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Communication

Dual-Hydrogen-Bond Donor and Brønsted Acid Cocatalysis Enables Highly Enantioselective Protio-Semipinacol Rearrangement Reactions

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ABSTRACT: A catalytic protio-semipinacol ring-expansion reaction has been developed for the highly enantioselective conversion of tertiary vinylic cyclopropyl alcohols into cyclobutanone products bearing α-quaternary stereogenic centers. The method relies on the cocatalytic effect of a chiral dual-hydrogen-bond donor (HBD) with hydrogen chloride. Experimental evidence is provided for a stepwise mechanism where protonation of the alkene generates a short-lived, high-energy carbocation, which is followed by C−C bond migration to deliver the enantioenriched product. This research applies strong acid/chiral HBD cocatalysis to weakly basic olefinic substrates and lays the foundation for further investigations of enantioselective reactions involving high-energy cationic intermediates.

Brønsted acid catalysis holds unique importance as a reactivity principle in both chemical and biological synthesis. In recent years, significant effort has been focused on controlling absolute stereochemical outcomes in acid-catalyzed reactions, with a primary approach involving the design and implementation of small-molecule chiral Brønsted acids.[1,2] A broad array of highly effective chiral catalysts of varying acidity have been identified, enabling the development of numerous important organic transformations with high enantioselectivity.[3] In this regard, particular success has been achieved in reactions engaging substrates bearing basic functional groups such as imines.[2,4] Extension of these systems to less basic substrate classes remains challenging, though noteworthy advances have been achieved recently for enantioselective reactions involving activation of carbonyl groups[5] or simple olefins.[6]

A complementary approach to asymmetric catalysis in reactions requiring substrate activation with strong Brønsted acids involves engaging neutral, chiral anion-binding catalysts capable of associating with the conjugate bases of achiral mineral acids. This strategy offers the potential to access chiral variants of Brønsted acids possessing an essentially unlimited range of acidities. To this end, chiral dual-hydrogen-bond donors (HBDs) have been utilized to impart enantioselectivity in transformations of imines and carbonyl compounds promoted by sulfonic acids or HCl (Figure 1A).[7,8] We sought to determine whether this cocatalysis concept could be extended to reaction of olefins that upon protonation generate carbocationic intermediates lacking heteroatom stabilization, focusing on the specific case of protio-semipinacol 1,2-ring-expansion processes (Figure 1B).

Traditionally, enantioselective semipinacol rearrangement reactions have relied on the use of electrophilic atom-transfer reagents to generate bridged cationic intermediates as the first

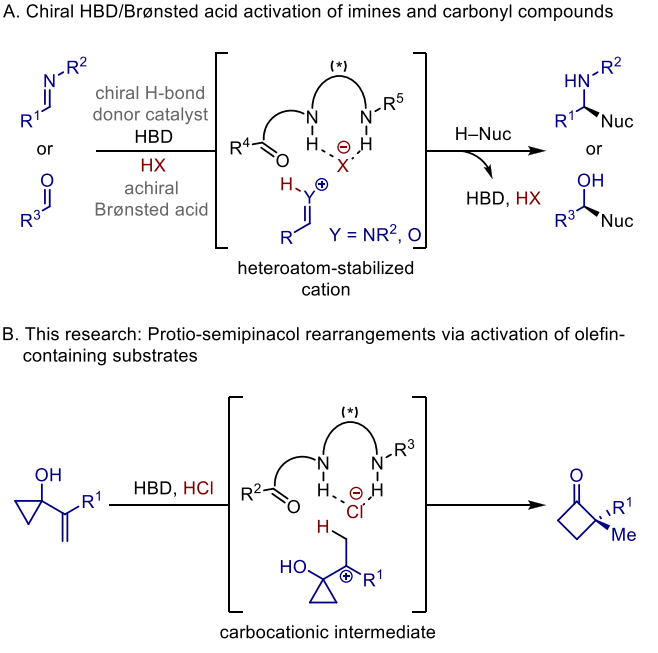

Figure 1. Chiral hydrogen-bond donor (HBD)/achiral Brønsted acid cocatalysis.

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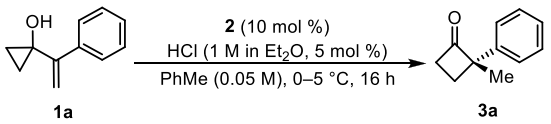
step in the 1,2-ring expansion process.[9,10] The few examples of enantioselective protio-semipinacol rearrangement methods that have been reported to date rely on substrates that undergo protonation to generate heteroatom-stabilized cationic intermediates.[11,12] This substrate limitation likely results from the challenges associated with generating and controlling the stereoselectivity of high-energy intermediates.[13] Given that chiral HBD catalysts have been demonstrated to induce high levels of enantiocontrol through networks of attractive noncovalent interactions in reactions proceeding through ionic mechanisms,[14] we considered whether the cooperative effect of an HBD with HCl may generate a chiral environment amenable to an enantioselective protio-semipinacol ring-expansion process that does not require heteroatom stabilization of the cationic intermediate. Here we describe the successful application of chiral HBD/HCl cocatalysis to the enantioselective isomerization of vinylic tertiary cyclopropyl alcohol substrates in semipinacol 1,2-ring-expansion reactions. The resulting method provides a versatile platform for accessing highly enantioenriched cyclobutanone products bearing α-quaternary centers.

