

Recent advances in the synthesis of fused and bridge oxacycles via Prins cyclization

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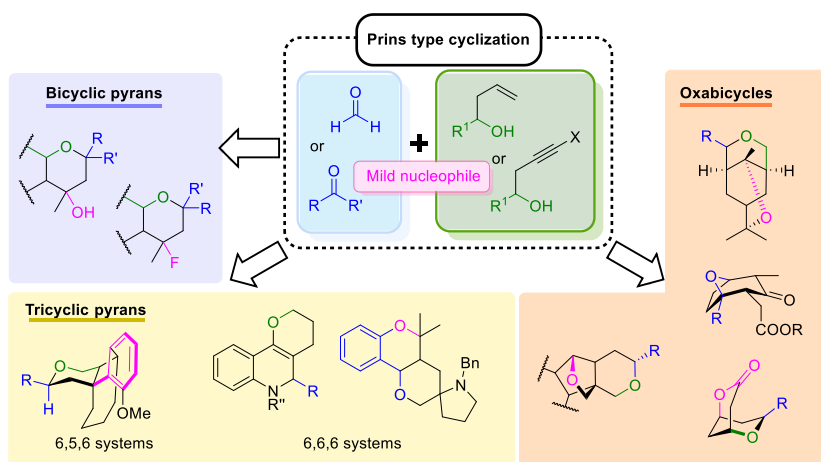
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Abstract

The Prins cyclization is a powerful and versatile synthetic platform for the construction of oxygen-containing heterocyclic frameworks of high relevance in medicinal chemistry and natural product total synthesis. Owing to the presence of heteroatoms, these motifs often display improved solubility, molecular recognition, and interactions with biological targets. Recent advances in Prins-based methodologies have significantly expanded the scope of this transformation, enabling the efficient synthesis of complex oxacyclic architectures under controlled and selective conditions. This review provides a critical overview of recent developments in Prins cyclizations for the construction of oxacycles: tetrahydropyrans and related oxygen-rich polycyclic systems.



Keywords: Prins cyclization, oxacycle, pyran, oxygenated bicycles

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1. Introduction

Heterocyclic molecules are organic compounds which are formed by a ring structure and at least one heteroatom (typically N, S or O). During the last decades, these molecules have displayed a broad range of applications in agrochemicals,¹ material sciences² and pharmaceuticals, and it is estimated that more than 70% of marketed drugs incorporate a heterocyclic scaffold as a key structural motif. The interest in heterocycles is due to the physicochemical properties provided by these scaffolds, such as enhanced aqueous solubility, modulation of pKa, and the ability to act as hydrogen-bond acceptors. These features, combined with their conformational rigidity, are essential for their biological activity in natural products. In addition, when these organic scaffolds are fused to other organic moieties, the resulting molecules commonly enhance their properties by providing multifunctional activities.^{3,4}

Among the various heteroatoms, oxygen-containing heterocycles (oxacycles) are widespread in nature. Tetrahydropyran derivatives are six-membered oxacycles which are especially prevalent due to their favourable balance between ring strain and conformational flexibility. This balance allows them to adopt low-energy chair conformations while effectively organizing substituents covering the three-dimensional space. As a result, tetrahydropyran motifs often play a decisive role in molecular recognition and biological activity.⁵ Similarly, six-membered dioxacycles, such as 1,3-dioxanes, are essential structural motifs. Beyond their conformational stability, 1,3-dioxanes often serve as rigid templates that enhance stereochemical control, serving as key frameworks in various natural products and synthetic intermediates.⁶

Besides these simple monocyclic oxacycles, more complex architectures containing multiple connected rings are also found in bioactive natural products. Fused oxacyclic systems - structures in which an oxacycle shares two adjacent atoms with another carbocyclic or heterocyclic system - are frequently found in chromenes,⁷ benzopyrans, hydrobenzopyrans,⁸ and terpene-derived polycyclic ethers. In addition, spirocyclic oxacycles - where two rings share a single common atom - have gained significant attention due to their unique three-dimensional architectures and promising biorelevance.⁹ Many of these oxacyclic systems have exhibited antiviral, anticancer, anti-inflammatory or neuroactive properties,¹⁰ making oxacycles crucial structural motifs, which play critical roles in determining the function of many drug molecules and natural products (Figure 1). For this reason, the development of efficient and economical methods for their synthesis is highly desirable.

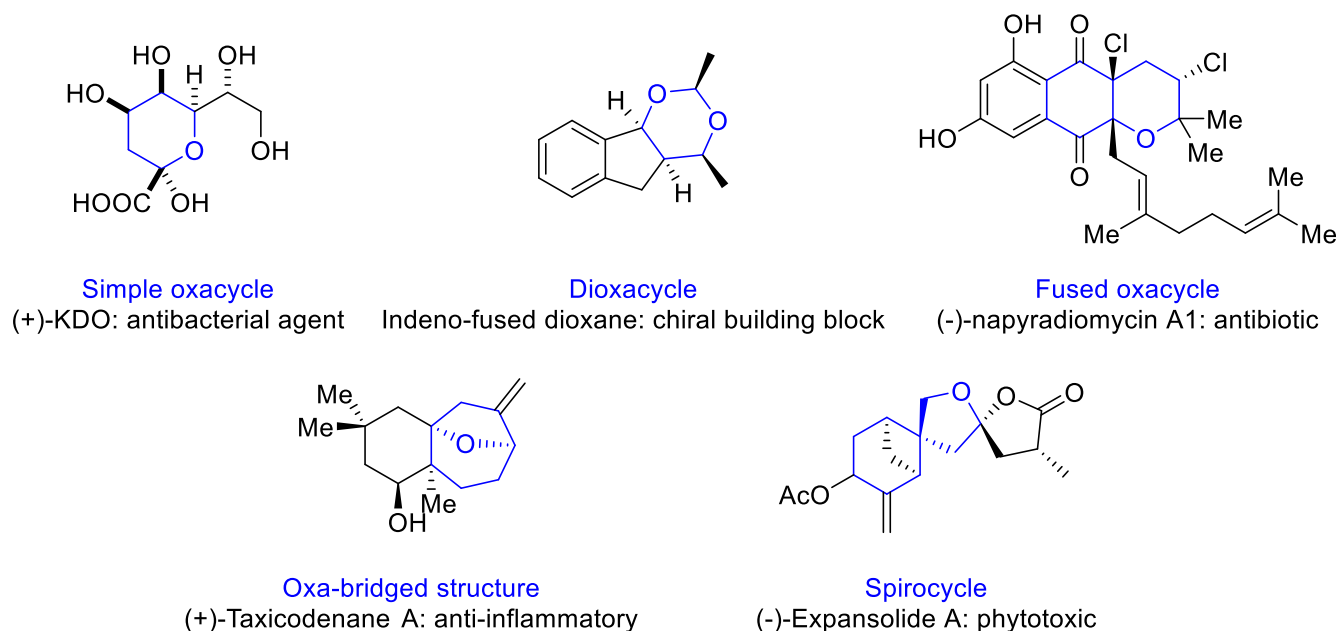
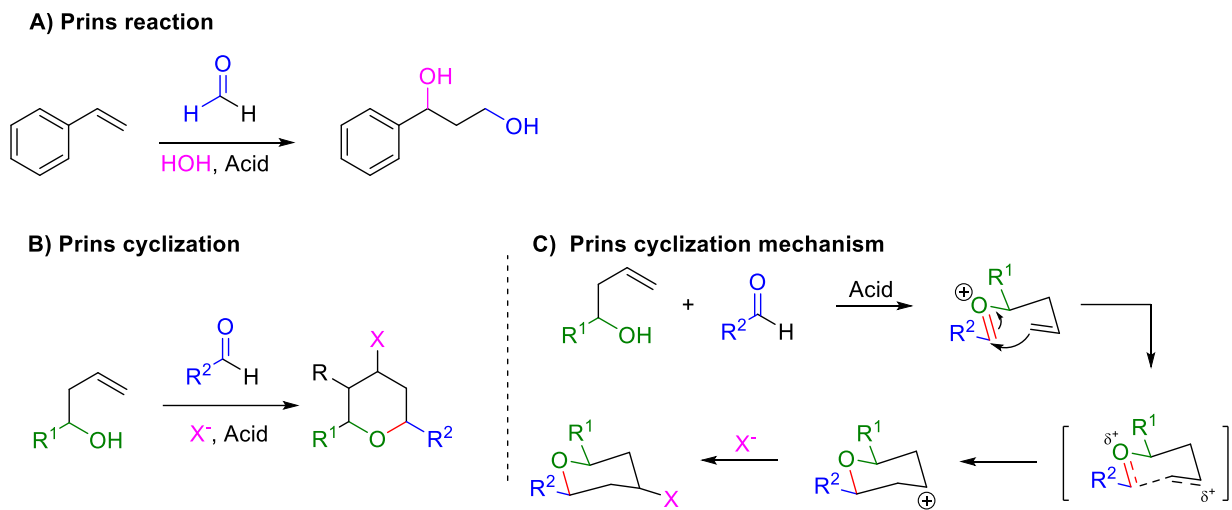


Figure 1. Types of oxacycles.^{4,6,11,12,13}

Numerous synthetic methodologies have been reported for the construction of oxygen-containing fused cycles, such as cycloadditions, radical processes, and transition-metal-catalyzed cyclizations. Nevertheless, these approaches present some disadvantages, e.g., cycloadditions require highly specialized and pre-activated substrates,¹⁰ radical processes present poor stereochemical control and undesired side reactions due to the high intermediate reactivity,¹⁴ and transition-metal-catalyzed cyclizations frequently depend on expensive, air-sensitive or toxic catalysts.¹⁵ Consequently, these methods demand the utilization of substrates with specific functional groups which limits the application of these methods in the synthesis of fused oxacyclic compounds and the exploration of functionalization processes. Therefore, the development of new strategies to synthesize fused oxygenated cyclic compounds with simple and readily available starting materials constitutes a significant opportunity in synthetic methodology.

