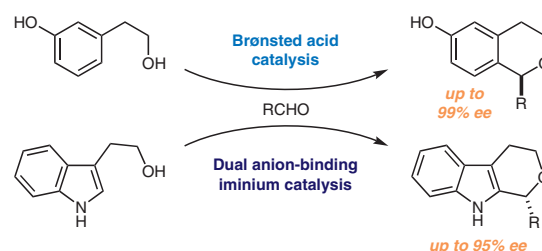


Catalytic Enantioselective Approaches to the oxa-Pictet–Spengler Cyclization and Other 3,6-Dihydropyran-Forming Reactions

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Abstract This Short Review provides an analysis of the state-of-the-art in catalytic enantioselective oxa-Pictet–Spengler cyclizations. Also discussed are other catalytic reactions providing access to enantio-enriched isochromans and tetrahydropyrano[3,4-*b*]indoles. Context is provided and remaining challenges are highlighted.

Key words oxa-Pictet–Spengler cyclization, isochromans, tetrahydropyrano[3,4-*b*]indoles, oxocarbenium ions, asymmetric catalysis, ion pairing

Among compounds containing a 3,6-dihydropyran core, isochromans and tetrahydropyrano[3,4-*b*]indoles have captured particular interest in the synthetic and medicinal chemistry communities. A small selection of compounds containing these core frameworks is shown in Figure 1. The isochroman heterocycle is a ubiquitous component of natural products often possessing intriguing bioactivities, such as ilexisochromane,¹ penicisochroman B,² and blapsin B.³ Synthetic isochromans include the antiapoptotic agent ISO-09⁴ and the 5-HT_{1D} agonist PNU-109291.⁵ Examples of bioactive tetrahydropyrano[3,4-*b*]indoles are the anti-inflammatory agent etodolac,⁶ the potent analgesic agent pemedolac,⁷ and the non-nucleoside inhibitor of hepatitis C virus HCV-371.⁸ The perhaps most desirable way to access isochromans and tetrahydropyrano[3,4-*b*]indoles in a stereocontrolled fashion is by means of the oxa-Pictet–Spengler cyclization; a process in which an oxocarbenium ion intermediate undergoes ring-closure onto a pendent

aryl substituent.⁹ In this Short Review, we provide examples of asymmetric oxa-Pictet–Spengler cyclizations that are under substrate control, discuss all known catalytic enantioselective variants of the oxa-Pictet–Spengler cyclization,¹⁰ and provide an overview of other catalytic enantioselective reactions that lead to isochromans and tetrahydropyrano[3,4-*b*]indoles. In addition, we outline remaining challenges in this area.

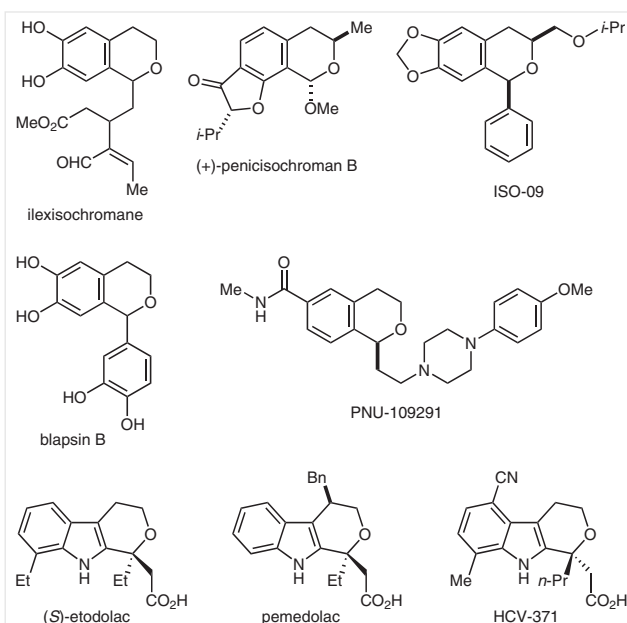


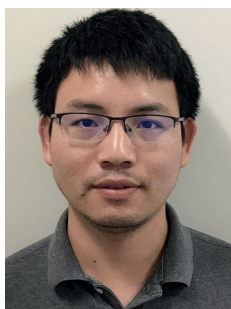
Figure 1 Examples of naturally occurring and artificial bioactive isochromans and tetrahydropyrano[3,4-*b*]indoles

The Pictet–Spengler reaction was discovered in 1911 and involves the HCl-promoted condensation of β -phenethylamine and formaldehyde dimethyl acetal to form 1,2,3,4-tetrahydroisoquinoline (Scheme 1).¹¹ The definition

of the Pictet–Spengler reaction was later expanded to include cyclizations of imines or iminium ions possessing a covalently linked aryl group that undergoes substitution upon ring-closure.¹² While the apparently first example of an oxa-Pictet–Spengler reaction dates back to 1935,¹³ when the synthesis of isochroman from chloroether **1** was disclosed in a patent by Buschmann and Michel (Scheme 1), the term oxa-Pictet–Spengler cyclization was coined by

Wünsch and Zott only in 1992.¹⁴ While it was found that β -phenylethanol can condense directly with formaldehyde or paraformaldehyde in the presence of aqueous HCl to form isochroman without the need to first isolate **1**, this approach inadvertently leads to side products containing chloromethyl groups on the phenyl ring (not shown).^{14,15} As outlined in Scheme 1, the general mechanism of the oxa-Pictet–Spengler reaction involves the formation of an oxo-

Biographical Sketches



Zhengbo Zhu was born and raised in Jiangxi, China. He earned his B.Sc. degree in the Department of Chemistry and Chemical Engineering at Nanjing University working with

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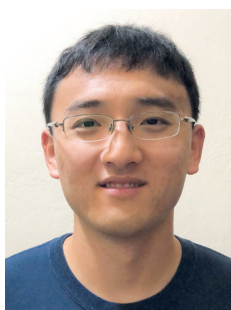
ty of Florida. His research focuses on asymmetric Brønsted acid catalysis and redox-neutral α -C–H bond functionalization of cyclic amines.



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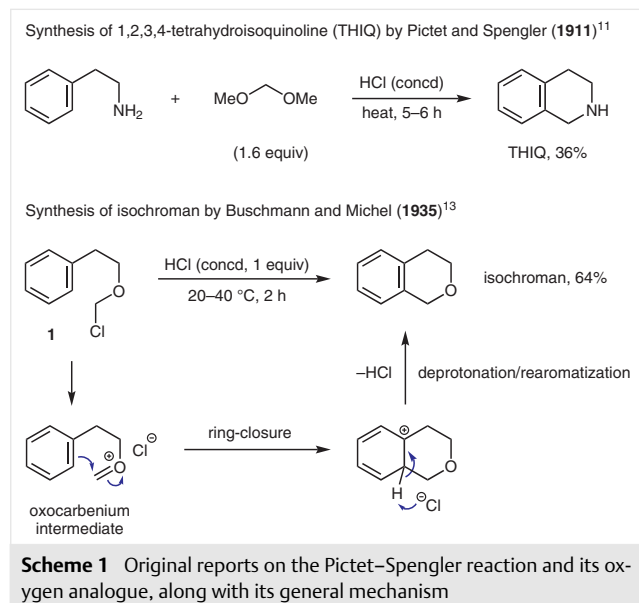


Daniel Seidel studied chemistry at the Friedrich-Schiller-Universität Jena, Germany, and at the University of Texas at Austin (Diplom 1998). He performed his graduate studies in the laboratory of Prof. Jonathan L.