Our studies on the cocatalytic effect of HCl and chiral HBDs in protio-semipinacol rearrangements were initiated using phenyl-substituted vinylic cyclopropyl alcohol **1a** as a model substrate. Drawing on prior work on the activation of aldehydes toward Prins cyclization reactions,[8] we found that thiourea derivative **2a** (10 mol %) and an ethereal solution of hydrochloric acid (5 mol %) in toluene promoted the isomerization of **1a** to the ring-expanded cyclobutanone **3a** in 97% yield with 83% ee (Table 1, entry 1). Extensive variation of the structure and nature of the chiral dual HBD cocatalyst revealed the best results for compounds with the general structure in **2** but a surprisingly flat enantioselectivity

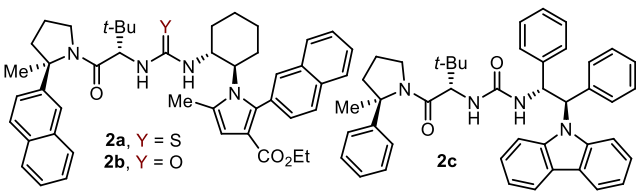
Table 1. Optimization of Reaction Conditions for the Protio-Semipinacol Rearrangement Reaction[a]



1a **3a**

entry	HBD[d]	deviation in condition	RSM (%)[b]	yield (%)[b]	ee (%)[c]
1	**2a**	none	n.d.	97	83
2	**2b**	none	19	77	84
3	**2c**	none	n.d.	88	92
4	**2c**	Et_2O in place of PhMe	90	n.d.	–
5	**2c**	22 °C instead of 0–5 °C	n.d.	88	90
6	**2c**	0.1 M in **1a**	n.d.	85	92
7	**2c**	10 mol % HCl	n.d.	87	92
8	**2c**	20 mol % HCl	n.d.	82	89

[a]Reactions were performed using 0.05 mmol of **1a** in toluene at 0–5 °C with 10 mol % **2** and 5 mol % HCl solution in Et_2O. [b]Determined by crude ^1H NMR analysis with mesitylene as an internal standard (RSM = remaining starting material). [c]Determined by GC analysis using a chiral stationary phase. [d]HBD structures:



landscape within that family of catalysts (see SI sections 2.3 and 13). For example, replacement of the thiourea moiety with a urea as in **2b** had little effect on the enantioselectivity (entry 2); however, the urea catalyst was found to be more stable toward the strongly acidic reaction conditions, avoiding Edman degradation pathways.[15] The carbazole-containing urea **2c** imparted the highest enantioselectivities of all catalysts tested, affording the ring-expanded cyclobutanone product in 88% yield with 92% ee (entry 3). Aromatic solvents such as toluene were found to be essential for good reactivity (entry 4), while the reaction performance was relatively insensitive to changes in temperature or concentration (entries 5 and 6). Optimal levels of enantioselectivity could be attained with different HCl/HBD ratios as long as [HCl] does not exceed that of the chiral catalyst (entries 7 and 8).[16]

The reaction conditions identified as optimal for the highly enantioselective catalytic rearrangement of **1a** were applied to a series of other styrenylcyclopropyl alcohol substates (Figure 2). Variations of the aryl component were generally well-tolerated (**3c**–**3h**), although products bearing strongly electron-donating (**3b**) or -withdrawing (**3m**) substituents were generated with lower enantioselectivities. Extension to nonconjugated alkyl-substituted vinylic cyclopropyl alcohol derivatives also proved possible, with excellent levels of enantiocontrol achieved with substrates bearing cyclohexyl, adamantyl, neopentyl, and *tert*-butyl substituents (**3i**–**3l**). However, limitations were encountered, with the conformationally flexible phenethyl derivative **3n** generated in high yield but modest enantioselectivity (53% ee). More highly substituted alkenyl derivatives (e.g., **1o**) and vinylic cyclobutanols (e.g., **1p**) proved to be unreactive under the cocatalytic conditions tested.

