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Enantioselective fluoride ring opening of aziridines enabled by cooperative Lewis acid catalysis

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This manuscript is dedicated to Professor Melanie S. Sanford on the occasion of her receiving the Tetrahedron Young Investigator Award

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ABSTRACT

The enantioselective ring opening of aziridines using a latent source of HF is described. A combination of two Lewis acids, (salen)Co and an achiral Ti(IV) cocatalyst, provided optimal reactivity and enantioselectivity for the *trans* β-fluoroamine product. The use of a chelating aziridine protecting group was crucial. Acyclic and cyclic *meso N*-picolinamide aziridines underwent fluoride ring opening in up to 84% ee, and the kinetic resolution of a piperidine-derived aziridine was performed with k_{rel}=6.6. The picolinamide group may be readily removed without epimerization of the fluoroamine. Preliminary studies revealed a bimetallic mechanism wherein the chiral (salen)Co catalyst delivers the nucleophile and the Ti(IV) cocatalyst activates the aziridine.

1. Introduction

The asymmetric ring opening of aziridines is a powerful strategy to access valuable enantioenriched β-substituted amines.[1] However, the use of halides as nucleophiles in this transformation has only recently been achieved. Jacobsen and Mita reported the desymmetrization of *meso* aziridines with HCl catalyzed by a bifunctional thiourea–phosphine,[2] and Ooi and co-workers accomplished both the desymmetrization and kinetic resolution of aziridines by TMSCl and TMSBr in combination with a chiral triazolium catalyst.[3]

From a synthetic standpoint, enantioenriched β-fluoroamines represent a desirable target.[4] By lowering the pK_a of neighboring amines, β-fluoro substitution affects a variety of properties relevant to medicinal chemistry, including metabolic stability, binding affinity, and bioavailability.[5] Work in our laboratory has revealed that the combination of benzoyl fluoride and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) serves as a latent source of HF for ring-opening reactions. The addition of a Lewis base catalyst to PhCOF/HFIP promotes the in situ generation of an amine–HF reagent that is effective in the ring opening of aziridines.[6] However, enantioselective fluoride ring opening could not be achieved with chiral amine catalysts (<15% ee); instead, a chiral auxiliary was employed for the asymmetric synthesis of β-fluoroamines. The lack of asymmetric induction is attributed to the variable, non-rigid structure of the active fluorinating reagent, an amine poly(hydrogen fluoride) species.

We previously reported the enantioselective ring opening of epoxides by fluoride catalyzed by the chiral Lewis acid (salen)Co.[7] Use of the same latent HF source, PhCOF/HFIP, enabled these reactions to occur under mild conditions and with high enantioinduction for the desymmetrization of *meso* epoxides and kinetic resolution of terminal epoxides. On the basis of detailed mechanistic investigations, we proposed that the active nucleophilic fluorine source is a cobalt bifluoride, which delivers fluoride to an epoxide substrate that is activated by another (salen)Co species.[8] The interaction between two chiral (salen)Co species in the transition state has been proposed to be key to the high enantioinduction observed for epoxide-opening reactions.[9]

In developing an asymmetric catalytic fluoride ring opening of aziridines, we envisioned taking advantage of the chiral metal fluoride generated from (salen)Co, PhCOF, and HFIP. Although (salen)Co(III) can act as a Lewis acid to activate epoxides, previous work has shown that (salen)Co(III) Lewis acids are not effective for the activation of protected aziridines, likely due to their increased

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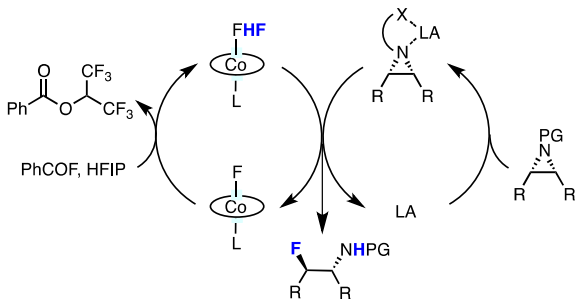
steric hindrance.[10] The Jacobsen group has approached this challenge by designing tridentate Schiff base ligands; the resulting Cr(III) complexes effect enantioselective opening of *N*-dinitrobenzyl aziridines by $TMSN_3$. Unfortunately, the relatively basic *N*-alkyl aziridines compatible with this catalyst undergo facile autocatalytic background reaction in the presence of PhCOF/HFIP.

We therefore considered whether a distinct Lewis acid could be used to activate the aziridine toward fluoride ring opening by (salen)CoF(HF). Shibasaki,[11] Kobayashi,[12] and Parquette and Rajan-Babu[13] have taken advantage of multimetallic chiral catalyst systems to achieve the highly asymmetric ring opening of aziridines by nucleophiles including azide, cyanide, anilines, and malonates. These systems rely on multidentate ligands that can coordinate to multiple metal centers; for aziridine opening, homopolymetallic systems are most often employed.[14] We anticipated that catalyst design could be simplified if a separate, readily available Lewis acid could be used in combination with our existing (salen)Co/PhCOF/HFIP system. In order to favor coordination of this Lewis acid to the substrate, we decided to install a chelating protecting group on the aziridine (Scheme 1). The proposed system represents an example of synergistic catalysis, in which both the nucleophile and the electrophile are activated by distinct catalysts.[15]



Scheme 1. Proposed catalytic cycle for aziridine ring opening.

2. Results and discussion

2.1. Optimization

We chose to initiate reaction development using the chiral Lewis acid catalyst and latent HF source that provided optimal reactivity and enantioselectivity in the epoxide ring-opening reaction.[7] Since we reasoned that (salen)Co(III) would be able to activate fluoride toward asymmetric nucleophilic delivery, but would not serve as a competent Lewis acid for the *N*-substituted aziridine, we evaluated a wide variety of achiral Lewis acid cocatalysts. In accordance with our design plan (Scheme 1), we tested aziridines functionalized with chelating protecting groups. Intriguingly, *N*-acyl aziridines bearing 2-azaarenes proved uniquely effective (2-pyridyl, 2-thiazolyl, 1-isoquinolinyl). All other aziridine protecting groups provided no observable β-fluoroamine or racemic product in the presence of a range of Lewis acid cocatalysts (Fig. 1). The picolinamide-protected aziridine **1a** was selected for further optimization. This auxiliary was introduced as a directing group for Pd-catalyzed C(sp^3)–H activation[16] and is proposed to act as a chelating protecting group in the cinchona alkaloid/Zn(II)-catalyzed desymmetrization of aziridines with phosphites.[17]

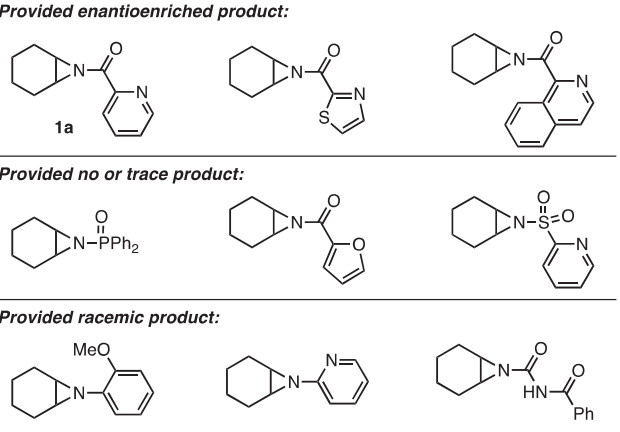
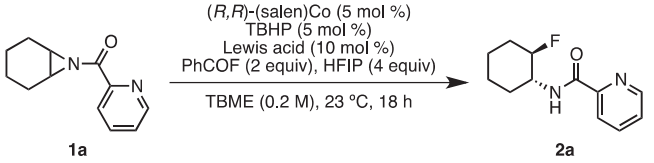


Fig. 1. Aziridines tested in the fluoride ring opening reaction.

