Synergetic Ion-Binding Catalysis Demonstrated via an Enantioselective, Catalytic [2,3]-Wittig Rearrangement

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ABSTRACT: Sigmatropic rearrangements number among the most powerful complexity-building transformations in organic synthesis but have remained largely insensitive to enantioselective catalysis due to the diffuse nature of their transition structures. Here, we describe a synergistic ion-binding strategy for asymmetric catalysis of anionic sigmatropic rearrangements. This approach is demonstrated with the enantioselective [2,3]-Wittig rearrangement of α-allyloxy carbonyl compounds to afford highly enantioenriched homoallylic alcohol products. Chiral thiourea catalysts are shown to engage reactive anions and their countercations through a cooperative set of attractive, noncovalent interactions. Catalyst structure–reactivity–selectivity relationship studies and computational analyses provide insight into catalyst–substrate interactions responsible for enantioinduction and allude to the potential generality of this catalytic strategy.

INTRODUCTION

As Doering and Roth wryly noted, sigmatropic rearrangements epitomize "no-mechanism" reactions.1 While these transformations have become staples of organic synthesis and have inspired landmark advances in diastereocatalysis,2–6 the highly diffuse nature of their transition structures and the absence of discrete intermediates have rendered sigmatropic rearrangements frustratingly insensitive to catalysis, especially enantioselective variants thereof.7–9 In a step toward overcoming these limitations, we have previously demonstrated that chiral, polyfunctional hydrogen-bond donor catalysts accelerate enantioselective sigmatropic rearrangements of neutral substrates, such as the Claisen rearrangement10–12 and Cope-type hydroamination,13 by cooperatively engaging the charge-separated components of the dipolar transition structures (Figure 1A). In parallel, our group and others have demonstrated that similar chiral, small-molecule hydrogen-bond donors can bind the anions of tight ion-pair intermediates, thereby disposing the cations toward enantioselective nucleophilic trapping (Figure 1B).14–18 An analogous cation-binding catalysis strategy developed around chiral crown ethers has been employed for a limited number of transformations (Figure 1B).19–21

Because sigmatropic rearrangements of anionic species proceed through transition structures involving far greater charge delocalization than their corresponding substrates and products, we hypothesized that precise control of the relative positions of the reactive anions and their countercations could enable selective transition-state stabilization. We thus became interested in determining if the principles of anion- and cation-binding catalysis could be integrated to enable such sigmatropic rearrangements, which have been traditionally recalcitrant toward catalytic enantiocontrol.7,8,22 We envisioned that a polyfunctional hydrogen-bond donor catalyst could engage a prochiral, anionic substrate, while complementary cation-binding elements could orient the countercation precisely to stabilize one diastereomeric transition structure preferentially, thereby inducing stereoselective rearrangement (Figure 1C).

Herein, we report the realization of this strategy with a highly enantioselective thiourea and Brønsted base cocatalyzed [2,3]-Wittig rearrangement of α-allyloxy carbonyl compounds. Application of the [2,3]-Wittig rearrangement to the synthesis of hindered homoallylic alcohol fragments in a variety of natural products and pharmaceutical agents stands as a testament to its utility.4,5,23–27 Furthermore, this intramolecular O–C allyl transfer is representative of the broader class of anionic sigmatropic rearrangements.28 While significant advances have been made toward enantioselective catalysis of rearrangements with related ylides,5,6,28–32 development of a general, catalytic, enantioselective [2,3]-Wittig rearrangement has lagged.7,8 Accordingly, the transformation has been the subject of intense interest, and during the preparation of this manuscript, two methods for the enantioselective [2,3]-Wittig rearrangement of allyloxyxindoles were disclosed.33,34 The work described here is complementary in scope to these methods, and we posit that the synergistic ion-binding approach it demonstrates can be extended to enable other anionic sigmatropic rearrangements and related transformations, which have hitherto resisted asymmetric catalysis.