Sessler, obtaining his Ph.D. in 2002. From 2002 to 2005, he was an Ernst Schering Postdoctoral Fellow in the group of Prof. David A. Evans at Harvard University. He started his independent career at Rutgers

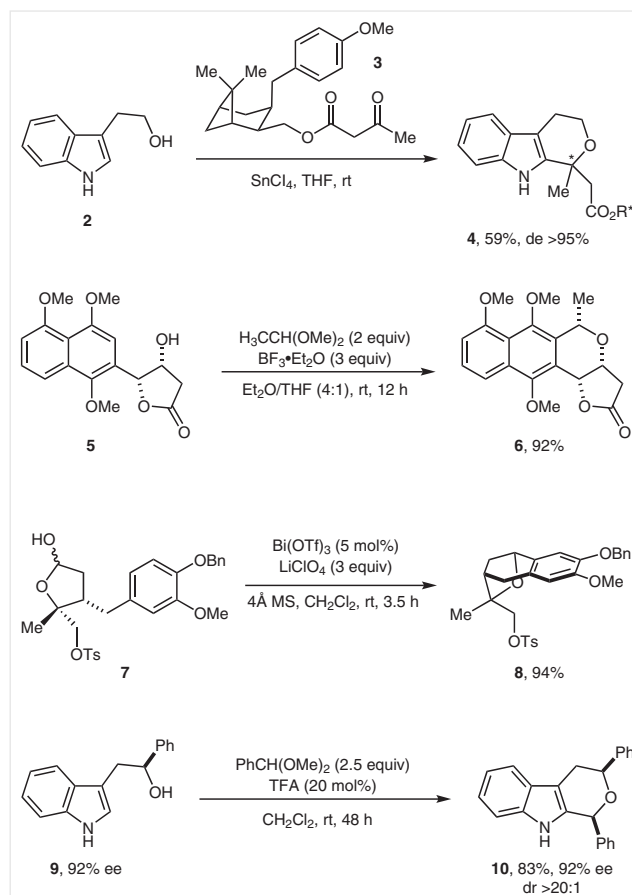
University in 2005 and was promoted to Associate Professor in 2011 and Full Professor in 2014. In the summer of 2017, his research group moved to the University of Florida.

carbenium ion, followed by ring closure and subsequent deprotonation/rearomatization. Both the Pictet–Spengler cyclization and the oxa-Pictet–Spengler cyclization can be viewed as variants of an intramolecular Friedel–Crafts alkylation.¹⁶ In addition, the oxa-Pictet–Spengler cyclization is mechanistically related to certain types of the Prins reaction.¹⁷



For the majority of the history of the oxa-Pictet–Spengler reaction, asymmetric variants were limited to cyclizations of enantioenriched starting materials.⁹ Several illustrative examples of such diastereoselective oxa-Pictet–Spengler cyclizations are provided in Scheme 2. A chiral auxiliary based approach was reported by Costa et al., utilizing β -ketoester **3** derived from (–)- β -pinene.¹⁸ Condensation of tryptophol (**2**)¹⁹ with β -ketoester **3** is facilitated by SnCl_4 , resulting in the formation of product **4** with excellent diastereoselectivity. Interestingly, the use of BF_3 etherate in place of SnCl_4 provides a 1:1 mixture of product diastereomers. The ratio of the starting materials and the amount of the Lewis acid are not specified in this report. Also, the absolute configuration of product **4** remains unknown. A highly diastereoselective oxa-Pictet–Spengler cyclization was reported by Fernandes and Brückner in the course of a synthesis of (+)-kalafungin.²⁰ Exposure of **5** to two equivalents of acetaldehyde dimethyl acetal and excess BF_3 etherate provides product **6** as a single diastereomer in excellent yield. As part of their synthesis of (–)-platensimycin, Eey and Lear explored the conversion of **7** into **8** via an interesting type of oxa-Pictet–Spengler cyclization under a variety of conditions.²¹ Although the reaction can be facilitated with a large excess of SnCl_4 (8 equiv), the optimal conditions involve exposure of **7** to a catalytic amount of $\text{Bi}(\text{OTf})_3$ (5 mol%) in the presence of lithium perchlorate (3 equiv) and molecular

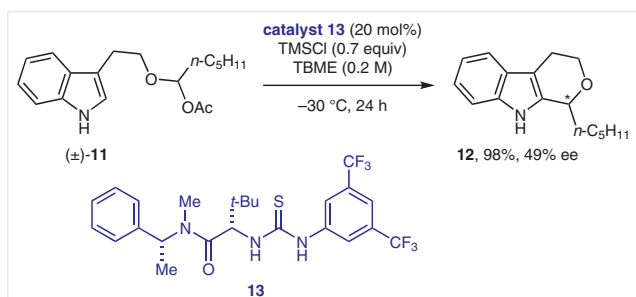
sieves in dichloromethane at room temperature, allowing for the isolation of polycyclic product **8** in excellent yield. A recent example of a Brønsted acid catalyzed diastereoselective oxa-Pictet–Spengler cyclization was reported by Da and co-workers.²² Tryptophol derivative **9**, derived from the enantioselective CBS reduction of the corresponding ketone, engages benzaldehyde dimethyl acetal in the presence of a catalytic amount of trifluoroacetic acid to furnish tetrahydropyrano[3,4-*b*]indole **10** in excellent yield and dr. Consistent with the expected mechanism of this transformation, the ee of product **10** matches that of the starting material **9**.



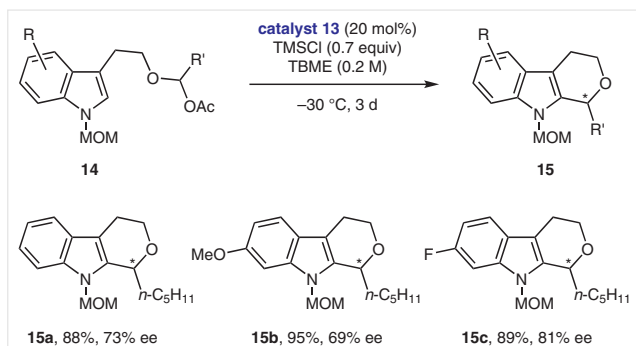
Scheme 2 Examples of diastereoselective oxa-Pictet–Spengler reactions with optically active starting materials

The first documented efforts toward developing a catalytic enantioselective variant of the oxa-Pictet–Spengler reaction were disclosed by Doyle in 2008.²³ Evaluation of a number of (thio)urea catalysts in direct condensations of tryptophol with a range of aldehydes and ketones, either in the absence or presence of various Brønsted and Lewis acid additives and dehydrating agents, was reported to lead to tetrahydropyrano[3,4-*b*]indole products with low levels of enantioinduction (<15% ee, not shown). Significant increases in reactivity and appreciable levels of enantioselectivity are observed with tryptophol-derived mixed acetoxy-

acetals such as **11**; precursors that enable the formation of the requisite oxocarbenium ion intermediates under milder conditions (Scheme 3). Exposure of **11** to trimethylsilyl chloride in the presence of thiourea catalyst **13** furnishes product **12** in excellent yield and encouraging 49% ee (absolute configuration not established). Higher levels of enantioselectivity are obtained with *N*-MOM protected tryptophol acetals **14** (Scheme 4). Reactions of acetals **14**, performed under identical conditions, provide the corresponding products **15** with up to 81% ee (absolute configuration of products not established). Promising preliminary results for catalytic enantioselective oxa-Pictet–Spengler cyclizations were also obtained with acetoxy-acetals derived from a number of β -heteroaryl ethanol (Scheme 5). Regarding the mechanism of these transformations, the hydrogen-bond donor²⁴ thiourea catalyst most likely interacts with chloride via anion-binding,²⁵ forming a chiral ion pair with the oxocarbenium ion.

