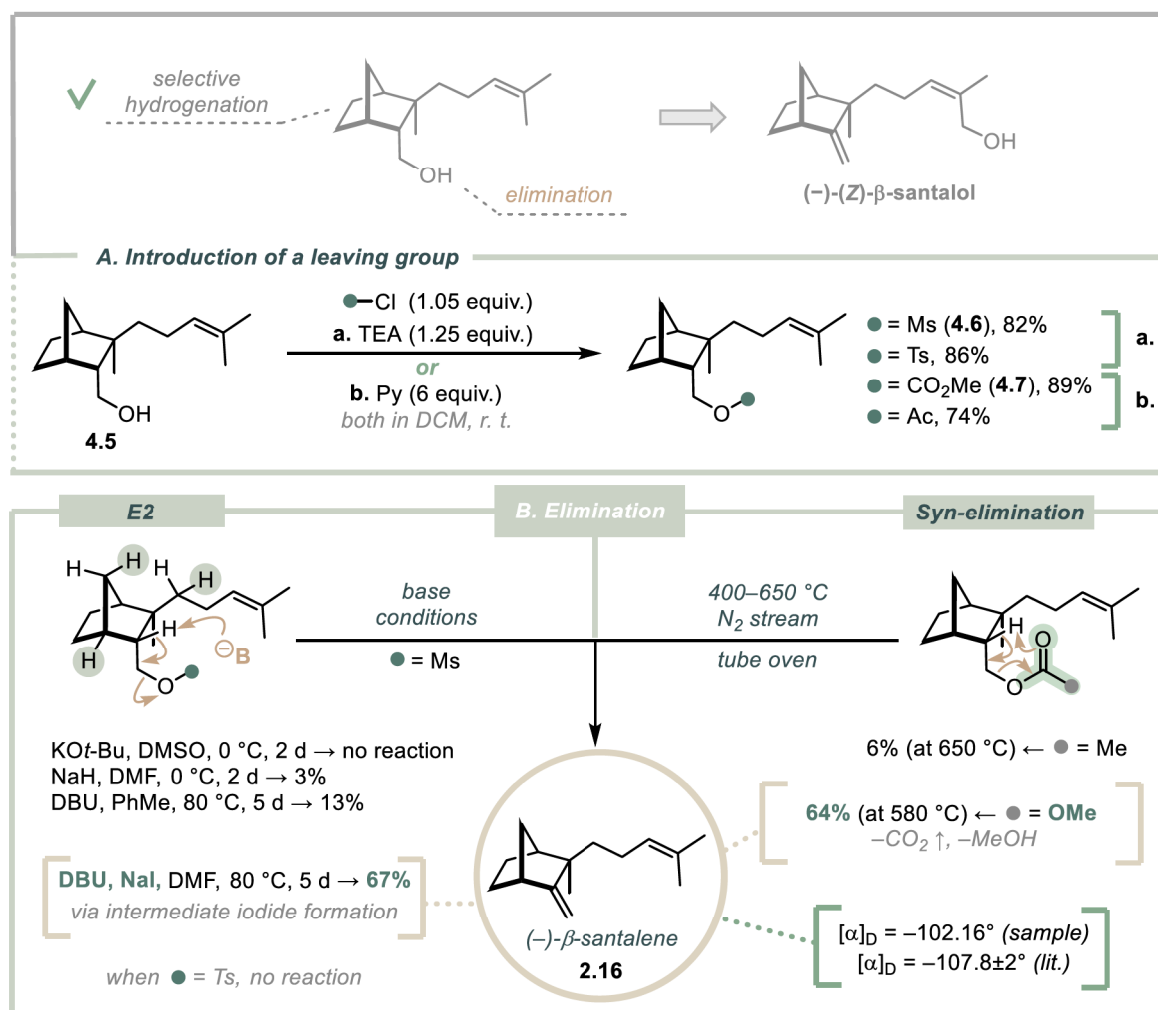


Figure 42. Attempted strategies towards the formation of *exo*-double bond.

Another appealing opportunity, particularly from an economic and practical standpoint, is the possibility of performing the elimination under pyrolytic conditions (Figure 42B). Ester pyrolysis is generally believed to proceed through a six-membered cyclic transition state as a *syn*-elimination. Although steric effects still play a role in these reactions,^{190,191} their influence is considerably reduced compared to E2 pathway, since ester pyrolysis is typically an intramolecular process. We therefore explored the thermal elimination of the readily available acetate and carbonate **4.7**. The acetate proved remarkably stable, with only traces of the elimination product observed even at 650 °C. In contrast, the carbonate was converting to the desired **2.16** already at 580 °C. This pronounced difference could stem from the fact that pyrolysis of carbonates releases gaseous CO₂ and MeOH, thus shifting the equilibrium toward

the product formation and facilitating the reaction compared to the release of AcOH in the case of acetates.

Under these optimized conditions, (–)-β-santalene **2.16** was obtained in 64% (87% based on the recovered starting material) yield after purification by passing the crude reaction mixture through a short silica gel plug: elution with pure pentane afforded the product, while the subsequent 3:1 pentane:MTBE wash recovered unreacted starting material (27%). Both isolated samples of (–)-β-santalene displayed spectroscopic and analytical data consistent with those reported in the literature.^{134,192–194}

4.3.3. Allylic Oxidation of (–)-β-Santalene to (–)-(Z)-β-Santalol

We next turned our attention to the final and the most demanding challenge of this total synthesis—the introduction of Z-allylic alcohol moiety. As discussed in Chapter 2.3.2, this particular transformation has been a major bottleneck in previous synthetic approaches, frequently dictating retrosynthetic disconnections and causing many promising strategies to fail at this stage.

At a first glance, allylic oxidation represents a well-developed area of organic synthesis, supported by a broad arsenal of reagents and methodologies, which found successful application in the synthesis of natural products.¹⁹⁵ Nevertheless, several persistent challenges continue to limit its applicability, including moderate yields, poor chemo- and stereoselectivity, and the tendency toward overoxidation. Among the available methods, the most reliable and frequently applied approach for the selective oxidation of alkenes to allylic alcohols involves selenium-based reagents, particularly selenium dioxide (SeO₂) in the Riley oxidation,¹⁹⁶ typically used in combination with oxidants such as *tert*-butyl hydroperoxide (TBHP) or diphenyl diselenide (Ph₂Se₂) with iodobenzene diacetate (PhI(OAc)₂). Other commonly employed strategies rely on chromium (VI) oxidants including: CrO₃, chromium trioxide–3,5-dimethylpyrazole complex, chromate salts, and pyridinium chlorochromate (PCC)/pyridinium dichromate (PDC), or transition-metal-catalyzed oxidations using TBHP as a terminal oxidant. However, the oxidation with the metal-based reagents most often leads to carbonyl products, thus requiring an additional reduction step to access the corresponding allylic alcohols, and typically exhibits the highest efficiency in the oxidation to cyclic enones (Figure 43A).¹⁹⁷

A particularly attractive from the atom-economic standpoint approach is oxidation with singlet oxygen generated under irradiation in the presence of a photosensitizer (Schenck ene reaction). While conceptually appealing, this reaction is difficult to adapt to complex substrates

with multiple reactive sites and it usually yields a mixture of products.^{198,199}

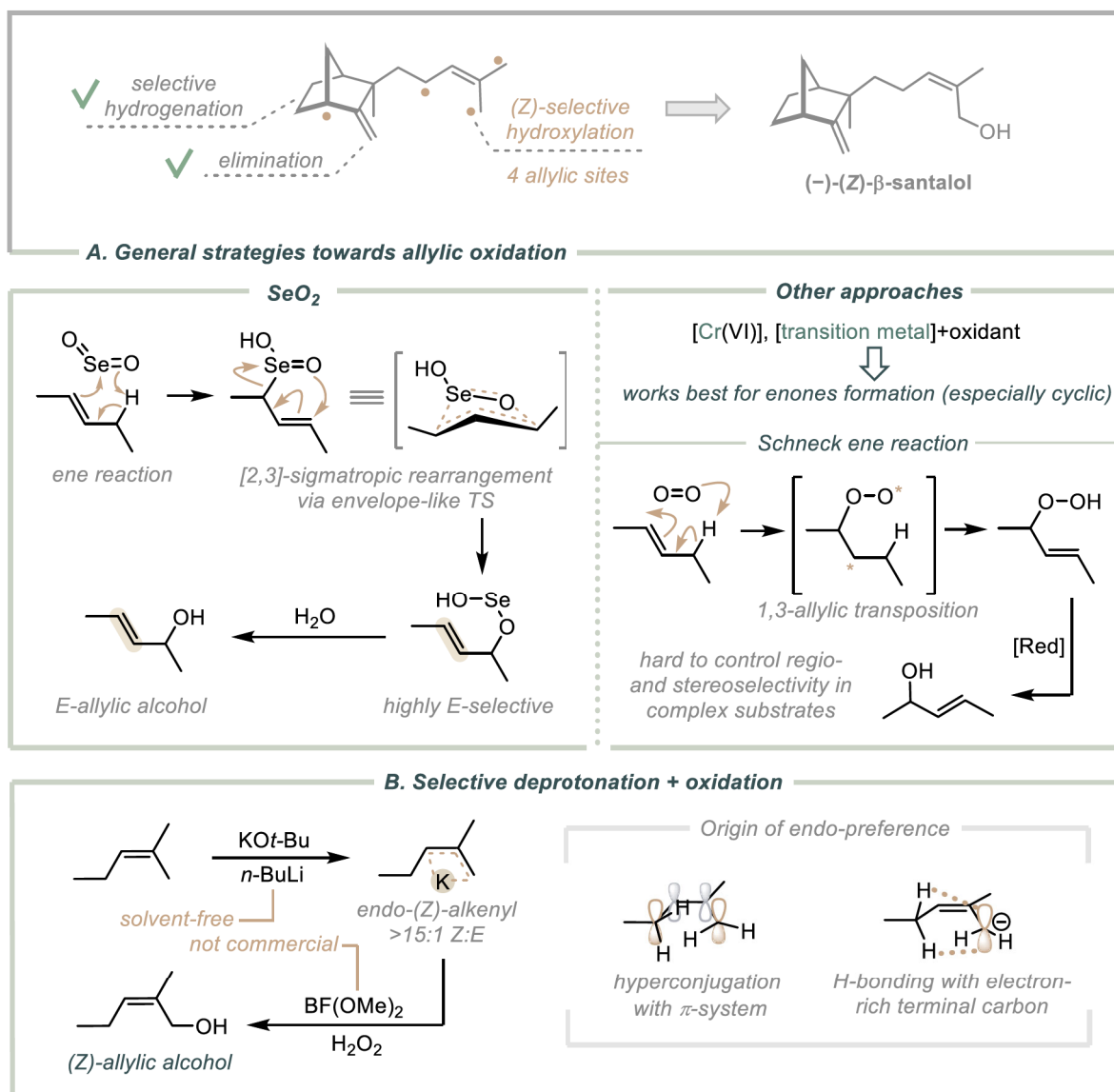
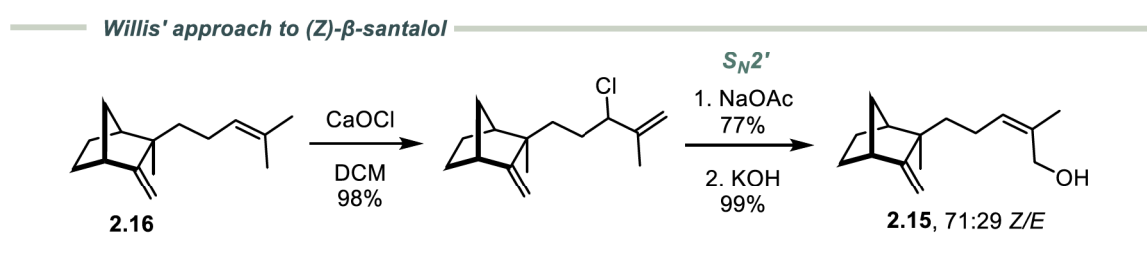


Figure 43. Possible approaches towards introduction of allylic alcohol moiety. *Radical or ionic charge.

Considering the limitations of metal-based oxidants and singlet oxygen, the selenium-based oxidants seemed to be the most promising option for our target transformation, motivating us to take a closer look to these reagents from a stereochemical point of view. In general, formation of *E*-substituted double bonds is thermodynamically favored due to the reduced steric strain. In SeO₂-mediated oxidations this preference is further reinforced by the reaction mechanism, which proceeds via an ene-type process followed by a [2,3]-sigmatropic rearrangement, occurring in an envelope-like transition state.^{200,201} This fact together with four potentially oxidizable allylic positions in (–)-β-santalene, renders SeO₂ oxidation unsuitable for our goals.

It's noteworthy that an alternative halogenation–substitution approach was previously developed by Willis at Fritzsche Dodge & Olcott Inc., who achieved allylic oxidation of β -santalene via CaOCl -mediated chlorination followed by $\text{S}_{\text{N}}2'$ displacement with a carboxylate nucleophile, ultimately affording (*Z*)- β -santalol in a 71:29 (*Z/E*) ratio after deprotection (Scheme 5).²⁰² A similar three-step protocol employing NaOCl was later patented by Isobionics, yielding β -santalol in a 65:35 (*Z/E*) ratio while avoiding the use of dry ice.²⁰³ Although both routes succeed in generating the desired allylic alcohol, they require multiple steps, produce considerable waste, and still fail to provide high stereoselectivity, motivating the search for a more direct and efficient solution.



Scheme 5. Three-step chlorination- $\text{S}_{\text{N}}2'$ approach to (*Z*)- β -santalol.

A particularly elegant and conceptually distinct strategy was proposed by Schlosser, utilizing the superbasic LICKOR system.^{204,205} During systematic studies of alkenyl metallated compounds generated via this protocol, Schlosser demonstrated that 2-alkenyl organometallics preferentially adopt the (*Z*)/*endo*-conformation,²⁰⁶ an effect rationalized by the intramolecular hydrogen bonding between the alkyl substituents and the electron-rich terminal carbon, as well as stabilizing hyperconjugative π -interactions.²⁰⁷ These intermediates can be efficiently trapped and oxidized to the corresponding allylic alcohols through either borylation–oxidation sequences or direct peroxide oxidation (Figure 43B). This methodology was later applied to the total syntheses of *epi*- β -santalol²⁰⁸ and α -santalol,²⁰⁹ both featuring the characteristic isoprenyl side chain oxidation with excellent *Z*-selectivity — no formation of the *E*-isomer was detected.

Intrigued by the potential of this approach and its demonstrated selectivity, we sought to adapt the Schlosser strategy for our synthetic route, aiming to render the process more sustainable and operationally simple. The main challenges associated with this method, are the preparation and handling of solvent-free *n*-BuLi and the oxidation step, which requires non-commercial and unstable fluorodimethoxyborane $\text{BF}(\text{OMe})_2$. We were pleased to find the report by Clanton,²¹⁰ which described an alternative superbasic system that eliminates the need for the solvent-free *n*-BuLi and non-commercial borane. In this system, potassium tetramethylpiperidide (KTMP) is generated in situ and used in combination with

triisopropoxyborane, enabling a highly region- and *Z*-selective conversion of alkenes to the corresponding allylic alcohols (Figure 44).

Encouraged by these findings, we applied the Clanton's procedure to our β -santalene substrate. Under the standard conditions reported in the original work, the reaction afforded (–)-(*Z*)- β -santalol in 27% yield with good *Z/E* selectivity (90:10 *Z/E*), while approximately 50% of the starting material was recovered. Subsequent optimization of reaction timing and reagent stoichiometry improved the yield to 48% (65% based on the recovered starting material), while maintaining the excellent stereoselectivity (97:3 *Z/E*). The NMR spectra and analytical data of the obtained (–)-(*Z*)- β -santalol were consistent with the reported literature data, confirming the identity and purity of the product. The isolated compound exhibited the characteristic sandalwood oil scent as well.

In an attempt to streamline the overall transformation, we explored the possibility of performing direct oxidation with TBHP or hydrogen peroxide, bypassing the borylation step. However, these conditions failed to yield the desired allylic alcohol.

