Communication

Enantioselective Tail-to-Head Cyclizations Catalyzed by Dual-Hydrogen-Bond Donors

Dennis A. Kutateladze, Daniel A. Strassfeld, and Eric N. Jacobsen

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Enantioselective Tail-to-Head Cyclizations Catalyzed by Dual-Hydrogen-Bond Donors

Dennis A. Kutateladze‡, Daniel A. Strassfeld‡, and Eric N. Jacobsen*

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138, United States

Supporting Information Placeholder

ABSTRACT: Chiral urea derivatives are shown to catalyze enantioselective tail-to-head cyclization reactions of neryl chloride analogues. Experimental data are consistent with a mechanism in which π-participation by the nucleophilic olefin facilitates chloride ionization and thereby circumvents simple elimination pathways. Kinetic and computational studies support a cooperative mode of catalysis wherein two molecules of the urea catalyst engage the substrate and induce enantioselectivity through selective transition state stabilization.

Carbocycles are ubiquitous motifs within natural and unnatural organic molecules, and their construction has been a primary research focus in synthetic organic chemistry since the inception of the field.[1] Terpenes and terpenoids constitute one of the most important classes of carbocyclic natural products from both structural and functional perspectives.[2] Their carbocyclic frameworks are constructed by terpene cyclase enzymes, which engage linear isoprenoid substrates of varying length.[3] Cyclization of these polyolefins is initiated either through protonation of an olefin or epoxide in head-to-tail (HT) cyclizations, or through abstraction of an allylic pyrophosphate leaving group in tail-to-head (TH) cyclizations (Figure 1A).[2-3] The reactivity of the resulting carbocationic intermediates is then modulated through a combination of substrate preorganization[5] and non-covalent stabilizing interactions[3,6] in the enzyme active site, resulting in selective rearrangements and carbon-carbon bond-forming reactions that ultimately give rise to an extraordinarily diverse array of natural products (Figure 1B).

The remarkable ability of cyclase enzymes to generate carbocationic intermediates and channel their reactivity along specific pathways has long captured the imagination of chemists and motivated efforts to deploy analogous strategies in synthesis.[7] However, the very features that make carbocations such powerful intermediates in biosynthesis also render their application outside of enzymatic chemistry quite challenging.[4,8] Nonetheless, over the last 60 years organic chemists have made significant progress in mimicking the HT synthesis of steroidal ring systems by leveraging the propensity of these reactions to proceed through concerted, stereospecific mechanisms.[9,10] In contrast, efforts to reproduce TH cyclizations using non-biological catalysts have generally resulted in unselective or thermodynamically controlled reactions.[4,11] Pioneering studies from the laboratories of Shenvi[4] and Tiefenbacher[12] have revealed strategies for extending carbocation lifetime, unlocking the potential for non-enzymatic mimics of TH polycyclizations, but catalyst control over enantioselectivity has remained elusive. To our knowledge, the only reported enantioselective TH cyclizations[13] employ a binol-derived leaving group as a chiral auxiliary.

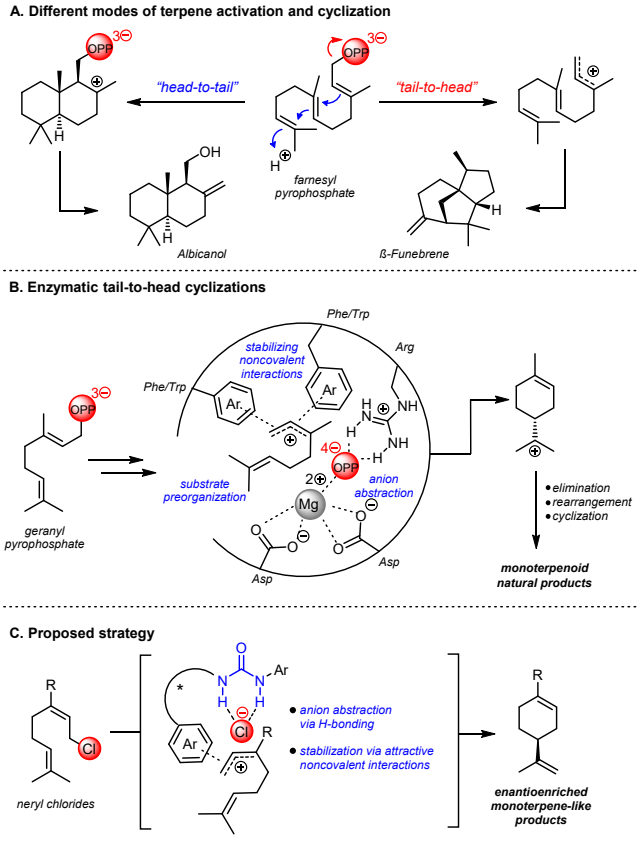

Figure 1. A) Head-to-tail and tail-to-head cyclization reactions. B) Schematic illustrating Nature's strategy for controlled ionization-dependent cyclizations. C) Proposed

strategy for enantioselective tail-to-head cyclizations catalyzed by chiral hydrogen-bond donors.