With quite general access to cyclobutanone products bearing α-quaternary stereocenters in hand, we sought to expand the utility of the products in a series of synthetic elaborations (Figure 3).[17] The model cyclobutanone **3a** was found to undergo completely stereospecific ring expansion under standard Baeyer–Villiger oxidation conditions to provide γ-lactone **4a** in excellent yield. Whereas ketone reduction with $NaBH_4$ proceeded with high relative stereoselectivity to afford cyclobutanol **5a** in a 12.8:1 ratio of diastereomers, other nucleophilic addition reactions proved to be less diastereoselective. For instance, the addition of vinyl Grignard to **3a** afforded a 3.4:1 ratio of separable diastereomers (**6a** and **6b**), and reductive amination provided benzylamine derivatives **7** as a 3.8:1 mixture. In every case, the major diastereomer was found to correspond to the product in which the nucleophilic addition occurred to the same face as the phenyl group.[18] This seemingly counterintuitive sense of relative stereoinduction is readily rationalized based on the conformational preferences of **3a**, which place the methyl substituent in a pseudoaxial position and minimize the steric effects of the phenyl group (see SI section 11.5 for computed conformers).

As a synthetic method, this asymmetric proto-semipinacol protocol affords a variety of readily elaborated cyclobutanones bearing α-quaternary stereocenters from vinylic cyclopropanol substrates. From a fundamental standpoint, the high levels of enantioselectivity achieved in these reactions raise the interesting question of how such high levels of chiral catalyst control ($\Delta\Delta G^{\ddagger}$ up to 2.1 kcal/mol at 4 °C) can be achieved in 1,2-ring expansion processes anticipated to have barriers below 6 kcal/mol.[19] To gain insight into the mechanism of catalysis and stereoinduction in the HBD–HCl cocatalytic reaction, we

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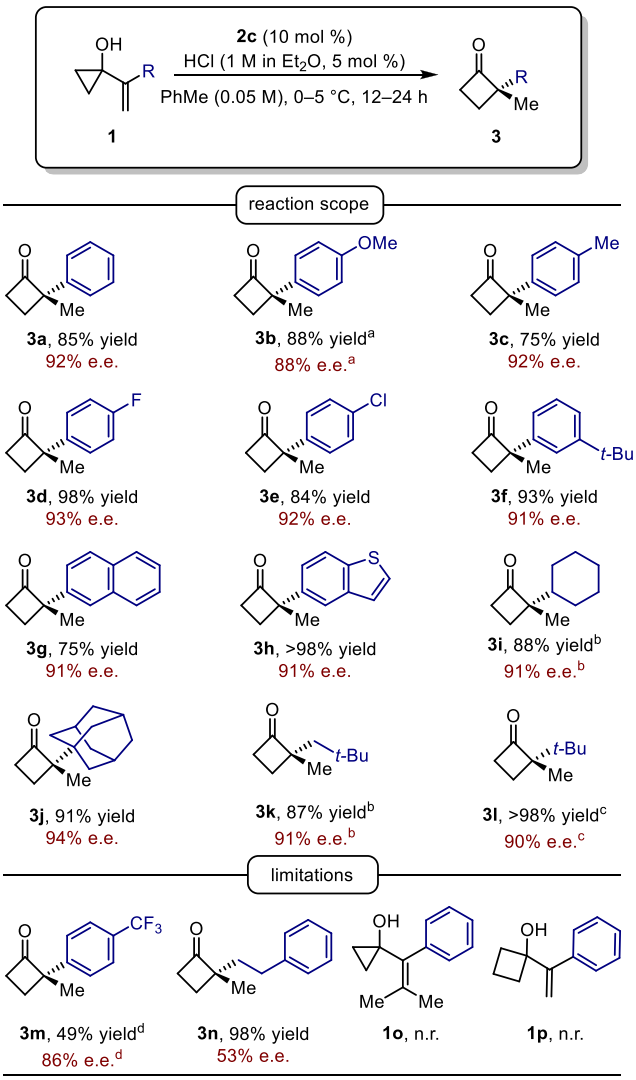

Figure 2. Protio-semipinacol ring-expansion reaction scope. Reactions were performed on a 0.25 mmol scale. Isolated yields are reported. [a]The reaction was run with 20 mol % **2c**. [b]Reactions were initiated at −78 °C and transferred to a −50 °C bath. [c]Reported as an average of three runs on a 0.025 mmol scale in toluene-d_8. The yield was determined by ^{1}H NMR analysis with mesitylene as an internal standard. [d]40% recovered **1m**; the reaction does not proceed to full conversion even with extended reaction times. n.r. = no reaction.

undertook a mechanistic investigation using a series of experimental and computational techniques.

In principle, the protio-semipinacol rearrangement reaction could proceed through either a concerted or stepwise reaction mechanism (Figure 4A). In a concerted mechanism, alkene protonation would be accompanied by C−C bond migration in a single step, whereas the distinguishing feature of a stepwise mechanism would be the intermediacy of a discrete carbocation formed via initial protonation of the alkene. Within the stepwise manifold, either the protonation or ring-expansion step could be rate- or enantiodetermining.

