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Communication

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Hydrogen Bonding Phase-Transfer Catalysis with Ionic Reactants: Enantioselective Synthesis of γ-Fluoroamines

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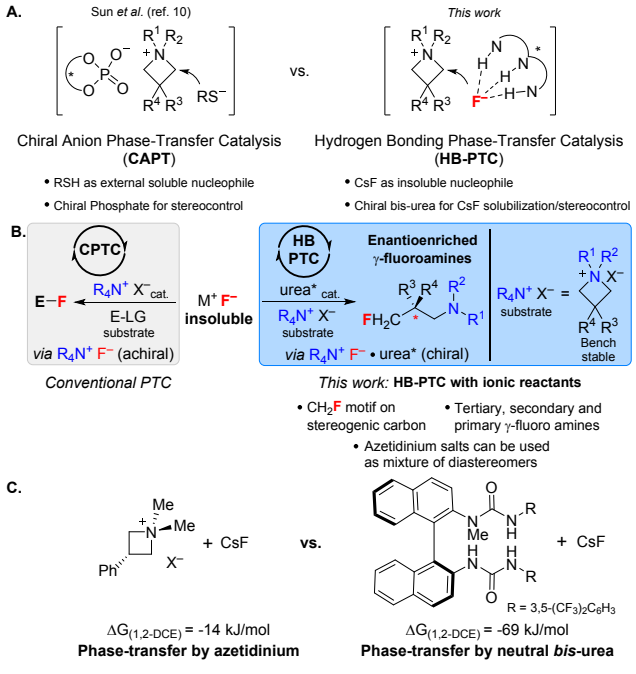
Supporting Information Placeholder

ABSTRACT: Ammonium salts are used as phase-transfer catalysts for fluorination with alkali metal fluoride. We now demonstrate that these organic salts, specifically azetidinium triflates, are suitable substrates for enantioselective ring opening with CsF and a chiral *bis*-urea catalyst. This process that highlights the ability of hydrogen bonding phase-transfer catalysts to couple two ionic reactants, affords enantioenriched γ-fluoroamines in high yields. Mechanistic studies underline the role of the catalyst for phase-transfer, and computed transition state structures account for the enantioconvergence observed for mixtures of achiral azetidinium diastereomers. The *N*-substituents in the electrophile influence reactivity, but the configuration at nitrogen is unimportant for enantioselectivity.

Asymmetric phase-transfer catalysis (PTC) is one of the most practical methods for enantioselective synthesis.[1] For many years, PTC approaches to asymmetric fluorinations have used F_2-derived electrophilic reagents and cationic or anionic chiral species for effective phase-transfer.[2] Inspired by nature's fluorinase,[3] we reported a complementary hydrogen bonding phase-transfer catalysis (HB-PTC) manifold, which employed alkali metal fluoride for asymmetric nucleophilic fluorinations.[4] Specifically, a chiral *N*-alkylated *bis*-urea served as hydrogen bond donor (HBD) catalyst to bring KF or CsF in solution. The process involves a chiral urea-fluoride complex capable of ion-pairing with *in situ* formed *meso* episulfonium or aziridinium ions. The ensuing enantioselective desymmetrization afforded enantioenriched β-fluorosulfides and β-fluoroamines. To date, all enantioselective fluorinations carried out under PTC use non-ionic substrates, including β-keto esters, alkenes, β-bromosulfides or β-chloroamines. An unexplored scenario in asymmetric C–F bond construction under PTC is the use of two ionic reactants. We became interested in this challenge as we envisioned that enantioselective desymmetrization of achiral azetidinium salts with fluoride would afford γ-fluoroamines of high value for medicinal chemistry.[5] Azetidinium salts[6] with non-nucleophilic counteranions are bench stable solids,[7a] and can be prepared from commercially or readily available azetidines.[7b–c] Few methods are available to access enantioenriched γ-fluoroamines,[8] and strategies for the enantioselective installation of CH_2F are scarce.[9]

