Catalytic Control in Cyclizations: from Computational Mechanistic Understanding to Selectivity Prediction

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CONSPECTUS: This Account describes the use of quantum chemical calculations to elucidate mechanism and develop catalysts to accomplish highly selective cyclization reactions. Chemistry is awash with cyclic molecules and the creation of rings is central to organic synthesis. Cyclization reactions, the formation of rings by the reaction of two ends of a linear precursor, have been instrumental in the development of predictive models for chemical reactivity, from Baldwin's classification and rules for ring closure to Woodward and Hoffmann's rules based on

the conservation of orbital symmetry and beyond. Ring-formation provides a productive and fertile testing ground for the exploration of catalytic mechanisms and of chemo-, regio-, diastereo- and enantioselectivity using computational and experimental approaches. The Account is organized around case studies from our laboratory, and illustrates the ways in which computations provide a deeper understanding of the mechanisms of catalysis in *5-endo* cyclizations, and how computational predictions can lead to the development of new catalysts for enhanced stereoselectivities in asymmetric cycloisomerizations.

We have explored the extent to which several cation-directed *5-endo* ring closing reactions may be considered as electrocyclic, and demonstrate that reaction pathways and magnetic parameters of transition structures computed using quantum chemistry are inconsistent with this notion, instead favoring a polar mechanism. A rare example of selectivity in favor of *5-endo-trig* ring closure is shown to result from subtle substrate effects which bias the reactant conformation out-of-plane, limiting the involvement of cyclic conjugation. The mode of action of a chiral ammonium counterion was deduced via conformational sampling of the transition state assembly, and coordinates to the substrate via a series of nonclassical hydrogen bonds. We describe how computational mechanistic understanding has led directly to the discovery of new catalyst structures for enantioselective cycloisomerizations. Calculations have revealed stepwise C-C bond formation and proton transfer dictate the exclusive *endo* diastereoselectivity of the intramolecular Michael addition to form 2-azabicyclo[3.3.1]nonane skeletons catalyzed by primary amines. These insights have led to development of a highly enantioselective catalyst with higher atom-economy than previous generations.

Transition-metal catalyzed cycloisomerizations are also explored here, where our theoretical investigations have uncovered an unexpected reaction pathway in the [5+2] cycloisomerization of ynamides. This leads to the design of new phosphoramidite ligands to enable a double stereodifferentiating cycloisomerizations in both matched and mismatched catalyst–substrate settings. Computational understanding of the factors responsible for regio-, enantio- and diastereocontrol are shown to lead to tangible predictions which lead to an acceleration of catalyst development for selective cyclizations.

■ INTRODUCTION

The construction of carbo- and heterocycles is central to the art of organic synthesis, driven by the large variety of mono- and polycyclic systems found in natural products and pharmaceuticals. It is therefore unsurprising that the development of new synthetic methods for cyclizations, in which a new ring is formed by the reaction of two ends of a linear molecule, continues to advance.¹ In particular, the use of catalytic methods which exert control over regio- and stereochemistry can enable highly selective cyclizations to be performed that are challenging to access by other means. In our recent research described in this Account, we have undertaken computational investigations to understand the mechanistic basis for these selectivities, and use this information as the rational basis for the development of new catalytic protocols in collaboration with several experimental groups.^{2,3}

We focus our attention on cycloisomerization reactions in this Account,⁴ in which all the atoms in the starting materials are present in the products. The application of theory to understanding ring-forming reactions is an area of considerable past success. Woodward and Hoffmann were able to rationalize and predict the occurrence of con- and disrotatory electrocyclic ring-closures, and hence diastereoselectivity,⁵ as a consequence of the conservation of orbital symmetry and Houk developed the concept of torquoselectivity to account for a substituent's preference to undergo inward or outward rotation.⁶ Aside from pericyclic transformations, based on available experimental data Baldwin formalized the classification of polar cyclizations,⁷ and with an appreciation of reactive trajectories favored by different functional groups, the relative favorability of different ring-closing modes could be predicted in due course.⁸ In practice, many cyclizations (such as those discussed in our Account) may defy simple categorization as either pericyclic or polar, making a straightforward prediction of reactivity difficult. We present the anionic cyclization of several systems for which both electrocyclic and polar mechanisms have been advanced in the literature, where we (and others) have used computations to elucidate the operative mechanism in each case.

Selectivity in cyclization reactions can be observed in terms of the size of the forming ring (i.e. regiocontrol) and we discuss a rare example of a formally-disfavored 5-*endo-trig* reaction where selectivity can be switched by a small change in substrate.⁹ Previously we have uncovered how enzyme catalysis can exert control to switch the innate regioselectivity of cyclizations to form natural product skeletons. In the case of asymmetric catalysis, the exertion of enantiocontrol in ring forming reactions requires an understanding of mechanism, but also of

the constellation of interactions which enable the catalyst to favor one pathway over another.¹⁰

From a computational perspective, the study of cyclization reactions avoids many of the substantial challenges associated with associative/dissociative reactions which occur in solution – principally by reducing a) the sizable uncertainties associated with changes in translational entropy¹¹ and b) the conformational degrees of freedom in intermediate and TS structures. Nonetheless, appreciation of the pitfalls of electronic structure theory, and understanding the requirements of an accurate description of thermochemical kinetics and dispersion are of importance, as is illustrated in all of the Accounts in this special issue. Throughout this Account, our optimizations have been performed with modern (dispersion-corrected) density functional methods¹² which either include a description of medium-range correlation through inclusion of the kinetic energy density (Mo6-2X¹³) or an explicit long-range correction for London-dispersion (wB97XD¹⁴). The absence of such a correction inevitably leads to quantitative error in the estimation of selectivities, but may also result in qualitatively incorrect structures particularly where noncovalent catalysis is involved.