Among the methodologies available for the construction of oxacycles, the Prins reaction has emerged as a powerful and versatile approach. The Prins reaction involves the acid-catalyzed condensation of an alkene with an aldehyde, yielding 1,3-diols (Scheme 1A). However, this classic version faces significant challenges, such as poor regioselectivity, the formation of complex mixtures of products due to carbocation rearrangements, and competition with elimination pathways that yield diene side-products.¹⁶ Due to these issues, this transformation evolved into the Prins cyclization (Scheme 1B), a process in which homoallylic alcohols react with aldehydes or related electrophiles catalyzed by Lewis or Brønsted acids. Under this approach (Scheme 1C), an oxocarbenium ion intermediate is generated, which undergoes an intramolecular cyclization to afford a tetrahydropyran framework with high levels of regio- and stereo-selective control.^{17,18} The interception of the resulting carbocation by internal or external nucleophiles provides access to a wide variety of substituted oxacycles. The broad functional-group tolerance, operational simplicity, and compatibility with cascade processes, have established Prins cyclization as a cornerstone transformation in oxacyclic chemistry. Recent years have witnessed impressive improvements in the development of new catalytic and enantioselective versions of this

transformation, allowing for more sustainable processes and better control over the molecular complexity of the resulting scaffolds.¹⁹



Scheme 1. Prototypical Prins reaction (A), General Prins cyclization (B) and its reaction mechanism (C).

Mechanistic studies have shown that the key step in the Prins cyclization is the formation of an oxocarbenium ion by condensation of the homoallylic alcohol with an activated carbonyl compound, followed by intramolecular cyclization through a chair-like transition state. Computational and experimental studies have demonstrated that the preferred geometry of this intermediate and the chair-like nature of the transition state are key factors governing the stereochemical outcome of the cyclization. Houk and Hoffmann illustrated that oxocarbenium ions preferentially adopt (*E*)geometry,²⁰ and Alder's density-functional-theory calculations revealed that the cyclization proceeds through a chair-like transition state in which substituents occupy pseudo-equatorial positions to minimize steric interactions.²¹ These mechanistic insights have enabled reliable prediction and rationalization of diastereoselectivity in the Prins cyclization.

Over the past decades, the scope of Prins chemistry has expanded far beyond simple monocyclic tetrahydropyrans. Tandem and domino variants have facilitated the rapid construction of fused bicyclic and polycyclic oxacyclic structures. These processes rely on the site-specific capture of the carbocation intermediate: while Prins/Friedel-Crafts locks the cation with an internal aromatic ring to form fused scaffolds,^{22,23} the alkynyl Prins utilizes alkynes to introduce an unsaturation,²⁴ and the Prins-Ritter reaction incorporates nitrogen functionality through nitrile trapping.²⁵ The synthetic versatility of these Prins-derived cascade processes is demonstrated by their extensive application in total synthesis of natural products.

This review summarizes recent developments reported between 2020 and 2026 in the synthesis of oxacycles in fused cyclic systems via Prins-based methodologies, highlighting reaction design, catalyst selection, and mechanistic features that govern selectivity and molecular complexity. Although spirocyclic oxacycles and dioxacycles are fundamental motifs in organic synthesis, they are beyond the scope of this work, which focuses specifically on the construction of fused architectures.

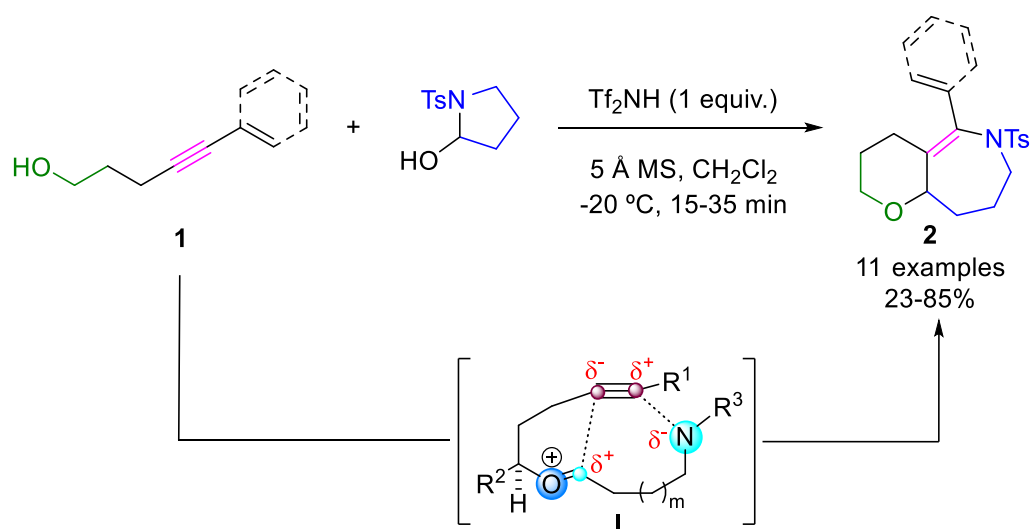
2. Bicyclic fused oxacycles

Over the past five years, the Prins reaction has evolved from a reliable method for the assembly of six-membered, oxygenated heterocycles, into a broadly applicable platform for the rapid construction of highly-substituted bicyclic, tricyclic, and bridged architectures.

Several methodologies now exploit Prins cyclizations within double- or triple-annulation sequences to assemble tricyclic cores and fused bis-heterocycles in a single operation. These contributions are unified by their reliance on strong Brønsted or Lewis acids to choreograph multiple bond-forming events, which align with the broader push toward more sustainable synthetic strategies.

Particularly, bicyclic oxacycles are essential motifs that appear in the structure of numerous natural products.²⁶ For this reason, several research groups have developed useful methodologies based on Prins cyclizations for the generation of diverse fused oxabicyclic scaffolds with demonstrated biological activity.

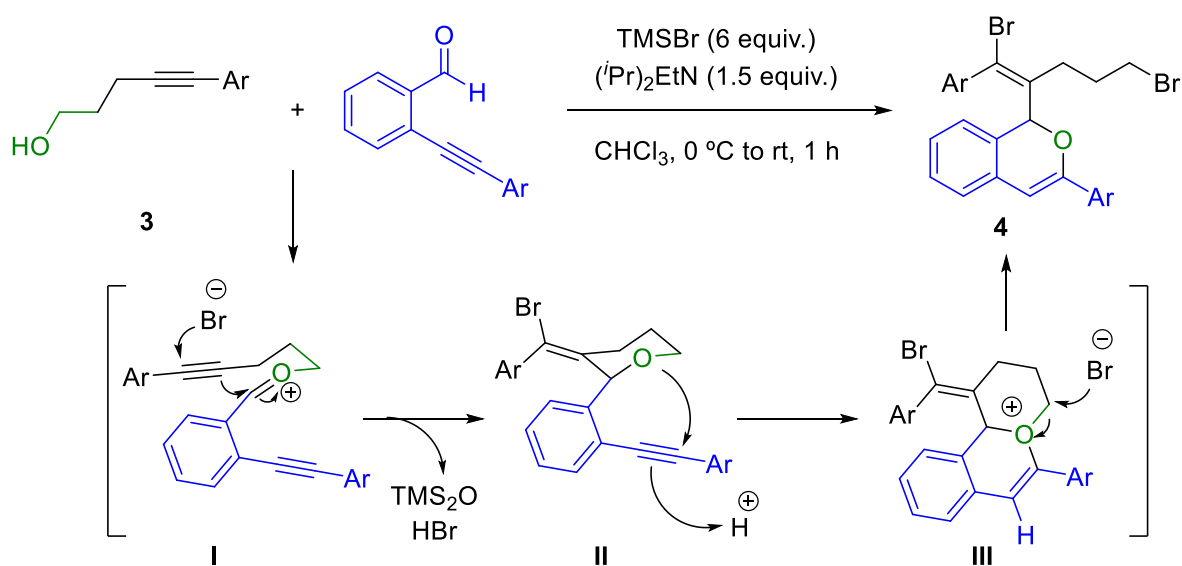
Abdul-Rashed and coworkers devised a conceptually distinctive, metal-free double annulation in which enyne or arenyne alcohols are combined with cyclic hemiaminals under strong Brønsted acid catalysis (e.g., triflimide) (Scheme 2). The hemiaminal functions as a “pincer” reagent, first generating an N-acyliminium ion that serves as an electrophile toward the enyne alcohol, and then deploys the sulfonamide nitrogen as a nucleophile to trap a vinyl cation formed during the intramolecular alkynyl Prins step. This design elegantly integrates iminium and oxocarbenium chemistry into a single cascade.²⁷ The outcome is the simultaneous formation of two heterocyclic rings and three new bonds (C–O, C–C, C–N), delivering unusual oxacyclo[3,2-c]-azepine (**2**) and -azocine architectures which are difficult to access via step-wise approaches. High diastereoselectivity is observed when chiral secondary alcohols are employed, reflecting efficient chirality transfer from the starting material into the fused-ring junction. While the requirement for strong acids and carefully designed hemiaminals may limit broad adoption, the conceptual advance lies in demonstrating that hemiaminals can be engineered as bifunctional reagents for orchestrating multi-bond-forming cationic cascades.



Scheme 2. Alkynyl Prins using cyclic hemiaminals as electrophiles by Abdul-Rashed and coworkers.

