Construction of Carbon–Fluorine Bonds Through Catalytic Nucleophilic Fluorination

Thesis by

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ABSTRACT

The importance of organofluorine compounds in disciplines such as agriculture, materials science and medicine has stimulated a long-standing interest among chemists in developing novel synthetic methods to access fluorine-containing molecules. Despite the tremendous success in the construction of $C(sp^2)$–F bonds, the synthesis of alkyl fluorides involving $C(sp^3)$–F bond formation remains relatively underdeveloped and relies heavily on electrophilic fluorinating agents (e.g., NFSI and SelectFluor). Nucleophilic alternatives (e.g., CsF and KF), although more economical and atom-efficient, have rarely been applied in fluorination reactions, probably because of facile side-reactions such as elimination that affords olefin. Herein, this dissertation primarily discusses the progress towards developing novel nucleophilic fluorination strategies, focusing on method development with preliminary mechanistic investigations.

Chapter I describes the development of a phosphine-catalyzed nucleophilic fluorination of tertiary alkyl halides under mild conditions. Unactivated[1] tertiary alkyl halides are converted to fluorides with AgF as fluorinating agent and economical PPh_3 as catalyst. Condition optimization, scope of substrates, study of functional-group compatibility and preliminary mechanistic studies have been included in this chapter.

Chapter II elaborates the development of copper-catalyzed enantioconvergent nucleophilic fluorination affording enantioenriched α-fluoroamides. Racemic α-chloro-α-arylacetamides are converted to enantioenriched α-fluoroamides with good enantioselectivity and yield under mild conditions, with copper, an earth-abundant metal, as catalyst and affordable CsF as nucleophilic fluorinating agent. Condition optimization, scope of substrates, study of functional-group compatibility, demonstration of synthetic application and preliminary mechanistic studies have been detailed in this chapter.

[1] In this dissertation, the term "unactivated" is utilized to describe functional groups not adjacent to conjugated systems (e.g., carbonyls, phenyls, nitriles, alkenes or alkynes) or π-donating systems (e.g., oxygen, nitrogen or sulfur atoms) directly or indirectly (e.g., adjacent to the derivatives or surrogates of functional groups described above).

Chapter III is temporarily embargoed.

PUBLISHED CONTENT AND CONTRIBUTIONS

This dissertation contains materials adapted with permission from the following publications:

1. Wang, Z.-Y.; Freas, D. J.; Fu, G. C. Phosphine Catalysis of the Fluorination of Unactivated Tertiary Alkyl Chlorides under Mild and Convenient Conditions. *J. Am. Chem. Soc.* **2023**, *145*, 25093–25097. doi: 10.1021/jacs.3c11042.

Z.-Y. W. participated in conceiving the project, optimization of condition, determination of scope of substrates, study of functional-group compatibility and mechanistic studies.

2. Wang, Z.-Y.; Fu, G. C. Copper-Catalyzed Enantioconvergent Nucleophilic Fluorination of Alkyl Electrophiles to Generate α-Fluoroamides. *J. Am. Chem. Soc.* **2026**, *148*, 14617–14623. doi: 10.1021/jacs.6c03178.

Z.-Y. W. participated in conceiving the project, optimization of condition, determination of scope of substrates, study of functional-group compatibility, synthetic applications and mechanistic studies.

Note: Z.-Y. W. and Zhuoyan Wang, the author of this dissertation, are the same individual.

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GENERAL INFORMATION AND ABBREVATIONS

The drafting of this dissertation is assisted with AI tools which helped improve the syntax and language presentation. Nevertheless, no assertions related to science were generated by AI, no complete sentences were directly replicated from AI-generated materials, no data is fabricated or altered by AI and none of the graphic presentations is delivered by AI. The author alone is held accountable for all the material in this dissertation.

Unless otherwise noted, reagents received from commercial suppliers were used as received. All reactions were performed under an atmosphere of dry nitrogen. Glassware was oven-dried at 150 °C for a minimum of 12 h, or flame-dried utilizing a gas flame under high vacuum. All solvents were either purified by passage through activated aluminum oxide in a solvent-purification system, or they were purchased from commercial suppliers and used as received.

NMR spectra were collected on a Bruker 400 MHz, Varian 500 MHz, or Varian 600 MHz spectrometer at ambient temperature (unless otherwise indicated); chemical shifts (δ) are reported in ppm downfield from tetramethylsilane, using the solvent resonance as an internal standard. FT-IR measurements were carried out on a Thermo Scientific Nicolet iS5 FT-IR spectrometer equipped with an iD5 ATR accessory. X-ray crystallographic analyses were carried out in the Caltech X-Ray Crystallography Facility. HRMS were acquired on an Agilent 1260 Infinity II HPLC, Agilent 6230 LC-TOF system in electrospray ionization (ESI+) mode, or by field ionization/field desorption ionization using a JEOL AccuTOF GC-Alpha (JMS-T2000GC) mass spectrometer interfaced with an Agilent 8890 GC system. GC-MS analyses were carried out on an Agilent 6890N GC-MS. SFC analyses were carried out on an Agilent 1260 Infinity II system with Daicel CHIRALPAK® or Daicel CHIRALCEL® columns (4.6 × 250 mm, particle size 5 μm), with samples prepared by dissolving the compound in *i*-PrOH. Flash column chromatography was performed using silica gel (SiliaFlash® P60, particle size 40-63 μm, Silicycle). Syringe filters were purchased from

VWR (nylon, 13 mm diameter, 0.22 μm pore). Melting points were measured using a Büchi Melting Point B-545 instrument (20 °C – 200 °C; gradient 0.5 °C/s).

The abbreviations and acronyms used in this dissertation are explained below. Certain abbreviations may also be noted in legends or footnotes.

$\{^1H\}$	proton-decoupled
^1H	proton
^{13}C	carbon-13
^{18}F	fluorine-18
^{19}F	fluorine-19
2-Me-THF	2-methyl-tetrahydrofuran
^{31}P	phosphorus-31
Å	angstrom(s)
A_X	anisotropic hyperfine coupling constant (of the atom X)
Ac	acetyl
aq.	aqueous
Ar	aryl group
ATR	attenuated total reflection
BINAP	(2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)
Boc	*t*-butoxycarbonyl
box	bisoxazoline
Bn	benzyl
br	broad

i-Bu	isobutyl
n-Bu	norm-butyl
c	concentration
°C	degrees Celsius
calcd	calculated
cat.	catalytic amount
CCDC	Cambridge Crystallographic Data Centre
c.f.	consult or compare to (Latin: confer)
cm^{-1}	wavenumber(s)
Cp	cyclopentadienyl
CW	continuous-wave
Cy	cyclohexyl
d	doublet or day(s)
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DCM	dichloromethane
n-Dec	*n*-decyl
DFB	1,2-difluorobenzene
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide

dr	diastereomeric ratio
e	electron
ee	enantiomeric excess
E	trans (entgegen) olefin geometry
E2	bimolecular elimination
e.g.	for example (Latin: exempli gratia)
EPR	electron paramagnetic resonance
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
F^2	square of structure factor
FI	field ionization
FD	field desorption
FDA	U.S. Food and Drug Administration
FT	Fourier transform
g	gram(s)
g	*g*-value
GC	gas chromatography
GHz	gigahertz

h	hour(s)
hept	heptet
HR	high resolution
HMDS	bis(trimethylsilyl)amide
HMPA	hexamethylphosphoramide
hv	light
HWE	Horner–Wadsworth–Emmons (reaction)
Hz	hertz
IC_{50}	half-maximal inhibitory concentration
ID	inner diameter
i.e.	that is (Latin: id est)
i-PrOH	isopropanol
IR	infrared spectroscopy
J	coupling constant
K	Kelvin
kCal	kilocalories
L*	chiral ligand
LDA	lithium diisopropylamide
m	multiplet
M	molar
m-	meta-
μ	micro

Me	methyl
MeOH	methanol
Mes	mesityl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
mm	millimeter(s)
mmol	millimole(s)
mol	mole(s)
m.p.	melting point
Ms	mesyl (methanesulfonyl)
MS	mass spectroscopy
MW	microwave
mW	milliWatt
m/z	mass-to-charge ratio
N	normal or molar
n	generic number
NCS	*N*-chlorosuccinimide
NFSI	*N*-fluorobenzenesulfonimide
nm	namometer(s)
NMR	nuclear magnetic resonance

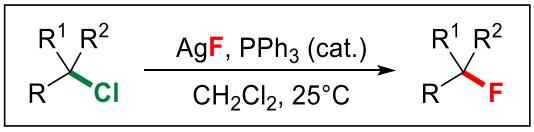
Nu	nucleophile
o-	ortho-
n-Oct	*n*-octyl
ORTEP	Oak Ridge thermal ellipsoid plot
p-	para-
PET	positron emission tomography
Ph	phenyl
PhMe	toluene
pin	pinacolato
ppm	parts per million
n-pent	*n*-pentyl
Pr	propyl
i-Pr	isopropyl
n-Pr	*norm*-propyl
i-PrOH	isopropanol
PPI	protein-protein interaction
PTFE	polytetrafluoroethylene
q	quartet
R	generic alkyl group
R	rectus
rac	racemic
ref.	reference

RMS	root-mean square
rpm	revolutions per minute
r.t.	room temperature
s	singlet
S	sinister
sat.	saturated
SFC	supercritical fluid chromatography
S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
t	time or triplet
TBAF	tetrabutylammonium fluoride
TBS	*t*-butyl(dimethyl)silyl
temp	temperature
TEMPO	2,2,6,6-tetramethylpiperidin-1-oxyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMEDA	*N,N,N′,N′*-tetramethylethylenediamine
TMS	trimethylsilyl
tol	tolyl
Ts	tosyl (*p*-toluenesulfonyl)
W	Watt

wt	weight
X	anionic ligand or halide
Z	number of molecules in an asymmetric unit
Z	cis (Zusammen) olefin geometry
[α]	specific rotation
δ	chemical shift
μL	microliter(s)

Chapter I

PHOSPHINE-CATALYZED NUCLEOPHILIC FLUORINATION OF TERTIARY ALKYL HALIDES



1. Introduction

Developing novel synthetic strategies to access organofluorine molecules has always been of substantial interest due to their applications in various fields such as agrochemicals, materials science, clinical treatment (e.g., PET leveraging ^{18}F decay) and pharmaceuticals. As a "paradoxical" element,[1] fluorine is considered both as xenobiotic, since very few natural pathways can construct carbon–fluorine bonds,[2] and as essential to life, because fluorine atoms are frequently introduced into molecules of pharmaceutical relevance. For example, more than 40% of the small-molecule drugs newly approved by FDA in 2018–2019 contain at least one fluorine; in 2023, this proportion is 37.5% (12 of 32).[3] The introduction of fluorine atoms in drug candidates imparts exquisite metabolic stability, customizable bioavailability and tunable polarity, taking advantage of the strength of C–F bonds (110 kCal/mol for CH_3–F[4]) and the high electronegativity of fluorine element.

Among the plethora of fluorine-bearing drug molecules, the predominant classes are aryl monofluorides and trifluoromethyl arenes, whereas alkyl monofluorides constitute only about 15% of all organofluorine compounds (Figure 1A).[5] Compared to strategies to synthesize aryl fluorides,[6] approaches for alkyl monofluorides are less developed (Figure 1B). Although radical and electrophilic fluorination methods, which employ electrophilic fluorinating agents such as NFSI, *N*-fluoropyridinium and SelectFluor, can efficiently furnish alkyl monofluorides, their broader application may be stemmed by high cost, hazardous production[7] and side reactions due to their oxidative nature. Nucleophilic

approaches utilizing alkali metal fluorides (or analogues) represent attractive alternatives, but competing reactions, particularly S_N2-type elimination, severely compromise the efficiency of fluorination, unless unhindered primary alkyl electrophiles are used as substrates.