As the distinguishing feature between the concerted and stepwise mechanisms is the formation of a discrete carbocation, we conducted a Hammett study to assess the degree of charge development in the product-committing step.[20] The log of relative reaction rates for styrenylcyclopropyl alcohol substrates bearing different *para* substituents correlated

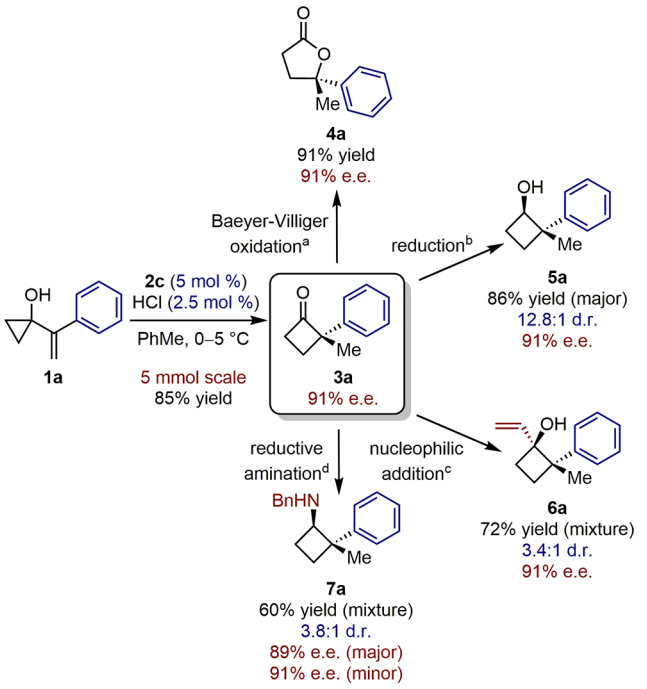

Figure 3. Elaborations of the cyclobutanone products. [a]**3a** (0.25 mmol), 77% *m*-CPBA (2.0 equiv), $NaHCO_3$ (2.0 equiv), CH_2Cl_2 (0.05 M), 0−5 °C. [b]**3a** (0.25 mmol), $NaBH_4$ (2.0 equiv), MeOH (0.05 M), −78 °C. [c]**3a** (0.25 mmol), $CeCl_3$ (1.6 equiv), vinylmagnesium bromide (0.92 M in THF, 2.5 equiv), THF (0.05 M), −78 °C. [d]**3a** (0.25 mmol), $Ti(OEt)_4$ (2.2 equiv), benzylamine (1.1 equiv), THF (0.05 M), 80 °C; then $NaBH_3CN$ (2.0 equiv), −78 °C.

extremely well with the Hammett σ parameter (R^2 = 0.997), affording a ρ value of −2.67 (Figure 4B). The magnitude of the ρ value is fully consistent with prior reports describing the generation of discrete benzyl cyclopropylcarbinyl carbocations.[21] The better correlation with the σ parameter instead of σ^+ (Figures S2 and S3) suggests that the aryl group is not fully conjugated with the alkene, a possibility reinforced by the comparable reaction rates observed with aryl- and alkyl-substituted vinylic cyclopropanols. While this correlation is most consistent with a stepwise process where protonation of the alkene is rate-determining, a highly asynchronous concerted mechanism could not be ruled out entirely on the basis of these data alone.

Further support for the stepwise nature of the rearrangement reaction was gleaned from heavy-atom kinetic isotope effect (KIE) studies. We reasoned that if protonation of the alkene is the rate-determining step, the migrating carbon would be minimally affected, and no primary KIE would be expected. Alternatively, if ring expansion is part of the rate-determining span (such as in a concerted asynchronous process or a stepwise process with rate-limiting ring expansion), a diagnostic primary KIE (computed to be 1.022; see SI section 11.3) would be predicted on the migrating carbon (Figure 4C). The $^{12}C/^{13}C$ isotope effects were determined using natural-abundance **1a** and the recently developed polarization-transfer methodology to enhance the ^{13}C signals.[22] We observed negligible isotope effects on the cyclobutanone carbons that arise from the cyclopropane but a distinctive isotope effect on the product methyl group (Figure 4C), closely matching those predicted for a reaction pathway where protonation is rate-determining.

