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Perspective

Asymmetric Ion-Pairing in Stereoselective Vinyl Polymerization

Cole C. Sorensen,[‡] Caleb T. Kozuszek,[‡] Meredith A. Borden, and Frank A. Leibfarth*

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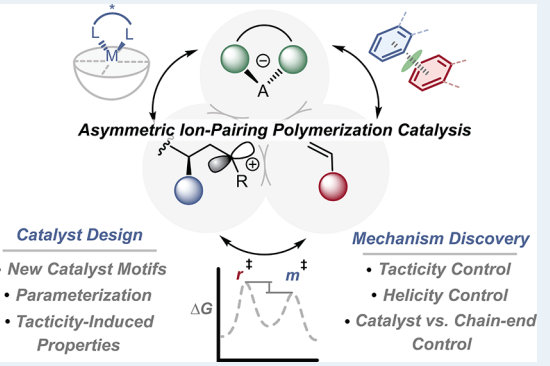
ABSTRACT: Controlling polymer tacticity is a key consideration in macromolecular synthesis due to the impact of stereochemistry on a material's thermomechanical and optical properties. Recently, inspired by work in small molecule catalysis, asymmetric ion-pairing has emerged as a valuable approach to control the stereochemistry of polymers made through chain growth polymerization of vinyl monomers. This Perspective outlines some of the challenges inherent to polymer stereocontrol as well as highlights recent catalyst development in the area of asymmetric ion-pairing that has enabled control of both the configuration and conformation of vinyl polymers. Several synthetic opportunities and mechanistic questions have been identified that will expand the impact of asymmetric ion-pairing in polymer synthesis.



KEYWORDS: *asymmetric ion-pairing, catalysis, polymers, tacticity, asymmetric polymerization, vinyl polymerizations*

INTRODUCTION

The stereochemistry of polymers has a significant influence on their thermomechanical and optical properties and therefore their application-specific functions.[1−4] For example, isotactic polypropylene is a tough semicrystalline thermoplastic produced on a multimillion-ton scale each year, while its atactic counterpart is a viscoelastic fluid with limited applications.[5,6] Historically, chemists have used two main strategies to control polymer stereochemistry: (1) employing chiral metal catalysts covalently bound to the growing polymer chain end and (2) leveraging templating Lewis acids in concert with chain-end control in anionic and radical polymerization mechanisms (Figure 1).[2] Given both the mechanistic limitations and monomer restrictions of using these two approaches, the types of polymers that can be synthesized with high stereoregularity is limited.[7,8] General stereocontrolled strategies that provide access to materials that complement existing stereoregular polymers are needed.

Asymmetric ion-pairing (AIP) catalysis is a burgeoning concept to control polymer stereochemistry in anionic and cationic polymerizations.[9−11] Giulio Natta disclosed the first use of AIP in 1961 for polymerization of benzofuran, which predates Merck's disclosure of asymmetric ion-pairing catalysis by 23 years.[12] Subsequently, Okamoto discovered helix-sense-selective polymerization to control polymer helicity in 1979.[13] There is renewed interest in leveraging AIP in controlling polymer stereochemistry that has led to promising improvements in material properties for a variety of polymers, including several systems where stereocontrolled polymerization was previously elusive. With further effort directed at catalyst design and mechanistic investigation, the field is primed to expand stereoselective polymerization methodology to provide access to unique stereoenriched polymers with differentiated properties.

AIP catalysis, wherein electrostatic interactions between a catalyst and a substrate of opposite charges dictate the stereochemical outcome of a transformation, has been an effective strategy to control stereoselectivity in small molecule catalysis for more than two decades.[9−11] Within AIP catalysis, reactions can be classified as either chiral ion-directed, in which the chiral catalyst is charged, or ion-binding, where a neutral chiral catalyst binds an ion that interacts with the reactive intermediate (Figure 2). The overarching challenge for AIP catalysis is the lack of directionality inherent to electrostatic interactions, which makes it difficult to place the source of chirality (i.e., the catalyst) in the correct spatial orientation to direct the desired transformation.

In order to achieve the exquisite selectivities characteristic of small molecule AIP transformations, a wide array of catalyst classes that leverage both attractive and repulsive noncovalent interactions (e.g., hydrogen bonding, pi-system interactions, Lewis acidity, etc.) have been developed.[14−18] As AIP strategies gain prominence in stereoselective polymerizations,

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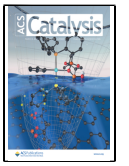

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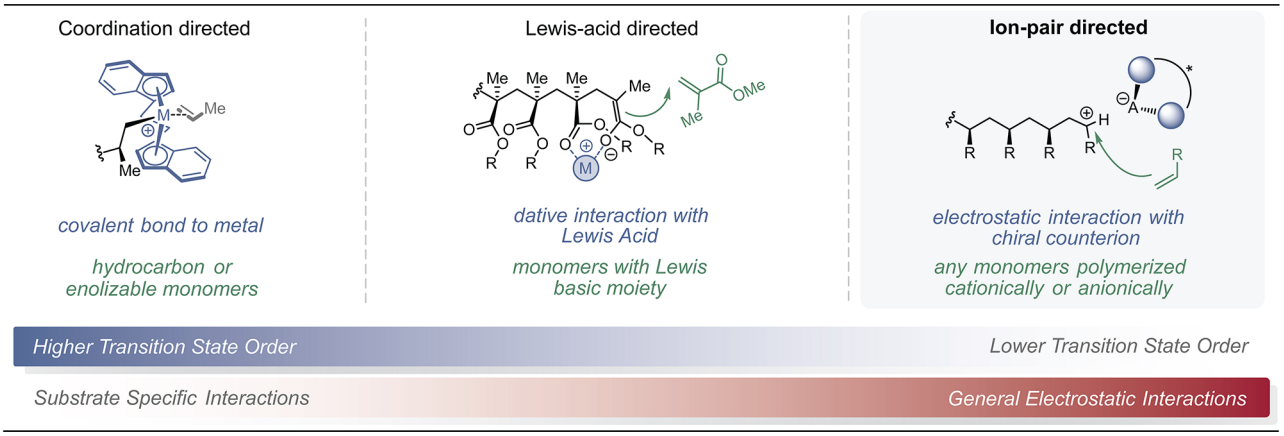

Figure 1. General approaches to directing monomer addition to a reactive chain end in stereoselective polymerization.

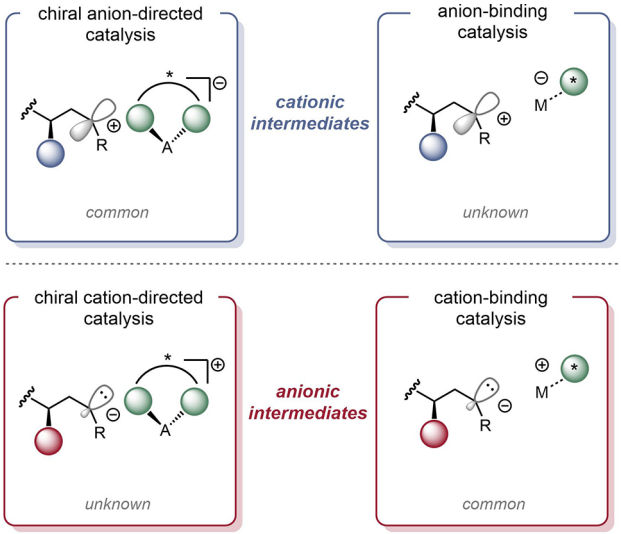

Figure 2. Modes of asymmetric ion-pairing in polymer science.

chemists can capitalize on this extensive body of work and the associated tools to understand mechanisms of stereoinduction to accelerate their efforts.