■ MECHANISMS OF CATION-PROMOTED ANIONIC CYCLIZATIONS

Our computations have focused on understanding the cyclizations of anionic systems. While formal classification of these reactions according to Baldwin's rules is straightforward, their characterization as electrocyclic (or indeed as non-electrocyclic), is an intriguing question. Collaborations with Prof. Martin Smith have led us to consider the a) 5-*endo-dig* closures involving isocyanide cyclizations¹⁵ and the b) 5-*endo-trig* closures involving enoate⁹ and imine¹⁶ (as studied by Tantillo) acceptors (Scheme 1).

Scheme 1. Catalytic cation-directed 5-*endo* ring closing reactions discussed in this account; a) 5-*endo-dig* anionic isocyanide cyclization; b) 5-*endo-trig* anionic cyclizations involving imine and enoate acceptors.

Implicit in the above classification of anionic ring-closures according to Baldwin's rules is the assumption of a polar mechanism. However, pericyclic arguments have also been advanced in the literature to interpret the reactivity shown in Scheme 1.^{16,17} For example, the pentadienyl anion embodies the same underlying Lewis structure as the forming ring systems in the examples above, and its ring closure proceeds through a disrotatory electrocyclicization. Thus both mechanistic extremes can be considered (Figure 1), and we reasoned that computational insight into the transition structures of these cyclizations would enable a more precise description to emerge.

Figure 1. Classification according to Baldwin's rules and the two mechanistic alternatives proposed for 5-endo-closure.

5-endo-dig cyclizations of isocyanides

5-endo-dig cyclizations are prevalent in the synthesis of aromatic heterocycles and Smith has reported the use of aromatic isonitriles in the cation-directed synthesis of indolenines via a 5-endo-dig closure (Scheme 2).^{15,18}

Scheme 2. Left: 5-endo-dig closure of isocyanides; Right: related cyclizations of nitrile ylides studied computationally.

The geometric demands of an obtuse approach trajectory required by alkynyl electrophiles make the 5-endo-dig closure challenging, in contrast to Baldwin's original prediction, which has been comprehensively redefined by Alabugin for anions and radicals.¹⁹ From a mechanistic perspective, both polar and anionic 6 π -electrocyclization scenarios are conceivable; indeed a pericyclic mechanism has been found computationally for the related cyclizations of nitrile-ylides,^{20,21} supported by energetic and magnetic criteria (Scheme 2). We have studied the cyclizations of isocyanides, combining computation and experiment to uncover the basis for the observed reactivity.¹⁵

Scheme 3. a) Computed reaction mechanism for the synthesis of the pyrroloindoline skeleton, comparing hydrogen-bonded and non-hydrogen-bonded cyclization pathways (CPCM-B2GP-PLYP/6-311++G(d,p) energies in kcal/mol); b) experimental studies into the role of the Brønsted acidic N-H proton.

Our computed reaction mechanism for a pyrroloindoline-forming isocyanide cascade-cyclization is shown in Scheme 2. Optimizations were performed with density functional theory corrected by an additive London-dispersion term (DFT-D) at the wB97XD/6-311++G(d,p) level, and the energetics refined with a perturbative double-hybrid functional B2GP-PLYP.²² For substrate **1** it is possible to locate two alternative TS structures for the initial ring-closure, **TS1** and **TS2**. In the second of these structures the isocyanide is activated by intramolecular hydrogen-bonding involving the amide N-H bond²³; this promotes the initial cyclization through stabilization of the developing negative charge at carbon in **TS2**. This computed mechanistic model provides an explanation for the ease of cyclization, and is supported by experimental studies. Removal of the amide N-H group by methylation results in no cyclization whatsoever, while N-D labelled starting material deuterium leads to significant incorporation in the product (erosion is due to solvent exchange) consistent with the proposed mechanism.

Figure 2. A. wB97XD/6-311++G(d,p) relative energies and GIAO-B3LYP/6-311++G(d,p) NICS(o)zz values along the reaction coordinate for comparative anionic 5-*endo*-cyclizations of isocyanide substrate **1** (TS2) and a pentadienyl anion (TS3); B. ACID plots (CSGT-B3LYP/6-311++G(d,p) level of theory generated with an 0.026 isosurface value), where R is abbreviated as Me.