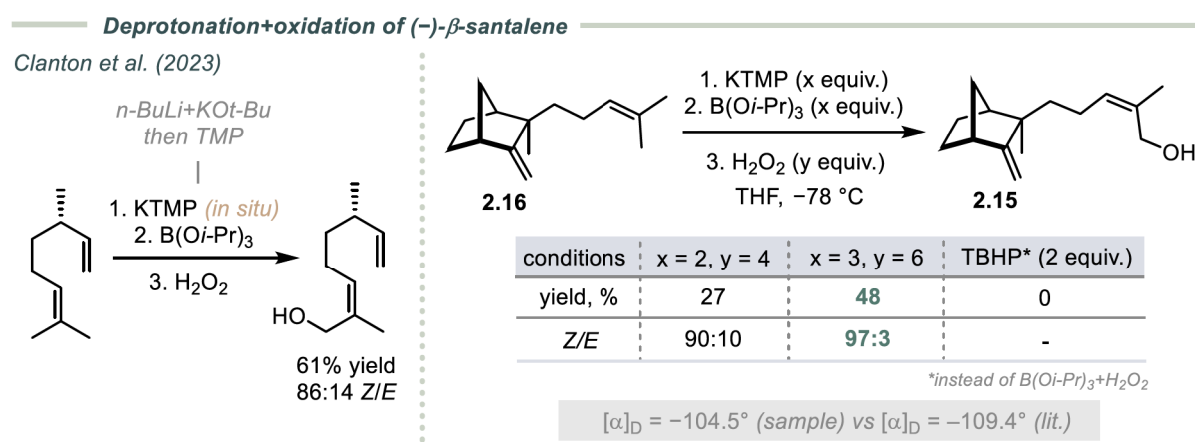


Figure 44. Allylic oxidation of (–)- β -santalene.

Overall, our enantioselective synthesis of (–)-(*Z*)- β -santalol requires just five steps and yields the target compound in 19% overall yield with excellent enantiomeric purity and a high *Z/E* ratio of the allylic alcohol. Importantly, the route relies exclusively on commercially available reagents, most of which are inexpensive bulk chemicals, with the exception of the chiral IDPi catalyst.

Across all stages of the process, only three chromatographic purifications were required: two rapid flash separations and one catalyst-recovery purification following the Diels–Alder step. The procedure employs low-toxicity, low-boiling solvents (MTBE, THF, EtOH), and

requires temperatures below 0 °C at just two steps (Figure 45). Taken together, this work establishes a concise, enantioselective, and operationally practical synthesis of (–)-(Z)-β-santalol, showcasing the synthetic potential of the developed organocatalytic Diels–Alder reaction.

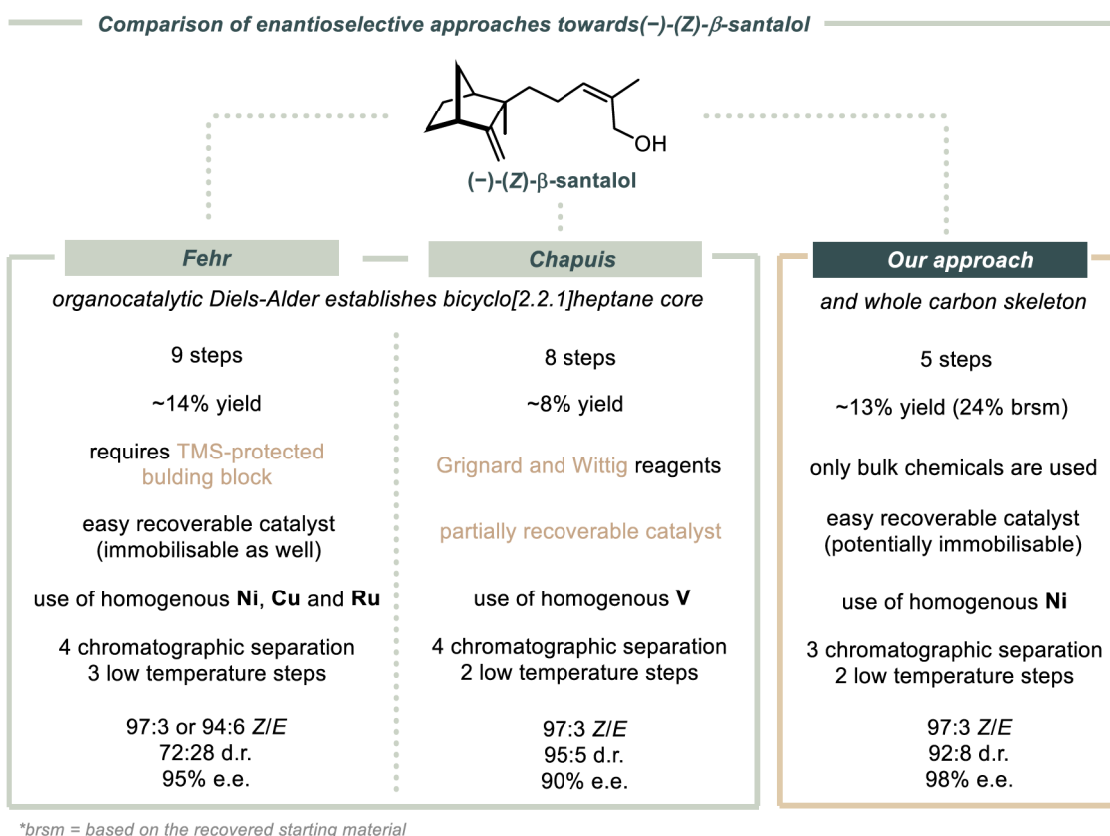


Figure 45. Comparison of the latest enantioselective approaches towards (–)-(Z)-β-santalol.

5. Summary

Considering the long and distinguished history of the Diels–Alder cycloaddition, new advancements in this field are rather final strokes on the grand picture of the reaction's methodology. Yet, such refinements remain of great importance, particularly when they result in a valuable synthetic application.

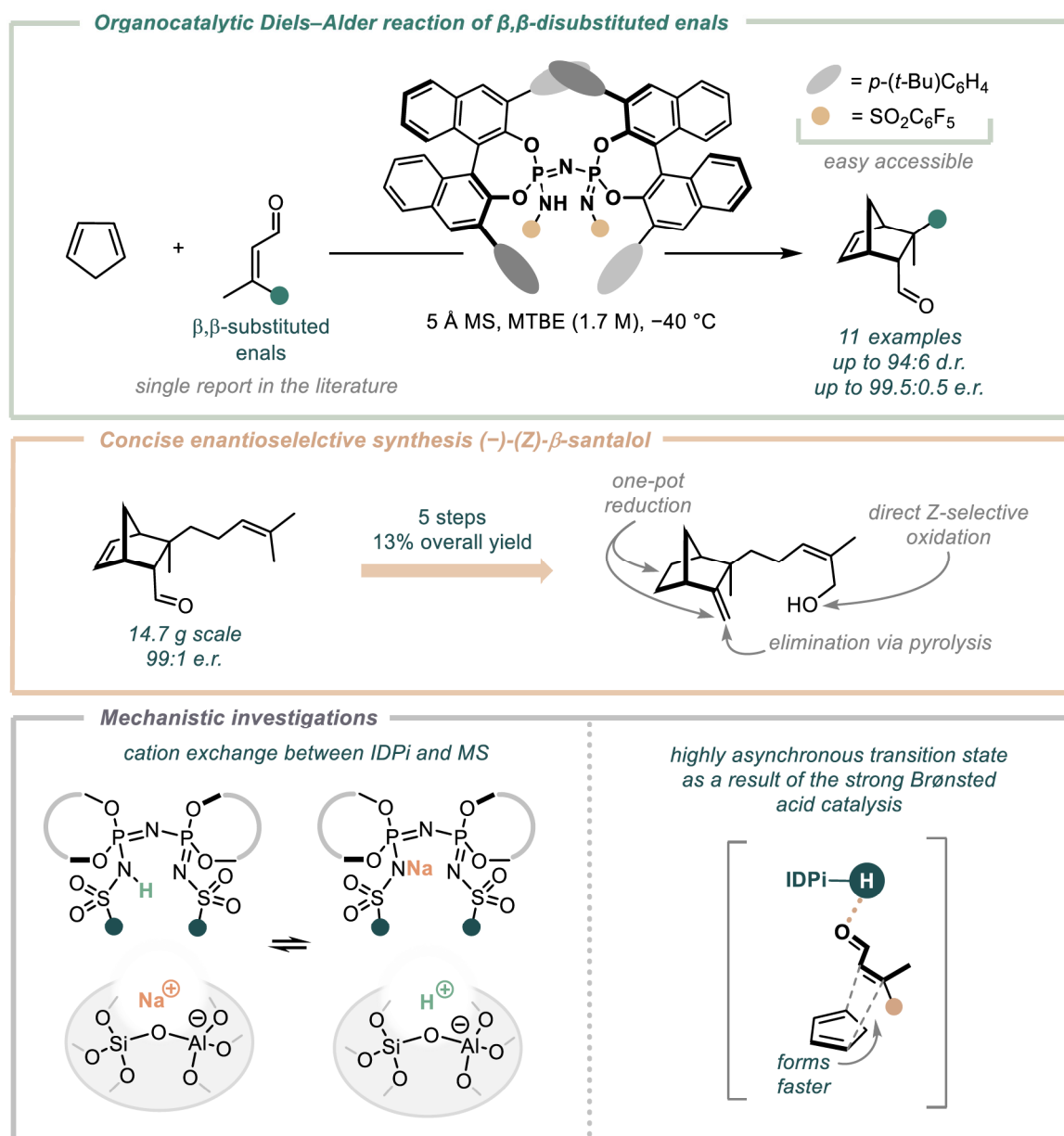


Figure 46. Key results of this work.

One of these enduring challenges lies in the enantioselective Diels–Alder reaction of β,β -disubstituted enals, a substrate class that combines high steric demand with in intrinsic lability, rendering them exceptionally poor dienophiles. Developing a catalytic system capable of overcoming these limitations would enable a direct and efficient access to complex chiral,

natural-product-like scaffolds from simple and inexpensive precursors.

Inspired by earlier works from our group and the versatility of IDPi catalysts, we set out to close the final gap in the reactivity landscape of enals. To our delight, we were able to identify an operationally simple and robust catalytic system capable of involving a variety of these challenging substrates in the target Diels-Alder reaction to yield the complex bicyclic products with consistently good yields and high stereoselectivity. The synthetic utility of the transformation is further reflected in the straightforward scalability and compatibility with *E/Z*-enal mixtures. We thus report the first general catalytic system for Diels-Alder reactions of β,β -disubstituted enals, delivering not only the desired reactivity but also unprecedented levels of stereocontrol (Figure 46).

The comprehensive mechanistic investigations provided valuable insight into the nature of the catalytic system and its stability under operational conditions. It was concluded that the reaction is promoted by Brønsted acidic form of the IDPi and proceeds via highly asynchronous yet concerted transition state, characteristic for strongly polarized, acid-activated dienophiles. ^{31}P NMR studies uncovered a dynamic equilibrium between the active Brønsted acid form of the IDPi and its sodium salt, generated through cation exchange with MS, which most importantly act as highly efficient drying agents, maintaining catalytic activity of the catalyst. While the sodium salt itself proved to be catalytically inactive, it might play a reservoir role, preventing the catalyst from decomposition as well as acid-induced side reactions of the enals.

The designed platform found a direct application in the concise, enantioselective total synthesis of (–)-(Z)- β -santalol. The key Diels-Alder reaction allowed to establish the entire carbon framework and all stereocenters in a single step. Compared to the previously reported enantioselective routes, our approach is significantly shorter, avoids the use of metal-based or stoichiometric chiral reagents, and relies exclusively on commercially available bulk chemicals, demonstrating promising sustainability. Furthermore, an efficient and direct strategy for the stereoselective introduction of the *Z*-allylic alcohol moiety was employed, addressing one of the major synthetic challenges in the synthesis of (–)-(Z)- β -santalol.

In conclusion, this work demonstrates the high versatility and synthetic utility of asymmetric Brønsted acid catalysis by tackling one of the most challenging Diels-Alder transformations. The developed methodology offers an enantioselective, practical and scalable route to the valuable chiral bicyclic scaffolds and, in particular, to (–)-(Z)- β -santalol. Beyond its direct synthetic impact, the study also provides mechanistic insight into the previously

overlooked interplay between IDPi catalysts and zeolite-based MS, used as a common additive in a variety of synthetic transformations.

6. Outlook

The developed catalytic system represents a significant step forward in extending the scope of Brønsted acid catalysis to the challenging class of β,β -disubstituted enals. Nonetheless, at its current state it still exhibits limitations in the substrate generality, particularly when confronted with more sterically encumbered or electronically demanding enals and dienes. Future research may therefore focus on the development of next-generation catalyst architectures capable of activating the whole range of substitution patterns, ultimately enabling a more general and unified platform for the asymmetric Diels–Alder reactions of enals.

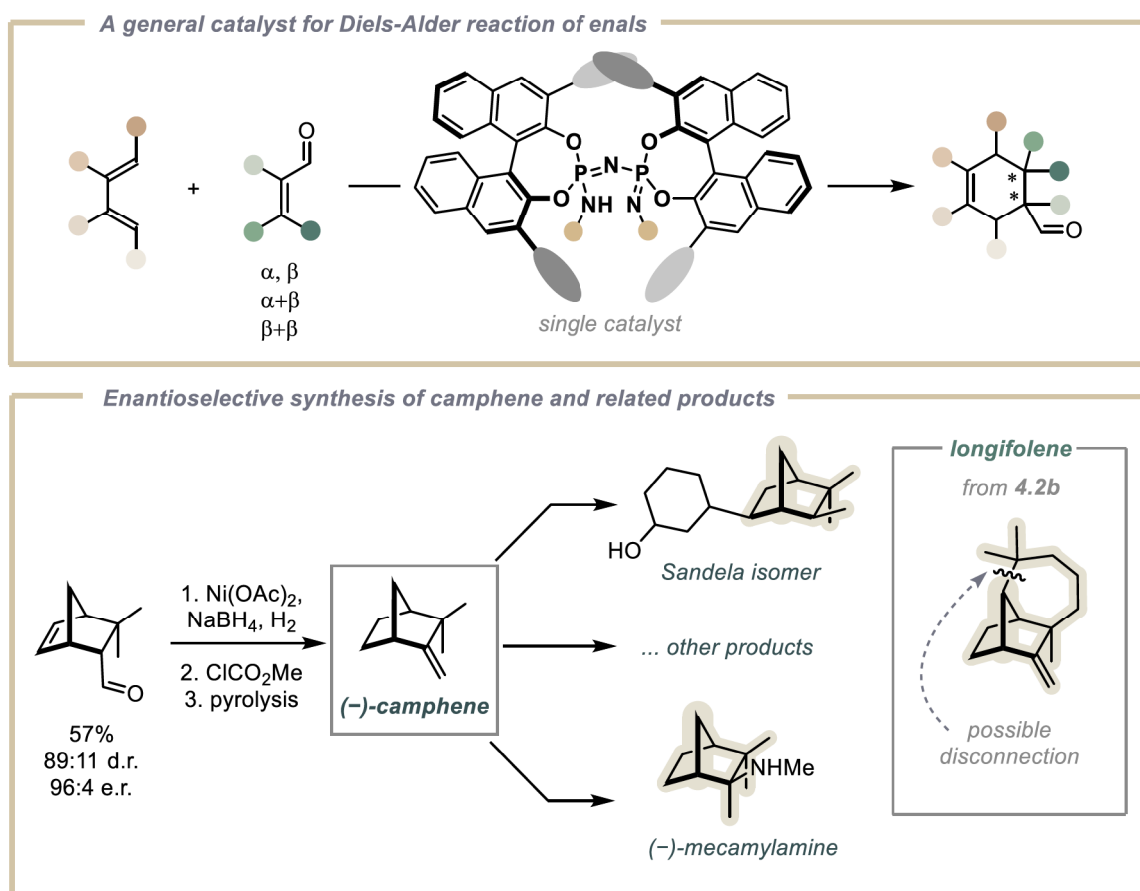


Figure 47. Future directions and conceptual outlook for this work.

The key Diels–Alder reaction between cyclopentadiene and geranial was capable to efficiently give rise to a complex terpenoid bicyclo[2.2.1]heptane scaffold of (–)-(Z)- β -santalol. Given that this scaffold can be found in other terpenes, the developed Diels–Alder reaction can be used in the asymmetric synthesis of the related natural products such as camphene and its derivatives, for example industrially produced sandalwood scent compound — Sandela,¹¹² or mecamylamine,^{211,212} antagonist of the nicotinic acetylcholine receptors. Another attractive application might be the total synthesis of tricyclic sesquiterpene longifolene,²¹³ demonstrating

the general synthetic potential of this catalytic platform.

Additionally, the physical properties of the reaction medium and interactions between IDPi, MS and reaction solvent might attract further attention. Prior studies have shown that Diels–Alder reactions can be significantly accelerated in highly polar lithium perchlorate solutions²¹⁴ due to the phenomenon described as “internal solvent pressure” as well as Lewis acidic properties of the solution. Interestingly, these same factors — enhanced local reactant concentration and Lewis acid activation — are also central to the catalytic behavior of zeolites in Diels–Alder reactions.²¹⁵ A deeper understanding of the interplay between these parameters and their modulation could open new avenues for enhancing the reactivity and selectivity of IDPi catalysts under mild conditions.