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RESULTS AND DISCUSSION

Development of Reaction Methodology. While the Wittig rearrangement has been most widely explored using strong Brønsted bases,23−27 we sought to develop a system that would trigger rearrangement under mild conditions and would thereby be compatible with a wide variety of functional groups, including dual hydrogen-bond donor catalysts. Accordingly, we deemed that an appropriate substrate should be sufficiently acidic to undergo selective deprotonation in the presence of ureas and thioureas ($pK_a \approx 9−20$)35 and that the alkoxide produced in the rearrangement step should be sufficiently basic to enable regeneration of a catalytic amount of Brønsted base. With these factors in mind, the Wittig rearrangement of di-tert-butyl-2-cinnamyloxy malonate (1a) was selected as a model reaction, and representative chiral hydrogen-bond donor catalyst classes were evaluated for their ability to induce enantioselective rearrangement in cooperation with a variety of organic and inorganic Brønsted bases (see Supporting Information for details). Through this study, the combination of dialkylthiourea 3 and cesium di-tert-butyl malonate ($\text{CsCH(CO}_2\text{Bu)}_2$) generated in situ emerged as a particularly promising dual catalyst system for effective enantiocontrol (entry 2).

Initial optimization efforts (see Supporting Information for details) revealed that enantioselectivity is moderately sensitive to substituents on the 2-arylpyrrolidine ($\text{Ar}_1$) and arylpyrrole ($\text{Ar}_2$) components of the thiourea catalyst. However, in all cases, the 2-arylpyrrolidino amides exist as slowly interconverting mixtures of ($E$)- and ($Z$)-rotamers, which can be readily detected and quantified by NMR spectroscopic analysis. Given the likelihood that the two rotameric forms of the thiourea catalyst exert differing degrees of enantiocontrol, potentially even in opposite directions, we sought to limit the opportunity for reaction through multiple competing pathways. Accordingly, the 2-arylpyrrolidine was alkylated to constrain the amide in exclusively the ($Z$)-rotameric form, thereby positioning the

![Figure 1. (A−C) Conceptual development of a synergistic ion-binding strategy for enantioselective catalysis of the [2,3]-Wittig rearrangement.](image)

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a Reactions were performed in duplicate on a 0.1 mmol scale and were quenched with the addition of 1.0 M aqueous hydrochloric acid. Values reported are the averages of two trials. $\text{Ar}_2 = 3,5$-bis(trifluoromethyl)phenyl. b Yields were determined by $\text{^1H NMR}$ integration relative to a mesitylene internal standard. c Enantiomeric excesses were determined by CSP-HPLC analysis. Positive ee indicates an excess of the ($R$)-enantiomer, while negative ee indicates an excess of the ($S$)-enantiomer. d $36 \text{h}$. e $4 \text{h}$.
aryl group proximal to the H-bond donor active site (see Supporting Information for NMR and crystallographic characterization).36 Catalysts bearing this constrained amide (4, 5, and 6) proved reactive and displayed improved enantioselectivity (entries 3–7). Complementary tuning of the arylpyrrole moiety revealed that catalysts 5b and 6b enable access to product 2a in high enantiomeric excess (entries 5 and 7), even with reduced catalyst loading (entry 8). While catalysts 5b and 6b may be used interchangeably, 5b is preferred for its greater synthetic accessibility.

The importance of each of the components of the thiourea was evinced through a series of structure–reactivity–enantioselectivity studies (Table 1). Truncation of the arylpyrrole moiety, as in cyclohexyl thiourea 7, or replacement of the 2-arylpyrrolidino amide with an unsubstituted N-pyrrolidino amide, as in catalyst 8, impairs stereoinduction significantly (entries 9 and 10). Furthermore, C₆-symmetric thiourea 9 affords low and reversed enantioselectivity relative to 8 (entry 11). These observations indicate that the arylpyrrole, the 2-arylpyrrolidine substituent, and the amide group all play crucial roles in enantiodifferentiation. The importance of the amide functional group has been noted in prior work with related catalysts and ascribed to the Lewis basic amide oxygen participating in stabilizing secondary interactions with reacting intermediates.37,38 While all of the dialkyl thioureas (3–9) examined afford good product yield, replacement of either the N-pyrrolidino amide or the arylpyrrole components with the privileged 3,5-bis(trifluoromethyl)phenyl motif 39 degrades both the reactivity and enantioselectivity of the system (entries 12 and 13). These results suggest that the acidity of the hydrogen-bond donor core must be carefully controlled and that weakly acidic dialkyl thioureas are well-suited to provide substrate activation while avoiding irreversible deprotonation under the basic reaction conditions.40

