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Hydrogen Bonding Phase-Transfer Catalysis with Potassium Fluoride: Enantioselective Synthesis of β-Fluoroamines

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ABSTRACT: Potassium fluoride (KF) is an ideal reagent for fluorination because it is safe, easy to handle and low-cost. However, poor solubility in organic solvents coupled with limited strategies to control its reactivity has discouraged its use for asymmetric C–F bond formation. Here, we demonstrate that hydrogen bonding phase transfer catalysis with KF provides access to valuable β-fluoroamines in high yields and enantioselectivities. This methodology employs a chiral *N*-ethyl bis-urea catalyst that brings solid KF into solution as a tricoordinated urea-fluoride complex. This operationally simple reaction affords enantioenriched fluoro-diphenidine (up to 50-g-scale) using 0.5 mol% of recoverable bis-urea catalyst.

The benefits of fluorine incorporation in organic molecules have been extensively studied and exploited in the agrochemical and pharmaceutical industry.[1] Fluorine substituents can alter the pK_a of neighboring groups, dipole moment, and properties such as metabolic stability, lipophilicity and bioavailability.[2] In this context, the demand for molecules featuring the fluorine substituent on a stereogenic carbon has accelerated the development of catalytic enantioselective fluorination methodologies.[3] Electrophilic fluorine sources of tailored reactivity have proved valuable for rapid advance of this field of research.[4] Asymmetric catalysis towards C–F bond formation using nucleophilic fluorine sources has progressed at a slower pace in part due to the difficulties in controlling fluoride reactivity.[5] Fluoride is solvated and poorly reactive in protic media, while unsolvated fluoride can react as a Brønsted base.[6] These issues have led to the development of reagents designed for *in situ* release of fluoride into solution.[5f, 7] Additional challenges for metal alkali fluorides are their hygroscopicity and poor solubility in organic solvents.[6] These characteristics have discouraged the use of potassium fluoride (KF) for asymmetric catalytic fluorination, despite the fact that this reagent is low cost, safe and easy to handle.[8]

Nature has evolved a fluorinase enzyme that makes use of a hydrogen bonded fluoride complex to enable C–F bond formation.[9] Inspired by this transformation, we prepared fluoride complexes derived from alcohols and ureas to study the effect of hydrogen bonding on fluoride reactivity.[10] These studies culminated with the discovery of hydrogen bonding phase-transfer catalysis (HB-PTC),[11] a new activation mode for PTC[12] whereby a neutral hydrogen bond donor urea catalyst acts as a transport agent to bring solid cesium fluoride, $CsF_{(s)}$ (lattice energy, 759 kJ/mol),[13] into solution in the form of a hydrogen bonded fluoride complex. This strategy afforded enantioenriched β-fluorosulfides with a chiral *N*-alkyl bis-urea catalyst U* (Fig. 1A), that adopts an *anti-syn* conformation and binds fluoride as a tricoordinated hydrogen bonded complex. At this stage, the prospect of using $KF_{(s)}$ under HB-PTC was tantalizing considering the advantages of this reagent compared to other fluorine sources (Fig. 1B).

Encouraged by initial calculations indicating that the energy required to solubilize $KF_{(s)}$ in dichloromethane is significantly reduced in the presence of bis-urea U* (see SI), we envisioned that asymmetric HB-PTC may be suitable for enantioselective fluorination with this more demanding fluoride source (lattice energy, 829 kJ/mol).[13] Precursors of *meso* aziridinium ions[14] were selected as substrates for this study because desymmetrization with KF affords high value enantioenriched β-fluoroamines that are of considerable interest for applications in medicinal chemistry, especially for central nervous system drug discovery,[15, 16] and catalyst design.[17] Specifically, we propose that a chiral bis-urea of type U* brings $KF_{(s)}$ into solution as a tricoordinated hydrogen bonded complex; ion pairing of this complex with *in situ* formed *meso* aziridinium ion followed by fluorination delivers the enantioenriched β-fluoroamine with release of the bis-urea catalyst (Fig. 1C).

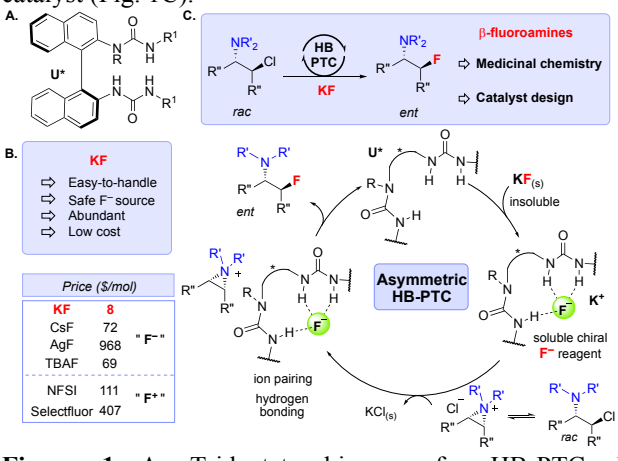
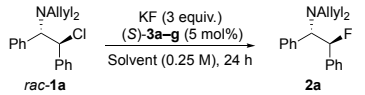


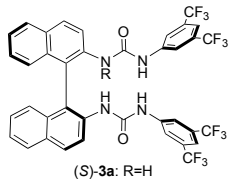
Figure 1 A. Tridentate bis-urea for HB-PTC. B. Advantages of KF. C. Synthesis of enantioenriched β-fluoroamines with $KF_{(s)}$, and proposed HB-PTC mechanism.

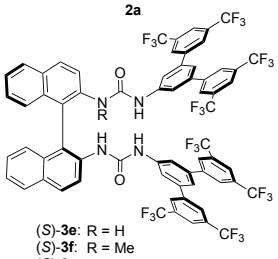
Most catalytic asymmetric methodologies towards β-fluoroamines require fluorinated building blocks,[18] but strategies featuring late stage enantioselective fluorination have been disclosed. Enamine catalysis and anionic phase transfer catalysis have been successfully applied using electrophilic fluorination reagents.[19] Catalytic enantioselective nucleophilic fluorinations towards β-fluoroamines have also appeared, but these reactions typically require hazardous HF reagents, or rely on *in situ* fluoride release from reagents of reduced atom economy.[20] These examples highlight the progress made toward accessing enantioenriched β-fluoroamines, and underline the demand for asymmetric catalytic methods for their synthesis using safe and readily available fluoride sources such as $KF_{(s)}$.

