Asymmetric Cooperative Catalysis of Strong Brønsted Acid–Promoted Reactions Using Chiral Ureas

Hao Xu, Stephan J. Zuend, Matthew G. Woll, Ye Tao, Eric N. Jacobsen*

Cationic organic intermediates participate in a wide variety of useful synthetic transformations, but their high reactivity can render selecting in competing pathways difficult to control. Here, we describe a strategy for inducing enantioselectivity in reactions of proto-iminium ions, wherein a chiral catalyst interacts with the highly reactive intermediate through a network of noncovalent interactions. This interaction leads to an attenuation of the reactivity of the iminium ion and allows high enantioselectivity in cycloadditions with electron-rich alkenes (the Povarov reaction). A detailed experimental and computational analysis of this catalyst system has revealed the precise nature of the catalyst-substrate interactions and the likely basis for enantioinduction.

The proton (H+) is the simplest, and arguably the most versatile, catalyst for organic reactions, mediating an extraordinary range of biological and synthetic transformations (1). Although a proton cannot be rendered chiral, enantioselective Brønsted acid catalysis is attainable through the influence of the acid’s conjugate base and through medium effects. The former strategy, involving the use of chiral acids, has proven particularly useful, as demonstrated in the design and application of chiral phosphoric acids (2–4), N-triflyl phosphanides (5), aryl sulfonic acids (6), and Lewis acid–(7, 8) or thiourea-assisted Brønsted acids (9, 10). The use of medium effects has been less straightforward, and chiral solvents have been investigated in asymmetric catalysis with comparably limited success (11). The recent discovery of anion-binding pathways (12, 13) in reactions catalyzed by chiral, small-molecule, H-bond donor catalysts such as urea and thiourea derivatives (14) suggests an alternative strategy that combines elements of both approaches. In this scenario, a chiral catalyst might associate with a protonated substrate through the counteranion and induce enantioselectivity in nucleophilic addition reactions to the cationic electrophile through specific secondary interactions with the charged species.

This idea was explored in the context of the formal [4+2] cycloaddition of N-aryl imines and electron-rich olefins, also known as the Povarov reaction (15). This Brønsted acid–catalyzed reaction affords tetrahydroquinoline derivatives with the concomitant generation of up to three contiguous stereogenic centers, and enantioselective Lewis acid–or phosphoric acid–catalyzed variants have been identified recently (16–18). The acid-catalyzed Povarov reaction between benzylidene aniline 1a and 2,3-dihydropyran 3 was selected as a model reaction (Fig. 1A), and a broad range of chiral urea and thiourea derivatives that were developed and studied previously in our laboratory, as well as several different Brønsted acids, were evaluated as catalysts for this transformation (table S1) (19). With this approach, we found that the combination of the bifunctional sulfanilamide urea derivative 1a (20) and ortho-nitrobenzenesulfonic acid (NBSA) catalyzed the model reaction with high enantioselectivity (Fig. 1, B and C, entry 1). The importance of both the urea and sulfanamide groups in the catalyst became evident in structure-reactivity/enantioselectivity studies. Thiourea derivative 1b is an efficient catalyst, but it induced lower enantio- and diastereoselectivity (Fig. 1C, entry 2), whereas the diastereoisomeric (R,S,S)-sulfanilamide urea 1e promoted a much slower and poorly selective reaction (Fig. 1C, entry 3). In addition, reactions catalyzed by phosphinic amide urea 1d displayed a modest selectivity, and pivalamide urea 1e and amino urea 1f both induced low reactivity and selectivity (Fig. 1C, entries 4 to 6). These results suggest a cooperative role for the urea and sulfanamide groups of 1a in the rate- and enantioselectivity-determining steps of the catalytic reaction.

Under optimized conditions, the Povarov reaction that is catalyzed by 1a was found to be applicable to different nucleophiles and a wide variety of N-aryl imines (Fig. 2, A and B). The highest enantioselectivities were observed in reactions that were carried out under cryogenic conditions with a 2:1 ratio of 1a to NBSA, which was used to ensure complete suppression of the racemic pathway catalyzed by NBSA alone. Lactam-substituted tetrahydroquinoline derivatives 6exo were obtained in high enantio- and diastereoselectivities by reaction of benzaldimines 2 with vinyl lactam 5. Tricyclic hexahydro- pyrrolo-[3,2-c]quinoline derivatives 8exo were generated in an analogous manner by the cyclization of N-Cbz–protected 2,3-dihydropyrole 7 with 2.

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Fig. 1. (A) Model Povarov reaction cocatalyzed by o-nitrobenzenesulfonic acid and chiral ureas/thioureas. (B) Some of the chiral catalysts evaluated in optimization studies. (C) Results of catalyst structure-reactivity/enantioselectivity studies. dr, diastereomeric ratio; ee, enantiomeric excess.