We hypothesized that it might be possible to achieve enantioselectivity in TH cyclizations with a small-molecule catalyst by mimicking nature's strategy of controlled generation and selective stabilization of key high-energy cationic intermediates and transition states. In particular, we sought to draw on advances in dual-hydrogen-bond-donor (HBD) catalysis, which have revealed that chiral urea and thioureas are capable of inducing enantioselectivity in reactions involving cationic intermediates generated by anion abstraction.[14] Moreover, specifically tailored HBD catalysts have been shown to induce enantioselectivity through non-covalent stabilizing interactions similar to those present in the active sites of cyclase enzymes.[10e,15] Herein we report the development of a urea-catalyzed enantioselective cyclization of neryl chloride derivatives (Figure 1C). Mechanistic analysis has provided key insights into the basis of reactivity and stereoinduction, including the revelation that π-participation by the nucleophilic olefin during ionization is critical to the success of the enantioselective transformation.

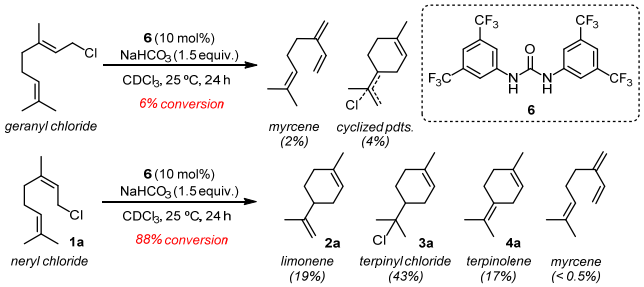

Figure 2. Differing reactivity observed in the urea-catalyzed cyclization of E and Z isomers. Conversions and yields were assessed from crude reaction mixtures using ^{1}H NMR with mesitylene as an internal quantitative standard.

In preliminary studies, geranyl chloride and neryl chloride (**1a**) were found to display dramatic differences in reactivity in the presence of the achiral bis-aryl urea **6** and a stoichiometric base (Figure 2). Geranyl chloride underwent a very slow reaction at room temperature, with significant formation of uncyclized elimination products. In contrast, the reaction of neryl chloride (**1a**) proceeded to high conversion under the same conditions, leading predominantly to the formation of cyclic products **2a-4a**. While enantioselective variants of the cyclization of **1a** could be promoted with chiral dual HBD catalysts, only very modest levels of enantioselectivity (up to 34% e.e.) were attained in the formation of limonene (**2a**) despite the evaluation of a wide assortment of chiral hydrogen-bond-donor catalysts and reaction conditions (see SI for details).

Recognizing that **1a** might be a particularly challenging substrate for asymmetric induction due to its limited structural features, we explored variations to the structure of the reactants. Introduction of a phenyl substituent as a potential catalyst-recognition element in place of the C3 methyl group (**1b**) led to significant improvements in enantioselectivity. Urea **7a** was identified as the optimal catalyst for this substrate, promoting cyclization to **2b** in 63% NMR yield and 87% e.e. at room temperature (Figure 3). In addition to **2b**, alkyl chloride **3b** was formed in 20% yield with similar e.e. (86%), consistent with both products arising from a common intermediate; **3b** could be converted to **2b** and **4b** in 83% combined yield (**2b**:**4b** = 10:1) via collidine-promoted elimination.[13b] The remainder of the mass balance consisted of two achiral cyclization products: 12% yield of tetrasubstituted olefin **4b** and 5% yield of conjugated diene **5b**, which we propose forms via a [1,2] hydride shift followed by elimination.[16] Consistent with our prior observations using geranyl chloride, the Z isomer of **1b** was found to undergo very slow reaction promoted by **7a** (5% conversion after 24 h), with **2b** generated in only 50% e.e. (see SI for details).