Anionic and cationic polymerization mechanisms are primed to leverage AIP to control stereochemistry because of the ionic intermediates that serve as their reactive chain ends. Traditional approaches for accessing stereoregular polymers synthesized by ionic mechanisms have relied on substrate control, where monomers with sterically bulky groups or chiral substituents are used for the sake of achieving high stereoregularities (Figure 3). These transformations require extensive monomer design and often achieve high tacticity values at the expense of material properties.[13,19−22] In contrast, recent developments in controlling stereochemistry with chiral catalysts has led to the development of new AIP polymerization methods where catalyst structure determines stereoselectivity. This has broadened the monomer scopes of these methods through catalyst−ligand design, thus providing access to stereoenriched polymers made from simple precursors that demonstrate attractive properties. The fledgling transition from monomer to catalyst design in controlling polymer stereochemistry parallels the advancements from substrate control with directing groups toward purely catalyst control in the fields of small molecule AIP catalysis, stereoselective photoredox chemistry, and C−H functionalization.[9−11,23−25]

In this Perspective, we highlight the recent developments in stereocontrolled polymerization using AIP catalysis. The Perspective is limited to applications of AIP catalysis for stereocontrolled polymerization of vinyl monomers due to their unique challenges.[2] This Perspective is broken into five sections where we discuss (1) the *general considerations of stereocontrolled polymerizations*, highlight examples in the field of (2) *configurational stereocontrol*, (3) *conformational stereocontrol*, and (4) *asymmetric polymerizations of disubstituted alkenes*, and share (5) *our perspective and outlook on the synthetic and mechanistic opportunities of the aforementioned fields*. AIP catalysis has been applied to select substrates in ring-opening, group transfer, and Lewis-pair polymerizations, but these examples are beyond the scope of this work.[26−30] Within the field of polymer chemistry, there is ambiguity in differentiating between initiators and catalysts; we elected to use the term

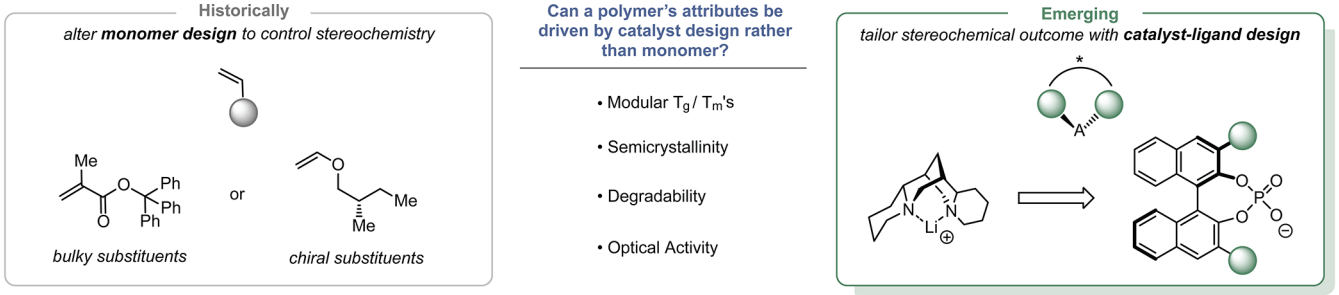

Figure 3. Controlling polymer stereochemistry using monomer-based approaches (left) to AIP catalyst design approaches (right) will broaden the scope of accessible stereoenriched polymers.

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catalyst in this Perspective as the structure is not incorporated into the polymer backbone and affects the transition state energy of more than one propagation event.[30] We aim to show the evolution of AIP catalyst design that has enabled stereocontrolled ionic polymerizations, while also outlining potential areas for further research.

GENERAL CONSIDERATIONS FOR STEREOCONTROLLED POLYMERIZATION

How to Define Good Selectivity. A challenge in polymer stereochemistry is that there is no agreed-upon value for the degree of stereocontrol required to represent an advance in the field. In small molecule asymmetric catalysis, typically >90% enantiomeric excess (% ee) is categorized as "good" and the higher the value the better. Enrichment of % ee provides more of one enantiomer, which is advantageous for asymmetric synthesis but does not change molecular properties. In contrast, most polymers demonstrate changes in their physical properties as a direct consequence of changes in their stereoregularity.[1]

Therefore, we propose that the degree of stereocontrol required to observe physical changes in the material (compared to its atactic counterpart) represents an advance worth reporting. For example, many isotactic materials become semicrystalline at high % *meso* diads (% *m*), which improves their mechanical properties.[31] Furthermore, achieving tacticity values above those which provide a step change in properties (i.e., approaching 100% *m* or *racemo* (% r) diads) is beneficial to gain a complete understanding of stereoselectivity−property relationships.

Challenges in Characterization. As compared to small molecules, the tools chemists have to evaluate tacticity are quite limited. While chiral chromatography (e.g., GC, HPLC, SFC) can reliably be used to determine enantiomeric excess for small molecules, polymer chemists typically rely on nuclear magnetic resonance (NMR) based techniques to determine tacticity. The number of possible stereoisomers in a vinyl polymer is 2^N, where N is the number of repeat units, which necessitates the analysis of relative stereochemistry denoted as *meso* or *racemo* diads, triads, and higher ordered sequences.[32,33] Tacticity of vinyl polymers is most often characterized by ^{13}C NMR because the large spectral window of ^{13}C NMR provides high resolution to identify diastereomeric substrates. The downside of ^{13}C NMR is the large material and time requirements to obtain sufficient resolution, which makes catalyst discovery resource intensive. ^{1}H NMR has also been applied in limited cases for tacticity characterization and typically requires elevated temperatures to resolve individual stereosequences and/or structurally simple polymers.[32,34,35] Further complications for characterization arise when the resonances required to identify polymer *meso* or *racemo* diads have not been previously assigned. Assignment is nontrivial and requires analysis by comparison, computational predictions, synthesis of small molecule analogues, and/or multidimensional NMR techniques, which makes the discovery of new tactic materials exceedingly difficult.

A recently reported improvement in tacticity characterization is the use of band-selective heteronuclear single quantum coherence spectroscopy (BS-HSQC).[36] This two-dimensional $^{1}H-^{13}C$ NMR experiment combines the benefits of ^{1}H sensitivity and ^{13}C resolution within a narrow spectral window to provide rapid experimentation time (typically around 5−15 min) for characterizing stereosequences. In our experience, BS-HSQC is also highly effective for peak deconvolution when assigning tacticity. However, further innovation in tacticity characterization would make the field of stereoselective polymerization more tractable and provide a means toward high-throughput experimentation, which can be highly effective for catalyst parametrization and design.[15,37]

Addressing Issues of Complexity. Tacticity is an indication of relative stereochemical configuration and is analogous to diastereoselectivity in small molecules, producing isotactic, syndiotactic, or higher order eutactic sequences (Figure 4A). As such, polymerizations can deliver stereoregular

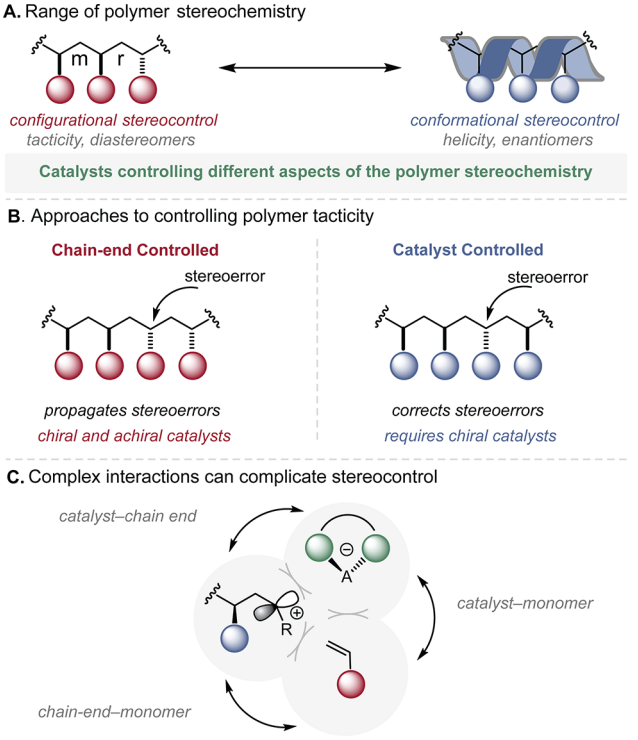

Figure 4. Stereochemical complexities unique to AIP catalysis in polymer science.

material from racemic or achiral catalysts since the propagating polymer itself is chiral. Catalysts that interact with the polymer chain end can impart stereocontrol through chain-end control, catalyst control, or a combination of both. Chain-end control arises from the chirality of the previously enchained monomer(s) influencing subsequent monomer addition. Catalyst control, also known as enantiomorphic site control, occurs when the chirality of the catalyst directs monomer addition. While the two mechanisms can both deliver stereoregular materials, chain-end controlled mechanisms propagate stereoerrors while catalyst-controlled mechanisms correct stereoerrors (Figure 4B). Therefore, they can produce two different materials with different stereochemical microstructures but identical reported tacticity values. Differentiating between chain-end and catalyst control is an important consideration in understanding the mechanism of stereoinduction and is most often analyzed by applying simple Markovian statistical methods to the triad distribution within a vinyl polymer.[32,38,39] Understanding the implications of the mechanism of stereocontrol on property outcomes is underexplored and will be enabled by the development of additional

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catalyst-controlled methods to control tacticity, especially in ionic polymerizations.