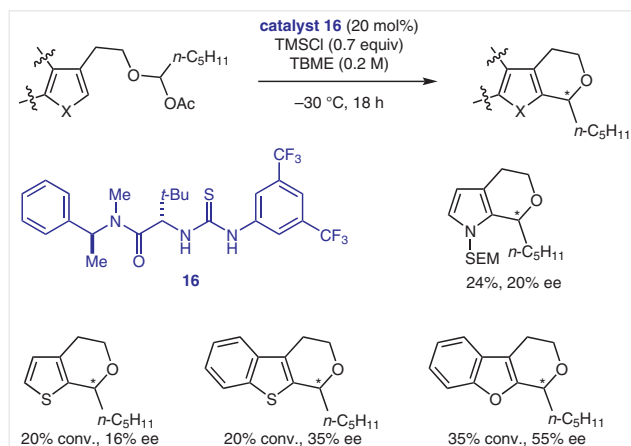


Scheme 3 Thiourea-catalyzed enantioselective oxa-Pictet–Spengler cyclization with mixed acetals derived from tryptophol



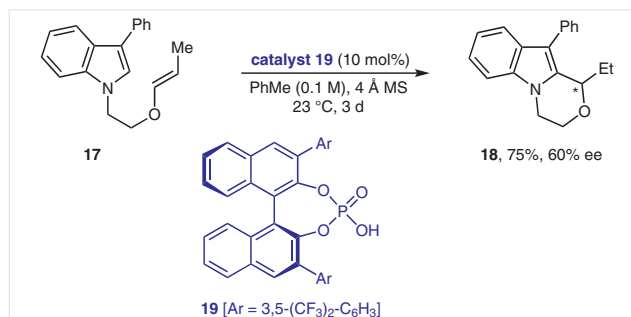
Scheme 4 Thiourea-catalyzed enantioselective oxa-Pictet–Spengler cyclization with *N*-MOM protected tryptophol acetals, selected scope

Another early example of a catalytic enantioselective oxa-Pictet–Spengler cyclization was reported by Scheidt and co-workers in 2013 (Scheme 6).²⁶ Chiral phosphoric acid catalyst **19** is capable of converting preformed enol



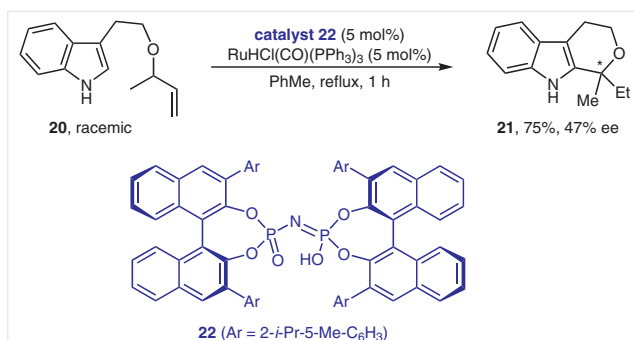
Scheme 5 Thiourea-catalyzed enantioselective oxa-Pictet–Spengler cyclizations involving various heterocycles

ether **17** into the corresponding cyclization product **18** with a moderate level of enantiocontrol (absolute configuration not established). Here, the intermediate oxocarbenium ion is generated by protonation of enol ether **17** by the chiral Brønsted acid **19**.²⁷



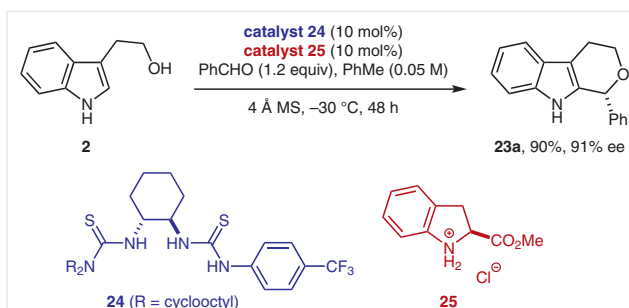
Scheme 6 Brønsted acid catalyzed enantioselective oxa-Pictet–Spengler cyclization with a preformed enol ether

Shortly thereafter, Nielsen and co-workers reported a related approach in which enol ethers are generated in situ from allyl ethers via a ruthenium catalyzed isomerization process (Scheme 7).²⁸ Application of this strategy to allyl ether **20**, in the presence of chiral imidodiphosphoric acid **22**, furnishes product **21** in good yield. While the enantioselectivity achieved in this reaction is only moderate (absolute configuration not established), this is the only example thus far that generates a tetrasubstituted stereogenic center in the course of an oxa-Pictet–Spengler cyclization. The *E/Z* selectivity of the initial isomerization step is unknown.

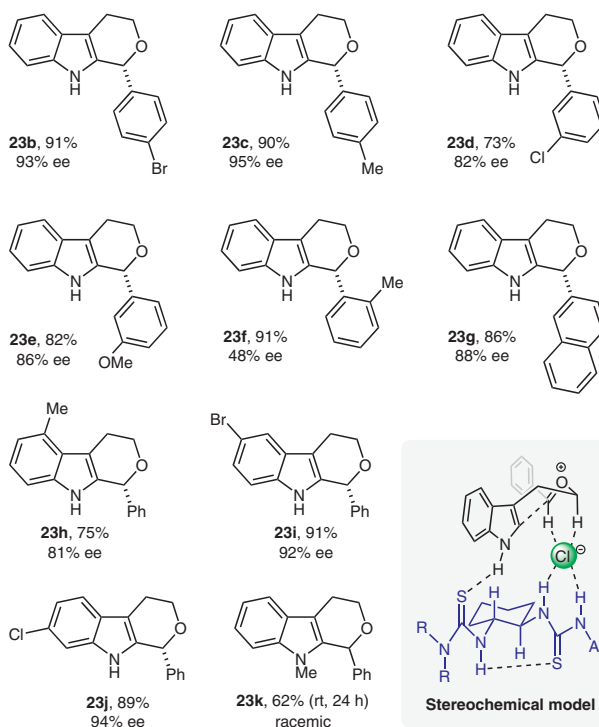


Scheme 7 Dually catalyzed enantioselective oxa-Pictet–Spengler cyclization of an allyl ether

The first highly enantioselective catalytic oxa-Pictet–Spengler cyclization was reported by our group in 2016 (Scheme 8).²⁹ In the presence of thiourea catalyst **24** and ammonium salt catalyst **25**, tryptophol (**2**) undergoes an oxa-Pictet–Spengler reaction with benzaldehyde to form product **23a** in excellent yield and ee. Substituted benzaldehydes also participate in this reaction. While *para*-substituted benzaldehydes provide products with excellent ee, *meta*-substitution leads to a slight drop-off in enantioselectivity, and *ortho*-substitution results in a significant erosion of ee (e.g., product **23f**). Substitution of the indole ring is compatible with the catalytic system, whereas aliphatic aldehydes are not viable reaction partners. Mechanistically, this method is based on a dual catalysis strategy that avoids the need for strongly acidic conditions commonly required for accessing oxocarbenium ions via direct condensation of aldehydes and alcohols. The ammonium salt catalyst **25** is thought to first engage the aldehyde to form an iminium ion³⁰ that then reacts with tryptophol, ultimately resulting in the formation of an oxocarbenium ion that likely interacts with the catalyst via anion-binding. A plausible transition state for the key C–C bond-forming step is shown in Scheme 8. This model is supported by the following observations: (1) there is a strong dependence on the nature of the anion with regard to reactivity and product ee; (2) The enantioselectivity of the reaction is solely dependent on catalyst **24** (e.g., almost identical results are obtained with the enantiomer of **25** or racemic **25**), and (3) The reaction with *N*-methyl tryptophol provides racemic product (e.g., product **23k**), indicating an important interaction of the indole N–H with a hydrogen-bond acceptor site on the catalyst (e.g., the S-atom of the electron-rich thiourea moiety) in the enantio-determining step of the reaction. Interestingly, catalyst **25** can be replaced with HCl to provide the product with nearly identical ee but in a significantly more sluggish reaction.