Variation of the electronic and steric properties of the C3 aryl substituent in **1** was explored in cyclization reactions catalyzed by **7a** (Figure 3). Electronic perturbation of the C3 aryl group of **1** revealed that the highest levels of e.e. were attained with electron-deficient substrates. Improved enantioselectivity was also observed upon substitution of the meta position with either electron-donating or withdrawing groups. While urea **7a** catalyzed the formation of limonene **2a** (R = Me) with low (< 10%) enantioselectivity, the cyclohexyl-substituted analog **2i** was formed in 76% e.e. It is therefore apparent both steric and electronic properties of the substrate play important roles in enantioinduction.

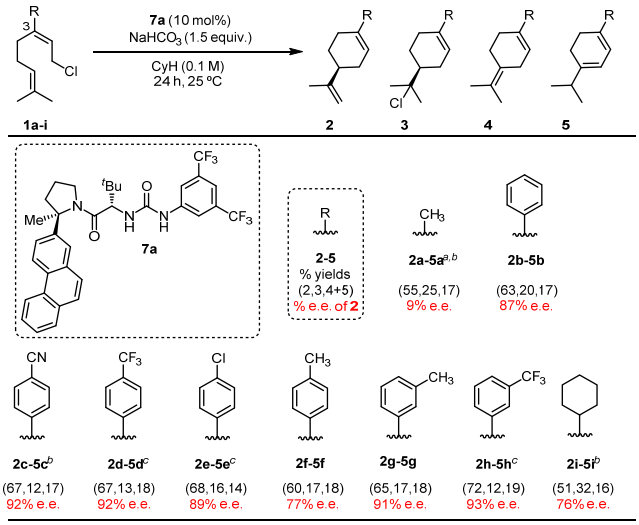

Figure 3. Substrate scope. All reactions were performed on 0.15 mmol scale and proceeded to complete conversion. E.e. values are for products **2a-i**. Alkyl chlorides **3b**, **3h**, and **3i** were generated in 86% e.e., 91% e.e., and 70% e.e., respectively. Conversions and yields were assessed from crude reaction mixtures using ^{1}H NMR with mesitylene as an internal standard. [a]Reaction run in C_6D_{12}; [b]72 hr. reaction time; [c]48 hr. reaction time.

The dramatic differences in reactivity and enantioselectivity observed in the **7a**-catalyzed cyclizations of the E and Z isomers of **1b** (*vide supra*) indicated that both the rate- and enantiodetermining steps differed for the two isomers, suggesting that they might react through fundamentally different mechanisms. While the Z isomer of **1b** must undergo rearrangement prior to cyclization,[17] the nucleophilic olefin of **1b** can interact with the allyl electrophile in a preorganized structure, potentially

facilitating chloride ionization through anchimeric assistance.[18]