An underappreciated complexity inherent to stereocontrolled vinyl polymerization is the impact of match−mismatch effects. Because propagation occurs at a chain end that contains stereocenters at previously enchained monomers, the use of a chiral catalyst produces a double diastereoselection scenario during polymerization with prochiral monomers (Figure 4C). In the event of using chiral monomers, triple diastereoselection scenarios are operative, where the stereochemistry of the monomer, catalyst, and chain end all influence the ultimate stereochemical outcome. Therefore, catalyst design cannot be pursued in isolation without an appreciation for the complex and interdependent interactions present during each stereodetermining, elementary step. Teasing out the individual interactions has been done experimentally in some examples, but a more rigorous understanding is required for the field to move toward mechanism-guided experimentation and use of computational methods where needed.[40−43]

Additional complexities arise when pursuing polymerization methods that control absolute stereochemistry, a type of asymmetric polymerization, for the generation of optically active polymers (Figure 4A). The majority of asymmetric polymerizations are achieved by controlling polymer helicity, which requires the combination of conformational stereocontrol by a chiral catalyst and bulky monomers whose polymers form stable secondary structures.[44] Further understanding of the role that AIP catalysis plays in imparting both stereochemical configurational and conformational control is an exciting opportunity in polymer catalysis.

EXAMPLES THAT HIGHLIGHT ADVANCES IN THE FIELD OF STEREOCHEMICAL CONFIGURATIONAL CONTROL

Difficulty of Overcoming Chain-End Control. Cationic polymerization of vinyl ethers was the first report of stereocontrolled polymerization and initiated the discussion of polymer stereochemistry.[45] Historically, bulky alkyl vinyl ethers like *tert*-butyl vinyl ether (*t*BuVE) have been polymerized to moderate isotacticity under chain-end control with small, achiral Lewis acids. Most notably, boron trifluoride etherate ($BF_3{\cdot}Et_2O$) was reported in 1948 as a catalyst for the synthesis of isotactic enriched semicrystalline poly(vinyl ethers), a polymer class that had previously only been synthesized as an atactic viscoelastic fluid.[19] Despite the development of modern chiral catalysts by Yamamoto, Aoshima, Leibfarth, and Liao, none have been able to polymerize *t*BuVE to levels of tacticity rivaling $BF_3{\cdot}Et_2O$ (Figure 5A).[31,41,46−49] These catalysts include chiral Lewis acids and Brønsted acids, some of which have been shown to operate under catalyst control for alkyl vinyl ethers.

In the model of stereocontrol for the polymerization of vinyl ethers proposed by Cram and co-workers (Figure 5B), the penultimate ether moiety binds to the propagating oxocarbenium, attenuating reactivity and biasing toward isotactic propagation because of the favorability of bulky pendant groups occupying an equatorial position in the 6-member cyclic chain-end chelate.[50] In this model, bulkier monomers like *t*BuVE are predicted to display stronger chain-end control for isotactic propagation. Chiral catalysts may disrupt inherent chain-end control associated with these sterically encumbered monomers without sufficiently differentiating between isotactic and syndiotactic propagation to improve tacticity. Evidence

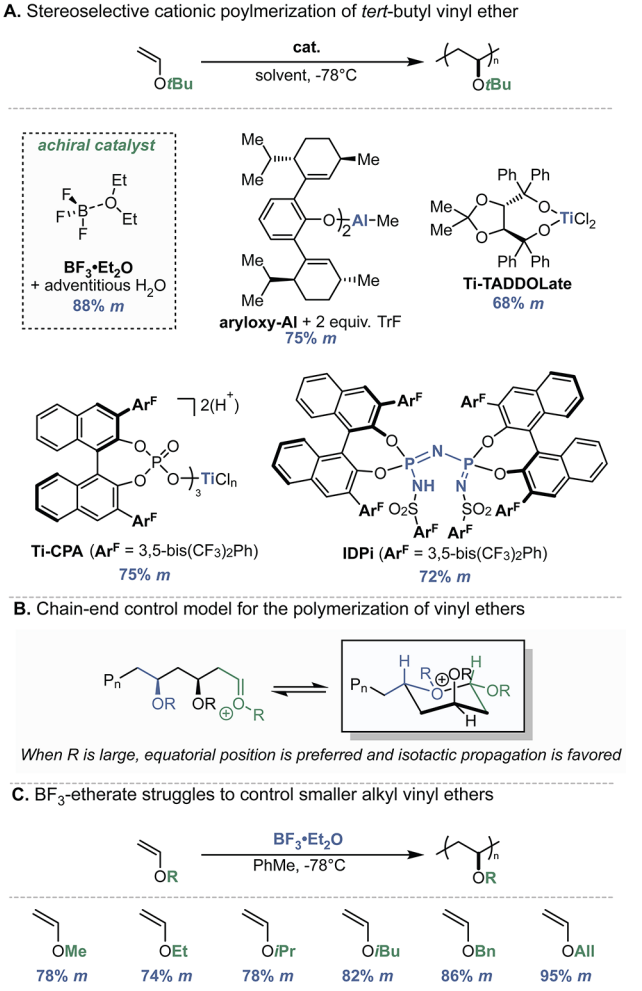

Figure 5. Challenges associated with stereocontrol of sterically encumbered *tert*-butyl vinyl ether.

supporting this hypothesis is observed for the $BF_3{\cdot}Et_2O$ catalyzed polymerizations of a variety of vinyl ethers; it is effective for *t*BuVE but struggles to control stereochemistry for less bulky alkyl vinyl ethers, has limited molecular weight control, and cannot be made chiral (Figure 5C).[51−53] Interestingly, $BF_3{\cdot}Et_2O$ provides 86% and 95% *m* for benzyl and allyl vinyl ether, respectively, potentially stemming from favorable cation−π interactions. This illustrates the complexity associated with stereoselective polymerization that may be difficult to predict experimentally.

One systematic approach to the application of asymmetric ion-pairing catalysis in the polymerization of *t*BuVE involved a series of chiral organoaluminum Lewis acid catalysts used in tandem with fluorine-containing initiators reported by the Yamamoto group in 2001.[46] C_1- and C_2-symmetric ligands were selected and compared to achiral organoaluminum Lewis acids, like methylaluminum bis(2,6-di-*t*-butyl-4-methylphenoxide) (MAD), showing increased isotacticity when using chiral Lewis acids relative to achiral Lewis acids. Initiator to catalyst ratio experiments led the authors to propose a chiral difluoroaluminate counteranion as the active counterion. They suggest that fluorine content is important to selectivity, which they credit to minimizing ion-pair distance and increasing covalent character between the chain end and catalyst. Although Yamamoto's chiral organoaluminum catalysts have been used to great effect in small molecule asymmetric

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catalysis, the levels of tacticity in poly(*t*BuVE) produced by these catalysts fell short of $BF_3{\cdot}Et_2O$ controls, likely due to destructive interactions between inherent chain-end control and catalyst contribution. While this report did not give particularly stereoenriched polymers, it was notably the first application of asymmetric ion-pairing catalysis to the polymerization of vinyl ethers and it illustrates the difficulty of controlling this particular substrate.