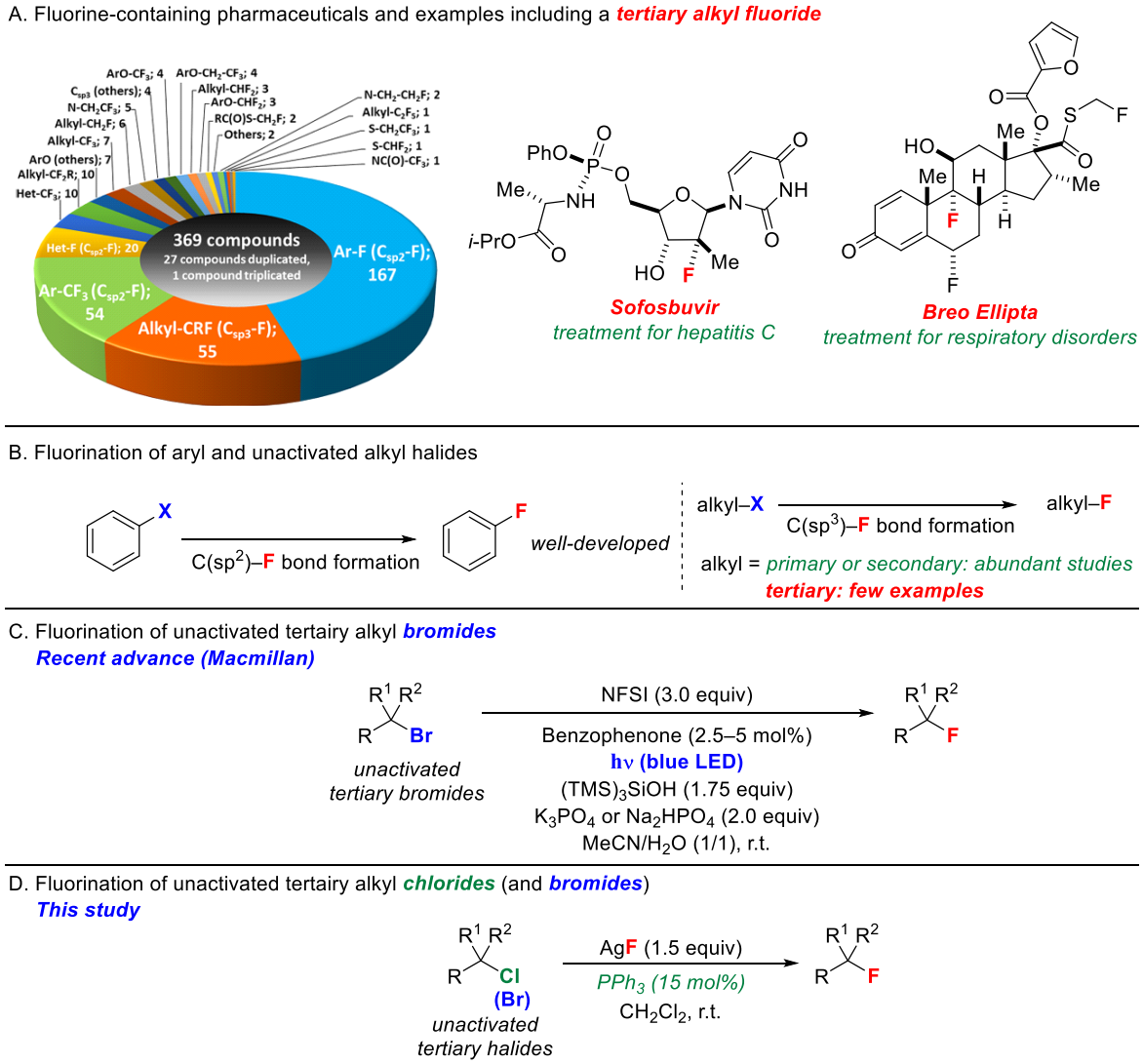


Figure 1. Fluorination of unactivated alkyl halides. (A) Classes of organofluorine molecules of pharmaceutical importance and selected examples of alkyl monofluorides. Pie chart is adapted from ref. 5. (B) Background: the synthesis of tertiary alkyl fluorides remains challenging. (C) Recent advances from Macmillan. (D) Mild and convenient nucleophilic fluorination of tertiary alkyl halides.

Halide exchange – substitution of an unactivated alkyl halide by fluoride – is a straightforward strategy to afford alkyl fluorides. Despite the success in the fluorination of

primary and secondary halides, synthesis of tertiary alkyl fluorides through halide exchange is underexplored and relies on electrophilic fluorination of alkyl bromides or iodides (Figure 1C).[8,9] Seminal studies on nucleophilic fluorination, on the other hand, have found only limited synthetic application due to their narrow scope[10] or the dependence on toxic agents (e.g., TlF).[11] The nucleophilic fluorination of tertiary alkyl chlorides is even rarer: we are only aware of fluorinations of adamantyl chlorides (not prone to H–Cl elimination)[12] and one example of fluorinating unactivated tertiary chlorides with a limited scope of substrates and 30 equiv of hazardous HF as the fluorine source.[13]

In this chapter, we describe the nucleophilic fluorination of unactivated tertiary alkyl chlorides (and bromides) with a wide range of substrates under mild and convenient conditions. Specifically, with commercially available AgF and inexpensive PPh_3 as catalyst, tertiary chlorides – even those of exacting steric demands – are converted to fluorides with good yield at room temperature. This catalytic process tolerates a broad array of functional groups, highlighting its potential in the late-stage modification of drug molecules.

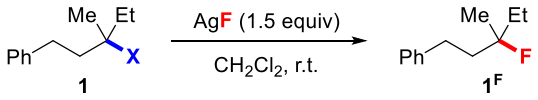
2. Optimization of conditions

Our initial investigations have found that tertiary bromide $\mathbf{1^{Br}}$ can react with AgF with promising yield of $\mathbf{1^{F}}$ in the presence of 10 mol% $NiBr_2$·glyme and 15 mol% pybox, whereas no fluorination product was observed without the catalyst (**Table 1**, entries 1–2). Control experiments later established C–F bond formation can still occur in the absence of $NiBr_2$·glyme, i.e., pybox alone suffices to deliver the fluorinated product (entry 3). Based on this finding, we hypothesize that pybox may coordinate with AgF, thereby enhancing its solubility in organic solvents. As such hypothesis implies that other Lewis-basic molecules may realize the nucleophilic fluorination similarly, we explored a wide range of inexpensive ligands and identified PPh_3 as an effective catalyst capable of fluorinating not only tertiary bromides but iodides and chlorides as well (entries 4–5, 7).

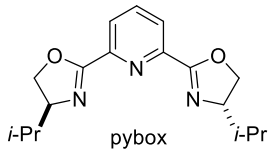
We thus decided to focus on the nucleophilic fluorination of tertiary chlorides, as they are the least explored and the most challenging (due to the strong C–Cl bond) among the

three halides. In the absence of PPh_3, only elimination, rather than fluorination, is observed (entry 8). Reduced loading of AgF or PPh_3 results in only modest loss of yield (entries 9–10) and this procedure is not sensitive to moisture or air, highlighting the robustness of this method (entries 11–12). The by-product of this method is usually olefin due to E2-type elimination.

Table 1. Initial Studies of the Catalytic Fluorination of Unactivated Tertiary Alkyl Halides[a]



entry	X	additional reagents	yield (%)
1	Br	none	<3
2	Br	$NiBr_2$•glyme (10 mol%), pybox (15 mol%)	56
3	Br	pybox (15 mol%)	59
4	**Br**	**PPh_3 (15 mol%)**	**69**
5	**I**	**PPh_3 (15 mol%)**	**70**
6	I	none	17
7	**Cl**	**PPh_3 (15 mol%)**	**79**
8	Cl	none	<3
9	Cl	PPh_3 (5.0 mol%)	73
10	Cl	PPh_3 (15 mol%), AgF (1.1, instead of 1.5, equiv)	73
11	Cl	PPh_3 (15 mol%), H_2O (1.0 equiv)	72
12	Cl	PPh_3 (15 mol%), under air in a closed vial[b]	70



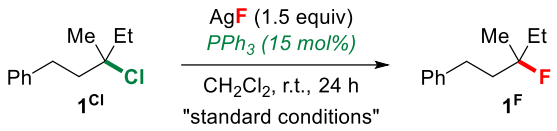
pybox

[a]Each entry represents the average yield of two runs (0.10-mmol scale). Yields were determined through analysis via ^{19}F NMR spectroscopy, with 4-fluorobiphenyl as the internal standard. Note: to ensure accurate assay, the offset frequency (o1p) in quantitative ^{19}F NMR should be set to the midpoint between the signals of the product and the internal standard. [b]The flask containing all reaction components was opened to air for 5 min, before capped and allowed to stir at r.t.

With the current optimized conditions at hand, we next examined the effect of different reaction parameters. The reaction time can be shortened from 24 h to 6 hours for $\mathbf{1^{Cl}}$ (entry 2). A stoichiometric amount of AgF was required for complete conversion, whereas alkali metal fluorides are not efficient fluorinating agents even with the presence of a sub-stoichiometric amount of AgF (entries 3–8). Solvents other than CH_2Cl_2 significantly suppressed the fluorination (entries 9–11). In particular, MeCN, previously employed by Easton in the fluorination of a tertiary alkyl bromide, affords only 23% yield. In addition to

PPh_3, either mono-phosphines or bis-phosphines are competent in catalyzing the nucleophilic fluorination except the electron-deficient $P(C_6F_5)_3$ (entries 12–15). On the other hand, 1,10-phenanthroline, as a representative nitrogen-containing ligand, proves to be ineffective (entry 16).

Table 2. Variation of reaction parameters: fluoride sources, solvents and ligands[a]



entry	variation from "standard conditions"	yield (%)
1	none	79
2	6 h, instead of 24 h	78
3	LiF, instead of AgF	<3
4	KF, instead of AgF	<3
5	KF (1.5 equiv) and AgF (0.5 equiv)	<3
6	CsF (1.5 equiv), instead of AgF	<3
7	CsF (1.5 equiv) and AgF (10 mol%)	<3
8	TBAF•3H_2O instead of AgF	<3
9	MeCN, instead of CH_2Cl_2	23
10	THF, instead of CH_2Cl_2	<3
11	PhMe, instead of CH_2Cl_2	<3
12	PCy_3, instead of PPh_3	17
13	P(*p*-anisyl)$_3$, instead of PPh_3	68
14	(rac)-tol-BINAP, instead of PPh_3 (48 h)	67
15	$P(C_6F_5)_3$, instead of PPh_3	<3
16	1,10-phenanthroline, instead of PPh_3	<3

[a]Each entry represents the average yield of two runs (0.10-mmol scale). Yields were determined through analysis via ^{19}F NMR spectroscopy, with 4-fluorobiphenyl as the internal standard.

3. Scope of Reactivity

The PPh_3-catalyzed nucleophilic fluorination is effective for the fluorination of unactivated tertiary chlorides of varying steric demands. In addition to β- and γ- substituted electrophiles, a tertiary chloride bearing an adjacent quaternary center undergoes fluorination with only slightly decreased yield (**3**–**5**). This procedure is also scalable: in a gram-scale reaction, 73% yield (1.05 g $\mathbf{1^F}$) is obtained with reduced loading of AgF (1.25, instead of 1.5, equiv).

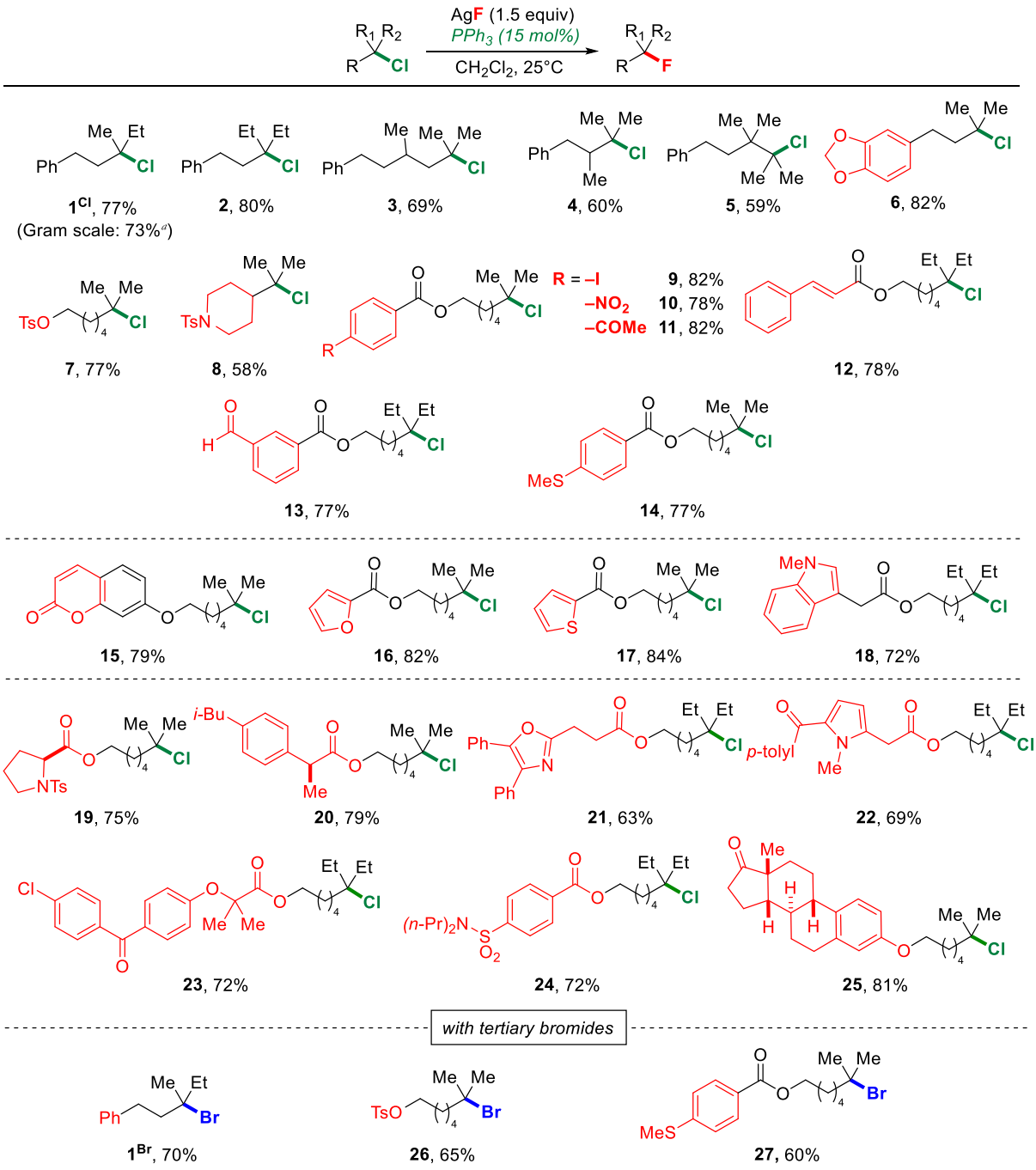


Figure 2. Phosphine-catalyzed nucleophilic fluorination of tertiary alkyl chlorides. Reactions were carried out on a 0.60–1.2 mmol scale unless otherwise noted (Yields represent an average of two runs). [a]Carried out on an 8.0-mmol scale with 1.25, instead of 1.5, equiv of AgF: 1.05 g of product (73% yield).