7. Experimental Section

General Information

Unless otherwise stated, all reactions were magnetically stirred and conducted in flame-dried glassware in anhydrous solvents under Ar, applying standard Schlenk techniques. Solid reagents were added through a weak Ar counter-flow. Cooling baths were prepared in Dewar vessels, filled with ice/water (0 °C), cooled acetone (> -78 °C) or dry ice/acetone (-78 °C). Heated silicon oil baths were used for reactions requiring elevated temperatures. Solvents were removed under reduced pressure at 40 °C using a rotary evaporator. All given yields are isolated yields of chromatographically and NMR spectroscopically pure materials, unless otherwise stated.

Chemicals

Chemicals were purchased from commercial suppliers and used without further purification unless otherwise stated. All starting aldehydes were purified by vacuum distillation and stored under Ar at -20 °C.

Geranial (95:5 *E/Z*) **4.1b-(E)**, neral (95:5 *Z/E*) **4.1b-(Z)** and geranylgeraniol were a kind gift of BASF. (*E*)-3,6,7-trimethylocta-2,6-dienal **4.1e** was obtained from KOFO MPI warehouse.

Solvents

Solvents were dried by distillation from an appropriate drying agent in the technical department of the Max-Planck-Institut für Kohlenforschung and received in Schlenk flasks under argon and stored over 4 Å MS when applicable.

Thin Layer Chromatography (TLC)

Was performed using silica gel pre-coated glass plates (SIL G-25, with fluorescent indicator UV254; Macherey-Nagel) which were visualized by irradiation with UV light (λ = 254 or 366 nm), *p*-anisaldehyde, basic KMnO₄, and/or phosphomolybdic acid (PMA) stains. Preparative thin-layer chromatography was performed on silica gel pre-coated glass plates SIL G-100, with fluorescent indicator UV254 (Macherey-Nagel).

Column Chromatography

Column chromatography was carried out using Merck silica gel (60 Å, 230–400 mesh, particle size 0.040–0.063 mm) using technical grade solvents. Elution was accelerated using Ar stream. Automated column chromatography was conducted on a Biotage® Isolera ISO-4SW

instrument, using Biotage® Sfär chromatography cartridges. All fractions containing a desired substance were combined and concentrated in vacuo, then redissolved in an appropriate solvent and filtered through cotton to remove silica residues.

Nuclear Magnetic Resonance Spectroscopy

^1H , ^{13}C , ^{19}F , ^{31}P NMR spectra were recorded on a Bruker Avance III 500 or a Bruker Avance Neo 600 MHz NMR spectrometer in a suitable deuterated solvent unless specified otherwise. The solvent employed and respective measuring frequency are indicated for each experiment. Chemical shifts were reported with Me_4Si serving as a reference. The resonance multiplicity is described as: s (singlet), d (doublet), t (triplet), q (quadruplet), p (pentet), hept (heptet), m (multiplet), and br (broad). All spectra were recorded at 298 K unless otherwise noted, processed with the program MestReNova 15.0.0, and coupling constants are reported as observed. The residual deuterated solvent signal relative to Me_4Si was used as the internal reference in ^1H NMR spectra.

Mass Spectrometry

Electrospray ionization (ESI) mass spectrometry was conducted on a Bruker ESQ 3000 spectrometer. High resolution mass spectrometry (HRMS) was performed on a Finnigan MAT 95 (EI) or Bruker APEX III FTMS (7 T magnet, ESI). The ionization method and mode of detection employed is indicated for the respective experiment and all masses are reported in atomic units per elementary charge (m/z) with an intensity normalized to the most intense peak.

Specific Rotations

Were measured with a Rudolph RA Autopol IV Automatic Polarimeter at the indicated temperature (T) with a sodium lamp (sodium D line, $\lambda = 589 \text{ nm}$). Measurements were performed in an acid resistant 1 mL cell (50 mm length) with concentrations ($\text{g}/(100 \text{ mL})$) reported in the corresponding solvent.

High-Performance Liquid Chromatography (HPLC)

Was performed on a Shimadzu LC-20AD liquid chromatograph SIL-20AC auto sampler, CMB-20A using Daicel/Merck columns with a chiral stationary phase. All solvents used were HPLC-grade solvents purchased from Sigma-Aldrich. The column employed and the respective solvent mixture are indicated for each experiment.

Gas Chromatography (GC)

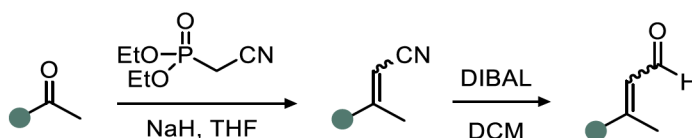
GC analyses on a chiral stationary phase were performed on HP 6890 and 5890 series instruments (split-mode capillary injection system, flame ionization detector (FID), hydrogen

carrier gas). The conditions employed are described in detail for the individual experiments.

Language corrections have been conducted with the assistance of the ChatGPT language model (GPT-5, OpenAI). Suggested corrections were carefully reviewed and selectively integrated to improve clarity and readability.

7.1. Substrates Synthesis

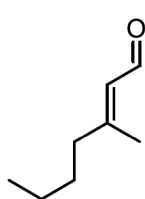
Synthesis via Horner–Wadsworth–Emmons reaction



The procedure was adopted from Dong et al.²¹⁶

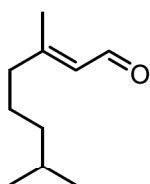
In a two-neck round-bottom flask under Ar diethyl cyanomethylphosphonate (1.2 equiv.) was dissolved in dry tetrahydrofuran (0.6 M) and cooled down to 0 °C. Sodium hydride (60% w/w in mineral oil, 1 equiv.) was slowly added, followed by addition of a solution of ketone (1 equiv.) in small amount of dry tetrahydrofuran. The resulting solution was kept stirring at room temperature for 6 h. After completion the reaction was quenched with water and extracted with DCM (3x). The combined organic phase was washed with water (3x), dried over anhydrous Na_2SO_4 and concentrated in vacuo.

The obtained residue was dissolved in DCM (1 M) and DIBAL (1 M in hexanes, 1.2 equiv.) was added dropwise at −78 °C under nitrogen atmosphere. The reaction mixture was kept at −20 °C for 2 h and monitored by TLC. After reaction was completed, EA (10 mL) was added to quench the remaining DIBAL. The reaction mixture was warmed up to room temperature followed by addition of another 10 mL of EA and 20 mL of saturated potassium sodium tartrate aqueous solution. The suspension was stirred vigorously for 2 h to give a biphasic mixture, which was separated and aqueous layer was extracted with EA (3x). The organic layers were combined, dried over Na_2SO_4 and then concentrated in vacuo. The residue was purified by automated silica gel column chromatography (MTBE:pentane from 0% to 25%) to give the corresponding alk-2-enals **4.1**.

(E)-3-Methylhept-2-enal (4.1c)

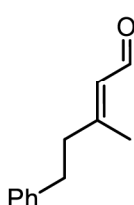
Obtained as a mixture of *E/Z* isomers (*E/Z*≈75:25), **(E)-4.1c** was separated using automated silica gel column chromatography (MTBE:pentane from 0% to 13%). Light yellow oil, 62.4% yield. The NMR spectroscopic data for **(E)-4.1c** is in agreement with the reported in literature.²¹⁷

¹H NMR (501 MHz, CDCl₃): δ 10.00 (d, *J* = 8.1 Hz, 1H), 5.91 – 5.86 (m, 1H), 2.27 – 2.20 (m, 2H), 2.17 (d, *J* = 1.3 Hz, 3H), 1.57 – 1.47 (m, 2H), 1.42 – 1.30 (m, 2H), 0.97 – 0.91 (m, 3H).

(E)-3,7-Dimethyloct-2-enal (4.1d)

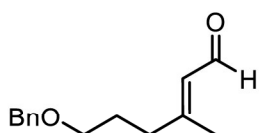
Obtained as a mixture of *E/Z* isomers (*E/Z*≈95:5) as a light yellow oil, 43.8% yield. The NMR spectroscopic data for **(E)-4.1d** is in agreement with the reported in literature.²¹⁸

¹H NMR (501 MHz, CDCl₃) δ 10.02 (d, *J* = 8.1 Hz, 1H), 5.90 (dp, *J* = 8.2, 1.3 Hz, 1H), 2.22 – 2.17 (m, 2H), 2.16 (d, *J* = 1.4 Hz, 3H), 1.62 – 1.48 (m, 1H+2H), 1.28 – 1.15 (m, 2H), 0.88 (d, *J* = 6.6 Hz, 6H).

(E)-3-Methyl-5-phenylpent-2-enal (4.1h)

Obtained as a mixture of *E/Z* isomers (*E/Z*≈65:35), **(E)-4.1h** was separated using automated silica gel column chromatography (MTBE:pentane from 0% to 12%). Light yellow oil, 55.0% yield. The NMR spectroscopic data for **(E)-4.1h** is in agreement with the reported in literature.²¹⁹

¹H NMR (501 MHz, CDCl₃) δ 9.99 (d, *J* = 8.0 Hz, 1H), 7.24 – 7.15 (m, 5H), 5.90 (dq, *J* = 8.0, 1.3 Hz, 1H), 2.85 – 2.74 (m, 2H), 2.56 – 2.50 (m, 2H), 2.19 (d, *J* = 1.4 Hz, 3H).

(E)-6-(Benzyloxy)-3-methylhex-2-enal (4.1j)

Obtained as a mixture of *E/Z* isomers (*E/Z*≈91:9) as a light yellow oil (961 mg, 4.41 mmol, 44.1% yield).

¹H NMR (501 MHz, CD₂Cl₂) δ 9.98 (d, *J* = 8.0 Hz, 1H_{maj}), 9.95 (d, *J* = 8.2 Hz, 1H_{min}), 7.45 – 7.23 (m, 5H_{maj+min}), 5.85 (ddq, *J* = 8.0, 2.5, 1.3 Hz, 1H_{maj+min}), 4.48 (s, 2H_{maj+min}), 3.49 (t, *J* = 6.2 Hz, 2H_{maj+min}), 2.72 – 2.64 (m, 2H_{min}), 2.40 – 2.27 (m, 2H_{maj}), 2.16 (d, *J* = 1.2 Hz, 3H_{maj}), 1.98 (d, *J* = 1.3 Hz, 3H_{min}), 1.87 – 1.78 (m, 2H_{maj+min}).

^{13}C NMR (126 MHz, CD_2Cl_2) δ 191.4, 164.1, 139.1, 128.7, 128.0, 127.9, 127.6, 73.3, 73.2, 73.2, 69.8, 37.6, 27.8, 17.7.

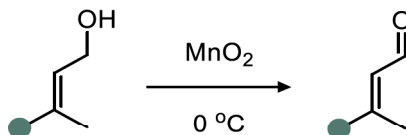
HRMS m/z (GC-EI): calcd. for $\text{C}_{14}\text{H}_{18}\text{O}_2\text{Na}$ ($[\text{M}+\text{Na}]^+$): 241.120450; found 241.120454.

4-Chloro-3-methylbut-2-enal (4.1k)

From *chloroacetone* and *triethyl phosphonoacetate* via Horner–Wadsworth–Emmons reaction and reduction with LiAlH_4 as described by Matsuda et al.²²⁰ The obtained allylic alcohol was oxidized as described in GP2 yielding the product as mixture of *E/Z* isomers (*E/Z* $\approx$ 76:24), (*E*)-**4.1k** was separated using automated silica gel column chromatography (MTBE:pentane from 0% to 6%), obtaining 327 mg (2.76 mmol, 27.6%) of yellow oil. Light and temperature sensitive compound, store at -78°C . The NMR spectroscopic data for (*E*)-**4.1k** is in agreement with the reported in literature.²²¹

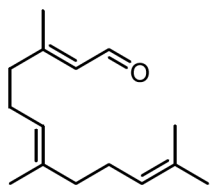
^1H NMR (501 MHz, CD_2Cl_2) δ 10.02 (d, $J = 7.6$ Hz, 1H), 6.07 (dq, $J = 7.6, 1.2$ Hz, 1H), 4.13 (d, $J = 1.0$ Hz, 2H), 2.24 (d, $J = 1.3$ Hz, 3H).

Synthesis via Oxidation of Alcohols



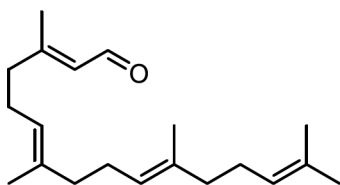
The procedure was adopted from Breinbauer et al.²²¹

In a two-neck flame dried round-bottom flask under Ar 1.0 g anhydrous 4 Å MS were transferred followed by addition of allylic alcohol substrate (1.0 equiv.) in DCM (0.10 M). Activated MnO_2 (8.0 equiv.) was added to the obtained mixture. The black reaction mixture was stirred for 8 h or until full consumption of starting alcohol was achieved (monitored by TLC). MnO_2 was removed by filtration through a pad of SiO_2 washing with DCM. The filtrate was collected and the solvent was evaporated under reduced pressure. The residue was purified by automated silica gel column chromatography (MTBE/pentane from 0% to 15%) to give the corresponding alk-2-enals **1**.

(2*E*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trienal (farnesal) (4.1f)

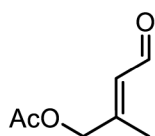
Obtained as a mixture of *E/Z* isomers (*E/Z*≈75:25), (***E***)-**4.1f** was separated using automated silica gel column chromatography (MTBE:pentane from 0% to 17%) as a light yellow oil, 75.5% yield. The NMR spectroscopic data for (***E***)-**4.1f** is in agreement with the reported in literature.²²²

¹H NMR (501 MHz, CDCl₃): δ 10.02 (d, *J* = 8.0 Hz, 1H), 5.94 – 5.88 (m, 1H), 5.14 – 5.05 (m, 2H), 2.32 – 2.20 (m, 4H), 2.19 (d, *J* = 1.2 Hz, 3H), 2.09 – 2.02 (m, 2H), 2.01 – 1.95 (m, 2H), 1.67 (brs, 3H), 1.66 – 1.60 (m, 6H).

(2*E*,6*E*,10*E*)-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraenal (4.1g)

Obtained as a mixture of *E/Z* isomers (*E/Z*≈96:4) as a light yellow oil, 92.0% yield. The NMR spectroscopic data for (***E***)-**4.1g** is in agreement with the reported in literature.²²²

¹H NMR (501 MHz, CDCl₃) δ 9.99 (d, *J* = 8.0 Hz, 1H), 5.91–5.86 (m, 1H), 5.13–5.05 (m, 3H), 2.26–2.18 (m, 4H), 2.17 (d, *J* = 1.3 Hz, 3H), 2.11–2.01 (m, 4H), 2.02–1.93 (m, 4H), 1.68 (d, *J* = 1.6 Hz, 3H), 1.63–1.57 (m, 9H).

2-Methyl-4-oxobut-2-en-1-yl acetate (4.1i)

Corresponding allylic alcohol obtained from 3-methyl-2-buten-1-ol as described by Barrero et al.²²³ oxidation product is obtained according to GP2 as mixture of *E/Z* isomers (*E/Z*≈95:5) as a light yellow oil, 39.2% yield. The NMR spectroscopic data for (***E***)-**4.1i** is in agreement with the reported in literature.²²⁴

¹H NMR (501 MHz, CD₂Cl₂) δ 10.07 (d, *J* = 7.9 Hz, 1H), 6.06–5.99 (m, 1H), 4.69–4.64 (m, 2H), 2.18 (dt, *J* = 1.5, 0.8 Hz, 3H), 2.15 (s, 3H).