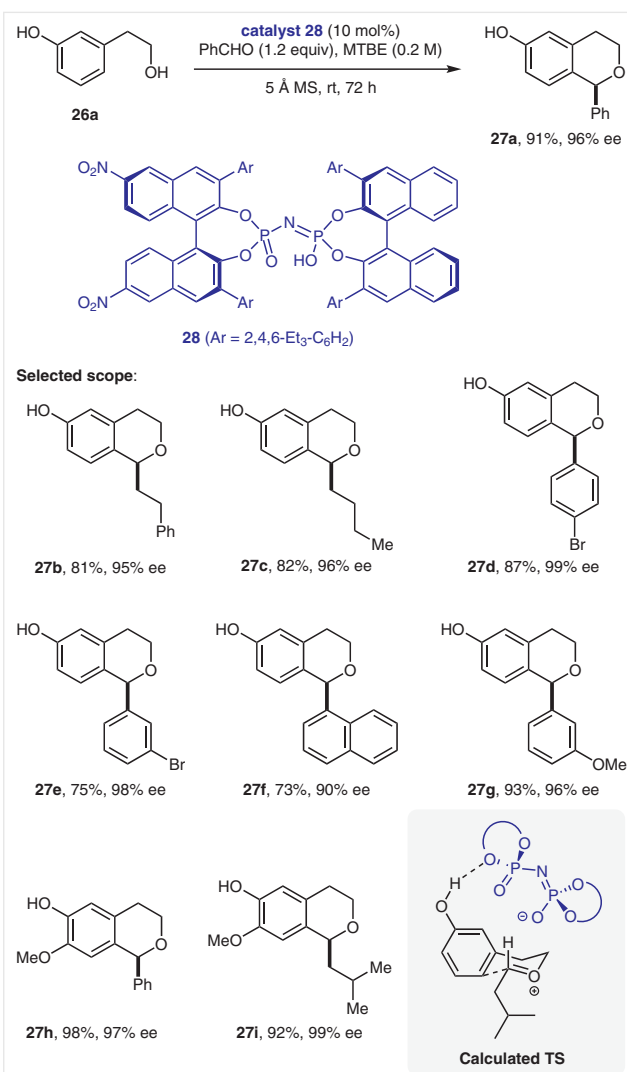
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Scheme 8 Dually catalyzed enantioselective oxa-Pictet–Spengler reactions of tryptophols with aldehydes

Nearly simultaneously to our report, the List group reported a distinct strategy for realizing highly enantioselective oxa-Pictet–Spengler cyclizations (Scheme 9).³¹ Nitrated imidodiphosphoric acid catalyst **28** was found to efficiently catalyze reactions of hydroxy-substituted β -phenylethanols with aldehydes. Catalyst **28** is significantly more active than the analogous imidodiphosphoric acid catalyst lacking the two nitro groups. The corresponding BINOL-based phosphoric acid **29** is also a competent catalyst but affords the products with significantly lower levels of enantioselectivity. Catalyst **28** provides products **27** with excellent ee values while accommodating a range of aromatic and aliphatic aldehydes, with the latter requiring elevated reaction

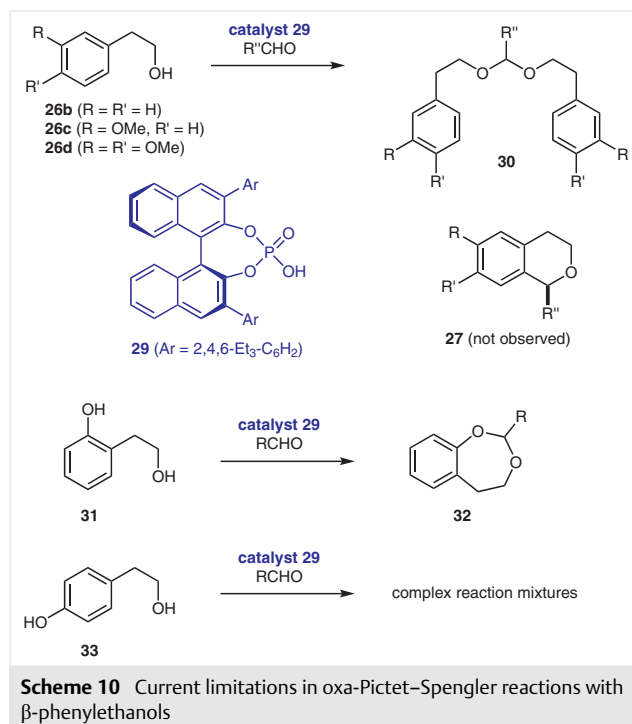
temperatures (50 °C). An additional methoxy group on **26a** is also tolerated. The proposed transition state for the C–C bond-forming step involves a critical hydrogen-bonding interaction of the catalyst anion with the phenol O–H moiety, as elucidated by DFT calculations. An alternate transition state in which ring-closure occurs in *ortho*- rather than *para*-position of the phenol O–H moiety was calculated to be 6.3 kcal/mol higher in free energy (not shown). Consistent with these calculations, these regioisomers are not observed.



Scheme 9 Imidodiphosphoric acid catalyzed enantioselective oxa-Pictet–Spengler reactions of hydroxy-substituted β-phenylethanols with aldehydes

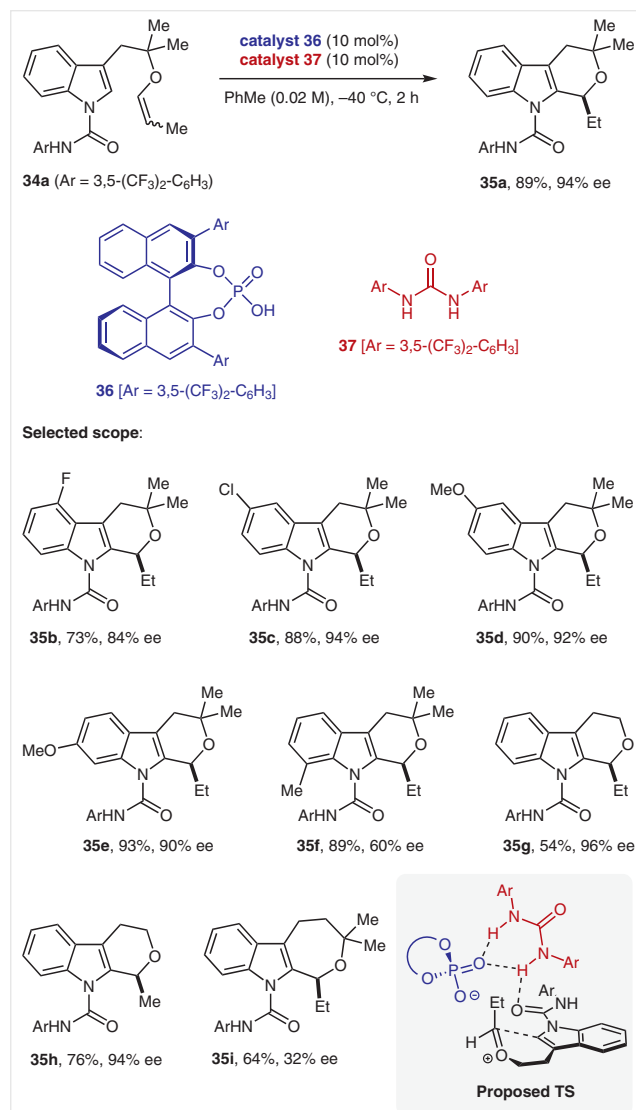
Interesting observations were made in the course of the List study, outlining remaining challenges (Scheme 10). Consistent with the calculated transition state depicted in Scheme 9, the presence of a 3-hydroxy substituent on the β-phenylethanol is a strict requirement. In the presence of

catalyst **29**, β-phenylethanols **26b–d** react with aldehydes to provide symmetrical acetals **30** as the only products. On the other hand, the 2-hydroxy substrate **31** undergoes formation of seven-membered cyclic acetal **32**, whereas **33** affords complex mixtures in reactions with aldehydes.