To examine the functional-group tolerance of the PPh_3-catalyzed fluorination, we have incorporated a sulfonamide, aryl iodide, nitroarene, ketone, and α,β-unsaturated ester into substrates (**8**–**12**), which afford tertiary alkyl fluorides with good yield. In particular,

functional groups prone to oxidation – e.g., an aldehyde and sulfide[14] – are tolerated in the catalysis (**13**–**14**), underscoring the complementarity of AgF-mediated nucleophilic fluorination to electrophilic methods. Heterocyclic aromatic rings such as furan, thiophene and an electron-rich indole[15] also remain intact over the course of fluorination (**15**–**18**). C–F bond formation can also be achieved under phosphine catalysis with a range of derivatives of natural products and bioactive compounds (**19**–**25**). Finally, we find the conditions developed for fluorination of tertiary chlorides can be applied to tertiary bromides without modification of conditions (**26**–**27**). We have not studied tertiary alkyl iodides due to their instability.

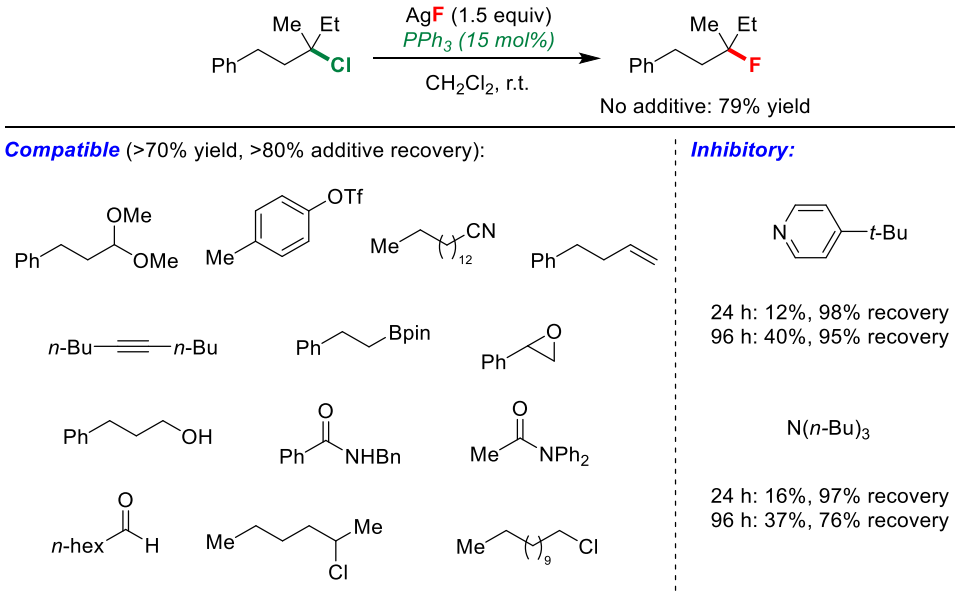


Figure 3. Study of functional-group compatibility. Each entry represents the average yield of two runs (0.10-mmol scale; reaction time: 24h). The yield of the fluorination product was determined through analysis via ^{19}F NMR spectroscopy, and the recovery of the additive was determined through analysis via GC, both using 4-fluorobiphenyl as the internal standard.

Through additive studies, we establish that additional functional groups such as an acetal, aryl triflate, nitrile, olefin, internal alkyne, alkylboronate ester, epoxide, alcohol and secondary and tertiary amide are compatible with the fluorination conditions, whereas a pyridine and a tertiary amine are inhibitory, probably due to their ability to bind silver. The AgF-mediated fluorination exhibits good chemoselectivity, as primary and secondary chlorides are unreactive when tertiary chlorides are fluorinated with good yield.

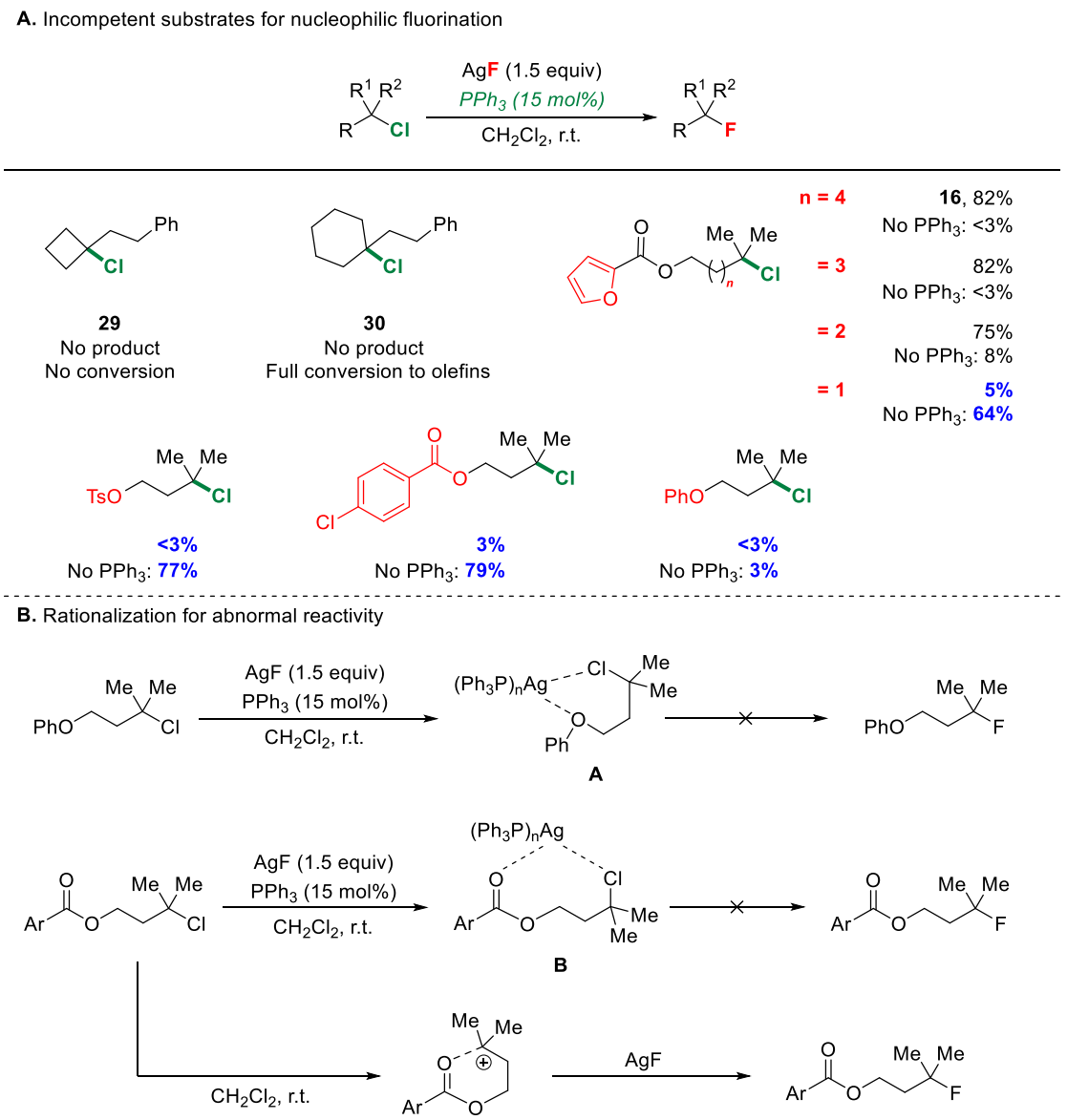


Figure 4. Observation of abnormal reactivity. (A) Incompetent substrates and tertiary chlorides exhibiting abnormal reactivity (poor yield *with* PPh_3 whereas good yield *without* PPh_3). (B) Rationalization for abnormal reactivity due to formation of Ag–substrate complexes.

The PPh_3-catalyzed fluorination is not devoid of limitations. For example, strained cyclic tertiary chlorides (e.g., **29**) may exhibit poor conversion, while unstrained substrates represented by **30** are prone to rapid elimination that affords olefin. Interestingly, if the tertiary chloride is placed proximal to a Lewis-basic group, fluorination occurs in the absence of PPh_3, while PPh_3 inhibits, rather than promotes, the nucleophilic fluorination. Such inversion of reactivity is only observed with substrates of a particular chain length (n = 1).

For a phenol ether, poor yield is obtained under conditions either with or without phosphines. The abnormal reactivity might be attributed to the formation of a meta-stable silver complexes chelated by the chloride and the Lewis-basic group (**A** and **B**). In ester substrates, a stable carbocation can form in the absence of phosphines, consequently trapped rapidly by the fluoride.

4. Preliminary Mechanistic Studies

With regard to mechanism, we hypothesize the fluorination may proceed through a silver-assisted S_N1 pathway. Interestingly, enantiopure tertiary chloride is converted to the fluoride with predominant *inversion* of stereochemistry. Although S_N1 reactions do not always produce fully racemized products from enantiopure starting materials,[16] the formation of a highly enantioenriched tertiary fluoride with stereochemical inversion suggests the involvement of a bulky silver complex which shields one face of the putative carbocation generated upon Ag-mediated heterolytic C–Cl bond cleavage.

To investigate the silver species involved in catalysis, we performed ^{31}P NMR studies. At the outset of the reaction, we observed a pair of ^{31}P doublets characteristic of a Ag–phosphine complex, consistent with the ^{31}P coupling with ^{107}Ag and ^{109}Ag, which occur in approximately equal natural abundance and both have nuclear spin +1/2. On the basis of the approximate $^{1}J(^{107}Ag–^{31}P)$ with that of $[Ag(P(p\text{-tol})_3)_4]^+$,[17] this species is assigned as $[Ag(PPh_3)_4]^+$. This assignment is further corroborated by the detection of the corresponding molecular mass in HRMS. As this complex is saturated in coordination (an 18 electron-complex), it may not be involved directly in the fluorination. Nevertheless, it may be converted to other species such as $[Ag(PPh_3)_2]^+$ (mass detected in HRMS) while AgF is gradually dissolved in CH_2Cl_2. In summary, the studies overall further support the hypothesis that ligands such as PPh_3 serve to enhance the solubility of AgF in CH_2Cl_2 – i.e., as phase-transfer catalysts – through coordination, although we are not able to determine the solubility of AgF in CH_2Cl_2 with the absence of phosphines through ^{109}Ag NMR.

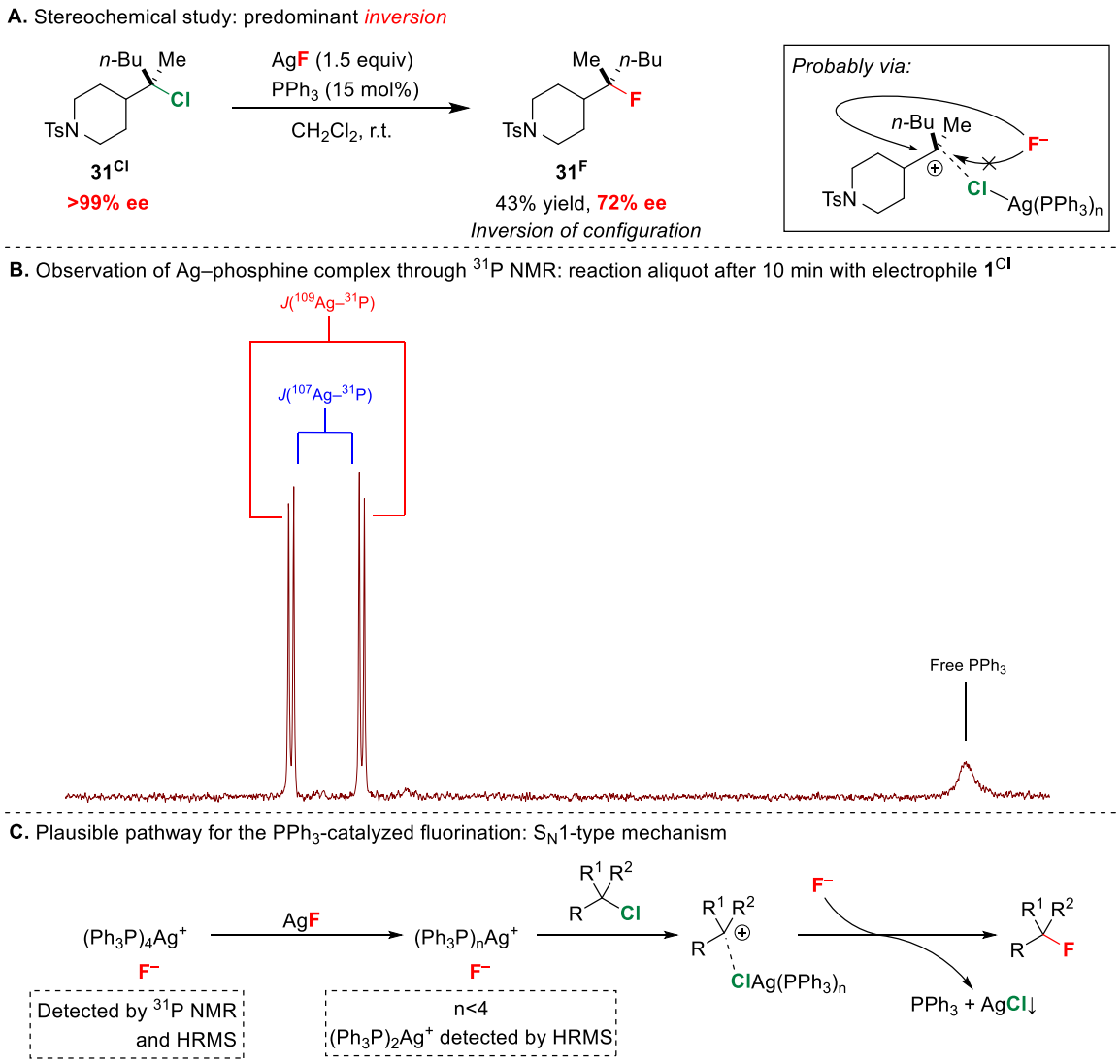


Figure 5. Preliminary mechanistic studies. (A) Stereochemical study with enantiopure tertiary alkyl chloride: predominant *inversion* of configuration. (B) Presence of Ag–phosphine complex through ^{31}P: spectrum of reaction aliquot at the outset of the fluorination. (C) Plausible pathway for the PPh_3-catalyzed fluorination: S_N1-type mechanism.