As the sole catalyst in the presence of PhCOF and HFIP in *tert*-butyl methyl ether (TBME), (*R*,*R*)-(salen)Co provided 79% yield of the desired β-fluoroamine **2a**; however, this product was generated in <10% ee (Table 1, entry 1). The addition of Lewis acid cocatalysts typically employed in aziridine-opening protocols (Y, Yb, Sc, Zn, Cu) to the (salen)Co-catalyzed protocol did not improve the enantioselectivity (entries 2–6). Interestingly, several oxophilic Lewis acids, including Al(O*i*-Pr)$_3$, $FeCl_3$, Zr(O*i*-Pr)$_4$, and Ti(O*i*-Pr)$_4$, provided significant enhancements in enantiomeric excess, up to 62% ee (entries 7–10).

Table 1
Optimization of Lewis acid cocatalyst[a]



Entry	Lewis acid	Yield[b] (%)	ee[c] (%)
1	None	79	7 (*S*,*S*)
2	Y(O*i*-Pr)$_3$	71	8 (*S*,*S*)
3	Yb(O*i*-Pr)$_3$	60	3 (*S*,*S*)
4	Sc(OTf)$_3$	0	n/a
5	Zn(OAc)$_2$	59	7 (*S*,*S*)
6	Cu(TFA)$_2$	25	0
7	Al(O*i*-Pr)$_3$	40	13 (*R*,*R*)
8	$FeCl_3$	58	31 (*R*,*R*)
9	Zr(O*i*-Pr)$_4$	61	41 (*R*,*R*)
10	Ti(O*i*-Pr)$_4$	66	62 (*R*,*R*)
11	**Ti(NMe$_2$)$_4$**	**79**	**83 (R,R)**
12	TiF_4[d]	79	56 (*R*,*R*)

[a] Reaction conditions: 0.1 mmol **1a**, 0.005 mmol (*R*,*R*)-(salen)Co, 0.005 mmol TBHP (5 M solution in decane), 0.01 mmol Lewis acid, 0.2 mmol PhCOF, 0.4 mmol HFIP, 0.5 mL TBME, 23 °C, 18 h. All reactions proceeded to >95% conversion.
[b] Determined by HPLC in the presence of diphenyl ether as a quantitative internal standard.
[c] Determined by chiral HPLC analysis.
[d] The cocatalyst was added as a 0.5 M solution in MeCN.

It is particularly remarkable that the addition of an *achiral* Lewis acid cocatalyst enables asymmetric induction by (*R*,*R*)-(salen)Co *despite a highly efficient unselective background reaction by the chiral catalyst*. Accordingly, we found that optimal enantioselectivity was achieved when a 2:1 molar ratio of Lewis acid relative to (salen)Co was employed. Ti(IV) species proved to be the most selective cocatalysts, and **2a** could be obtained in 83% ee in the presence of Ti(NMe$_2$)$_4$ (entry 11).

In previous studies, we observed that aerobic oxidation of the commercially available (salen)Co(II) complex to the catalytically active (salen)Co(III) species occurs in the presence of HFIP; however, this slow in situ oxidation gives rise to an induction period.[8] For aziridine opening by PhCOF/HFIP, we found that pre-oxidized catalysts provided superior performance. The (salen)Co(II) precatalyst can be rapidly oxidized in situ prior to the reaction by anhydrous *tert*-butyl hydroperoxide (TBHP). For substrates requiring extended reaction times, (salen)Co(III)OCH(CF$_3$)$_2$·HFIP, readily prepared from (salen)Co(II) and HFIP,[8] provides optimal results.

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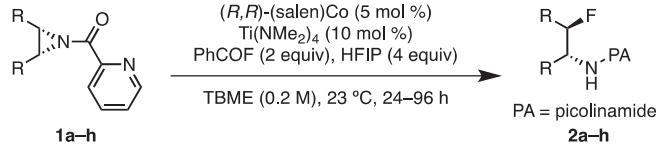
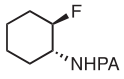
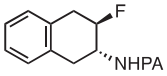
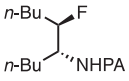
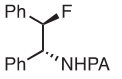
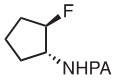
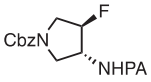
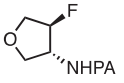
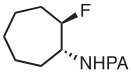
Further optimization was attempted by modifying the steric and electronic nature of the picolinamide protecting group. Substitution at the 6-position of the picolinamide was not tolerated, presumably because this hinders *N*,*O*-chelation by the Lewis acid. Electron-withdrawing and -donating substituents elsewhere on the pyridine ring had little effect on the enantioselectivity. Additionally, Ti(IV) cocatalysts bearing chiral ligands were evaluated; while these chiral catalysts did not provide superior results to $Ti(NMe_2)_4$, these data offered mechanistic insight into the synergistic interaction between the Lewis acid cocatalysts (vide infra).

2.2. Substrate scope

With this protocol in hand, we sought to explore the substrate scope of the dual Lewis acid-catalyzed aziridine ring opening. A variety of *meso* aziridines **1a**–**h** were synthesized by amide coupling of the corresponding N–H aziridine and picolinic acid. On preparative scale, **2a** was isolated in 93% yield and 84% ee (Table 2, entry 1). Promisingly, **2a** may be recrystallized from *i*-PrOH by slow evaporation to provide the *trans* β-fluoroamine in 95% ee.

Table 2
Substrate scope



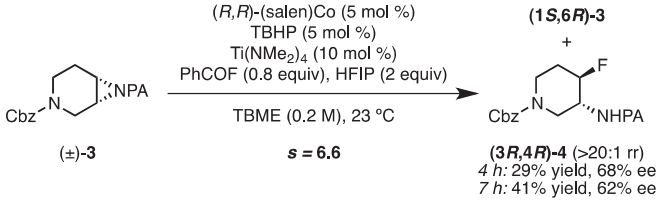
Entry	Conditions[a]	Product		Yield[b] (%)	ee[c] (%)
1	A		**2a**	93 (51)	84 (95)
2	A		**2b**	66 (56)	80 (97)
3	B		**2c**	75	63
4	B		**2d**	51	48
5	A		**2e**	46	56
6[d]	B		**2f**	48	75
7[d,e]	B		**2g**	27	32
8[e]	B		**2h**	33	12

[a] A: 5 mol % (salen)Co(II), 5 mol % TBHP (5 M in decane), 24 h; B: 5 mol % (salen)Co(III)$OCH(CF_3)_2 \cdot HOCH(CF_3)_2$, 48 h. Data are the average of two experiments. Yields based on recovered **2** and ees in parentheses are for products recrystallized from *i*-PrOH.
[b] Isolated yield on 0.2–0.5 mmol scale.
[c] Enantiomeric excesses determined by chiral HPCL.
[d] Reaction time: 96 h.
[e] One run.

Dihydronaphthalene-derived aziridine **1b** also performed well in the reaction, delivering **2b** in 66% yield and 80% ee (97% ee after recrystallization, entry 2). Acyclic aliphatic aziridines such as **1c** are also competent substrates, providing the β-fluoroamine as a single diastereomer in 63% ee (entry 3), but *cis*-diphenyl aziridine **1d** suffered from a number of side reactions leading to depressed yield and enantioselectivity (entry 4). The major side products for the reaction of **1d** arose from cationic rearrangements leading to *trans* aziridine[18] as well as *cis* and *trans* oxazolines.