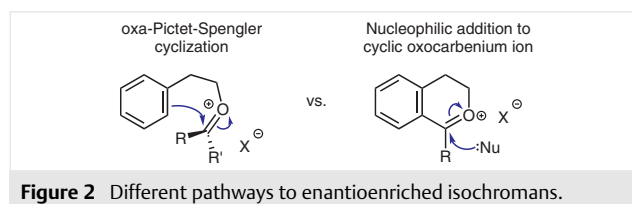
In 2018, Scheidt and co-workers published an alternate strategy to access tetrahydropyrano[3,4-*b*]indoles in highly enantioenriched form.³² A combination of chiral phosphoric acid catalyst **36** and achiral urea catalyst **37** facilitates cyclizations of tryptophol-derived enol ethers such as **34a** to generate oxa-Pictet–Spengler products with high levels of enantioselectivity (e.g., **35a**). The presence of a urea-type protecting group on the tryptophol nitrogen is a crucial design element of this approach (vide infra). While chiral phosphoric acid **36** is capable of catalyzing the reaction in the absence of urea **37**, reaction rates are dramatically retarded (incomplete reaction after 18 h vs. complete reaction within 15 min) and afford product **35a** in only 36% ee (not shown). Regarding the scope of this transformation, substitution of different indole ring positions is readily accommodated. While most products contain a *gem*-dimethyl group adjacent to the tetrahydropyrano oxygen atom, products lacking these substituents are also obtained with excellent ee values. Interestingly, this study contains the only example thus far reported in which a seven-membered ring is constructed enantioselectively in the course of an oxa-Pictet–Spengler cyclization, albeit in only 32% ee (product **35i**). As an application of their method, the authors reported a facile synthesis of coixspirolactam **C** from oxa-Pictet–

Spengler product **35h**. Regarding the mechanism of this transformation, it was proposed that a network of hydrogen-bonding interactions is responsible for achieving high levels of reactivity and enantiocontrol (see proposed TS in Scheme 11). Specifically, the thiourea catalyst is thought to bind to the chiral phosphate anion via dual hydrogen bonding while engaging in an additional hydrogen-bonding interaction with the carbonyl group of the protonated substrate.

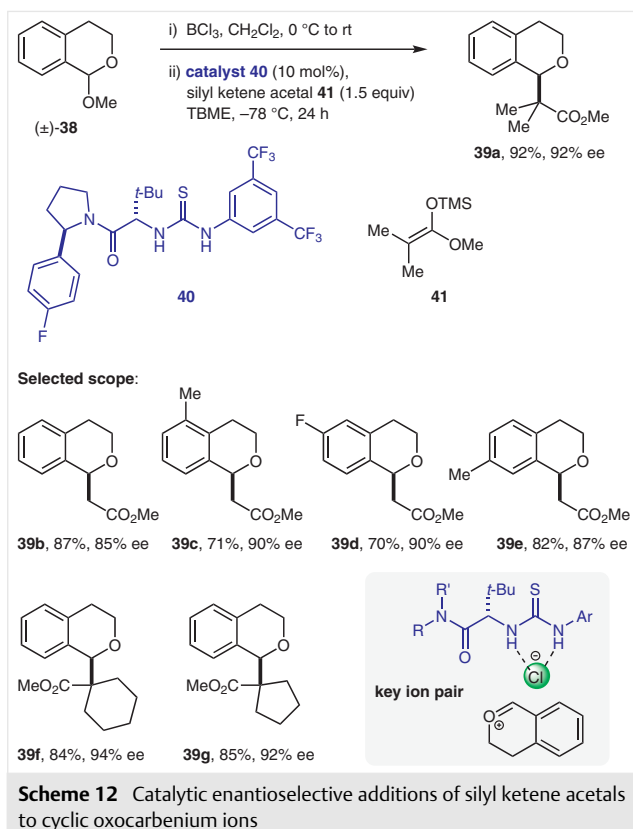


Scheme 11 Dually catalyzed enantioselective oxa-Pictet–Spengler reactions of tryptophol-derived enol ethers

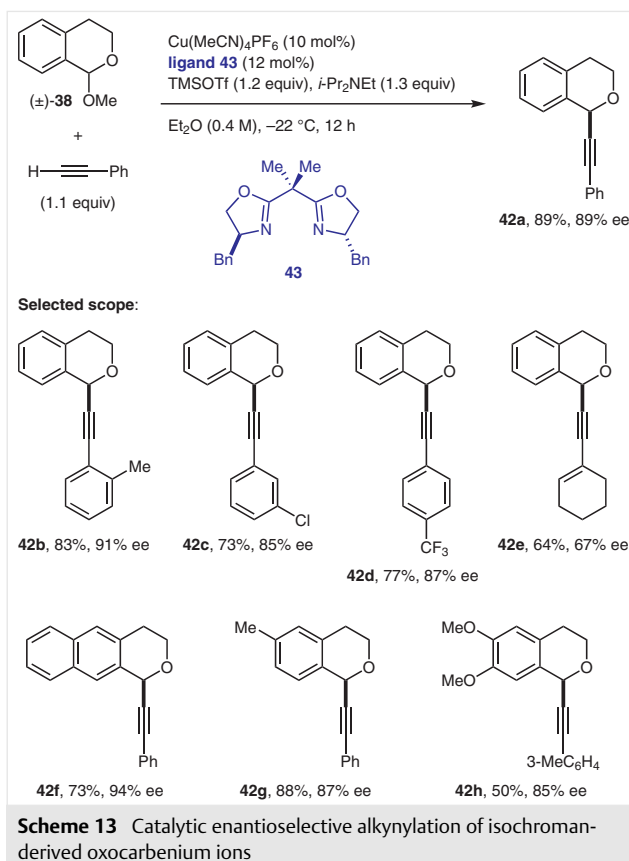
While not aiming to be complete, the following section provides an overview of catalytic enantioselective reactions that lead to oxa-Pictet–Spengler type products by alternate pathways also involving the intermediacy of oxocarbenium ions. As exemplified in the synthesis of enantioenriched isochromans, nucleophilic additions to cyclic oxocarbenium ions provide an alternative to the oxa-Pictet–Spengler cyclization (Figure 2). While cyclic isochroman-type oxocarbenium ions are more stable than their corresponding acyclic counterparts by virtue of conjugation with the fused and necessarily coplanar aryl ring, they offer an expanded array of opportunities for designing enantioselective variants. To render oxa-Pictet–Spengler cyclizations catalytic and enantioselective, the anion X[−] has to be homochiral (e.g., conjugate base of a chiral Brønsted acid catalyst). Alternatively, if achiral, X[−] has to be tightly associated with a chiral anion receptor catalyst (or catalyst ensemble) in order to facilitate the ring-closure step in an enantioselective fashion. These modes of enantiocontrol are also available in nucleophilic additions to cyclic oxocarbenium ions. In addition, the otherwise achiral nucleophile can be rendered chiral by interaction with a chiral catalyst. Nucleophiles can be carbon- or heteroatom-based, enabling the formation of monosubstituted isochromans via a reductive process.



A 2008 landmark study by the Jacobsen group accomplished the first catalytic enantioselective synthesis of 1-substituted isochromans (Scheme 12).^{33,34} Treatment of isochroman-derived acetal **38** with BCl₃ results in the in situ formation of 1-chloroisochroman (not shown), which is then converted into product **39a** upon treatment with silyl ketene acetal **41** in the presence of thiourea catalyst **40**. Binding of the chloride counter anion of the transient oxocarbenium ion to thiourea catalyst **40** is thought to form a chiral ion pair responsible for controlling the facial selectivity in the silyl ketene acetal addition step. Isochromans containing substituents on different positions of the aryl ring and a range of silyl ketene acetals participate in this transformation to provide products **39** in good yields and excellent ee values.