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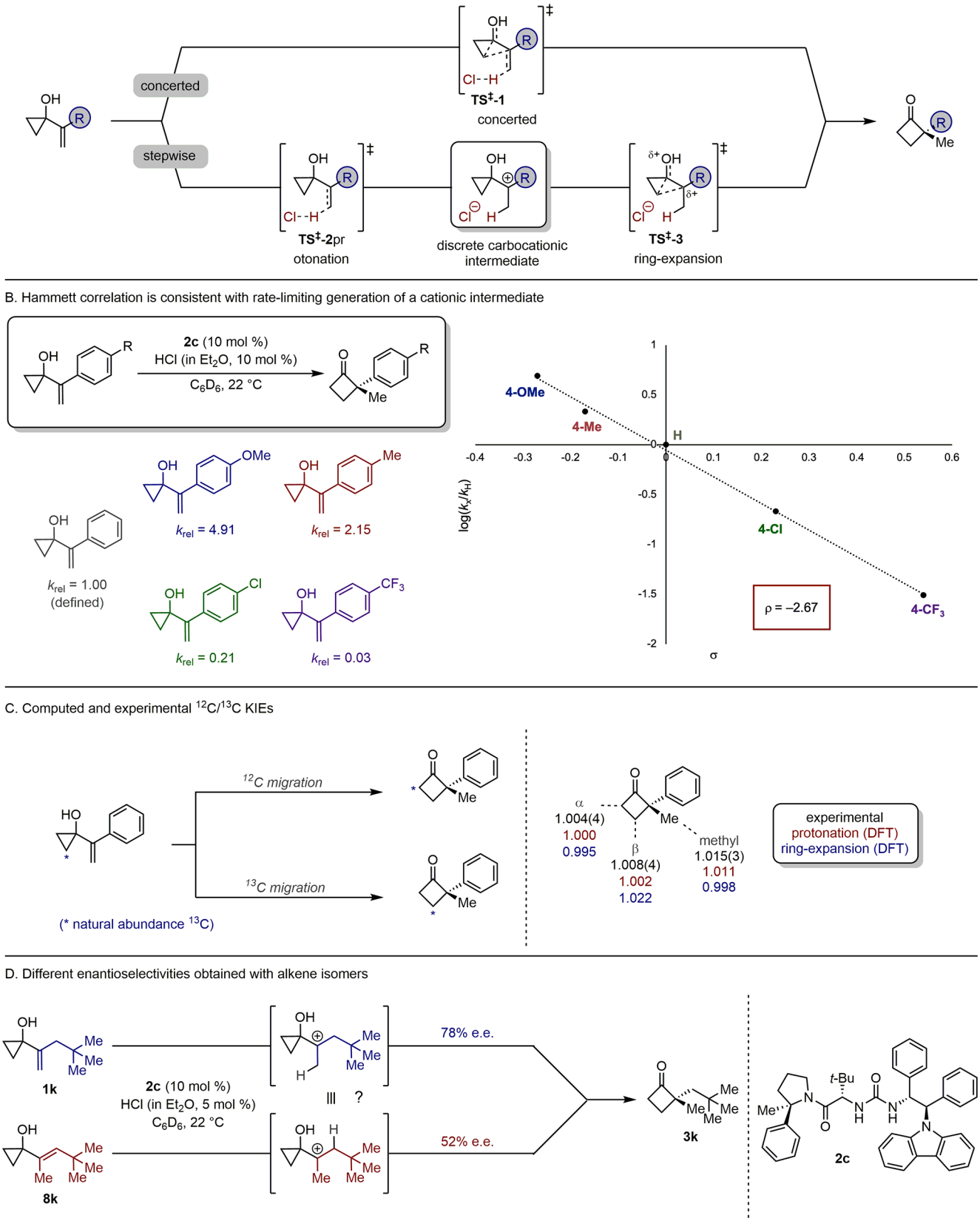

Figure 4. (A) Plausible mechanistic pathways for the protio-semipinacol rearrangement reaction. (B) Hammett correlation to evaluate the degree of charge buildup in the rate-determining step. (C) Experimental (black) and computed (red or blue) $^{12}C/^{13}C$ KIEs determined at the α-, β-, and methyl carbons of cyclobutanone **3a**. (D) Reaction of isomeric alkenyl cyclopropanols.

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While the experimental data outlined above provide compelling evidence that the semipinacol rearrangement reaction proceeds through a stepwise pathway with rate-limiting protonation, in principle either or both of the steps in that mechanism might be enantiodetermining. If skeletal rearrangement from a discrete cationic intermediate (**TS**‡-**3** in Figure 4A) is fully enantiodetermining, then identical enantioselectivity should be obtained for the different alkene isomers that undergo the protio-semipinacol rearrangement via the same carbocation. To test this possibility, the isomeric alkenyl cyclopropyl alcohols **1k** and **8k** were subjected separately to cocatalytic reaction conditions (C_6D_6, 22 °C). The cyclobutanone product **3k** was obtained with substantially different ee values (Figure 4D), suggesting that the carbocationic intermediate remains catalyst-bound and does not fully equilibrate to render these two intermediates identical. While this result precludes ring expansion from a fully equilibrated, discrete carbocation as the selectivity-determining step, either protonation or ring expansion from a catalyst-bound intermediate could still be enantiodetermining.