Kuan and coworkers developed a TMSBr-promoted intramolecular cyclization of (*o*-arylethynyl) benzyl ethers to generate *1H*-isochromenes structural motifs which are frequently encountered in more complex azaphilonoids, polyketide natural products and related frameworks (Scheme 3). The reaction proceeds via the formation of a vinyl carbocation stabilized by conjugated aryl groups, followed by intramolecular attack of the benzyl ether oxygen to form the pyran ring (**4**). This represents a rare example in which a benzyl ether activation is exploited not merely for deprotection, but also as a constructive element of a ring-forming sequence.

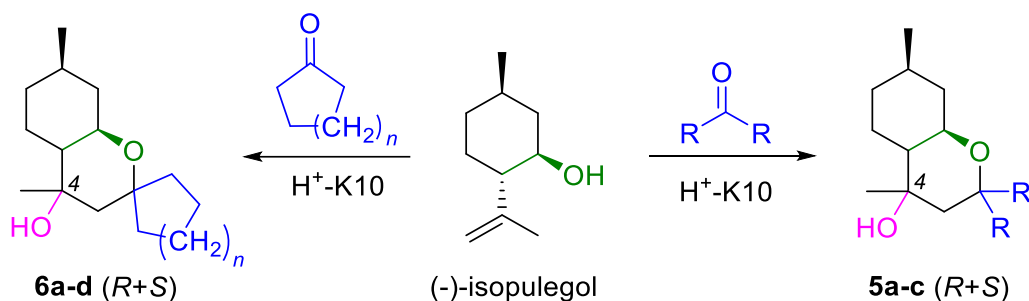
The one-pot variant was also furnished in which the required benzyl ether intermediate is generated *in situ* through an alkynyl Prins cyclization between alkynyl benzaldehydes and alkynyl alcohols in TMSBr. The initial tetrahydropyran formed via Prins cyclization undergoes ring opening and rearrangement under the influence of HBr and TMSBr to yield the final *1H*-isochromene, effectively stitching together two alkynyl fragments into a bicyclic framework.²⁸ This method exhibits wide substituent tolerance, yet it is sensitive to strongly electron-withdrawing groups, which attenuates the nucleophilicity of the benzyl oxygen, and destabilizes the cationic intermediates. This sensitivity delineates a current boundary condition for further expansion towards highly electron-poor systems.



Scheme 3. Mechanistic proposal for *1H*-isochromene derivatives' synthesis.

Another example is the synthesis of octahydro-*2H*-chromenes carried out by Volcho and coworkers to obtain new chiral heterocyclic compounds derived from natural substances, such as the monoterpene (-)-isopulegol (Scheme 4).²⁹ In this instance, they synthesized novel agents against influenza A and B viruses with an octahydro-*2H*-chromene framework from the Prins cyclization of (-)-isopulegol and different symmetric aliphatic and cyclic ketones. The reaction was performed employing montmorillonite clay K10 pretreated with 1 M HCl (H⁺-K10) as a catalyst, at room temperature without solvent for 2 h (2.5 h in the case of acetone). The use of clay H⁺-K10 allows, in some cases, the reduction of the amount of dehydration products formed during the reaction outcome, as well as increasing the yields of the target octahydro-*2H*-chromen-4-ols. The yield decreased when using ketones with a larger carbon backbones and with a larger ring size. Furthermore, in

reactions with pentanone and heptanone, only trace amounts of 4*S*-isomers were obtained. When using cyclic ketones, the 4*S*-isomer was only produced in the reaction between (-)-isopulegol and cyclopentanone.



Scheme 4. Synthesis of antiviral and analgesic isopulegol-derived octahydro-2*H*-chromenols.

Isopulegol-derived chromenols exhibited potent antiviral activity against influenza A H1N1 Puerto Rico 8/34, with IC_{50} values ranging from 7.5 μM for the lead compound **4*R*-5a** (acetone-derived, $\text{SI} = 189$) to >100 μM for derivatives bearing longer alkyl chains. Spirocyclic chromenols showed size-dependent activity: cyclopentanone **4*R*-6a** was highly potent ($\text{IC}_{50} = 8.4 \mu\text{M}$, $\text{SI} = 96$) whereas cyclohexanone **4*R*-6b** ($\text{IC}_{50} = 18.3 \mu\text{M}$, $\text{SI} = 34$) and larger rings (**6c**, **6d**, $\text{SI} \sim 3$) exhibited lower antiviral activity and, in some cases, reduced selectivity index and increased cytotoxicity. In parallel, analgesic screening (10 $\text{mg}\cdot\text{kg}^{-1}$ p.o.) of acetone and 3-pentanone derivatives (**4*R*-5a**, **4*R*-5b**) suppressed writhing by 44–57%; 4-heptanone derivative **4*R*-5c** showed hot-plate activity, while free-OH spirocycles **6a–d** were inactive. Overall, 4*R*-acetone and spirocyclopentyl chromenols demonstrated dual therapeutic potential, the size of substituents in the C2 and C4 stereochemistry being critical to control dual antiviral/analgesic profiles.^{29,30}

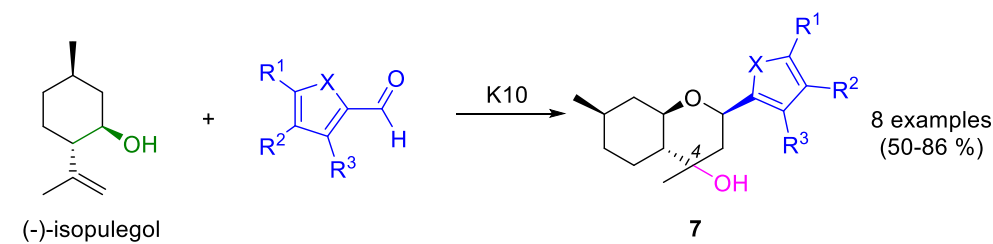
Table 1. Scope of the reaction with aliphatic or cyclic ketones, yields and diastereomeric ratios.

<i>n</i>	Product	Yield (%)	4 <i>R</i> :4 <i>S</i>	R	Product	Yield (%)	4 <i>R</i> :4 <i>S</i>
1	4<i>R</i>-6a + 4<i>S</i>-6a	26	17:1	Me	4<i>R</i>-5a + 4<i>S</i>-5a	57	3:1
2	4<i>R</i>-6b	30	-	Et	4<i>R</i>-5b	28	-
3	4<i>R</i>-6c	17	-	Pr ⁿ	4<i>R</i>-5c	19	-
4	4<i>R</i>-6d	17	-				

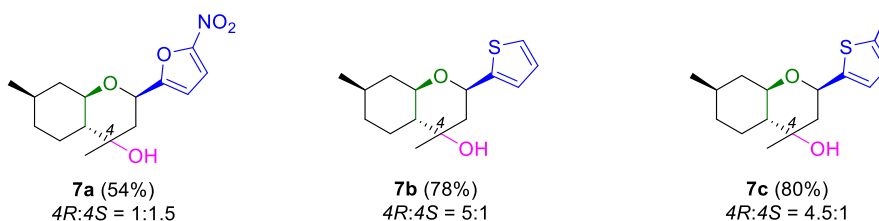
The reaction was also performed using aldehydes as electrophiles, but the antiviral activity obtained for the derived compounds was only moderate.²⁹ However, when aldehydes with heteroaromatic thiophene and furan substituents were employed in the presence of K10 as catalyst, highly-potent, analgesically-active compounds bearing the octahydro-2*H*-chromenol framework were obtained.

The reaction worked with furanic and thiophene aldehydes with different substituents (Scheme 5). Depending on the aldehyde employed, the reaction time was 60 (for **7a**), 90 (for **7b**) or 120 minutes (for **7c**), at room temperature without solvent, while using K10 as an acid catalyst. Under these conditions, nine products

were obtained as mixtures of diastereoisomers, with the 4*R*-isomer as the major component, in yields ranging from 54 to 86%. When the *in vivo* tests for these compounds were done, thienyl-2-substituted derivatives were found to exhibit significant analgesic activity in the acetic acid-induced writhing model. Compound **7a** was particularly strong, additionally demonstrating analgesic activity in the hot plate test at an oral dose of 1 mg/kg, with effects persisting for at least 24 h while displaying very low acute toxicity (LD₅₀ > 4500 mg/kg).³¹



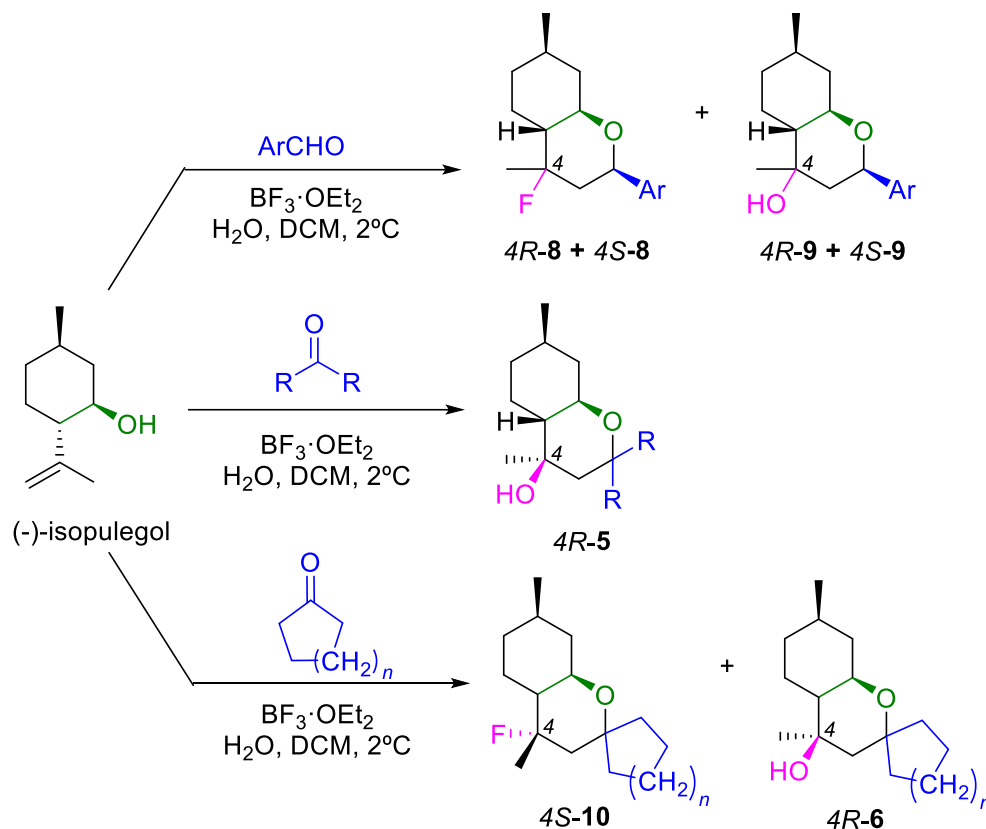
Selected examples:



Scheme 5. Synthesis of octahydro-2*H*-chromenols with analgesic activity from isopulegol and furanic or thiophene aldehydes.