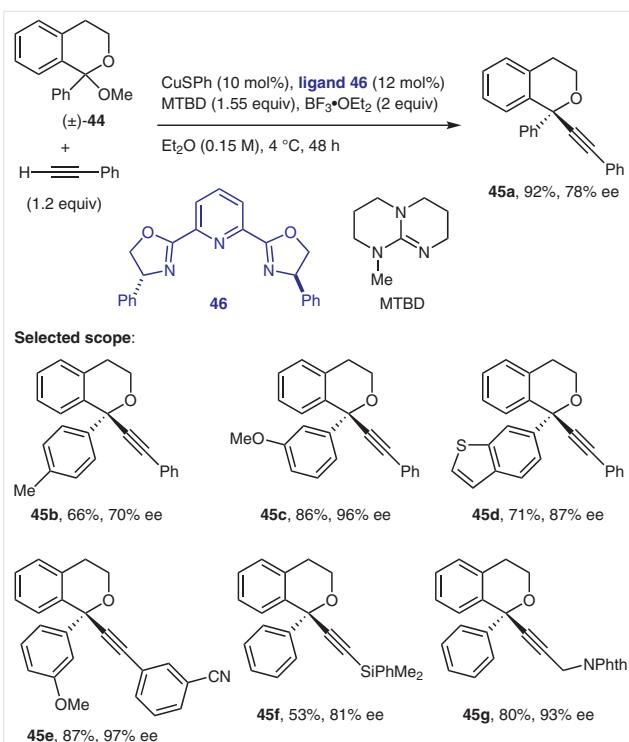


In 2011, Watson and co-workers reported a conceptually different strategy for the catalytic enantioselective addition of nucleophiles to isochroman-derived oxocarbenium ions (Scheme 13).³⁵ Specifically, catalytic enantioselective alkynylation of acetal **38** with phenylacetylene is achieved with a Cu(I) complex of bisoxazoline ligand **43**. Hünig's base facilitates the formation of a chiral Cu acetylide complex that adds to the oxocarbenium ion derived from acetal **38** and TMSOTf. The reaction tolerates substituents on different positions of the isochroman aryl ring and is applicable to a range of terminal alkynes. Some products are somewhat sensitive to oxidative decomposition (e.g., lactone formation). This is particularly true for product **42h** (the yield shown corresponds to the product obtained from subsequent reduction of the alkyne moiety to the corresponding alkane via hydrogenation). An impressive extension of this chemistry was reported in 2015 (Scheme 14).³⁶ A modified catalyst system derived from Pybox ligand **46** enables the synthesis of highly enantioenriched isochromans **45** from 1-substituted isochroman ketals **44**. This is a rare example

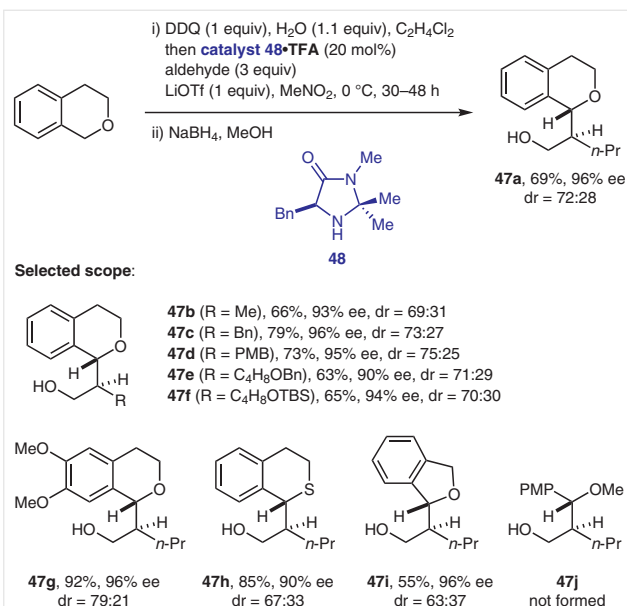


of a catalytic enantioselective process generating isochromans containing challenging tetrasubstituted stereogenic centers.

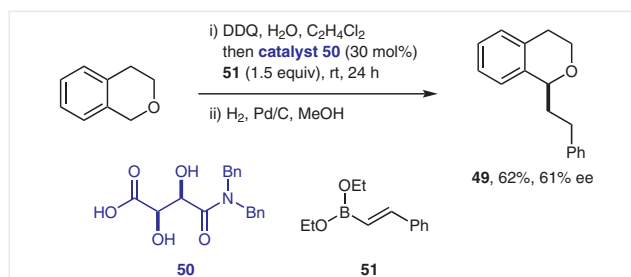
Acetals such as **38** are typically obtained from their corresponding isochromans via an oxidative process. In 2014, the Liu group reported a strategy that obviates the need for preparing acetals in a separate step (Scheme 15).^{37,38} Oxocarbenium ions are accessed in situ by oxidation of isochromans with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Addition of the aldehyde substrate is facilitated by catalyst **48** via an enamine mechanism. Reduction of the initially formed aldehyde products with sodium borohydride provides substituted isochromans (e.g., **47a–g**) and related products with excellent levels of enantioselectivity, albeit with moderate diastereoselectivity. As part of this study, the Liu group achieved the catalytic enantioselective addition of boronic ester **51** to isochroman (Scheme 16). This reaction is facilitated by tartaric-acid-derived catalyst **50** and provides product **49** with moderate ee after hydrogenation in situ.³⁹



Scheme 14 Formation of tetrasubstituted stereogenic centers via catalytic enantioselective alkylation of isochroman-derived oxocarbenium ions



Scheme 15 Catalytic enantioselective addition of enolizable aldehydes to isochromans

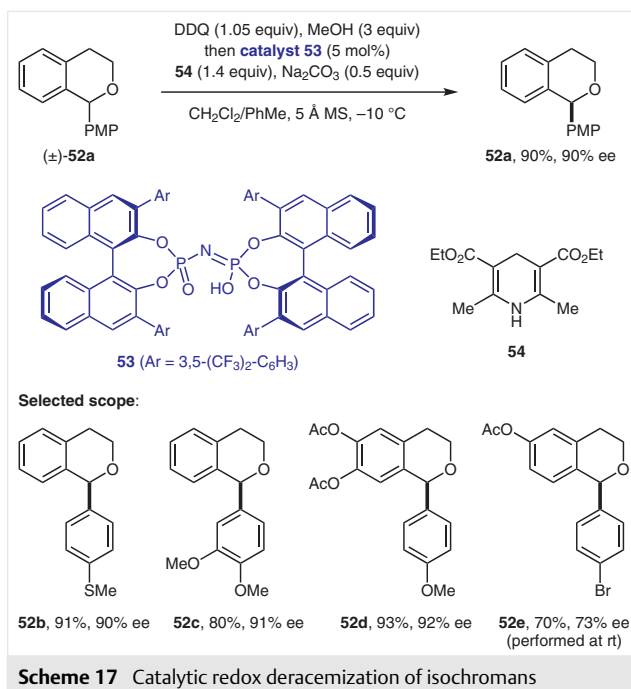


Scheme 16 Catalytic enantioselective addition of a boronic ester to isochroman

In 2017, the Liu group reported an interesting redox deracemization strategy that provides highly enantioenriched isochromans **52** (Scheme 17).⁴⁰ Racemic starting materials such as (±)-**52a** are oxidized in situ by DDQ to the corresponding oxocarbenium ions, which initially form acetals in the presence of methanol. The subsequent reduction step with Hantzsch ester **54** is rendered enantioselective by imidodiphosphoric acid catalyst **53**. In a subsequent study, similar products were obtained by reduction of preformed racemic acetals (not shown).⁴¹ Products **52a** could potentially be obtained more directly via an oxa-Pictet–Spengler cyclization from the corresponding β-phenylethanols. However, current limitations make this an elusive goal (see discussion centered around Scheme 10). The Liu group further applied their redox deracemization strategy to the synthesis of highly enantioenriched tetrahydropyrano[3,4-*b*]indoles, as highlighted in Scheme 18.⁴² For these substrates, SPINOL-derived phosphoric acid **55** and Hantzsch ester **56** provide optimal results. Tetrahydropyrano[3,4-*b*]indoles containing an aryl substituent are typically obtained in excellent yields and ee values. Unfortunately, just like the previously discussed oxa-Pictet–Spengler reaction of tryptophol is incompatible with aliphatic aldehydes (see Scheme 8), the deracemization process does not tolerate 1-alkyl substituents as these substrates fail to undergo oxidation under the standard reaction conditions.

Another strategy for synthesizing enantioenriched isochromans, different from everything discussed thus far, involves reactions in which the enantio-determining step is C–O bond formation. Scheme 19 highlights seminal work in this area, published by Kitamura and co-workers in 2011.⁴³ Ruthenium complex **59**, at a catalyst loading of only 0.1 mol%, facilitates intramolecular dehydrative *O*-allylation of **57** to furnish 1-vinyl isochroman **58a** in excellent yield and ee in a sequence that proceeds via the intermediacy of a Ru- π -allyl species.