Both dr and ee were determined by supercritical fluid chromatography analysis using commercially available chiral columns.

Fig. 2. (A and B) Asymmetric Povarov reactions catalyzed by 1a/NBSA with enamide 5 and enecarbamate 7 as the nucleophilic reacting partners. Molecular sieves (5 Å) serve to sequester water introduced with the hygroscopic NBSA reagent, thereby preventing competing imine hydrolysis pathways. See tables S2 and S3 for yields and selectivities obtained with each substrate. (C) Martinelline (11), a natural-product inhibitor of bradykinin B1 and B2 receptor antagonist (24). The enantioselective catalytic Povarov method provides an efficient enantioselective route to this natural product and its analogs (25), thereby solving a longstanding synthetic challenge.

The cooperative activity of an acid and a chiral organic molecule may represent a general strategy for asymmetric catalysis (9, 10), and we thus undertook a detailed experimental and computational study to elucidate the mechanism of catalysis in the Povarov reaction and the basis for the high levels of stereoselectivity induced by 1a. Similar enantioselectivities were achieved with a variety of sulfonic acids under homogeneous conditions, and we selected the 1a/HOTf cocatalyzed reaction between 2a and 3 as a model for mechanistic analysis (HOTf, triflic acid, HO3SCF3). The reaction between 2a (0.2 to 0.8 M) and 3 (0.4 to 1.6 M) promoted by catalytic quantities of HOTf (0.2 to 2.0 mM) and in toluene was monitored by reaction calorimetry and 1H nuclear magnetic resonance (NMR) spectroscopy (table S4). Kinetic analysis of reactions carried out at 28°C revealed a first-order dependence on [HOTf], and a zeroth-order dependence on imine concentration more rapidly in the Povarov reaction, but uniform high enantioselectivities were obtained despite these reactivity differences.

Povarov reactions between glyoxylate imines 9a or 9b with 2,3-dihydropyrrole 7 provide the endo products in high enantioselectivity. This represents a direct route to the core tetrathiopyrroloquinoline structure of a variety of important, biologically active compounds (21–23), including Martinelline (11, Fig. 2C), a naturally occurring nonpeptide natural product that has been identified as a bradykinin B1 and B2 receptor antagonist (24). The enantioselective catalytic Povarov method provides an efficient enantioselective route to this natural product and its analogs (25), thereby solving a longstanding synthetic challenge.

Although moderate diastereoselectivities favoring the exo diastereomer were obtained in this case (8exo/8endo = 1.4 to 4:2:1), this product was also generated in high diastereomeric excess (ee) (90 to 98% ee) and could be isolated in diastereomerically pure form in useful yields (45 to 73%). In general, imines derived from electron-deficient aldehydes—especially imines derived from glyoxylate esters—underwent reaction more rapidly in the Povarov reaction, but uniformly high enantioselectivities were obtained despite these reactivity differences. Povarov reactions between glyoxylate imines 9a or 9b with 2,3-dihydropyrrole 7 provide the endo products in high enantioselectivity. This represents a direct route to the core tetrathiopyrroloquinoline structure of a variety of important, biologically active compounds (21–23), including Martinelline (11, Fig. 2C), a naturally occurring nonpeptide natural product that has been identified as a bradykinin B1 and B2 receptor antagonist (24). The enantioselective catalytic Povarov method provides an efficient enantioselective route to this natural product and its analogs (25), thereby solving a longstanding synthetic challenge.

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The solubility of 2a·HOTf increases by a factor of 4 in the presence of achiral urea 12 through the formation of the 1:1 complex (Fig. 3A). 'H NMR chemical shifts of the formyl proton are sensitive probes of charge separation in iminium ions (26). We observed that the 1:1 complex of 2a·HOTf with achiral urea 12 exhibits a 0.14 parts per million (ppm) up-field shift of the 'H NMR resonance of the formyl proton of 2a·HOTf, consistent with increased charge separation. These observations can be attributed to a hydrogen-bonding interaction between 12 and the triflate anion of 2a·HOTf that leads to both solubilization and greater charge separation between the iminium ion and the triflate anion.

Markedly different effects are observed when 2a·HOTf is treated with solutions of bifunctional sulfinamidourea 1a, which increases the solubility of 2a·HOTf by more than one order of magnitude; however, dissolution is accompanied by a 0.92-ppm down-field shift of the 'H NMR resonance of the formyl proton of 2a·HOTf, which is consistent with a less–charge-separated
iminium ion. Computational analysis (27) of the ternary 2aHOTf1a complex suggests the basis for the observed effect. Four energetic minima of comparable stability were identified (Fig. 3B), with the 1a-triflate complex acting as a dual H-bond acceptor through the triflate and sulfimamide groups, and the iminium ion acting as a dual H-bond donor through the iminium nitrogen and formyl protons (28).

