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

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Supporting Information

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 industries. Fluorine substituents can alter the pKa of neighboring groups, dipole moment, and properties such as metabolic stability, lipophilicity and bioavailability. In this context, the demand for molecules featuring the fluorine substituent on a sterogenic carbon has accelerated the development of catalytic enantioselective fluorination methodologies. Electrophilic fluorine sources of tailored reactivity have proved valuable for rapid advance of this field of research. Asymmetric catalysis toward C–F bond formation using nucophile fluorine sources has progressed at a slower pace in part due to the difficulties in controlling fluoride reactivity. Fluoride is solvated and poorly reactive in protic media, while unsolvated fluoride can react as a Brønsted base. These issues have led to the development of reagents designed for in situ release of fluoride into solution. Additional challenges for metal alkali fluorides are their hygroscopicity and poor solubility in organic solvents. 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.

Nature has evolved a fluorinase enzyme that makes use of a hydrogen bonded fluoride complex to enable C–F bond formation. Inspired by this transformation, we prepared fluoride complexes derived from alcohols and ureas to study the effect of hydrogen bonding on fluoride reactivity. These studies culminated with the discovery of hydrogen bonding phase-transfer catalysis (HB-PTC), a new activation mode for PTC whereby a neutral hydrogen bond donor urea catalyst acts as a transport agent to bring solid cesium fluoride, CsF(lattice energy, 759 kJ/mol), into solution in the form of a hydrogen bonded fluoride complex. This strategy afforded enantioenriched β-fluorosulphides with a chiral N-alkyl bis-urea catalyst U* (Figure 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 fluoride sources (Figure 1B).

Encouraged by initial calculations indicating that the energy required to solubilize KF(s) under HB-PTC was tantalizing considering the advantages of this reagent compared to other fluoride sources (Figure 1B).

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.

Received: November 30, 2018  
Published: January 28, 2019
were selected as substrates for this study because desymmetrization with KF affords high value enantioenriched \( \beta \)-fluoroamines that are of considerable interest for applications in medicinal chemistry, especially for central nervous system drug discovery,\textsuperscript{15,16} and catalyst design.\textsuperscript{17} Specifically, we propose that a chiral bis-urea of type U\textsuperscript{*} brings KF\textsubscript{s} into solution as a tricoordinated hydrogen bonded complex; ion pairing of this complex with \textit{in situ} formed meso aziridinium ion followed by fluorination delivers the enantioenriched \( \beta \)-fluoroamine with release of the bis-urea catalyst (Figure 1C).

Most catalytic asymmetric methodologies toward \( \beta \)-fluoroamines require fluorinated building blocks,\textsuperscript{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.\textsuperscript{19} Catalytic enantioselective nucleophilic fluorinations toward \( \beta \)-fluoroamines have also appeared, but these reactions typically require hazardous HF reagents, or rely on \textit{in situ} fluoride release from reagents of reduced atom economy.\textsuperscript{20} These examples highlight the progress made toward accessing enantioenriched \( \beta \)-fluoroamines, and underline the demand for asymmetric catalytic methods for their synthesis using safe and readily available fluoride sources such as KF\textsubscript{s}.

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

The reaction of rac-1a and KF (3 equiv) in dichloromethane at r.t. with 5 mol% of urea (S)-3a afforded \( \beta \)-fluoroamine 2a in >99% yield, but no control over enantioselectivity was observed (\( \text{e.r.} = 55:45 \) (Table 1, entry 1)). This result however demonstrated that HB-PTC enables fluorination with KF. The N-alkylated catalysts (S)-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 \( \text{e.r.} \). The \( \text{e.r.} \) (up to 90:5:95) was increased with N-alkylated catalysts (S)-3f and (S)-3g featuring an extended polytrifluoromethylated terphenyl \( \pi \)-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 \( \text{e.r.} \)). The optimized conditions consist of treating rac-1a with KF (5 equiv) and (S)-3g (10 mol%) in CH\textsubscript{2}Cl\textsubscript{2} at \( \sim 15 \degree \text{C} \) for 72 h (Table 1, entry 11).

With the optimal reaction conditions in hand, we studied the scope of the reaction (Scheme 1). Substrates with a range of different amines were subjected to enantioselective fluorination. The fluorinated analogue of the analgesic lefatemin\textsuperscript{22} 2b possessing two methyl groups on nitrogen was obtained in 65% yield and 95:5 \( \text{e.r.} \). Various \( \text{N} \)-heterocycles were tolerated including motifs frequently encountered in FDA approved drugs (e.g., piperidine, piperazine, pyrrolidine, morpholine);\textsuperscript{23} this was demonstrated with the synthesis of \( \beta \)-fluoroamines 2c–i that were obtained in good yields and high enantioselectivities (up to 94% yield and 96:4 \( \text{e.r.} \)). Within this series, asymmetric HB-PTC gave access to fluorinated analogues of NMDA receptor antagonists 2e (MT-45)\textsuperscript{24a} and 2g (diphenidine) in high enantioselectivity.\textsuperscript{24b–d} The reaction is highly effective for substrates possessing two different \( \text{N} \)-substituents that may lead to two diastereomeric \textit{meso} aziridinium ions as exemplified with the synthesis of 2i, 2j and 2k that were obtained with \( \text{e.r.} \) reaching 96:4. Various substituents on the phenyl ring of the substrates are compatible including electron-donating and electron-withdrawing groups. \( \beta \)-Fluoroamines 2l–2s were synthesized in good yields and \( \text{e.r.} \) (up to 87% yield and 96:4 \( \text{e.r.} \)). A study comparing KF and CsF indicates that comparable yields could be obtained by 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 \textit{meso} aziridinium precursors were also evaluated. Asymmetric catalytic fluorination occurred smoothly at room temperature in \( \text{a,a,a-trifluorotoluene} \), and afforded the cyclic \( \beta \)-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 \degree \text{C}, and afforded 2a in 76% yield and 93:7 \( \text{e.r.} \) (Scheme 2A). N-Deprotection of \( \beta \)-fluoroamine 2a under Pd(0) catalysis\textsuperscript{21} afforded \( \beta \)-fluoroamine 4 in 72% yield with no erosion of \( \text{e.r.} \). A single recrystallization gave 4 in high enantiopurity (99:8:0 \( \text{e.r.} \)). Reductive amination of 4 with acetaldehyde yielded fluorinated epiphenidine 5 as a single enantiomer,\textsuperscript{24e} an

