Asymmetric nucleophilic fluorination under hydrogen bonding phase-transfer catalysis

Gabriele Pupo,[1†] Francesco Ibba,[1†] David M. H. Ascough,[1†] Anna Chiara Vicini,[1] Paolo Ricci,[1] Kirsten E. Christensen,[1] Lukas Pfeifer,[1] John Richard Morphy,[2] John M. Brown,[1] Robert S. Paton,[1] Véronique Gouverneur[1]*

[1] University of Oxford, Chemistry Research Laboratory, 12 Mansfield Road, OX1 3TA, Oxford (UK).

[2] Medicinal Chemistry, Eli Lilly and Company Limited, Erl Wood Manor, Sunninghill Road, GU20 6PH, Windlesham (UK).

[†] These authors have contributed equally to this work.

* Corresponding author. E-mail: veronique.gouverneur@chem.ox.ac.uk

Abstract: Common anionic nucleophiles such as those derived from inorganic salts have not been used for enantioselective catalysis because of their insolubility. Here, we disclose that merging hydrogen bonding and phase-transfer catalysis provides an effective mode of activation for nucleophiles that are insoluble in organic solvents. This catalytic manifold relies on hydrogen bonding complexation to render nucleophiles soluble and reactive, while simultaneously inducing asymmetry in the ensuing transformation. We demonstrate the concept using a chiral bis-urea catalyst to form a tridentate hydrogen bonding complex with fluoride from its cesium salt, thereby enabling highly efficient enantioselective ring-opening of episulfonium ion. This

fluorination method is synthetically valuable considering the scarcity of alternative protocols and points the way to wider application of the catalytic approach with diverse anionic nucleophiles.

One Sentence Summary: A chiral urea catalyst that transports fluoride ion by hydrogen bonding enables enantioselective fluorination with alkali metal fluorides.

Phase-transfer catalysis (PTC) (*1*) has progressed enormously with the appearance of powerful asymmetric methods based on lipophilic chiral cationic (*2*) or anionic salts (*3*) as catalysts. Despite these advances, an outstanding challenge is asymmetric synthesis where the solid phase reagent is a simple inorganic salt. Herein, we propose a solution, based on anion recognition by hydrogen bonding, to enable asymmetric PTC in organic media with poorly soluble inorganic nucleophiles. For proof-of-concept, we focused on the activation of alkali metal fluorides for the enantioselective installation of sp^3 C–F, a highly important functional group for applications in pharmaceutical sciences (*4*–*6*).

Catalytic enantioselective fluorination is dominated by methods employing electrophilic fluorinating reagents (*7*). Although alkali metal fluorides are abundant and inexpensive, their low solubility and high Brønsted basicity have hindered their application to asymmetric nucleophilic fluorination (*8*–*12*). Both cationic (*13*) and anionic (*3*) PTC have been successfully applied to asymmetric electrophilic fluorinations (Fig. 1A). Phase-transfer agents enabling nucleophilic rather than electrophilic fluorination have been extensively investigated, and the most common approach to enhance metal fluorides' reactivity in organic solvents entails metal encapsulation with a crown-ether (*14, 15*). Despite these advances, enantioselective fluorination with metal fluorides under PTC remains an unsolved problem. This state of play prompted us to formulate a strategy that embraces the poor solubility of metal fluorides in organic solvents and the capacity of fluoride to engage in H-bonding interactions. Fluoride-, and more generally anion-abstraction with a hydrogen bond donor (HBD) catalyst (*16–21*), has been explored to activate electrophiles via chiral ion pairs that react with an external nucleophile (Fig. 1B). Here, we introduce an alternative scenario where the H-bonded fluoride complex itself is the nucleophile for fluorination. We envisioned that a chiral HBD could act as a solid-liquid phase-transfer catalyst enabling enantioselective nucleophilic fluorination with a metal fluoride insoluble in organic media. The *in situ* formed H-bonded fluoride complex would become soluble and capable of mediating fluorination of an organic substrate with release of the HBD catalyst (Fig. 1C). Complexation of fluoride with HBDs is well documented, but has not been explored to access enantioenriched alkyl fluorides (*22–24*). We reported that urea-fluoride complexes are suitable reagents for the nucleophilic substitution of alkyl bromides, the reactive species being a 1:1 urea-fluoride complex (*25*). We therefore selected ureas as catalysts capable of bringing insoluble alkali metal fluorides (e.g. KF or CsF) into non-polar solution. For substrate choice, we sought inspiration from the fluorinase enzyme. The only known fluorination reaction in nature involves *S*-adenosyl-L-methionine with a sulfonium leaving group, and proceeds via an S_N2 pathway leading to a primary alkyl fluoride product (Fig. 1D). We focused on β-bromosulfides as model substrates because i) they form highly electrophilic episulfonium ions that readily undergo diastereospecific bond-forming reactions with nucleophiles (*21*), ii) the positively charged sulfur of the episulfonium ion can interact with the *in situ* formed urea-fluoride complex in a manner reminiscent of the HB-fluoride-sulfonium pre-reaction complex characteristic of the enzyme (*26–29*), iii) *meso*-episulfonium ions are suitable for enantioselective desymmetrization with a chiral urea catalyst, iv) the fluorination products contain both fluorine and sulfur, which are important elements in drug design, thus underlining the value of the products for medicinal chemistry (*4–6, 30*).