With optimized hydrogen-bond donor catalysts in hand, we carried out a systematic evaluation of inorganic Brønsted base cocatalysts. Substituting sodium or potassium carbonate for cesium carbonate leads to a complete suppression of reactivity,41,42 omission of di-tert-butyl malonate leads to highly variable yields and enantioselectivities. While the reaction exhibits little to no conversion for the competitive background reaction at elevated concentrations of alkali metal cations,43–47 the identity of the ester substituent (R₃) has a small effect on the reaction outcome (e.g., 2a–2c), with di-tert-butyl malonates generally affording the highest enantioselectivities. Prior computational studies have demonstrated that the allyl group accumulates significant partial negative charge in a typical rearrangement transition structure.48–50 Consistent with such charge buildup, substrates with aryl and electron-withdrawing substituents (R₃) capable of stabilizing an allylic anion undergo facile rearrangement, while alkyl-substituted substrates (such as 1s) undergo reaction more sluggishly. Notably, substrates bearing trisubstituted alkenes (R₂ ≠ H, for 1d–f) or ortho-
substituted arenes (1m,n) undergo rearrangement with modestly reduced rates, nonetheless affording products in good to excellent enantioemic excess under the optimized conditions. Heteroaromatic substrates (1p–r) are also largely compatible with the optimized conditions, affording rearrangement products in good enantiomeric excess. The limitations of the methodology are illustrated with substrates 1s–w. The terminally disubstituted 1u preferentially undergoes [1,2]-rearrangement at 23 °C and only affords the [2,3]-rearrangement product with low conversion and stereoselectivity at reduced temperatures. Substrates possessing substitution at the allylic position (1v) or (Z)-alkenes (1w) also exhibit very poor reactivity (Table 2B). These observations indicate that the steric environment around each of the allylic termini is defined precisely in the enantioselectivity-determining step, consistent with the notion that the olefin substituent (R²) must adopt a pseudoequatorial orientation to avoid A¹,³ strain in an envelope-like rearrangement transition structure (Figure 1C).⁵,²³

Identification of the Enantioselectivity-Determining Step. Given the potential for mechanistic insights to inform a general approach to asymmetric catalysis of anionic sigmatropic rearrangements, we undertook a series of experimental and computational studies to elucidate the basis for enantioselectivity in the thiourea-catalyzed [2,3]-Wittig rearrangement. Reaction progress kinetic analysis with substrate 1c revealed that the rate of the reaction is independent of catalyst concentration under synthetically relevant conditions.⁵¹ This observation suggests that mass transport or proton transfer is rate-determining and indicates that enantioinduction occurs after the rate-determining event. Accordingly, we were required to apply probes other than simple kinetic analysis to determine the identity of the enantioselectivity-determining step.

Stereoselective [2,3]-Wittig rearrangements employ stoichiometric chiral ligands have been shown to proceed via rate- and enantioselectivity-determining deprotonation followed by stereospecific rearrangement.²⁻⁶ In the catalytic system described here, deprotonation, substrate-binding, or rearrangement could, in principle, be enantiodetermining. To distinguish between these possibilities, isotope effects were measured for substrates deuterated at the α (1a-d₁₆) and allylic (1a-d₂₅₆₇₈) positions (Scheme 1A,B). A significant inverse isotope effect (k_H/k_D = 0.53 at 50% conversion) was determined by absolute rate measurements. The fact that an inverse effect is observed is irreconcilable with a primary kinetic isotope effect (KIE) resulting from irreversible deprotonation, but it is indicative of an equilibrium isotope effect (EIE).⁵⁵ Consistent with this assertion, hydrogen–deuterium scrambling at the α-positions of 1a and CsCH(CO₂Bu)₂ is observed by NMR spectroscopy at intermediate conversion. This indicates that only mechanisms involving reversible deprotonation of 1a-d₁₆ are plausible, thereby ruling out the possibility of enantiodetermining deprotonation. Furthermore, in an intermolecular competition experiment, substrate 1a-d₁₆ binds a normal secondary kinetic isotope effect (k_H/k_D = 1.19). Isotopic substitution at this site is unlikely to impact deprotonation or substrate binding, and KIEs of similar magnitude have been observed for analogously deuterated allyl vinyl ethers and 1,5-dienes undergoing Claisen and Cope rearrangements, respectively.⁶⁶,⁶⁷ Accordingly, this KIE is diagnostic of enantioselectivity-determining rearrangement.