Preliminary studies identified the stilbene-derived β-chloro-*N*-diallylamine **1a** as a suitable aziridinium ion precursor for the proposed enantioselective fluorination towards β-fluoroamine (Table 1) (see SI for details). This substrate features a tertiary amine rarely encountered in the context of late stage asymmetric fluorination,[3] and the product of fluorination belongs to the 1,2-diphenylethylamine family of NMDA receptor antagonists.[21] We opted for *N*-allyl substitution to allow release of the primary amine *via* Pd-catalyzed deallylation post-fluorination.[22]

Table 1. Optimization of Reaction Conditions.







Entry	Cat.	Solvent	T (°C)	Yield[a]	e.r.[b]
1	**3a**	DCM	rt	>99%	55:45
2	**3b**	DCM	rt	98%	85:15
3	**3c**	DCM	rt	>99%	86:14
4	**3d**	DCM	rt	83%	86:14
5	**3e**	DCM	rt	77%	55:45
6	**3f**	DCM	rt	72%	88:12
7	**3g**	DCM	rt	80%	90.5:9.5
8[c]	**3g**	DCM	0	80%	93:7
9[c]	**3g**	$CHCl_3$[d]	0	90%	93.5:6.5
10[c]	**3g**	1,2-DFB	0	58%	94:6
11[c]	**3g**	$CHCl_3$[d]	–15	71%[e]	95:5

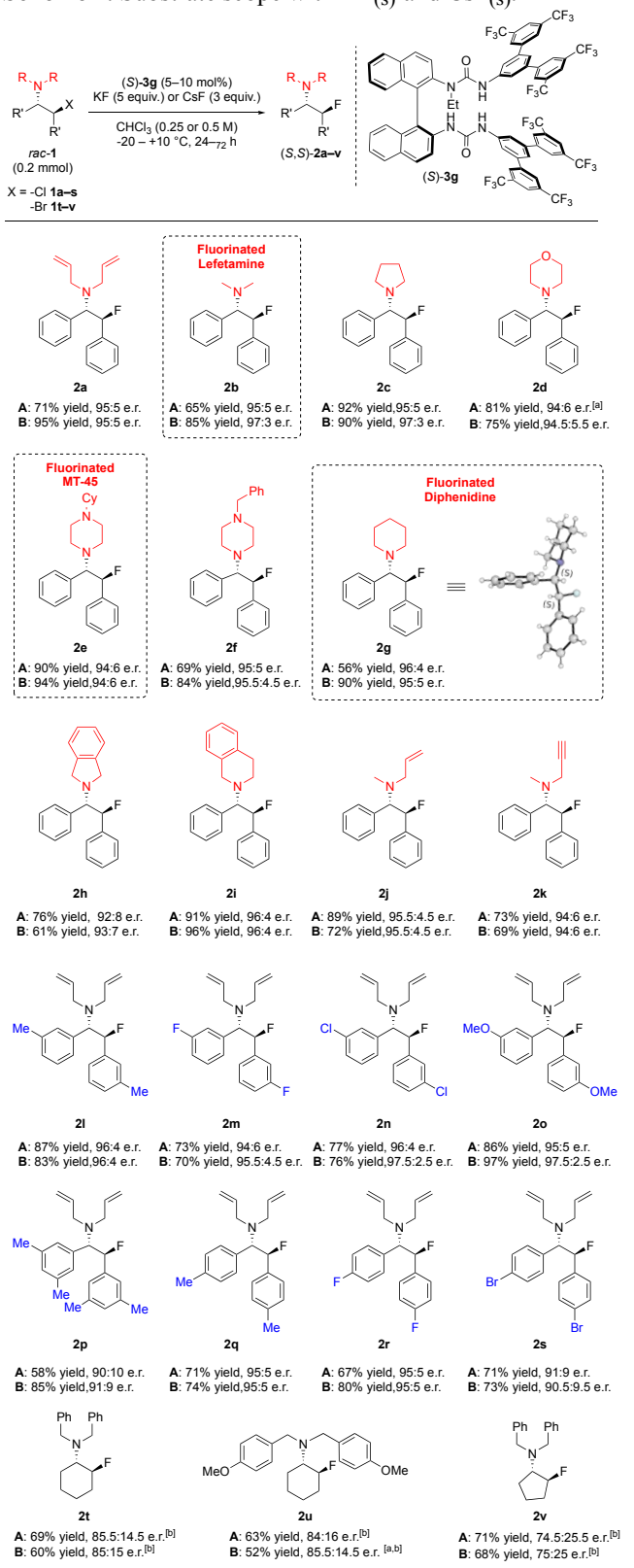
Reaction conditions: 0.05 mmol of **1a**, 0.25 M, (*S*)-**3a–g** (5 mol%), stirring at 1200 rpm for 24 h. [a] Determined by ^{19}F-NMR using 4-fluoroanisole as internal standard; [b] e.r. = enantiomeric ratio determined by HPLC; [c] 0.5 M, 5 equiv. of KF, 10 mol% of **3g**; [d] $CHCl_3$ was filtered on basic alumina to remove residual HCl; [e] Yield of isolated product after 72 h.