Racemic β-bromosulfides were conveniently prepared from the corresponding *cis*-epoxides via a two-step epoxide-ring opening/bromination sequence, or via a one-pot protocol from the corresponding *cis*-alkene (fig. S5-S7). Preliminary experiments (fig. S1) revealed that **1a** performed particularly well under the designed catalytic conditions (Fig. 2A). No fluorination occurred at room temperature when **1a** was treated with 1.2 equiv. of CsF in toluene, acetonitrile or dichloromethane (0.25 M); in contrast, C–F bond formation took place in the presence of 10 mol% of urea **2a** (*31*) affording the desired product **3a** in yields up to 80% in CH_2Cl_2. Retention of configuration occurred, an observation consistent with fluoride attack on an *in situ* formed episulfonium ion. The reaction also proceeded with KF under urea catalysis, but this reagent required significantly longer time (table S1). This solid liquid phase-transfer manifold has advantages over the use of soluble fluoride sources such as AgF or *n*-$Bu_4NF{\cdot}3H_2O$, not least because it generates reactive fluoride at controllable low concentration and offers the possibility to induce asymmetry with a chiral non-racemic urea catalyst. Excision of the catalyst's HBD groups, or reduction of acidity through substituent effects led to no reaction or a decrease in reactivity (table S1). No product was formed with the corresponding thiourea (fig. S3), prompting the use of urea catalysts for subsequent studies. These data gave insight into the parameters enabling catalysis, and suggested that urea–fluoride HB is a key interaction to enable C–F bond formation.

Computational analysis of the reaction catalyzed by urea **2a** and the corresponding uncatalyzed pathway was undertaken to gain more insight (Fig. 2B). The thermodynamics of phase-transfer were evaluated by combining experimental CsX formation free energies with density functional theory (DFT)-computed data in an anion exchange process (fig. S9). The reaction is initiated by ionization of *rac*-**1k** to form the tight episulfonium-bromide ion pair **ii**, with a barrier to auto-ionization of 90 kJ/mol (**i**‡). Following ion pair dissociation, uncatalyzed halide anion exchange (**iii-iv**) of free bromide for free fluoride in solution is unfavorable by 34 kJ/mol, the much higher lattice energy of CsF relative to CsBr playing a crucial role. Unfavorable ion transport is therefore responsible for the prohibitively high energetic span of the uncatalyzed pathway (122 kJ/mol). The key catalytic role of the urea is in promoting anion-exchange through preferential stabilization of fluoride in solution. With urea **2a**, anion exchange becomes favorable by 17 kJ/mol, due to the stronger H-bonding of F^- over Br^- to the catalyst. The lower reactivity of fluoride sources such as KF arises from larger differences in lattice energies between the metal fluoride and bromide salts, which disfavor ion transport (table S9). Fluoride delivery (via TS **vi**‡**)** to form the product is irreversible, even in the presence of catalyst, with a barrier to the reverse reaction of 135 kJ/mol, indicating that the product is not susceptible to racemization and that this step is enantio-determining using a chiral urea catalyst. In the fluoride delivery transition structure (TS), the phenyl ring on the α-carbon stabilizes the TS by aligning its π system with the forming/breaking bonds (table S10).

Activation of otherwise insoluble fluoride by a urea ligand provides a platform for asymmetric catalysis (Fig. 2C). We considered axially chiral C_2-symmetric ureas derived from BINAM ([1,1'-binaphthalene]-2,2'-diamine) (*32*) because these systems can be readily tuned through structural modification. After initial optimization, **1a** underwent fluorination with (*S*)-**4a** (10 mol%) (*32*) in 1,2-difluorobenzene at room temperature affording (+)-**3a** after 1.5 h in > 95% yield and an enantiomeric ratio (e.r.) of 86:14 (table S2). Catalysts (*S*)-**4b–e** modified at the binaphthyl core or presenting a phenyl instead of the 3,5-(trifluoromethyl)phenyl group were less effective (fig. S2). The presence of two urea motifs within catalyst **4a** prompted us to interrogate which H-bond interactions are necessary for reactivity and enantioselectivity, experimentally and computationally.

Molecular dynamics (MD) simulations of the solution-phase conformation of **4a** binding cesium fluoride indicated that isomerism of one urea proximal to the binaphthyl core from *anti-anti* to *anti-syn* was likely, and DFT calculations reinforced the energetic preference for the resulting tridentate H-bonding mode (tables S14, S15). Experimentally, the fluorination of *rac*-**1a** was carried out with the corresponding mono- and di-methylated catalysts to probe the requirements for effective H-bonding (fig. S2). These catalysts were less effective or ineffective with the exception of **4f**, methylated at the N-H that is predicted computationally not to interact with fluoride. This catalyst is as active as **4a** and enhances enantiocontrol (> 95% yield, 88:12 e.r.). The replacement of the *N*-methyl group with a larger alkyl group (**4g–h**), and further optimization (– 30 ºC) afforded (+)-**3a** in 90% yield (95.5:4.5 e.r.).