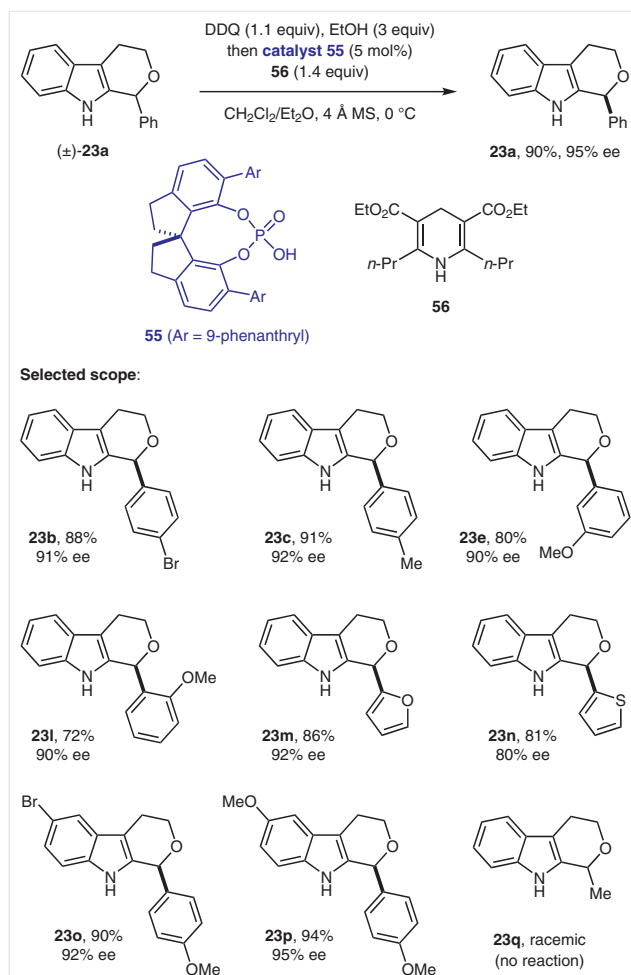
A mechanistically distinct approach published by White and co-workers in 2016 accomplishes the synthesis of related isochroman products by intramolecular catalytic enantioselective allylic C–H oxidation (Scheme 20).⁴⁴ A



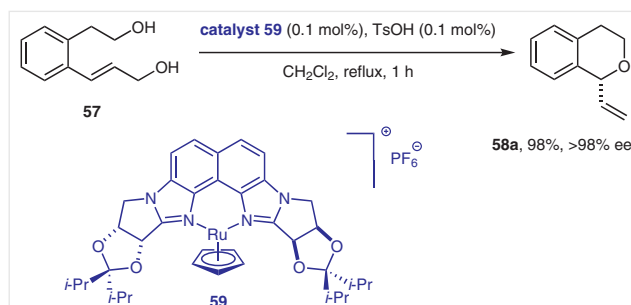
complex derived from palladium acetate and ligand **61**, in the presence of diphenylphosphinic acid, catalyzes the transformation of β-arylethanols such as **60** to 1-vinyl isochromans **58**, and the products are obtained with excellent levels of enantioselectivity. 2,6-Dimethylbenzoquinone (2,6-DMBQ) serves as the terminal oxidant in this process.

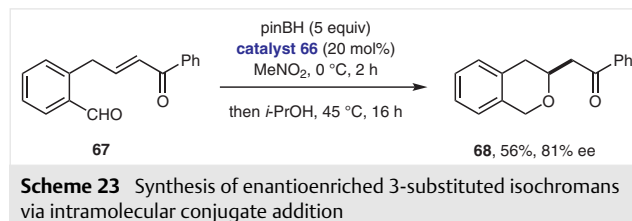
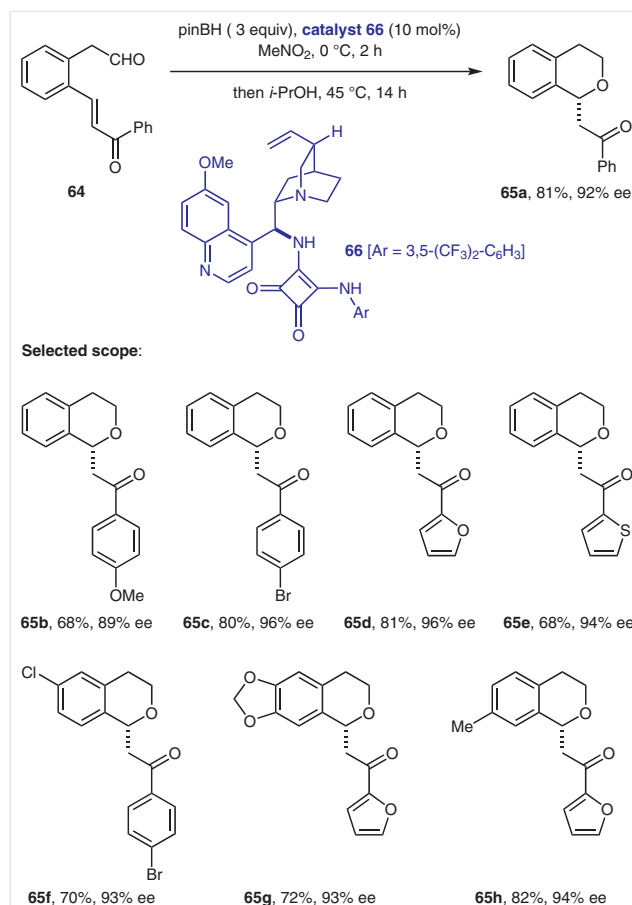
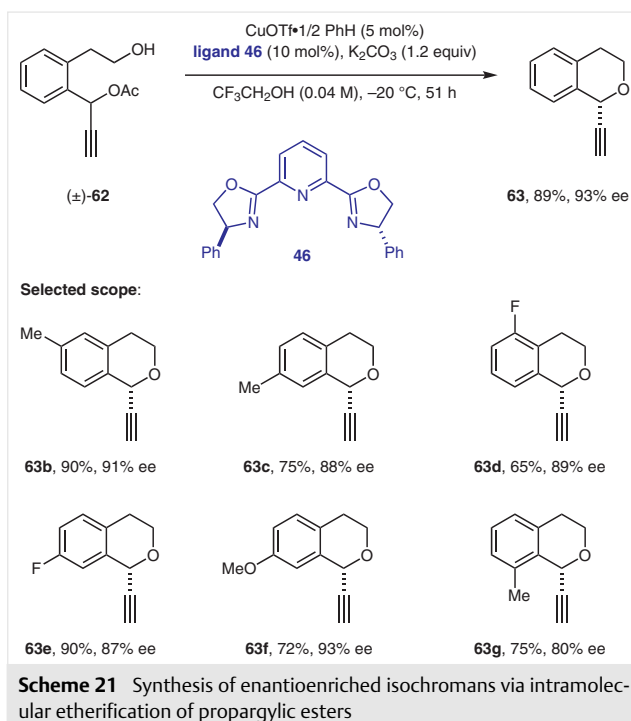
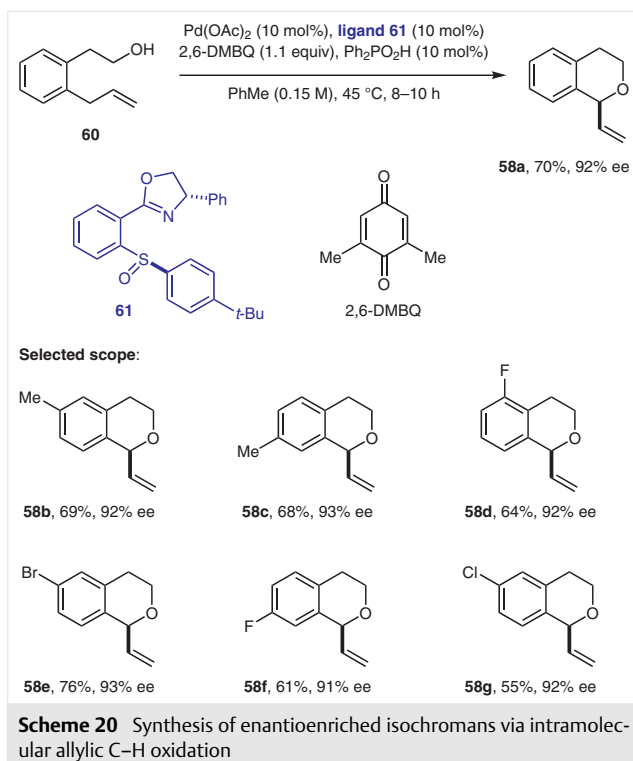
The catalytic enantioselective synthesis of 1-alkynyl isochromans was reported by Nishibayashi and co-workers in 2019 (Scheme 21).⁴⁵ A Cu(I)-complex derived from Pybox ligand **46** catalyzes the enantioselective intramolecular etherification of propargylic esters (e.g., **62**) to provide products **63** in good to excellent yields and ee values. A nonlinear relationship exists between the enantiopurity of ligand **46** and product, leading the authors to propose the intermediacy of a dicopper-allenylidene species.