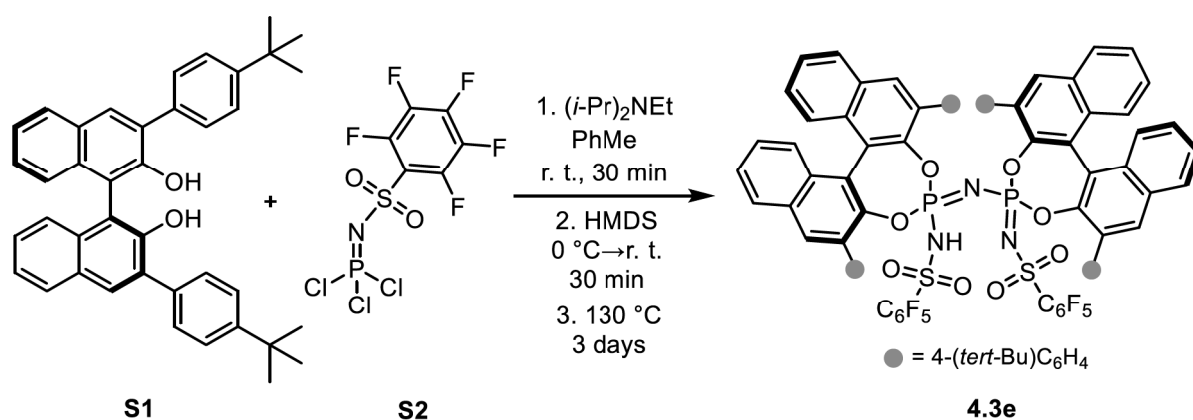
7.2. IDPi Catalyst Synthesis

IDPi catalysts **4.3a-d**, **4.3f** were prepared according to the literature procedures.^{10,225}

(*S,S*)-(4-*tert*-butylphenyl)-C₆F₅ IDPi (**4.3e**)

Starting materials — ((perfluorophenyl)sulfonyl)phosphorimidoyl trichloride **S2** and 3,3'-disubstituted BINOL **S1** — were synthesized according to previously reported procedures.²²⁶

The IDPi catalysts were prepared according to previously reported procedures with slight modifications. The spectroscopic data is in agreement with the previous reports.²²⁶

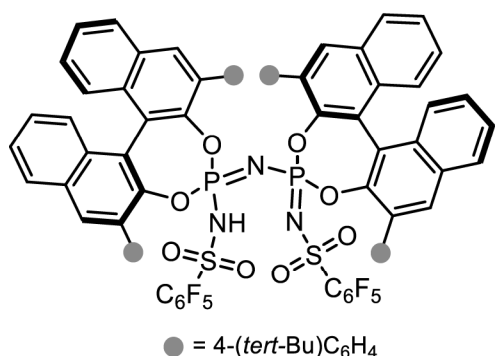


BINOL (1.0 equiv. 7.26 mmol, 4000.0 mg) and phosphazene reagent (1.1 equiv., 7.99 mmol, 3055.0 mg) were loaded into Schlenk flask under Ar followed by addition of 60.0 mL of PhMe, resulting mixture was stirred at r. t. until clear solution was obtained. To the obtained solution (*i*-Pr)₂NEt (16.0 equiv., 44.12 mmol, 7.60 mL) was added and resulting mixture left stirring at r. t. for 30 min (monitored by TLC following BINOL consumption). Then the mixture was cooled in ice bath and bis(trimethylsilyl)amine (HMDS, 0.5 equiv., 3.63 mmol, 758.0 mL) was added. The cooling bath was removed and the reaction mixture was stirred for additional 30 min and then immersed into the preheated to 120 °C oil bath.

After 3 days the mixture was carefully quenched with 10% aqueous HCl (70 mL) and extracted with DCM (3x100 mL). The combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure.

The residue was purified by silica gel column chromatography eluting with *n*-hexane:MTBE 4:1→2:1 v/v. After evaporation of solvent, the collected solid was dissolved in 10 mL of DCM and passed through acidified DOWEX 50WX8 column eluting with DCM. The obtained solution was evaporated and the obtained solid was azeotropically dried using PhMe

delivering IDPi **4.3e** as an off-white solid in 48.0% yield (1.74 mmol, 2899.0 mg).



¹H NMR (600 MHz, CD₂Cl₂) δ 8.21 (ddt, *J* = 8.2, 1.3, 0.6 Hz, 2H), 8.08 (s, 2H), 8.00 (d, *J* = 8.4 Hz, 2H), 7.91 (s, 2H), 7.74 (ddd, *J* = 8.2, 6.8, 1.1 Hz, 2H), 7.61 – 7.56 (m, 2H), 7.53 (ddd, *J* = 8.4, 6.8, 1.3 Hz, 2H), 7.42 (s, 8H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.38 – 7.36 (m, 4H), 6.75 (bd, *J* = 8.6 Hz, 4H), 6.70 (bs, 1H, NH), 6.62 (bd, *J* = 8.6 Hz, 4H), 1.26 (s, 18H), 0.93 (s, 18H).

¹³C NMR (151 MHz, CD₂Cl₂) δ 151.4, 150.6, 144.2 (dd, *J* = 259.9, 11.5 Hz), 143.9 (t, *J* = 5.1 Hz), 143.8 (t, *J* = 5.7 Hz), 143.5 (dt, *J* = 261.3, 13.3 Hz), 137.4 (bdt, *J* = 256.8, 14.8 Hz), 134.5 (t, *J* = 1.3 Hz), 133.4 (t, *J* = 1.8 Hz), 133.3, 132.8, 132.4, 132.1, 132.1, 131.7, 131.5, 130.8, 129.5, 129.3, 129.2, 128.7, 127.6, 127.19, 127.16, 127.1, 127.0, 126.2, 125.0, 123.7 (t, *J* = 1.4 Hz), 123.0 (t, *J* = 1.3 Hz), 117.6 (t, *J* = 14.1 Hz), 34.8, 34.6, 31.3, 31.2.

¹⁹F NMR (565 MHz, CD₂Cl₂) δ –135.61 (d, *J* = 20.7 Hz), –146.45 (bs), –160.42 (bt, *J* = 21.0 Hz).

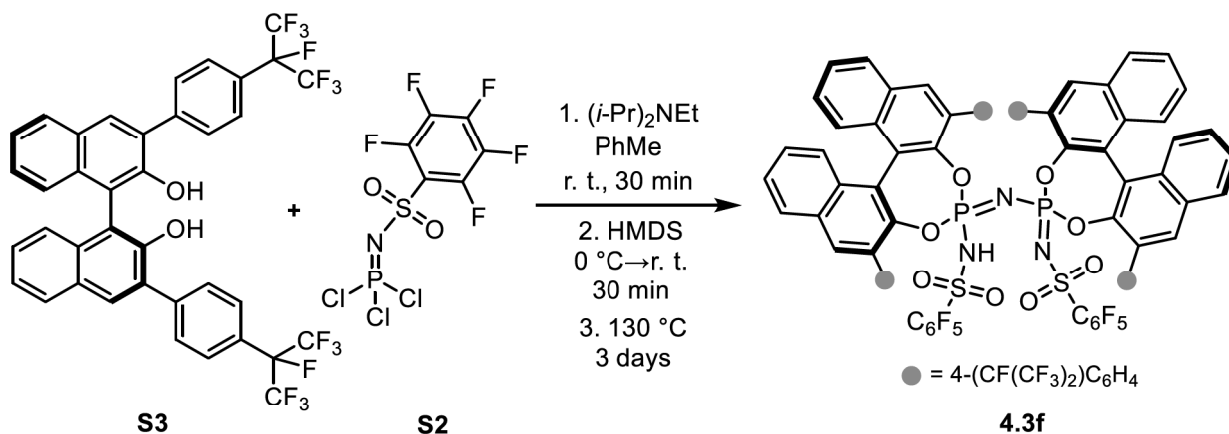
³¹P NMR (203 MHz, CD₂Cl₂) δ –7.91.

HRMS *m/z* (ESI): calcd. for C₉₂H₇₂F₁₀N₃O₈P₂S₂ ([M-H][–]): 1662.4082; found 1662.4067.

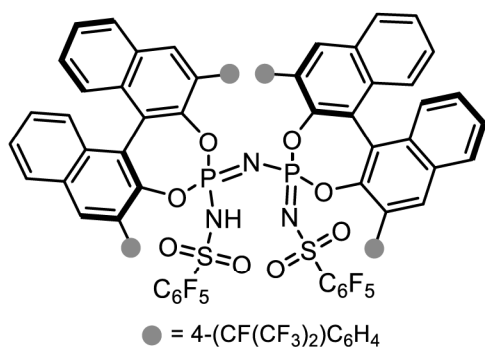
TLC in DCM R_f = 0.32.

(*S,S*)-(4-(perfluoropropan-2-yl)phenyl)-C₆F₅ IDPi (**4.3h**)

Following the procedure for IDPi synthesis described above with BINOL **S3** (0.186 mmol, 144.0 mg) synthesized as described by Díaz-Oviedo et al.²²⁷ and phosphazene reagent **S2** as starting materials.



The product is obtained in 69.6% yield (0.064 mmol, 136 mg).



¹H NMR (501 MHz, CD₂Cl₂) δ 8.31 (d, *J* = 8.2 Hz, 2H), 8.17 (brs, 2H), 8.11 – 8.04 (m, 4H), 7.86 – 7.79 (m, 2H), 7.69 – 7.64 (m, 10H), 7.63 – 7.55 (m, 2H), 7.44 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 4H), 7.05 (d, *J* = 8.2 Hz, 4H), 6.78 (d, *J* = 8.2 Hz, 4H).

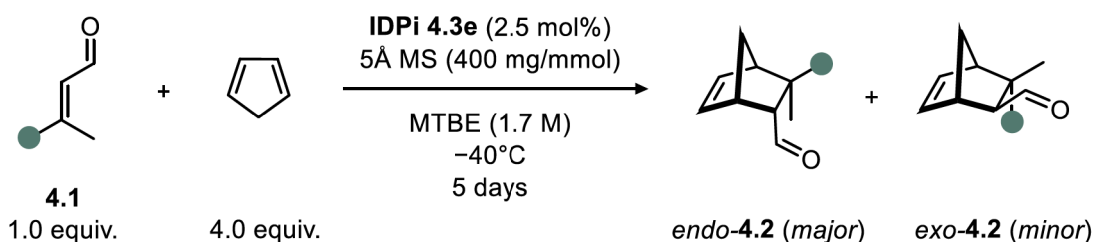
Representative ¹³C spectrum could not be obtained due to insufficient material.

¹⁹F NMR (471 MHz, CD₂Cl₂) δ -75.51 (ddt, *J* = 302.6, 18.1, 9.2 Hz, 12F), -76.35 (ddt, *J* = 128.0, 19.0, 9.7 Hz, 12F), -136.17 (d, *J* = 27.5 Hz, 4F), -145.85–-146.13 (m, 2F), -160.16–-160.65 (m, 4F), -181.24–-181.68 (m, 2F), -182.88–-183.35 (m, 2F).

³¹P NMR (203 MHz, CD₂Cl₂) δ -6.33.

HRMS *m/z* (ESI): calcd. for C₈₈H₃₇F₃₈N₃O₈P₂S₂ ([M-H]⁻): 2110.091332; found 2110.091407.

TLC in DCM R_f = 0.20.

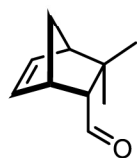
7.3. Organocatalytic Diels-Alder Reaction of β,β -Substituted Enals

Activated (130°C , 2 d, high vacuum) molecular sieves $5\text{ \AA}$ (80.0 mg), and IDPi catalyst **3e** (0.025 equiv., 2.5 mol%, 0.005 mmol, 8.3 mg) were introduced in a flame-dried glass vial under Ar. MTBE (1.7 M, 120 μL) was added, and the resulting suspension was stirred at rt for 15 min. The reaction mixture was then cooled in a dry ice bath, followed by the addition of cyclopentadiene **2** (4.0 equiv., 0.8 mmol, 66.0 μL). After stirring for 10 min in the dry ice bath, the enal substrate **1** (1.0 equiv., 0.2 mmol) was added. The mixture was then transferred to a cryostat maintained at -40°C and stirred for 5 d, unless otherwise specified.

Upon completion of the reaction, the mixture was quenched with triethylamine (0.03 equiv.) and allowed to warm to rt. The molecular sieves were removed by filtration through a short pad of Celite®, washed with MTBE, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography using *n*-pentane/MTBE (9:1) as eluent, unless otherwise noted.

Racemate Synthesis

The racemic samples were synthesized as described in GP3 using 1:1 *S,S*:*R,R* enantiomers catalyst mixture on 0.05 mmol scale. The racemic products were isolated using thin-layer preparative chromatography.

(1*S*,2*R*,4*R*)-3,3-dimethylbicyclo[2.2.1]hept-5-ene-2-carbaldehyde (4.2a)

Using **4.1a** as enal. The product is obtained as mixture of isomers *endo*/*exo* = 88:12. Yield 57.0%, 17.1 mg, 0.114 mmol, colorless oil.

$^1\text{H NMR}$ (501 MHz, CD_2Cl_2) δ 9.77 (d, $J = 3.4\text{ Hz}$, 1H_{min}), 9.33 (d, $J = 4.2\text{ Hz}$, 1H_{maj}), 6.33 – 6.29 (m, $2\text{H}_{\text{maj} + \text{min}}$), 6.24 (dd, $J = 5.7, 3.1\text{ Hz}$, 1H_{min}), 6.16 (dd, $J = 5.7, 3.1\text{ Hz}$, 1H_{min}) 3.01 –

2.96 (m, 1H_{maj}), 2.98 – 2.94 (m, 1H_{min}), 2.48 – 2.43 (m, 1H_{maj}), 2.43 (dd, $J = 4.2, 3.3$ Hz, 1H_{maj}), 1.74 – 1.68 (m, 1H_{min+maj}), 1.49 – 1.47 (m, 1H_{maj+min}), 1.30 (s, 3H_{maj}), 1.17 (s, 3H_{min}), 1.03 (s, 3H_{min}), 0.91 (s, 3H_{maj}).

¹³C NMR (126 MHz, CD₂Cl₂) δ 206.4_{maj}, 205.7_{min}, 138.3_{maj}, 137.8_{min}, 135.2_{min}, 133.6_{maj}, 62.8_{maj}, 60.6_{min}, 54.2_{maj}, 47.4_{maj}, 46.4_{min}, 46.2_{maj}, 45.1_{maj}, 31.8_{maj}, 29.7_{min}, 25.9_{min}, 23.7_{maj}.

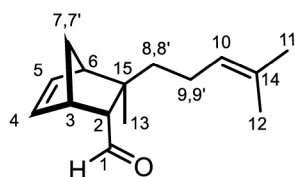
HRMS m/z (GC-EI): calcd. for C₁₀H₁₄O ([M]⁺): 150.103915; found 150.103890.

GC (29.5 m BGB-178, injection temperature: 220 °C; 70 °C – iso 5 min, 1 °C/min, 110 °C; 8 °C/min, 220 °C iso 10 min, 0.5 bar H₂).

$t_{R1} = 20.58$ min (*minor*), $t_{R2} = 20.97$ min (*minor*), $t_{R3} = 22.43$ min (*major*), $t_{R4} = 22.91$ min (*major*); e.r. 59:41 (*minor*) = (18% e.e.), e.r. (*major*) = 96:4 (92% e.e.).

$[\alpha]_D^{25} = -19.13$ ($c = 0.486$, CHCl₃).

(1*S*,2*R*,3*R*,4*R*)-3-methyl-3-(4-methylpent-3-en-1-yl)bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (4.2b)



Using geranial (*E*)-**4.1b** as enal. The product is obtained as mixture of isomers *endo/exo* = 87:13. Yield 62.9%, 27.5 mg, 0.126 mmol, light yellow oil.

¹H NMR (501 MHz, CDCl₃) δ 9.77 (d, $J = 3.2$ Hz, 1H-1_{min}), 9.34 (d, $J = 4.0$ Hz, 1H-1_{maj}), 6.34 (dd, $J = 5.7, 2.9$ Hz, 1H-4_{maj}), 6.29 (dd, $J = 5.7, 3.1$ Hz, 1H-5_{maj}), 6.21 (dd, $J = 5.7, 2.9$ Hz, 1H-4_{min}), 6.14 (dd, $J = 5.7, 3.1$ Hz, 1H-5_{min}), 5.14 – 5.07 (m, 1H-10_{maj}), 5.09 – 5.02 (m, 1H-10_{min}), 3.07 – 2.91 (m, 1H-3_{maj}), 2.60 – 2.53 (m, 1H-6_{maj}), 2.52 – 2.49 (m, 1H-2_{maj}), 2.48 – 2.46 (m, 1H-2_{min}), 2.12 – 2.02 (m, 2H-9,9'_{maj}), 2.02 – 1.94 (m, 2H-9,9'_{min}), 1.72 – 1.66 (m, 10H-11_{maj}, 12_{maj}, 8,8'_{maj}, 7,7'_{maj}), 0.91 (s, 3H-13_{maj}+13_{min}).