We were intrigued to establish whether the key carbocyclization step, via **TS2**, exhibits any characteristics of a pericyclic 6 π -electrocyclization as had been suggested. The principal computational criteria we have used to make this distinction are structural, energetic and magnetic. A cyclical delocalization of electrons associated with pericyclic reactivity leads to TS aromaticity and results in distinct magnetic properties.²⁴ Nucleus Independent Chemical Shift (NICS) computations²⁵ directly probe the ring current, and can further be refined to isolate magnetic effects related to aromaticity exclusively.²⁶ The NICSzz value represents the response perpendicular to the delocalized ring of electrons and reflects aromaticity, and is not contaminated by irrelevant in-plane components. We evaluated the NICS(o)zz tensor along the intrinsic reaction coordinate (IRC) at the center of the forming 5-membered ring in the isocyanide cyclization and compared this result with the analogous cyclization of an alkenyl anion via **TS3** (Figure 2). For the isocyanide, the NICSzz value

steadily increases along the IRC, while for the all carbon analogue a minimum value -20.4 ppm occurs at **TS3** (for reference, benzene gives a value of -14.5 ppm). On this evidence, **TS2** does not display the characteristic aromaticity of a pericyclic (i.e. electrocyclic) ring closure. The polar-electrocyclic mechanistic distinction between **TS2** and **TS3** is further reinforced through visualizing the anisotropy of the current-induced density (ACID), as developed by Herges.²⁷ In this approach, clockwise/counterclockwise ring currents depict aromaticity/antiaromaticity, while the absence of ring currents correspond to a break in ring conjugation.²⁴ A closed circuit and diamagnetic ring current indicate aromaticity in pericyclic **TS3**. In contrast, isocyanide cyclization **TS2** displays a breached ring current due to the absence of cyclic delocalization in the polar mechanism.

5-*endo*-trig selective cyclizations

5-*endo*-trig cyclizations are generally considered to be kinetically unfavorable, as described by Baldwin's rules.²⁸ Consequently, kinetically-controlled closures of this type are rare. This is usually ascribed to difficulties in achieving the stereoelectronically-prescribed approach trajectories in the TS. We turned to quantum chemical calculations to understand the surprising observation of a highly enantio- and diastereoselective 5-*endo*-trig cyclization catalyzed by a chiral ammonium salt (Scheme 1b).⁹ Our computational studies prompted the re-examination of different substrates using an achiral catalyst, leading to the discovery that different nucleophilic components undergo different cyclization modes - an ester leads exclusively to 5-*exo*-trig cyclization, while a malonate leads exclusively to 5-*endo*-trig cyclization (Figure 3).

Figure 3. The mode of cyclization is dictated by the nucleophilic component: an ester leads exclusively to 5-*exo*-trig cyclization, while a malonate leads exclusively to 5-*endo*-trig cyclization.

Figure 4. Computed CPCM-Mo6-2X/6-311++G(d,p) free-energy profiles for competing 5-endo-trig and 5-exo-trig ring closure, comparing diester (malonate) and monoester substrates. Despite a switch in the favored reaction pathway between the two substrates, the TS structures show similar trajectories of attack: nucleophilic trajectories are not decisive in controlling selectivity.

Computations, performed at the CPCM-Mo6-2X/6-311++G(d,p) level of theory, are shown in Figure 6 and clearly illustrate that the selectivity of enolate **2** to undergo 5-endo-trig closure is kinetically controlled. 5-Endo-trig TS5 is 8.7 kcal/mol more stable than the competing 5-exo-trig TS4, and cyclization is computed to be irreversible. The cyclization of enolate **3**, with only a single anion-stabilizing group, confirm that a complete switch in selectivity is to be expected: 5-endo-trig TS7 is kinetically disfavored relative to the 5-exo-trig closure TS6 by 9.6 kcal/mol. Comparison of the TS geometries for each mode of closure (Figure 4, RHS) shows that the nucleophilic trajectory of exo-attack proceeds along an angle closer to that expected from stereoelectronic considerations – however, this is true for both of the substrates. The fact that they give opposite selectivities forces us to conclude that geometric and/or stereoelectronic constraints are not decisive in the observed outcome of this irreversible ring-closure.

How does this difference in selectivity relate to the mechanism of cyclization? There are two feasible mechanistic extremes: an anionic 5-endo-trig polar reaction and a suprafacial 6 π -electrocyclization. IUPAC defines an electrocyclic rearrangement in terms of the “formation of a σ -bond between the termini of a fully conjugated linear π -electron system and a decrease by one in the number of π -bonds”. The enolate geometry in **2** is planar, while that in **3** is rotated away from of planarity by 50° due to the larger

malonate group (Figure 4). The extent of linear π -conjugation is thus reduced in **2**, arguing against the involvement of pericyclic character in the observed 5-endo-trig selectivity.

Figure 5. Change in NICS_{zz} values along an axis perpendicular to ring plane for ring-closure TS structures: archetype 5-endo-trig and 6 π -electrocyclic structures shown with TS5 and TS6.

We have further characterized the nature of the unusual 5-endo-trig closure by NICS_{zz} calculations. For 5-endo-trig cyclizations Alabugin has discovered the presence of a 5-center, 6-electron σ -aromatic orbital array involving the nucleophilic lone pair, the target alkene π bond and a σ_{CC} bridge can result in TS aromaticity.²⁹ This has further led to the classification of such cyclizations as “aborted” [2,3]-sigmatropic shifts. This would give rise to in-plane TS aromaticity, while an electrocyclic mechanism would show out-of-plane TS aromaticity. However, neither are evident

from analysis of the NICS_{zz} values along an axis running through and perpendicular to the ring-plane (Figure 5). A maximum value of 13 ppm is computed at the center of **TS5**, indicating that TS aromaticity – of either the σ or π -variety – does not contribute to the observed 5-*endo*-trig reactivity. **TS5** embodies a 5-*endo*-trig nucleophilic cyclization. In contrast, **TS6** displays some of the characteristics of an electrocyclization: disrotatory closure is apparent along the IRC, and the NICS_{zz} values either side of the ring plane are negative (approximately -10 ppm). The lack of both aromaticity and disrotation in the transition structure are key features that indicate the reaction is better described as non-pericyclic. Baldwin himself suggested that conventional rules for closure may not apply to concerted electrocyclic processes in which geometric changes other than inversions are often observed. What we observe is quite the opposite—it is the favorability of the polar mechanism (and corresponding absence of electrocyclic character) in **TS5** that makes the 5-*endo*-trig cyclization so facile.