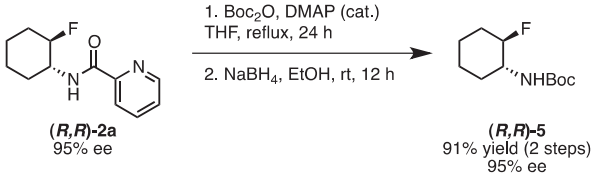
Other ring sizes performed modestly in the asymmetric fluorination reaction. Five-membered cyclic aziridines delivered fair yields, and fluoroamines **2e** and **2f** with cyclopentane and pyrrolidine backbones were obtained with 56 and 75% ee, respectively (entries 5 and 6). A dihydrofuran-derived aziridine (**1g**), however, underwent sluggish ring opening with low enantioselectivity (entry 7). Cycloheptane substrate **1h** also performed poorly, providing only 12% ee (entry 8). Significant amounts of oxazoline were also observed in these reactions and the enantioselectivities of the reactions decreased over time, indicative of catalyst inhibition or degradation. The oxazoline side product arises from the Lewis acid-catalyzed Gabriel–Heine rearrangement, in which acylaziridines are isomerized to the corresponding oxazolines.[19] Interestingly, the oxazoline byproducts are generated with measurable ee, suggesting that (salen)Co is involved in the isomerization.[20]

β-Fluoroamines derived from unsymmetrical aziridines represent valuable building blocks for medicinal chemistry. For example, the *trans* 3-amino-4-fluoropiperidine core has appeared in numerous patents.[21] Previous work has shown that nucleophilic attack on 3,7-diazabicyclo[4.1.0]heptane occurs preferentially at the position distal to the inductively electron-withdrawing heteroatom;[22] however, asymmetric reactions of this substrate to arrive at valuable enantioenriched products have not been reported. Gratifyingly, the kinetic resolution of aziridine **3** occurred with a selectivity factor (*s*)[23] of 6.6, providing 3-amino-4-fluoropiperidine **4** as a single regioisomer in 29% yield and 68% ee after 4 h, and 41% yield and 62% ee after 7 h (Scheme 2).



Scheme 2. Kinetic resolution of piperidine **3** by regioselective fluoride ring opening.

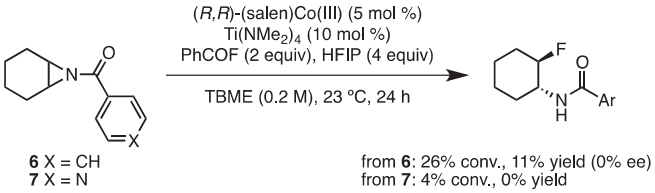
Importantly, the picolinamide group can be readily removed under mild conditions without epimerization of the β-fluoroamine. Product **2a** (95% ee) was subjected to Boc protection and the amide was subsequently cleaved by $NaBH_4$ to furnish (*R*,*R*)-**5** in 91% yield and 95% ee (Scheme 3). The absolute configuration of the β-fluoroamine products was determined by comparison to the literature data (**5**) and X-ray crystallography (**2b**[24]): notably, (*R*,*R*)-(salen)Co provides the *opposite* absolute configuration for the aziridine ring opening compared to epoxide ring opening, which generates (*S*,*S*)-fluorohydrins.[7]



Scheme 3. Deprotection of **2a**.

2.3. Mechanistic studies

2.3.1. Control experiments: protecting group. To confirm that the unique reactivity observed for the picolinamide-protected aziridines **1** arises from chelation to the Lewis acid, rather than simply an electronic effect, we synthesized benzamide- and isonicotinamide-protected aziridines **6** and **7** (Scheme 4). Under the cocatalytic reaction conditions, both aziridines displayed poor reactivity, and benzamide-protected **6** delivered only 11% yield of the fluoroamine in racemic form. No fluorinated product was detected in the reaction of isonicotinamide-protected aziridine **7**, which underwent only 4% conversion.



Scheme 4. Control experiments with aziridines **6** and **7**. Conversions, yields, and ees determined by chiral HPLC.

2.3.2. Nonlinear effects with scalemic (salen)Co. The fluorination of **1a** was performed with 0–100% ee (*R,R*)-(salen)Co, and a linear relationship between %ee of **2a** and %ee of the catalyst was observed (Chart 1). The lack of nonlinear effects on enantioselectivity is consistent with either a mechanism in which the (salen)Co species do not interact, or one in which the (salen)Co species interact but the homo- and heterochiral pathways occur with equal rates.[25]

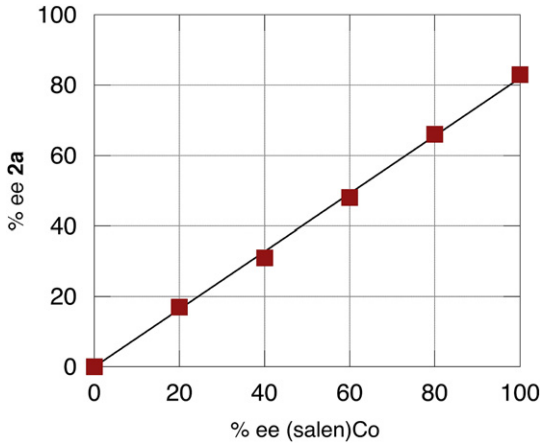


Chart 1. %ee of **2a** versus %ee of (salen)Co for the ring opening of **1a** (red squares) and linear fit.

2.3.3. Reactions with a linked (salen)Co catalyst. Linked (salen)Co catalyst **8** (Fig. 2) has been shown to accelerate the fluoride ring opening of epoxides and provide improved ees for the fluorohydrin products; together with nonlinear effects, substituent effects, and kinetic data, this effect is consistent with a ring-opening reaction in which the Co center both activates the epoxide and delivers the nucleophile.[9a] However, **8** provided no rate acceleration and depressed ee relative to monomeric (salen)Co for the aziridine ring-opening reactions. Therefore, the linear relationship between %ee of **2a** and %ee of (salen)Co is best ascribed to a mechanism in which this catalyst plays only one role in the ring opening. This scenario also provides a rationale for the observation that the absolute stereochemistry of the aziridine ring opening is the opposite of that for the epoxide opening.

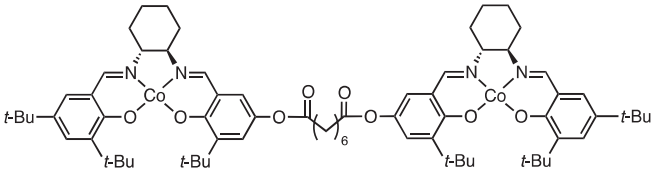


Fig. 2. Linked (salen)Co catalyst (*R,R,R,R*)-**8**.