¹³C NMR (126 MHz, CDCl₃) δ 206.8 (1_{maj}), 206.1 (1_{min}), 138.3 (5_{maj}), 137.4 (5_{min}), 135.4 (4_{min}), 134.1 (4_{maj}), 131.7 (14_{maj}), 131.5 (14_{min}), 124.3 (10_{maj}), 61.7 (2_{maj}), 60.1 (2_{min}), 52.7 (6_{maj}), 52.6 (6_{min}), 48.8 (15_{maj}), 47.2 (7,7'_{maj}), 46.0 (7,7'_{min}), 45.9 (3_{maj}), 44.4 (8,8'_{maj}), 44.2 (3_{min}), 42.6 (8,8'_{min}), 27.0 (11_{min}), 25.7 (11_{maj}), 24.0 (9,9'_{min}), 23.7 (9,9'_{maj}), 22.4 (13_{min}), 20.5 (13_{maj}), 17.7 (12_{maj}), 17.6 (12_{min}).

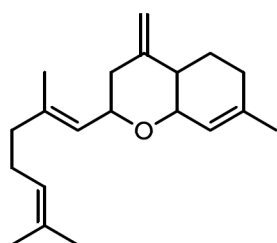
HRMS m/z (GC-EI): calcd. for C₁₅H₂₂O ([M]⁺): 218.166515; found 218.166530.

GC (29.5 m BGB-178, injection temperature: 220 °C; 100 °C – iso 5 min, 1 °C/min, 230 °C iso 10 min, 0.5 bar H₂).

t_{R1} = 88.41 min (minor), t_{R2} = 91.15 min (minor), t_{R3} = 97.38 min (major), t_{R4} = 99.10 min (major); e.r. (minor) = 93:7 (86% e.e.), e.r. (major) = 99:1 (98% e.e.)

$[\alpha]_D^{25} = -66.55$ ($c = 0.565$, CHCl₃).

(*E*)-2-(2,6-dimethylhepta-1,5-dien-1-yl)-7-methyl-4-methylene-3,4,4a,5,6,8a-hexahydro-2H-chromene (4.2b-SP)



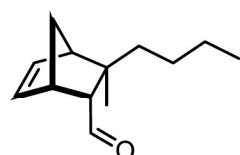
Isolated from the crude reaction mixture *via* consecutive CC eluting with 100% pentane and then thin-layer preparative chromatography eluting with 100% pentane.

¹H NMR (600 MHz, CDCl₃) δ 5.44 (dq, $J = 2.7, 1.4$ Hz, 1H), 5.26 (dq, $J = 8.1, 1.3$ Hz, 1H), 5.10 (thept, $J = 7.0, 1.4$ Hz, 1H), 4.77 (q, $J = 1.6$ Hz, 1H), 4.64 (q, $J = 1.6$ Hz, 1H), 4.19 (ddd, $J = 11.0, 8.1, 3.0$ Hz, 1H), 3.61 (dhept, $J = 9.4, 3.7$ Hz, 1H), 2.24 (dd, $J = 13.4, 3.0$ Hz, 1H), 2.18 (ddt, $J = 13.4, 11.0, 1.8$ Hz, 1H), 2.15 – 2.06 (m, 3H), 2.04–1.99 (m, 3H), 1.99–1.91 (m, 2H), 1.69–1.67 (m, 9H), 1.60–1.59 (m, 3H), 1.52–1.43 (m, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 148.3, 138.9, 137.0, 131.8, 125.5, 124.2, 123.8, 105.1, 80.0, 76.4, 44.3, 42.7, 39.6, 30.6, 26.5, 25.8, 23.1, 22.6, 17.8, 17.1.

HRMS m/z (GC-EI): calcd. for C₂₀H₃₀O ([M]⁺): 286.229665; found 286.229673.

(1*S*,2*R*,3*R*,4*R*)-3-butyl-3-methylbicyclo[2.2.1]hept-5-ene-2-carbaldehyde (4.2c)



Using **4.1c** as enal. The product is obtained as mixture of isomers *endo/exo* = 94:6. Yield 65.6%, 24.9 mg, 0.130 mmol, colorless oil.

¹H NMR (501 MHz, CD₂Cl₂) δ 9.73 (d, $J = 3.2$ Hz, 1H_{min}), 9.30 (d, $J = 4.0$ Hz, 1H_{maj}), 6.31 (dd, $J = 5.7, 2.9$ Hz, 1H_{maj}), 6.28 (dd, $J = 5.7, 3.2$ Hz, 1H_{maj}), 6.19 (dd, $J = 5.7, 3.0$ Hz, 1H_{min}), 6.12 (dd, $J = 5.7, 3.1$ Hz, 1H_{min}), 2.98 – 2.93 (m, 1H_{maj}), 2.59 – 2.57 (m, 1H_{min}), 2.55 – 2.47 (m, 1H_{maj}), 2.47 – 2.42 (m, 1H_{maj}), 2.42 – 2.40 (m, 1H_{min}), 1.69 (dt, $J = 8.7, 1.7$ Hz, 1H_{maj}), 1.51 –

1.42 (m, 2H_{maj+min}), 1.37 – 1.23 (m, 5H_{maj+min}), 0.91 (t, $J = 7.1$ Hz, 3H_{maj+min}), 0.85 (s, 3H_{maj+min}).

¹³C NMR (126 MHz, CD₂Cl₂, *endo*-major isomer is reported) δ 206.5, 138.2, 134.1, 61.6, 48.7, 47.0, 45.9, 44.1, 29.7, 27.1, 23.5, 20.3, 13.8.

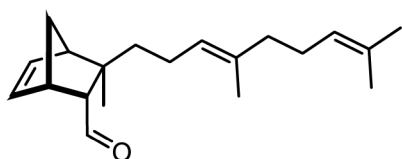
HRMS m/z (GC-ESI): calcd. for C₁₃H₂₄N₁O ([M+NH₄]⁺): 210.185239; found 210.185170.

GC (29.5 m BGB-178, injection temperature: 220 °C; 100 °C – iso 5 min, 2 °C/min, 180 °C; 5 °C/min, 220 °C iso 10 min, 0.5 bar H₂).

$t_{R1} = 17.35$ min (minor), $t_{R2} = 17.74$ min (minor), $t_{R3} = 18.35$ min (major), $t_{R4} = 18.83$ min (major); e.r. (minor) = 51:49 (2% e.e.), e.r. (major) = 98:2 (96% e.e.)

$[\alpha]_D^{25} = -16.98$ ($c = 0.502$, CHCl₃).

(1*S*,2*R*,3*R*,4*R*)-3-((*E*)-4,8-dimethylnona-3,7-dien-1-yl)-3-methylbicyclo[2.2.1]hept-5-ene-2-carbaldehyde (4.2f)



Using **4.1f** (farnesal) as enal. The product is obtained as mixture of isomers *endo/exo* = 89:11. Yield 63.2%, 36.2 mg, 0.126 mmol, light yellow oil.

¹H NMR (501 MHz, CD₂Cl₂) δ 9.76 (d, $J = 3.1$ Hz, 1H_{min}), 9.33 (d, $J = 3.9$ Hz, 1H_{maj}), 6.34 (dd, $J = 5.7$, 2.9 Hz, 1H_{maj}), 6.29 (dd, $J = 5.7$, 3.2 Hz, 1H_{maj}), 6.22 (dd, $J = 5.7$, 3.0 Hz, 1H_{min}), 6.15 (dd, $J = 5.7$, 3.0 Hz, 1H_{min}), 5.14 (tq, $J = 7.1$, 1.4 Hz, 1H_{maj+min}), 5.10 (tdt, $J = 5.7$, 2.9, 1.4 Hz, 1H_{maj+min}), 3.00 – 2.95 (m, 1H_{maj+min}), 2.58 – 2.55 (m, 1H_{maj+min}), 2.51 – 2.47 (m, 1H_{maj+min}), 2.12 – 2.03 (m, 5H_{maj+min}), 2.00 – 1.95 (m, 2H_{maj+min}), 1.73 – 1.70 (m, 1H_{maj+min}), 1.69 – 1.66 (m, 3H_{maj+min}), 1.63 – 1.61 (m, 3H_{maj+min}), 1.61 – 1.58 (m, 4H_{maj+min}), 1.48 – 1.44 (m, 1H_{maj+min}), 1.16 (s, 3H_{min}), 0.90 (s, 3H_{maj}).

¹³C NMR (126 MHz, CD₂Cl₂) δ 206.7_{maj}, 206.2_{min}, 138.6_{maj}, 137.7_{min}, 135.8_{min}, 135.5_{maj}, 135.3_{min}, 134.6_{maj}, 131.7_{maj+min}, 124.8_{maj}, 124.75_{min}, 124.71_{maj}, 124.68_{min}, 62.1_{maj}, 60.5_{min}, 53.2_{maj}, 53.0_{min}, 49.1_{maj+min}, 47.5_{maj+min}, 46.3_{maj}, 44.8_{maj}, 44.6_{min}, 43.0_{min}, 40.1_{maj+min}, 27.12_{maj}, 27.08_{min}, 25.8_{maj+min}, 24.3_{min}, 24.0_{maj}, 22.6_{min}, 20.7_{maj}, 17.8_{maj+min}, 16.1_{maj+min}.

HRMS m/z (GC-ESI): calcd. for C₂₀H₃₀ONa ([M+Na]⁺): 309.21889; found 309.21885.

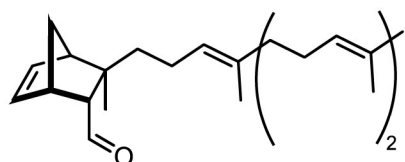
HPLC (Chiralpak IB-N3, 100% *n*-heptane, 298 K, 220 nm).

$t_{R1} = 7.53$ min (minor), $t_{R2} = 8.04$ min (major), $t_{R3} = 12.40$ min (minor), $t_{R4} = 14.77$ min (major);

e.r. (*minor*) = 99:1 (98% e.e.), e.r. (*major*) = 99:1 (98% e.e.).

$[\alpha]_D^{25} = -67.59$ ($c = 0.505$, CHCl_3).

(1*S*,2*R*,3*R*,4*R*)-3-methyl-3-((3*E*,7*E*)-4,8,12-trimethyltrideca-3,7,11-trien-1-yl)bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (4.2g)



Using **4.1g** as enal. The product is obtained as mixture of isomers *endo/exo* = 88:12. Yield 60.0%, 42.5 mg, 0.120 mmol, light yellow oil.

^1H NMR (501 MHz, CD_2Cl_2) δ 9.75 (d, $J = 3.2$ Hz, 1H_{min}), 9.32 (d, $J = 3.9$ Hz, 1H_{maj}), 6.32 (dd, $J = 5.7, 2.9$ Hz, 1H_{maj}), 6.28 (dd, $J = 5.7, 3.1$ Hz, 1H_{maj}), 6.21 (dd, $J = 5.7, 3.0$ Hz, 1H_{min}), 6.13 (dd, $J = 5.7, 3.1$ Hz, 1H_{min}), 5.16 – 5.05 (m, $3\text{H}_{\text{maj+min}}$), 2.99 – 2.93 (m, $1\text{H}_{\text{maj+min}}$), 2.57 – 2.53 (m, $1\text{H}_{\text{maj+min}}$), 2.49 – 2.46 (m, $1\text{H}_{\text{maj+min}}$), 2.10 – 2.01 (m, $6\text{H}_{\text{maj+min}}$), 2.02 – 1.93 (m, $5\text{H}_{\text{maj+min}}$), 1.71 – 1.68 (m, $1\text{H}_{\text{maj+min}}$), 1.66 (d, $J = 1.4$ Hz, $3\text{H}_{\text{maj+min}}$), 1.62 (d, $J = 1.3$ Hz, $3\text{H}_{\text{maj+min}}$), 1.60 – 1.57 (m, $7\text{H}_{\text{maj+min}}$), 1.46 – 1.42 (m, $1\text{H}_{\text{maj+min}}$), 1.15 (s, 3H_{min}), 0.89 (s, 3H_{maj}).

^{13}C NMR (126 MHz, CD_2Cl_2) δ 206.3_{maj}, 205.7_{min}, 138.2_{maj}, 137.3_{min}, 135.4_{min}, 135.1_{maj}, 134.9_{maj+min}, 134.2_{maj}, 131.1_{maj}, 124.4_{maj}, 124.3_{maj}, 124.2_{maj}, 124.1_{min}, 61.6_{maj}, 60.0_{min}, 52.7_{maj}, 52.6_{min}, 48.7_{maj}, 47.0_{maj+min}, 45.9_{maj+min}, 44.4_{maj}, 44.2_{min}, 42.6_{min}, 39.71_{maj}, 39.67_{maj+min}, 39.7_{min}, 26.8_{maj}, 26.6_{maj}, 26.5_{min}, 25.4_{maj}, 23.9_{min}, 23.6_{maj}, 22.2_{min}, 20.3_{maj}, 17.4_{maj}, 15.68_{maj}, 15.65_{maj+min}.

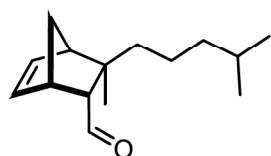
HRMS m/z (GC-EI): calcd. for $\text{C}_{25}\text{H}_{38}\text{ONa}$ ($[\text{M}+\text{Na}]^+$): 377.28149; found 377.28159.

HPLC (Chiralpak IB-N3, 100% *n*-heptane, 298 K, 220 nm).

$t_{\text{R}1} = 7.52$ min (*minor*), $t_{\text{R}2} = 8.08$ min (*major*), $t_{\text{R}3} = 11.34$ min (*minor*), $t_{\text{R}4} = 13.40$ min (*major*); e.r. (*minor*) = 99:1 (98% e.e.), e.r. (*major*) = 98:2 (96% e.e.).

$[\alpha]_D^{25} = -71.05$ ($c = 0.485$, CHCl_3).

(1*S*,2*R*,3*R*,4*R*)-3-methyl-3-(4-methylpentyl)bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (4d)



Using **4.1d** as enal. The product is obtained as mixture of isomers *endo/exo* = 87:13. Yield 68.0%, 30 mg, 0.136 mmol, light yellow oil.

¹H NMR (501 MHz, CD₂Cl₂) δ 9.74 (d, *J* = 3.2 Hz, 1H_{min}), 9.31 (d, *J* = 4.0 Hz, 1H_{maj}), 6.31 (dd, *J* = 5.7, 2.9 Hz, 1H_{maj}), 6.27 (dd, *J* = 5.7, 3.1 Hz, 1H_{maj}), 6.19 (dd, *J* = 5.7, 3.0 Hz, 1H_{min}), 6.16–6.11 (m, 1H_{min}), 2.97–2.93 (m, 1H_{maj+min}), 2.55–2.50 (m, 1H_{maj+min}), 2.47–2.43 (m, 1H_{maj+min}), 1.71–1.69 (m, 1H_{maj+min}), 1.68–1.65 (m, 1H_{maj+min}), 1.57–1.53 (m, 3H_{maj+min}), 1.47–1.43 (m, 2H_{maj+min}), 1.40–1.34 (m, 2H_{maj+min}), 1.19 (s, 3H_{min}), 1.18 (s, 3H_{min}), 1.16 (s, 3H_{min}), 0.88 (s, 3H_{maj}), 0.87 (s, 3H_{maj}), 0.86 (s, 3H_{maj})..

¹³C NMR (126 MHz, CD₂Cl₂) δ 206.7_{maj}, 206.1_{min}, 138.4_{maj}, 136.0_{min}, 135.9_{min}, 134.2_{maj}, 62.3_{min}, 61.8_{maj}, 52.9_{maj}, 52.2_{min}, 47.9_{min}, 47.2_{maj}, 46.3_{min}, 46.0_{maj}, 44.7_{maj}, 44.5_{min}, 39.9_{maj}, 39.7_{min}, 28.1_{maj}, 27.2_{min}, 23.3_{maj+min}, 22.8_{maj+min}, 22.5_{maj+min}, 22.3_{maj}, 22.2_{min}, 20.6_{min}, 20.5_{maj}.

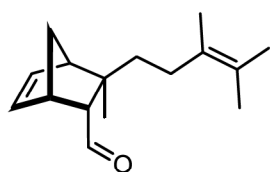
HRMS *m/z* (GC-EI): calcd. for C₁₅H₂₄O ([M]⁺): 220.182165; found 220.182190.

GC (29.5 m BGB-178, injection temperature: 220 °C; 100 °C – iso 5 min, 2 °C/min, 180 °C; 5 °C/min, 220 °C iso 10 min, 0.5 bar H₂).

*t*_{R1} = 70.73 min (minor), *t*_{R2} = 71.61 min (minor), *t*_{R3} = 73.93 min (major), *t*_{R4} = 75.94 min (major); e.r. (minor) = 81:19 (62% e.e.), e.r. (major) = 98:2 (96% e.e.)

[α]_D²⁵ = –20.67 (*c* = 0.328, CHCl₃).