Figure 6. The most stable B97D/6-31G(d) TS for the cyclization reaction with a chiral ammonium counterion present. C-H...O hydrogen bonds and C-H... π interactions are responsible for chiral recognition, while a steric interaction arises at the position of X, giving rise to the erosion of selectivity with an increase in size.

Having characterized the mechanism of ring-closure we also sought to understand the high level and sense of enantioselectivity. This was probed by exploring the geometry of the substrate:catalyst complex computationally, in order to dissect the noncovalent interactions responsible for asymmetric catalysis.³⁰ The location of transition structures for chemical systems with multiple degrees of freedom requires careful consideration, and in our case in-house Monte-Carlo conformational routines to sample the binding pose utilizing a semi-empirical Hamiltonian corrected for dispersion and hydrogen-bonding (PM6-DH2), were used.³¹ Subsequent reoptimizations were carried out at the B97D/6-31G(d) level of theory for structures within 10 kJ/mol of the most stable. The resulting calculated absolute sense of stereoinduction agrees with experiment. In the most favorable conformation (Figure 6), the close contacts occur between the positively charged ammonium α -hydrogens of the catalyst and negatively charged ester-oxygen atoms of the substrate, the catalyst acting as an “oxyanion hole”. Cannizarro and Houk³² have shown such hydrogen

bonding interactions of ammonium cations to be the strongest of this type of non-classical CH...O hydrogen bonding interactions³³ evaluated so far. A further anchoring point is provided by a cation- π interaction between the benzene ring and an α -hydrogen lying just 2.5 Å above the ring center. In the computed structure the substrate aromatic ring orients a hydrogen atom at the C7-position (*para*- to the nucleophilic group) towards the face of a naphthyl group in the catalyst. From our computational model, we expected that an increase in the size of this substituent should result in unfavorable steric interactions between substrate and catalyst along the major pathway: experimentally, the enantioselectivity is progressively eroded by a larger group in this C7-position, while C6-substitution has a negligible effect in accord with the model.

The related 5-*endo*-trig closure of imines has been studied computationally by Tantillo and colleagues,³⁴ in which diastereoselectivity is dependent on the identity of the ammonium counterion (Figure 7). With a malonate nucleophilic group, the conformational behavior of the anion reflects that described above, being twisted out of the aromatic plane. Since cyclic delocalization is minimized, the computed NICS values show no evidence of aromaticity in the cyclization (with an E-imine). Diastereoselective ring-closure is computed to favor the *cis*-disposition of the two phenyl rings, both kinetically and in terms of the stability of cyclized adduct due to the presence of attractive aromatic interactions.³⁵ With an achiral ammonium counterion this is indeed the major diastereomer formed. Evidently the chiral benzylcinchonidinium counterion must overcome this inherent preference to account for the selectivity in favor of the opposite diastereomer.

Figure 7. Cyclization of the delocalized 2-azapentadienyl anion favors a 5-*endo*-trig Mannich process with an *E*-imino substituent. Favorable aromatic-interactions favor the *cis*-diastereomer: catalyst-dependent diastereoselectivity likely results from the ability of catalysts

to overwhelm the inherent stereochemical preference of cyclization.

The Brønsted-acid catalyzed cyclization of α,β -unsaturated hydrazones has also been classified previously as an electrocyclic transformation (Figure 8).³⁶ However, Thiel and colleagues have shown computationally³⁷ that this reaction is more accurately described in terms of a 5-*endo* polar-mechanism. Compared with the symmetrical 6π -electrocyclic closure of a pentadienyl anion, the cyclization TS has a lower activation barrier, shows a lack of a disrotatory reaction coordinate, and has smaller reduction in NICS value at the TS, which all point towards polar character. An alternative classification, which is not mutually exclusive, as a pseudo-pericyclic TS is also discussed due to the planar TS structure. The defining characteristics of a pseudo-pericyclic mechanism³⁸ are low or nonexistent barriers, planar transition structure geometries,^{39,40} and cyclic reactions that are allowed irrespective of the number of atoms.

Figure 8. Comparison of the Brønsted-acid catalyzed cyclization of an α,β -unsaturated hydrazones against a 6π -

electrocyclization highlights the importance of polar/pseudo-pericyclic character.

■ COMPUTATIONAL CATALYST DESIGN FOR ASYMMETRIC CYCLIZATIONS

Ring-closure offers the potential for the generation of new stereogenic centers within the cyclized product, which raises the prospect of catalytic stereocontrol. For an achiral starting material, enantiocontrol over absolute stereochemistry comes from the use, or development, of a suitable chiral catalyst. Where existing stereocenters are already present in the linear reactant, the diastereoselectivity of cyclization can be enhanced or reduced by a chiral catalyst, depending on whether matched or mismatched control between substrate and catalyst occurs. Starting from a mechanistic approach to understanding a cyclization we have reported examples of the development of new chiral catalysts and ligands where selectivity has been optimized through computational understanding and design in both enantioselective and diastereoselective settings.