5. Conclusion

In this chapter we have addressed a previously unsolved challenge: the development of a versatile and convenient method for the fluorination of unactivated tertiary alkyl chlorides. The process, which employs AgF as the nucleophilic fluorine source and inexpensive PPh_3 as catalyst, is characterized by its broad scope, robustness, operational simplicity, mild conditions and good functional-group compatibility. In fact, we have noticed recent reports

utilizing this strategy either in the synthesis of tertiary fluorides[18] or, as a cornerstone, in the development of more convenient, phosphine-free fluorination methods leveraging mechanochemistry.[19]

6. Experimental Session

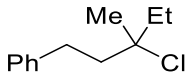
A. Preparation of Electrophiles

The yields have not been optimized.

General Procedure 1 (GP–1): Chlorination/bromination of tertiary alcohols.

Typical scale: 10 mmol of substrate. A 100-mL round-bottom flask equipped with a PTFE stir bar was charged with LiCl (2.0 equiv) and aqueous HCl (12 M; 20 mL). The solution was cooled to 0 °C, and then the tertiary alcohol was added dropwise, either neat or dissolved in a minimal amount of CH_2Cl_2, over 5 min. The reaction mixture was allowed to warm to rt, and it was stirred for 12 h. The mixture was then diluted with Et_2O (20 mL) and water (20 mL), and the organic layer was separated. The residual Et_2O in the aqueous layer was recovered by diluting with water (25 mL) and Et_2O (10 mL) (twice) and then saturated aqueous $NaHCO_3$ (25 mL) and Et_2O (10 mL) (twice). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated to provide the crude product.

The bromination of tertiary alcohols utilized the same procedure, with LiBr and aqueous HBr (48 wt%) used in place of LiCl and aqueous HCl.



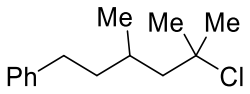
(3-Chloro-3-methylpentyl)benzene ($\mathbf{1^{Cl}}$). Compound $\mathbf{1^{Cl}}$ was synthesized according to **GP–1** and purified by vacuum distillation (250 mbar, 75 °C). Colorless oil. Yield: 4.52 g, 85%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 2H), 7.29 – 7.23 (m, 3H), 2.92 – 2.77 (m, 2H), 2.21 – 2.01 (m, 2H), 1.99 – 1.83 (m, 2H), 1.64 (s, 3H), 1.10 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.9, 128.52, 128.48, 126.0, 74.8, 45.7, 37.0, 31.3, 29.3, 9.3.

FT-IR (film): 2972, 1497, 1454, 1380, 1031, 806, 743, 607, 628, 553, 505 cm^{-1}.

HRMS (FI^+-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{12}H_{17}Cl]^{+\bullet}$: 196.1019, found: 196.1024.



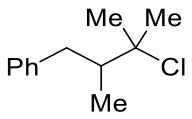
(5-Chloro-3,5-dimethylhexyl)benzene (3). Compound **3** was synthesized according to **GP-1** and purified by flash column chromatography (100% hexanes). Colorless oil. Yield: 1.17 g.

^{1}H NMR (400 MHz, CDCl3) δ 7.34 – 7.29 (m, 2H), 7.25 – 7.17 (m, 3H), 2.76 – 2.56 (m, 2H), 1.90 (dd, *J* = 14.3, 3.6 Hz, 1H), 1.86 – 1.66 (m, 3H), 1.61 (s, 6H), 1.60 – 1.52 (m, 1H), 1.10 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, CDCl3) δ 142.7, 128.4, 128.3, 125.7, 71.5, 52.8, 40.7, 33.5, 33.2, 32.9, 29.9, 22.0.

FT-IR (film): 2925, 1496, 1453, 1370, 1116, 1031, 745, 697, 570, 509 cm^{-1}.

HRMS (FI^+-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{14}H_{21}Cl]^{+\bullet}$: 224.1332, found: 224.1341.



(3-Chloro-2,3-dimethylbutyl)benzene (4). Compound **4** was synthesized according to **GP–1** and purified by vacuum distillation (75 °C, 250 mTorr). Colorless oil. Yield: 2.12 g.

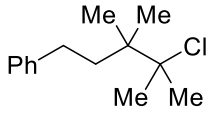
According to ^{1}H NMR spectroscopic analysis, compound **4** contains ~3% of a rearranged isomer, (2-chloro-2,3-dimethylbutyl)benzene, which cannot be separated from compound **4**.

^{1}H NMR (400 MHz, CDCl3) δ 7.33 – 7.27 (m, 2H), 7.24 – 7.16 (m, 3H), 3.24 (dd, *J* = 13.1, 2.7 Hz, 1H), 2.24 (dd, *J* = 13.1, 11.0 Hz, 1H), 2.00 (dqd, *J* = 11.0, 6.7, 2.6 Hz, 1H), 1.65 (dd, *J* = 22.9, 1.5 Hz, 6H), 0.90 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, CDCl3) δ 141.3, 129.2, 128.3, 125.9, 75.2, 48.1, 38.8, 31.2, 29.5, 14.5.

FT-IR (film): 2975, 1495, 1454, 1370, 1125, 1077, 776, 737, 698, 632, 573, 499, 466 cm-1.

HRMS (FI^{+}-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{12}H_{17}Cl]^{+\bullet}$: 196.1019, found: 196.1024.



(4-Chloro-3,3,4-trimethylpentyl)benzene (5). Compound **5** was synthesized according to **GP–1** and purified by recrystallization from acetone and water. White waxy solid. Yield: 1.86 g, 46%.

According to ^{1}H NMR spectroscopic analysis, compound **5** contains ~11% of a rearranged isomer, (3-chloro-3,4,4-trimethylpentyl)benzene, which cannot be separated from compound **5**.

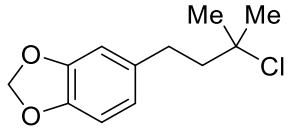
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H), 7.23 – 7.16 (m, 3H), 2.66 – 2.58 (m, 2H), 1.80 – 1.72 (m, 2H), 1.60 (s, 6H), 1.14 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.1, 128.4 (2), 125.8, 80.1, 41.8, 39.6, 31.6, 28.5, 22.1.

FT-IR (film): 2973, 1601, 1491, 1453, 1378, 1145, 1125, 1097, 1030, 921, 819, 749, 696, 614, 568, 520, 463, 424 cm^{-1}.

HRMS (FI^{+}-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{14}H_{21}Cl]^{+\bullet}$: 224.1332, found: 224.1340.

m.p.: 46.0 °C.



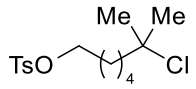
5-(3-Chloro-3-methylbutyl)benzo[d][1,3]dioxole (6). Compound **6** was synthesized according to **GP–1** and purified by flash column chromatography (2% EtOAc in hexanes). Colorless oil. Yield: 2.82 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (d, *J* = 7.9 Hz, 1H), 6.70 (d, *J* = 1.7 Hz, 1H), 6.67 – 6.63 (m, 1H), 5.92 (s, 2H), 2.80 – 2.63 (m, 2H), 2.09 – 1.87 (m, 2H), 1.63 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.6, 145.7, 135.6, 121.1, 108.9, 108.2, 100.8, 70.5, 48.2, 32.5, 31.4.

FT-IR (film): 2972, 1502, 1488, 1441, 1370, 1244, 1189, 1159, 1094, 1038, 927, 861, 804, 771, 636, 563, 532, 421 cm^{-1}.

HRMS (FI^+-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{12}H_{15}O_2Cl]^{+\bullet}$: 226.0761, found: 226.0772.



6-Hydroxy-6-methylheptyl 4-methylbenzenesulfonate (7). Compound **7** was synthesized according to **GP–1** and purified by flash column chromatography (10% EtOAc in hexanes).

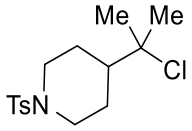
Colorless oil. Yield: 1.53 g, 80%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 4.03 (t, *J* = 6.4 Hz, 2H), 2.44 (s, 3H), 1.73 – 1.62 (m, 4H), 1.53 (s, 6H), 1.48 – 1.38 (m, 2H), 1.38 – 1.27 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7, 133.2, 129.9, 127.9, 70.9, 70.4, 45.7, 32.4, 28.7, 25.4, 24.4, 21.7.

FT-IR (film): 2940, 1598, 1454, 1356, 1174, 1097, 953, 813, 755, 727, 662, 553 cm^{-1}.

HRMS (FD^+-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{15}H_{23}O_3ClS]^{+\bullet}$: 318.1056, found: 318.1056.



4-(2-Chloropropan-2-yl)-1-tosylpiperidine (8). Compound **8** was synthesized according to **GP–1** and purified by recrystallization from EtOAc and hexanes. White solid. Yield: 1.80 g, 62%.

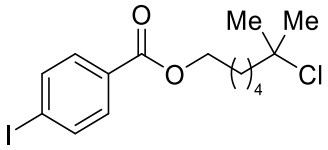
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 3.92 – 3.84 (m, 2H), 2.43 (s, 3H), 2.27 – 2.12 (m, 2H), 1.95 – 1.90 (m, 2H), 1.59 – 1.39 (m, 3H), 1.50 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5, 133.0, 129.6, 127.8, 72.9, 48.2, 46.5, 29.9, 26.9, 21.5.

FT-IR (film): 2980, 1597, 1461, 1372, 1333, 1302, 1250, 1161, 1113, 1089, 1055, 926, 870, 808, 728, 653, 638, 584, 548, 517, 494, 411 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $[C_{15}H_{23}NO_2ClS]^+$: 316.1133, found: 316.1133.

m.p.: 127.0 °C.



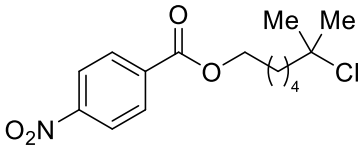
6-Chloro-6-methylheptyl 4-iodobenzoate (9). Compound **9** was synthesized according to **GP–1** and purified by flash column chromatography on silica gel (3% EtOAc in hexanes). Colorless oil. Yield: 1.74 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.78 (m, 2H), 7.76 – 7.72 (m, 2H), 4.31 (t, *J* = 6.7 Hz, 2H), 1.85 – 1.73 (m, 4H), 1.60 – 1.52 (m, 2H), 1.57 (s, 6H), 1.50 – 1.40 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 137.7, 131.0, 129.9, 100.6, 71.0, 65.2, 45.9, 32.5, 28.6, 26.2, 24.8.

FT-IR (film): 2939, 1717, 1586, 1466, 1392, 1369, 1265, 1176, 1101, 1007, 845, 752, 682, 627, 571, 462 cm^{-1}.

HRMS (FD^+-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{15}H_{20}O_2ClI]^{+\bullet}$: 394.0197, found: 394.0201.



6-Chloro-6-methylheptyl 4-nitrobenzoate (10). Compound **10** was synthesized according to **GP–1** and purified by flash column chromatography on silica gel (5% → 10% EtOAc in hexanes). White solid. Yield: 1.47 g.

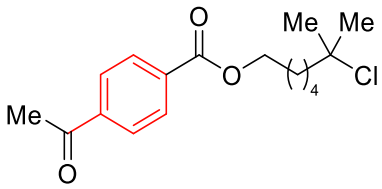
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 – 8.26 (m, 2H), 8.23 – 8.18 (m, 2H), 4.38 (t, *J* = 6.6 Hz, 2H), 1.89 – 1.73 (m, 4H), 1.63 – 1.53 (m, 2H), 1.57 (s, 6H), 1.52 – 1.42 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8, 150.5, 135.8, 130.7, 123.6, 71.0, 66.0, 45.9, 32.5, 28.6, 26.1, 24.8.

FT-IR (film): 2949, 1715, 1598, 1521, 1468, 1347, 1319, 1278, 1126, 1104, 1059, 1012, 974, 871, 813, 787, 713, 570, 504 cm^{-1}.

HRMS (FD^+-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{15}H_{20}NO_4Cl]^{+\bullet}$: 313.1081, found: 313.1056.

m.p.: 42.5 °C.



6-Chloro-6-methylheptyl 4-acetylbenzoate (11). Compound **11** was synthesized according to **GP–1** and purified by flash column chromatography on silica gel (12% EtOAc/hexanes).

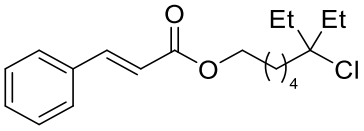
Colorless oil. Yield: 1.36 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.3 Hz, 2H), 8.00 (d, *J* = 8.1 Hz, 2H), 4.35 (t, *J* = 6.7 Hz, 2H), 2.64 (s, 3H), 1.87 – 1.72 (m, 4H), 1.61 – 1.53 (m, 2H), 1.57 (s, 6H), 1.52 – 1.41 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.6, 165.8, 140.2, 134.2, 129.8, 128.2, 71.0, 65.5, 45.9, 32.5, 28.6, 26.9, 26.2, 24.8.

FT-IR (film): 2940, 1719, 1688, 1406, 1357, 1258, 1108, 1016, 957, 859, 768, 741, 696, 611, 589, 572 cm^{-1}.

HRMS (FD^+-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{17}H_{23}O_3Cl]^{+\bullet}$: 310.1336, found: 310.1322.



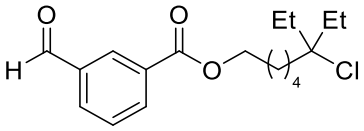
6-Chloro-6-ethyloctyl cinnamate (12). Compound **12** was synthesized according to **GP–1** and purified by flash column chromatography on silica gel (5% EtOAc in hexanes). Colorless oil. Yield: 1.90 g.