(1*S*,2*R*,3*R*,4*R*)-3-(3,4-dimethylpent-3-en-1-yl)-3-methylbicyclo[2.2.1]hept-5-ene-2-carbaldehyde (4.2e)



Using 3,6,7-trimethylocta-2,6-dienal as enal. The product is obtained as mixture of isomers *endo/exo* = 87:13. Yield 61.3%, 28.5 mg, 0.122 mmol, light yellow oil.

¹H NMR (501 MHz, CD₂Cl₂) δ 9.76 (d, *J* = 3.2 Hz, 1H_{min}), 9.33 (d, *J* = 3.9 Hz, 1H_{maj}), 6.34 (dd, *J* = 5.7, 2.9 Hz, 1H_{maj}), 6.30 (dd, *J* = 5.7, 3.2 Hz, 1H_{maj}), 6.25 (dd, *J* = 5.7, 3.0 Hz, 1H_{min}), 6.16 (dd, *J* = 5.7, 3.1 Hz, 1H_{min}), 3.00–2.95 (m, 1H_{maj+min}), 2.61–2.54 (m, 1H_{maj+min}), 2.50–2.47 (m, 1H_{maj+min}), 2.16–2.02 (m, 2H_{maj+min}), 1.72 (dt, *J* = 8.8, 1.7 Hz, 1H_{maj+min}), 1.66–1.62 (m, 1H_{maj+min}), 1.47 (dt, *J* = 8.8, 1.8 Hz, 1H_{maj+min}), 1.17 (s, 3H_{min}), 0.91 (s, 3H_{maj}).

¹³C NMR (126 MHz, CD₂Cl₂) δ 206.8_{maj}, 206.1_{min}, 138.6_{maj}, 137.7_{min}, 135.8_{min}, 134.5_{maj}, 128.0_{maj+min}, 124.1_{maj}, 123.7_{min}, 62.2_{maj}, 60.7_{min}, 53.0_{maj}, 52.8_{min}, 49.1_{maj+min}, 47.5_{maj+min}, 46.4_{min}, 46.3_{maj}, 44.6_{min}, 43.0_{maj}, 30.7_{min}, 30.4_{maj}, 22.5_{min}, 20.7_{maj}, 20.62_{min}, 20.57_{maj}, 20.1_{maj+min}, 18.7_{maj}, 18.6_{min}.

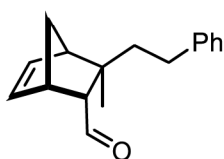
HRMS m/z (GC-EI): calcd. for $C_{16}H_{24}O$ ($[M]^+$): 232.182715; found 232.182722.

2D HPLC (1st dimension: PVA-SIL, 100% *n*-heptane, 308 K; 2nd dimension: Chiralcel OD-3, *n*-heptane/2-propanol = 99.5:0.5, 298 K; 210 nm)

t_{R1} = 5.375 min (minor), t_{R2} = 6.110 min (minor), t_{R3} = 5.293 min (minor), t_{R4} = 7.237 min (major);
e.r. (minor) = >99.5:0.5 (99% e.e.), e.r. (major) = >99.5:0.5 (99% e.e.)

$[\alpha]_D^{25} = -44.93$ (c = 0.552, $CHCl_3$).

(1*S*,2*R*,3*R*,4*R*)-3-methyl-3-phenethylbicyclo[2.2.1]hept-5-ene-2-carbaldehyde (4.2h)



Using **4.1h** as enal. Reaction time was increased to 7 days. The product is obtained as mixture of isomers *endo/exo* = 88:12. Yield 46.0%, 22.1 mg, 0.092 mmol, light yellow oil.

¹H NMR (501 MHz, CD_2Cl_2) δ 9.79 (d, J = 3.2 Hz, 1H_{min}), 9.37 (d, J = 3.9 Hz, 1H_{maj}), 7.32–7.17 (m, 5H_{maj+min}), 6.37 (dd, J = 5.7, 2.9 Hz, 1H_{maj}), 6.33 (dd, J = 5.7, 3.1 Hz, 1H_{maj}), 6.25 (dd, J = 5.7, 3.0 Hz, 1H_{min}), 6.17 (dd, J = 5.7, 3.0 Hz, 1H_{min}), 3.04–2.99 (m, 1H_{maj+min}), 2.74–2.67 (m, 2H_{maj+min}), 2.64–2.60 (m, 1H_{maj+min}), 2.58–2.54 (m, 1H_{maj+min}), 1.96–1.88 (m, 1H_{maj+min}), 1.87–1.77 (m, 1H_{maj+min}), 1.74 (dd, J = 9.0, 1.7 Hz, 1H_{maj+min}), 1.49 (dd, J = 8.9, 1.8 Hz, 1H_{maj+min}), 1.25 (s, 3H_{min}), 0.99 (s, 3H_{maj}).

¹³C NMR (126 MHz, CD_2Cl_2) δ 206.23, 142.83, 138.21, 134.22, 128.33, 128.28, 125.67, 61.60, 52.76, 48.84, 47.07, 46.63, 45.93, 31.46, 20.33.

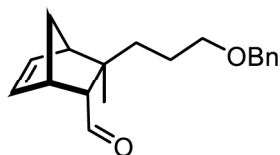
HRMS m/z (GC-EI): calcd. for $C_{17}H_{20}NaO$ ($[M+Na]^+$): 263.14064; found 263.14065.

2D HPLC (1st dimension: PVA-SIL, 100% *n*-heptane, 308 K; 2nd dimension: Chiralcel OD-3, *n*-heptane/2-propanol = 99:1, 298 K; 210 nm)

t_{R1} = 9.967 min (minor), t_{R2} = 12.165 min (minor), t_{R3} = 11.539 min (major), t_{R4} = 15.889 min (major); e.r. (minor) = >99.5:0.5 (99% e.e.), e.r. (major) = >99.5:0.5 (99% e.e.)

$[\alpha]_D^{25} = -22.45$ (c = 0.545, $CHCl_3$)

(1*S*,2*R*,3*R*,4*R*)-3-(3-(benzyloxy)propyl)-3-methylbicyclo[2.2.1]hept-5-ene-2-carbaldehyde (4.2j)



Using **4.1j** as enal. The product is obtained as mixture of isomers *endo/exo* = 88:12. Yield 70.0%, 40.0 mg, 0.140 mmol, transparent oil.

¹H NMR (501 MHz, CD₂Cl₂) δ 9.74 (d, *J* = 3.2 Hz, 1H_{min}), 9.31 (d, *J* = 3.9 Hz, 1H_{maj}), 7.35 – 7.26 (m, 1H_{maj+min}), 6.33 (dd, *J* = 5.7, 2.9 Hz, 1H_{maj}), 6.29 (dd, *J* = 5.8, 3.1 Hz, 1H_{maj}), 6.21 (dd, *J* = 5.7, 3.0 Hz, 1H_{min}), 6.14 (dd, *J* = 5.7, 3.1 Hz, 1H_{min}), 4.48 (s, 2H_{maj}), 4.45 (s, 2H_{min}), 3.48 (t, *J* = 6.2 Hz, 2H_{maj}), 3.41 (t, *J* = 6.5 Hz, 2H_{min}), 2.98 – 2.95 (m, 1H_{maj+min}), 2.55 – 2.53 (m, 1H_{maj+min}), 2.47 – 2.43 (m, 1H_{maj+min}), 1.72 – 1.65 (m, 5H_{maj}), 1.59 – 1.55 (m, 5H_{min}), 1.45 (dt, *J* = 8.8, 1.8 Hz, 1H_{maj+min}), 1.13 (s, 3H_{min}), 0.87 (s, 3H_{maj}).

¹³C NMR (75 MHz, CD₂Cl₂) δ 206.7_{maj+min}, 139.3_{min}, 138.5_{maj}, 136.1_{min}, 134.5_{maj}, 130.3_{maj+min}, 128.6_{maj+min}, 127.9_{maj+min}, 127.7_{maj+min}, 73.1_{maj+min}, 71.3_{maj}, 71.2_{min}, 61.9_{maj}, 60.2_{min}, 48.9_{maj+min}, 47.4_{maj+min}, 46.2_{maj}, 44.7_{min}, 41.1_{maj+min}, 30.0_{maj+min}, 26.1_{min}, 25.8_{maj}, 20.6_{maj+min}.

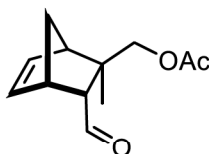
HRMS *m/z* (GC-EI): calcd. for C₁₉H₂₄O₂Na₁ ([M+Na]⁺): 307.167400; found 307.167410.

2D HPLC (YMC PVA-SIL *n*-heptane/2-propanol = 99.8:0.2, 308 K, 220 nm; Chiralpak IB-N3, *n*-heptane/2-propanol = 99:1, 298 K, 220 nm).

*t*_{R1} = 4.833 min (minor), *t*_{R2} = 5.091 min (minor), *t*_{R3} = 5.151 min (major), *t*_{R4} = 5.864 min (major); e.r. (minor) = 96:4 (92% e.e.), e.r. (major) = 98.5:1.5 (97% e.e.)

[α]_D²⁵ = −61.40 (*c* = 0.589, CHCl₃).

((1*R*,2*R*,3*R*,4*S*)-3-formyl-2-methylbicyclo[2.2.1]hept-5-en-2-yl)methyl acetate (**4.2i**)



Using **4.1i** as enal. The product is obtained as mixture of isomers *endo/exo* = 83:17. Yield 50.8%, 21.2 mg, 0.102 mmol, transparent oil.

¹H NMR (501 MHz, CD₂Cl₂) δ 9.78 (d, *J* = 2.6 Hz, 1H_{min}), 9.40 (d, *J* = 3.2 Hz, 1H_{maj}), 6.38 (dd, *J* = 5.7, 3.0 Hz, 1H_{maj}), 6.26 (dd, *J* = 5.7, 3.2 Hz, 1H_{maj}), 6.20 – 6.18 (m, 2H_{min}), 4.14 (d, *J* = 10.8 Hz, 1H_{maj+min}), 4.04 (d, *J* = 10.9 Hz, 1H_{maj+min}), 3.07 – 3.02 (m, 1H_{maj+min}), 2.69 – 2.65 (m, 1H_{maj \ min}), 2.57 – 2.52 (m, 1H_{maj \ min}), 2.07 (s, 3H_{maj}), 2.05 (s, 3H_{min}), 1.66 (dt, *J* = 9.1, 1.7 Hz, 1H_{maj+min}), 1.48 (dt, *J* = 9.1, 1.8 Hz, 1H_{maj+min}), 1.21 (s, 3H_{min}), 0.97 (s, 3H_{maj}).

¹³C NMR (75 MHz, CD₂Cl₂) δ 205.0_{maj}, 204.8_{min}, 171.2_{maj+min}, 137.3_{maj}, 137.0_{min}, 136.6_{min},

135.7_{maj}, 73.1_{maj}, 72.5_{min}, 59.4_{maj}, 57.0_{min}, 51.5_{min}, 50.1_{maj}, 48.0_{min}, 47.0_{maj}, 46.3_{maj+min}, 45.9_{maj}, 44.2_{min}, 21.3_{min}, 20.9_{maj}, 19.6_{maj+min}.

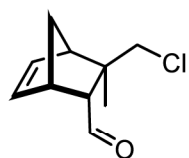
HRMS m/z (GC-EI): calcd. for C₁₂H₁₆O₃Na ([M+Na]⁺): 231.099715; found 231.099721.

GC (24.5 m Ivadex-1, injection temperature: 220 °C; 100 °C – iso 10 min, 1 °C/min, 180 °C – iso 10 min; 5 °C/min, 220 °C – iso 10 min; 0.5 bar H₂).

t_{R1} = 34.30 min (*minor*), t_{R2} = 34.66 min (*minor*), t_{R3} = 35.39 min (*major*), t_{R4} = 36.24 min (*major*); e.r. (*minor*) = 66:34 (32% e.e.), e.r. (*major*) = 97:3 (94% e.e.).

$[\alpha]_D^{25} = -57.70$ ($c = 0.310$, CHCl₃).

(1*S*,2*R*,3*R*,4*R*)-3-(chloromethyl)-3-methylbicyclo[2.2.1]hept-5-ene-2-carbaldehyde (4.2k)



Using **4.1k** as enal. The product is obtained as mixture of isomers *endo/exo* = 88:12. Yield 32.7%, 12.1 mg, 0.065 mmol, transparent oil.

¹H NMR (501 MHz, CD₂Cl₂) δ 9.77 (d, $J = 2.6$ Hz, 1H_{min}), 9.41 (d, $J = 2.7$ Hz, 1H_{maj}), 6.38 (dd, $J = 5.7, 2.9$ Hz, 1H_{maj+min}), 6.25 (dd, $J = 5.7, 3.2$ Hz, 1H_{maj+min}), 3.72 (d, $J = 10.7$ Hz, 1H_{maj+min}), 3.64 (d, $J = 10.8$ Hz, 1H_{maj+min}), 3.08–3.03 (m, 1H_{maj+min}), 2.72–2.69 (m, 1H_{maj+min}), 2.65 (t, $J = 3.1$ Hz, 1H_{maj+min}), 1.62 (dt, $J = 9.1, 1.7$ Hz, 1H_{maj+min}), 1.50 (dt, $J = 9.1, 1.9$ Hz, 1H_{maj+min}), 1.30 (s, 3H_{min}), 1.05 (s, 3H_{maj}).

¹³C NMR (126 MHz, CD₂Cl₂) δ 204.64_{maj}, 204.55_{min}, 137.12_{maj}, 137.08_{min}, 136.9_{min}, 136.0_{maj}, 60.6_{maj}, 58.5_{min}, 56.9_{maj}, 56.0_{min}, 52.32_{min}, 51.35_{maj}, 49.9_{maj+min}, 46.9_{maj}, 46.7_{min}, 45.9_{maj}, 44.6_{min}, 21.5_{min}, 20.0_{maj}.

HRMS m/z (GC-EI): calcd. for C₁₀H₁₃ClO₁Na₁ ([M+Na]⁺): 207.055263; found 207.055260.

GC (29.5 m BGB-176, injection temperature: 220 °C; 100 °C–iso 5 min, 1 °C/min, 180 °C; 5 °C/min, 220 °C iso 10 min, 0.5 bar H₂).

t_{R1} = 60.03 min (*minor*), t_{R2} = 60.66 min (*minor*), t_{R3} = 64.43 min (*major*), t_{R4} = 65.19 min (*major*); e.r. (*minor*) = 93:7 (86% e.e.), e.r. (*major*) = 99:1 (98% e.e.).

$[\alpha]_D^{25} = -31.27$ ($c = 0.366$, CHCl₃).

7.4. Total Synthesis of (–)-(Z)- β -Santalol

Upscaling of the Diels-Alder Reaction to 100 mmol

Activated (dried in high vacuum oven at 130 °C for 2 days) molecular sieves 5 Å (35.0 g) and IDPi catalyst **4.3e** (1.48 mol%, 1.48 mmol, 2.47 g) were loaded into a flame-dried two-necked 250 mL round-bottom flask equipped with a stirring bar under Ar flow. MTBE (1.7 M, 60.0 mL) was added and the obtained mixture was stirred for 15 min at room temperature. Then the reaction vessel was cooled down in dry ice bath and cyclopentadiene (2.5 equiv., 250.0 mmol, 20.6 mL) was added. The resulting mixture was stirred for 10 min in dry ice before adding geranial **4.1b-(E)** (1 equiv., 100.0 mmol, 17.1 mL). The reaction vessel was placed in –40 °C cryostat filled with EtOH as cooling agent and stirred for 7 days.

After completion of the reaction, it was quenched by the addition of triethylamine (0.03 equiv., 0.4 mL) and allowed to warm up to room temperature. Molecular sieves were removed by filtration through a fritted glass filter and obtained solution was concentrated under reduced pressure.

The crude product was purified by column chromatography hexane/MTBE (9:1) to afford 14.7 g (67.4% yield) of the pure product **4.2b** with 87:13 *endo/exo* ratio and 99:1 e.r. (*endo*) as yellowish oil. (We attempted to perform vacuum distillation of the product from the crude reaction mixture as well, but it resulted in the severe reduction of the yield of the product, probably due to the side reactions taking place at elevated temperatures and presence of other reactive compounds in the reaction mixture).

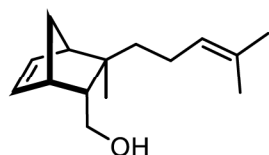
The catalyst was recovered by washing the chromatography column with hexane/MTBE (1:1) and acidified over Dowex® resin. After drying in high vacuum at 40 °C for 24 hours 2.40 g (97.2%) of the IDPi catalyst were recovered.