Organocatalytic intramolecular Michael-cycloisomerization

In collaboration with Dixon and colleagues, we described how the desymmetrization of a prochiral cyclohexanone through an intramolecular Michael addition to α, β -unsaturated esters can be catalyzed using a chiral primary amine (Figure 9).⁴¹ Before turning to the enantioselective reaction it was discovered that small primary amines, such as *n*-butylamine, give rise to exclusive formation of the (contra-steric) *endo*-diastereomer of the Michael adduct. We have investigated the mechanistic origins of this selectivity, with computations carried out at the Mo6-2X/6-311+G(d,p) level of theory, with implicit (CPCM) solvation by CH_2Cl_2 .

Figure 9. Intramolecular (Michael) cycloisomerization catalyzed by primary amines (A) importance of enamine geometry; (B) diastereo-selectivity of Michael addition; (C) TS for the aminothiurea-catalyzed transformation; (D) analysis of the competing thiourea-catalyzed pathways leading to formation of the enantiomeric *endo*-Michael adducts. CPCM-Mo6-2X/6-311+G(d,p) Gibbs free energies in kcal/mol.

Assuming condensation of amine and substrate occur, enamine-catalysis was considered: we found that with a simple amine catalyst only the *s-trans* enamine is competent to react, since the N-H must be oriented towards the ester to avoid substantial charge separation: proton transfer occurs in the C...C forming TS, which is not possible for the *s-cis* enamine conformer. We were able to dismiss the possibility of a concerted cycloisomerization (an intramolecular ene reaction) since this was associated with a high activation barrier of 33.4 kcal/mol. Instead, C...C formation and proton N-H...C proton transfer occur in a stepwise fashion: the *endo*-diastereomer results from the requirement that the proton must be delivered to the ester α -carbon, which is only possible with this relative stereochemistry. Formation of the *exo*-diastereomer would require the intervention of an intermolecular proton source, since the intramolecular transfer is now geometrically impossible. None of the

exo-diastereomer was observed experimentally, in support of our model.

Experimentally, a bifunctional thiourea/primary amine catalyst derived from a chiral cyclohexanediamine was found to control the asymmetric cyclization with 96% ee. Based on the stepwise cyclization mechanism established with the simpler catalyst, we obtained the free energy profile with the chiral catalyst in which the *tert*-leucine side-chain was abbreviated as a methyl group (**Figure 9 C&D**). Conformers for each TS were sampled in a Monte Carlo approach with the semi-empirical PM6-DH2 method as described previously, and refined by CPCM-Mo6-2X/6-311+G(d) optimizations. We located TSs in which C-C bond formation occurs leading to four diastereomeric Michael adducts. As with the achiral example, the *endo*-diastereomer was preferred. Unlike the achiral example, both enamine geometries are viable reactive intermediates since the thiourea can stabilize the developing oxyanion through

coordination. The reactive enamine geometry differs between the two pathways, with the *s-cis* enamine yielding the major enantiomer and the *s-trans* enamine yielding the minor enantiomer, although both conformations benefit from stabilizing hydrogen-bonding interactions between ester and thiourea. Energetic discrimination between Michael transition states results from differing conformations of the cyclohexylthiourea functional group. Our computational studies predicted that the *tert*-leucine fragment would exert no additional stereocontrolling effect, since in each TS this side chain is oriented well away from the rest of the system bulk. Accordingly, the Me substituted catalyst was then synthesized and tested in the cyclization to validate the computational prediction of high enantioselectivity, and showed good quantitative agreement between experiment and theory, giving 97% ee and no evidence of the minor diastereomer. Through our detailed DFT calculations, a new low-molecular-weight catalyst was thus

developed based on our mechanistic understanding of the cycloisomerization.

Stereoselective [5+2]-cycloisomerization

In transition-metal catalyzed cyclizations, we have studied how the ligand can exert control over enantioselectivity⁴² and regioselectivity.⁴³ More recently this has led to collaborative efforts with Anderson and colleagues to explore computational-led design of ligands for asymmetric higher-order cycloisomerizations. Combining detailed DFT calculations with experiment has enabled the discovery of a highly reactive Rh:phosphoramidite catalyst for the stereoselective [5+2]-cycloisomerization of ynamide-vinylcyclopropanes to [5.3.0]-azabicycles (**Figure 10**).⁴⁴ Evans and Baik have reported the optimization of diastereoselectivity through substrate modification in the Rh-catalyzed [2+2+1] cyclization (Pauson-Khand reaction) based on a computational understanding of the polarization in the competing TS structures.⁴⁵

Figure 10. Diastereoselective ynamide [5+2] cycloisomerization. (A) enantiodetermining/rate-limiting step; (B) stereochemical possibilities associated with ynamide coordination to a chiral Rh-phosphoramidite; (C) transition state model for computational ligand design. Calculations were performed at SMD- ω B97XD/6-311++G(d,p)/LanL2TZ// ω B97XD/6-31G(d)/LanL2DZ level of theory.

Investigation on intermolecular Rh-catalysed [5+2] cycloisomerizations of enynes have been reported by Yu, Houk and Wender and suggest that oxidative addition into the vinylcyclopropane is the first step on

the catalytic pathway.⁴⁶ We considered this, and alternative proposals, with calculations at the ω B97XD/6-311++G(d,p) level of theory and found that the ynamide substrate behaves rather differently (Fig.