The reaction of *rac*-**1a** and KF (3 equiv) in dichloromethane at rt with 5 mol% of urea (*S*)-**3a** afforded β-fluoroamine **2a** in >99% yield, but no control over enantioselectivity was observed (e.r. = 55:45) (Table 1, entry 1). This result however demonstrated that HB-PTC enables fluorination with KF. The *N*-alkylated catalysts **3b–d** capable of forming tricoordinated hydrogen bonded complex with fluoride did improve enantiocontrol (Table 1, entries 2–4, up to >99% yield and 86:14 e.r.). The e.r. (up to 90.5:9.5) was increased with *N*-alkylated catalysts **3f** and **3g** featuring an extended poly-trifluoromethylated terphenyl π-system (Table 1, entries 6–7). Further reaction condition optimization (see SI for details) afforded **2a** in good yields and high enantioselectivity (71% yield of isolated product, 95:5 e.r.). The optimized conditions consist of treating *rac*-**1a** with KF (5 equiv.) and **3g** (10 mol%) in $CHCl_3$ at –15 °C for 72 h (Table 1, entry 11).

With the optimal reaction conditions in hand, we studied the scope of the reaction (Scheme 2). Substrates with a range of different amines were subjected to enantioselective fluorination. The fluorinated analogue of the analgesic lefetamine[22] **2b** possessing two methyl groups on nitrogen was obtained in 65% yield and 95:5 e.r.. Various *N*-heterocycles were tolerated including motifs frequently encountered in FDA approved drugs (*e.g.* piperidine, piperazine, pyrrolidine, morpholine);[23] this is demonstrated with the synthesis of β-fluoroamines **2c–i** that were obtained in good yields and high enantioselectivities (up to 94% yield and 96:4 e.r.). Within this series, asymmetric HB-PTC gave access to fluorinated analogues of NMDA receptor antagonists **2e** (MT-45)[24a] and **2g** (diphenedine) in high enantioselectivity.[24b-d] The reaction is highly effective for substrates possessing two different *N*-substituents that may lead to two diastereomeric *meso* aziridinium ions as exemplified with the synthesis of **2i, 2j** and **2k** that were obtained with e.r. reaching 96:4. Various substituents on the phenyl ring of the substrates are compatible including electron-donating and electron-withdrawing groups. β-Fluoroamines **2l–2s** were synthesized in good yields and e.r. (up to 87% yield and 96:4 e.r.). A study comparing KF and CsF indicates that comparable yields could be obtained by simply increasing the excess of KF (5 vs. 3 equiv.), and the reaction concentration (0.5 vs. 0.25 M). The enantiomeric ratios were unaffected by the nature of the alkali fluoride. Departing from diaryl-based substrates, six- and five-membered cyclic *meso* aziridinium precursors were also evaluated. Asymmetric catalytic fluorination occurred smoothly at room temperature in α,α,α-trifluorotoluene, and afforded the cyclic β-fluoroamines **2t-v** in good yields and with moderate enantioselectivity.

The catalyst loading was reduced to 3 mol% for the reaction on a 1.1 g scale of **1a**. This fluorination was performed at 5 °C, and afforded **2a** in 76% yield and 93:7 e.r. (Scheme 3A). *N*-Deprotection of β-fluoroamine **2a** under Pd(0) catalysis[21] afforded β-fluoroamine **4** in 72% yield with no erosion of e.r.. A single recrystallization gave **4** in high enantiopurity (99.8:0.2 e.r.). Reductive amination of **4** with acetaldehyde yielded fluorinated ephenidine **5** as a single enantiomer,[24e] an additional NMDA receptor antagonist of the 1,2-diphenylethylamine family.

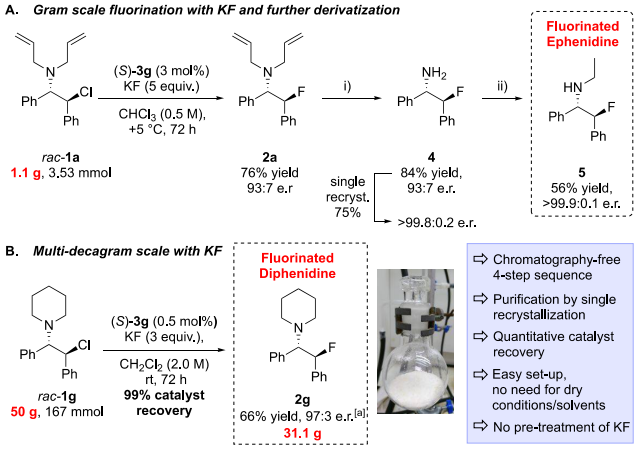
Scheme 2. Substrate scope with $KF_{(s)}$ and $CsF_{(s)}$.



Conditions **A**: **1** (0.2 mmol), KF (5 equiv.), (*S*)-**3g** (5–10 mol%), $CHCl_3$ (0.5 M). Conditions **B**: **1** (0.2 mmol), CsF (3 equiv.), (*S*)-**3g** (5-10 mol%), $CHCl_3$ (0.25 M). [a]15 mol% of catalyst used. [b]Reaction performed in α,α,α-trifluorotoluene. Structure of (*S*,*S*)-**2g** determined by single-crystal x-ray diffraction. Absolute configuration of all products assigned by analogy with (*S*,*S*)-**2g**.

In order to demonstrate the applicability of the methodology to multidecagram synthesis, we further optimized the process (Scheme 3B, see SI for details). Multigram quantities of substrate *rac*-**1g** were prepared *via* a chromatography-free epoxidation/ring-opening/chlorination sequence from commercially available *cis*-stilbene (48% yield over three steps). The fluorination of *rac*-**1g** was performed at room temperature on a 50-g-scale using a smaller excess of KF (3 equiv.), and 0.5 mol% of catalyst (*S*)-**3g** for 72h; this was made possible by increasing the concentration to 2 M and replacing chloroform with dichloromethane. The catalyst (*S*)-**3g** was separated from the product **2g** *via* acid/base work-up, and the crude product was purified with a single recrystallization in MeOH to afford **2g** in 66% yield and 97:3 e.r.. The catalyst was quantitatively recovered and recycled without loss of efficiency with respect to both yield and enantioselectivity. Noteworthy, the reaction set-up is operationally simple, does not require dry solvents, is carried out under air, and KF is used without any pre-treatment.

Scheme 3. A. Gram scale fluorination of **1a** enabling access to enantiopure fluorinated ephenidine. B. 50-g-scale reaction for the synthesis of fluorinated diphenidine.