^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 16.0 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.42 – 7.36 (m, 3H), 6.45 (d, J = 16.0 Hz, 1H), 4.21 (t, J = 6.7 Hz, 2H), 1.86 – 1.69 (m, 8H), 1.52 – 1.38 (m, 4H), 0.96 (t, J = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 144.7, 134.5, 130.3, 128.9, 128.1, 118.2, 79.5, 64.6, 40.2, 33.4, 28.7, 26.3, 23.9, 8.8.

FT-IR (film): 2941, 1710, 1637, 1450, 1381, 1308, 1269, 1201, 1164, 978, 863, 835, 766, 710, 683, 610, 573, 485 cm^{-1}.

HRMS (FD^+-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{19}H_{27}O_2Cl]^{+\bullet}$: 322.1700, found: 322.1696.



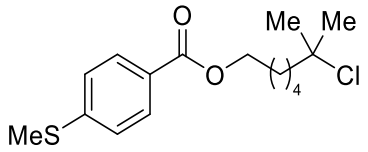
6-Chloro-6-ethyloctyl 3-formylbenzoate (13). Compound **13** was synthesized according to **GP–1** and purified by flash column chromatography on silica gel (6% EtOAc in hexanes). Colorless oil. Yield: 2.01 g.

^1H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.62 – 8.51 (m, 1H), 8.33 (dt, J = 7.7, 1.5 Hz, 1H), 8.11 (dt, J = 7.8, 1.4 Hz, 1H), 7.73 – 7.62 (m, 1H), 4.40 (t, J = 6.7 Hz, 2H), 1.91 – 1.73 (m, 8H), 1.54 – 1.46 (m, 4H), 0.98 (t, J = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.4, 165.5, 136.5, 135.2, 133.1, 131.5, 131.2, 129.3, 79.4, 65.6, 40.2, 33.3, 28.6, 26.3, 23.9, 8.8.

FT-IR (film): 2941, 1721, 1702, 1603, 1459, 1381, 1283, 1185, 1162, 1101, 1074, 964, 819, 747, 700, 677, 647, 609 cm^{-1}.

HRMS (FD^+-MS) *m/z* $[M–H]^{+\bullet}$ calcd for $[C_{18}H_{24}O_3Cl]^{+\bullet}$: 323.1414, found: 323.1417.



6-Chloro-6-methylheptyl 4-(methylthio)benzoate (14). Compound **14** was synthesized according to **GP–1** and purified by flash column chromatography on silica gel (5% → 10% EtOAc in hexanes). White solid. Yield: 1.45 g.

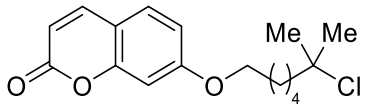
^1H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.91 (m, 2H), 7.27 – 7.23 (m, 2H), 4.31 (t, *J* = 6.6 Hz, 2H), 2.52 (s, 3H), 1.87 – 1.71 (m, 4H), 1.61 – 1.52 (m, 2H), 1.57 (s, 6H), 1.50 – 1.39 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 145.3, 129.9, 126.6, 124.9, 71.1, 64.9, 45.9, 32.4, 28.7, 26.2, 24.9, 14.9.

FT-IR (film): 2983, 2939, 1698, 1593, 1470, 1403, 1368, 1272, 1185, 1126, 1110, 1058, 1013, 953, 841, 822, 759, 688, 559, 524, 478 cm^{-1}.

HRMS (FD^+-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{16}H_{23}O_2ClS]^{+\bullet}$: 314.1107, found: 314.1098.

m.p.: 37.5 °C.



7-((6-Chloro-6-methylheptyl)oxy)-2H-chromen-2-one (15). Compound **15** was synthesized according to **GP–1** and purified by flash column chromatography on silica gel (15% EtOAc in hexanes). Yield: 1.84 g, 80%.

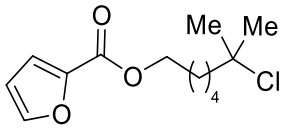
^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 9.5 Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H), 6.82 (dd, J = 8.6, 2.4 Hz, 1H), 6.78 (d, J = 2.3 Hz, 1H), 6.22 (d, J = 9.5 Hz, 1H), 4.01 (t, J = 6.4 Hz, 2H), 1.88 – 1.79 (m, 2H), 1.79 – 1.72 (m, 2H), 1.60 – 1.46 (m, 4H), 1.56 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 161.3, 155.9, 143.5, 128.8, 112.94, 112.92, 112.4, 101.4, 71.1, 68.5, 45.9, 32.5, 28.9, 26.1, 24.9.

FT-IR (film): 2951, 1713, 1606, 1505, 1472, 1395, 1373, 1349, 1281, 1234, 1199, 1158, 1123, 1044, 1004, 988, 889, 855, 826, 759, 731, 629, 617, 522, 456, 428 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $[C_{17}H_{22}O_3Cl]^+$: 309.1252, found: 309.1246.

m.p.: 65.0 °C.



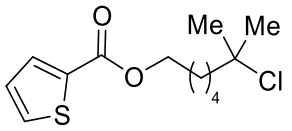
6-Chloro-6-methylheptyl furan-2-carboxylate (16). Compound **16** was synthesized according to **GP–1** and purified by flash column chromatography on silica gel (3% EtOAc in hexanes). Colorless oil. Yield: 1.75 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, J = 1.7, 0.9 Hz, 1H), 7.17 (dd, J = 3.5, 0.9 Hz, 1H), 6.50 (dd, J = 3.5, 1.7 Hz, 1H), 4.31 (t, J = 6.7 Hz, 2H), 1.83 – 1.71 (m, 4H), 1.58 – 1.51 (m, 2H), 1.56 (s, 6H), 1.49 – 1.39 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 146.2, 144.8, 117.8, 111.8, 71.0, 64.9, 45.9, 32.4, 28.6, 26.1, 24.8.

FT-IR (film): 2940, 1715, 1581, 1473, 1399, 1370, 1292, 1230, 1179, 1115, 1076, 1012, 960, 885, 761, 616, 596, 571 cm^{-1}.

HRMS (FI^+-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{13}H_{19}O_3Cl]^{+\bullet}$: 258.1023, found: 258.1031.



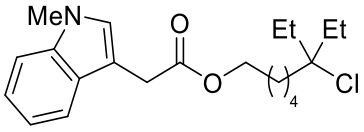
6-Chloro-6-methylheptyl thiophene-2-carboxylate (17). Compound **17** was synthesized according to **GP–1** and purified by flash column chromatography on silica gel (3% EtOAc in hexanes). Colorless oil. Yield: 1.10 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, J = 3.7, 1.3 Hz, 1H), 7.55 (dd, J = 5.0, 1.3 Hz, 1H), 7.10 (dd, J = 5.0, 3.8 Hz, 1H), 4.30 (t, J = 6.6 Hz, 2H), 1.82 – 1.72 (m, 4H), 1.60 – 1.52 (m, 2H), 1.57 (s, 6H), 1.49 – 1.33 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 134.0, 133.3, 132.2, 127.7, 71.0, 65.1, 45.9, 32.4, 28.7, 26.1, 24.8.

FT-IR (film): 2940, 1705, 1525, 1419, 1358, 1256, 1224, 1093, 1073, 1038, 860, 750, 718, 630, 571 cm^{-1}.

HRMS (FD^+-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{13}H_{19}O_2ClS]^{+\bullet}$: 274.0794, found: 274.0802.



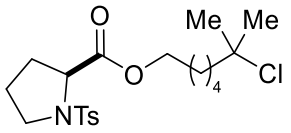
6-Chloro-6-ethyloctyl 2-(1-methyl-1H-indol-3-yl)acetate (18). Compound **18** was synthesized according to **GP–1** and purified by flash column chromatography on silica gel (5% → 8% EtOAc in hexanes). Pale yellow oil. Yield: 2.58 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.60 (m, 1H), 7.33 – 7.28 (m, 1H), 7.26 – 7.21 (m, 1H), 7.16 – 7.10 (m, 1H), 7.05 (s, 1H), 4.11 (t, J = 6.7 Hz, 2H), 3.77 (s, 5H), 1.77 (q, J = 7.4 Hz, 4H), 1.72 – 1.60 (m, 4H), 1.44 – 1.26 (m, 4H), 0.95 (d, J = 7.3 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 136.9, 127.7 (2), 121.8, 119.1, 119.0, 109.3, 106.9, 79.5, 64.8, 40.1, 33.3, 32.7, 31.3, 28.6, 26.2, 23.9, 8.8.

FT-IR (film): 2941, 1731, 1461, 1375, 1330, 1247, 1148, 1064, 1013, 834, 730, 609, 427 cm^{-1}.

HRMS (FD^+-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{21}H_{30}NO_2Cl]^{+\bullet}$: 363.1965, found: 363.1975.



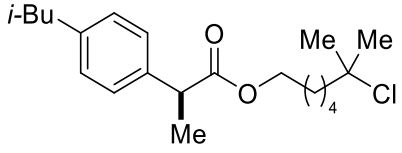
6-Chloro-6-methylheptyl tosyl-*L*-prolinate (19). Compound **19** was synthesized according to **GP–1** and purified by flash column chromatography on silica gel (10% → 20% EtOAc in hexanes). Colorless oil. Yield: 1.79 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.3 Hz, 2H), 7.31 (dd, J = 8.6, 0.8 Hz, 2H), 4.29 (dd, J = 8.1, 4.0 Hz, 1H), 4.19 – 4.05 (m, 2H), 3.53 – 3.44 (m, 1H), 3.36 – 3.26 (m, 1H), 2.42 (s, 3H), 2.08 – 1.89 (m, 3H), 1.80 – 1.71 (m, 3H), 1.70 – 1.62 (m, 2H), 1.56 (s, 6H), 1.55 – 1.46 (m, 2H), 1.43 – 1.32 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 143.5, 135.4, 129.6, 127.5, 71.1, 65.3, 60.5, 48.4, 45.9, 32.4, 31.0, 28.4, 25.9, 24.8, 24.7, 21.6.

FT-IR (film): 2981, 1747, 1598, 1452, 1347, 1282, 1156, 1093, 1012, 815, 708, 662, 591, 547 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $[C_{20}H_{30}NO_4ClS]^+$: 416.1657, found: 416.4658.



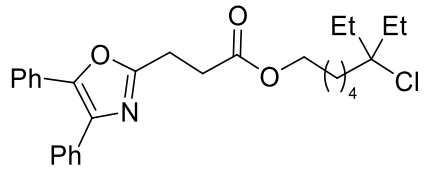
6-Chloro-6-methylheptyl *(S)*-2-(4-isobutylphenyl)propanoate (20). Compound **20** was synthesized according to **GP–1** and purified by flash column chromatography on silica gel (3% EtOAc in hexanes). Colorless oil. Yield: 2.79 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.18 (m, 2H), 7.11 – 7.07 (m, 2H), 4.07 (td, J = 6.6, 1.8 Hz, 2H), 3.68 (q, J = 7.2 Hz, 1H), 2.45 (d, J = 7.2 Hz, 2H), 1.85 (dt, J = 13.3, 6.7 Hz, 1H), 1.72 – 1.56 (m, 4H), 1.55 (s, 6H), 1.49 (d, J = 7.2 Hz, 3H), 1.47 – 1.38 (m, 2H), 1.32 – 1.21 (m, 2H), 0.90 (d, J = 6.6 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 140.5, 137.9, 129.3, 127.2, 71.0, 64.6, 45.9, 45.2, 45.0, 32.4, 30.2, 28.5, 25.9, 24.7, 22.4, 18.5.

FT-IR (film): 2951, 1732, 1512, 1464, 1369, 1331, 1200, 1162, 1070, 1022, 848, 729, 572 cm^{-1}.

HRMS (FD^+-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{21}H_{33}O_2Cl]^{+\bullet}$: 352.2169, found: 352.2157.



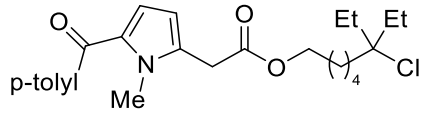
6-Chloro-6-ethyloctyl 3-(4,5-diphenyloxazol-2-yl)propanoate (21). Compound **21** was synthesized according to **GP–1** and purified by flash column chromatography on silica gel (10% EtOAc in hexanes). Viscous colorless oil. Yield: 1.92 g.

^1H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.61 (m, 2H), 7.60 – 7.55 (m, 2H), 7.39 – 7.29 (m, 6H), 4.13 (t, J = 6.7 Hz, 2H), 3.19 (dd, J = 8.2, 6.8 Hz, 2H), 2.91 (dd, J = 8.2, 6.9 Hz, 2H), 1.75 (q, J = 7.3 Hz, 4H), 1.72 – 1.61 (m, 4H), 1.47 – 1.30 (m, 4H), 0.94 (t, J = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 161.8, 145.4, 135.1, 132.5, 129.0, 128.7, 128.6, 128.5, 128.1, 127.9, 126.5, 79.5, 64.8, 40.1, 33.3, 31.2, 28.6, 26.1, 23.9, 23.6, 8.8.

FT-IR (film): 2941, 1734, 1571, 1502, 1445, 1166, 1057, 1025, 962, 834, 762, 693, 674, 607, 522 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $[C_{28}H_{35}NO_3Cl]^+$: 468.2300, found: 468.2296.



6-Chloro-6-ethyloctyl 2-(1-methyl-5-(4-methylbenzoyl)-1*H*-pyrrol-2-yl)acetate (22). Compound **22** was synthesized according to **GP–1** and purified by flash column chromatography on silica gel (10% EtOAc in hexanes). Viscous yellow oil. Yield: 1.64 g.