Transition Metal Catalyzed Cationic AIP. Contemporary catalysts for stereoselective cationic polymerization control polymer stereochemistry for a more diverse array of substrates by combining the inherent control imparted by chain-end conformation with a chiral counterion. In particular, chiral 1,1′-bi-2-naphthol (BINOL) based Brønsted acid catalysts, which have found widespread application in small molecule AIP catalysis, have emerged as a useful scaffold to develop stereoselective cationic polymerizations.[40,47,48,54] In 2019, the Leibfarth group reported a catalyst for stereoselective polymerization of vinyl ethers involving a BINOL-based chiral phosphoric acid (CPA).[31] While the CPA alone was not active enough to initiate cationic polymerization, addition of a Lewis acid provided poly(alkyl vinyl ether)s with various degrees of selectivity for isotactic enchainment. A thorough screen of both CPA and metal identity found that a combination of $TiCl_4(THF)_2$ and a BINOL-CPA with 3,5-bis-(trifluoromethyl)phenyl substitution at the 3,3′ position provided the highest selectivities (Figure 6A).

Markovian statistical analysis of stereotriad distribution revealed a strong bias for catalyst control. Catalyst control was credited as the reason for this method's high substrate generality, giving 88−93% *m* for ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, and *iso*-amyl vinyl ether. This substrate generality allowed for the synthesis of semicrystalline isotactic poly(vinyl ether) copolymers with tunable glass transition temperatures (T_g) and melting temperatures (T_m) by copolymerizing monomers with different pendant groups.[55] To date, this is the only catalyst system reported for the stereoselective (co)polymerization of vinyl ethers to operate under a strongly catalyst-controlled mechanism.

A follow-up mechanistic study of this catalyst system used chemical kinetics, Eyring analysis of stereoselectivity, additive experiments, and match−mismatch experiments to elucidate catalyst mechanism and give insight into catalyst structure (Figure 6B).[40] A chiral CPA-Ti complex is proposed to abstract a chloride from the Markovnikov adduct of a vinyl ether and HCl, thus providing a carbocation to initiate polymerization and an anionic CPA-Ti complex that serves as a chiral counterion. Notably, match−mismatch effects were observed with chiral vinyl ethers (Figure 6A); enantioenriched alkyl vinyl ethers with a chiral center at either the α- or β-position from the ether oxygen were polymerized with either (*R*)-CPA or (*S*)-CPA titanium catalyst. The chirality matched catalyst−enantiomer combination provided 3% higher *meso* diad content compared to the mismatched case, fitting well with the catalyst-controlled mechanism. Monomer structure−stereoselectivity trends were investigated. Vinyl ethers containing longer linear alkyl groups provided higher isotacticity, while increased branching at the α-position yielded lower isotacticity. Kinetic analysis revealed a pronounced ligand deceleration effect that resulted in the observed rate constant for the CPA-Ti complex to be eight times lower than the unligated $TiCl_4$.

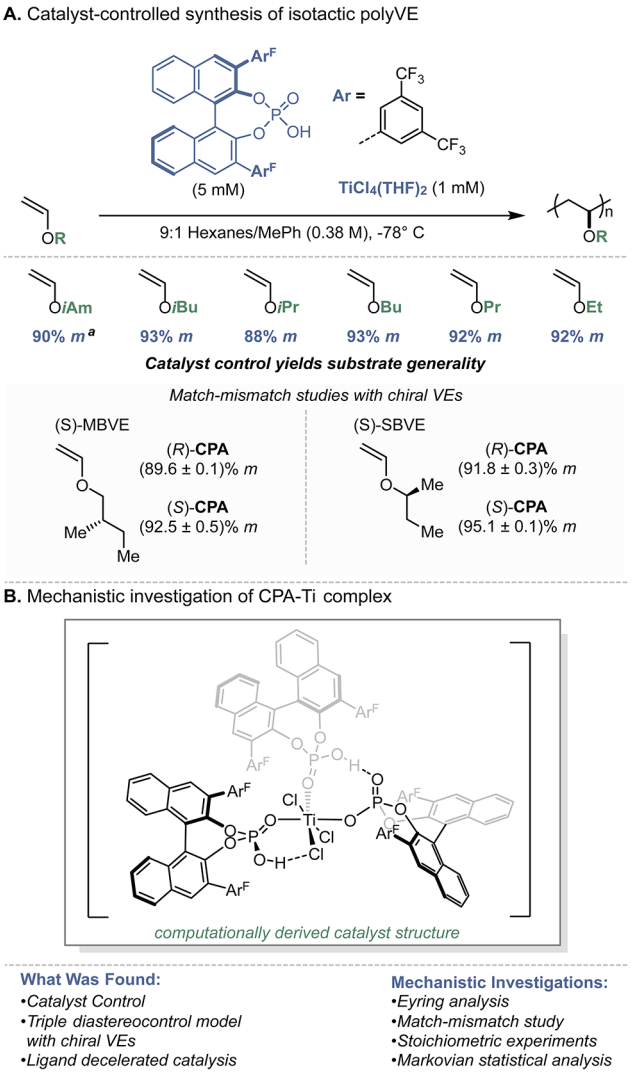

Figure 6. Catalyst-controlled stereoselective cationic polymerization enables substrate generality. [a]$TiCl_4$ used in the reaction instead of $TiCl_4(THF)_2$.

An Eyring analysis of stereoselectivity showed linearity from −78 to −40 °C, and a $\Delta\Delta G^{\ddagger}$ of 0.73 kcal/mol was calculated under the assumption of a two-state model. A crystal structure of the CPA-Ti catalyst could not be obtained, but ligand-to-metal ratio experiments and density functional theory (DFT) geometry calculations indicated that a 3:1 CPA:Ti complex was the ground state structure of the catalyst species, with three phosphate ligands bound on the same plane of the octahedral Ti center (Figure 6B).

Another chiral titanium catalyst was reported by the Aoshima group in 2020 utilizing widely available and well-studied $\alpha,\alpha,\alpha',\alpha'$-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) ligands.[41] It was found that a Ti-TADDOLate complex was able to initiate cationic polymerization in the presence of an isobutyl vinyl ether-HCl adduct, giving a vinyl ether-derived carbocation to initiate polymerization and an anionic Ti-TADDOLate complex to act as the chiral counterion. A brief Lewis acid screen illustrated the dependence of metal identity on stereoselectivity. In all cases, chiral ligands outperformed the achiral 1,1-diphenylethanol control ligand (Figure 7A). A similar phenomenon has been seen in

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various systems, highlighting the importance of chirality in the catalysts.[46,56]

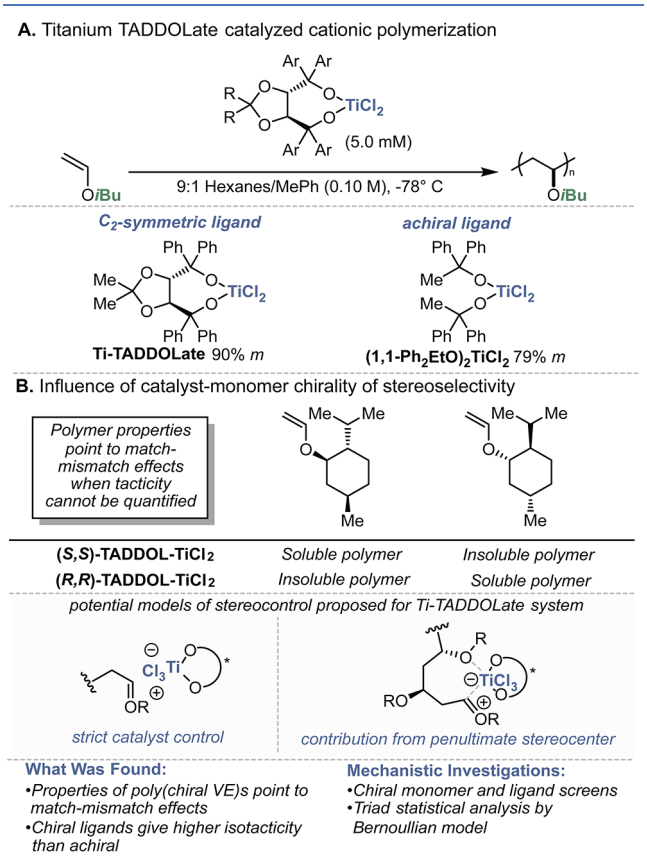

Figure 7. Chiral titanium TADDOLate catalyst for vinyl ether polymerization.