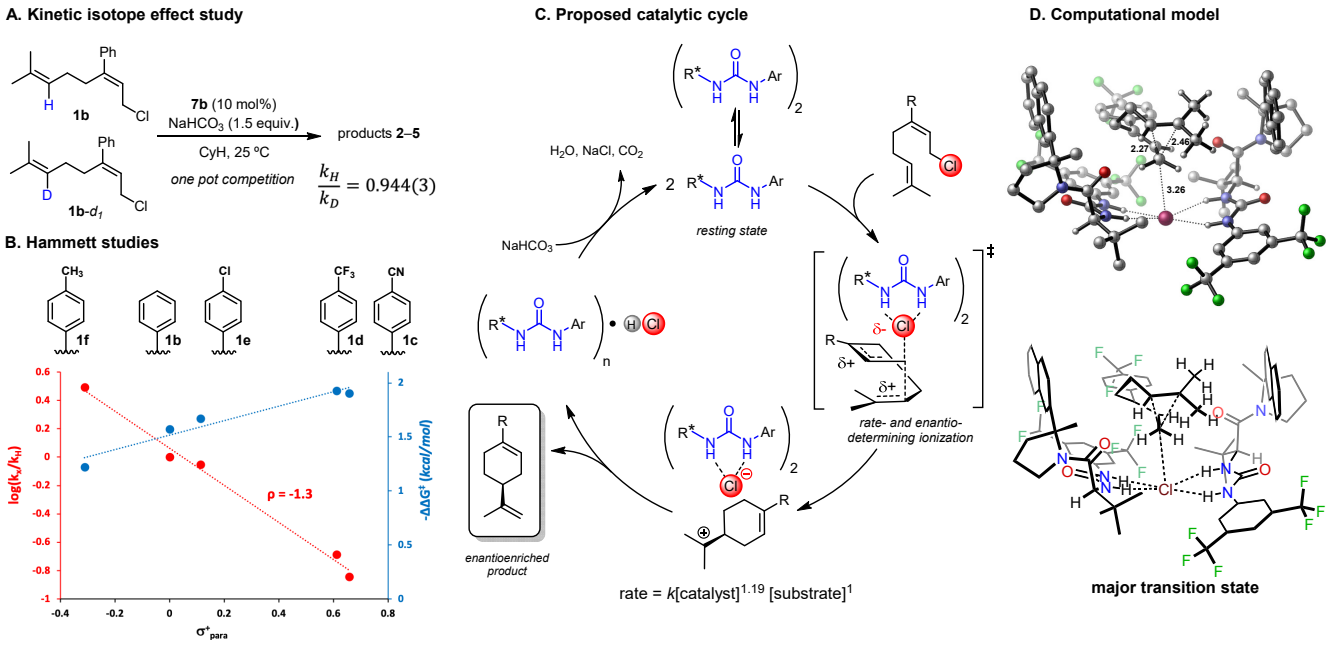

Figure 4. Mechanistic studies. A) One-pot competition secondary H/D KIE experiment. B) Hammett studies. In red: Relative rates of cyclization of **1b-1f** promoted by catalyst **7b**. In blue: Enantioselectivities (expressed as $-\Delta\Delta G^{\ddagger} = RT\ln$(enantiomer ratio), T = 25 °C) in the formation of **2b-2f** promoted by **7a**. C) Proposed catalytic cycle based on the KIE data and the experimentally determined rate law. D) Transition state model for the pathway leading to the major enantiomeric product in the cyclization of **1d**. Key bond lengths are reported in Angstroms. Calculations were carried out at PCM (CyH) – B3LYP-D3(BJ)/6-311+G(d,p) // B3LYP/6-31G(d).

The role of the nucleophilic olefin in the rate-determining step of the cyclization of **1b** was assessed in a kinetic isotope effect (KIE) experiment.[19] Starting material recovered from one-pot competition experiments between **1b** and **1b**-d_1 revealed enrichment in the protio isotopologue corresponding to k_H/k_D = 0.944(3) (Figure 4A). This small, secondary inverse KIE is consistent with direct involvement of the distal olefin in the rate-determining step, with partial rehybridization of the vinylic carbon from sp^2 to sp^3 and a small degree of C–C bond formation in the transition state.[20,21]

Hammett analysis conducted using catalyst **7b** established that reaction rate correlates linearly with σ^+_{para} in the reactions of **1b-1f** (Figure 4B), consistent with the buildup of positive charge on the C3 carbon during the rate-determining step. Enantioselectivity values for the same substrates also correlate directly with σ^+_{para}. The increased levels of asymmetric induction in electron-deficient substrates may be a consequence of differential extents of olefin participation during chloride displacement. For electron-deficient substrates, a higher degree of anchimeric assistance from the distal olefin would be expected on the basis of a diminished ability to support positive charge at C3. A greater degree of C–C bond formation would be expected to result in a more highly ordered enantiodetermining transition state.[18g]

Kinetic analysis of the reaction catalyzed by urea **7b** revealed a first-order dependence of rate on substrate **1b**, 0th order dependence on base, and a kinetic order in catalyst of 1.19 (see SI for details). Aryl pyrrolidine urea and thiourea hydrogen-bond donors such as **7** are prone to dimerization both in the solid state and in nonpolar organic solvents,[22] so a mixed resting state of monomeric and dimeric **7b** could account for the observed non-integer order in catalyst. This possibility was supported through isothermal titration calorimetric studies, which revealed the presence of a roughly 70:30 equilibrium mixture of dimeric and monomeric **7b** in cyclohexane at $[\mathbf{7b}]_{total}$ = 0.01 M (see SI for details). Thus, the observed kinetic order in [**7b**] can be ascribed to a mixed dimer-monomer resting state and a rate-determining transition state containing two molecules of catalyst. Based on the results of the kinetic analyses, Hammett studies, and the KIE experiment, we propose the catalytic cycle depicted in Figure 4C, where concerted rate- and enantioselectivity-determining chloride ionization and carbon-carbon bond formation is promoted through the cooperative action of two molecules of the urea catalyst.[14d,23]