Based on these data, we selected catalyst (*S*)-**4h** to study the scope of this process (Fig. 3A). Variation of the substituents on the carbon backbone of the electrophile revealed that aryl groups with meta- and para-positioned electron-donating and electron-withdrawing functionalities are compatible, affording the desired products (*S*,*S*)-**3a-l** in high yields and enantioselectivities. The sulfur substituent can also be modified with phenylethyl affording the products with the highest enantioselectivity. By this route, a gram quantity of **1d** underwent fluorination affording (*S*,*S*)-**3d** in 51% overall yield as a single enantiomer (>99.9:0.1 e.r.) after one recrystallization. Despite recent interest in the preparation and properties of molecules containing the F–C–C–S(O)$_n$ (*n* = 0, 1 and 2) motif (*30, 33*), no alternative method to access these scaffolds in enantiopure form has been developed to date.

The linear relationship between the enantiopurity of catalyst and product indicates that one chiral urea is involved in the enantiodetermining step (fig. S4). Following extensive MD simulation of the reactive ion pair, more than thirty DFT-calculated TSs were optimized for catalysts (*S*)-**4f** and (*S*)-**4h** with substrate **1k** (fig. S24, S27). A Boltzmann ensemble of competing (*S*)-**4h** TSs predicted (*S*,*S*)-product formation (supported by single-crystal x-ray diffraction) (fig. S33) in 96.5:3.5 e.r. (at 243.15 K), a result which aligns with the experimental value (91:9 e.r.). The alkylated urea adopts an *anti*-*syn* conformation in both the fluoride complex and the populated TSs, which were subsequently found to overlay well with the x-ray structure of tetrabutylammonium fluoride·**4h** (TBAF·**4h**) (fig. S32), in terms of catalyst conformation, fluoride binding mode, and position of the cation (Fig. 3B) (fig. S28). In the lowest energy TSs (Fig. 3C), the catalyst interacts favorably with the substrate through cation-π and CH-π non-covalent interactions (fig. S30). Catalyst:substrate non-covalent interactions are similar in competing TSs; however, shorter distances in the major TS are consistent with preferential binding. Substrate conformation also contributes to the sense of selectivity. Phenyl ring rotation adjacent to the site of nucleophilic substitution is unfavorable, due to loss of conjugation, and is more pronounced in the less favorable (i.e. minor) pathway contributing half of $\Delta\Delta G^{\ddagger}$ (fig. S29). Only in the major TS can the substrate dock into the catalyst, with a full complement of non-covalent interactions, whilst maintaining phenyl conjugation.

Due to the early TS position along the intrinsic reaction coordinate (IRC) pathway, all three H---F interactions remain bonded in the TS (<1.9 Å), but lengthen over the IRC pathway due to charge neutralization. This effect is strongest for H-bond 3, which lengthens at 1.8 to 3.5x the rate of the other H-bonds, resulting in bidentate binding. In forming the major enantiomer, a significant lengthening of H-bond 2 also occurs along the IRC pathway once the C–F bond is fully formed, resulting in one dominant H-bond with the product (fig. S31). The evolution of H-bonds closely mimics the fluorinase enzymatic mechanism, with the bidentate urea (H-bonds 1 and 2) mimicking Ser 158A and the alkylated urea (H-bond 3) mimicking the role of Thr 80A (*28*).

We have introduced hydrogen bonding phase-transfer catalysis (HB PTC), and have applied this approach to asymmetric nucleophilic fluorination with a metal fluoride. The protocol employs a safe fluoride source and a readily accessible urea-catalyst, avoiding transition metals and the need to exclude air and moisture. Beyond fluorination, we anticipate that many inexpensive nucleophiles insoluble in organic solvents can be productively applied to enantioselective catalysis using this approach. More generally, this research opens new opportunities in the design of chiral catalysts for enantioselective catalysis.

Acknowledgments

We thank R. Surgenor for selected experiments. **Funding:** This work was supported by the EU Horizon 2020 Research and Innovation Programme (Marie Skłodowska-Curie agreements 675071 and 316882), EPSRC (EP/R010064, SBM-CDT EP/L015838/1), and Lilly Research Award Program. We acknowledge the University of Oxford Advanced Research Computing facility (**http://dx.doi.org/10.5281/zenodo.22558**) and the Extreme Science and Engineering Discovery Environment (XSEDE) through allocation TG-CHE180006. **Author**

contributions: G.P. and F.I. performed the experimental work in collaboration with A.C.V.. Preliminary experiments and binding studies were performed by P.R. and L.P.. The computational studies were performed by D.M.H.A. and R.S.P., and K.E.C. acquired the x-ray data. All authors contributed to the design of the experimental and computational work, to data analysis, discussed the results, and commented on the manuscript. R.S.P. and V.G. wrote the manuscript. V.G. conceived and supervised the project. All authors declare no conflicting interests. **Data and materials availability:** Crystallographic data are available free of charge from the Cambridge Crystallographic Data Centre under references CCDC 1812187 and CCDC 1812188. Additional optimization and mechanistic data are provided in the supplementary materials.