Prins cyclization of (-)-isopulegol with carbonyl compounds proceeds efficiently in the presence of Lewis acids such as BF₃·OEt₂, which acts not only as a Lewis acid catalyst, but also as a fluoride source, thus enabling access to the C4-fluorinated products (Scheme 6). Thus, this methodology not only provides access to the previously synthesized octahydro-2*H*-chromen-4-ols using alternative catalytic systems, but also expands the synthetic scope with the preparation of fluorinated octahydro-2*H*-chromenes. This kind of These kinds of fluorinated derivatives constitute a valuable synthetic tool, as fluorine incorporation is known to modulate

lipophilicity, metabolic stability, and electrostatic interactions, thereby, ultimately enhancing the bioactivity of these medicinally-relevant molecules.



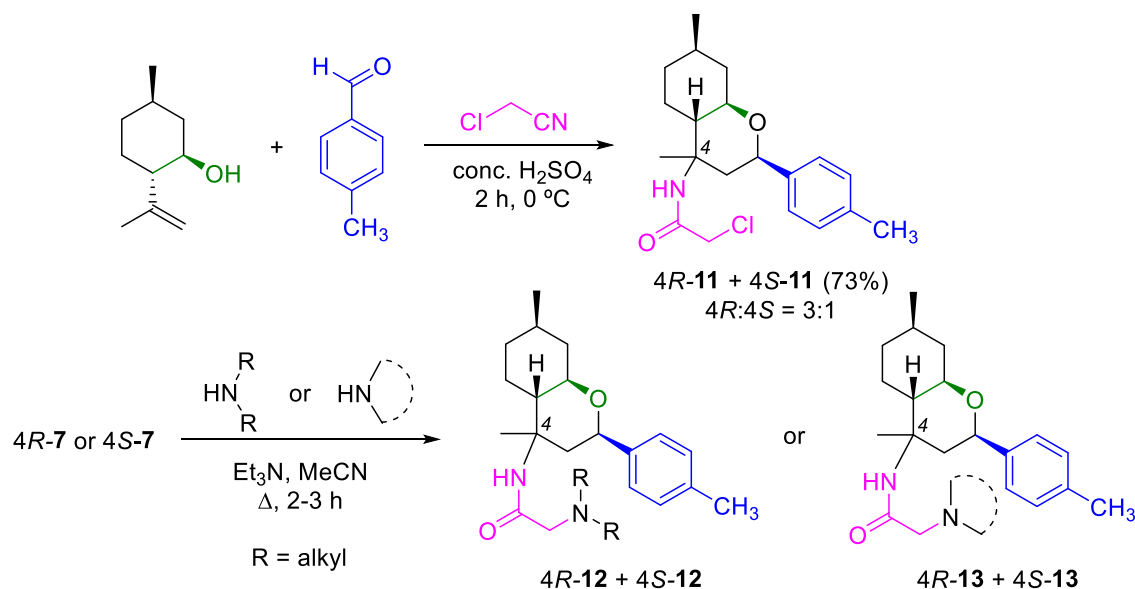
Scheme 6. Synthesis of 4-fluorinated-octahydro-2H-chromenes and octahydro-2H-chromen-4-ols.

The optimal conditions for the Prins cyclization of (-)-isopulegol with carbonyl compounds were 2°C for the temperature, and dichloromethane as the solvent. The time required to complete the process was controlled by GC until full conversion of (-)-isopulegol was achieved. A wide range of products were obtained by employing aromatic aldehydes. All of the products were based on a diastereomeric mixture of isomers 4R and 4S, with 4R being the major isomer and, in some cases, the only product. When using aliphatic ketones, only the 4R-chromen-4-ol was produced, while, when using cyclic ketones, a mixture of 4S-fluorinated chromene and 4R-hydroxylated chromene was obtained.³²

Fluorinated-octahydro-2H-chromenes obtained from (-)-isopulegol were evaluated primarily for antiviral activity against influenza A H1N1 in infected MDCK cells, measuring both inhibitory potency (IC_{50}) and cytotoxicity (CC_{50}) to calculate the selectivity index SI ($\text{CC}_{50}/\text{IC}_{50}$). The fluorinated derivatives generally showed markedly improved antiviral profiles compared with their hydroxy-analogues, combining low micromolar IC_{50} values with high SIs. The best compounds maintained activity across different influenza A strains, indicating that C4 fluorination enhances both potency and selectivity, rather than simply preserving the activity of the parent chromenols.⁷

Another methodology employed to synthesize highly analgesic compounds is a tricomponent Prins-Ritter reaction between (-)-isopulegol, an aromatic *p*-substituted aldehyde, such as *p*-toluenaldehyde, and

chloroacetonitrile (Scheme 7). This cyclization occurs using concentrated sulfuric acid for 2 hours to provide an isomeric mixture of diastereomers 4*R* and 4*S*. The stereoselectivity of the process is thermodynamically controlled, so the diastereomeric ratio changes depending on the temperature. In this process, Prins cyclization generates a carbocation in position 4, which is later captured by the nitrile via Ritter reaction, producing two diastereomers that are possible to separate by recrystallization. The subsequent reaction of one of the isomers with a secondary or cyclic amine gives rise to a mixture of *N*-(octahydro-2*H*-chromen-4-yl)-2-amidoacetamides (4*R* + 4*S*) in good yields.²⁵ The *p*-substitution of the aldehyde has also been varied (R = H, F, *i*-Pr, OCH₃) to expand the synthetic scope of the Prins-Ritter cyclization. The subsequent reaction of 4*S*-isomer with morpholine produces the final products 4*S*-**13a-d** in very good yields (84-92%).³³



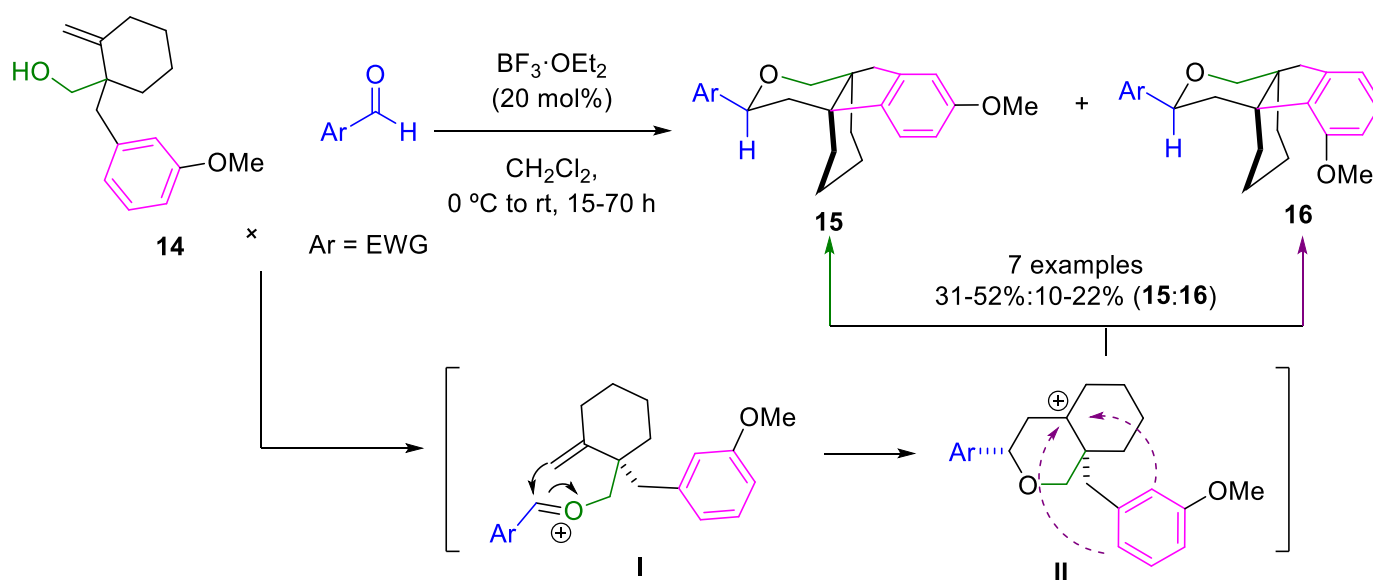
Scheme 7. Prins-Ritter cyclization and subsequent reaction with amines to form *N*-(octahydro-2*H*-chromen-4-yl)-2-amidoacetamides.

3. Tricyclic fused oxacycles

In addition to the construction of oxacycles by using Prins' cyclization, this methodology can be embedded within domino and cascade sequences to deliver densely functionalized tricyclic and fused polycyclic cores from relatively simple acyclic or monocyclic precursors. The following transformations illustrate how the fine-tuning of electronic properties, nucleophile identity, and media effects can be exploited to steer cationic intermediates toward specific architectures.