While [1,2]-Wittig rearrangements have been shown to proceed through radical cleavage/recombination, the [2,3]-

### Scheme 1. Evidence for Enantioselectivity-Determining Rearrangement by a Concerted Mechanism

#### A. Equilibrium Isotope Effect

![Image](image1.png)

**Ph**

Ph

CO₂Bu

CO₂Bu

CO₂Bu

CH₂CO₂Bu₁₂₂

C₆H₅₂, 23 °C

k_H/k_D = 0.53 at 50% conversion

**Amin**

CO₂Bu

CO₂Bu

**1a or 1a-d₁₆**

**2a**

#### B. Competition Kinetic Isotope Effect

![Image](image2.png)

**Ph**

Ph

CO₂Bu

CO₂Bu

CO₂Bu

CH₂CO₂Bu₁₂₂

C₆H₅₂, 23 °C

k_H/k_D = 1.19 (1.09 per D)

**1a**

**1a-d₂₅₆₇₈**

**2a-d₂**

#### C. Crossover Experiment

![Image](image3.png)

**Ph**

Ph

CO₂Bu

CO₂Bu

CO₂Bu

CH₂CO₂Bu₁₂₂

C₆H₅₂, 23 °C

**1g**

**1g-d₁₆**

**2g**

**2a**
Scheme 2. Proposed Catalytic Cycle

Figure 2. Computed transition structures. (A) Energy-minimized lowest-energy transition structure for the [2,3]-Wittig rearrangement of 1a (leading to (R)-2a) in the active site of catalyst 5a, calculated at the M06-2x/6-31G(d)/SDD(Cs)/PCM(cyclohexane) level of density functional theory. (B) Analogous view of the transition structure leading to the minor enantiomer ((S)-2a). This transition structure places the allyl fragment exo to Cs⁺ and is disfavored relative to the structure in A by 1.4 kcal mol⁻¹ to 2.1 kcal mol⁻¹ using free energies or zero-point corrected electronic energies, respectively. Select bond distances are shown in angstroms. Carbon-bound hydrogen atoms are omitted for clarity. Black rods represent the π-faces of the arylpyrrole and arylpyrrolidine moieties forming an “aromatic box” around Cs⁺.
interactions resulted in much higher-energy structures. The lack of a specific role for the thiourea sulfur is consistent with the observation that the urea analogue of 4 is also a competent catalyst (see Supporting Information for details).

Taken together, these results illustrate that the cesium cation serves a central role in the structural organization of the intermediate ground state and transition structures, precisely orienting the substrate toward the hydrogen-bond donor portion of the catalyst. On the basis of the computational model, enantiodifferentiation thus may be ascribed to two key features distinguishing the major and minor transition structures. First, the N−H···O(carbonyl) hydrogen bond is 0.2 Å longer in the major transition structure leading to (R)-2a than in the minor transition structure leading to (S)-2a, while the N−H···O(ether) hydrogen bond is 0.1 Å shorter in the major transition structure than in the minor transition structure. Because negative charge must be redistributed from O(carbonyl) to O(ether) over the course of the rearrangement, these differences in hydrogen bond distances are consistent with greater stabilization of the transition state leading to the major enantiomer of product. Second, the migrating allyl group is positioned endo to Cs⁺ in the major transition structure leading to (R)-2a but exo to Cs⁺ en route to (S)-2a. Such an endo-preference is preceded for diastereoselective [2,3]-Wittig rearrangements. Consistent with the observations here, the preference is generally attributed to an attractive, electrostatic interaction between the negative charge accumulating on the migrating allyl fragment and the cationic character of the carbonyl carbon or its associated Lewis acid.48−50 Altogether, these subtle distinctions illustrate the advantages that a synergistic ion-binding strategy offers for achieving enantiocontrol.