Figure Legends

Fig. 1. Catalytic reaction design. (A) Enantioselective electrophilic fluorination under PTC. (B) Electrophile activation under hydrogen bonding catalysis. (C) Proposed enantioselective nucleophilic fluorination under hydrogen bonding PTC; urea-catalyzed fluorination of an episulfonium ion precursor with an alkali metal fluoride (M^+F^-). (D) Hydrogen bonded fluoride complex for nucleophilic fluorination of *S*-adenosyl-L-methionine catalyzed by the fluorinase enzyme.

Fig. 2. Reaction development. (A) Urea-catalyzed fluorination of *rac*-**1a**. (B) Computed Gibbs energy profile (ωB97X-D3/(ma)-def2-TZVPP/COSMO(CH_2Cl_2)//M06-2X/def2-SVP(TZVPPD)/

CPCM(CH_2Cl_2) at 298.15 K in kJ/mol) for urea-catalyzed (**2a**) fluorination of *rac*-**1k**, compared with the uncatalyzed reaction. (C) Enantioselective nucleophilic fluorination of *rac*-**1a** catalyzed by (*S*)-**4a–h**; rt, room temperature.

Fig. 3. Scope and mechanistic insights. (A) Substrate scope. Absolute configuration was assigned by x-ray diffraction analysis of **3d**. (B) Single crystal structure of TBAF·**4h** overlaid with the DFT-predicted solvated structure of CsF·**4h** (excluding cations). (C) Competing major and minor transition states (DFT) leading to either enantiomer.

References

1. K. Maruoka, Ed., *Asymmetric Phase Transfer Catalysis* (Wiley-VCH, Weinheim, Germany, 2008).

2. T. Ooi, K. Maruoka, Recent advances in asymmetric phase-transfer catalysis. *Angew. Chem. Int. Ed.* **46**, 4222–4226 (2007).

3. V. Rauniyar, A. D. Lackner, G. L. Hamilton, F. D. Toste, Asymmetric electrophilic fluorination using an anionic chiral phase-transfer catalyst. *Science* **334**, 1681–1684 (2011).

4. K. Müller, C. Faeh, F. Diederich, Fluorine in pharmaceuticals: looking beyond intuition. *Science* **317**, 1881–1886 (2007).

5. S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **37**, 320–330 (2008).

6. I. Ojima, Ed., *Fluorine in Medicinal Chemistry and Chemical Biology* (Wiley-Blackwell, Chichester, UK, 2009).

7. X. Yang, T. Wu, R. J. Phipps, F. D. Toste, Advances in catalytic enantioselective fluorination, mono-, di-, and trifluoromethylation, and trifluoromethylthiolation reactions. *Chem. Rev.* **115**, 826–870 (2015).

8. J. A. Kalow, A. G. Doyle, Enantioselective ring opening of epoxides by fluoride anion promoted by a cooperative dual-catalyst system. *J. Am. Chem. Soc.* **132**, 3268–3269 (2010).

9. M. H. Katcher, A. G. Doyle, Palladium-catalyzed asymmetric synthesis of allylic fluorides. *J. Am. Chem. Soc*. **132**, 17402–17404 (2010).

10. J. A. Kalow, A. G. Doyle, Mechanistic investigations of cooperative catalysis in the enantioselective fluorination of epoxides. *J. Am. Chem. Soc.* **133**, 16001–16012 (2011).

11. M. H. Katcher, A. Sha, A. G. Doyle, Palladium-catalyzed regio- and enantioselective fluorination of acyclic allylic halides. *J. Am. Chem. Soc.* **133**, 15902–15905 (2011).

12. S. Suzuki, T. Kamo, K. Fukushi, T. Hiramatsu, E. Tokunaga, T. Dohi, Y. Kita, N. Shibata, Iodoarene-catalyzed fluorination and aminofluorination by an Ar–I/HF·pyridine/*m*CPBA system. *Chem. Sci.* **5**, 2754–2760 (2014).

13. X. Wang, Q. Lan, S. Shirakawa, K. Maruoka, Chiral bifunctional phase transfer catalysts for asymmetric fluorination of β-keto esters. *Chem. Commun.* **46**, 321–323 (2010).

14. C. L. Liotta, H. P. Harris, Chemistry of naked anions. I. Reactions of the 18-crown-6 complex of potassium fluoride with organic substrates in aprotic organic solvents. *J. Am. Chem. Soc.* **96**, 2250–2252 (1974).

15. V. H. Jadhav, H. J. Jeong, W. Choi, D. W. Kim, Crown ether metal complex fluoride salt as a facile and low hygroscopic fluoride source for nucleophilic fluorination. *Chem. Eng. J.* **270**, 36–40 (2015).

16. J. A. Birrell, J. N. Desrosiers, E. N. Jacobsen, Enantioselective acylation of silyl ketene acetals through fluoride anion-binding catalysis. *J. Am. Chem. Soc.* **133**, 13872–13875 (2011).