The additional stabilizing interactions involving the catalyst-sulfimamide group and iminium formyl proton group have a pronounced effect on the rate of the Povarov reaction. Kinetic analysis of the reaction between 2a and 3 that was cocatalyzed by HOTf and chiral sulfimamideurea 1a under homogeneous conditions revealed that 1a induces a substantial decrease in reaction rate (Fig. 3D). In contrast, the simple achiral urea 12 has a slight accelerating effect (Fig. 3F).

In the presence of 1a, the reaction rate can be expressed by a two-term rate law in which the pathway catalyzed by HOTf alone dominates at low [1a], and a HOTf/1a cocatalyzed pathway dominates at high [1a] (Eq. 2). A binding constant of \( K = 9000 \pm 2000 \text{ M}^{-1} \) for the interaction between 1a and 2aHOTf can be determined from the kinetic data (Fig. 3D and fig. S11). This relatively high value stands in sharp contrast to the much weaker binding between chiral H-bond donors and neutral substrates (29, 30), but is consistent with binding constants determined between tetraalkylammonium salts and ureas and thioureas (31, 32).

\[
\text{Rate} = \frac{d[4]}{dt} = k_{\text{rac}}[\text{imine-HOTf}][3] + k_{\text{asym}}[\text{imine-HOTf}1a][3] \tag{2}
\]

Here, \( k_{\text{asym}} \) is the second-order rate constant for the enantioselective cycloaddition between 2aHOTf1a and 3.

The observation of tight binding between proto-iminium-triflate 2aHOTf and sulfimamide urea 1a serves to explain how high enantioselectivity is obtained during the formation of 4a, even under conditions where the HOTf-catalyzed racemic pathway is several times more rapid than the enantioselective pathway (Fig. 3, C and E). The equilibrium constant for complex formation is sufficiently high that virtually no free iminium ion exists, and the reaction is thus channeled through the asymmetric pathway. The enantioselectivity in the formation of 4aexo is increased further to synthetically useful levels by carrying out the reaction at lower temperatures (that is, −55°C, 97% ee).

To glean insight into the basis for stereoinduction in the Povarov reaction by sulfimamideurea catalyst 1a, we carried out a full experimental and computational analysis of the mechanism of addition of dihydrofuran 3 to the protioiminium sulfate 2HOTf1a. In principle, any of several elementary steps in this process may represent the rate- and enantioselectivity-determining event (Fig. 4A, steps a to d). The absence of a primary kinetic isotope effect on the ortho hydrogens of the aniline group of 2 indicates that re aromatization (step d) is kinetically rapid (Fig. 4B). A positive Hammett correlation was obtained in the analysis of the effect of anilino substituents on the rate of reaction (\( \rho = +1.96 \pm 0.06, \text{fig. S17} \)). This result indicates that either the first step of a stepwise process (step a) or a concerted cycloaddition (step c) may be rate-limiting, but it is inconsistent with the cyclization step of a stepwise process (step b) representing the slow step. Definitive distinction between steps a and c is more challenging (33), but the kinetic isotope effect data suggest that partial rehybridization of the ortho-carbon of the aniline occurs in the rate-limiting step (34), and this is indicative of a concerted, albeit highly asynchronous [4+2] cycloaddition. This conclusion was supported by a computational analysis of the reaction leading to 4exo, which predicts that the lowest-energy pathway involves an endothermic cycloaddition and a comparatively rapid deprotonation/rearomatization step (fig. S19).

The catalyst-bound iminium ions depicted in Fig. 3B each have one \( \pi \) face exposed to solvent.