10A): metallacyclopentene was computed to occur prior to insertion into the vinylcyclopropane, as the stereodetermining step. We attribute to the additional stabilization of the forming Rh(III) intermediate in the oxidative coupling step provided by the electron-rich ynamide. In the solid-state phosphoramidite ligands are known to coordinate a cationic Rh-center in a bidentate fashion, with the principal Rh-P bond supplemented by the η^2 -coordination of one of the ligand's phenyl rings with the metal center.⁴⁷ The chiral environment created by this coordination mode was envisaged to discriminate between different binding modes of the substrate, leading to the selectivity over Rh-coordination to the alkene enantioface. Therefore, the possible coordination geometries of the enynamide were exhaustively considered, favoring the *P-trans-ene/Up* mode (as shown in **Fig. 10B**).

With the above model in hand, our computations emphasized the importance of two interactions involving the chiral ligand in the key TS: a Rh-arene interaction (between metal and ligand) and a stabilizing aromatic interaction between the ynamide substituent and the naphthyl group of phosphoramidite ligand (**Fig. 10C**).³⁵ Based on this transition state model we reasoned the modulation these key interactions parameters would have an effect upon the enantioselectivity of the cycloisomerization. We computed the selectivity of several modified ligands, and found that substitution at the para-position of the ligand phenyl rings had a sizable effect: electron releasing methoxy groups led to a predicted erosion in overall rate and enantioselectivity, while withdrawing fluoro groups were computed to exert the opposite effect, increasing the rate and selectivity. This computed trend in reactivity and enantioselectivity, namely $F > H > OMe$, results from a weakened metal-arene interaction in the TS which is compensated for through stronger coordination of the alkynyl and alkenyl groups. Further experimental verification correlated well with the predicted data and the new designed *p-F* ligand showed a dramatic enhancement of rate and selectivity in the cyclization compared with the parent ligand (*p-H*). The application of this catalyst/ligand combination to a number of enantioselective transformations, and diastereoselective transformations of single enantiomer substrates showed the designed *p-F* ligand to be superior in rate and enantioselectivity across a range of substrates, as well as successful in both the matched and mismatched double-stereodifferentiating setting (i.e. competing catalyst vs. substrate stereocontrol). This work demonstrates the powerful role of density functional level of theory (DFT) computations in understanding asymmetric catalysis, leading to quantitative computational-led design of new, highly selective ligands.

■ CONCLUSIONS AND PROSPECTS

The investigations described here show how computational mechanistic insights lead to tangible predictions governing the selectivities of ring-closing reactions. A combination of structural, energetic and magnetic parameters obtained from calculation has played a role in redefining the mechanisms of anionic cyclizations. Mechanistic proposals of electrocyclic character in 5-*endo* closures should be viewed with caution in light of the fact that the catalytically relevant examples studied here are dominated by polar (or alternatively pseudo-pericyclic) character. The utility of computational models in making tangible predictions in stereoselective cyclizations has been shown, in the successful development of new organo- and transition metal catalysts for cycloisomerizations. Computational understanding of the factors responsible for regio-, enantio- and diastereocontrol can accelerate the development of catalysts in this way. Challenges remain in the efficient sampling of transition structures for flexible systems, and current efforts in this direction are currently on-going in our group.

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Author Contributions

The manuscript was written through contributions of both authors, who have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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Robert Paton is from Stockport (born 1981) in the North of England and completed undergraduate and graduate studies at the University of Cambridge. From