[a] After single recrystallization; the product from crude reaction mixture has an e.r. = 92:8

Reaction conditions: i) Thiosalicyclic acid (2.5 equiv.), $Pd(dba)_2$ (10 mol%), dppb (10 mol%), THF, 60 °C, 12 h; ii) CH_3CHO (5 equiv), $NaBH(OAc)_3$ (3 equiv.), MeOH (0.2 M), rt, 3 h (1 mmol scale). Derivatization of **4** confirmed its (*S*,*S*) absolute configuration (see SI).[5g]

The reaction was investigated computationally by molecular dynamics (MD) simulations, and density functional theory (DFT) calculations (see SI for full details).[25] MD simulations in chloroform confirmed that *N*-alkylated catalyst **3g** forms a stable and persistent tridentate fluoride complex, with the alkylated urea in an *anti-syn* conformation.[26] MD was further used for conformational sampling for DFT calculations,[11,27] resulting in 15 DFT optimized transition structures (TSs) for ring-opening.

A Boltzmann ensemble of competing TSs predicted preferential (*S*,*S*) product formation from catalyst (*S*)-**3g** (supported by single-crystal x-ray diffraction of (*S*,*S*)-**2g**). Further, the computed selectivity of 95:5 e.r. at 278.15 K compares favorably with experimental values. The most stable competing TSs contributing towards major and minor product formation are shown in Figure 2A. The *N*-substituents of the aziridinium ion are pointing away from

the catalytic pocket, into solvent, explaining wide substituent tolerance in these positions (Fig. 2Bi). In both TSs, the aziridinium ion docks with the catalyst backbone - favorable cation–π interactions between naphthyl ring and aziridinium Cα-H protons are present (Fig. 2Bii).[28]

We used various energy decomposition analyses to rationalize the origins of enantioselectivity.[29-31] The cation–π interaction is stronger in the major TS based on truncated models - in the absence of this interaction the selectivity is reduced by 1.5 kJ/mol. Steric crowding in the minor TS also leads to unfavorable geometric distortion (Fig. 2Biii). These combined effects contribute approximately half of $\Delta\Delta G^{\ddagger}$. The remainder is due to substrate conformation (Fig. 2Biv), favoring conjugation of the phenyl ring with the forming and breaking bonds (benzylic S_N2). On the basis of dihedral angles, the minor TS is 20° further from conjugation than the major (see SI for more details of this analysis).[32]

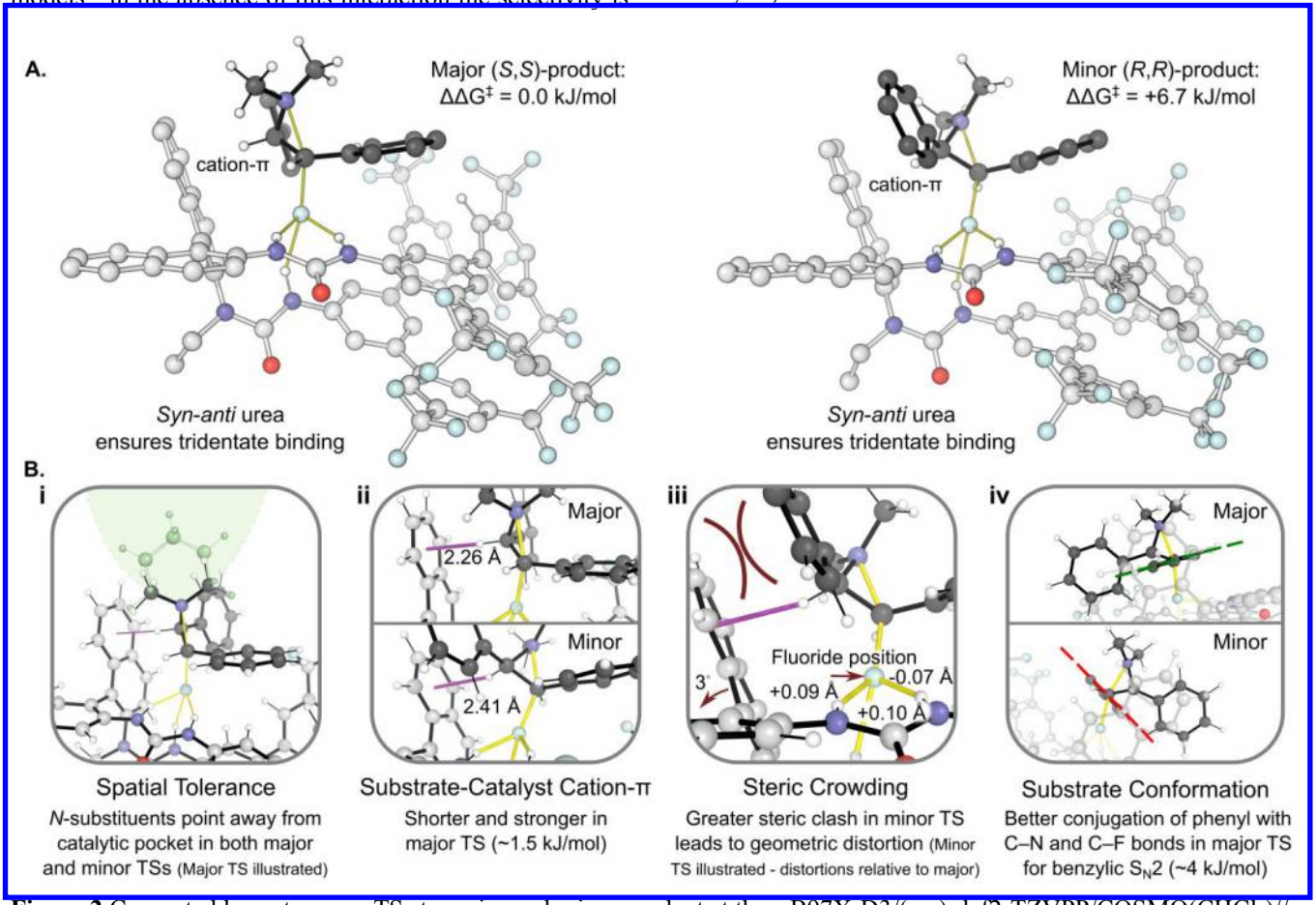


Figure 2 Computed lowest energy TSs to major and minor product at the ωB97X-D3/(ma)-def2-TZVPP/COSMO($CHCl_3$)//M06-2X/def2-SVP(TZVPPD)/CPCM($CHCl_3$) level of theory, with highlights rationalizing substituent tolerance and origins of enantioselectivity.