### Table 1. Optimization of Reaction Conditions\textsuperscript{a}

| entry | cat. | solvent | \( T \) (\degree \text{C}) | yield\textsuperscript{b} | \( \text{e.r.} \) |
|-------|------|---------|----------------|----------------|----------------|
| 1     | 3a   | DCM     | r.t.           | >99%           | 55:45         |
| 2     | 3b   | DCM     | r.t.           | 98%            | 85:15         |
| 3     | 3c   | DCM     | r.t.           | >99%           | 86:14         |
| 4     | 3d   | DCM     | r.t.           | 83%            | 86:14         |
| 5     | 3e   | DCM     | r.t.           | 77%            | 55:45         |
| 6     | 3f   | DCM     | r.t.           | 72%            | 88:12         |
| 7     | 3g   | DCM     | r.t.           | 80%            | 90:5:95       |
| 8\textsuperscript{d} | 3g | DCM     | 0              | 80%            | 93:5:6:5      |
| 9\textsuperscript{d} | 3g | CH\textsubscript{2}Cl\textsubscript{e} | 0              | 90%            | 93:5:6:5      |
| 10    | 3g   | 1,2-DFB | 0              | 58%            | 94:6          |
| 11\textsuperscript{d} | 3g | CH\textsubscript{2}Cl\textsubscript{f} | \textit{15} | 71%            | 95:5          |

\( \text{a} \text{Reaction conditions: 0.05 mmol of 1a, 0.25 M, (S)-3a–g (5 mol%), stirring at 900 rpm for 24 h.} \text{b} \text{Determined by} \textsuperscript{19} \text{F-NMR using 4-fluoroanisole as internal standard.} \text{c} \text{e.r. = enantiomeric ratio determined by HPLC.} \text{d} \text{0.5 M, 5 equiv of KF, 10 mol% of 3g.} \text{e} \text{CH\textsubscript{2}Cl\textsubscript{2} was filtered on basic alumina to remove residual HCl.} \text{f} \text{Yield of isolated product after 72 h.} \)
additional NMDA receptor antagonist of the 1,2-diphenylethylamine family.

In order to demonstrate the applicability of the methodology to multidecagram synthesis, we further optimized the process (Scheme 2B, 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)\textsubscript{3}g for 72 h; this was made possible by increasing the concentration to 2 M and replacing chloroform with dichloromethane. The catalyst (S)\textsubscript{3}g was separated from the product 2g via acid/base workup, and the crude product was purified with a single recrystallization in MeOH to a 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. Noteworthily, the reaction setup is operationally simple, does not require dry solvents, is carried out under air, and KF is used without any pretreatment.

The reaction was investigated computationally by molecular dynamics (MD) simulations, and density functional theory (DFT) calculations (see SI for full details). MD simulations in chloroform confirmed that N-alkylated catalyst (S)\textsubscript{3}g forms a stable and persistent tridentate fluoride complex, with the alkylated urea in an anti-syn conformation. MD was further used for conformational sampling for DFT calculations, resulting in 15 DFT optimized transition structures (TSs) for ring-opening of diaryl-based aziridinium, leading to 2b. A Boltzmann ensemble of competing TSs predicted preferential (S,S) product formation from catalyst (S)\textsubscript{3}g (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 toward 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 (Figure 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 (Figure 2Bii).

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 (Figure 2Biii). These combined effects contribute approximately half of ΔΔG‡. The remainder is due to substrate conformation (Figure 2Biv), favoring conjugation of the phenyl ring with the forming and breaking bonds (benzylic Sν2). 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

In summary, we have shown that asymmetric HB-PTC enables enantioselective fluorination of racemic β-haloamines 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 pretreatment 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

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b12568.

Additional optimization and mechanistic data, computational methods and energies (PDF)

Molecular dynamics input and DFT xyz coordinates (ZIP)

Crystallographic data (CIF)

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§These authors contributed equally to this work.

### Notes

The authors declare no competing financial interest. Crystallographic data are available free of charge from the Cambridge Crystallographic Data Centre under references CCDC 1880527–1880530.

### ACKNOWLEDGMENTS

We thank Dr P. Ricci for preliminary experiments. This work was supported by the EU Horizon 2020 Research and Innovation Programme (Marie Skłodowska-Curie agreements
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