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■ REFERENCES

- (1) Moyano, A.; Rios, R. Asymmetric Organocatalytic Cyclization and Cycloaddition Reactions. *Chem. Rev.* **2011**, *111*, 4703–4832.
- (2) Tantillo, D. J. Using Theory and Experiment to Discover Catalysts for Electrocyclizations. *Angew. Chem. Int. Ed.* **2009**, *48*, 31–32.
- (3) Houk, K. N.; Cheong, P. H.-Y. Computational prediction of small-molecule catalysts *Nature* **2008**, *455*, 309–313.
- (4) Watson, I. D. G.; Toste, F. D. Catalytic Enantioselective Carbon-Carbon Bond Formation Using Cycloisomerization Reactions. *Chem. Sci.* **2012**, *3*, 2899–2919.
- (5) Woodward, R. B.; Hoffmann, R. Stereochemistry of Electrocyclic Reactions. *J. Am. Chem. Soc.* **1965**, *87*, 395–397.
- (6) Houk, K. N. Stereoselective Electrocyclizations and Sigmatropic Shifts of Strained Rings: Torquoelectronics! in *Strain and Its Implications in Organic Chemistry* (A. de Meijere and S. Blechert, Editors) **1989**, 25.
- (7) Baldwin, B. J. E. Rules for Ring Closure. **1976**, 734, 734–736.
- (8) Alabugin, I. V.; Gilmore, K. Finding the right path: Baldwin “Rules for Ring Closure” and stereoelectronic control of cyclizations. *Chem. Commun.* **2013**, 49, 11246–11250.
- (9) Johnston, C. P.; Kothari, A.; Sergeieva, T.; Okovytyy, S. I.; Jackson, K. E.; Paton, R. S.; Smith, M. D. Catalytic Enantioselective Synthesis of Indanes by a Cation-Directed 5-Endo-Trig Cyclization. *Nature Chem.* **2015**, *7*, 171–177.
- (10) Hotta, K.; Chen, X.; Paton, R. S.; Minami, A.; Li, H. Swaminathan, K. T.; Mathews, I. I.; Watanabe, K.; Oikawa, H.; Houk, K. N.; Kim, C. Y. Enzymatic Catalysis of Anti-Baldwin Ring-Closure in Polyether Biosynthesis. *Nature* **2012**, *483*, 355–358.
- (11) Plata, R. E.; Singleton, D. A. A Case Study of the Mechanism of Alcohol-Mediated Morita Baylis-Hillman Reactions. the Importance of Experimental Observations. *J. Am. Chem. Soc.* **2015**, *137*, 3811–3826.
- (12) Grimme, S. Density Functional Theory with London Dispersion Corrections. *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **2011**, *1*, 211–228.
- (13) Zhao, Y.; Truhlar, D. The Mo6 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four Mo6-class functionals and 12 other functionals. *Theor. Chem. Acc.* **2008**, *120*, 215–241.
- (14) Chai, J.-D.; Head-Gordon, M. Long-range corrected hybrid density functionals with damped atom-atom dispersion corrections. *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615–6620.
- (15) Knipe, P. C.; Gredičak, M.; Cernijenko, A.; Paton, R. S.; Smith, M. D. Phase-Transfer-Catalysed Synthesis of Pyrroloindolines and Pyridoindolines by a Hydrogen-Bond-Assisted Isocyanide Cyclization Cascade. *Chem. Eur. J.* **2014**, *20*, 3005–3009.
- (16) Maciver, E.; Thompson, S.; Smith, M. Catalytic Asymmetric 6 π Electrocyclization: Enantioselective Synthesis of Functionalized Indolines. *Angew. Chem. Int. Ed.* **2009**, *48*, 9979–9982.
- (17) Vicario, J. L.; Badia, D. Enantioselective 6 π Electrocyclizations: Pushing the Limits in Organocatalytic Pericyclic Reactions. *ChemCatChem* **2010**, *2* (4), 375–378.
- (18) Li, M.; Woods, P. A.; Smith, M. D. Cation-Directed Enantioselective Synthesis of Quaternary-Substituted Indolenines. *Chem. Sci.* **2013**, *4*, 2907–2911.
- (19) Alabugin, I. V.; Gilmore, K.; Manoharan, M. Rules for Anionic and Radical Ring Closure of Alkynes. *J. Am. Chem. Soc.* **2011**, *133*, 12608–12623.
- (20) Fabian, W. M. F.; Kappe, C. O.; Bakulev, V. A. Ab Initio and Density Functional Calculations on the Pericyclic vs Pseudopericyclic Mode of Conjugated Nitrile Ylide 1,5-Electrocyclizations. *J. Org. Chem.* **2000**, *65*, 47–53.
- (21) Cabaleiro-Lago, E. M.; Rodríguez-Otero, J.; Hermida-Ramón, J. M. Evaluation of Magnetic Properties as a Criterion for the Elucidation of the Pseudopericyclic Character of 1,5-Electrocyclizations in Nitrile Ylides. *J. Phys. Chem. A* **2003**, *107*, 4962–4966.
- (22) Karton, A.; Tarnopolsky, A.; Lamère, J. F.; Schatz, G. C.; Martin, J. M. L. Highly Accurate First-Principles Benchmark Data Sets for the Parametrization and Validation of Density Functional and Other Approximate Methods. Derivation of a Robust, Generally Applicable, Double-Hybrid Functional for Thermochemistry and Thermochemical Kinetics. *J. Phys. Chem. A* **2008**, *112*, 12868–12886.
- (23) Jones, G. O.; Li, X.; Hayden, A. E.; Houk, K. N. Danishefsky, S. J. The Coupling of Isonitriles and Carboxylic Acids Occurring By Sequential Concerted Rearrangement Mechanisms. *Org. Lett.*, **2008**, *10*, 4093–4096.
- (24) Schleyer, P. von R.; Wu, J. I.; Cossío, F. P.; Fernández, I. Aromaticity in Transition Structures. *Chem. Soc. Rev.* **2014**, *43*, 4909–4921.
- (25) Chen, Z.; Wannere, C. S.; Corminboeuf, C.; Puchta, R.; Schleyer, P. v. R. Nucleus-Independent Chemical Shifts (NICS) as an Aromaticity Criterion. *Chem. Rev.* **2005**, *105*, 3842–3888.
- (26) Feixas, F.; Matito, E.; Poater, J.; Solà, M. Quantifying Aromaticity with Electron Delocalisation Measures. *Chem. Soc. Rev.* **2015**, *44*, 6434–6451.
- (27) Geuenich, D.; Hess, K.; Köhler, F.; Herges, R. Anisotropy of the Induced Current Density (ACID), a

General Method To Quantify and Visualize Electronic Delocalization. *Chem. Rev.* **2005**, *105*, 3758–3772.

(28) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. 5-Endo-trigonal reactions: a disfavoured ring closure. *J. Chem. Soc., Chem. Commun.* **1976**, 736–738.

(29) Gilmore, K.; Manoharan, M.; Wu, J. I.-C.; Schleyer, P. V. R.; Alabugin, I. V. Aromatic Transition States in Nonpericyclic Reactions: Anionic 5-Endo Cyclizations Are Aborted Sigmatropic Shifts. *J. Am. Chem. Soc.* **2012**, *134*, 10584–10594.

(30) Paton, R. S. Dissecting non-covalent interactions in oxazaborolidinium catalyzed cycloadditions of maleimides. *Org. Biomol. Chem.* **2014**, *12*, 1717–1720.