In summary, we have shown that asymmetric HB-PTC enables enantioselective fluorination of racemic β-chloroamines with KF, an ideal fluoride source based on safety, availability and cost. The resulting β-fluoroamines are obtained in high yields and enantiomeric ratios. This reaction uses a novel *N*-ethylated bis-urea catalyst that transports KF in solution as a chiral tricoordinated bis-urea/fluoride complex. Subsequent ion-pairing with *in situ* formed *meso* aziridinium ion enables enantioselective C–F bond formation. The method stands out as it is operationally simple, can be performed in an open vessel, and does not require dry solvents or pre-treatment of KF. A 50-g-scale reaction was performed for the synthesis of an enantioenriched fluorinated analogue of diphenidine, an NMDA receptor antagonist. We anticipate that the advantages of this novel HB-PTC process will offer new prospects in fluorination chemistry both in academia and industry.

ASSOCIATED CONTENT

Supporting Information

Data and materials availability: Additional optimization and mechanistic data are provided in the Supporting Information. Computational methods, energies and coordinates are provided in the Supporting Information. Crystallographic data are available free of charge from the Cambridge Crystallographic Data Centre under references CCDC 1880527-1880530. The Supporting Information is available free of charge on the ACS Publications website.

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Notes
The authors declare no competing financial interests.

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REFERENCES

(1) (a) *Fluorine in Medicinal Chemistry and Chemical Biology* Ojima, I., Ed., Wiley-Blackwell, Chichester, UK, 2009; 1 (b) *Fluorine in Pharmaceutical and Medicinal Chemistry* Gouverneur, V., Müller, K., Eds., Imperial College Press, London, UK, 2012; c) Jeschke, P. "The Unique Role of Fluorine in the Design of Active Ingredients for Modern Crop Protection" *ChemBioChem* **2004**, *5*, 570.

(2) (a) Müller, K.; Faeh, C.; Diederich, F. "Fluorine in Pharmaceuticals: Looking Beyond Intuition" *Science* **2007**, *317*, 1881. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. "Fluorine in medicinal chemistry" *Chem. Soc. Rev.* **2008**, 37, 320. (c) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. "Applications of Fluorine in Medicinal Chemistry" *J. Med. Chem.*, **2015**, *58*, 8315.

(3) (a) Yang, X; Wu, T.; Phipps, R. J.; Toste F. D. "Advances in Catalytic Enantioselective Fluorination, Mono-, Di-, and Trifluoromethylation, and Trifluoromethylthiolation Reactions" *Chem. Rev.*, **2015**, *115*, 826. (b) Lozano, O.; Gouverneur, V. "Asymmetric Fluorination, Monofluoromethylation, Difluoromethylation, and Trifluoromethylation Reactions" in *Science of Synthesis*, Evans, P.A. Ed; Thieme; **2011**, Volume 3: Stereoselective Synthesis 3. (c) Zhu, Y.; Han, J.; Wang, J.; Shibata, N.; Sodoka, M.; Soloshonok, V. A.; Coelho, J. A. S.; Toste, F. D. "Modern Approaches for Asymmetric Construction of Carbon Fluorine Quaternary Stereogenic Centers: Synthetic Challenges and Pharmaceutical Needs" *Chem. Rev.* **2018**, *118*, 3887.

(4) (a) Timofeeva, D. T.; Ofial, A. R.; Mayr, H. "Kinetics of Electrophilic Fluorinations of Enamines and Carbanions: Comparison of the Fluorinating Power of N–F Reagents" *J. Am. Chem. Soc.*, **2018**, *140*, 11474; (b) Rozatian, N.; Ashworth, I. W.; Sandford, G.; Hodgson, D. R. W. "A quantitative reactivity scale for electrophilic fluorinating reagents", *Chem. Sci.* **2018**, *9*, 8692.

(5) (a) Scheidt, F.; Schäfer, M.; Sarie, J. C.; Daniluc, C. G., Molloy, J. J; Gilmour R. "Enantioselective, Catalytic Vicinal Difluorination of Alkenes" *Angew. Chem. Int. Ed.* **2018**, *57*, 16431. (b) Mennie, K. M.; Banik, S. M.; Reichert, E. C.; Jacobsen, E. N. "Catalytic Diastereo- and Enantioselective Fluoroamination of Alkenes" *J. Am. Chem. Soc.* **2018**, *140*, 4797. (c) Zhu, J.; Tsui C. G.; Lautens, M. "Rhodium-Catalyzed Enantioselective Nucleophilic Fluorination: Ring Opening of Oxabicyclic Alkenes" *Angew. Chem. Int. Ed.* **2012**, *51*, 12353. (d) Katcher, M. H.; Doyle, A. G. "Palladium-catalyzed asymmetric synthesis of allylic fluorides" *J. Am. Chem. Soc.* **2010**, *132*, 17402. (e) Katcher, M. H.; Sha, A.; Doyle, A. G. "Palladium-catalyzed regio- and enantioselective fluorination of acyclic allylic halides" *J. Am. Chem. Soc.* **2011**, *133*, 15902; (f) Kalow, J. A.; Doyle, A. G. "Enantioselective Ring Opening of Epoxides by Fluoride Anion Promoted by a Cooperative Dual-Catalyst System" *J. Am. Chem. Soc.* **2010**, *132*, 3268; (g) Kalow, J. A.; Doyle, A. G. "Enantioselective fluoride ring opening of aziridines enabled by cooperative Lewis acid catalysis" *Tetrahedron* **2013**, *69*, 5702.