The Ti-TADDOLate system was used by Aoshima and co-workers to polymerize bioderived chiral vinyl ethers.[41] The resultant material properties may point to match−mismatch effects, demonstrating yet another dependence of catalyst chirality on the stereochemical outcome (Figure 7B). Enantiopure (1*S*,2*R*,4*R*)-menthyl vinyl ether was found to form insoluble polymer in a variety of solvents when (*R*,*R*)-TADDOL-$TiCl_2$ was used but soluble polymer was formed with (*S*,*S*)-TADDOL-$TiCl_2$, with the inverse true for the enantiomer of the monomer. It was hypothesized that this difference could be due to match−mismatch effects, where the solubility was related to isotacticity with more stereoregular materials being less soluble in an array of solvents. Quantitative tacticity determination by ^{13}C NMR was not possible, however, due to peak convolution. Bernoullian statistics for chain-end control did not fit the polymers obtained from this system, but no conclusions were drawn about potential contribution from catalyst control. Two different mechanisms of stereocontrol were proposed (Figure 7B), either strict catalyst control or penultimate-monomer contribution where the penultimate pendant ether forms a 7-member chelate with the titanium counterion, similar to the 6-member chelate chain end proposed by Cram and co-workers[50] for chain-end control (Figure 5B).

Asymmetric Organocatalysts for Cationic AIP. While transition metal chiral catalysts provided isotactic poly(vinyl ether)s with high stereoselectivity, they required high catalyst loading and limited the scope of monomer substrates. In response, a number of groups pursued the discovery of single-component Brønsted acids as catalysts. Specifically, BINOL-based catalysts with higher acidity, *N*-sulfonyl phosphoramides (NPAs), phosphoamidimidates (PADIs), and imidodiphosphorimidate (IDPi), have provided isotactic poly(vinyl ether)s under mild reaction conditions.

Sterically confined IDPi catalysts are known to be highly active and stereoselective catalysts for many small molecule transformations. For example, IDPis catalyzed the addition of carbon nucleophiles to highly reactive, unbiased aliphatic oxocarbenium ion intermediates with high conversion and excellent stereoselectivity, illustrating the promise of these catalysts in controlling the cationic polymerization of alkyl vinyl ethers.[57] Exploring this catalyst class for cationic polymerization, the Leibfarth group reported the polymerization of alkyl vinyl ethers with chiral BINOL-based Brønsted acid catalysts (Figure 8A).[47] While NPAs gave relatively low

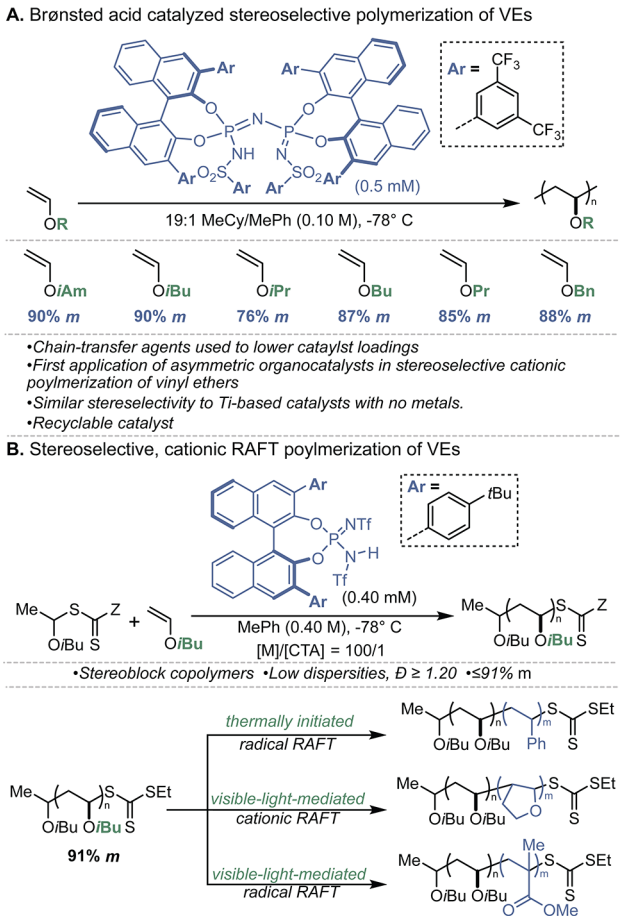

Figure 8. Discrete Brønsted acid catalysts expand amenable monomers and architectures for cationic polymerization.

selectivity, IDPi catalysts provided high selectivity for isotactic enchainment. Substitution of the catalysts at the 3,3′-position had a significant effect on stereoselectivity, with the 3,5-bis(trifluoromethyl)phenyl group providing the highest stereoselectivity.

The isotactic poly(vinyl ether)s demonstrated high molecular weights compared to other stereoselective methods, which the authors attributed to the confinement of the IDPi catalysts reducing chain-transfer events. The isotactic polymers were semicrystalline materials with T_m ranging from 40 to 140 °C.

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The IDPi catalysts enabled access to isotactic poly(benzyl vinyl ether), which was inaccessible by previous stereoselective methods that used titanium Lewis acids. The material demonstrated a T_m of 140 °C, which is higher than the T_m of high-density polyethylene and illustrates its potential for further structure−property evaluation.

An additional benefit to the use of single component Brønsted acids catalysts was the ability to use well-known chain transfer agents (CTAs) for cationic reversible addition−fragmentation chain-transfer (RAFT) polymerization to facilitate control of molecular weight, dispersity, and architecture. The Leibfarth group[47] reported that thioacetal CTAs, which are incompatible with the state-of-the-art Lewis acid catalysts, could be used with IDPi catalysts to reduce catalyst loading to part per thousand (ppt) levels and tune molecular weight, although living character and low dispersity was not achieved. Additionally, the IDPi catalysts could be recovered after polymer precipitation and recycled for further polymerizations.

Concurrent to the Leibfarth group's publication,[47] the Liao group reported a comprehensive screen of Brønsted acid catalysts for the polymerization of vinyl ethers,[48] followed by the application of PADI catalysts for the stereoselective polymerization of a range of vinyl ethers (Figure 8B).[54] These advances enabled the stereoselective cationic RAFT polymerization using trithiocarbonate and dithiocarbamate CTAs to generate low dispersity ($Đ$ = 1.2) isotactic poly(vinyl ether)s that could then undergo chain-extension to form a variety of stereoblock copolymers. Unlike the previous catalysts reported by Leibfarth and co-workers, the 4-*t*-butylphenyl substitution at the 3,3′-position of the BINOL scaffold was shown to give the greatest selectivity with PADI catalysts. This departure from precedent motivates further efforts in catalyst discovery for this application and points to the need for a more complete mechanistic understanding of structure−stereoselectivity relationships to design future catalysts.

Despite the recent attention to stereoselective cationic polymerization, many fundamental questions remain regarding the role of the catalyst in each elementary step of polymerizations. For example, while many of the discussed catalysts have regularly achieved >98:2 enantiomeric ratio in a series of small molecule reactions that proceed through oxocarbenium ion intermediates, they struggle to rise above 90% *m* selectivity in the polymerization of alkyl vinyl ethers. In a polymerization, the number of stereoisomers that arise from the presence of previously enchained monomers and relevant transition states greatly increases, which may account for the reduced stereoselectivity. Enantio-discrimination of the oxocarbenium ion chain end is further impeded by the early transition state produced by the highly exothermic nature of vinyl polymerizations.[58,59] This illustrates the difficulty of translating existing small molecule catalysts to the complex interactions present during polymerization and the need for a greater understanding of the underlying interactions at play in AIP polymerization. To move toward a more intentional approach to catalyst design, more information is needed on catalyst and counterion structure and what noncovalent interactions give rise to stereoselectivity. Specific models for directed monomer addition during propagation would be valuable.