**Fig. 4.** (A) Possible mechanisms and rate-limiting steps in the asymmetric Povarov reaction. Z, an electron-donating or withdrawing substituent. (B) Kinetic isotope-effect experiments to distinguish between different possible rate-limiting steps. (C) Geometry and energy-minimized lowest-energy transition structure for cycloaddition calculated at the B3LYP/6-31G(d) level of density functional theory. Selected bond distances are shown in angstroms. Ar, 3,5-(CF3)2C6H3. (D) Alternate view of the structure in (C) highlighting the stabilizing \( \pi-\pi \) interaction between the aryl groups of the catalyst and the iminium ion undergoing cycloaddition. (E) Analogous view of the transition structure leading to the minor enantiomer of product. This transition structure lacks stabilizing \( \pi-\pi \) interactions and is disfavored relative to the structure in (D) by 1.3 kcal/mol in calculations using the B3LYP/6-31G(d) method, and by 3.6 to 3.9 kcal/mol using M05-2X/6-31+G(d,p) or MP2/6-31G(d) single-point calculations. See table S17 for further details.
and the other π face shielded by the catalyst, and are all expected to be energetically accessible under the reaction conditions. Computational analyses using either density functional theory or ab initio methods (Fig. 4, C to E) predict that the enantioselectivity-determining cycloaddition occurs preferentially with complex 1, leading to the experimentally observed (R)-enantiomer of product 4aexo. The lowest-energy cycloaddition transition structure displays iminium N–H···O sulfonamide and formyl C–H···O sulfonate hydrogen bonds (Fig. 4C), and is predicted to have ≥1.3 kcal/mol lower energy than alternatives arising from complexes II to IV, which is consistent with the experimental data. The basis for enantioselectivity may be ascribed to a stabilizing π–π interaction between the (CF3)2-C6H3N component of the catalyst and the cationic amine moiety of the substrate. This interaction is evident in transition structures leading to the major enantiomer of 4aexo (Fig. 4D), but it is absent in transition structures leading to the minor enantiomer (Fig. 4E).

Enantioselective catalysis by 1a of a strong Brønsted acid–catalyzed Povarov reaction thus involves tight binding to a highly reactive cationic intermediate through multiple, specific H-bonding interactions, and these noncovalent interactions are maintained in the subsequent stereo-determining cycloaddition event. One of the four energetically accessible ground-state complexes undergoes reaction with the nucleophile preferentially, illustrating the utility of bifunctional catalyst 1a to control precisely the outcome of this reaction through noncovalent interactions alone. Given the known ability of urea and thiourea derivatives to bind a wide range of anions, the strategy demonstrated here is applicable, in principle, to cationic intermediates with a variety of counterion structures.

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Supporting Online Material
www.sciencemag.org/cgi/content/full/327/5968/986/DC1 Materials and Methods
SOM Text
Figs. S1 to S19
Tables S1 to S17
References
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100-Million-Year Dynasty of Giant Planktivorous Bony Fishes in the Mesozoic Seas
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Large-bodied suspension feeders (planktivores), which include the most massive animals to have ever lived, are conspicuously absent from Mesozoic marine environments. The only clear representatives of this trophic guild in the Mesozoic have been an enigmatic and apparently short-lived Jurassic group of extinct pachycormid fishes. Here, we report several new examples of these giant bony fishes from Asia, Europe, and North America. These fossils provide the first detailed anatomical information on this poorly understood clade and extend its range from the lower Middle Jurassic to the end of the Cretaceous, showing that this group persisted for more than 100 million years. Modern large-bodied, planktivorous vertebrates diversified after the extinction of pachycormids at the Cretaceous–Paleogene boundary, which is consistent with an opportunistic refilling of vacated ecospaces.

The largest vertebrates—fossil or living—are marine suspension feeders. Modern clades adopting this ecological strategy diversified in the Paleogene (66 to 23 million years ago) (1–3) and include baleen whales and four independent lineages of cartilaginous fishes (sharks and rays) (4). In striking contrast to the array of giant suspension feeders found in Cenozoic marine environments, this guild has appeared to be absent during most of the Mesozoic, an interval that is marked by the ecological ascendance of modern planktivore groups (5, 6). Possible candidates have been proposed (7, 8), but the clearest examples of large-bodied planktivores in the Mesozoic seas have been a handful of bony fishes confined to a brief 20-million-year window during the Jurassic (Callovian-Tithonian, 165 to 145 million years ago) and known almost exclusively from European deposits (9–12). These enigmatic taxa belong to the extinct family Pachycormidae (the dagger symbol indicates extinct groups), a stem-teleost clade that is otherwise composed of pelagic predators convergent upon tunas and billfishes (10). Giant pachycormids include the largest bony fish of all time (the ~9 m T. Leedischthys) (9, 13), but their short stratigraphic range had implied that they were an inconsequential component of

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Editor's Summary

Acid Assistance

Protons are quite versatile catalysts of organic reactions, but because they are achiral, they cannot induce stereoselectivity on their own. One productive way around this problem has been to use chiral conjugate bases and perform reactions in media where the bases remain tightly attracted to protonated substrates. Xu et al. (p. 986; see the Perspective by Schreiner) thoroughly explored the mechanism of an alternative approach, in which an achiral acid was used in conjunction with a second, chiral molecule (a urea derivative) for catalysis. High selectivity was attained with this method in the coupling of aryl imines with olefins. Extensive kinetic and computational studies showed that the acid and its chiral partner acted cooperatively in binding the substrates, optimizing the tradeoff between speed and selectivity.