2.3.4. Role of the Ti(IV) cocatalyst. In the aziridine ring opening reactions, we consistently observed a small amount of *N,N*-dimethylbenzamide as a byproduct, which is produced by the reaction of benzoyl fluoride with the $Ti(NMe_2)_4$ cocatalyst. Indeed, when $Ti(NMe_2)_4$ and 4 equiv PhCOF were combined in $CDCl_3$ in an NMR tube, the reaction mixture turned orange and became warm. A yellow precipitate was formed upon standing for several minutes. Addition of MeCN slightly solubilized this precipitate and the resulting suspension displayed a ^{19}F NMR resonance consistent with a terminal Ti–F (+135.0 ppm relative to $CFCl_3$). Dialkylaminotitanium fluorides, $TiF_n(NR_2)_{4-n}$, have been previously prepared by alternative methods; these species exhibit insolubility and complex concentration- and temperature-dependent equilibria between oligomeric species via bridging fluorides.[26] The species obtained from $Ti(NMe_2)_4$ and PhCOF is a competent cocatalyst, providing 67% yield and 67% ee for the ring opening of **1a** under the standard conditions; TiF_4 provides 56% ee, despite its poor solubility in organic solvents (Table 1, entry 12). This observation raises the possibility that the nucleophilic fluorine source in the ring-opening reaction is in fact a titanium fluoride complex. However, in the absence of PhCOF, **2a** is not observed in the reaction of **1a** with pregenerated dimethylaminotitanium fluoride (2 equiv), (salen)Co, and HFIP. Therefore, ligand exchange of $Ti(NMe_2)_4$ with PhCOF may increase the Lewis acidity of this catalyst, but the resulting titanium fluoride is not the source of fluoride for aziridine opening.[27]

2.3.5. Matched–mismatched effects with chiral Ti(IV) cocatalysts. In light of our data, we propose a mechanism in which fluoride is delivered by (salen)Co, as in the epoxide-opening reaction, and the Ti(IV) cocatalyst activates the aziridine by chelating to the picolinamide protecting group (Fig. 3). Based on our previous studies, we propose that the nucleophilic fluorine species is a cobalt(III) bifluoride.

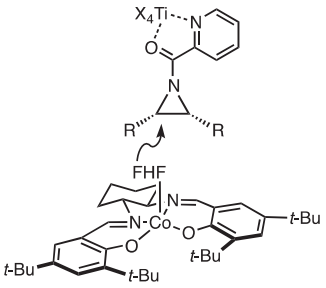


Fig. 3. Proposed mechanism for ring opening.

The proposed synergistic interaction between the cocatalysts is further supported by experiments with chiral Ti(IV) cocatalysts.[28] When TiF_2X_2 catalysts generated from chiral diols are used in the reaction of **1a**, modest matched–mismatched effects on enantioselectivity are observed for the diastereomeric combinations of the catalysts (Scheme 5). These matched–mismatched effects are consistent with a cooperative interaction between the two chiral catalysts.

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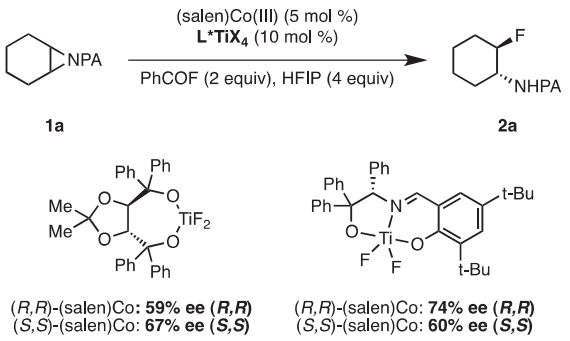

Scheme 5. Matched–mismatched effects for the reaction of **1a** with (salen)Co and chiral Ti(IV) catalysts.

3. Conclusion

We have described the first asymmetric catalytic fluoride ring opening of aziridines. This protocol generates valuable *trans* β-fluoroamine products through the desymmetrization of *meso* aziridines in up to 84% ee. Additionally, the catalytic fluorination may be applied to the kinetic resolution of a racemic substrate. Keys to the success of this reaction are the use of PhCOF and HFIP as a latent source of HF and the application of the picolinamide protecting group to enable Lewis acid activation of the aziridine. Intriguingly, an achiral Lewis acid is required in addition to (salen)Co to achieve enantioselectivity for the ring opening. Preliminary mechanistic studies reveal a synergistic interaction between the catalysts, in which (salen)Co serves to deliver fluoride and Ti(IV) activates the aziridine. The discovery of new applications of benzoyl fluoride as a latent fluoride source for asymmetric catalytic transformations is ongoing in our laboratory.

4. Experimental

4.1. General information

Unless otherwise noted, reactions were carried out in oven-dried glassware under a N_2 atmosphere. Commercial reagents were used as received with the following exceptions. Dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), and toluene were dried by passing through activated alumina columns; acetonitrile (CH_3CN) was dried by passing through a column of activated molecular sieves. *tert*-Butyl methyl ether (TBME) was distilled from CaH_2 and stored over 3 Å molecular sieves (8–12 mesh), which had been flame-dried under reduced pressure. 1,1,1,3,3,3-Hexafluoroisopropanol (HFIP) was distilled from powdered activated 3 Å molecular sieves and stored over activated 3 Å molecular sieves (8–12 mesh). Commercial benzoyl fluoride (PhCOF) was filtered through SiO_2, eluting with pentanes, and solvent was removed in vacuo; it was stored in a plastic vial in a desiccator containing $CaSO_4$. $Ti(NMe_2)_4$ (>99%) was purchased in ampules, transferred to oven-dried vials fitted with a Mininert valve cap, and stored in a dessicator. Reactions were monitored by LC/MS or thin-layer chromatography (TLC) on EMD Silica Gel 60 F_{254} plates, visualizing with fluorescence quenching, $KMnO_4$, ninhydrin, or ceric ammonium molybdate (CAM). Automated column chromatography was performed using SiliCycle SiliaFlash F60 (40–53 μm, 60 Å) in SNAP cartridges on a Biotage Isolera 4.

Proton and carbon nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were recorded on a Bruker 500 AVANCE spectrometer (500 and 125 MHz). Chemical shifts for protons are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$=δ 7.26 ppm, MeOH=3.31 ppm). Chemical shifts for carbon are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to the central carbon resonance of the solvent residual peak ($CDCl_3$=δ 77.16 ppm, MeOH=49.00 ppm). ^{19}F spectra were recorded on a Bruker NB 300 spectrometer (282 MHz); chemical shifts are reported in parts per million (ppm) and are referenced to $CFCl_3$ (δ 0 ppm). NMR data are represented as follows: chemical shift (δ ppm), multiplicity, coupling constant in hertz (Hz), integration. Reversed-phase liquid chromatography/mass spectrometry (LC/MS) was performed on an Agilent 1260 Infinity analytical LC and Agilent 6120 Quadrupole LCMS system, using electrospray ionization/atmospheric-pressure chemical ionization (ESI/APCI), and UV detection at 254 and 280 nm. High-resolution mass spectra were obtained on an Agilent 6220 using electrospray ionization time-of-flight (ESI-TOF). FTIR spectra were recorded on a Perkin–Elmer Spectrum 100 and are reported in terms of frequency of absorption (cm^{-1}). High-pressure liquid chromatography (HPLC) was performed on an Agilent 1200 series instrument using Chiracel OD-H (25 cm×0.46 cm), Chiralpak AS-H (25 cm×0.46 cm), and Chiralpak AD-H (25 cm×0.46 cm) columns equipped with the corresponding guard columns (1 cm×0.4 cm). Gas chromatography (GC) was performed on an Agilent 7890A series instrument equipped with a J&W Scientific Cyclodex-B column (30 m×0.25 mm). Optical rotations were recorded on a Jasco P-1010 polarimeter using a 1-mL cell with a 0.5 dm path length; concentration (c) is in g/100 mL and $[\alpha]_D$ values are in degrees.