EXAMPLES THAT HIGHLIGHT ADVANCES IN THE FIELD OF STEREOCHEMICAL CONFORMATIONAL CONTROL

AIP Enabled Stereoselective Helix-Sense-Selective Anionic Polymerization. Chain-end control of stereochemistry is well developed for anionic polymerization, partially due to dative interactions of lithium countercations with the penultimate enchained monomer. The use of achiral anionic organolithium initiators has furnished high stereoregularity (% *m* and % *r*) for methacrylates, acrylates, acrylamides, vinylpyridines, and styrenics.[60−67] Moving beyond the configurational control engendered by achiral catalysts, the use of a chiral counterion can also exert conformational stereocontrol (e.g., control of polymer helicity) through AIP catalysis.[4,44] Control of polymer helicity is known as a helix-sense-selective polymerization (HSSP) and functions orthogonally to control of polymer configuration (e.g., tacticity) (Figure 4A). When polymer conformation is paired with sterically encumbered monomers that hinder polymer chain collapse, the formation of thermally and solution-stable helices can be achieved to produce an optically active material. Thermally stable and optically active helical polymers are specialty commercial materials for high-value applications such as chiral stationary phases for high-pressure liquid chromatography, biomimetic polymers, and chiral optoelectronic applications.[44] These materials present an opportunity for the rapid synthesis of stable chiral materials from prochiral feedstocks whose optical activity arises solely from their helicity.

The anionic polymerization of methacrylates with chiral alkyl lithium initiators reported by Okamoto and co-workers in 1979 was the first example of a HSSP.[13] In subsequent work, monomer and catalyst design principles have been developed.[13,44] A principle requirement for all anionic HSSPs is the steric bulk of the pendent group on the ester, which directs helix formation through a teleinduction mechanism through interactions with previously enchained monomers. Rigorous mechanistic experimentation has shown the importance of enantioselectivity at low molecular weights (i.e., dimer, trimers, etc.) on helicity; the stereochemistry of these oligomers is translated to the resulting helicity of the polymer similar to a chain-end control mechanism for biasing tacticity.[62] Nearly all of these methods exhibit high levels of tacticity control simultaneous to conformational control, which has been proposed to help engender stable helices through conformational effects.

A series of reports highlight the sensitivity of anionic HSSP to small changes in monomer sterics, which is reported to drastically change the stability of the formed helices (Figure 9A).[21,68,69] For example, changing from triphenyl- to diphenylmethyl-methacrylate or swapping the carbon−oxygen bond for silicon−oxygen (i.e., extending the bond length) induces rapid helix racemization. Accordingly, much of the field has sought to exhaustively optimize monomer structure to elicit high helicity, with a goal of increasing the magnitude of the optical rotation and separation factor of enantiomeric small molecules in chromatographic separations using these chiral polymers as a stationary phase.

As a consequence of the focus on monomer design, little catalyst development has been pursued over the last 40 years. This is partially due to the high efficacy of established methods that utilize alkyl lithiums in conjunction with spartiene, DDB,

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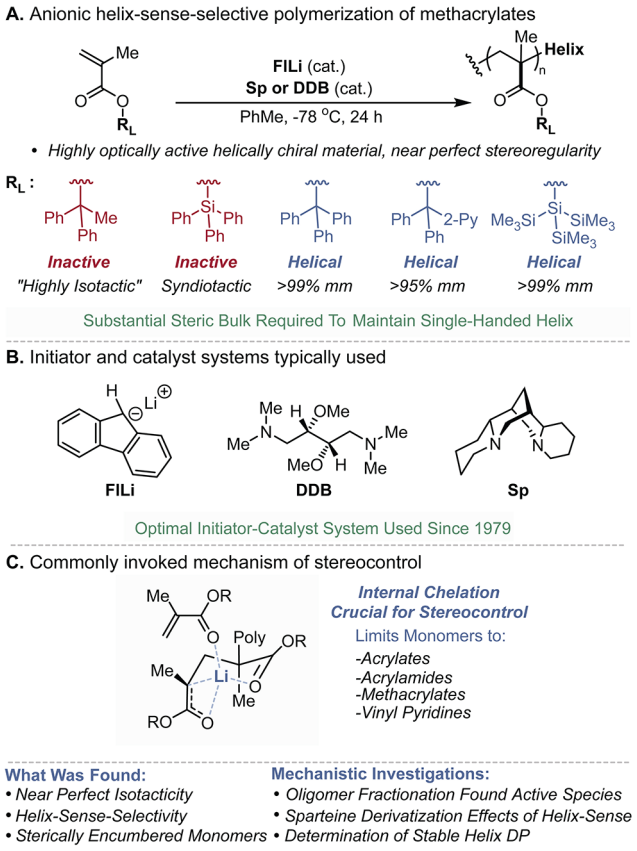

Figure 9. Controlling polymer helicity and tacticity during anionic polymerization.

or related scaffolds as ligands for the polymerization of sterically bulky methacrylates (Figure 9B). The proposed mechanism of stereocontrol, which includes dative intra- and intermolecular interactions between the Lewis acid, chain end, and incoming monomer, respectively (Figure 9C), provides high selectivity. Consequently, these interactions currently limit anionic HSSP methods to Lewis-basic containing monomers.[70]

Given both the success of anionic HSSP for a limited set of monomers and the limited catalyst development in this area, we propose that substantial opportunities exist for catalyst design to access helical polymers whose synthesis does not rely on substrate coordination through a purely catalyst-controlled mechanism. Development of catalyst-controlled approaches for helix-sense selectivity and tacticity could provide access to a broader library of helical polymers and methods that do not require cryogenic temperatures and long reaction times.

Stereoselective Helix-Sense-Selective Cationic Polymerization. In contrast to anionic methods, cationic polymerization provides complementary reactivity for the polymerization of electron rich monomers. As described previously, a number of approaches have been reported to access stereoregular polymers via cationic polymerization using Brønsted or Lewis acid catalysis. The extension of configurational stereocontrol to conformational stereocontrol in cationic polymerization (i.e., helix sense-selective cationic polymerization) has been an outstanding problem. A complementary challenge more broadly in the field of stereoselective polymerizations is the independent control of tacticity and helicity, which has the implication of tuning different aspects of the bulk material properties (e.g., semicrystallinity vs optical activity) independently.

The Leibfarth group recently reported the first example of a stereoselective cationic HSSP of a vinyl monomer, *N*-vinylcarbazole (NVC), using chiral scandium bis(oxazoline) (BOX) Lewis acids.[56] The proposed mechanism was that ionization of a hemiaminal of NVC and methanol initiated polymerization and generated a chiral counteranion concomitantly, which provided a highly isotactic and helically enriched polymer (Figure 10A). Use of a chiral substituted BOX ligand

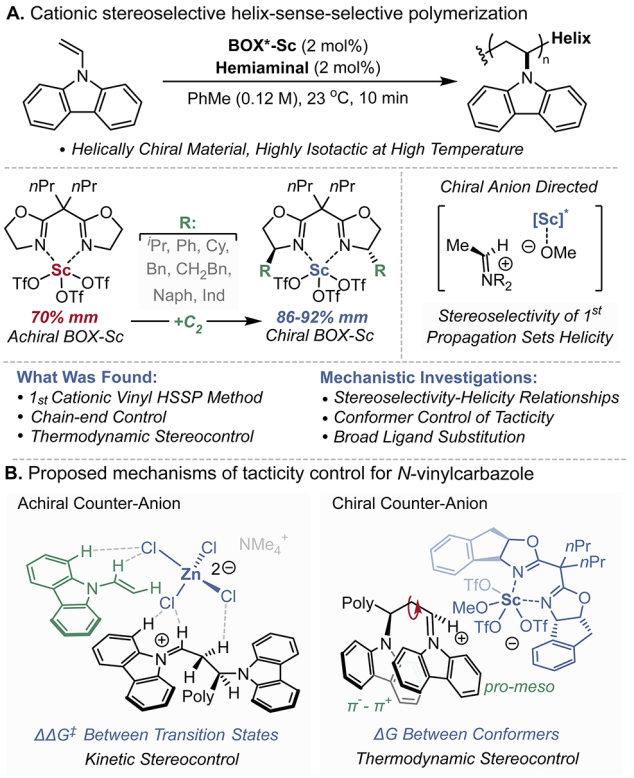

Figure 10. Expanding helix-sense-selective polymerization to cationic methods.

led to a marked increase in tacticity across the board (70% to >85% *mm*, at room temperature) compared to an achiral variant, highlighting the importance of the chiral character of the counterion (Figure 10A). The use of substituted but racemic BOX ligands produced the same tacticity as the enantioenriched ligands but did not result in a helical polymer, demonstrating that ligand chirality translates to polymer helicity.