In 2018, Sun and co-workers reported the desymmetrization of azetidinium salts with mercaptobenzothiazoles and a chiral phosphate catalyst (Scheme 1A, LHS).[10] This pioneering study encouraged experimentation applying this anionic PTC approach (CAPT) with TBAF or CsF; none of our attempts yielded γ-fluoroamines (Scheme S6). This result prompted the use of HB-PTC as an alternative manifold. Mechanistically, achiral azetidinium salts could themselves act as phase-transfer agents enabling solubilization of solid alkali metal fluoride as azetidinium fluoride. Indeed, ammonium salts,[11a–c] pyridinium salts[11d] and imidazolium-based ionic liquids[11e] have been used as phase-transfer catalysts for non-enantioselective fluorination reactions with KF or CsF (Scheme 1B, LHS).[11f-g] Such cationic phase-transfer scenario (CPTC) would transform *in situ* formed azetidinium fluoride into racemic γ-fluoroamine. We envisioned that HB-PTC using a chiral *bis*-urea catalyst could offer a viable approach for the desymmetrization of achiral azetidinium salts with alkali metal fluoride (Scheme 1A and 1B, RHS). This scenario is not without challenges because the use of two pre-formed ionic reactants implies high concentration of ions in solution, a drastic change when compared to transformations featuring transiently formed ion pairs.[4a-b] Significant variation in fluorination kinetics and competitive binding events (*e.g.* azetidinium counter-anion X^- vs. F^-) can be expected.[12] Computational studies indicated that a neutral *N*-methyl chiral *bis*-urea[4a] binds a CsF unit more strongly than 1,1-dimethyl azetidinium ion in 1,2-dichloroethane (ΔG_{urea} = −69 kJ/mol, ΔG_{azet} = −14 kJ/mol) (Scheme 1C).[13a]



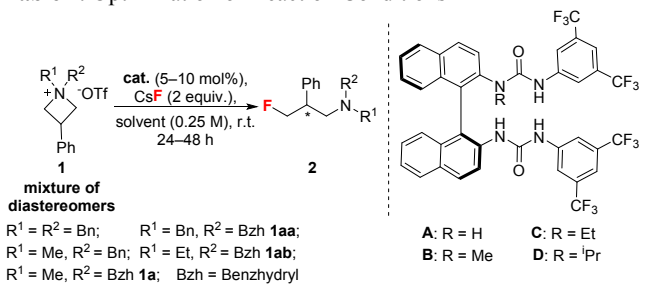
Scheme 1. A. Desymmetrization of azetidinium salts. **B.** $R_4N^+X^-$ as catalyst (CPTC) vs. $R_4N^+X^-$ as substrate (HB-PTC). **C.** Computational binding studies ($R_4N^+X^-$ treated as dissociated).

Encouraged by these findings,[13b] we surmised that azetidinium salts (R_4N^+X) could undergo enantioselective fluorination with an alkali metal fluoride (M^+F^-), in the presence of a chiral HBD catalyst (urea*) if orchestrated hydrogen-bonding and ion metathesis

generate the soluble chiral ion pair $[R_4N]^+[F•urea*]^-$. This species could undergo C–F bond formation with release of the enantioenriched γ-fluoroamine and catalyst. Herein, we describe the development of this unusual PTC process featuring two ionic reactants and demonstrate that achiral azetidinium salts are amenable to desymmetrization with CsF and a chiral BINAM-derived *bis*-urea catalyst.

Preliminary investigations unveiled details on the impact of the structural features of azetidinium salts on reactivity (Table 1).

Table 1. Optimization of Reaction Conditions



Entry	R^1	R^2	cat.	solvent	Yield[a]	e.r.[b]
1	Bn	Bn	A	CH_2Cl_2	traces	//
2	Me	Bn	A	CH_2Cl_2	traces	//
3	Me	Bzh	A	CH_2Cl_2	14%	55:45
4	Me	Bzh	B	CH_2Cl_2	20%	55:45
5	Me	Bzh	C	CH_2Cl_2	20%	75:25
6	Me	Bzh	D	CH_2Cl_2	45%	74:26
7	Me	Bzh	D	$CHCl_3$	56%	67:33
8	Me	Bzh	D	1,2-DFB	47%	79:21
9	Me	Bzh	D	1,2-DCE	51%	81:19
10	Et	Bzh	D	1,2-DCE	40%	96:4
11[c, d]	Et	Bzh	D	1,2-DCE	93%	96:4
12	Bn	Bzh	D	1,2-DCE	>95%	96:4
13[c, e]	Bn	Bzh	D	1,2-DCE	98%	96:4