4.2. Representative procedure for synthesis of substrates

*4.2.1. 7-Azabicyclo[4.1.0]heptan-7-yl(pyridin-2-yl)methanone (**1a**).* To a solution of 7-azabicyclo[4.1.0]heptane[29] (0.55 mL, 94 wt %, 5.0 mmol) in anhydrous CH_2Cl_2 (25 mL) at 23 °C were added picolinic acid (0.62 g, 5.0 mmol), 4-dimethylaminopyridine (0.67 g, 5.5 mmol), and *N*,*N*-diisopropylcarbodiimide (0.86 mL, 5.5 mmol). The reaction mixture was stirred for 16 h, and the suspension was diluted with hexanes, filtered, and concentrated. The crude reaction mixture was purified by column chromatography (5–40% EtOAc/hexanes with 0.5% Et_3N) to provide the title compound as a white solid (0.83 g, 82% yield); mp 65.0–66.0 °C (lit.[17a] 65.0–67.0 °C). The product was stored at −10 °C. Spectral data were in agreement with the literature values.[6]

*4.2.2. Pyridin-2-yl(1a,2,7,7a-tetrahydro-1H-naphtho[2,3-b]azirin-1-yl)methanone (**1b**).* Prepared from 1a,2,7,7a-tetrahydro-1*H*-naphtho[2,3-*b*]azirine.[30] FTIR (thin film, cm^{-1}) 3050, 1668, 1434, 1316; ^1H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, J=3.9 Hz, 1H), 7.92 (d, J=7.8 Hz, 1H), 7.75 (td, J=7.7, 1.6 Hz, 1H), 7.39 (dd, J=7.4, 4.8 Hz, 1H), 7.16–7.10 (m, 2H), 7.10–7.01 (m, 2H), 3.53 (d, J=16.6 Hz, 2H), 3.29 (s, 2H), 3.21 (d, J=16.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.85, 150.99, 149.30, 136.74, 132.51 (2C), 129.46 (2C), 126.80 (2C), 126.41, 123.87, 37.49 (2C), 29.49 (2C); HRMS (ESI^+) calculated for $C_{16}H_{15}N_2O$ ($[M+H]^+$): 251.1179; found: 251.1178.

*4.2.3. (cis-2,3-Dibutylaziridin-1-yl)(pyridin-2-yl)methanone (**1c**).* Prepared from *cis*-2,3-dibutylaziridine.[31] FTIR (thin film, cm^{-1}) 2957, 1673, 1585, 1439, 1332, 1147, 996; ^1H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, J=3.7 Hz, 1H), 8.09 (d, J=7.8 Hz, 1H), 7.82 (t, J=7.0 Hz, 1H), 7.44 (dd, J=6.4, 4.8 Hz, 1H), 2.63 (d, J=4.3 Hz, 2H), 2.00–1.77 (m, 2H), 1.80–1.28 (m, 10H), 0.94 (t, J=7.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.41, 151.08, 149.28, 136.85, 126.50, 124.05, 42.90 (2C), 29.65 (2C), 27.59 (2C), 22.72 (2C), 14.22 (2C); HRMS (ESI^+) calculated for $C_{16}H_{25}N_2O$ ($[M+H]^+$): 261.1961; found: 261.1962.

*4.2.4. (cis-2,3-Diphenylaziridin-1-yl)(pyridin-2-yl)methanone (**1d**).* Prepared from *cis*-2,3-diphenylaziridine.[32] FTIR (thin film, cm^{-1}) 3050, 1679, 1584, 1438, 1413, 1328, 1243, 1092, 911; ^1H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, J=4.6 Hz, 1H), 8.16 (d, J=7.8 Hz, 1H), 7.81 (td, J=7.7, 1.4 Hz, 1H), 7.43 (dd, J=7.5, 4.8 Hz, 1H), 7.30 (d, J=6.9 Hz, 4H), 7.23–7.10 (m, 6H), 4.21 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.69, 150.35, 149.68, 136.98, 134.23 (2C), 128.16 (4C), 127.90 (4C),

127.39 (2C), 126.85, 124.30, 46.75 (2C); HRMS (ESI^+) calculated for $C_{20}H_{17}N_2O$ ($[M+H]^+$): 301.1335; found: 301.1337.

*4.2.5. 6-Azabicyclo[3.1.0]hexan-6-yl(pyridin-2-yl)methanone (**1e**).* Prepared from 6-azabicyclo[3.1.0]hexane.[33] FTIR (thin film, cm^{-1}) 2960, 1655, 1520, 1436, 1393, 1183, 1140, 997; ^1H NMR (500 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.09 (d, J=7.8 Hz, 1H), 7.81 (t, J=7.7 Hz, 1H), 7.42 (dd, J=7.4, 4.9 Hz, 1H), 3.31 (s, 2H), 2.22–2.14 (m, 2H), 1.74–1.61 (m, 3H), 1.30–1.19 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.55, 151.17, 149.44, 136.88, 126.36, 123.85, 43.85 (2C), 27.03 (2C), 19.40; HRMS (ESI^+) calculated for $C_{11}H_{13}N_2O$ ($[M+H]^+$): 189.1022; found: 189.1023.

*4.2.6. Benzyl 6-picolinoyl-3,6-diazabicyclo[3.1.0]hexane-3-carboxylate (**1f**).* Prepared from benzyl 3,6-diazabicyclo[3.1.0]hexane-3-carboxylate.[32] FTIR (thin film, cm^{-1}) 2877, 1699, 1668, 1585, 1423, 1390, 1348, 1313, 1211, 1126, 1089, 1040, 995, 914; ^1H NMR (500 MHz, $CDCl_3$) δ 8.67 (d, J=4.6 Hz, 1H), 7.97 (d, J=7.8 Hz, 1H), 7.76 (t, J=7.7 Hz, 1H), 7.43 (dd, J=7.3, 4.9 Hz, 1H), 7.37–7.25 (m, 5H), 5.03 (d, J=3.1 Hz, 2H), 4.11 (d, J=12.1 Hz, 1H), 4.03 (d, J=12.3 Hz, 1H), 3.55–3.52 (m, 1H), 3.50–3.47 (m, 1H), 3.39 (d, J=1.7 Hz, 1H), 3.37 (d, J=1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.31, 155.01, 150.32, 149.32, 137.09, 136.60, 128.56 (2C), 128.12, 128.06 (2C), 126.90, 123.94, 67.08, 46.61, 46.05, 41.14, 40.98; HRMS (ESI^+) calculated for $C_{18}H_{18}N_3O_3$ ($[M+H]^+$): 324.1343; found: 324.1341.

*4.2.7. 3-Oxa-6-azabicyclo[3.1.0]hexan-6-yl(pyridin-2-yl)methanone (**1g**).* Prepared from 3-oxa-6-azabicyclo[3.1.0]hexane.[32] FTIR (thin film, cm^{-1}) 2861, 1667, 1585, 1439, 1387, 1360, 1318, 1077, 906, 767; ^1H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, J=4.5 Hz, 1H), 8.14 (d, J=7.8 Hz, 1H), 7.83 (td, J=7.8, 1.6 Hz, 1H), 7.45 (dd, J=7.0, 5.3 Hz, 1H), 4.05 (d, J=10.0 Hz, 2H), 3.66–3.49 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.21, 150.84, 149.07, 137.08, 126.69, 124.02, 66.42 (2C), 41.24 (2C); HRMS (ESI^+) calculated for $C_{10}H_{11}N_2O_2$ ($[M+H]^+$): 191.0815; found: 191.0814.