The construction of propellane architectures bearing a hexahydroindeno[2,1-*c*]pyran subunit exhibits the power of Prins-based cascades for addressing sterically congested scaffolds that are, otherwise, difficult to access. In a representative contribution, Piva and coworkers reported a highly regioselective domino Prins/Friedel-Crafts cyclization of cyclic homoallylic alcohols (derived from ethyl cyclohexanone carboxylate)

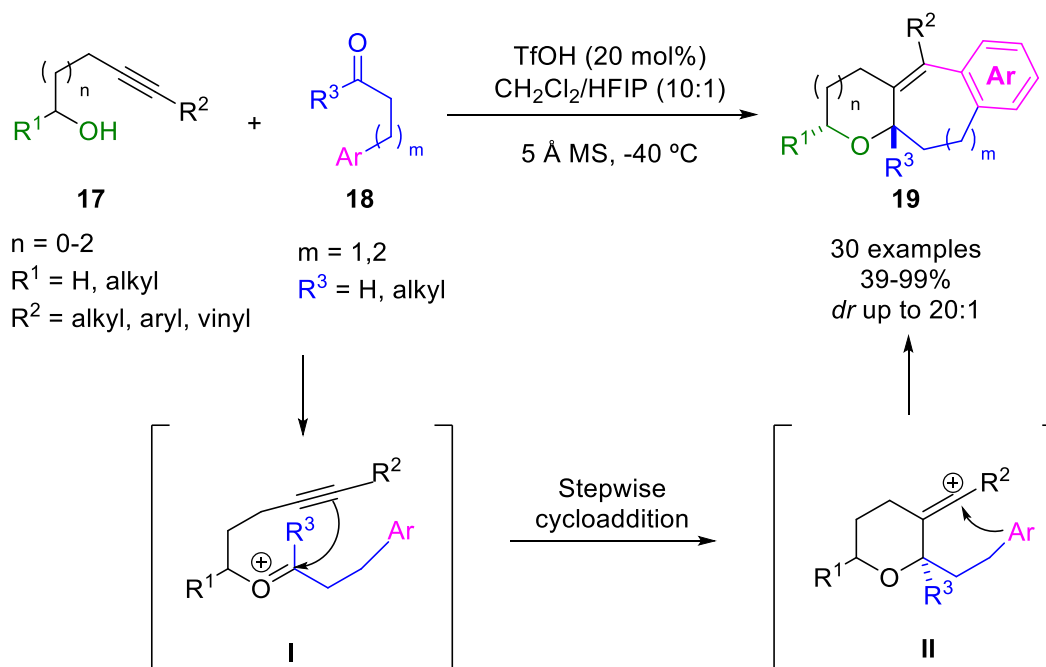
with aldehydes under $\text{BF}_3 \cdot \text{OEt}_2$ catalysis, furnishing [4.4.3]propellane derivatives in a single step (Scheme 8).³⁴ The key tetrahydropyranyl carbocation intermediate is generated via a conventional Prins cyclization, but its downstream fate is governed by the electronic nature of a tethered arene, providing a clear demonstration of cationic pathway control by aryl substitution. A salient mechanistic feature of this system is the requirement for an electron-rich aromatic ring to promote the intramolecular Friedel–Crafts step-over competitive elimination. Electron-neutral phenyl substituents favor isochromene formation via deprotonation, whereas, introduction of a methoxy group sufficiently enhances arene nucleophilicity to divert the manifold toward propellane formation, and suppress the undesired pathway. The reaction proceeds with high regioselectivity, delivering, predominantly, the isomer in which the methoxy group is *p*-substituted to the newly formed C–C bond, a result that can be rationalized by a transition state that minimizes steric congestion at the reacting positions. This method tolerates a range of electron-poor aldehydes and provides moderate yields of the desired propellanes, illustrating both the synthetic opportunities and current limitations in efficiency for such heavily congested systems.



Scheme 8. Propellane derivatives' synthesis featuring the hexahydroindenol[2,1-c]pyran subunit by Piva and coworkers.

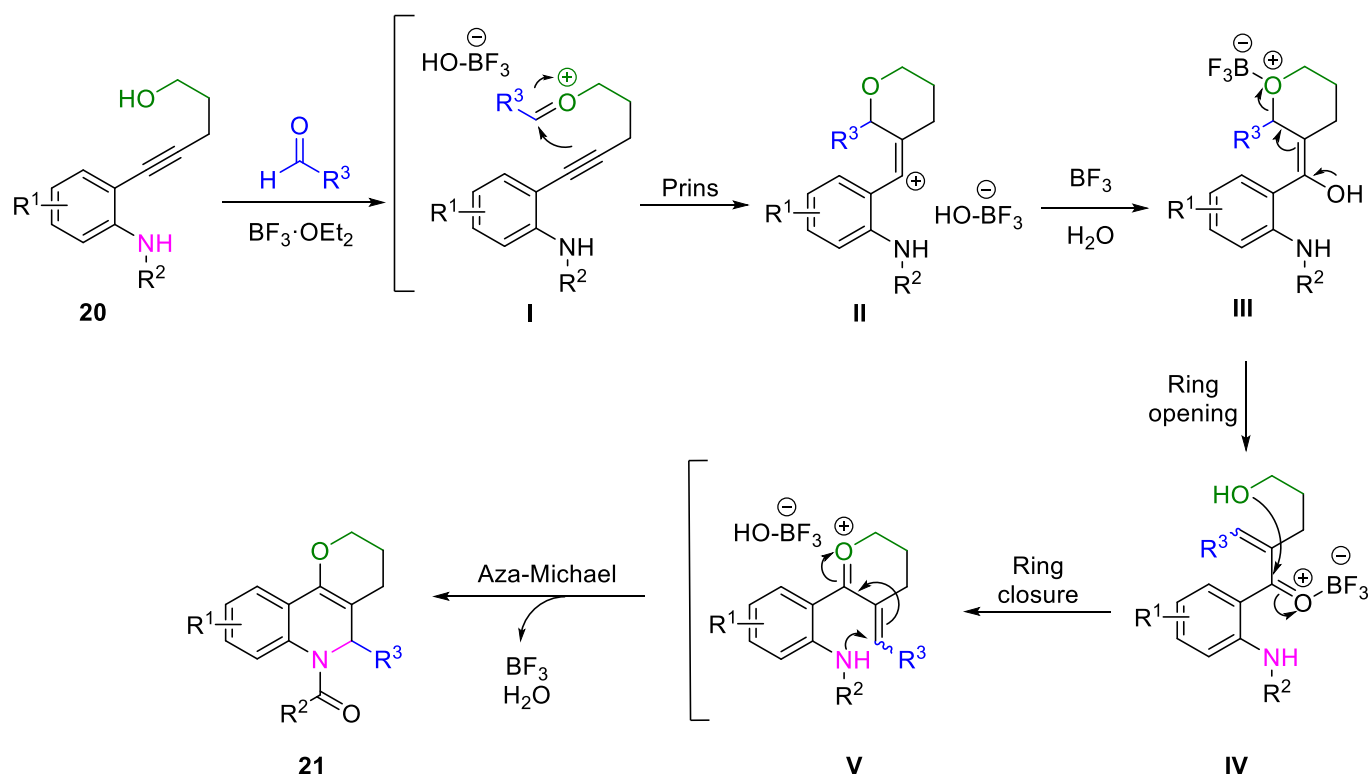
Embedding an alkynyl component within Prins cascades has opened new avenues for constructing linearly-fused heterocyclic systems through, formally, cycloaddition-like steps nested in cationic networks (Scheme 9). Hernandez and Frontier developed a Brønsted acid-catalyzed alkynyl Prins coupling/carbocyclization in which aldehydes are condensed with alkynyl alcohols bearing pendant arenes or heterocycles, leading to oxocarbenium ions that are intercepted intramolecularly by an alkyne. The resulting vinyl cation is subsequently trapped by the tethered arene, highlighting how alkyne activation and intramolecular nucleophilic capture can be orchestrated in a single cationic sequence.²⁴ The use of a mixed solvent system (DCM/HFIP) is crucial in this context, as HFIP stabilizes the highly reactive carbocationic intermediates and, thereby, broadens the scope to include electron-rich and heteroaromatic nucleophiles such as indoles and benzofurans. Under optimized conditions (TfOH, molecular sieves), a diverse array of fused

heterotricyclic scaffolds, including hexahydrobenzo[*f*]isochromenes, can be accessed with good diastereocontrol, particularly when secondary alcohols are used as chiral-information carriers. This work illustrates how solvent engineering and Brønsted acid choice can be combined to reconcile high reactivity with functional group tolerance, yet also underscores the fact that strongly deactivating substituents at the arene can still compromise cascade efficiency.



Scheme 9. Carbocyclization cascade from the construction of fused polycyclic scaffolds by Frontier and coworkers.