Reaction conditions: 0.05 mmol of **1**, 0.25M, 10 mol% cat., 900 rpm stirring, 24 h; [a] Determined by ^{19}F NMR (4-fluoroanisole as internal standard); [b] e.r. = enantiomeric ratio, determined by HPLC; [c] Yield of isolated product. [d] 72 h, 10 mol% cat.; [e] 48 h, 5 mol% cat.

3-Phenyl *N*,*N*-dibenzyl and *N*-methyl-*N*-benzyl azetidinium triflates afforded traces of product with CsF and catalyst (*S*)-**A** (Table 1, entries 1–2). When *N*-methyl-*N*-benzhydryl substrate **1a** was employed, the desired γ-fluoroamine was obtained in poor yield and enantioselectivity (Table 1, entry 3). Notably, **1a** reacted with CsF in 1,2-DCE in the absence of catalyst to afford γ-fluoroamine (±)-**2a** in 8% yield (Table S1). When this reaction was carried out using the *N*-alkylated *bis*-urea catalysts (*S*)-**B**, (*S*)-**C** or (*S*)-**D**, **2a** was obtained in moderate yield and enantiomeric ratio (e.r.) (Table 1, entries 4–6). Solvent screening showed the superiority of 1,2-DCE (Table 1, entries 7–9, up to 81:19 e.r.). In addition to the benzhydryl group, the second *N*-substituent also influenced reactivity and enantioselectivity, with benzyl and ethyl being superior to methyl (Table 1, entries 10–13, up to 96:4 e.r.). After optimization, the reaction of **1aa** (d.r. 1:1.1) in 1,2-DCE with CsF (2 equiv.) and *N*-isopropyl *bis*-urea catalyst (*S*)-**D** (5 mol%) at r.t. afforded γ-fluoroamine **2aa** in 98% yield and 96:4 e.r. (Table 1, entry 13). *N*-Ethyl azetidinium triflate **1ab** required longer reaction time (72 h) and higher catalyst loading (10 mol %) to afford **2ab** (93% yield, 96:4 e.r., Table 1, entry 11). These findings were encouraging because azetidinium salts can be used as mixture of diastereomers, and both benzhydryl and benzyl groups are cleavable releasing a primary amine amenable to myriad transformations.

The benefit of the *N*-benzhydryl group on reactivity prompted further investigation.[14] Fluorination reactions performed on differently *N*,*N*-disubstituted azetidinium salts under homogeneous conditions (TBAF·$3H_2O$, 1,2-DCE, no catalyst) showed benzhydryl being superior to all other *N*-substituents (Scheme S4). The increased reactivity of *N*-benzhydryl azetidinium salts is therefore unconnected with phase-transfer. Computed transition state structures (TSs) for the fluorination of seven azetidinium ions by free fluoride (homogeneous conditions) show that increased experimental yields are consistent with smaller computed activation barriers. *N*-Benzhydryl azetidinium ions have barriers to fluorination ~ 6 kJ/mol lower than the corresponding *N*-benzyl substrate. This can be traced to increased reactant strain: *N*-benzhydryl azetidinium ions have more elongated C–N bonds and earlier fluoride delivery TS positions compared to the methyl or benzyl substrates (Figure 1).