Having established the stoichiometry and general features of the key selectivity-determining transition state, we sought to explore the factors responsible for enantioinduction through the use of computational modeling (see SI for computational details). Density functional theory (DFT) calculations identified energy-minimized transition state structures for the major and minor enantiomeric cyclization pathways of **1d** promoted by two molecules of **7b**.[24] Consistent with experimental observations, chloride ionization was characterized by olefinic participation (Figure 4D, forming C–C

bond: 2.27 Å, breaking C–Cl bond: 3.26 Å). The lowest energy computed cyclization transition state is partially encapsulated within the dimeric catalyst assembly, with catalyst naphthyl groups positioned in close proximity to developing positive charge. The mode by which the aryl substituents on the catalyst influence enantioselectivity was assessed experimentally. Kinetic analysis conducted on the cyclization of **1b** using catalysts **7a**-**7d** revealed a positive correlation between reaction rate and enantioselectivity (Figure 5).[25] Decomposition of the observed rate into contributions from the major and minor enantiomeric pathways[15c] reveals that the effect is far more pronounced for the major pathway; the catalyst aryl pyrrolidine stabilizes the transition state leading to the minor enantiomer to a lesser extent. Thus, it can be concluded that stabilizing aromatic interactions are at least partially responsible for enantioinduction.[26]

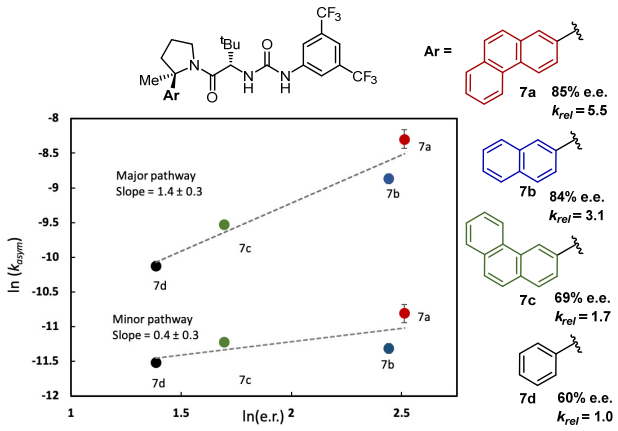

Figure 5. Effect of catalyst aryl substituents on reaction rate and enantioselectivity.

In summary, we have developed a highly enantioselective cyclization reaction of neryl chloride analogues catalyzed by chiral ureas. Reactions proceed through a concerted pathway in which π-participation by the nucleophilic olefin facilitates ionization of the leaving group, thereby avoiding direct elimination products. A network of attractive non-covalent interactions involving two molecules of the urea serves to stabilize the cyclization transition state and induce enantiocontrol. Concerted mechanisms have been proposed to play key roles in enzymatic[3b,27] and synthetic reactions[9,28] involving formal cationic intermediates, and they likely underlie the attainment of high chemo- and enantioselectivity in the present system. Future studies will be aimed at leveraging the principles uncovered here toward more complex transformations such as polycyclization reactions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Experimental procedures and characterization data of catalyst and substrate syntheses, procedures and analytical data for enantioselective reactions, details of mechanistic studies, and computational studies (PDF)

Crystallographic data for **2d** (CIF)

AUTHOR INFORMATION

Corresponding Author

*jacobsen@chemistry.harvard.edu

Author Contributions

‡These authors contributed equally.

Notes

The authors declare no competing financial interest.

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(17) A 1,3 transposition of the chloride to the benzylic position would be required followed either by $S_N1(2)$' attack of the nucleophilic olefin or further 1,3 rearrangement to form **1b**. Alternatively, **Z-1b** could undergo sequential ionization, allyl cation isomerization, and attack of the nucleophilic olefin. For a discussion on the plausibility of allyl cation isomerization, see ref. 12a.
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(19) Catalyst **7b** was used and was found to promote cyclization of **1b** to **2-5b** in quantitative yield and similar e.e. of **2b** (86%) as compared to the reaction catalyzed by **7a**. See SI for details.
(20) A similar k_H/k_D KIE of 0.925 was reported by Bunton and co-workers in solvolysis studies of neryl chloride. See reference 18b.
(21) Rapid, reversible ionization followed by rate-limiting olefin addition to an allyl cation intermediate cannot be ruled out a priori but would be expected to involve a significant degree of rehybridization at the nucleophilic carbon and therefore display a much larger inverse secondary KIE.
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(23) Enantioselectivities were observed to be invariant as a function of [**7b**] at 5, 10, and 15 mol% loadings, rendering highly unlikely any participation of a competitive monomeric pathway.
(24) On the basis of prior mechanistic studies from our group (see ref. 22), we assumed a 4-H binding geometry to chloride. Transition states characterized by 2-H binding to chloride were not modeled.
(25) There is no detectable background reaction of **1** under the reaction conditions in the absence of catalysts **7**.
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