These investigations expand the concept of cocatalysis between strong achiral Brønsted acids and chiral HBDs beyond activation of heteroatom-containing functional groups. The disclosed protio-semipinacol rearrangement reaction provides access to highly enantioenriched cyclobutanones bearing α-quaternary stereocenters. Through a series of physical-organic experiments (linear free energy relationship studies, $^{12}C/^{13}C$ KIEs), we elucidate a stepwise reaction pathway where protonation of the alkene in the cyclopropyl alcohol substrate is rate-determining but in principle either or both steps could be enantiodetermining. The intriguing question of how such high levels of enantioinduction can be achieved in reactions involving short-lived reactive intermediates is the topic of continuing studies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c02960.

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

Accession Codes

CCDC 2264585 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews, see: (a) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. Complete Field Guide to Asymmetric BINOL-Phosphate Derived Brønsted Acid and Metal Catalysis: History and Classification by Mode of Activation; Brønsted Acidity, Hydrogen Bonding, Ion Pairing, and Metal Phosphates. *Chem. Rev.* **2014**, *114*, 9047−9153. (b) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. Addition and Correction to Complete Field Guide to Asymmetric BINOL-Phosphate Derived Brønsted Acid and Metal Catalysis: History and Classification by Mode of Activation; Brønsted Acidity, Hydrogen Bonding, Ion Pairing, and Metal Phosphates. *Chem. Rev.* **2017**, *117*, 10608−10620.

(2) For seminal reports, see: (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. Enantioselective Mannich-Type Reaction Catalyzed by a Chiral Brønsted Acid. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566−1568. (b) Uraguchi, D.; Terada, M. Chiral Brønsted Acid-Catalyzed Direct Mannich Reactions via Electrophilic Activation. *J. Am. Chem. Soc.* **2004**, *126*, 5356−5357.

(3) For reviews, see: (a) Akiyama, T.; Mori, K. Stronger Brønsted Acids: Recent Progress. *Chem. Rev.* **2015**, *115*, 9277−9306. (b) Schreyer, L.; Properzi, R.; List, B. IDPi Catalysis. *Angew. Chem., Int. Ed.* **2019**, *58*, 12761−12777.

(4) For selected recent advances, see: (a) Rueping, M.; Antonchick, A. P. Catalytic Asymmetric Aminoallylation of Aldehydes: A Catalytic Enantioselective Aza-Cope Rearrangement. *Angew. Chem., Int. Ed.* **2008**, *47*, 10090−10093. (b) Varlet, T.; Matišić, M.; Van Elslande, E.; Neuville, L.; Gandon, V.; Masson, G. Enantioselective and

Diastereodivergent Synthesis of Spiroindolenines via Chiral Phosphoric Acid-Catalyzed Cycloaddition. *J. Am. Chem. Soc.* **2021**, *143*, 11611−11619. (c) Huang, D.; Li, X.; Xu, F.; Li, L.; Lin, X. Highly Enantioselective Synthesis of Dihydroquinazolinones Catalyzed by SPINOL-Phosphoric Acids. *ACS Catal.* **2013**, *3*, 2244−2247.

(5) For selected examples, see: (a) Zhou, H.; Zhou, Y.; Bae, H. Y.; Leutzsch, M.; Li, Y.; De, C. K.; Cheng, G.-J.; List, B. Organocatalytic stereoselective cyanosilylation of small ketones. *Nature* **2022**, *605*, 84−89. (b) Díaz-Oviedo, C. D.; Maji, R.; List, B. The Catalytic Asymmetric Intermolecular Prins Reaction. *J. Am. Chem. Soc.* **2021**, *143*, 20598−20604. (c) Kikuchi, J.; Aramaki, H.; Okamoto, H.; Terada, M. F_{10}BINOL-derived chiral phosphoric acid-catalyzed enantioselective carbonyl-ene reaction: theoretical elucidation of stereochemical outcomes. *Chem. Sci.* **2019**, *10*, 1426−1433. (d) Rueping, M.; Theissmann, T.; Kuenkel, A.; Koenigs, R. M. Highly Enantioselective Organocatalytic Carbonyl-Ene Reaction with Strongly Acidic, Chiral Brønsted Acids as Efficient Catalysts. *Angew. Chem., Int. Ed.* **2008**, *47*, 6798−6801.

(6) For selected examples, see: (a) Tsuji, N.; Kennemur, J. L.; Buyck, T.; Lee, S.; Prévost, S.; Kaib, P. S. J.; Bykov, D.; Farès, C.; List, B. Activation of olefins via asymmetric Brønsted acid catalysis. *Science* **2018**, *359*, 1501−1505. (b) Zhang, P.; Tsuji, N.; Ouyang, J.; List, B. Strong and Confined Acids Catalyze Asymmetric Intramolecular Hydroarylation of Unactivated Olefins with Indoles. *J. Am. Chem. Soc.* **2021**, *143*, 675−680.

(7) (a) Mita, T.; Jacobsen, E. N. Bifunctional Asymmetric Catalysis with Hydrogen Chloride: Enantioselective Ring Opening of Aziridines Catalyzed by a Phosphinothiourea. *Synlett* **2009**, *2009*, 1680−1684. (b) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. Asymmetric Cooperative Catalysis of Strong Brønsted Acid-Promoted Reactions Using Chiral Ureas. *Science* **2010**, *327*, 986−990.