((1S,2R,3R,4R)-3-methyl-3-(4-methylpent-3-en-1-yl)bicyclo[2.2.1]hept-5-en-2-yl) methan-ol (4.4)

To a stirred solution of aldehyde obtained in previous step (1.0 equiv., 13.78 mmol, 3.02 g) in EtOH (0.17 M, 80.0 mL) was added NaBH₄ (1.5 equiv., 20.68 mmol, 782.0 mg) at room temperature and stirring was continued for 3 h. The reaction mixture was diluted with Et₂O (80.0 mL), washed with H₂O (3x150 mL) and saturated aqueous NaCl (200 mL), dried over anhydrous MgSO₄ and concentrated under reduced pressure to give crude alcohol which was

purified by column chromatography pentane/MTBE (4:1) to afford the pure product in 92.3% yield (2.79 g, 12.68 mmol) as colorless oil.

The product is obtained as mixture of isomers *endo/exo* = 87:13, NMR data for the major (*endo*) diastereomer is reported.



¹H NMR (501 MHz, CDCl₃) δ 6.23 (dd, *J* = 5.7, 3.1 Hz, 1H), 6.18–6.13 (m, 1H), 5.13 (tdd, *J* = 7.2, 2.9, 1.5 Hz, 1H), 3.45 (dd, *J* = 10.5, 6.1 Hz, 1H), 3.27–3.19 (m, 2H+1H), 2.90–2.85 (m, 1H), 2.46–2.41 (m, 1H), 2.04 (dq, *J* = 12.7, 6.7 Hz, 2H), 1.68 (bs, 3H), 1.66–1.58 (m, 3H+1H), 1.58–1.49 (m, 1H), 1.51–1.38 (m, 2H), 0.75 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 138.6, 133.9, 131.3, 125.1, 64.8, 53.3, 51.4, 46.7, 45.5, 44.8, 43.8, 25.8, 23.9, 18.9, 17.8.

HRMS *m/z* (GC-EI): calcd. for C₁₅H₂₄O₁ ([M]⁺): 220.182165; found 220.182270.

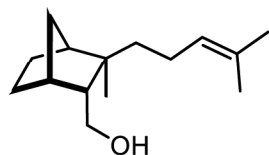
[α]_D²⁵ = −17.59 (*c* = 0.71, CHCl₃)

((1*R*,2*R*,3*R*,4*S*)-3-methyl-3-(4-methylpent-3-en-1-yl)bicyclo[2.2.1]heptan-2-yl)methanol (4.5)

The procedure is adopted from Baldovini and Solladié.¹⁴⁰

To a solution of Ni(OAc)₂·4H₂O (0.20 equiv., 585.0 mg, 2.35 mmol) in 95% ethanol (100.0 mL) was added in one portion a solution of NaBH₄ (0.16 equiv., 71.1 mg, 1.88 mmol) and NaOH (0.008 equiv., 3.8 mg, 0.094 mmol) in aqueous ethanol (35.0 mL EtOH + 0.5 mL of H₂O). The reaction flask was purged with H₂ and the unsaturated alcohol from the previous step (1.0 equiv., 2.59 g, 11.75 mmol) was added as a solution in 20 mL of EtOH. The obtained reaction mixture was stirred at room temperature for 3 h under H₂ atmosphere.

The reaction mixture was then poured into 1 M HCl (150 mL) and extracted with diethyl ether (2x100 mL). The organic phases were washed with brine, dried over MgSO₄ and evaporated to afford the crude product which was purified by column chromatography pentane/MTBE (4:1) to afford the pure product in 82.0% yield (2.14 g, 9.63 mmol) as colorless oil.



¹H NMR (501 MHz, CDCl₃) mixture of two diastereomers *endo/exo* = 88:12, NMR data for the major diastereomer is reported. δ 5.08 (dddd, J = 8.5, 5.7, 2.9, 1.4 Hz, 1H), 3.61 (d, J = 7.8 Hz, 2H), 2.30–2.24 (m, 1H), 1.96–1.85 (m, 1H+2H), 1.67 (d, J = 1.5 Hz, 3H), 1.65–1.54 (m, 3H+3H), 1.51–1.44 (m, 1H), 1.40–1.23 (m, 4H), 1.19 (dt, J = 9.7, 1.7 Hz, 1H), 0.81 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 131.1, 125.0, 61.3, 51.7, 47.2, 44.7, 39.9, 39.3, 37.0, 25.7, 24.6, 22.9, 20.7, 17.6, 17.0.

HRMS m/z (API-MS): calcd. for C₁₅H₂₄O₁Na₁ ([M+Na]⁺): 245.187584; found 245.187410.

$[\alpha]_D^{25} = -3.55$ (c = 0.56, CHCl₃)

One-Pot Procedure for Reduction of Aldehyde and C=C Bond

To a solution of Ni(OAc)₂·4H₂O (0.20 equiv.) in 95% ethanol was added in one portion a solution of NaBH₄ (0.16 equiv.) and NaOH (0.008 equiv.) in aqueous ethanol. The reaction flask was purged with H₂ and the unsaturated alcohol (1.0 equiv.) was added as a solution in EtOH. The obtained reaction mixture was stirred at room temperature for 3 h under H₂ atmosphere.

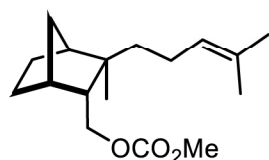
Then NaBH₄ (2.0 equiv.) was added and the reaction was left overnight at room temperature.

The reaction mixture was then poured into 1 M HCl (150 mL) and extracted with diethyl ether (2x100 mL). The organic phases were washed with brine, dried over MgSO₄ and evaporated to afford the crude product, which was purified by column chromatography pentane/MTBE (4:1) to afford the pure product in overall 70.6% yield (2.35 g, 10.59 mmol) starting with 15.0 mmol of aldehyde **4.2b**.

Methyl (((1*R*,2*R*,3*R*,4*S*)-3-methyl-3-(4-methylpent-3-en-1-yl)bicyclo[2.2.1]heptan-2-yl)methyl) carbonate (4.7**)**

To a solution of the alcohol (1.0 equiv., 1.43 g, 6.42 mmol) and pyridine (6 equiv., 38.52 mmol, 3.13 mL) in DCM (20 mL) cooled in an ice bath methyl chloroformate (1.5 equiv., 0.75 mL, 9.63 mmol) was slowly added. After the addition was complete, stirring was continued at 0°C overnight. The reaction mixture was carefully washed with 1 M HCl (2x100 mL) and then

with saturated solution of NaHCO_3 (150 mL). Aqueous layer was extracted with DCM (100 mL), organic layers were combined and washed with brine (200 mL) and finally dried over anhydrous Na_2SO_4 . The solvent was evaporated to afford the crude product which was purified by column chromatography pentane/MTBE (9:1) to afford the pure product in 88.7% yield (1.59 g, 5.69 mmol).



Mixture of two diastereomers *endo/exo* = 90:10, NMR data for the major diastereomer is reported.

^1H NMR (501 MHz, CDCl_3) δ 5.08 (tdp, J = 6.9, 4.2, 1.4 Hz, 1H), 4.16 – 4.11 (m, 2H), 3.76 (s, 3H), 2.28 – 2.22 (m, 1H), 1.96 – 1.85 (m, 1H+2H), 1.83 – 1.75 (m, 1H), 1.67 (bs, 3H), 1.65 – 1.58 (m, 2H+3H), 1.41 – 1.24 (m, 5H), 1.20 (dt, J = 9.8, 1.7 Hz, 1H), 0.84 (s, 3H).

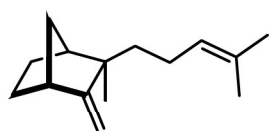
^{13}C NMR (126 MHz, CDCl_3) δ 156.3, 131.5, 125.3, 67.6, 55.0, 48.1, 47.6, 44.8, 40.4, 40.1, 37.4, 26.1, 24.9, 23.2, 21.2, 18.0, 17.6.

HRMS m/z (API-MS): calcd. for $\text{C}_{17}\text{H}_{28}\text{O}_3\text{Na}_1$ ($[\text{M}+\text{Na}]^+$): 303.193064; found 303.193094.

$[\alpha]_{\text{D}}^{25} = -14.36$ (c = 0.59, CHCl_3)

(1*S*,2*R*,4*R*)-2-methyl-3-methylene-2-(4-methylpent-3-en-1-yl)bicyclo[2.2.1]heptane, (–)- β -santalene (2.16)

The carbonate obtained in the previous step (1.12 g, 4.0 mmol) was pyrolyzed at 580 °C (10 ml/min, quartz tube, N_2) in a tube oven. Obtained oil was purified column chromatography pentane/MTBE (100:1) to afford the pure product in 64.0% (522.5 mg, 2.55 mmol or 87.3% brsm) yield as yellowish oil. After washing the chromatography column with *n*-pentane/MTBE (10:1), 302.6 mg (27.0%, 1.08 mmol) of the remaining carbonate were recovered.



^1H NMR (501 MHz, CD_2Cl_2) mixture of two diastereomers *endo/exo* = 92:8, NMR data for the major diastereomer is reported δ 5.10 (tp, J = 7.1, 1.4 Hz, 1H), 4.72 (bs, 1H), 4.47 (bs, 1H), 2.65 (dd, J = 4.5, 1.8 Hz, 1H), 2.14 (bd, J = 4.1 Hz, 1H), 2.06 – 1.88 (m, 2H), 1.73 – 1.59 (m, 3H+3H+3H), 1.46 – 1.34 (m, 2H), 1.29 – 1.16 (m, 4H), 1.05 (s, 3H).

^{13}C NMR (126 MHz, CD_2Cl_2) δ 167.1, 131.4, 125.5, 99.7, 47.4, 45.2, 45.1, 41.7, 37.5, 30.2, 25.9, 24.1, 24.0, 22.9, 17.7.

HRMS m/z (API-MS): calcd. for $C_{15}H_{25}$ ($[M+H]^+$): 205.19508; found 205.19502.

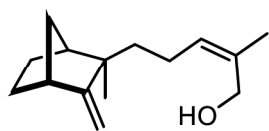
$[\alpha]_D^{25} = -102.16$ ($c = 0.69$, $CHCl_3$).

The spectroscopic data and physical properties are in accordance with the literature.^{193,228}

(*Z*)-2-methyl-5-((1*S*,2*R*,4*R*)-2-methyl-3-methylenebicyclo[2.2.1]heptan-2-yl)pent-2-en-1-ol, (–)-(*Z*)- β -santalol (2.15)

*The procedure is adopted from Clanton et al.*²¹⁰

To solution of potassium *tert*-butoxide (3 equiv., 444.8 mg, 3.96 mmol) in THF (20 mL) cooled down to -78°C 2.5 M *n*-BuLi in hexanes (3 equiv., 1.60 mL, 3.96 mmol) was added dropwise. The resulting yellow solution was stirred for 15 min before adding dropwise 2,2,6,6-tetramethylpiperidine (3 equiv., 0.67 mL, 3.96 mmol). The obtained solution was further stirred for 15 min before adding solution (–)- β -santalene (1 equiv., 270.0 mg, 1.32 mmol) in 2 mL of THF. The reaction mixture was stirred for 1 hour at -78°C . Then triisopropylborate (3 equiv., 0.91 mL, 3.96 mmol) was added and the reaction was allowed to warm to room temperature. Aqueous hydrogen peroxide solution (35%, 6 equiv., 0.77 mL, 7.93 mmol) was added slowly and the reaction was stirred for an additional 1 hour. The reaction was diluted with water (70 mL) and extracted with MTBE (3x30 mL), washed with 1 M HCl (20 mL), and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4 , concentrated and purified by column chromatography: starting with *n*-pentane/MTBE (100:1) delivered (–)- β -santalene **6** ($R_f = 0.95$, 68.5 mg, 0.34 mmol, 25.7% recovered) and moving to *n*-pentane/EA = 4:1 to afford the pure product in 48.2% (or 65.3% brsm) yield ($R_f = 0.45$, 140.1 mg, 0.64 mmol).



^1H NMR (501 MHz, $CDCl_3$) mixture of *endo/exo* = 92:8 and *Z/E* = 97:3.
 δ 5.27 (td, $J = 7.5, 1.6$ Hz, 1H), 4.72 (s, 1H), 4.46 (s, 1H), 4.10 (s, 2H), 2.65 (dd, $J = 4.5, 1.7$ Hz, 1H), 2.11 (d, $J = 4.2$ Hz, 1H), 2.09 – 1.98 (m, 2H), 1.78 – 1.74 (m, 3H), 1.72 – 1.59 (m, 3H+1H(OH)), 1.46 – 1.35 (m, 2H), 1.27 – 1.20 (m, 3H), 1.04 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.2, 134.6, 128.9, 99.8, 61.7, 47.3, 45.12, 45.07, 41.9, 37.4, 30.1, 24.0, 23.6, 22.8, 21.3.

HRMS m/z (API-MS): calcd. for $C_{15}H_{24}O_1Na_1$ ($[M+Na]^+$): 243.171934; found 243.171850.

$[\alpha]_{\text{D}}^{25} = -104.47$ ($c = 0.52$, CHCl_3)

HPLC (Chiralpak IG-3, *n*-heptane/2-propanol = 99.5:0.5, 294 K, 210 nm).

$t_{\text{R}1} = 15.31$ min (minor diastereomer, not baseline separation), $t_{\text{R}2} = 18.48$ min (*major*), $t_{\text{R}3} = 20.81$ min (*major*); e.r. (*major*) = 99:1 (98% e.e.).

The spectroscopic data and physical properties are in accordance with the literature.^{136,229–231}

7.5. Mechanistic Investigations

Synthesis of sodium salt of 4.3e (4.3e - Na salt)

In a glass vial 8.0 mg of **4.3e** were dissolved in 300 μL of DCM followed by addition of 300 μL of distilled water. Then Na_2CO_3 (1.5 equiv., 0.0073 mmol, 0.8 mg) was added to the vial. The obtained biphasic mixture was vigorously stirred for 3 hours and then centrifuged to separate the layers. The upper layer was removed using syringe, the remaining organic solution was evaporated to dryness and then dried in high vacuum at 40 $^\circ\text{C}$ for 2 days.

^{31}P NMR (203 MHz, CD_2Cl_2) δ 1.13.

Preparation of NH_4NO_3 treated MS (H-5 Å MS)

5 Å MS (5 g) were combined with 200 mL of freshly prepared 1 M NH_4NO_3 solution in round-bottom flask equipped with a condenser. The resulting mixture was vigorously stirred with 80 $^\circ\text{C}$ for 5 h. The mixture was then filtered through a fritted glass filter several times (using the same filter) and the obtained solid was used in the ion exchange procedure described above again. After filtration the solid residue washed several times with distilled water and transferred to a beaker for drying overnight at room temperature, followed by 12 h drying in oven at 120 $^\circ\text{C}$.

The obtained solid was calcinated in an electric heated furnace (Dekema Austromat 654i G2) at 550 $^\circ\text{C}$ for 6 h, heating rate was 1 $^\circ\text{C}/\text{min}$. Next, the obtained material was cooled to room temperature and transferred to a Schlenk flask for storage.

Comparison of MS before and after Diels-Alder reaction

Powder XRD analysis

The possible changes in the crystal structure of MS due to participation in reaction processes or decomposition were attempted to detect using powder XRD analysis. Three samples were prepared:

1 – 5 Å MS high vacuum oven dried at 125 $^\circ\text{C}$, stored under Ar (black) – standard approach for big scales;

2 – 5 Å MS flame torch dried in a reaction vial under vacuum (red) – alternative

approach, convenient for small scales;

3 – 5 Å MS recovered after reaction and dried at 80 °C in an oven for 24 (blue).