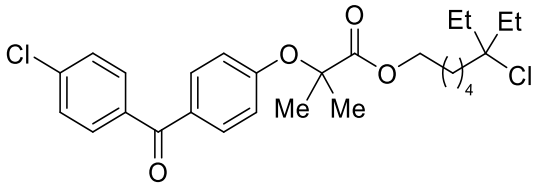
^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 7.7 Hz, 2H), 6.67 (d, J = 4.0 Hz, 1H), 6.11 (d, J = 4.1 Hz, 1H), 4.15 (t, J = 6.7 Hz, 2H), 3.95 (s, 3H), 3.71 (s,

2H), 2.42 (s, 3H), (q, J = 7.4 Hz, 4H), 1.73 – 1.64 (m, 4H), 1.47 – 1.29 (m, 4H), 0.94 (t, J = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 185.9, 169.5, 141.9, 137.3, 134.6, 131.4, 129.5, 128.7, 122.3, 109.4, 79.4, 65.4, 40.1, 33.3, 33.2, 33.0, 28.5, 26.1, 23.8, 21.6, 8.8.

FT-IR (film): 2941, 1736, 1624, 1480, 1455, 1373, 1262, 1172, 1067, 1041, 976, 882, 833, 790, 748, 704, 619, 480 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $[C_{25}H_{35}NO_3Cl]^+$: 432.2300, found: 432.2297.



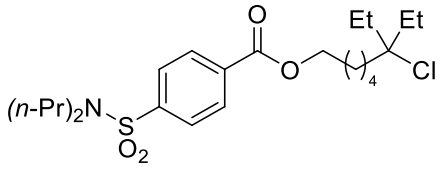
6-Chloro-6-ethyloctyl 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoate (23). Compound **23** was synthesized according to **GP–1** and purified by flash column chromatography on silica gel (10% EtOAc in hexanes). Viscous colorless oil. Yield: 3.01 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.69 (m, 4H), 7.50 – 7.44 (m, 2H), 6.92 – 6.85 (m, 2H), 4.19 (t, J = 6.6 Hz, 2H), 1.76 (q, J = 7.4 Hz, 4H), 1.70 (s, 6H), 1.68 – 1.62 (m, 4H), 1.44 – 1.32 (m, 2H), 1.31 – 1.20 (m, 2H), 0.94 (t, J = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2, 173.8, 159.7, 138.4, 136.4, 132.0, 131.2, 130.3, 128.6, 117.2, 79.4, 79.3, 65.7, 40.1, 33.3, 28.3, 26.0, 25.5, 23.8, 8.8.

FT-IR (film): 2941, 1733, 1654, 1597, 1505, 1461, 1383, 1283, 1248, 1171, 1136, 1089, 1014, 952, 926, 852, 836, 761, 739, 679, 653, 575, 521, 478 cm^{-1}.

HRMS (FD^+-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{27}H_{34}O_4Cl]^{+\bullet}$: 492.1834, found: 492.1818.



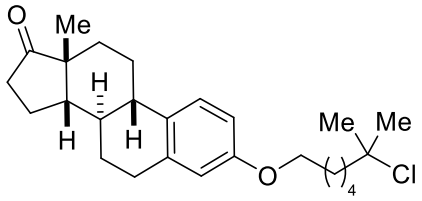
6-Chloro-6-ethyloctyl 4-(*N*,*N*-dipropylsulfamoyl)benzoate (24). Compound **24** was synthesized according to **GP–1** and purified by flash column chromatography on silica gel (7% EtOAc in hexanes). Viscous colorless oil. Yield: 3.09 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.6 Hz, 2H), 7.87 (d, J = 8.5 Hz, 2H), 4.36 (t, J = 6.6 Hz, 2H), 3.13 – 3.08 (m, 4H), 1.88 – 1.71 (m, 8H), 1.63 – 1.43 (m, 8H), 0.95 (t, J = 7.4 Hz, 6H), 0.87 (t, J = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3, 144.2, 133.7, 130.2, 127.0, 79.4, 65.7, 49.9, 40.2, 33.3, 28.6, 26.3, 23.9, 22.0, 11.2, 8.8.

FT-IR (film): 2968, 1721, 1460, 1343, 1270, 1158, 1106, 1087, 991, 862, 765, 740, 694, 601, 561, 448 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $[C_{23}H_{38}NO_4ClS]^+$: 460.2283, found: 460.2276.



(8*R*,9*S*,13*S*,14*S*)-3-((6-Chloro-6-methylheptyl)oxy)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one (25). Compound **25** was synthesized according to **GP–1** and purified by flash column chromatography on silica gel (10% EtOAc in hexanes). White solid. Yield: 1.67 g.

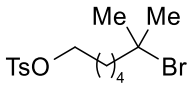
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (dd, J = 8.7, 1.0 Hz, 1H), 6.71 (dd, J = 8.6, 2.8 Hz, 1H), 6.65 (d, J = 2.7 Hz, 1H), 3.94 (t, J = 6.4 Hz, 2H), 2.96 – 2.83 (m, 2H), 2.50 (dd, J = 18.8, 8.6 Hz, 1H), 2.45 – 2.34 (m, 1H), 2.31 – 2.20 (m, 1H), 2.20 – 2.09 (m, 1H), 2.09 – 1.92 (m, 3H), 1.86 – 1.73 (m, 4H), 1.70 – 1.37 (m, 10H), 1.58 (s, 6H), 0.91 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 221.0, 157.1, 137.7, 131.9, 126.3, 114.5, 112.1, 71.2, 67.7, 50.4, 48.0, 46.0, 44.0, 38.4, 35.9, 32.5, 31.6, 29.7, 29.3, 26.6, 26.2, 25.9, 24.9, 21.6, 13.9.

FT-IR (film): 2934, 2862, 1737, 1608, 1499, 1453, 1370, 1281, 1234, 1161, 1055, 1006, 819, 749, 697, 615, 570 cm^{-1}.

HRMS (FD^+-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{26}H_{37}O_2Cl]^{+\bullet}$: 416.2482, found: 416.2470.

m.p.: 115.5 °C.



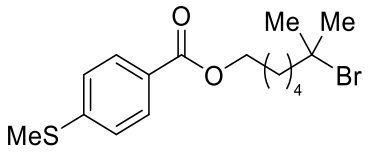
6-Hydroxy-6-methylheptyl 4-methylbenzenesulfonate (26). Compound **26** was synthesized according to **GP–1** and purified by flash column chromatography (10% EtOAc in hexanes). Colorless oil. Yield: 1.80 g, 62%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 4.04 (t, J = 6.4 Hz, 2H), 2.45 (s, 3H), 1.80 – 1.60 (m, 4H), 1.72 (s, 6H) 1.52 – 1.41 (m, 2H), 1.40 – 1.29 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7, 133.2, 129.9, 127.9, 70.4, 68.1, 47.2, 34.2, 28.7, 25.6, 25.3, 21.7.

FT-IR (film): 2939, 2864, 1598, 1452, 1359, 1177, 1120, 1098, 905, 825, 760, 728, 665 cm^{-1}.

HRMS (FD^+-MS) *m/z* $[M–HBr]^{+\bullet}$ calcd for $[C_{15}H_{23}O_3S]^{+\bullet}$: 283.1368, found: 283.1365.



6-Bromo-6-methylheptyl 4-(methylthio)benzoate (27). Compound **27** was synthesized according to **GP–1** and purified by flash column chromatography on silica gel (5% → 10% EtOAc in hexanes). Pale yellow liquid. Yield: 1.08 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.7 Hz, 2H), 7.25 (d, J = 8.7 Hz, 2H), 4.31 (t, J = 6.6 Hz, 2H), 2.52 (s, 3H), 1.85 – 1.77 (m, 4H), 1.76 (s, 6H), 1.65 – 1.55 (m, 2H), 1.53 – 1.43 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 145.3, 129.9, 126.6, 124.9, 68.3, 64.9, 47.4, 34.3, 28.7, 26.1, 26.1, 14.9.

FT-IR (film): 2919, 2860, 1712, 1594, 1443, 1384, 1264, 1180, 1106, 1015, 960, 842, 759, 688 cm^{-1}.

HRMS (FD^+-MS) *m/z* $[M–H]^{+\bullet}$ calcd for $[C_{16}H_{22}O_2BrS]^{+\bullet}$: 358.0602, found: 358.0598.

B. Fluorination of Unactivated Tertiary Alkyl Halides

General Procedure 2 (GP–2). Fluorination.

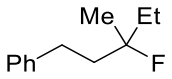
An oven-dried 40-mL vial equipped with a cross-shaped PTFE stir bar (19 mm diameter; 9.5 mm height) and a PTFE-lined cap was evacuated and backfilled with nitrogen once.

If the starting material is a non-viscous liquid: PPh_3 (31 mg, 0.12 mmol) and AgF (152 mg, 1.2 mmol) were added to the vial. The vial was sealed with a PTFE-lined cap, and then evacuated and backfilled with nitrogen (three cycles) to establish an inert atmosphere. Anhydrous CH_2Cl_2 (8 mL) was then added, and the mixture was stirred for 10 min. The alkyl chloride (0.80 mmol) was then introduced into the vial using a microsyringe.

If the starting material is a viscous liquid or a solid: PPh_3 (31.4 mg, 0.12 mmol), AgF (152 mg, 1.2 mmol), and the alkyl chloride (0.80 mmol) were added to the vial. The vial was evacuated and backfilled with nitrogen (three cycles), and then anhydrous CH_2Cl_2 (8 mL) was added to the vial via syringe.

In both cases, the nitrogen line attached to the 40-mL vial was then disconnected, and the puncture site was sealed using vacuum grease. The interface between the cap and the vial was wrapped with electrical tape. The reaction mixture was then stirred vigorously (~1500 rpm) for 24 h, maintained at 25 °C using an oil bath. Next, the reaction mixture was filtered

through a pad of silica gel. The vial, cap, and pad of silica gel were rinsed with Et_2O, and the combined organic washings were transferred to a round-bottom flask. The solution was then concentrated, and the crude product was purified using flash column chromatography on silica gel.



(3-Fluoro-3-methylpentyl)benzene ($\mathbf{1^F}$). The title compound was synthesized from (3-chloro-3-methylpentyl)benzene $\mathbf{1^{Cl}}$ according to **GP–2**. The compound was purified by flash column chromatography on silica gel (2% Et_2O in hexanes). Colorless oil.

Run 1: 110 mg, 76% yield. Run 2: 112 mg, 78% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.25 (m, 2H), 7.24 – 7.16 (m, 3H), 2.71 (dd, J = 9.5, 7.9 Hz, 2H), 2.01 – 1.81 (m, 2H), 1.79 – 1.60 (m, 2H), 1.37 (d, J = 21.8 Hz, 3H), 0.97 (t, J = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.2, 128.5, 128.3, 125.9, 97.4 (d, J = 167.7 Hz), 41.1 (d, J = 23.0 Hz), 32.3 (d, J = 23.7 Hz), 30.0 (d, J = 5.5 Hz), 23.7 (d, J = 25.0 Hz), 8.1 (d, J = 7.0 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –146.6 (s).

FT-IR (film): 2975, 1496, 1455, 1379, 1191, 1031, 930, 876, 757, 727, 697, 514 cm^{-1}.

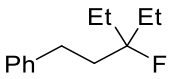
HRMS (FI^+-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{12}H_{17}F]^{+\bullet}$: 180.1314, found: 180.1309.

Gram-scale synthesis: A flame-dried 250-mL round-bottom flask equipped with a PTFE stir bar and a rubber septum was evacuated and backfilled with nitrogen once. PPh_3 (315 mg, 1.2 mmol) and AgF (1.27 g, 10.0 mmol) were added to the flask, and then the flask was evacuated and backfilled with nitrogen (three cycles). CH_2Cl_2 (80 mL) was added via a syringe, a nitrogen balloon was attached, and 3-chloro-3-methylpentyl)benzene ($\mathbf{1^{Cl}}$; 1.57 g, 8.0 mmol) was added via a syringe. The mixture was allowed to stir vigorously (>1200 rpm) at r.t. for 24 h. Next, the reaction mixture was filtered through a pad of silica gel. The flask, septum, and pad of silica gel were rinsed with Et_2O, and the combined organic washings

were concentrated. The crude product was purified using flash column chromatography on silica gel, employing 2% Et_2O in hexanes as the eluent.

Run 1: 1.05 g, 73% yield. Run 2: 1.05 g, 73% yield.

The reaction was carried out according to **GP–2** with $\mathbf{1^{Br}}$. Run 1: 102 mg, 71% yield. Run 2: 100 mg, 69% yield.



(3-Ethyl-3-fluoropentyl)benzene ($\mathbf{2^F}$). The title compound was synthesized from (3-ethyl-3-chloropentyl)benzene **2** according to **GP–2**. The compound was purified by flash column chromatography on silica gel (2% Et2O in hexanes). Colorless oil.

Run 1: 126 mg, 81% yield. Run 2: 121 mg, 78% yield.

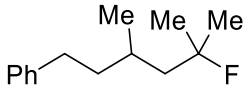
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H), 7.24 – 7.17 (m, 3H), 2.73 – 2.62 (m, 2H), 1.99 – 1.83 (m, 2H), 1.80 – 1.62 (m, 4H), 0.94 (t, J = 7.5 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.3, 128.5, 128.3, 125.9, 99.3 (d, J = 169.9 Hz), 38.3 (d, J = 23.1 Hz), 29.7 (d, J = 5.8 Hz), 29.0 (d, J = 23.8 Hz), 7.8 (d, J = 7.3 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –154.6 (s).

FT-IR (film): 2971, 1496, 1455, 1365, 1031, 971, 907, 752, 716, 696, 512 cm^{-1}.

HRMS (FI^+-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{13}H_{19}F]^{+\bullet}$: 194.1471, found: 194.1465.