*4.2.8. 8-Azabicyclo[5.1.0]octan-8-yl(pyridin-2-yl)methanone (**1h**).* Prepared from 8-azabicyclo[5.1.0]octane.[34] FTIR (thin film, cm^{-1}) 2927, 1663, 1519, 1464, 1435, 1326, 1178, 1155, 997, 820; ^1H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, J=3.9 Hz, 1H), 8.07 (d, J=7.8 Hz, 1H), 7.81 (td, J=7.7, 1.5 Hz, 1H), 7.42 (dd, J=6.5, 4.7 Hz, 1H), 2.82 (d, J=2.8 Hz, 2H), 2.14–1.96 (m, 4H), 1.74–1.48 (m, 5H), 1.38–1.28 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.82, 151.10, 149.54, 136.79, 126.35, 124.01, 42.22 (2C), 31.60, 29.19 (2C), 25.64 (2C); HRMS (ESI^+) calculated for $C_{13}H_{17}N_2O$ ($[M+H]^+$), 217.1335; found: 217.1333.

*4.2.9. Benzyl 7-picolinoyl-3,7-diazabicyclo[4.1.0]heptane-3-carboxylate (**3**).* Prepared from benzyl 3,7-diazabicyclo[4.1.0]heptane-3-carboxylate.[35] FTIR (thin film, cm^{-1}) 2929, 1680, 1673, 1585, 1415, 1319, 1242, 1216, 1137, 1107, 1046, 995, 906, 828; ^1H NMR (500 MHz, $CDCl_3$) δ 8.73–8.61 (m, 1H), 8.15–8.02 (m, 1H), 7.87–7.74 (m, 1H), 7.51–7.40 (m, 1H), 7.38–7.27 (m, 5H), 5.13 (s, 2H), 4.20–3.93 (m, 2H), 3.70–3.53 (m, 1H), 3.47–3.22 (m, 1H), 3.13, 2.85 (m, 2H), 2.46–2.18 (m, 1H), 2.11–1.87 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, peaks corresponding to rotamers indicated by *) δ 177.23, 177.10*, 155.61, 155.54*, 150.44, 149.51, 149.45*, 136.97, 136.92*, 136.76, 128.57 (2C), 128.10, 127.98 (2C), 126.76, 124.19, 124.13*, 67.27, 42.52, 42.43*, 38.48, 38.30*, 36.03, 35.79*, 35.75, 35.35*, 23.95, 23.50*; HRMS (ESI^+) calculated for $C_{19}H_{20}N_3O_3$ ($[M+H]^+$): 338.1499; found: 338.1497.

4.3. Representative procedures for the desymmetrization of *meso* aziridines

*Method A: N-((2R,3R)-3-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)picolinamide (**2b**).* To a suspension of (*R*,*R*)-(salen)Co (6.0 mg, 0.010 mmol) in TBME (1 mL) were added TBHP (2 μL, 0.01 mmol) and $Ti(NMe_2)_4$ (4.7 μL, 0.020 mmol), followed by HFIP (84 μL, 0.80 mmol), **1b** (50 mg, 0.20 mmol), and PhCOF (44 μL, 0.40 mmol). The reaction mixture was sealed and stirred at 23 °C for 24 h then poured onto SiO_2 and purified by column chromatography (5–40% EtOAc/hexanes) to obtain the title compound as a white solid: 63% yield (34 mg), 78% ee; 70% yield (38 mg), 82% ee. Compound **2b** (64 mg) was recrystallized from IPA to obtain the product in 97% ee and 56% yield (36 mg). The absolute configuration was assigned by X-ray crystallography (see Supplementary data). FTIR (thin film, cm^{-1}) 3363, 3062, 3023, 2932, 1670, 1520, 1466, 1435, 1020, 998; ^1H NMR (500 MHz, $CDCl_3$) δ 8.54–8.48 (m, 1H), 8.21 (d, J=7.8 Hz, 1H), 8.15 (d, J=7.1 Hz, 1H), 7.86 (td, J=7.7, 1.7 Hz, 1H), 7.43 (ddd, J=7.6, 4.8, 1.1 Hz, 1H), 7.23–7.18 (m, 2H), 7.17–7.11 (m, 2H), 5.07 (dddd, J=12.7, 6.6, 6.6, 5.3 Hz, 1H), 4.72–4.64 (m, 1H), 3.47 (dt, J=16.8, 5.0 Hz, 1H), 3.31 (ddd, J=22.3, 17.2, 5.1 Hz, 1H), 3.17 (td, J=17.5, 6.5 Hz, 1H), 2.89 (dd, J=16.9, 7.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.61, 149.58, 148.20, 137.57, 132.81 (d, ^4J=1.4 Hz), 132.18 (d, ^3J=6.8 Hz), 129.35, 129.20, 126.82, 126.78, 126.52, 122.42, 89.10 (d, ^1J=177.4 Hz), 48.44 (d, ^2J=22.6 Hz), 33.46 (d, ^2J=21.6 Hz), 32.75 (d, ^3J=4.3 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −182.77 (dddt, J=50.1, 22.5, 17.9, 5.1 Hz); HRMS (ESI^+) calculated for $C_{16}H_{16}FN_2O$ ($[M+H]^+$): 271.1241; found: 271.1244; $[\alpha]_D^{21}$ −41.5 (*c* 1.0, $CHCl_3$), 79% ee; HPLC (Chiracel OD-H, 10% IPA/hexane, 1 mL/min): t_R(major)=17.3, t_R(minor)=13.0 min.

*Method B: N-((5R,6R)-6-fluorodecan-5-yl)picolinamide (**2c**).* To a solution of (*R*,*R*)-(salen)Co(III)OCH$(CF_3)_2\cdot$HFIP (9.4 mg, 0.010 mmol) in TBME (0.5 mL) was added $Ti(NMe_2)_4$ (4.7 μL, 0.020 mmol), followed by HFIP (84 μL, 0.80 mmol) and PhCOF (44 μL, 0.40 mmol). Compound **1c** (52 mg, 0.20 mmol) was charged as a solution in TBME (0.5 mL) and the reaction mixture was stirred under N_2 at 23 °C for 48 h. The reaction mixture was poured onto SiO_2 and purified by column chromatography (5–40% Et_2O/hexanes) to obtain the title compound as a clear oil: 80% yield (45 mg), 67% ee; 70% yield (39 mg), 58% ee. FTIR (thin film, cm^{-1}) 3385, 2956, 2932, 2861, 1680, 1518, 1466, 1434, 998; ^1H NMR (500 MHz, $CDCl_3$) δ 8.59–8.56 (m, 1H), 8.20 (d, J=7.8 Hz, 1H), 8.10 (d, J=10.0 Hz, 1H), 7.86 (td, J=7.7, 1.6 Hz, 1H), 7.44 (ddd, J=7.5, 4.8, 1.0 Hz, 1H), 4.60 (dddd, J=47.4, 8.8, 4.2, 1.4 Hz, 1H), 4.22 (dddd, J=29.0, 17.2, 7.5, 1.4 Hz, 1H), 1.77–1.64 (m, 3H), 1.56–1.23 (m, 9H), 0.90–0.85 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.45, 149.74, 148.29, 137.47, 126.35, 122.52, 95.50 (d, ^1J=172.9 Hz), 51.69 (d, ^2J=18.9 Hz), 32.23 (d, ^3J=3.0 Hz), 31.77 (d, ^2J=20.8 Hz), 28.38, 27.55 (^{3}d, J=4.8 Hz), 22.71, 22.58, 14.14, 14.12; ^{19}F NMR (282 MHz, $CDCl_3$) δ −196.06 (dddd, J=46.6, 31.4, 29.4, 14.5 Hz); HRMS (ESI^+) calculated for $C_{16}H_{26}FN_2O$ ($[M+H]^+$): 281.2024; found: 281.2025; $[\alpha]_D^{21}$ +14.5 (*c* 1.4, $CHCl_3$), 67% ee; HPLC (Chiralpak AD-H, 1% IPA/hexane, 1 mL/min): t_R(major)=26.9, t_R(minor)=29.0 min.