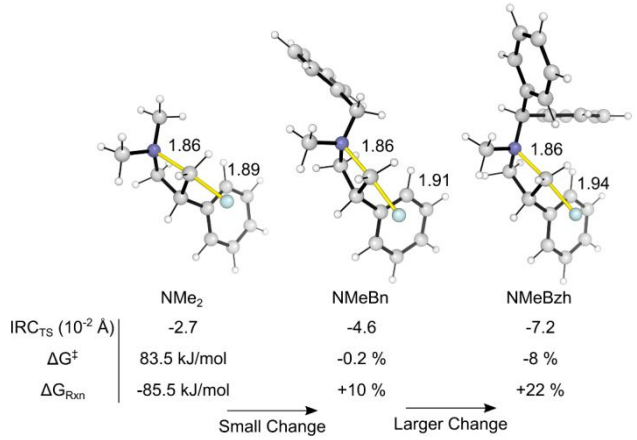


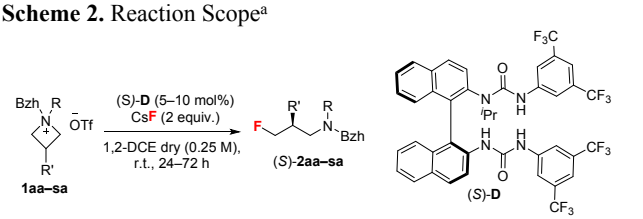
Figure 1. Effect of *N*-benzhydryl on reactivity (Me, Bn and Bzh series). IRC position calculated as C–N minus C–F distance.[15]

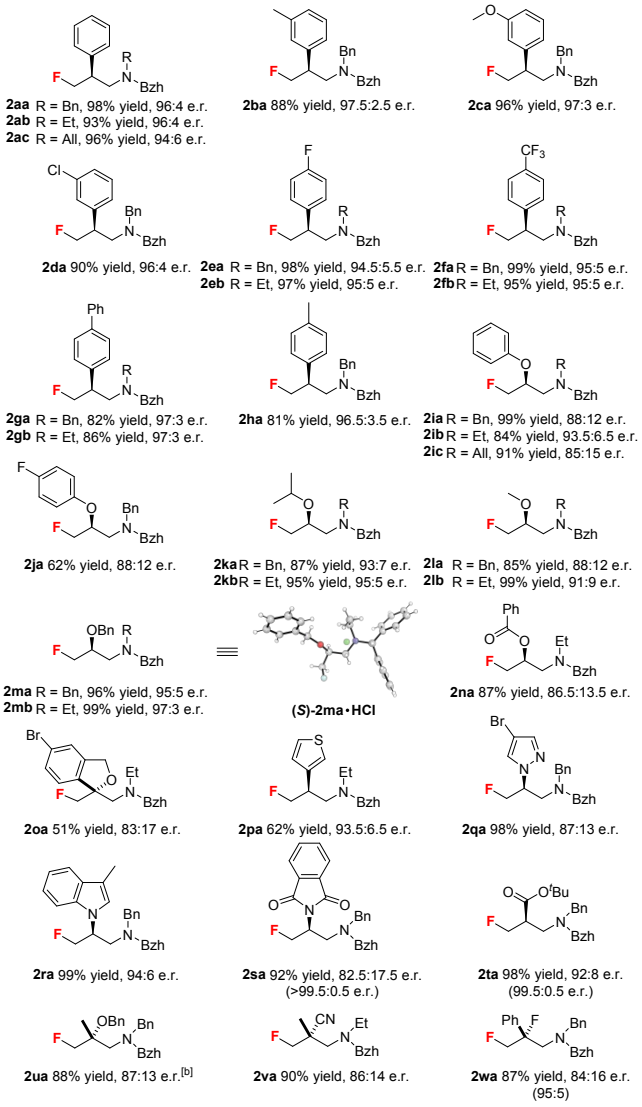
The scope of γ-fluoroamine synthesis was examined next. High yields and enantioselectivities were obtained with 3-aryl azetidinium triflates. Substrates bearing aromatic groups with electron-withdrawing and electron-donating substituents at *meta* or *para* positions were converted with excellent yields and enantioselectivities (**2aa**–**2ha**, up to 99% yield, 97.5:2.5 e.r.). Heteroaromatic groups such as thiophene (**2pa**), pyrazole (**2qa**) and indole (**2ra**) were compatible, representing pharmaceutically relevant motifs (up to 99% yield, 94:6 e.r.). Additional highlights are the suitability of *N*-allyl azetidinium salts (**2ac**, **2ic**), the tolerance of the reaction to 3-aryloxy- (**2ia**–**2ja,** up to 99% yield, 93.5:6.5 e.r.), 3-alkoxy- (**2ka**–**2mb**), and 3-phtalimido- groups (**2sa**), as well as the synthesis of enantioenriched γ-fluoroamines **2oa, 2va**–**2ua** featuring a tetrasubstituted stereogenic carbon. Furthermore, **2ta** bearing an ester group stands out as an immediate precursor to enantioenriched fluorinated β-lactams and β-amino acids.[16] Tertiary fluoride **2wa** was accessed in good yield and moderate enantioselectivity. Substrates mono- or bis-alkylated at position 3 were less successful (Scheme S7).[13a] Single-crystal X-ray diffraction analysis of **2ma**·HCl and **3ab** (Scheme 3A) enabled the assignment of the absolute configuration (*S*-catalyst affords *S*-product).[17]