(8) (a) Kutateladze, D. A.; Jacobsen, E. N. Cooperative Hydrogen-Bond-Donor Catalysis with Hydrogen Chloride Enables Highly Enantioselective Prins Cyclization Reactions. *J. Am. Chem. Soc.* **2021**, *143*, 20077−20083. (b) Kutateladze, D. A.; Wagen, C. C.; Jacobsen, E. N. Chloride-Mediated Alkene Activation Drives Enantioselective Thiourea and Hydrogen Chloride Co-Catalyzed Prins Cyclizations. *J. Am. Chem. Soc.* **2022**, *144*, 15812−15824.

(9) For reviews, see: (a) Wang, B.; Tu, Y. Q. Stereoselective Construction of Quaternary Carbon Stereocenters via a Semipinacol Rearrangement Strategy. *Acc. Chem. Res.* **2011**, *44*, 1207−1222. (b) Wang, S.-H.; Li, B.-S.; Tu, Y.-Q. Catalytic Asymmetric Semipinacol Rearrangements. *Chem. Commun.* **2014**, *50*, 2393−2408. (c) Zhang, X.-M.; Li, B.-S.; Wang, S.-H.; Zhang, K.; Zhang, F.-M.; Tu, Y.-Q. Recent Development and Applications of Semipinacol Rearrangement Reactions. *Chem. Sci.* **2021**, *12*, 9262−9274.

(10) For examples of asymmetric semipinacol rearrangements of vinylic cyclopropanols, see: (a) Romanov-Michailidis, F.; Guénée, L.; Alexakis, A. Enantioselective Organocatalytic Fluorination-Induced Wagner−Meerwien Rearrangement. *Angew. Chem., Int. Ed.* **2013**, *52*, 9266−9270. (b) Romanov-Michailidis, F.; Guénée, L.; Alexakis, A. Enantioselective Organocatalytic Iodination-Initiated Wagner−Meerwein Rearrangement. *Org. Lett.* **2013**, *15*, 5890−5893. (c) Romanov-Michailidis, F.; Pupier, M.; Guénée, L.; Alexakis, A. Enantioselective Halogenative Semi-Pinacol Rearrangement: A Stereodivergent Reaction on a Racemic Mixture. *Chem. Commun.* **2014**, *50*, 13461−13464. (d) Romanov-Michailidis, F.; Romanova-Michaelides, M.; Pupier, M.; Alexakis, A. Enantioselective Halogenative Semi-Pinacol Rearrangement: Extension of Substrate Scope and Mechanistic Investigations. *Chem. - Eur. J.* **2015**, *21*, 5561−5583. (e) Xie, Y.-Y.; Chen, Z.-M.; Luo, H.-Y.; Shao, H.; Tu, Y.-Q.; Bao, X.; Cao, R.-F.; Zhang, S.-Y.; Tian, J.-M. Lewis Base/Brønsted Acid Co-catalyzed Enantioselective Sulfenylation/Semipinacol Rearrangement of Di- and Trisubstituted Allylic Alcohols. *Angew. Chem., Int. Ed.* **2019**, *58*, 12491−12496.

(11) (a) Zhang, Q.-W.; Fan, C.-A.; Zhang, H.-J.; Tu, Y.-Q.; Zhao, Y.-M.; Gu, P.; Chen, Z.-M. Brønsted Acid Catalyzed Enantioselective Semipinacol Rearrangement for the Synthesis of Chiral Spiroethers. *Angew. Chem., Int. Ed.* **2009**, *48*, 8572−8574. (b) Zhang, E.; Fan, C.-A.; Tu, Y.-Q.; Zhang, F.-M.; Song, Y. L. Organocatalytic Asymmetric Vinylogous α-Ketol Rearrangement: Enantioselective Construction of Chiral All-Carbon-Quaternary Stereocenters in Spirocyclic Diketones via Semipinacol-Type 1,2-Carbon Migration. *J. Am. Chem. Soc.* **2009**, *131*, 14626−14627. (c) Liang, T.; Zhang, Z.; Antilla, J. C. Chiral Brønsted Acid Catalyzed Pinacol Rearrangement. *Angew. Chem., Int. Ed.* **2010**, *49*, 9734−9736. (d) Schneider, A.; Ruppert, J.; Lystbæk, T. B.; Bastian, S.; Hauer, B. Expanding the Cation Cage: Squalene-Hopene Cyclase-Mediated Enantioselective Semipinacol Rearrangement. *ACS Catal.* **2023**, *13*, 1946−1951.