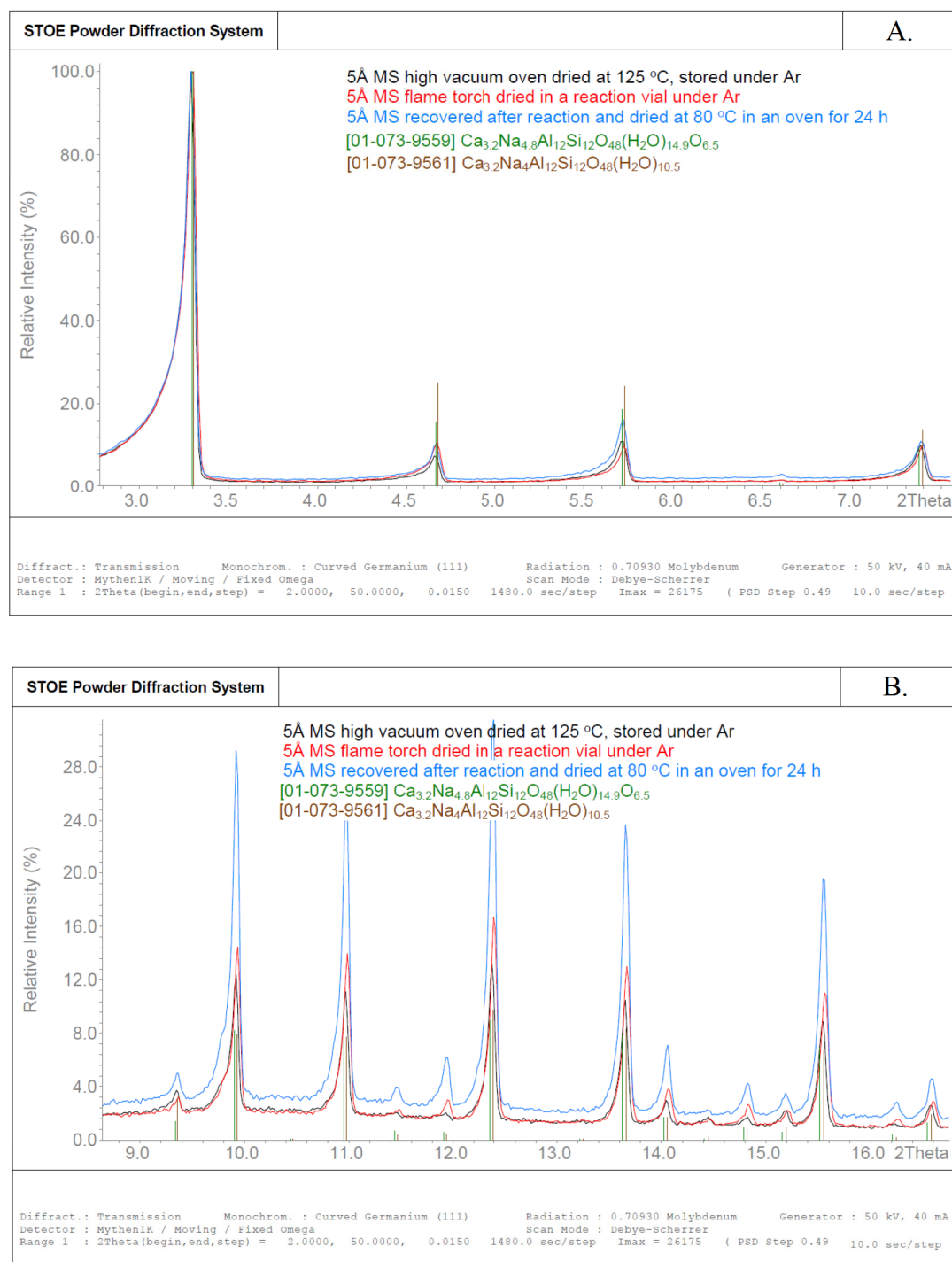


Figure 48. Comparison of XRD patterns of 5 Å MS before and after the Diels-Alder reaction, and reference patterns of the corresponding zeolites. A. Zoom-in 0.0 to 8.0 2θ ; B. Zoom-in 8.5 to 16.5 2θ

The data was collected using Stoe STADI P Transmission Powder Diffractometer,

equipped with a molybdenum ($\lambda = 0.70930 \text{ \AA}$) X-ray source, curved germanium primary monochromators, and a Mythen detector.

The obtained data compared with the database references as well, namely calcium sodium aluminum silicate hydrates $\text{Ca}_{3.2}\text{Na}_{4.8}\text{Al}_{12}\text{Si}_{12}\text{O}_{48}(\text{H}_2\text{O})_{14.9}\text{O}_{6.5}$ [01-073-9559] (green) and $\text{Ca}_{3.2}\text{Na}_4\text{Al}_{12}\text{Si}_{12}\text{O}_{48}(\text{H}_2\text{O})_{10.5}$ [01-073-9561] (brown) representing corresponding LTA zeolites. The crystal structure of the prepared samples wasn't affected in all cases and was in accordance with the referenced compounds, as can be seen from the matching of XRD patterns (Figure 48). It thus can be concluded that MS do not undergo significant decomposition during flame drying and the reaction course. MS sample obtained after the reaction (3, blue) displayed slight shifts of the key peaks as well as slightly increased intensity of them, indicating the increase of electron density inside the channels. In case of zeolites it might indicate presence of the of guest molecules, for example water.

Performed TGA-MS analysis of the sample 3 showed total loss of mass of 19.5% which corresponds to the loss of water detected by MS and in accordance with typical adsorbing capacity of 5 Å MS (20–21% w/w). No other adsorbed compounds were detected in significant amounts in the sample.

¹³C Kinetic Isotope Effect (KIE) at Natural Abundance

For the determination of ¹³C KIE at natural abundance 100 mg of alcohol **4.4** were used. *Major (endo)* isomer was separated using preparative HPLC (Kromasil 100-5-C18, acetonitrile/water = 50:50, 42.5 mL/min, 13.5 MPa, 308 K; retention time (*endo*) = 62.5 min).

Table 5. Crude dataset of the ¹³C KIE measurements

#	Integrals				Relative Integrals			
	C3	C4	C5	C6	C3	C4	C5	C6
1	1.7224	1.6377	1.6320	1.6692	1.0000	1.0000	0.9966	0.9691
2	1.7246	1.6264	1.6319	1.6574	1.0000	1.0000	1.0034	0.9610
3	1.7222	1.6346	1.6220	1.6587	1.0000	1.0000	0.9923	0.9631
4	1.7302	1.6261	1.6198	1.6526	1.0000	1.0000	0.9961	0.9551
5	1.7229	1.6271	1.6154	1.6608	1.0000	1.0000	0.9928	0.9639
6	1.7290	1.6252	1.6301	1.6565	1.0000	1.0000	1.0030	0.9580
7	1.7199	1.6255	1.6208	1.6540	1.0000	1.0000	0.9971	0.9617
8	1.7172	1.6267	1.6228	1.6495	1.0000	1.0000	0.9976	0.9606
average					1.000	1.000	0.997	0.962
					± 0.000	± 0.000	± 0.004	± 0.004

KIE ($^{12}\text{C}/^{13}\text{C}$)					KIE ($^{12}\text{C}/^{13}\text{C}$)				
#	C3	C4	C5	C6	#	C3	C4	C5	C6
1	1.000	1.000	1.003	1.032	5	1.000	1.000	1.007	1.037
2	1.000	1.000	0.997	1.041	6	1.000	1.000	0.997	1.044
3	1.000	1.000	1.008	1.038	7	1.000	1.000	1.003	1.040
4	1.000	1.000	1.004	1.047	8	1.000	1.000	1.002	1.041
average						1.000	1.000	1.003	1.040
						± 0.000	± 0.000	± 0.004	± 0.004

Catalyst stability in the presence of MTBE and water

As mentioned in the chapter 4.2.5 in the absence of MS we detected slow decomposition of IDPi.

To test these five samples were prepared by dissolving 5.0 mg of IDPi **4.3e** in 300 mL of MTBE in a flame dried NMR tubes with toluene- d_8 inlet. Optionally 15 mg of 5 Å MS were added. The samples were monitored using ^{31}P NMR over period of several days at room temperature. To ensure homogeneity and emulate reaction condition samples were periodically shaken using vortex mixer (every ~8 h). The representative ^{31}P NMR shown in Figure 49.

As can be seen in sample 2 after one day in MTBE without MS IDPi starts to slowly convert to a new product. As it was shown Chapter 4.3.5 by ^1H - ^{31}P correlation spectra this product most probably corresponds to the alkylation of the IDPi inner core **4.3-IDPi-A**.

After 5 days (sample 3) further decomposition to **4.3e-iIDP** starting to be observed (most probably accelerated by slow penetration of water from air). The presence of *iIDP* was corroborated by mass spectroscopy as well. We couldn't detect **4.3-IDPi-A** at the same mass spectrum however, most probably since it can not produce characteristic negatively charged ion.

On the opposite hand, in the presence of MS (samples 4 and 5) IDPi **4.3e** appeared to be stable for the period of 5 days, showing no decomposition to the **4.3e-iIDP** and only traces of the alkylation product **4.3-IDPi-A**.

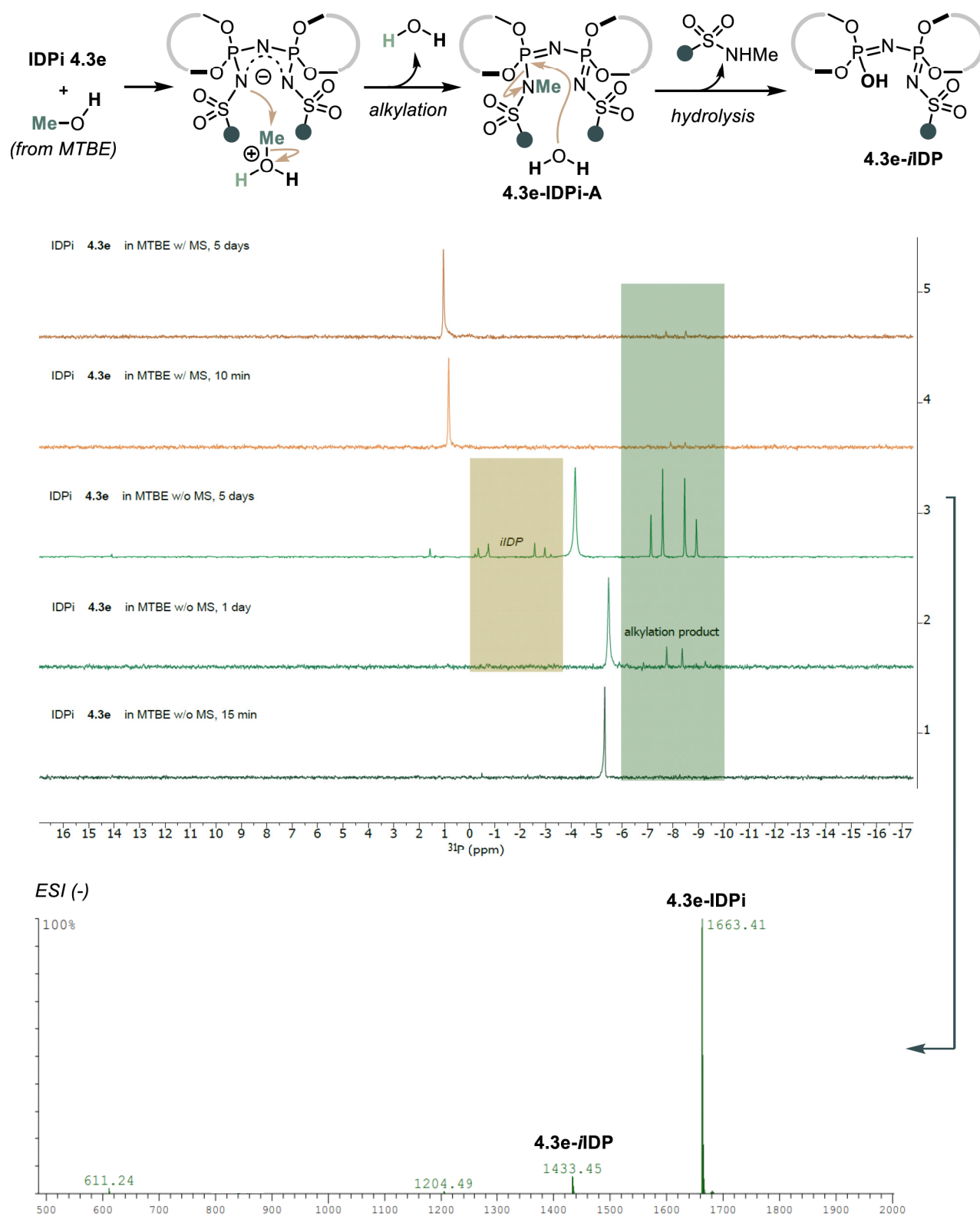
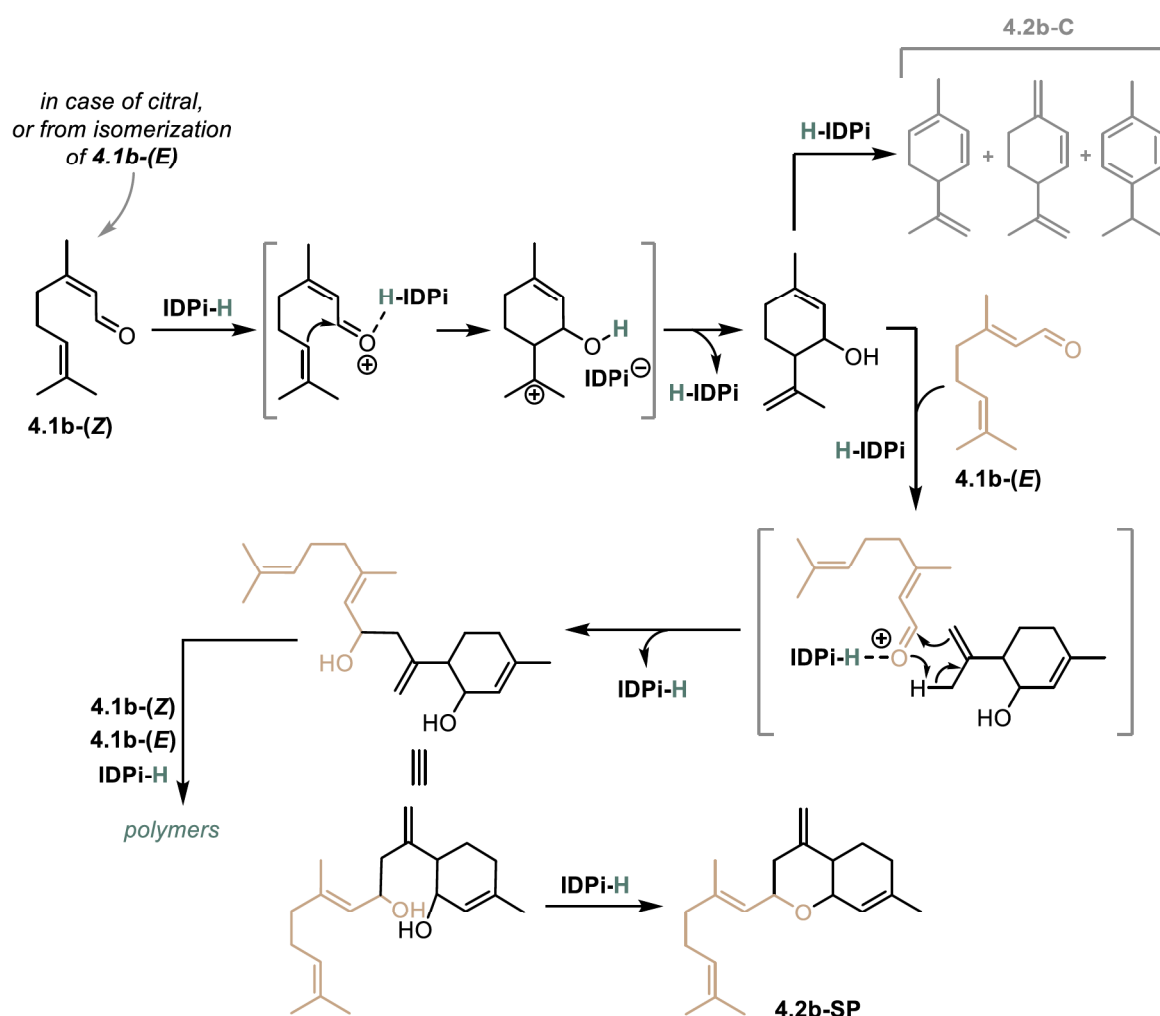


Figure 49. Possible alkylation/decomposition mechanism, NMR spectra of 4.3e in MTBE and the mass spectrum of the sample 3.

Possible mechanism of 4.2b-SP and 4.2b-C formation

The formation of **4.2b-SP** can be rationalized by IDPi-catalyzed cyclization of the **4.1b-(Z)** present when citral mixture is used, or arising from the isomerization of geranial **4.1b-(E)**. The resulting cyclic alcohol of the acid-catalyzed Prins/ene-reaction can then undergo further acid-catalyzed dehydration resulting in the formation of **4.2b-C** or engage in second Prins/ene reaction with **4.1b-(E)** present in excess compared to **4.1b-(Z)**. The resulting diol is then perfectly set up for the formation of the final tetrahydropyran fragment of **4.2b-SP**. Alternatively the diol can engage in further reaction with **4.1b-(E)** or **4.1b-(Z)** resulting in the formation of the complex polymeric mixtures (Scheme 6).



Scheme 6. Possible mechanistic pathways of the side reactions.

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