17. A. G. Doyle, E. N. Jacobsen, Small-molecule H-bond donors in asymmetric catalysis. *Chem. Rev.* **107**, 5713–5743 (2007).

18. K. Brak, E. N. Jacobsen, Asymmetric ion-pairing catalysis. *Angew. Chem. Int. Ed.* **52**, 534–561 (2013).

19. S. M. Banik, A. Levina, A. M. Hyde, E. N. Jacobsen, Lewis acid enhancement by hydrogen-bond donors for asymmetric catalysis. *Science* **358**, 761–764 (2017).

20. R. J. Phipps, G. L. Hamilton, F. D. Toste, The progression of chiral anions from concepts to applications in asymmetric catalysis. *Nat. Chem.* **4**, 603–614 (2012).

21. S. Lin, E. N. Jacobsen, Thiourea-catalysed ring opening of episulfonium with indole derivatives by means of stabilizing non-covalent interactions. *Nat. Chem.* **4**, 817–823 (2012).

22. J.–W. Lee, M. T. Oliveira, H. B. Jang, S. Lee, D. Y. Chi, D. W. Kim, C. E. Song, Hydrogen-bond promoted nucleophilic fluorination: concept, mechanism and applications in positron emission tomography. *Chem. Soc. Rev.* **45**, 4638–4650 (2016).

23. S. Liang, G. B. Hammond, B. Xu, Hydrogen bonding: regulator for nucleophilic fluorination. *Chem. Eur. J.* **23**, 17850–17861 (2017).

24. K. M. Engle, L. Pfeifer, G. W. Pidgeon, G. T. Giuffredi, A. L. Thompson, R. S. Paton, J. M. Brown, V. Gouverneur, Coordination diversity in hydrogen-bonded homoleptic fluoride–alcohol complexes modulates reactivity. *Chem. Sci.* **6**, 5293–5302 (2015).

25. L. Pfeifer, K. M. Engle, G. W. Pidgeon, H. A. Sparkes, A. L. Thompson, J. M. Brown, V. Gouverneur, Hydrogen-bonded homoleptic fluoride–diarylurea complexes: structure, reactivity, and coordinating power. *J. Am. Chem. Soc.* **138**, 13314–13325 (2016).

26. D. O'Hagan, C. Schaffrath, S. L. Cobb, J. T. G. Hamilton, C. D. Murphy, Biochemistry: biosynthesis of an organofluorine molecule. *Nature* **416**, 279 (2002).

27. C. Dong, F. Huang, H. Deng, C. Schaffrath, J. B. Spencer, D. O'Hagan, J. H. Naismith, Crystal structure and mechanism of a bacterial fluorinating enzyme. *Nature* **427**, 561–565 (2004).

28. X. Zhu, D. A. Robinson, A. R. McEwan, D. O'Hagan, J. H. Naismith, Mechanism of enzymatic fluorination in *Streptomyces cattleya*. *J. Am. Chem. Soc.* **129**, 14597–14604 (2007).

29. D. O'Hagan, H. Deng, Enzymatic fluorination and biotechnological developments of the fluorinase. *Chem. Rev.* **115**, 634–649 (2015).

30. C. Thiehoff, M. C. Holland, C. Daniliuc, K. N. Houk, R. Gilmour, Can acyclic conformational control be achieved *via* a sulfur–fluorine *gauche* effect?. *Chem. Sci.* **6**, 3565–3571 (2015).

31. P. R. Schreiner, Metal-free organocatalysis through explicit hydrogen bonding interactions. *Chem. Soc. Rev.* **32**, 289–296 (2003).

32. E. M. Fleming, T. McCabe, S. J. Connon, Novel axially chiral bis-arylthiourea-based organocatalysts for asymmetric Friedel–Crafts type reactions. *Tetrahedron Lett.* **47**, 7037–7042 (2006).

33. Z. Yuan, H-Y. Wang, X. Mu, P. Chen, Y.-L. Guo, G. Liu, Highly selective Pd-catalyzed intermolecular fluorosulfonylation of styrenes. *J. Am. Chem. Soc.* **137**, 2468–2471 (2015).

34. H. Y. Kim, K. Oh, Highly diastereo- and enantioselective aldol reaction of methyl α-isocyanoacetate: a cooperative catalysis approach. *Org. Lett*. **13**, 1306–1309 (2011).

35. C. B. Tripathi, S. Mukherjee, Lewis base catalysis by thiourea: *N*-bromosuccinimide-mediated oxidation of alcohols. *J. Org. Chem.* **77**, 1592–1598 (2012).

36. S. –H. Lee, H. Matsushita, B. Clapham, K. D. Janda, The direct conversion of carbamates to ureas using aluminum amides. *Tetrahedron* **60**, 3439–3443 (2004).

37. G. Jakab, A. Hosseini, H. Hausmann, P. R. Schreiner, Mild and selective organocatalytic iodination of activated aromatic compounds. *Synthesis* **45**, 1635–1640 (2013).