Diverse substitution of the BOX ligand resulted in changes in both tacticity and helicity; however, ligands that improved one did not necessarily improve the other. To better understand this previously unobserved behavior in HSSPs, mechanistic studies were pursued to understand the distinct pathways that engender such behavior. It was found that the enantioselectivity of the first propagation event from the prochiral iminium ion generated upon initiation strongly influenced polymer helicity, which indicated that each subsequent monomer addition to a diastereotopic chain end proceeded with high stereocontrol (Figure 10A). Therefore, the first monomer addition is stereochemically distinct from every other propagation event, which leads to complex catalyst design principles where a ligand that is effective for tacticity

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control does not necessarily lead to high helix-sense selectivity and vice versa.

In contrast to the kinetic control of polymer helicity, a thermodynamic mechanism was invoked for tacticity. The orbital overlap between the electron-deficient carbazolium propagating chain end and the previously enchained monomer was supported through density functional theory (DFT) calculations to stabilize an eclipsed conformation, which blocks one face of the chain end for monomer addition (Figure 10B). The substitution and chirality of the counterion influences the thermodynamic stability of each conformation of the poly(NVC) chain end and, in using high performing ligands, promotes a pro-*meso* stereochemistry. This mechanistic hypothesis is contrary to another polymerization method of NVC reported by Aoshima and co-workers that utilizes an achiral $ZnCl_4^{2-}$ counterion. They propose that tacticity is influenced primarily by a kinetic stereocontrol mechanism, with a significant difference in $\Delta\Delta G^{\ddagger}$ between *meso* and *racemo* monomer addition to the reactive chain end at low temperatures.[35,42] Comparing these two approaches, the thermodynamic stereocontrol mechanism enables isoselective polymerization at room temperature and may be applicable to other monomers with strong intermolecular interactions. In contrast, the kinetic stereocontrol mechanism is more reliant on empirical catalyst discovery but has the potential to be generalized beyond monomers with extended π-systems. In both cases, further mechanistic understanding is important to drive innovations in method development and materials discovery.

EXAMPLES THAT HIGHLIGHT ADVANCES IN THE FIELD OF ASYMMETRIC POLYMERIZATION

Asymmetric Polymerization of Cyclic Alkenes. In contrast to vinyl monomers, the polymerization of cyclic, nonsymmetrical alkenes produces optically active polymers with absolute stereochemical configurational control. This concept was defined by Okamoto as asymmetric polymerization and is exemplified by the lack of a pseudomirror plane in the polymer backbone and the presence of a ditactic stereosequence, meaning there are two neighboring stereocenters per enchained monomer.[4] The first report of asymmetric polymerization was the AIP polymerization of benzofuran in 1961.[12,71] Typically, the asymmetric polymerization of benzofuran proceeds through chiral anion directed catalysis, where the precatalyst is in the form of $MX_{3-n}L_n$ or $M_2X_4L_2$ and M = Ti, Al, or Sn and L = diols, alcohols, amino alcohols, and amino acids. Chiral aluminum catalysts were used in the initial report by Natta[12] through the addition of various amino- and beta-amino acids to $AlCl_3$. At the time, the lack of structural information on the catalyst limited development. This was partially ameliorated by expanding to discrete menthol bound aluminum complexes that provided elucidation of structure−activity−selectivity relationships.[12] Hayakawa et al. found that either aluminum(menthol)chloride monomeric or dimeric catalyst structures led to polymer; the monomeric catalyst was significantly more active but not asymmetric selective, whereas the dimer was highly asymmetric selective but required 2 days to reach 4.1% conversion of monomer (Figure 11A).[72] This example demonstrated how ligand decelerated catalysis can play a crucial role to achieve high selectivity in cationic polymerization, similar to the stereoselective polymerization of vinyl ethers by titanium BINOL complexes.

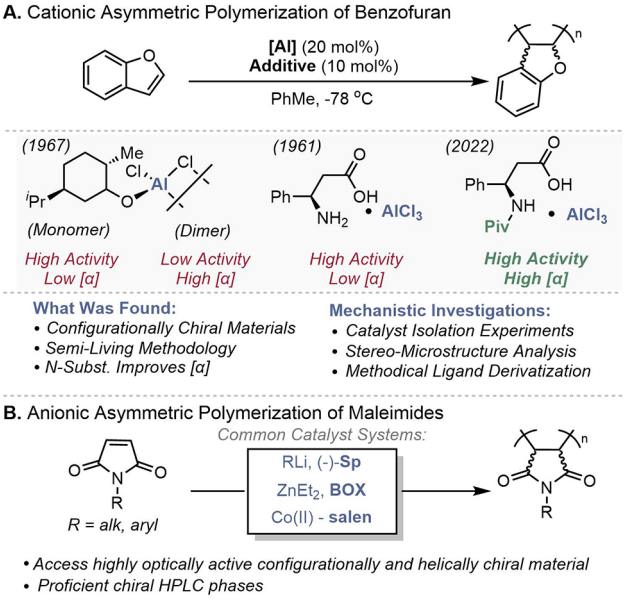

Figure 11. Asymmetric polymerization of disubstituted monomers yield configurationally chiral polymers.

More recently, Kamigaito and co-workers revisited the initial system disclosed by Natta[12] for the polymerization of benzofuran.[73] Through a more rigorous mechanistic investigation and ligand derivatization, they were able to achieve the highest optical activities ($[\alpha]$) to date for poly(benzofuran) (93.4°), which enabled a polymerization that demonstrated semiliving character, the characterization of the relevant optically active stereosequences, and the realization of molecular weights greater than 500 kDa. As an example of structure−selectivity relationships uncovered, (*S*)-β-phenylalanine as a ligand for $AlCl_3$ provided high activity but low selectivity. Changing the chiral substituent from Ph or moving to α-amino acids displayed a minimal change in enantioselectivity. However, introducing steric bulk at the nitrogen with acetyl, benzoyl, *iso*propyl, and pivoyl groups led to a marked increase in enantioselectivity while maintaining high activity. While no crystal structure of the catalyst was disclosed, the simple ligand substitution presents a modular way of tuning enantioselectivity for the synthesis of a valuable polymer. The polymers obtained were characterized via ^{13}C NMR through comparison with other cyclic alkenyl ethers, and the authors deduced that the *threo*-diisotactic sequence was responsible for the high optical activity. Moreover, initiating polymerization in the presence of an aromatic thioether CTA allowed for the synthesis of stereoblock copolymers.

Asymmetric polymerization that proceeds through a formal anionic mechanism is also well-known for maleimides with alkyl or aryl nitrogen substitution (Figure 11B).[44] Various catalyst systems have been found effective, such as alkyl lithium sparteine, dialkyl Zn-BOX, and Co-Salen complexes.[74,75] Like poly(benzofuran), the optical activity of these materials stems from their absolute configuration. An exception to this is when the nitrogen substitution is naphthyl, which provides a polymer that is both configurationally and helically chiral and leads to an extremely high optical activity.

PERSPECTIVE AND OUTLOOK

Synthetic Opportunities to Access Novel Stereodefined Polymers. Given the recent recognition of AIP as

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a conceptual approach to conduct stereoselective polymerization, there are many opportunities to expand its generality and utility. In the following paragraphs, we identify a number of outstanding problems in the field where the development of stereoselective polymerization methods, possibly through an AIP approach, would expand the library of accessible stereoregular polymers and stereosequences to provide materials with differentiated properties (Figure 12A).

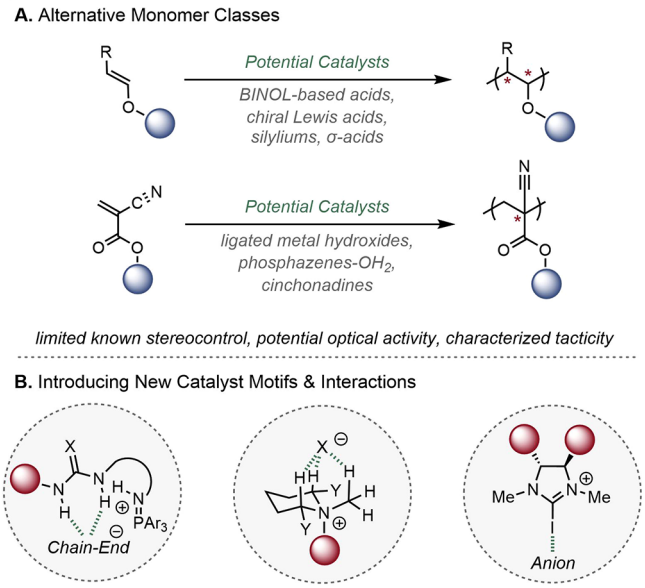

Figure 12. Potential synthetic opportunities for AIP polymerization.