This new catalytic protocol enabled the preparative scale synthesis of γ-fluoroamines **3aa** and **3ab** (Scheme 3A). The reaction of one gram of **1aa** was conducted with a lower catalyst loading (3 mol%) and no compromise in e.r. relative to the smaller scale reaction. Deprotection and a single recrystallization gave the primary γ-fluoroamine **3aa** in 99:1 e.r. A similar protocol afforded enantioenriched secondary γ-fluoroamine **3ab** in 98.5:1.5 e.r. The

synthesis of the fluorinated analogue of Lorcaserin,[18] a selective serotonin 2C receptor agonist, FDA-approved for chronic-weight management, illustrates the value of the method for accessing valuable pharmaceutical motifs (Scheme 3B).

Scheme 2. Reaction Scope[a]

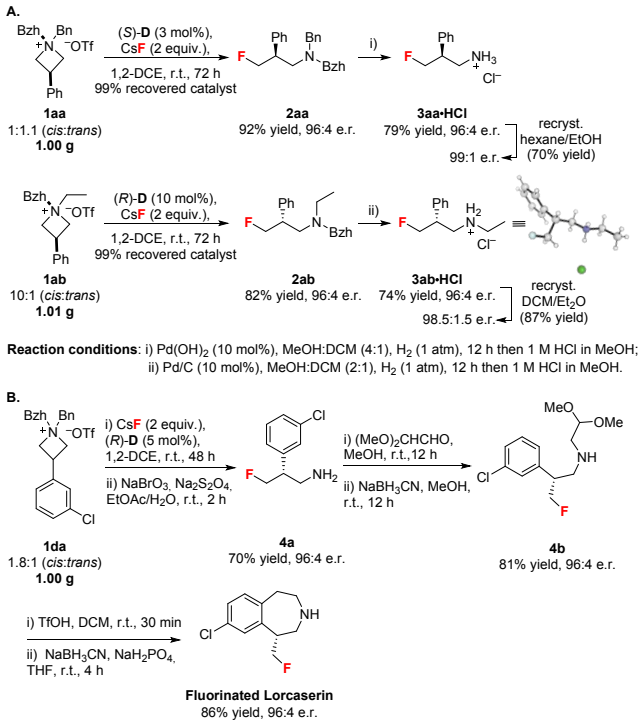




[a] 0.1 mmol scale, except for **1sa**, **1ta**, **1wa** (0.5–1 mmol scale). Absolute configuration assigned by analogy to (*S*)-**2ma** for all products except **2oa**, **2ua**–**2wa** featuring a tetrasubstituted stereogenic carbon; [b] 20 mol% cat. In parenthesis, e.r after single recrystallization.