*4.3.1. N-((1R,2R)-2-Fluorocyclohexyl)picolinamide (**2a**).* Method A, **1a** (40 mg, 0.20 mmol), 5–40% EtOAc/hexanes with 0.5% Et_3N: 94% yield (42 mg), 83% ee; 92% yield (41 mg), 85% ee. Compound **2a** (350 mg) was recrystallized by from IPA to obtain the product in 95% ee and 51% yield (180 mg). White solid. Spectral data were in were in agreement with the literature values;[6] $[\alpha]_D^{21}$ −36.5 (*c* 0.7, $CHCl_3$), 84% ee; HPLC (Chiralpak AS-H, 10% IPA/hexane, 1 mL/min): t_R(major)=13.1, t_R(minor)=14.8 min.

*4.3.2. N-((1R,2R)-2-Fluoro-1,2-diphenylethyl)picolinamide (**2d**).* Method B, **1d** (60 mg, 0.20 mmol), 5–15% acetone/hexanes: 42% yield (27 mg), 48% ee; 59% yield (38 mg), 48% ee. White solid. FTIR (thin film, cm^{-1}) 3383, 3063, 3034, 2932, 1676, 1512, 1465, 1455, 1435, 998, 697; ^1H NMR (500 MHz, $CDCl_3$) δ 8.88 (d, J=8.9 Hz, 1H), 8.59 (d, J=4.7 Hz, 1H), 8.10 (d, J=7.8 Hz, 1H), 7.81 (td, J=7.7, 1.2 Hz, 1H), 7.43 (dd, J=6.9, 4.5 Hz, 1H), 7.38–7.27 (m, 10H), 5.84 (dd,

J=45.9, 4.4 Hz, 1H), 5.61 (ddd, J=21.5, 9.1, 4.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.95, 149.50, 148.32, 138.32 (d, ^3J=1.8 Hz), 137.45, 136.79 (d, ^2J=20.6 Hz), 128.73 (d, ^3J=1.5 Hz), 128.72 (2C), 128.42 (2C), 128.05, 127.53 (d, ^3J=0.5 Hz, 2C), 126.49, 126.11, 126.05, 122.47, 95.60 (d, ^1J=180.9 Hz), 57.64 (d, ^2J=21.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −188.37 (dd, J=46.0, 21.5 Hz); HRMS (ESI$^+$) calculated for $C_{20}H_{18}FN_2O$ ([M+H]$^+$), 321.1398; found: 321.1394; [á]$_D^{21}$ −4.5 (*c* 1.0, $CHCl_3$), 48% ee; HPLC (Chiralpak AS-H, 5% IPA/hexane, 1 mL/min): t_R(major)=22.9, t_R(minor)=16.8 min.

*4.3.3. N-((1R,2R)-2-Fluorocyclopentyl)picolinamide (**2e**).* Method A, **1e** (75 mg, 0.40 mmol), 5–40% EtOAc/hexanes: 43% yield (36 mg), 50% ee; 48% yield (40 mg), 61% ee. White solid. FTIR (thin film, cm^{-1}) 3378, 3059, 2964, 2877, 1662, 1516, 1465, 1434, 998, 957, 820; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, J=4.7 Hz, 1H), 8.20 (br d, J=7.8 Hz, 1H), 7.94 (d, J=3.0 Hz, 1H), 7.86 (td, J=7.7, 1.1 Hz, 1H), 7.44 (dd, J=7.1, 5.2 Hz, 1H), 5.06 (ddd, J=9.6, 6.8, 3.5 Hz, 1H), 4.54–4.45 (m, 1H), 2.30 (ddd, J=13.5, 13.2, 7.6 Hz, 1H), 2.05–1.82 (m, 4H), 1.71–1.61 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.15, 149.67, 148.12, 137.60, 126.46, 122.37, 98.72 (d, ^1J=179.5 Hz), 56.41 (d, ^2J=28.2 Hz), 31.11 (d, ^2J=21.9 Hz), 30.27 (d, ^3J=1.8 Hz), 21.63 (d, ^3J=1.4 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −175.65 (ddddd, J=46.0, 29.3, 28.4, 18.2, 0.9 Hz); HRMS (ESI$^+$) calculated for $C_{11}H_{14}FN_2O$ ([M+H]$^+$), 209.1085; found: 209.1088; $[\alpha]_D^{22}$ −11.8 (*c* 1.2, $CHCl_3$), 61% ee; HPLC (Chiralpak AS-H, 5% IPA/hexane, 1 mL/min): t_R(major)=24.4, t_R(minor)=23.4 min.

*4.3.4. (3R,4R)-Benzyl 3-fluoro-4-(picolinamido)pyrrolidine-1-carboxylate (**2f**).* Method B, 96 h, **1f** (162 mg, 0.400 mmol), 7–60% EtOAc/hexanes: 47% yield (80 mg), 78% ee; 49% yield (84 mg), 72% ee. Yellow oil. FTIR (thin film, cm^{-1}) 3290, 3062, 2953, 2890, 1697, 1667, 1515, 1418, 1357, 1338, 1212, 1185, 1104, 997, 955, 766, 696; ^{1}H NMR (500 MHz, MeOD) δ 8.61 (d, J=4.3 Hz, 1H), 8.08 (d, J=7.8 Hz, 1H), 7.95 (td, J=7.7, 1.5 Hz, 1H), 7.57–7.53 (m, 1H), 7.41–7.27 (m, 5H), 5.18 (dm, J_{HF}=50.5 Hz, 1H), 5.15 (s, 2H), 4.71–4.62 (m, 2H), 3.93–3.63 (m, 4H); ^{13}C NMR (125 MHz, MeOD, mixture of rotamers, indicated by *) δ 166.97, 156.66, 156.60*, 150.51, 149.81, 138.86, 137.94, 129.55, 129.17, 129.16*, 129.00, 128.99*, 128.05, 123.37, 95.31 (d, J=182.1 Hz), 94.53* (d, ^1J=183.2 Hz), 68.35, 55.57 (d, ^2J=29.9 Hz), 54.72* (d, J=29.2 Hz), 51.52 (d, J=26.7 Hz), 51.34* (d, J=26.7 Hz), 50.08, 49.85*; ^{19}F NMR (282 MHz, MeOD, mixture of rotamers, indicated by *) δ −181.46 (dddd, J=49.1, 36.1, 25.3, 12.8 Hz), −181.84* (dddd, J=48.8, 37.6, 25.2, 12.7 Hz); HRMS (ESI$^+$) calculated for $C_{18}H_{19}FN_3O_3$ ([M+H]$^+$): 344.1405; found: 344.1403; $[\alpha]_D^{22}$ +30.7 (*c* 1.3, $CHCl_3$), 72% ee; HPLC (Chiralpak AD-H, 17.5% IPA/hexane, 0.9 mL/min): t_R(major)=15.6, t_R(minor)=17.3 min.