In conclusion, the experimental and computational analyses presented for the enantioselective [2,3]-Wittig rearrangement provide strong evidence for a mechanistic model in which the chiral thiourea catalyst engages both the reactive anion and its counterion through a cooperative set of attractive, noncovalent interactions. Specifically, we advance that the polyfunctional catalyst stabilizes the enantiodetermining rearrangement transition state through the synergistic action of anion-binding and cation-binding motifs. These include the thiourea, which forms hydrogen bonds to the nascent alkoxide, along with the catalyst arenes and amide, which encapsulate the cesium cation through cooperative cation−π and Lewis base interactions. We envision that the features responsible for reactivity and selectivity may be extended to cooperative activation of other anionic, prochiral intermediates with polyfunctional hydrogen-bond donor catalysts. Accordingly, this activation mode has the potential to enable enantioselective approaches to important organic transformations, such as the oxy-Cope rearrangement or Ireland−Claisen rearrangement, that have hitherto resisted asymmetric catalysis. Our ongoing attention is directed toward the realization of these aims.

■ METHODS

General Procedure for the Asymmetric [2,3]-Wittig Rearrangement Catalyzed by 5b. In an N₂-atmosphere glovebox, a 10 mL round-bottom flask was charged with cesium carbonate (3.1 mg, 0.010 mmol, 10 mol %), catalyst 5b (6.0 mg, 0.010 mmol, 10 mol %), and a PTFE-coated magnetic stir bar. Di-tert-butyl malonate (22 μL, 0.10 mmol, 1.0 equiv) and anhydrous cyclohexane (2.0 mL) were then added. The flask was sealed, removed from the glovebox, and stirred (750 rpm) for 12 h at 23 °C over which time the reaction mixture became uniformly turbid. After 12 h, the reaction flask was cooled to 10 °C in a cryogenic cooling bath, and a stock solution of the desired substrate in anhydrous cyclohexane (2.0 mL, 50 mM, 0.10 mmol, 1.0 equiv) was injected directly into the precooled reaction mixture. The septum was quickly sealed with electrical tape and plastic parafilm, and the reaction was maintained at 10 °C in the cooling bath with rapid stirring. After the indicated time, the reaction was quenched with the addition of 1 M aqueous hydrochloric acid (1.0 mL), diluted with ethyl ether and allowed to warm to ambient temperature. The layers were partitioned, and the aqueous layer was extracted with additional ethyl ether. The organic extracts were filtered through sodium sulfate and concentrated. The yield was determined from integration of the ¹H NMR spectrum of the crude reaction mixture relative to an internal standard added after workup. The homoallylic alcohol product, 2a, was purified by silica gel chromatography (on a pipet column), eluting with an appropriate ethyl ether/dichloromethane/pentane solvent mixture, and the enantiomeric excess was determined by chiral stationary phase−high performance liquid chromatographic (CSP-HPLC) analysis or chiral stationary phase−gas chromatographic (CSP-GC) analysis. The absolute configuration of 2c was determined by X-ray crystallographic analysis, and the configurations of all other products were assigned by analogy.

■ ASSOCIATED CONTENT

 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscentsci.6b00125.

Procedures and data for mechanistic experiments, computational results, and the syntheses and characterization data for the substrates and catalysts (PDF). Crystallographic data for compounds 2c (CCDC 1471722), 3a (CCDC 1471720), 4a (CCDC 1471719), and CsCH(CO₂Bu)₂ (CCDC 1471721) (CIF).

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Notes

The authors declare no competing financial interest.

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(55) In general, equilibrium deuterium isotope effects (EIE) reflect the energetic preference for exchangeable deuteria to concentrate at the bond with the largest force constant. In the present case, the observed inverse EIE indicates that under the reaction conditions the pKd of CHD(2)CO2Bu+ is higher than that of the substrate. The origin of this effect has not been established but could be attributable to the formation of an aggregated network of CsCH(CO2Bu)+ and CH2=CO2Bu− molecules, resulting in preferential partitioning of deuterium within that network.


(65) Frisch, M. J. et al. Gaussian 09, Revision D.01; Gaussian Inc.: Wallingford, CT, 2009; see Supporting Information for full citation.