38. M. Shi, X. –G. Liu, Asymmetric Morita-Baylis-Hillman reaction of arylaldehydes with 2-cyclohexen-1-one catalyzed by chiral bis(thio)urea and DABCO. *Org. Lett.* **10**, 1043–1046 (2008).

39. R. Holakovský, M. März, R. Cibulka, Urea derivatives based on a 1,1′-binaphthalene skeleton as chiral solvating agents for sulfoxides. *Tetrahedron: Asymmetry* **26**, 1328–1334 (2015).

40. M. C. Mimmi, M. Gullotti, L. Santagostini, R. Pagliarin, L. De Gioia, E. Monzani, L. Casella, Synthesis and conformational studies of a chiral octadentate ligand derived from (*R*)-

1,1′-binaphthyl-2,2′-diamine and its dinuclear zinc(ii) and nickel(ii) complexes. *Eur. J. Inorg. Chem.* **21**, 3934–3944 (2003).

41. K. H. Kim, D. –W. Lee, Y. –S. Lee, D. –H. Ko, D. –C. Ha, Enantioselective oxidative coupling of methyl 3-hydroxy-2-naphthoate using mono-*N*-alkylated octahydrobinaphthyl-2,2′-diamine ligand. *Tetrahedron* **60**, 9037–9042 (2004).

42. A. Crespo–Peña, D. Monge, E. Martín-Zamora, E. Álvarez, R. Fernández, J. M. Lassaletta, Asymmetric formal carbonyl-ene reactions of formaldehyde tert-butyl hydrazone with α-keto esters: dual activation by bis-urea catalysts. *J. Am. Chem. Soc.* **134**, 12912–12915 (2012).

43. X. Pu, X. Qi, J. M. Ready, Allenes in asymmetric catalysis: asymmetric ring opening of meso-epoxides catalyzed by allene-containing phosphine oxides. *J. Am. Chem. Soc.* **131**, 10364–10365 (2009).

44. N. Ajvazi, S. Stavber, Direct halogenation of alcohols with halosilanes under catalyst- and organic solvent-free reaction conditions. *Tetrahedron Lett.* **57**, 2430–2433 (2016).

45. G. K. Helmkam, D. J. Pettitt, Mechanism of the desulfurization of episulfides with methyl iodide. *J. Org. Chem.* **29**, 3258–3262 (1964).

46. S. E. Denmark, T. Vogler, Synthesis and reactivity of enantiomerically enriched thiiranium ions. *Chem. Eur. J.* **15**, 11737–11745 (2009).

47. P. Sokkalingam, C. –H. Lee, Highly sensitive fluorescence “turn-on” indicator for fluoride anion with remarkable selectivity in organic and aqueous media. *J. Org. Chem.* **76**, 3820–3828 (2011).

48. P. Kuzmič, Program DYNAFIT for the analysis of enzyme kinetic data: application to HIV proteinase. *Anal. Biochem.* **237**, 260–273 (1996).

49. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian 09, Revision D.01, Gaussian, Inc., Wallingford CT (2016).

50. Y. Zhao, D. G. Truhlar, The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals. *Theor. Chem. Acc.* **120**, 215–241 (2008).

51. F. Weigend, R. Ahlrichs, Balanced basis sets of split valence, triple zeta valence and quadruple zeta valence quality for H to Rn: design and assessment of accuracy. *Phys. Chem. Chem. Phys.* **7**, 3297–3305 (2005).

52. A. Hellweg, D. Rappoport, Development of new auxiliary basis functions of the Karlsruhe segmented contracted basis sets including diffuse basis functions (def2-SVPD, def2-TZVPPD, and def2-QVPPD) for RI-MP2 and RI-CC calculations. *Phys. Chem. Chem. Phys.* **17**, 1010–1017 (2015).

53. D. Rappoport, F. Furche, Property-optimized Gaussian basis sets for molecular response calculations. *J. Chem. Phys.* **133**, 134105 (2010).

54. T. Leininger, A. Nicklass, W. Küchle, H. Stoll, M. Dolg, A. Bergner, The accuracy of the pseudopotential approximation: non-frozen-core effects for spectroscopic constants of alkali fluorides XF (X = K, Rb, Cs). *Chem. Phys. Lett.* **255**, 274–280 (1996).

55. V. Barone, M. Cossi, Quantum calculation of molecular energies and energy gradients in solution by a conductor solvent model. *J. Phys. Chem. A.* **102**, 1995–2001 (1998).

56. M. Cossi, N. Rega, G. Scalmani, V. Barone, Energies, structures, and electronic properties of molecules in solution with the C-PCM solvation model. *J. Comput. Chem.* **24**, 669–681 (2003).

57. Y. Takano, K. N. Houk, Benchmarking the conductor-like polarizable continuum model (CPCM) for aqueous solvation free energies of neutral and ionic organic molecules. *J. Chem. Theory Comput.* **1**, 70–77 (2005).

58. R. S. Paton, I. Funes-Ardois, GoodVibes.py, doi:10.5281/zenodo.60811.

59. S. Grimme, Supramolecular binding thermodynamics by dispersion-corrected density functional theory. *Chem. Eur. J.* **18**, 9955–9964 (2012).