(31) Rotatable torsions in each diastereomeric transition state were sampled using an in-house uniform-usage directed MCMC conformational search (1000 steps) interfaced to a version of Mopac, during which the forming bond was constrained; MOPAC2012, J. J. P. Stewart, Stewart Computational Chemistry, Colorado Springs, CO, USA, <http://OpenMOPAC.net> (2012)

(32) Cannizzaro, C. E.; Houk, K. N. Magnitudes and Chemical Consequences of $R_3N(+)-C-H...O=C$ Hydrogen Bonding. *J. Am. Chem. Soc.* **2002**, *124*, 7163–7169.

(33) Johnston, R. C.; Cheong, P. H.-Y. C-H...O Non-Classical Hydrogen Bonding in the Stereomechanics of Organic Transformations: Theory and Recognition. *Org. Biomol. Chem.* **2013**, *11*, 5057–5064.

(34) Sharma, K.; Wolstenhulme, J. R.; Painter, P. P.; Yeo, D.; Grande-Carmona, F.; Johnston, C. P.; Tantillo, D. J.; Smith, M. D. Cation-Controlled Enantioselective and Diastereoselective Synthesis of Indolines: An Autoinductive Phase-Transfer Initiated 5-Endo-Trig Process. *J. Am. Chem. Soc.* **2015**, *137*, 13414–13424.

(35) Krenske, E. H.; Houk, K. N. Aromatic Interactions as Control Elements in Stereoselective Organic Reactions. *Acc. Chem. Res.* **2013**, *46*, 979–989.

(36) Müller, S.; List, B. A Catalytic Asymmetric 6 π Electrocyclization: Enantioselective Synthesis of 2-Pyrazolines. *Angew. Chem. Int. Ed.* **2009**, *48*, 9975–9978.

(37) Heggen, B.; Patil, M.; Thiel, W. Cyclization of an α , β -Unsaturated Hydrazone Catalyzed by a BINOL-Phosphoric Acid: Pericyclic or Not? *J. Comput. Chem.* **2016**, *37*, 280–285.

(38) Ross, J. A.; Seiders, R. P.; Lemal, D. M. An extraordinarily facile sulfoxide automerization. *J. Am. Chem. Soc.* **1976**, *98*, 4325–4327.

(39) Silva López, C.; Nieto Faza, O.; Freindorf, M.; Kraka, E.; Cremer, D. Solving the Pericyclic-Pseudopericyclic Puzzle in the Ring-Closure Reactions of 1,2,4,6-Heptatetraene Derivatives. *J. Org. Chem.* **2016**, *81*, 404–414.

(40) Paton, R. S.; Steinhardt, S. E.; Vanderwal, C. D.; Houk, K. N. Unraveling the Mechanism of Cascade Reactions of Zincke Aldehydes. *J. Am. Chem. Soc.* **2011**, *133*, 3895–3905.

(41) Gammack-Yamagata, A. D.; Datta, S.; Jackson, K. E.; Stegbauer, L.; Paton, R. S.; Dixon, D. J. Enantioselective Desymmetrization of Prochiral Cyclohexanones via Organocatalytic Intramolecular Michael Additions to α,β -Unsaturated Esters. *Angew. Chem. Int. Ed.* **2015**, *127*, 4981–4985.

(42) Sladojevich, F.; Fuentes de Arriba, A. L.; Yang, T.; Ferrali, A.; Paton, R. S.; Dixon, D. J. Mechanistic investigations on the enantioselective Conia-ene reaction catalyzed by cinchona-derived amino urea pre-catalysts and Cu(I). *Chem. Eur. J.* **2013**, *19*, 14286–14295.

(43) Daniels, D. S. B.; Jones, A. S.; Thompson, A. L.; Paton, R. S.; Anderson, E. A. Ligand Bite Angle-dependent Palladium-catalyzed Cyclization of Propargylic Carbonates to 2-Alkynyl Azacycles or Cyclic Dienamides. *Angew. Chem. Int. Ed.* **2014**, *53*, 1915–1920.

(44) Straker, R. N.; Peng, Q.; Mekareeya, A.; Paton, R. S.; Anderson, E. A. Computational Ligand Design in Enantio- and Diastereoselective Ynamide [5+2] Cycloisomerization. *Nature Commun.* **2016**, *7*, 10109.

(45) Baik, M.; Mazumder, S.; Ricci, P.; Sawyer, J. R.; Song, Y.; Wang, H.; Evans, P. A. Computationally Designed and Experimentally Confirmed Diastereoselective Rhodium-Catalyzed Pauson-Khand Reaction at Room Temperature. *J. Am. Chem. Soc.* **2011**, *133*, 7621–7623.

(46) Yu, Z.-X.; Wender, P. A.; Houk, K. N. On the Mechanism of $[Rh(CO)_2Cl]_2$ -Catalyzed Intermolecular (5 + 2) Reactions between Vinylcyclopropanes and Alkynes. *J. Am. Chem. Soc.* **2004**, *126*, 9154–9155.

(47) Mikhel, I. S.; Rüegger, H.; Butti, P.; Camponovo, F.; Huber, D.; Mezzetti, A. A Chiral Phosphoramidite beyond Monodentate Coordination: Secondary π -Interactions Turn a Dangling Aryl into a Two-, Four-, or Six-Electron Donor in d6 and d8 Complexes. *Organometallics* **2008**, *27*, 2937–2948.