AIP catalysis has been most successful for cationic polymerization in terms of its application to a variety of monomer substrates. Despite this success, there are limited reports of the stereoselective polymerization of 1,2-disubstituted alkenes, for example, propenyl ethers, to generate a ditactic polymer.[76,77] Given these polymers typically have high glass transition temperatures and are proposed as more sustainable alternatives to current glassy thermoplastics, control of their stereochemistry would enable a larger diversity of properties from these readily available and underexplored monomers.[78−80] A complementary goal is a continued pursuit of methods that provide stereoselective polymerization under living conditions, which would provide access to stereoblock materials or complex polymer architectures that could alter crystallization and thermomechanical and optical properties.

For anionic polymerization, the majority of work has been focused on HSSP of sterically encumbered monomers with a limited diversity of catalysts. Given the breadth of chiral cation catalysts in the small molecule literature, we hypothesize AIP will be applicable to a broader set of building blocks made through anionic polymerization.[14,81,82] For example, it should be possible to synthesize materials from more acidic monomers that have traditionally been inaccessible. One such example is the polymerization of cyanoacrylates, whose stereoselective polymerization has not been explored.[83] Poly(cyanoacrylates) are used extensively in commercial adhesive applications, and controlling their stereochemistry could lead to materials with increased toughness or adhesive strength from readily available building blocks. Beyond cyanoacrylates, anionic polymerization has been effective for the synthesis of optically active helical materials, but development of catalyst-controlled mechanisms could deliver optically active asymmetric materials without the requirement for bulky monomers, thus broadening the potential scope of materials with high-value applications such as chiral stationary phases.

The pursuit of these exciting applications at the interface of asymmetric catalysis and polymer synthesis can build upon the variety of conceptual approaches and accompanying privileged catalytic scaffolds in small molecule AIP catalysis. For example, hydrogen bonding catalysts, which include ureas, thioureas, and squaramides, among others, have been used extensively in an anion-binding approach to control the stereochemistry of reactions that proceed through prochiral intermediates.[18] While anion-binding catalysis using both halogen-binding and hydrogen-bonding catalysts has been reported for controlled cationic polymerization, no asymmetric varieties are currently known;[84,85] therefore, we propose that opportunities exist for the development of mild stereoselective cationic polymerizations that also achieve controlled characteristics.[86] To achieve this lofty goal, the exploration of multifunctional catalysts that leverage directional interactions, such as H-bonding, Lewis basic interactions, and π-stacking, in addition to electrostatic interactions could provide a more structured transition state (Figure 12B).

Mechanism-Guided Discovery of Stereoselective Polymerizations. To increase the utility of AIP catalysis in polymer science, a more thorough mechanistic evaluation of the polymerizations will be necessary, as well as an understanding of the role the catalyst plays in engendering the stereochemical outcome (Figure 13A). Overall, a deeper

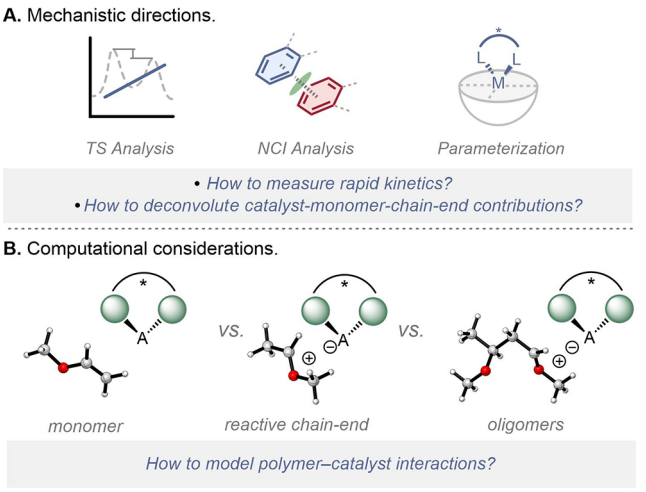

Figure 13. Complexities in using computational tools in polymerization optimization.

understanding of the mechanism will lead to better designed monomers, catalysts, and systems for achieving designer materials. Classical physical organic tools such as kinetic isotope effects, Eyring analysis, and kinetic studies can all be used to learn about the mechanism of these reactions.[87] One challenge in studying the mechanisms of these transformations in the context of polymerization is rapid kinetics; therefore, adoption of modern tools like stopped-flow NMR methods or ReactIR by the polymer community is essential for studying these reactions.[88] Physical organic macromolecular chemistry offers additional tools to study the mechanism of these reactions such as evaluating match−mismatch effects with chiral monomers or assessing the chain-end versus catalyst

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control through analysis of the stereotriads.[32] Teasing out the effects of these polymer-specific phenomena will require detailed studies of how polymer properties are impacted by stereochemistry, which will necessitate careful polymer characterization by calorimetry, scattering, and dynamic mechanical studies.

Complementary to detailed experimental studies, DFT is an enabling tool to support mechanistic understanding. Applying atomistic DFT approaches to study polymerization mechanisms, however, poses a number of challenges. Polymers are inherently large and have significant structural flexibility, making it challenging to compute their ground state structure. As such, it is typical to cut the polymer into a small surrogate species, but there is no systematic approach for determining how much of the polymer structure is required to obtain an accurate sense of the relevant transition states (Figure 13B). Particularly in systems in which chain-end control of stereoselectivity is operative, accurately describing the chain end with just one or two monomer units may not capture the 3-dimensional complexity of the reaction coordinate. For example, since the model of penultimate ether binding in vinyl ether polymerization is commonly invoked, a minimum of 3 repeat units is required. This is significantly more computationally expensive and for alkyl vinyl ethers introduces large conformational space that potentially makes extracting accurate quantitative values challenging. Ultimately, finding approaches to combine DFT with targeted experimental studies will aid in understanding the elementary steps required for a catalyst to control stereochemistry, which will help in designing improved catalysts, expanding the scope of potential stereocontrolled polymerizations, and accessing alternative stereochemical outcomes.

In conjunction with DFT, data science tools are becoming more prevalent to uncover mechanistic insights in small molecule asymmetric catalysis.[58,89,90] Applying multivariate linear regression techniques or machine learning could accelerate the discovery of conditions to deliver diverse stereoregular materials. However, one challenge translating these techniques into the realm of polymer science is acquiring the requisite amount of data. Compared to chiral chromatography techniques, determining % *m* through ^{13}C NMR is both material and time intensive. Improving the techniques available to rapidly determine selectivity using a small amount of polymer will expand opportunities to use data science strategies for stereoselective polymerization.

The application of AIP in polymerizations provides a potentially general conceptual approach to control the configurational and conformational stereochemistry of polymers. The pursuit of AIP for stereoselective polymerization has provided synthetic insights into asymmetric catalysis broadly and provided access to stereoregular polymers with thermomechanical properties that are different than their atactic counterparts. Initial work in the field has demonstrated the potential of AIP catalysis in both cationic and anionic polymerizations, as well as for accessing optically active materials. By expanding the classes of catalysts being applied to these reactions, understanding the mechanism of stereocontrol, and leveraging computational techniques, AIP will continue to transform the way chemists think about controlling tacticity in polymer synthesis.

AUTHOR INFORMATION

Corresponding Author

Frank A. Leibfarth − *Department of Chemistry, University of North Carolina, Chapel Hill, North Carolina 27599, United States;* orcid.org/0000-0001-7737-0331; Email: FrankL@email.unc.edu

Authors

Cole C. Sorensen − *Department of Chemistry, University of North Carolina, Chapel Hill, North Carolina 27599, United States;* orcid.org/0000-0002-0705-9406

Caleb T. Kozuszek − *Department of Chemistry, University of North Carolina, Chapel Hill, North Carolina 27599, United States*

Meredith A. Borden − *Department of Chemistry, University of North Carolina, Chapel Hill, North Carolina 27599, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.3c00040

Author Contributions

‡C.C.S. and C.T.K. contributed equally.

Notes

The authors declare no competing financial interest.

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