(6) (a) Lee, J-W.; Oliveira, M. T.; Jang, H. B.; Lee, S.; Chi, D. Y.; Kim, D. W.; Song, C. E. "Hydrogen-bond promoted nucleophilic fluorination: concept, mechanism and applications in positron emission tomography" *Chem. Soc. Rev.,* **2016**, *45*, 4638. (b) Liang, S.; Hammond, G. B.; Xu, B. "Hydrogen bonding: regulator for nucleophilic fluorination" *Chem. Eur. J.* **2017**, *23*, 17850.

(7) Neumann, C. N.; Ritter, T. "Late-Stage Fluorination: Fancy Novelty or Useful Tool?" *Angew. Chem. Int. Ed.*, 2015, 54, 3216.

(8) See Figure 1b for comparison with other commercially available nucleophilic and electrophilic sources of fluorine.

(9) (a) O'Hagan, D.; Schaffrath, C.; Cobb, S. L.; Hamilton, J. T. G.; Murphy, C. D. "Biosynthesis of an organofluorine molecule" *Nature* **2002**, *416*, 279; (b) Dong, C.; Huang, F.; Deng, H.; Schaffrath, C.; Spencer, J. B., O'Hagan, D.; Naismith, J. H. "Crystal structure and mechanism of a bacterial fluorinating enzyme" *Nature* **2004**, *427*, 561; (c) Zhu, X.; Robinson, A.; McEwan, R.; O'Hagan, D.; Naismith, J. H. "Mechanism of enzymatic fluorination in streptomyces cattleya" *J. Am. Chem. Soc.* **2007**, *129*, 14597. (d) O'Hagan, D.; Deng, H. "Enzymatic fluorination and biotechnological developments of the fluorinase" *Chem. Rev.* **2015**, *115*, 634.

(10) (a) Engle, K. M.; Pfeifer, L.; Pidgeon, G. W.; Giuffredi, G. T.; Thompson, A. L.; Paton, R. S.; Brown, J. M.; Gouverneur, V. "Coordination diversity in hydrogen-bonded homoleptic fluoride–alcohol complexes modulates reactivity" *Chem. Sci.* **2015**, *6*, 5293. (b) Engle, K. M.; Pfeifer, L.; Pidgeon, G. W.; Sparkes, H. A.; Thompson, A. L.; Brown, J. M.; Gouverneur, V. "Hydrogen-bonded homoleptic fluoride–diarylurea complexes: structure, reactivity, and coordinating power" *J. Am. Chem. Soc.* **2016**, *138*, 13314.

(11) Pupo, G.; Ibba, F.; Ascough, D. M. H.; Vicini, A. C.; Ricci, P.; Christensen, K. E.; Pfeifer, L.; Morphy, J. R.; Brown, J. M.; Paton, R. S. Gouverneur, V. "Asymmetric nucleophilic fluorination under hydrogen bonding phase-transfer catalysis" *Science*, **2018**, *360*, 638.

(12) For recent reports/reviews on PTC, see: (a) Shirikawa, S.; Maruoka, K. "Recent Developments in Asymmetric Phase-Transfer Reactions", *Angew. Chem. Int. Ed.* **2013**, *52*, 4312. (b) Brak, K; Jacobsen, E. N. "Asymmetric Ion-Pairing Catalysis" *Angew. Chem.*

Int. Ed. **2013**, *52*, 534. (c) Phipps, R. J.; Hamilton, G. L.; Toste, F. D. "The Progression of Chiral Anions from Concepts to Application in Asymmetric Catalysis" *Nat. Chem.* **2012**, *4*, 603.

(13) Handbook of Chemistry and Physics, 85th edition, Lide, D. R., Ed., CRC Press, New York, U.S.A., **2004**, 12.

(14) For a previous report on the desymmetrization of *meso* aziridinium ions with oxygen nucleophiles: Hamilton, G. L.; Kanai, T.; Toste, F. D. "Chiral Anion-Mediated Asymmetric Ring Opening of *meso*-Aziridinium and Episulfonium Ions" *J. Am. Chem. Soc.* **2008**, 130, 14984.

(15) (a) Morgenthaler, M.; Schweizer, E.; Hoffmann-Roder, F.; Benini, F.; Martin, R. E.; Jaeschke, G.; Wagner, B.; Fischer, H.; Bendels, S.; Zimmerli, D.; Schneider, J.; Diederich, F.; Kansy, M.; Muller, K. "Predicting and Tuning Physicochemical Properties in Lead Optimization: Amine Basicities" *ChemMedChem* **2007**, *2*, 1100. (b) Briggs, C. R. S.; O'Hagan D.; Howard, J. A. K.; Yufit, D. S. "The C–F bond as a tool in the conformational control of amides" *J. Fluorine Chem.* **2003**, *119*, 9.

(16) For selected examples of drugs containing this motif, see: (a) Sofia, M. J.; Bao, D.; Chang, W.; Du, J.; Nagarathnam, D.; Rachakonda, S.; Reddy, P. G.; Ross, B. S.; Wang, P.; Zhang, H.–R.; Bansal, S.; Espiritu, C.; Keilman, M.; Lam, A.M.; Micolochick Steuer, H. M.; Niu, C.; Otto, M. J.; Furman P. A. "Discovery of a β-D-20-Deoxy-20-r-fluoro-20-β-C-methyluridine Nucleotide Prodrug (PSI-7977) for the Treatment of Hepatitis C Virus" *J. Med. Chem*. **2010**, *53*, 7202. (b) Sato, K.; Hoshino, K.; Tanaka, M.; Hayakawa, I.; Osada, Y.; "Antimicrobial Activity of DU-6859, a New Potent Fluoroquinolone, against Clinical Isolates" *Antimicrob. Agents Chemother*. **1992**, *36*, 1491. (f) Murray, T. K.; Whalley, K.; Robinson, C. S.; Ward, M. A.; Hicks, C. A.; Lodge, D.; Vandergriff, J. L.; Baumbarger, P.; Siuda, E.; Gates, M.; Ogden, A. M.; Skolnick, P.; Zimmerman, D. M.; Nisenbaum, E. S.; Bleakman, D.; O'Neill, M. J. "LY503430, a Novel α-Amino-3-hydroxy-5-methylisoxazole-4- propionic Acid Receptor Potentiator with Functional, Neuroprotective and Neurotrophic Effects in Rodent Models of Parkinson's Disease" *J. Pharmacol. Exp. Ther.* **2003**, *306*, 752.