(5-Fluoro-3,5-dimethylhexyl)benzene ($\mathbf{3^F}$). The title compound was synthesized from (5-chloro-3,5-dimethylhexyl)benzene **3** according to **GP–2**. The compound was purified by flash column chromatography on silica gel (2% Et_2O in hexanes). Colorless oil.

Run 1: 114 mg, 69% yield. Run 2: 114 mg, 69% yield.

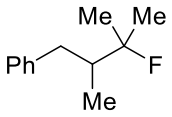
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H), 7.22 – 7.15 (m, 3H), 2.62 (dddd, J = 29.8, 13.5, 10.2, 5.6 Hz, 2H), 1.83 – 1.60 (m, 3H), 1.58 – 1.44 (m, 2H), 1.35 (d, J = 21.3 Hz, 6H), 1.03 (d, J = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.8, 128.4, 128.3, 125.6, 96.1 (d, J = 165.3 Hz), 47.9 (d, J = 21.5 Hz), 40.1 (d, J = 1.3 Hz), 33.3, 28.9 (d, J = 1.9 Hz), 27.6 (d, J = 24.9 Hz), 27.0 (d, J = 25.0 Hz), 21.2 (d, J = 2.2 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –135.8 (s).

FT-IR (film): 2927, 1496, 1454, 1372, 1171, 1031, 863, 745, 697, 512, 476 cm^{-1}.

HRMS (FI^+-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{14}H_{21}F]^{+\bullet}$: 208.1627, found: 208.1622.



(3-Fluoro-2,3-dimethylbutyl)benzene (4^F). The title compound was synthesized from (4-chloro-3,4-dimethylpentyl)benzene **4** (1.2-mmol scale) according to **GP–2**. The compound was purified by flash column chromatography on silica gel (2% Et_2O in hexanes). Colorless oil. The desired product contained ~4% (according to ^{1}H and ^{19}F NMR spectroscopy) of an isomer, which originated in alkyl chloride **4** (see Section A).

Run 1: 127 mg, 59%. Run 2: 130 mg, 60%.

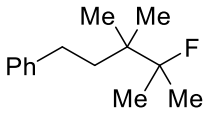
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.23 – 7.15 (m, 3H), 3.06 (dd, J = 13.0, 2.9 Hz, 1H), 2.16 (dd, J = 13.0, 11.3 Hz, 1H), 1.97 (ddtd, J = 18.1, 11.2, 6.9, 3.0 Hz, 1H), 1.38 (dd, J = 22.0, 2.9 Hz, 6H), 0.81 (d, J = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.3, 129.2, 128.3, 125.9, 98.1 (d, J = 167.1 Hz), 45.1 (d, J = 21.6 Hz), 37.7 (d, J = 5.8 Hz), 25.2 (d, J = 25.0 Hz), 23.3 (d, J = 25.0 Hz), 14.1 (d, J = 7.0 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –137.8 (s). (^{19}F{^{1}H} NMR for the isomer: –148.5 (s).)

FT-IR (film): 2979, 1494, 1454, 1388, 1373, 1256, 1152, 1083, 940, 903, 875, 845, 756, 725, 698, 579, 502, 457 cm^{-1}.

HRMS (FI^+-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{12}H_{17}F]^{+\bullet}$: 180.1314, found: 180.1310.



(4-Fluoro-3,3,4-trimethylpentyl)benzene (5^F). The title compound was synthesized from (4-fluoro-3,3,4-trimethylpentyl)benzene **5** (1.2-mmol scale) according to **GP–2**. The compound was purified by flash column chromatography on silica gel (2% Et_2O in hexanes). Colorless oil.

The desired product contained ~11% (according to ^1H and ^{19}F NMR spectroscopy) of an isomer, which originated in alkyl chloride **5** (see Section A).

Run 1: 121 mg, 58%. Run 2: 124 mg, 59%.

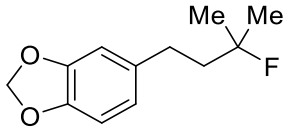
^1H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.22 – 7.16 (m, 3H), 2.67 – 2.58 (m, 2H), 1.69 – 1.59 (m, 2H), 1.34 (d, J = 22.2 Hz, 6H), 1.04 (d, J = 0.9 Hz, 6H).

^{13}C NMR (101 MHz, CDCl3) δ 143.4, 128.39, 128.38, 125.7, 100.3 (d, J = 171.3 Hz), 40.11 (d, J = 3.3 Hz), 40.07 (d, J = 20.3 Hz), 31.2 (d, J = 2.3 Hz), 23.1 (d, J = 25.4 Hz), 21.9 (d, J = 5.3 Hz).

$^{19}F\{^1H\}$ NMR (376 MHz, CDCl3) δ –145.8 (s). ($^{19}F\{^1H\}$ NMR for the isomer: –160.2 (s).)

FT-IR (film): 2972, 1604, 1495, 1455, 1377, 1241, 1158, 1069, 1030, 935, 862, 803, 747, 698, 588, 516, 487 cm^{-1}.

HRMS (FI^+-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{14}H_{21}F]^{+\bullet}$: 208.1627, found: 208.1621.



5-(3-Fluoro-3-methylbutyl)benzo[*d*][1,3]dioxole (6^F). The title compound was synthesized from 5-(3-chloro-3-methylbutyl)benzo[*d*][1,3]dioxole **6** according to **GP–2**. The compound was purified by flash column chromatography on silica gel (2% Et_2O in hexanes). Colorless oil.

The title compound coeluted with olefin side products (no other impurities) that were not separable via chromatography. The yield was therefore determined via ^1H NMR

spectroscopy: the ratio between the multiplet at δ 1.83 – 1.92 (2H, alkyl fluoride) versus at δ 5.91 – 5.92 (2H, alkyl fluoride plus olefins) allowed the determination of the ratio of alkyl fluoride : olefins and the yield.

Run 1: 171 mg, with 1.00 : 0.27 ratio of **6^{F}**: olefins (molar ratio). 82% yield.

Run 2: 168 mg, with 1.00 : 0.23 ratio of **6^{F}**: olefins (molar ratio). 82% yield. Run 3: 170 mg, with 1.00 : 0.25 ratio of **6^{F}**: olefins (molar ratio). 82% yield.

Run 4: 169 mg, with 1.00 : 0.27 ratio of **6^{F}**: olefins (molar ratio). 81% yield. The eluent for this run was 1% Et_2O in pentane.

The spectral data were collected for pure compound obtained by preparative TLC.

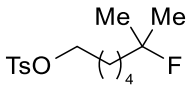
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (dd, J = 7.9, 0.9 Hz, 1H), 6.69 (d, J = 1.7 Hz, 1H), 6.64 (ddt, J = 7.8, 1.6, 0.7 Hz, 1H), 5.92 (s, 2H), 2.69 – 2.61 (m, 2H), 1.97 – 1.80 (m, 2H), 1.40 (d, J = 21.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.6, 145.6, 135.9, 120.9, 108.8, 108.2, 100.8, 95.3 (d, J = 165.7 Hz), 43.6 (d, J = 22.8 Hz), 30.0 (d, J = 5.4 Hz), 26.7 (d, J = 24.7 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –138.9 (s).

FT-IR (film): 2980, 1503, 1489, 1441, 1372, 1241, 1187, 1096, 1038, 927, 885, 810, 782, 753, 632, 606, 474, 426 cm^{-1}.

HRMS (FI^{+}-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{12}H_{15}O_2F]^{+\bullet}$: 210.1056, found: 210.1049.



6-Fluoro-6-methylheptyl 4-methylbenzenesulfonate (7^{F}). The title compound was synthesized from 6-chloro-6-methylheptyl 4-methylbenzenesulfonate **7** according to **GP–2**. The compound was purified by flash column chromatography on silica gel (9% → 12% Et_2O in pentane). Colorless oil.

Run 1: 189 mg, 78% yield. Run 2: 183 mg, 76% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 7.8 Hz, 2H), 4.02 (t, J = 6.4 Hz, 2H), 2.44 (s, 3H), 1.70 – 1.58 (m, 2H), 1.59 – 1.46 (m, 2H), 1.33 – 1.29 (m, 4H), 1.29 (d, J = 21.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7, 133.2, 129.8, 127.9, 95.5 (d, J = 164.7 Hz), 70.5, 41.1 (d, J = 22.8 Hz), 28.7, 26.6 (d, J = 24.7 Hz), 25.7, 23.3 (d, J = 5.2 Hz), 21.6.

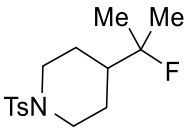
^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –137.9 (s).

FT-IR (film): 2941, 1598, 1465, 1356, 1114, 1097, 953, 813, 757, 662, 575, 553 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $[C_{15}H_{23}O_3FSNa]^+$: 325.1245, found: 325.1234.

The reaction was carried out according to **GP–2** with **26**.

Run 1: 157 mg, 65% yield. Run 2: 154 mg, 64% yield.



4-(2-Fluoropropan-2-yl)-1-tosylpiperidine (8^F). The title compound was synthesized from 4-(2-chloropropan-2-yl)-1-tosylpiperidine **8** according to **GP–2**. The compound was purified by flash column chromatography on silica gel (8% → 15% EtOAc in hexanes). White solid.

Run 1: 142 mg, 59% yield. Run 2: 137 mg, 57% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 3.91 – 3.82 (m, 2H), 2.43 (s, 3H), 2.25 – 2.16 (m, 2H), 1.81 – 1.71 (m, 2H), 1.50 – 1.38 (m, 3H), 1.26 (d, J = 22.0 Hz, 6H).

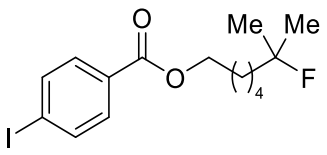
^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5, 133.0, 129.6, 127.7, 96.6 (d, J = 167.0 Hz), 46.5, 45.2 (d, J = 22.8 Hz), 26.1 (d, J = 6.2 Hz), 24.2 (d, J = 25.0 Hz), 21.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ –140.2 – –140.8 (m).

FT-IR (film): 2959, 1598, 1469, 1381, 1335, 1308, 1254, 1094, 1058, 1040, 926, 886, 833, 813, 772, 730, 650, 595, 547, 504, 482, 461, 427 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $[C_{15}H_{23}NO_2FS]^+$: 300.1429, found: 300.1424.

m.p.: 113.5 °C.



6-Fluoro-6-methylheptyl 4-iodobenzoate (9^F). The title compound was synthesized from 6-chloro-6-methylheptyl 4-iodobenzoate **9** according to **GP–2**. The compound was purified by flash column chromatography on silica gel (2% → 5% Et2O in pentane). Colorless oil.

Run 1: 249 mg, 82% yield. Run 2: 246 mg, 81% yield.

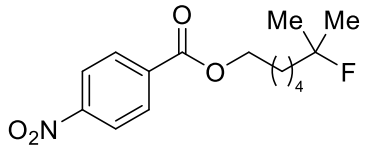
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.78 (m, 2H), 7.76 – 7.71 (m, 2H), 4.31 (t, J = 6.6 Hz, 2H), (pent, J = 7.0 Hz, 2H), 1.69 – 1.56 (m, 2H), 1.48 – 1.42 (m, 4H), 1.34 (d, J = 21.5 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 137.7, 131.0, 129.9, 100.6, 95.6 (d, J = 164.6 Hz), 65.2, 41.3 (d, J = 22.8 Hz), 28.6, 26.7 (d, J = 24.8 Hz), 26.4, 23.6 (d, J = 5.1 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –137.7 (s).

FT-IR (film): 2939, 1717, 1586, 1466, 1392, 1372, 1265, 1176, 1108, 1007, 845, 752, 682, 462 cm^{-1}.

HRMS (FI^+-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{15}H_{20}O_2FI]^{+\bullet}$: 378.0492, found: 378.0488.



6-Fluoro-6-methylheptyl 4-nitrobenzoate (10^F). The title compound was synthesized from 6-chloro-6-methylheptyl 4-nitrobenzoate **10** according to **GP–2**. The compound was purified by flash column chromatography on silica gel (4% → 8% Et_2O in pentane). Colorless oil.

Run 1: 186 mg, 78% yield. Run 2: 186 mg, 78% yield.

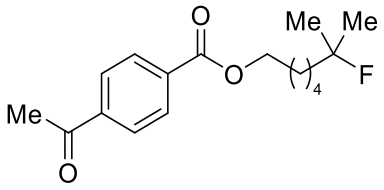
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 – 8.26 (m, 2H), 8.23 – 8.17 (m, 2H), 4.38 (t, J = 6.7 Hz, 2H), 1.87 – 1.75 (m, 2H), 1.69 – 1.57 (m, 2H), 1.51 – 1.44 (m, 4H), 1.34 (d, J = 21.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 150.5, 135.8, 130.7, 123.5, 95.6 (d, J = 164.7 Hz), 66.0, 41.2 (d, J = 22.8 Hz), 28.6, 26.7 (d, J = 24.9 Hz), 26.3, 23.6 (d, J = 5.0 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –138.0 (s).

FT-IR (film): 2941, 1722, 1608, 1527, 1467, 1348, 1269, 1102, 958, 873, 785, 758, 716, 502 cm^{-1}.

HRMS (FD^+-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{15}H_{20}NO_4F]^{+\bullet}$: 297.1376, found: 297.1371.



6-Fluoro-6-methylheptyl 4-acetylbenzoate (11^F). The title compound was synthesized from 6-chloro-6-methylheptyl 4-acetylbenzoate **11** according to **GP–2**. The compound was purified by flash column chromatography on silica gel (5% → 10% EtOAc in pentane). Colorless oil.

Run 1: 187 mg, 80% yield. Run 2: 195 mg, 83% yield.