60. J. Contreras-García, E. R. Johnson, S. Keinan, R. Chaudret, J. –P. Piquemal, D. N. Beratan, W. Yang, NCIPLOT: A program for plotting noncovalent interaction regions. *J. Chem. Theory Comput.* **7**, 625–632 (2011).

61. E. R. Johnson, S. Keinan, P. Mori Sánchez, J. Contreras–García, A. J. Cohen, W. Yang, Revealing noncovalent interactions. *J. Am. Chem. Soc.* **132**, 6498–6506 (2010).

62. F. Neese, The ORCA program system. *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **2**, 73–78 (2012).

63. J. –D. Chai, M. Head-Gordon, Long-range corrected hybrid density functionals with damped atom–atom dispersion corrections. *Phys. Chem. Chem. Phys.* **10**, 6615–6620 (2008).

64. Y. –S. Lin, G. –D. Li, S. –P. Mao, J. –D. Chai, Long-range corrected hybrid density functionals with improved dispersion corrections. *J. Chem. Theory Comput.* **9**, 263–272 (2013).

65. S. Grimme, J. Antony, S. Ehrlich, H. Krieg, A consistent and accurate *ab initio* parametrization of density functional dispersion correction (DFT-D) for the 94 elements H-Pu. *J. Chem. Phys.* **132**, 154104 (2010).

66. J. Zheng, X. Xu, D. G. Truhlar, Minimally augmented Karlsruhe basis sets. *Theor. Chem. Acc.* **128**, 295–305 (2011).

67. A. Klamt, G. Schüürmann, COSMO: a new approach to dielectric screening in solvents with explicit expressions for the screening energy and its gradient. *J. Chem. Soc., Perkin Trans. 2*, 799–805 (1993).

68. K. Raghavachari, G. W. Trucks, J. A. Pople, M. Head-Gordon, A fifth-order perturbation comparison of electron correlation theories. *Chem. Phys. Lett.* **157**, 479–483 (1989).

69. Spartan ’16., Wavefunction, Inc., Irvine, CA, (2016).

70. T. A. Halgren, Merck molecular force field. I. Basis, form, scope, parameterization, and performance of MMFF94. *J. Comput. Chem.* **17**, 490–519 (1996).

71. C. Møller, M. S. Plesset, Note on an approximation treatment for many-electron systems. *Phys. Rev.* **46**, 618–622 (1934).

72. H. J. C. Berendsen, D. van der Spoel, R. van Drunen, GROMACS: A message-passing parallel molecular dynamics implementation. *Comput. Phys. Commun.* **91**, 43–56 (1995).

73. E. Lindahl, B. Hess, D. van der Spoel, GROMACS 3.0: a package for molecular simulation and trajectory analysis. *J. Mol. Model.* **7**, 306–317 (2001).

74. D. Van Der Spoel, E. Lindahl, B. Hess, G. Groenhof, A. E. Mark, H. J. C. Berendsen, GROMACS: Fast, flexible, and free. *J. Comput. Chem.* **26**, 1701–1718 (2005).

75. B. Hess, C. Kutzner, D. Van Der Spoel, E. Lindahl, GROMACS 4: algorithms for highly efficient, load-balanced, and scalable molecular simulation. *J. Chem. Theory Comput.* **4**, 435–447 (2008).

76. S. Pronk, S. Páll, R. Schulz, P. Larsson, P. Bjelkmar, R. Apostolov, M. R. Shirts, J. C. Smith, P. M. Kasson, D. van der Spoel, B. Hess, E. Lindahl, GROMACS 4.5: a high-throughput and highly parallel open source molecular simulation toolkit. *Bioinformatics* **29**, 845–854 (2013).

77. M. J. Abraham, T. Murtola, R. Schulz, S. Páll, J. C. Smith, B. Hess, E. Lindah, GROMACS: High performance molecular simulations through multi-level parallelism from laptops to supercomputers. *SoftwareX*. **1–2**, 19–25 (2015).

78. W. L. Jorgensen, J. Tirado-Rives, The OPLS [optimized potentials for liquid simulations] potential functions for proteins, energy minimizations for crystals of cyclic peptides and crambin. *J. Am. Chem. Soc.* **110**, 1657–1666 (1988).

79. W. L. Jorgensen, D. S. Maxwell, J. Tirado-Rives, Development and testing of the OPLS all-atom force field on conformational energetics and properties of organic liquids. *J. Am. Chem. Soc.* **118**, 11225–11236 (1996).

80. Schrödinger Release 2017-2, Schrödinger, LLC, New York, NY, (2017).

81. C. I. Bayly, P. Cieplak, W. D. Cornell, P. A. Kollman, A well-behaved electrostatic potential based method using charge restraints for deriving atomic charges: the RESP model. *J. Phys. Chem.* **97**, 10269–10280 (1993).

82. W. D. Cornell, P. Cieplak, C. I. Bayly, P. A. Kollman, Application of RESP charges to calculate conformational energies, hydrogen bond energies, and free energies of solvation. *J. Am. Chem. Soc.* **115**, 9620–9631 (1993).