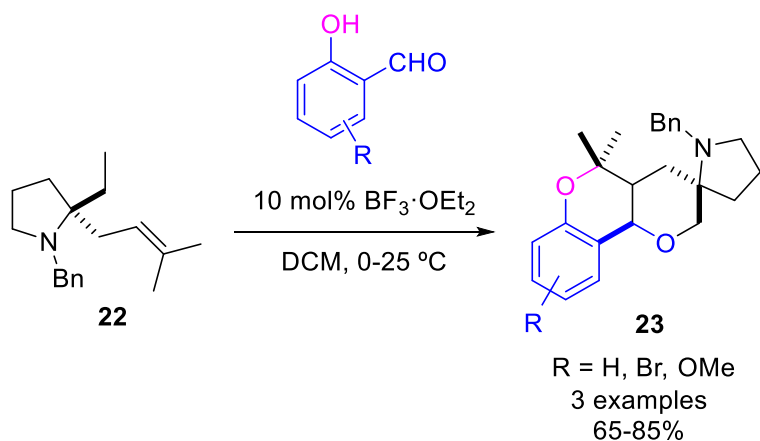
The integration of nitrogen into fused ring systems via Prins-based cascades has also been achieved through metal-free sequences that merge alkynyl Prins cyclization with intramolecular aza-Michael addition (Scheme 10). Biswas and Saikia reported that *o*-alkynol amines or ureas undergo $\text{BF}_3 \cdot \text{OEt}_2$ promoted reactions with aldehydes in DCM to give dihydropyrano[3,2-*c*]quinoline and isochromeno[4,3-*c*]quinoline cores. The cascade operates through a dihydropyranylidene cation that is initially trapped to form an enol, which then undergoes ring opening to a conjugated enone, setting the stage for intramolecular aza-Michael closure by the pendant nitrogen nucleophile.³⁵



Scheme 10. Plausible mechanism for dihydropyranoquinoline scaffolds' synthesis by means of an alkynyl Prins-aza-Michael addition cascade.

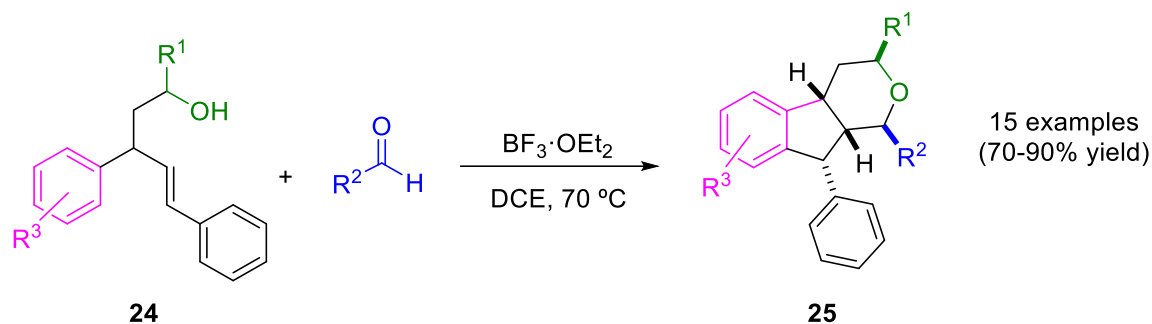
This methodology is known for its broad functional-group compatibility and for the innate “value-added” character of the products, which can be further elaborated through C–C bond-forming processes such as Pd-catalyzed intramolecular Heck reactions and Rh(III)-catalyzed annulations. The latter provide highly fluorescent pentacyclic ammonium salts, suggesting that carefully designed Prins/aza-Michael cascades can provide N,O-heterocycles.

In a similar methodology, (3,5)-oxonium–ene cyclizations provide an alternative platform for constructing spirocyclic and fused frameworks in which an oxocarbenium ion engages a pendant alkene via an ene-type process (Scheme 11). Subba Reddy and coworkers harnessed γ -hydroxyolefins derived from proline and $\text{BF}_3 \cdot \text{OEt}_2$ catalysis to access 7-oxa-1-azaspiro[4.5]decane scaffolds (**23**), thereby, leveraging chiral-pool starting materials to impart stereochemical control. The reaction is consistent with a cyclization through a chair-like transition state, enabling high diastereoselectivity by placing substituents in pseudo-equatorial positions.³⁶



Scheme 11. Synthesis of fused tetrahydropyrans by Subba Reddy and coworkers.

Other types of tandem Prins processes have been used to synthesize tricyclic oxacycles, such as the Prins-Friedel-Craft reaction developed to form in a stereoselective manner hexahydroindeno[2,1-c]pyran derivatives **25** with four stereogenic centres, from 3,5-diphenylpent-4-en-1-ol and aliphatic or aromatic aldehydes. After performing an optimization with several catalysts the best conditions for the reaction were $\text{BF}_3 \cdot \text{OEt}_2$ (10 mol%) in 1,2-dichloroethane, at $70 \text{ }^\circ\text{C}$ during 2-8 hours. In this manner, it has been possible to obtain a wide variety of products with different types of electronic substituents and with high stereoselectivity and very good yields. Furthermore, it has also been possible to vary the substitution of the starting alcohol, thereby broadening the synthetic scope of the reaction.³⁷

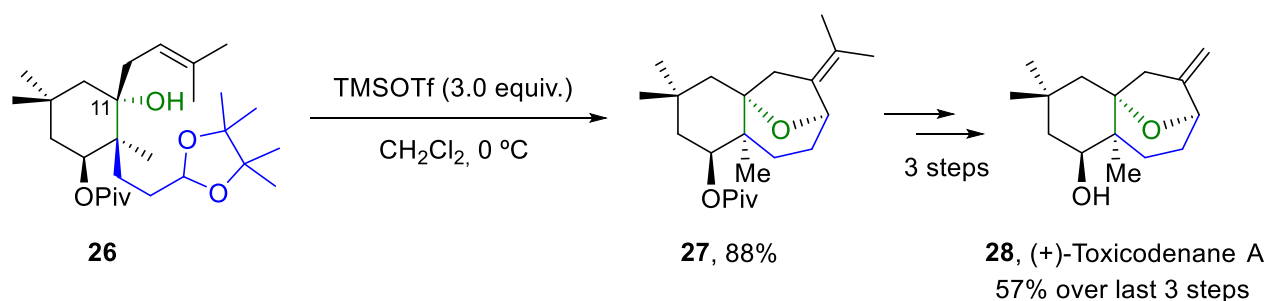


Scheme 12. Stereoselective Prins-Friedel-Craft cyclization to form hexahydroindeno[2,1-c]pyran derivatives **25**.

4. Bridged oxacycles

The latest generation of Prins-based methodologies demonstrates that cationic cascades can be harnessed not only for fused and spirocyclic systems, but also for architecturally-demanding bridged frameworks, including oxa-bridged tricycles central to natural-product synthesis. These case studies are instructive in showing how subtle changes in olefin substitution, bridge length, and reaction conditions can modulate ring-size outcomes and bridge connectivity.

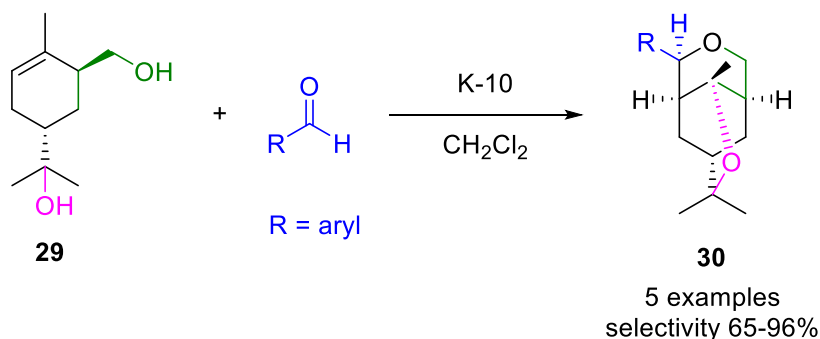
Toxicodenanes, or [5.4.0] and [6.3.0] oxa-bridged tricyclic cores, provide a stringent testbed for evaluating the capacity of Prins cascades to install multiple rings and stereocentres with high fidelity (Scheme 13). Han and coworkers reported an enantioselective total synthesis of (+)-toxicodenane **28** in nine steps. The pivotal oxa-bridged tricyclic core arose from treatment of a tertiary alcohol bearing a pendant acetal and alkene with TMSOTf, triggering a transacetalation/Prins cascade that forms the [6.6.5] scaffold present in intermediate **27** in high yield.¹² In a subsequent divergent study, the authors systematically probed the factors controlling ring size and regioselectivity in the cyclization step, demonstrating that the steric environment of the olefinic trap directs the preference for 6-*endo* versus 5-*endo* closure.³⁸ Terminal olefins favored the formation of oxatricyclotridecanes (6-membered ether rings), whereas, more substituted olefins favored oxatricyclododecanes (5-membered ether rings), mirroring the substitution pattern in the natural product.



Scheme 13. Synthesis of (+)-toxicodenane A's (**28**) oxa-bridge substructure by Han and coworkers.

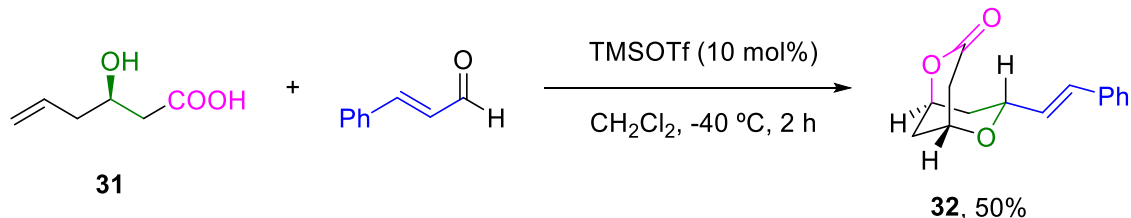
Heterogeneous acid catalysts have emerged as attractive alternatives to homogeneous Lewis and Brønsted acids for Prins-type transformations, particularly in the context of renewable feedstocks. Sidorenko and coworkers compared acid-modified halloysite nanotubes and montmorillonites for the condensation of 8-hydroxy-6-hydroxymethylimonene (from α -pinene) with thiophene-2-carbaldehyde, identifying montmorillonite K-10 as the most effective catalyst for the synthesis of 1,8-cineole derivatives via a Prins reaction, followed by intramolecular etherification.