(17) Aufiero, M.; Gilmour, R. "Informing Molecular Design by Stereoelectronic Theory: The Fluorine Gauche Effect in Catalysis" *Acc. Chem. Res.,* **2018**, *51*, 1701.

(18) (a) Guan, Y.; Han, Z.; Li, X.; You, C.; Tan, X.; Lv, H.; Zhang, X. "A cheap metal for a challenging task: nickel- catalyzed highly diastereo- and enantioselective hydrogenation of tetrasubstituted fluorinated enamides" *Chem. Sci.* **2019**, *10*, 252. (b) Vara, B. A.; Johnston, J. N. "Enantioselective Synthesis of β-Fluoro Amines via β-Amino α-Fluoro Nitroalkanes and a Traceless Activating Group Strategy" *J. Am. Chem. Soc.* **2016**, *138*, 13794; (c) Vaithiyanathan, V.; Kim, J.; Liu, Y.; Yan, H; Song, C. S. "Direct Access to Chiral β-Fluoroamines with Quaternary Stereogenic Center through Cooperative Cation-Binding Catalysis" *Chem. Eur. J.* **2017**, *23*, 1268. (d) Trost, B. M.; Saget, T.; Lerchen, A.; Hung, C. J. "Catalytic Asymmetric Mannich Reactions with Fluorinated Aromatic Ketones: Efficient Access to Chiral β -Fluoroamines" *Angew. Chem*. **2016**, *128*, 791. (e) Cosimi, E., Engl O. D., Saadi, J., Ebert, M-O Wennemers, H. "Stereoselective Organocatalyzed Synthesis of a-Fluorinated β-Amino Thioesters and Their Application in Peptide Synthesis" *Angew. Chem. Int. Ed.* **2016**, *55*, 13127. (f) Mizuta, S. Shibata, S.; Goto, Y.; Furukawa, T.; Nakamura, S.; and Toru, T. "Cinchona Alkaloid-Catalyzed Enantioselective Monofluoromethylation Reaction Based on Fluorobis(phenylsulfonyl)methane Chemistry Combined with a Mannich-type Reaction" *J. Am. Chem. Soc.* **2007**, *129*, 6394.

(19) (a) Fadeyi, O. O.; Lindsley, C. W. "Rapid General Access to Chiral β-Fluoroamines and β,β-Difluoroamines *via* Organocatalysis" *Org. Lett.* **2009***, 11,* 943; (b) O'Reilly, M. C.; Lindsley, C. W. "A general, enantioselective synthesis of β- and γ-fluoroamines" *Tetrahedron Lett.* **2013**, *54*, 3627. (c) Phipps, R. J.; Hiramatsu, K.; Toste, F. D. "Asymmetric Fluorination of Enamides: Access to α-Fluoroimines Using an Anionic Chiral Phase-Transfer Catalyst" *J. Am. Chem. Soc*. **2012**, *134*, 8376.

(20) (a) Lu, D. –F.; Zhu, C. –L.; Sears, J. D.; Xu, H., "Iron(II)-Catalyzed Intramolecular Olefin Aminofluorination" *J. Am. Chem. Soc.* **2016**, *138*, 11360. For approaches based on hypervalent iodine reagents/catalysts in combination with HF sources, see: (b) Suzuki, S.; Kamo, T.; Fukushi, K.; Hiramatsu, T.; Tokunaga, E.; Dohi, T.; Kita, Y.; Shibata, N. "Iodoarene-catalyzed fluorination and aminofluorination by an Ar–I/HF·pyridine/mCPBA system" *Chem. Sci.* **2014**, *5*, 2754. (c) Mennie, K. M.; Banik, S. M.; Reichert, E. C.; Jacobsen, E. N. "Catalytic Diastereo- and Enantioselective Fluoroamination of Alkenes" *J. Am. Chem. Soc.* **2018**, *140*, 4797. (d) Kong, W.; Feige, P.; De Haro, T.; Nevado, C. *Angew. Chem. Int. Ed.* **2013**, *52*, 2469. For approaches that generate HF *in situ*, see reference **5f**.

(21) Duthion, B.; Pardo, D. G.; Cossy, J. "Enantioselective Synthesis of β-Fluoroamines from β-Amino Alcohols: Application to the Synthesis of LY503430" *Org. Lett.,* **2010**, *12,* 4620.

(22) Janiri, L.; Persico, M. A.; Tempesta, E. "Dual effect of Lephetamine on spontaneous and evoked neuronal firing in the somatosensory cortex of the rat" *Neuropharmacology*, **1989**, *28*, 1405.

(23) Vitaku, E.; Smith, D. T.; Njardarson J. T. "Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals" *J. Med. Chem*. **2014**, *57*, 10257.