83. F. Duarte, R. S. Paton, Molecular recognition in asymmetric counteranion catalysis: understanding chiral phosphate-mediated desymmetrization. *J. Am. Chem. Soc.* **139**, 8886–8896 (2017).

84. D. A. Case, D. S. Cerutti, T. E. Cheatham III, T. A. Darden, R. E. Duke, T. J. Giese, H. Gohlke, A. W. Goetz, D. Greene, N. Homeyer, S. Izadi, A. Kovalenko, T.S. Lee, S. LeGrand, P. Li, C. Lin, J. Liu, T. Luchko, R. Luo, D. Mermelstein, K. M. Merz, G. Monard, H. Nguyen, I. Omelyan, A. Onufriev, F. Pan, R. Qi, D. R. Roe, A. Roitberg, C. Sagui, C. L. Simmerling, W. M. Botello-Smith, J. Swails, R. C. Walker, J. Wang, R. M. Wolf, X. Wu, L. Xiao, D. M. York and P. A. Kollman, AMBER 2017, University of California, San Francisco (2017).

85. D. Van Der Spoel, P. J. van Maaren, C. Caleman, GROMACS molecule & liquid database. *Bioinformatics* **28**, 752–753 (2012).

86. S. Chen, S. Yi, W. Gao, C. Zuo, Z. Hu, Force field development for organic molecules: modifying dihedral and 1–n pair interaction parameters. *J. Comput. Chem.* **36**, 376–384 (2015).

87. U. Essmann, L. Perera, M. L. Berkowitz, T. Darden, H. Lee, L. G. Pedersen, A smooth particle mesh Ewald method. *J. Chem. Phys.* **103**, 8577–8593 (1995).

88. B. Hess, H. Bekker, H. J. C. Berendsen, J. G. E. M. Fraaije, LINCS: A linear constraint solver for molecular simulations. *J. Comput. Chem.* **18**, 1463–1472 (1997).

89. G. Bussi, D. Donadio, M. Parrinello, Canonical sampling through velocity rescaling. *J. Chem. Phys.* **126**, 014101 (2007).

90. M. Parrinello, A. Rahman, Crystal structure and pair potentials: a molecular-dynamics study. *Phys. Rev. Lett.* **45**, 1196–1199 (1980).

91. M. Parrinello, A. Rahman, Polymorphic transitions in single crystals: a new molecular dynamics method. *J. Appl. Phys.* **52**, 7182–7190 (1981).

92. X. Daura, K. Gademann, B. Jaun, D. Seebach, W. F. van Gunsteren, A. E. Mark, Peptide folding: when simulation meets experiment. *Angew. Chem. Int. Ed.* **38**, 236–240 (1999).

93. J. R. Pliego Jr., J. M. Riveros, New insights on reaction pathway selectivity promoted by crown ether phase-transfer catalysis: Model *ab initio* calculations of nucleophilic fluorination. *J. Mol. Catal. A Chem.* **363–364**, 489–494 (2012).

94. N. F. Carvalho, J. R. Pliego Jr., Theoretical design and calculation of a crown ether phase-transfer-catalyst scaffold for nucleophilic fluorination merging two catalytic concepts. *J. Org. Chem.* **81**, 8455–8463 (2016).

95. W. M. Haynes, D. R. Lide, T. J. Bruno, *CRC Handbook of Chemistry and Physics* (Taylor & Francis Inc., Boca Raton, 97th ed., 2017).

96. Y. Marcus, A. Loewenschuss, Chapter 4. Standard entropies of hydration of ions. *Annu. Reports Sect. "C" (Physical Chem.)* **81**, 81–135 (1984).

97. D. O'Hagan, Recent developments on the fluorinase from Streptomyces cattleya. *J. Fluor. Chem.* **127**, 1479–1483 (2006).

98. L. Palatinus, G. Chapuis, SUPERFLIP – a computer program for the solution of crystal structures by charge flipping in arbitrary dimensions. *J. Appl. Cryst.* **40**, 786–790 (2007).

99. P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, CRYSTALS version 12: software for guided crystal structure analysis. *J. Appl. Cryst.* **36**, 1487 (2003).

100. R. I. Cooper, A. L. Thompson, D. J. Watkin, CRYSTALS enhancements: dealing with hydrogen atoms in refinement. *J. Appl. Cryst.* **43**, 1100–1107 (2010).

101. H. D. Flack, On enantiomorph-polarity estimation. *Acta Cryst.* **A39**, 876–881 (1983).

102. H. D. Flack, G. Bernardinelli, Reporting and evaluating absolute-structure and absolute-configuration determinations. *J. Appl. Cryst.* **33**, 1143–1148 (2000).

103. R. W. W. Hooft, L. H. Straver, A. L. Spek, Determination of absolute structure using Bayesian statistics on Bijvoet differences. *J. Appl. Cryst.* **41**, 96–103 (2008).

Supplementary Materials

Materials and Methods

Figures S1-S33

Tables S1-S31

References (*34*-*103*)