A particularly instructive outcome is the strong solvent dependence of product distribution, e.g., methylene chloride promotes highly selective formation of 1,8-cineole derivatives, whereas solvent-free or aqueous conditions favor an alternative pathway via a triol intermediate, culminating in 1,4-cineole products (Scheme 14).³⁹



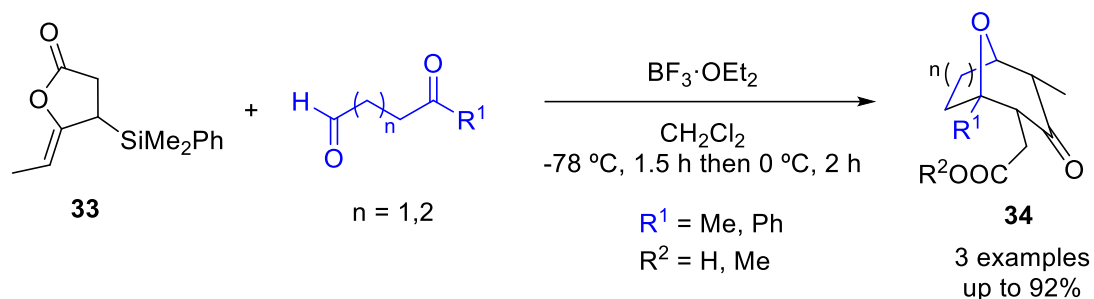
Scheme 14. Prins cyclization using heterogeneous catalysts, by Sidorenko, Murzin, and coworkers.

The first diastereoselective total synthesis of a bicyclic styryl lactone featuring a 2,6-dioxabicyclo[3.3.1]nonan-3-one core illustrates the utility of Prins/lactonization sequences for the rapid construction of bridged lactones. Biradar and coworkers employed cinnamaldehyde and a chiral homoallylic carboxylic acid (*R*)-3-hydroxyhex-5-enoic acid using TMSOTf to promote a Prins cyclization followed by intramolecular esterification. The tethered carboxyl group serves as an internal trap for the carbocation or derived alcohol, obviating the need for external nucleophiles and simplifying reaction design.⁴⁰ This tandem process delivers the target as a single diastereomer with optical rotation matching that of the natural product, underscoring both the stereochemical precision and step economy achievable with Prins-based strategies when nucleophilic traps are pre-installed within the substrate.



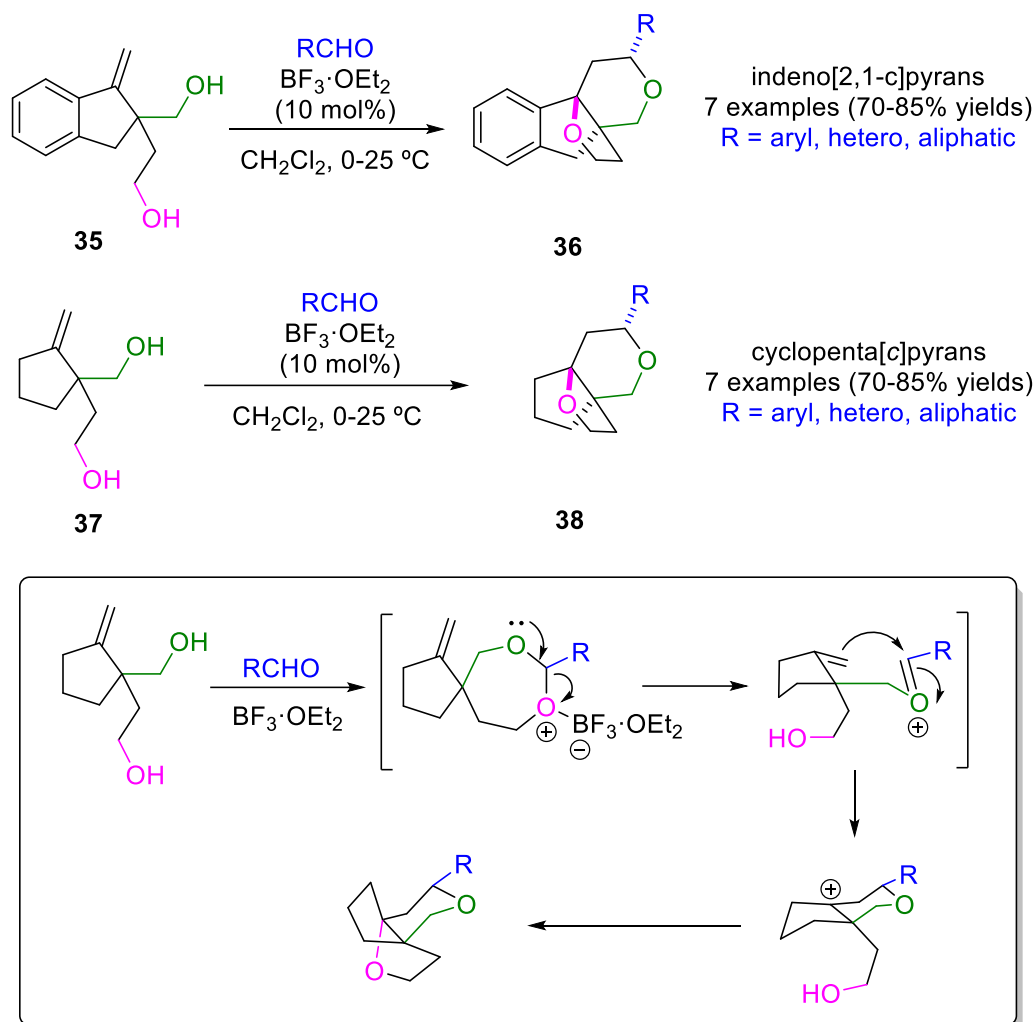
Scheme 15. Synthesis of **32** reported by Biradar, Subba Reddy, and coworkers.

Sakaguchi and coworkers introduced a tandem Hosomi–Sakurai/Prins cyclization that leverages a β -silyl- γ -ethylidene- γ -butyrolactone (Scheme 16). Upon treatment with ketoaldehydes or cyclic ketones in the presence of Lewis acids, the silyl group facilitates an initial allylsilane-type addition to the carbonyl (Hosomi–Sakurai reaction), generating an intermediate that then participates in an intramolecular Prins cyclization with a second carbonyl unit. This sequence exemplifies how classical allylsilane chemistry can be fused with Prins reactivity to access higher-order-oxygenated frameworks.⁴¹ When ketoaldehydes were employed, the method provided fused oxabicyclic systems, such as 8-oxabicyclo[3.2.1]octanes (**34**), in high yields, with excellent control over relative stereochemistry in the tetrahydropyranone ring. The approach significantly expands the repertoire of Prins-based methods for constructing bridged-oxygenated skeletons from relatively simple starting materials, and highlights the strategic potential of preinstalled silyl groups for both reactivity activation and stereocontrol. Future extensions might focus on asymmetric variants and on incorporating additional nucleophilic partners to further enrich molecular complexity in a single synthetic operation.



Scheme 16. Oxabicyclo derivatives' synthesis via Prins cyclization by Sakaguchi and coworkers.

Prins cascade cyclizations can also be a useful methodology to form highly-functionalized indeno[2,1-*c*]pyrans **36** and cyclopenta[*c*]pyrans **38** from indanic and cyclopentyl-*exo*-olefinic diols (Scheme 17). In this case, the reaction in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ (10 mol%) in dichloromethane at 0-25 $^\circ\text{C}$ gave dioxacycles with three contiguous stereogenic centres in good yields and high diastereoselectivity, due to the preferential intramolecular closure from the equatorial face, the least sterically impeded. The scope included aromatic, heteroaromatic and aliphatic aldehydes.⁴²



Scheme 17. Prins cascade cyclizations to generate indeno[2,1-c]pyrans and cyclopenta[c]pyrans.

Conclusions

Recent applications of the Prins cyclization for the synthesis of oxacycles of varying complexity have been reviewed, including tetrahydropyrans, 1*H*-isochromenes, bridged oxacycles, and polycyclic systems. Several of these oxacycles were found to exhibit interesting biological properties and/or occur in natural products, such as 2*H*-chromenes synthesized from (-)-isopulegol, which show antiviral and analgesic activities. Significant advances have been made in the development of enantioselective methodologies, enabling access to chiral compounds with high diastereoselectivity under chiral reaction environments. These strategies expand the synthetic scope, allowing the preparation of complex oxygenated architectures from diverse types of starting materials.

Overall, the Prins cyclization continues to provide a versatile platform for constructing biologically-relevant oxacycles, from simple acyclic or monocyclic systems to intricate bridged and polycyclic structures. Further exploration of catalytic systems, stereoselective methodologies, and cascade variants is expected to enhance synthetic utility and enable the preparation of new natural product analogues and drug-like molecules.