(12) For a stereospecific example of a protio-semipinacol ring-expansion reaction, see: Poteat, C. M.; Lindsay, V. N. G. Stereospecific Synthesis of Enantioenriched Alkylidenecyclobutanones via Formal Vinylidene Insertion into Cyclopropanone Equivalents. *Org. Lett.* **2021**, *23*, 6482−6487.

(13) (a) Naredla, R. R.; Klumpp, D. A. Contemporary Carbocation Chemistry: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 6905−6948. (b) Nistanaki, S. K.; Williams, C. G.; Wigman, B.; Wong, J. J.; Haas, B. C.; Popov, S.; Werth, J.; Sigman, M. S.; Houk, K. N.; Nelson, H. M. Catalytic Asymmetric C−H Insertion Reactions of Vinyl Carbocations. *Science* **2022**, *378*, 1085−1091.

(14) (a) Brak, K.; Jacobsen, E. N. Asymmetric Ion-Pairing Catalysis. *Angew. Chem., Int. Ed.* **2013**, *52*, 534−561. (b) Knowles, R. R.; Jacobsen, E. N. Attractive Noncovalent Interactions in Asymmetric Catalysis: Links between Enzymes and Small Molecule Catalysts. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 20678−20685.

(15) Edman, P. Method for Determination of the Amino Acid Sequence in Peptides. *Acta Chem. Scand.* **1950**, *4*, 283−293.

(16) While small effects on reaction selectivity were observed with increased HCl loading and reaction concentration with the model substrate, the standard conditions were found to afford measurably better results with other substrates (see Table S3 for further details).

(17) For synthetic applications of cyclobutane derivatives, see: (a) Lee-Ruff, E.; Mladenova, G. Enantiomerically Pure Cyclobutane Derivatives and Their Use in Organic Synthesis. *Chem. Rev.* **2003**, *103*, 1449−1484. (b) Namyslo, J. C.; Kaufmann, D. E. The Application of Cyclobutane Derivatives in Organic Synthesis. *Chem. Rev.* **2003**, *103*, 1485−1538.

(18) The relative configuration of products **5**−**7** was assigned based on diagnostic NOE cross-peaks and supported by computational analysis (see SI section 6.5).

(19) For references discussing barriers to cationic rearrangements, see: (a) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books: Sausalito, CA, 2006; p 657. (b) Olah, G. A.; Reddy, V. P.; Prakash, G. K. S. Long-Lived Cyclopropylcarbinyl Cations. *Chem. Rev.* **1992**, *92*, 69−95. (c) Ammal, S. C.; Yamataka, H.; Aida, M.; Dupuis, M. Dynamics-Driven Reaction Pathway in an Intramolecular Rearrangement. *Science* **2003**, *299*, 1555−1557. (d) Weitman, M.; Major, D. T. Challenges Posed to Bornyl Diphosphate Synthase: Diverging Reaction Mechanisms in Monoterpenes. *J. Am. Chem. Soc.* **2010**, *132*, 6349−6360. (e) Tantillo, D. J. The carbocation continuum in terpene biosynthesis−where are the secondary cations? *Chem. Soc. Rev.* **2010**, *39*, 2847−2854. (f) Major, D. T.; Weitman, M. Electrostatically Guided Dynamics−The Root of Fidelity in a Promiscuous Terpene Synthase? *J. Am. Chem. Soc.* **2012**, *134*, 19454−19462. (g) Ghigo, G.; Maranzana, A.; Tonachini, G. *Memory Effects* in Carbocation Rearrangements: Structural and Dynamic Study of the Norborn-2-en-7-ylmethyl-X Solvolysis Case. *J. Org. Chem.* **2013**, *78*, 9041−9050. (h) Castiñeira Reis, M.; López, C. S.; Nieto Faza, O.; Tantillo, D. J. Pushing the limits of concertedness. A waltz of wandering carbocations. *Chem. Sci.* **2019**, *10*, 2159−2170.

(20) Hammett, L. P. The Effect of Structure upon the Reactions of Organic Compounds. Benzene Derivatives. *J. Am. Chem. Soc.* **1937**, *59*, 96−103.

(21) Kirmse, W.; Krzossa, B.; Steenken, S. Laser Flash Photolysis Study of Arylcyclopropylcarbenium Ions: Cation Stabilizing Abilities of Cyclopropyl and Phenyl Groups. *J. Am. Chem. Soc.* **1996**, *118*, 7473−7477.

https://doi.org/10.1021/jacs.3c02960
J. Am. Chem. Soc. 2023, 145, 15036−15042

(22) Kwan, E. E.; Park, Y.; Besser, H. A.; Anderson, T. L.; Jacobsen, E. N. Sensitive and Accurate ^{13}C Kinetic Isotope Effect Measurements Enabled by Polarization Transfer. *J. Am. Chem. Soc.* **2017**, *139*, 43−46.

https://doi.org/10.1021/jacs.3c02960
J. Am. Chem. Soc. 2023, 145, 15036−15042