Further experimentation was undertaken to gain more insight on this process: (i) the reaction of **1aa** with 1 equiv. of $[(S)\text{-}\mathbf{D}\cdot F]^-[n Bu_4N]^+$ formed *in situ* or pre-formed from $n Bu_4N^+F^-\cdot 3H_2O$ in 1,2-DCE (0.25 M) afforded **2aa** in 30% yield and 96:4 e.r.; this result confirms the involvement of $[(S)\text{-}\mathbf{D}\cdot F]^-$ for enantiocontrol (Scheme S5), and highlights the detrimental impact of water on yield (Table S5); (ii) exchanging OTf^- of **1aa** with PF_6^- gave **2aa** in identical e.r. (96:4), but in only 31% yield (Table S6). This observation indicates that the counter-anion influences the efficacy of phase transfer, and advocates against anion binding catalysis. This is further supported by NMR studies which showed the stronger binding preference of the catalyst for fluoride compared to other anions ($F^- >> TfO^- \sim BF_4^- > PF_6^-$);[13a] (iii) the linear relationship between the enantiopurity of catalyst and product supports the involvement of a single urea catalyst in the enantiodetermining step (Table S7); (iv) when diastereomerically pure *N*-methyl substituted *cis*-**1a** or *trans*-**1a** was subjected to asymmetric fluorination under standard reaction conditions, fluoroamine (*S*)-**2a** was formed with a comparable e.r. (80.5:19.5 and 80:20, respectively, Table S4).

Scheme 3. A. Gram-Scale Reactions and Deprotection. **B.** Enantioselective Synthesis of Fluorinated Lorcaserin.



Finally, we turned our attention towards the origin of enantioconvergence for this transformation. The TSs for fluorination of **1a**, mediated by catalyst (*S*)-**D** were computed using density functional theory (DFT).[19] An ensemble of TSs was optimized for both *cis* and *trans* substrates (Figure 2). With *cis* substrate (major diastereomer), both $\mathbf{TS_{Major}}$-***cis*** and $\mathbf{TS_{Minor}}$-***cis*** feature a face-to-face π-interaction between the phenyl in the 3-position of the substrate and the catalyst (Figure 2Ai), orienting the substrate in the catalytic pocket. In contrast, the benzhydryl groups point in different directions. In $\mathbf{TS_{Major}}$-***cis*** the azetidinium ion adopts its favored conformation, with an intramolecular CH---π interaction worth approximately 2-5 kJ/mol (Figure 2Aii). In $\mathbf{TS_{Minor}}$-***cis***, this is compensated by an aromatic edge-to-face interaction of the benzhydryl group with the catalyst BINAM backbone (Figure 2Aiii). When computed with *N*-ethyl substituent (**1ab**), (*S*)-catalyst affords (*S*)-product with 91:9 e.r., consistent with the experimental enantioselectivity of 96:4 e.r. Comparison of $\mathbf{TS_{Major}}$-***cis*** with the lowest energy TS to major product with *trans* substrate, $\mathbf{TS_{Major}}$-***trans***, shows remarkable similarity, with excellent superposition of catalyst, fluoride and substrate, with the only exception being reversal of configuration at nitrogen, resulting in the sterically demanding benzhydryl group pointing in a different direction (Figure 2B). The enantioconvergence of the diastereomers originates from the azetidinium *N*-substituents projecting away from the catalyst, and the resulting indifference to the configuration at nitrogen.[20]