(24) (a) Natsuka, K; Nakamura, H. Negoro, T.; Hitoshi, U.; Nishimura, H. "Studies on 1-Substituted 4-(l,2-Diphenylethyl)piperazine Derivatives and their analgesic activities. Structure-Activity relationships of l-Cycloalkyl-4-(l,2-diphenylethyl)piperazines" *J. Med. Chem.* **1978**, *21*, 1265; (b) Sahai, M. A.; Davidson, C.; Dutta, N.; Opacka-Juffry, J. "Mechanistic Insights into the Stimulant Properties of Novel Psychoactive Substances (Nps) and Their Discrimination by the Dopamine Transporter—in Silico and in

Vitro Exploration of Dissociative Diarylethylamines" *Brain Sci.* **2018**, *8*, 63. (c) Luethi, D.; Hoener, M. C.; Liechti, M. E. "Effects of the new psychoactive substances diclofensine, diphenidine, and methoxphenidine on monoaminergic systems" *Eur. J. Pharmacol.*, **2018**, *819*, 242. (d) Berger, M. L.; Schweifer, A.; Rebernik, P.; Hammerschmidt, F. "NMDA Receptor Affinities of 1,2-Diphenylethylamine and 1-(1,2-Diphenylethyl)Piperidine Enantiomers and of Related Compounds" *Bioorganic Med. Chem.* **2009**, *17*, 3456; (e) Kang, H.; Park, P. Bortolotto, Z. A.; Brandt, S. D.; Colestock, T.; Wallach, J.; Collingridge, G. L.; Lodge, D. "Ephenidine: A new psychoactive agent with ketamine-like NMDA receptor antagonist properties" *Neuropharmacology,* **2017**, *112*, 144.

(25) Calculations were performed at the ωB97X-D3/(ma)-def2-TZVPP/COSMO($CHCl_3$)//M06-2X/def2-SVP(TZVPPD)/CPCM($CHCl_3$) level of theory. Optimizations and frequency analyses were performed in Gaussian 09, revision D.01, and single point energy corrections in ORCA 3.0.3. MD simulations were performed in GROMACS 5.1.4, using the OPLS-AA 2005 force field, in explicit chloroform solvent. See supporting information for full details of computational methods.

(26) For a preliminary ^{1}H and ^{19}F NMR study on binding of the urea catalyst (*S*)-**3g** with fluoride anion in solution (DCM-d_2), see the Supporting Information.

(27) Duarte, F.; Paton, R. S. "Molecular Recognition in Asymmetric Counteranion Catalysis − Understanding Chiral Phosphate-Mediated Desymmetrization" *J. Am. Chem. Soc.* **2017**, *139*, 8886.

(28) Kennedy, C. R.; Lin, S.; Jacobsen, E. N. "The Cation–π Interaction in Small-Molecule Catalysis" *Angew. Chem. Int. Ed.* **2016**, *55*, 12596.

(29) For general information on EDA approaches, see: (a) Zhao, L.; Hopffgarten, M. von; Andrada, D. M.; Frenking, G. "Energy Decomposition Analysis" *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **2018**, *8*, e1345. (b) Bickelhaupt, F. M.; Houk, K. N. "Analyzing Reaction Rates with the Distortion / Interaction-Activation Strain Model" *Angew. Chem. Int. Ed.* **2017**, *56*, 10070. (c) Fernández, I.; Bickelhaupt, F. M. "The Activation Strain Model and Molecular Orbital Theory: Understanding and Designing Chemical Reactions" *Chem. Soc. Rev.* **2014**, *43*, 4953.

(30) For selected examples of truncated/fragment models, see: (a) Maji, R.; Mallojjala, S. C.; Wheeler, S. E. "Chiral Phosphoric Acid Catalysis: From Numbers to Insights" *Chem. Soc. Rev.* **2018**, *47*, 1142. (b) Maji, R.; Champagne, P. A.; Houk, K. N.; Wheeler, S. E. "Activation Mode and Origin of Selectivity in Chiral Phosphoric Acid-Catalyzed Oxacycle Formation by Intramolecular Oxetane Desymmetrizations" *ACS Catal.* **2017**, *7*, 7332. (c) Seguin, T. J.; Wheeler, S. E. "Electrostatic Basis for Enantioselective Brønsted-Acid-Catalyzed Asymmetric Ring Openings of Meso-Epoxides" *ACS Catal.* **2016**, *6*, 2681. (d) Nguyen, Q. N. N.; Lodewyk, M. W.; Bezer, S.; Gagné, M. R.; Waters, M. L.; Tantillo, D. J. "Effects of Helix Macrodipole and Local Interactions on Catalysis of Acyl Transfer by α-Helical Peptides" *ACS Catal.* **2015**, *5*, 1617.

(31) For selected examples of the distortion/interaction-activation strain model, see: (a) Chen, S.; Zheng, Y.; Cui, T.; Meggers, E.; Houk, K. N. "Arylketone π-Conjugation Controls Enantioselectivity in Asymmetric Alkynylations Catalyzed by Centrochiral Ruthenium Complexes" *J. Am. Chem. Soc.* **2018**, *140*, 5146. (b) Chen, S.; Houk, K. N. "Origins of Stereoselectivity in Mannich Reactions Catalyzed by Chiral Vicinal Diamines" *J. Org. Chem.* **2018**, *83*, 3171. (c) Chen, S.; Huang, X.; Meggers, E.; Houk, K. N. "Origins of Enantioselectivity in Asymmetric Radical Additions to Octahedral Chiral-at-Rhodium Enolates: A Computational Study" *J. Am. Chem. Soc.* **2017**, *139*, 17902. (d) Zhang, S. Q.; Taylor, B. L. H.; Ji, C.-L.; Gao, Y.; Harris, M. R.; Hanna, L. E.; Jarvo, E. R.; Houk, K. N.; Hong, X. "Mechanism and Origins of Ligand-Controlled Stereoselectivity of Ni-Catalyzed Suzuki-Miyaura Coupling with Benzylic Esters: A Computational Study" *J. Am. Chem. Soc.* **2017**, *139*, 12994. (e) Maji, R.; Champagne, P. A.; Houk, K. N.; Wheeler, S. E. "Activation Mode and Origin of Selectivity in Chiral Phosphoric Acid-Catalyzed Oxacycle Formation by Intramolecular Oxetane Desymmetrizations" *ACS Catal.* **2017**, *7*, 7332.

(32) Dihedral angles were measured between the conjugating phenyl ring and the C–C bond of the aziridinium ring (Fig. S2). The optimum dihedral angle was estimated by performing a dihedral scan of the fluoride delivery TS with a small, achiral urea. The dihedral in the major TS, is approximately 7° from optimum, and in the minor, 27° (Fig. S13).

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