References

1. Edmunds, A.J.F. Triazine Herbicides. *Bioactive Heterocyclic Compound Classes: Agrochemicals*; Clemens Lamberth, C., Dinges, J.; Wiley VCH: Weinheim, 2012. Chapter 1, pp 1–20.
2. Mori, H. *Polym. J.*, **2021**, *53*, 975-987.
<https://doi.org/10.1038/s41428-021-00497-9>
3. Patel, G.; Banerjee, S. *Curr. Org. Chem.*, **2020**, *24*, 2566–2587.
<https://doi.org/10.2174/1385272824999200709125717>
4. Martin, S. F. *J. Org. Chem.*, **2017**, *82*, 10757–10794. <https://doi.org/10.1021/acs.joc.7b01368>
5. Budakoti, A; Mondal, P.K.; Verma, P.; Khamrai, J. *Beilstein J. Org. Chem.*, **2021**, *17*, 932–963.
<https://doi.org/10.3762/bjoc.17.77>
6. Snieckus, V.; Board, J. *Synfacts*, **2017**, *13*, 351. <https://doi.org/10.1055/s-0036-1590191>
7. Ilyina, I. V.; Patrusheva, O. S.; Zarubaev, V. V.; Misiurina, M. A.; Slita, A. V.; Esaulkova, I. L.; Korchagina, D. V.; Gatilov, Y. V.; Borisevich, S. S.; Konstantin, P. V.; Salakhutdinov, N. F. *Bioorg. Med. Chem. Lett.*, **2021**, *31*, 127677. <https://doi.org/10.1016/j.bmcl.2020.127677>
8. Yanagihara, M; Kishimoto, N; Nakahara, K.; Abe, T.; Miura, S.; Lin, B.; Fumimoto, M.; Haruta, J.; Misumi, S.; Arisawa, M.; Murai, K. *Chem. Eur. J.*, **2023**, *29*, e202300677.
<https://doi.org/10.1002/chem.202300677>
9. Subba Reddy, B. V.; Nair, P. N.; Antony, A.; Srivastava, N. *Eur. J. Org. Chem.*, **2017**, *2017*, 5484–5496.
<https://doi.org/10.1002/ejoc.201700633>
10. Wang, C.; Liu, Y.; Wan, J. P. *Org. Lett.*, **2025**, *27*, 3983–3987.
<https://doi.org/10.1021/acs.orglett.5c00946>
11. Meng, S.; Guo, W.; Liu, L.; Zheng, J.; Wang, Q. *ChemistrySelect*, **2022**, *7*, e202202760.

<https://doi.org/10.1002/slct.202202760>

12. Qin, X. L.; Wu, G. J.; Han, F. S. *Org. Lett.*, **2021**, *23*, 8570–8574.
<https://doi.org/10.1021/acs.orglett.1c03293>
13. Subba Reddy, B. V.; Reddy, S. G.; Reddy, M. R.; Bhadra, M. P.; Sarma, A. V. S. *Org. Biomol. Chem.*, **2014**, *12*, 7257–7260. <https://doi.org/10.1039/C4OB01188K>
14. Sinka, V.; Martín, V. S.; Cruz, D. A.; Padrón, J. I. *Eur. J. Org. Chem.*, **2020**, *2020*, 6704–6717.
<https://doi.org/10.1002/ejoc.202000850>
15. Deokar, D. B.; Patra, R.; Kumar, Y. B.; Sridhar, B.; Soujanya, Y.; Likhar, P. R. *Org. Lett.*, **2025**, *27*, 1287–1292.
<https://doi.org/10.1021/acs.orglett.5c00018>
16. Peña, L. F.; Barbero, A. *Org. Lett.*, **2024**, *26*, 5202–5207.
<https://doi.org/10.1021/acs.orglett.4c01806>
17. Díez-Poza, C.; Barbero, H.; Díez-Varga, A.; Barbero, A. *Prog. Heterocycl. Chem.*, **2018**, *30*, 13–41.
<https://doi.org/10.1016/B978-0-08-102788-2.00002-7>
18. Olier, C.; Kaafarani, M.; Gastaldi, S.; Bertrand, M. P. *Tetrahedron*, **2010**, *66*, 413–445.
<https://doi.org/10.1016/j.tet.2009.10.069>
19. Reyes, E.; Prieto, L.; Uria, U.; Carrillo, L.; Vicario, J. L. *ACS Omega*, **2022**, *7*, 31621–31627.
<https://doi.org/10.1021/acsomega.2c04765>
20. Broeker, J. L.; Hoffmann, R. W.; Houk, K. N. *J. Am. Chem. Soc.*, **1991**, *113*, 5006–5017.
<https://doi.org/10.1021/ja00013a041>
21. Ikeda, S.; Miyashita, H.; Taniguchi, M.; Kondo, H.; Okano, M. Sato, Y.; Odashima, K. *J. Am. Chem. Soc.*, **2002**, *124*, 12060–12061.
<https://doi.org/10.1021/ja0202863>
22. Sidorenko, A. Y.; Kurban, Y. M.; Kravtsova, A. V.; Il'ina, I. V.; Li-Zhulanov, N. S.; Korchagina, D. V.; Sánchez-Velandia, J. E.; Aho, A.; Volcho, K. P.; Salakhutdinov, N. F.; Murzin, D. Y.; Agabekov, V. E. *Appl. Catal., A*, **2022**, *629*, 118395.
<https://doi.org/10.1016/j.apcata.2021.118395>
23. Kindala, T. J.; Takatori, K.; Nagumo, S. *J. Org. Chem.*, **2025**, *90*, 1514–1530.

- <https://doi.org/10.1021/acs.joc.4c02451>
24. Hernandez, J. J.; Frontier, A. J. *Chem. Sci.*, **2022**, *13*, 13548-13553.
<https://doi.org/10.1039/D2SC04750K>
25. Li-Zhulanov, N. S.; Kuznetsova, V. A.; Gatilov, Y. V.; Volcho, K. O.; Khvostov, M. V.; Tolstikova, T. G.; Salakhutdinov, N. F. *Russ. Chem. Bull.*, **2023**, *72*, 2430–2438.
<https://doi.org/10.1007/s11172-023-4044-2>
26. Wang, M.; Tietjen, I.; Chen, M.; Williams, D. E.; Daoust, J.; Brockman, M. A.; Andersen, R. J. *J. Org. Chem.*, **2016**, *81*, 11324–11334. <https://doi.org/10.1021/acs.joc.6b02312>
27. Abdul-Rashed, S.; Alachouzos, G.; Brennessel, W. W.; Frontier, A. J. *Org. Lett.*, **2020**, *22*, 4350–4354.
<https://doi.org/10.1021/acs.orglett.0c01351>
28. Kuan, T.-H.; Kotipalli, T.; Chen, C.-C.; Hou, D.-R. *Org. Biomol. Chem.*, **2021**, *19*, 10390–10402.
<https://doi.org/10.1039/D1OB01941D>
29. Ilyina, I. V.; Zarubaev, V. V.; Lavrentieva, I. N.; Shtro, A. A.; Esaulkova, I. L.; Korchagina, D. V.; Borisevich, S. S.; Volcho, K. P.; Salakhutdinov, N. F. *Bioorg. Med. Chem. Lett.*, **2018**, *28*, 2061–2067.
<https://doi.org/10.1016/j.bmcl.2018.04.057>
30. Il'ina, I. V.; Korchagina, D. V.; Morozova, E. A.; Tolstikova, T. G.; Volcho, K. P.; Salakhutdinov, N. F. *Russ. Chem. Bull.*, **2019**, *68*, 1061–1066. <https://doi.org/10.1007/s11172-019-2520-5>
31. Nazimova, E.; Pavlova, A.; Mikhalchenko, O.; Ilyina, I. V.; Korchagina, D.; Tolstikova, T.; Volcho, K. P.; Salakhutdinov, N. F. *Med. Chem. Res.*, **2016**, *25*, 1369–1383.
<https://doi.org/10.1007/s00044-016-1573-3>
32. Il'ina, I. V.; Patrusheva, O. S.; Korchagina, D. V.; Volcho, K. P.; Salakhutdinov, N. F. *Chem. Heterocycl. Compd.*, **2020**, *56*, 867–874.
<https://doi.org/10.1007/s10593-020-02743-z>
33. Li-Zhulanov, N.S.; Nikolaichuk, K. M.; Gatilov, Y. V.; Volcho, K.; Khvostov, M. V.; Tolstikova, T. G.; Salakhutdinov, N.F. *Dokl. Chem.*, **2023**, *512*, 242–248. <https://doi.org/10.1134/S0012500823600694>
34. Nassar, Y.; Fache, F.; Pelotier, B.; Piva, O. *Synthesis*, **2022**, *54*, 4622–4628. <https://doi.org/10.1055/a-1882-8128>
35. Biswas, S.; Saikia, A. K. *J. Org. Chem.*, **2024**, *89*, 14454–14471. <https://doi.org/10.1021/acs.joc.4c01916>
36. Raju, N. P.; Reddy, B. J. M.; Khan, P. R.; Aita, S.; Reddy, G. J.; Sridhar, B.; Subba Reddy, B. V. *Tetrahedron Lett.*, **2022**, *107*, 154101.

<https://doi.org/10.1016/j.tetlet.2022.154101>

37. Subba Reddy, B. V.; Reddy, G. N.; Reddy, M. R.; Lakshmi, J. K.; Jagadeesh, B.; Sridhar, B. *Asian J. Org. Chem.*, **2015**, *4*, 1266–1272.

<https://doi.org/10.1002/ajoc.201500218>

38. Qin, X-L.; Wu, G-J.; Han, F-S. *J. Org. Chem.*, **2022**, *87*, 3223–3233. <https://doi.org/10.1021/acs.joc.1c02928>

39. Sidorenko, A.Y.; Khalimonyuk, T. V.; Kurban, Y. M.; Ilyina, I. V.; Li-Zhulanov, N.; Patrusheva, O. S.; Aho, A.; Heinmaa, I.; Volcho, K.; Salakhutdinov, N. F.; Murzin, D. *Appl. Catal., A*, **2025**, *691*, 120070.

<https://doi.org/10.1016/j.apcata.2024.120070>

40. Biradar, D. O.; Mane, Y. D.; Narsaiah A. V.; Subba Reddy, B. V. *Results Chem.*, **2023**, *5*, 100717.

<https://doi.org/10.1016/j.rechem.2022.100717>

41. Ariyoshi, S.; Sakaguchi, K.; Nishimura, T. *J. Org. Chem.*, **2021**, *86*, 11884–11894.

<https://doi.org/10.1021/acs.joc.1c01284>

42. Subba Reddy, B. V.; Raju, N. P.; Someswarao, B.; Jagan Mohan Reddy, B.; Sridhar, B.; Kiran Kumar, S. *Org. Biomol. Chem.*, **2015**, *13*, 4733–4736. <https://doi.org/10.1039/c5ob00518c>

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