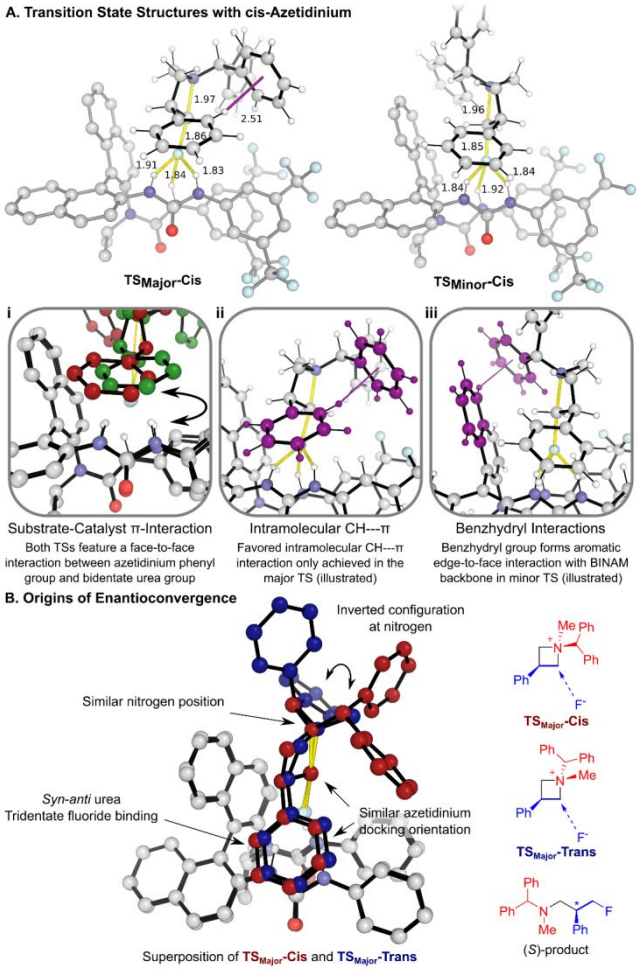


Figure 2. Computed TSs for fluorination of **1a**. **A.** TSs with *cis*-**1a** and key structural features. **B.** Origin of enantioconvergence of *cis*-**1a** and *trans*-**1a** demonstrated through the structural similarity of the most favorable TSs with each diastereomer of substrate.

In conclusion, this study provides new insights on HB-PTC and its application to high value fluorine-containing molecules. Neutral *N*-alkylated *bis*-urea catalysts are more effective at fluoride binding than azetidinium ions, a feature enabling efficient enantioselective ring opening with CsF for the synthesis of γ-fluoroamines. Considering that the use of ammonium salts as substrates is uncommon in asymmetric catalysis,[21] the principles outlined here may encourage further studies to transform ionic starting materials into enantioenriched products applying HB-PTC.

ASSOCIATED CONTENT

Optimization/mechanistic data are provided in the Supporting Information which is available free of charge on the ACS publications website. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (1973306-07) and can be obtained free of charge.

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Author Contributions

§ These authors contributed equally to this work.

Notes

The authors declare no competing financial interests.

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12) (a) Turnover of the productive fluorination pathway will be influenced by a change in substrate cation concentration (i.e. pre-formed azetidinium versus in situ formed episulfonium). In previous work (reference 4a), the episulfonium ion pair lies at +48 kJ/mol compared to the unionized precursor, corresponding to an equilibrium constant of 4 x 10^{-9} at r.t. For a detailed analysis of concentration effects in catalysis, refer to 12c-e; (b) High concentrations of substrate counter-anion will also increase competitive binding of the hydrogen bonding catalyst, potentially hindering HB-PTC and/or facilitating alternative anion-binding pathways; (c) Kozuch, S.; Shaik, S. How to Conceptualize Catalytic Cycles? The Energetic Span Model. *Acc. Chem. Res.* **2011**, *44*, 101; (d) Kozuch, S.; Shaik, S. Kinetic-Quantum Chemical Model for Catalytic Cycles: The Haber-Bosch Process and the Effect of Reagent Concentration. *J. Phys. Chem. A* **2008**, *112*, 6032; (e) Uhe, A.; Kozuch, S.; Shaik, S. Automatic Analysis of Computed Catalytic Cycles. *J. Comput. Chem.* **2011**, *32*, 978.

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14) *N*-Benzhydryl azetidinium salts also feature in the study of Sun and co-workers (reference 10a).

15) A larger variation in key metrics occurs on changing from Bn to Bzh. $\Delta G^{\ddagger}$ was measured relative to TBAF + $Azet^{+}$. ΔG_{Rxn} measures the release of ring strain of the ion upon fluorination with TBAF.

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19) (a) Calculations were performed using Gaussian 16 Rev. A.03 for optimization and frequency calculations, with single point energy corrections performed with ORCA 4.2.0. The CPCM(1,2-DCE)/ωB97X-D3/(ma)-def2-TZVPP//CPCM(1,2-DCE)/M06-2X/def2-SVP(D) level of theory was used for all calculations. Full computational details, including precise definition of the basis sets, are provided in the supporting information. (b) Thermochemistry is evaluated at 298.15 K, at 1 M standard concentration.

20) The full ensemble of computed TSs for reaction *cis*-**1a** and *trans*-**1a** are provided in the SI.

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