*4.3.5. N-((3R,4S)-4-Fluorotetrahydrofuran-3-yl)picolinamide (**2g**).* Method B, 96 h, **1g** (95 mg, 0.50 mmol), 12–100% EtOAc/hexanes: 27% yield (28 mg, 85% purity), 32% ee. Off-white solid. FTIR (thin film, cm^{-1}) 3369, 3061, 2970, 2869, 1717, 1665, 1514, 1466, 1383, 1351, 1279, 1075, 998, 904, 769, 713; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, J=4.6 Hz, 1H), 8.19 (d, J=7.8 Hz, 1H), 8.12 (br s, 1H), 7.87 (td, J=7.7, 1.4 Hz, 1H), 7.46 (dd, J=7.5, 4.8 Hz, 1H), 5.21 (dd, J=52.2, 3.6 Hz, 1H), 4.71 (dd, J=13.1, 6.2 Hz, 1H), 4.26–3.84 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.40, 149.11, 148.30, 137.67, 126.78, 122.40, 95.91 (d, ^1J=184.3 Hz), 72.29 (d, ^2J=24.0 Hz), 71.18, 55.68 (d, ^2J=28.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −176.09 (dddd, J=51.6, 37.1, 29.0, 14.1 Hz); HRMS (ESI$^+$) calculated for $C_{10}H_{12}FN_2O_2$ ([M+H]$^+$), 211.0877; found: 211.0880; HPLC (Chiracel OD-H, 10% IPA/hexane, 1 mL/min): t_R(major)=14.7, t_R(minor)=12.6 min.

*4.3.6. N-((1R,2R)-2-Fluorocycloheptyl)picolinamide (**2h**).* Method B, **1h** (87 mg, 0.40 mmol), 2–20% EtOAc/hexanes: 33% yield (31 mg), 12% ee. Clear oil. FTIR (thin film, cm^{-1}) 3371, 2932, 3862, 1666, 1520, 1465, 1435, 998; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56–8.53 (m, 1H), 8.24–8.21 (br m, 1H), 8.20 (d, J=7.8 Hz, 1H), 7.84 (td, J=7.7, 1.6 Hz, 1H), 7.42 (ddd, J=7.5, 4.8, 1.0 Hz, 1H), 4.63 (dm, J_{HF}=48.2 Hz, 1H), 4.28 (ddddd, J=17.3, 8.7, 8.7, 8.6, 3.2 Hz, 1H), 2.03–1.93 (m, 3H), 1.82–1.59 (m, 5H), 1.59–1.44 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.93, 149.97, 148.11, 137.51, 126.31, 122.39, 96.46 (d, ^1J=173.8 Hz), 55.24 (d, ^2J=21.8 Hz), 31.89 (d, ^2J=21.2 Hz), 30.29 (d, ^3J=7.6 Hz), 27.95, 24.45, 21.34 (d, ^3J=8.2 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −169.35 (m); HRMS (ESI$^+$) calculated for $C_{13}H_{18}FN_2O$ ([M+H]$^+$): 237.1398; found: 237.1401; HPLC (Chiralpak AS-H, 10% IPA/hexane, 1 mL/min): t_R(major)=11.2, t_R(minor)=12.1 min.

4.4. Procedure for the kinetic resolution of 3

*4.4.1. (3R,4R)-Benzyl 4-fluoro-3-(picolinamido)piperidine-1-carboxylate (**4**).* (*R*,*R*)-(salen)Co (12 mg, 0.020 mmol) was suspended in TBME (1 mL) and TBHP (4 μL, 0.02 mmol) and Ti(NMe$_2$)$_4$ (9.5 μL, 0.040 mmol) were added via syringe. Compound **3** (135 mg, 0.400 mmol) and HFIP (84 μL, 0.80 mmol) were added as a solution in TBME (1 mL), followed by PhCOF (35 μL, 0.32 mmol). The reaction mixture was sealed and stirred at 23 °C for 4 or 7 h, then quenched with 7 M methanolic ammonia (4 mL) and stirred vigorously for 15 min. The red solution was poured into 1 M NaOH (10 mL) and extracted with DCM (3×5 mL). The combined organic layers were washed with saturated brine (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by column chromatography on SiO_2 (7–60% EtOAc/hexanes) to obtain the title product as a yellow oil. The 4-h reaction provided **4** in 29% yield (42 mg) and 68% ee (s=6.9), with 65% yield recovered **3** (87 mg) in 29% ee. The 7-h reaction provided **4** in 41% yield (59 mg) and 62% ee (s=6.4). FTIR (thin film, cm^{-1}) 3362, 3062, 2932, 2858, 1697, 1675, 1519, 1466, 1433, 1314, 1269, 1229, 1139, 998; ^{1}H NMR (500 MHz, MeOD) δ 8.62 (d, J=4.4 Hz, 1H), 8.10 (d, J=7.8 Hz, 1H), 7.97 (td, J=7.7, 1.6 Hz, 1H), 7.56 (ddd, J=7.5, 4.8, 1.0 Hz, 1H), 7.34 (d, J=25.0 Hz, 5H), 5.15 (s, 2H), 4.79 (ddd, J=48.8, 12.0, 8.2 Hz, 1H), 4.16 (ddd, J=17.1, 8.6, 4.7 Hz, 1H), 4.12–4.06 (m, 1H), 3.94 (d, J=1.2 Hz, 1H), 3.29–3.16 (m, 2H), 2.20–2.08 (m, 1H), 1.84–1.72 (m, 1H); ^{13}C NMR (125 MHz, MeOD) δ 166.74, 156.90, 150.54, 149.79, 138.88, 137.92, 129.56, 129.16, 128.90, 128.01, 123.26, 90.89 (d, J=179.8 Hz), 68.63, 51.34 (d, J=20.71 Hz), 46.11 (d, J=5.3 Hz), 41.93, 30.66; ^{19}F NMR (282 MHz, MeOD) δ −185.20 (dm, J_{HF}=49.4 Hz); HRMS (ESI$^+$) calculated for $C_{19}H_{21}FN_3O_3$ ([M+H]$^+$): 358.1561; found: 358.1558; $[\alpha]_D^{22}$ +17.8 (*c* 1.1, $CHCl_3$), 68% ee; HPLC (Chiralpak AD-H, 15% IPA/hexane, 0.9 mL/min): t_R(major)=19.6, t_R(minor)=24.3 min. The absolute stereochemistry was assigned in analogy to **2a**,**b**.

4.5. Procedure for the deprotection of 2a

*4.5.1. tert-Butyl ((1R,2R)-2-fluorocyclohexyl)carbamate (**5**).* To a refluxing solution of **2a** (181 mg, 0.814 mmol, 95% ee) and 4-dimethylaminopyridine (10 mg, 0.081 mmol) in THF (3.3 mL) was added di-*tert*-butyl dicarbonate portionwise (8×0.19 mL, 6.51 mmol total) over 24 h. Upon completion, the reaction mixture was concentrated in vacuo and purified by column chromatography on SiO_2 (5–40% EtOAc/hexanes) to obtain *tert*-butyl ((1*R*,2*R*)-2-fluorocyclohexyl)(picolinoyl)-carbamate as a white solid (249 mg, 95% yield). *N*-Boc-**2a** (247 mg) was dissolved in EtOH (6 mL) and $NaBH_4$ (116 mg, 3.06 mmol) was charged. The reaction mixture was stirred at 23 °C for 12 h, then quenched with 1 M NaOH (10 mL) and extracted with Et_2O (3×10 mL). The combined organics were washed with saturated brine (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by column chromatography on SiO_2 (5–40% Et_2O/hexanes) to obtain **5** as a white solid in 96% yield (159 mg, 91% yield over two steps). The enantiomeric excess was determined to be 95% by chiral GC. Spectral data were in agreement with the literature values; $[\alpha]_D^{22}$ −34.7 (*c* 1.1, $CHCl_3$), 95% ee; GC (Cyclodex-B, 130 °C isotherm, 1 mL/min):

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t_R(major)=33.3, t_R(minor)=34.0 min. The absolute configuration of the product was assigned as (*R*,*R*) on the basis of comparison to the literature data for (*S*,*S*)-**5** ($[\alpha]_D^{22}$ +27.5 (*c* 1.01, $CHCl_3$), 99% ee).[6]

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.01.062.

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