In 2015, Ghorai and co-workers reported a catalytic enantioselective method for the synthesis of highly enantio-enriched 1-substituted isochromans (Scheme 22).⁴⁶ This method is based on intramolecular conjugate addition. Reduction of the aldehyde functionality of ketoaldehydes such as **64** by pinacolborane (pinBH) provides an alkoxyboronate intermediate that then undergoes conjugate addition to form products **65** with excellent ee values. Reactions are catalyzed by quinine-derived squaramide-containing bi-functional organocatalyst **66** and exhibit a broad scope. This method also enables the synthesis of isochromans containing a substituent in the 3-position. An example is pro-

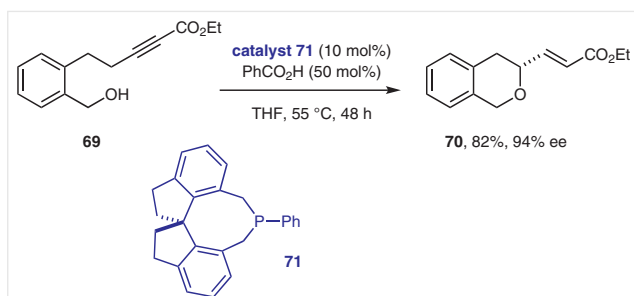


vided in Scheme 23. Ketoaldehyde **67**, a constitutional isomer of **64**, undergoes reduction followed by intramolecular conjugate addition to provide product **68** in 81% ee.



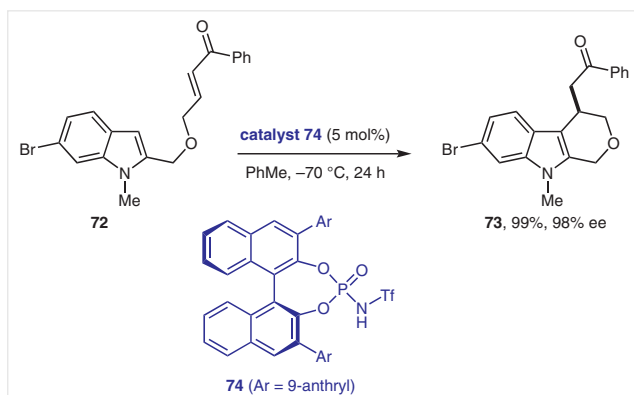


Another rare example of a catalytic enantioselective process leading to isochromans containing a substituent in the 3-position was reported in 2009 (Scheme 24).⁴⁷ As part of a broader effort directed at preparing a range of structurally diverse compounds, Chung and Fu achieved the catalytic enantioselective synthesis of isochroman **70** from α,β -alkynyl ester **69**. This isomerization reaction is catalyzed by chiral phosphine **71**, operating in concert with benzoic acid.



Scheme 24 Synthesis of enantioenriched 3-substituted isochromans via phosphine-catalyzed isomerization of α,β -alkynyl esters

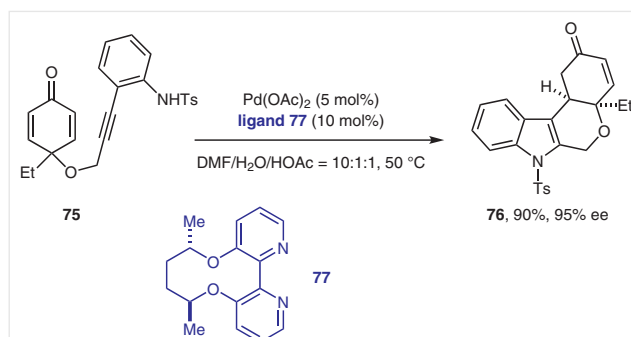
Examples of catalytic enantioselective reactions that provide enantioenriched tetrahydropyrano[3,4-*b*]indoles containing substituents in other than the 1-position are shown in Scheme 25 and Scheme 26. In 2011, the You group achieved enantioselective intramolecular Friedel–Crafts alkylation reactions of indolyl enones (e.g., **72**), providing products such as **73** with exceptional efficiency (Scheme 25).⁴⁸ Reactions are catalyzed by chiral *N*-triflyl phosphoramidate **74**, a catalyst that is remarkably active at $-70\text{ }^{\circ}\text{C}$. In earlier work published in 2009, the same group showed that products such as **73** can be obtained by olefin cross-metathesis/Friedel–Crafts alkylation cascades using a compatible combination of a Ru catalyst and a chiral phosphoric acid catalyst (not shown).⁴⁹



Scheme 25 Synthesis of enantioenriched tetrahydropyrano[3,4-*b*]indoles by intramolecular Friedel–Crafts alkylation

Highly enantioenriched tetrahydropyrano[3,4-*b*]indoles containing a fused ring and two stereogenic centers (e.g., **76**) can be prepared from substrates such as **75**, as reported by Lu and co-workers in 2017.⁵⁰ This transformation involves a Pd(II)-catalyzed aminopalladation/1,4-addition sequence that is facilitated by chiral bipyridine ligand **77**.

As is clear from the transformations discussed in this Short Review, access to highly enantioenriched isochromans and tetrahydropyrano[3,4-*b*]indoles by means of



Scheme 26 Synthesis of enantioenriched tetrahydropyrano[3,4-*b*]indoles by a Pd-catalyzed cascade reaction

asymmetric catalysis has improved dramatically over the past 10 years, with most advances having emerged only in the past 5 years. It is also clear that significant challenges remain. Although highly desirable, for instance for a more efficient synthesis of drug molecules such as etodolac, methods that efficiently install tetrasubstituted stereogenic centers remain rare and have largely been limited to additions to cyclic oxocarbenium ions (Scheme 14). Thus far, there is only one example with low enantioselectivity in which a tetrasubstituted stereogenic center was generated via an oxa-Pictet–Spengler cyclization (Scheme 7). Pictet–Spengler cyclizations of tryptophols or β -arylethanol with ketones or ketone surrogates would provide the most direct access to isochromans and tetrahydropyrano[3,4-*b*]indoles containing a tetrasubstituted stereogenic center in the 1-position. While such reactions are well known in a racemic sense, catalytic enantioselective variants have remained elusive. In addition, highly enantioselective oxa-Pictet–Spengler reactions of tryptophols have not yet been accomplished with aliphatic aldehydes, and reactions with β -phenylethanol require the presence of a hydroxyl group in a specific position of the aryl ring. All three of the highly enantioselective oxa-Pictet–Spengler reactions reported to date (Scheme 8, Scheme 9, and Scheme 11) require the presence of hydrogen-bonding donor or acceptor sites on the alcohol substrate. However, encouraging findings such as those summarized in Scheme 6 suggest that such reactions could potentially be rendered highly enantioselective in the absence of obvious directing groups. Overall, there is cause for optimism that many of these limitations will be addressed in the not-too-distant future. We look forward to learning about new advances and hope that this Short Review will motivate others to tackle the remaining challenges.

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