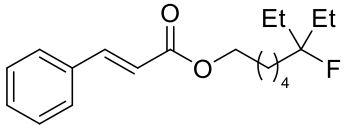
^1H NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.10 (m, 2H), 8.03 – 7.99 (m, 2H), 4.35 (t, J = 6.6 Hz, 2H), 2.64 (s, 3H), 1.84 – 1.77 (m, 2H), 1.71 – 1.57 (m, 2H), 1.49 – 1.45 (m, 4H), 1.34 (d, J = 21.5 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.6, 165.8, 140.2, 134.2, 129.8, 128.2, 95.6 (d, J = 164.6 Hz), 65.5, 41.3 (d, J = 22.8 Hz), 28.6, 26.8, 26.7 (d, J = 24.8 Hz), 26.4, 23.6 (d, J = 5.0 Hz).

$^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –137.8 (s).

FT-IR (film): 2940, 1719, 1688, 1407, 1373, 1259, 1178, 1108, 1016, 958, 860, 768, 696, 611, 589, 499 cm^{-1}.

HRMS (FD^+-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{17}H_{23}O_3F]^{+\bullet}$: 294.1631, found: 294.1629.



6-Ethyl-6-fluorooctyl cinnamate (12^F). The title compound was synthesized from 6-ethyl-6-chlorooctyl cinnamate **12** according to **GP–2**. The compound was purified by flash column chromatography on silica gel (3% → 5% Et_2O in pentane). Pale yellow oil.

Run 1: 190 mg, 78% yield. Run 2: 192 mg, 78% yield.

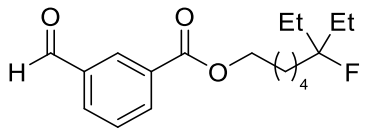
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 16.0 Hz, 1H), 7.54 – 7.52 (m, 2H), 7.41 – 7.37 (m, 3H), 6.45 (d, J = 16.0 Hz, 1H), 4.21 (t, J = 6.7 Hz, 2H), 1.73 (m, 2H), 1.68 – 1.54 (m, 6H), 1.50 – 1.33 (m, 4H), 0.89 (t, J = 7.5 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 144.7, 134.5, 130.3, 128.9, 128.1, 118.2, 99.5 (d, J = 169.1 Hz), 64.6, 36.0 (d, J = 23.0 Hz), 29.1, 28.8 (d, J = 16.0 Hz), 26.5, 23.0 (d, J = 5.6 Hz), 7.7 (d, J = 7.0 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –154.1 (s).

FT-IR (film): 2942, 1711, 1637, 1450, 1309, 1269, 1201, 1165, 979, 911, 864, 766, 710, 684, 574, 484 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $[C_{19}H_{27}O_2FNa]^+$: 306.1995, found: 306.1992.



6-Ethyl-6-fluorooctyl 3-formylbenzoate (13^{F}). The title compound was synthesized from 6-ethyl-6-chlorooctyl 3-formylbenzoate **13** according to **GP–2**. The compound was purified by flash column chromatography on silica gel (7% → 12% Et_2O in pentane). Colorless oil.

Run 1: 188 mg, 76% yield. Run 2: 191 mg, 77% yield.

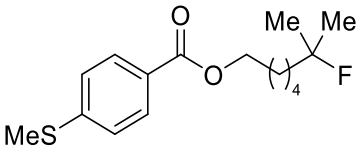
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.08 (s, 1H), 8.52 (td, J = 1.7, 0.6 Hz, 1H), 8.30 (dt, J = 7.7, 1.5 Hz, 1H), 8.08 (dt, J = 7.7, 1.5 Hz, 1H), 7.62 (t, J = 7.7 Hz, 1H), 4.37 (t, J = 6.6 Hz, 2H), 1.85 – 1.78 (m, 2H), 1.69 – 1.53 (m, 6H), 1.52 – 1.34 (m, 4H), 0.88 (t, J = 7.5 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.5, 165.5, 136.6, 135.2, 133.0, 131.6, 131.2, 129.3, 99.5 (d, J = 169.3 Hz), 65.6, 36.0 (d, J = 23.1 Hz), 29.1, 28.8 (d, J = 17.7 Hz), 26.5, 23.0 (d, J = 5.5 Hz), 7.7 (d, J = 7.0 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –154.2 (s).

FT-IR (film): 2943, 1720, 1702, 1603, 1461, 1382, 1283, 1185, 1163, 1103, 1075, 961, 911, 818, 748, 701, 678, 647, 475 cm^{-1}.

HRMS (FD^{+}-MS) *m/z* $[M–H]^{+\bullet}$ calcd for $[C_{18}H_{25}O_3F]^{+\bullet}$: 307.1710, found: 307.1712.



6-Fluoro-6-methylheptyl 4-(methylthio)benzoate (14^{F}). The title compound was synthesized from 6-chloro-6-methylheptyl 4-(methylthio)benzoate **14** according to **GP–2**. The compound was purified by flash column chromatography on silica gel (4% → 8% Et2O in pentane). Colorless oil.

Run 1: 186 mg, 78% yield. Run 2: 182 mg, 76% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.91 (m, 2H), 7.28 – 7.25 (m, 2H), 4.33 (t, J = 6.6 Hz, 2H), 2.54 (s, 3H), 1.84 – 1.76 (m, 2H), 1.72 – 1.58 (m, 2H), 1.52 – 1.45 (m, 4H), 1.36 (d, J = 21.5 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 145.3, 129.9, 126.6, 124.9, 95.6 (d, J = 164.6 Hz), 64.9, 41.3 (d, J = 22.9 Hz), 28.7, 26.8 (d, J = 25.0 Hz), 26.4, 23.7 (d, J = 5.2 Hz), 14.9.

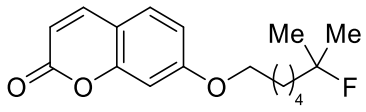
^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –137.6 (s).

FT-IR (film): 2939, 1711, 1593, 1437, 1372, 1266, 1180, 1107, 1014, 966, 842, 757, 690, 480 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $[C_{16}H_{23}O_2FSNa]^+$: 321.1295, found: 321.1299.

The reaction was carried out according to **GP–2** with **27**.

Run 1: 139 mg, 58% yield. Run 2: 149 mg, 62% yield.



7-((6-Fluoro-6-methylheptyl)oxy)-2H-chromen-2-one (15^{F}). The title compound was synthesized from 7-((6-chloro-6-methylheptyl)oxy)-2H-chromen-2-one **15** according to **GP–2**. The compound was purified by flash column chromatography on silica gel (10% → 20% EtOAc in pentane). White solid.

Run 1: 186 mg, 80% yield. Run 2: 183 mg, 78% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 9.4 Hz, 1H), 7.36 (d, J = 8.5 Hz, 1H), 6.83 (dd, J = 8.6, 2.5 Hz, 1H), 6.80 (d, J = 2.4 Hz, 1H), 6.24 (d, J = 9.5 Hz, 1H), 4.02 (t, J = 6.4 Hz, 2H), 1.88 – 1.81 (m, 2H), 1.71 – 1.57 (m, 2H), 1.54 – 1.43 (m, 4H), 1.35 (d, J = 21.4 Hz, 6H).

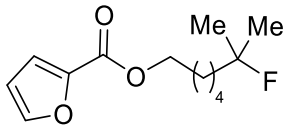
^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 161.3, 155.9, 143.5, 128.7, 112.98, 112.95, 112.4, 101.3, 95.6 (d, J = 164.6 Hz), 68.5, 41.3 (d, J = 22.9 Hz), 28.9, 26.7 (d, J = 24.7 Hz), 26.3, 23.7 (d, J = 5.1 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –137.8 (s).

FT-IR (film): 2939, 2864, 1710, 1606, 1558, 1506, 1473, 1408, 1395, 1372, 1348, 1278, 1231, 1201, 1158, 1119, 1089, 1042, 1007, 988, 892, 865, 846, 831, 760, 735, 711, 632, 616, 551, 486, 458, 417 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $[C_{17}H_{21}O_3FNa]^+$: 315.1267, found: 315.1263.

m.p.: 58.0 °C.



6-Fluoro-6-methylheptyl furan-2-carboxylate (16^{F}). The title compound was synthesized from 6-chloro-6-methylheptyl furan-2-carboxylate **16** according to **GP–2**. The compound was purified by flash column chromatography on silica gel (3% → 4% EtOAc in hexanes). Colorless oil.

Run 1: 158 mg, 82% yield. Run 2: 159 mg, 82% yield.

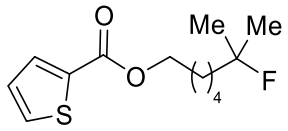
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dt, J = 1.5, 0.6 Hz, 1H), 7.17 (dt, J = 3.5, 0.6 Hz, 1H), 6.50 (dd, J = 3.5, 1.7 Hz, 1H), 4.30 (t, J = 6.7 Hz, 2H), 1.82 – 1.70 (m, 2H), 1.67 – 1.54 (m, 2H), 1.44 (dq, J = 7.5, 3.8 Hz, 4H), 1.33 (d, J = 21.5 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 146.2, 144.9, 117.8, 111.8, 95.6 (d, J = 164.6 Hz), 64.9, 41.3 (d, J = 22.8 Hz), 28.7, 26.6 (d, J = 24.8 Hz), 26.3, 23.6 (d, J = 5.2 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –137.6 (s).

FT-IR (film): 2941, 1716, 1581, 1474, 1373, 1293, 1230, 1178, 1116, 1076, 1012, 961, 884, 760, 616, 597 cm^{-1}.

HRMS (FI^+-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{13}H_{19}O_3F]^{+\bullet}$: 242.1318, found: 242.1313.



6-Fluoro-6-methylheptyl thiophene-2-carboxylate (17^F). The title compound was synthesized from 6-chloro-6-methylheptyl thiophene-2-carboxylate **17** according to **GP–2**. The compound was purified by flash column chromatography on silica gel (4% → 6% Et_2O in pentane). Colorless oil.

Run 1: 173 mg, 84% yield. Run 2: 173 mg, 84% yield.

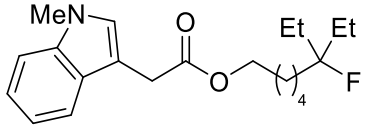
^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, J = 3.8, 1.3 Hz, 1H), 7.55 (dd, J = 5.0, 1.3 Hz, 1H), 7.10 (dd, J = 5.0, 3.7 Hz, 1H), 4.30 (t, J = 6.6 Hz, 2H), 1.80 – 1.73 (m, 2H), 1.67 – 1.58 (m, 2H), 1.47 – 1.40 (m, 4H), 1.34 (d, J = 21.5 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 134.0, 133.3, 132.2, 127.7, 95.7 (d, J = 164.6 Hz), 65.1, 41.3 (d, J = 22.8 Hz), 28.7, 26.7 (d, J = 24.9 Hz), 26.4, 23.7 (d, J = 5.2 Hz).

$^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –137.6.

FT-IR (film): 2940, 1706, 1526, 1419, 1373, 1358, 1257, 1224, 1093, 1074, 860, 750, 718 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $[C_{13}H_{19}O_2FSNa]^+$: 281.0982, found: 281.0987.



6-Ethyl-6-fluorooctyl 2-(1-methyl-1H-indol-3-yl)acetate (18^F). The title compound was synthesized from 6-ethyl-6-chlorooctyl 2-(1-methyl-1H-indol-3-yl)acetate **18** according to **GP–2**. The compound was purified by flash column chromatography on silica gel (5% → 12% EtOAc in pentane). Yellow oil.

Run 1: 199 mg, 72% yield. Run 2: 198 mg, 71% yield.

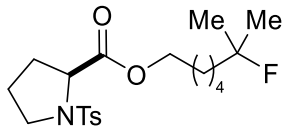
^{1}H NMR (400 MHz, CDCl3) δ 7.62 (d, J = 7.9 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.16 – 7.11 (m, 1H), 7.05 (s, 1H), 4.11 (t, J = 6.7 Hz, 2H), 3.77 (s, 5H), 1.72 – 1.48 (m, 8H), 1.33 (pent, J = 3.6 Hz, 4H), 0.89 (t, J = 7.5 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 136.9, 127.7 (2), 121.7, 119.1, 119.0, 109.3, 107.0, 99.5 (d, J = 169.1 Hz), 64.8, 35.9 (d, J = 23.1 Hz), 32.7, 31.3, 29.0 (d, J = 23.8 Hz), 28.6, 26.4, 22.9 (d, J = 5.6 Hz), 7.7 (d, J = 7.0 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –154.1 (s).

FT-IR (film): 2941, 1731, 1462, 1375, 1330, 1246, 1139, 1013, 970, 911, 737, 427 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $[C_{21}H_{30}NO_2F]^+$: 348.2334, found: 348.2332.



6-Fluoro-6-methylheptyl tosyl-*L*-prolinate (19^{F}). The title compound was synthesized from 6-chloro-6-methylheptyl tosyl-*L*-prolinate **19** (0.60-mmol scale) according to **GP–2**. The compound was purified by flash column chromatography on silica gel (15% → 25% EtOAc in pentane). Colorless oil.

Run 1: 180 mg, 75% yield. Run 2: 178 mg, 74% yield.

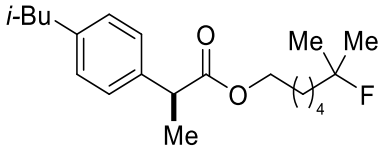
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 4.35 – 4.28 (m, 1H), 4.20 – 4.06 (m, 2H), 3.58 – 3.44 (m, 1H), 3.40 – 3.28 (m, 1H), 2.45 (s, 3H), 2.17 – 1.91 (m, 3H), 1.83 – 1.73 (m, 1H), 1.72 – 1.57 (m, 4H), 1.54 – 1.30 (m, 4H), 1.35 (d, J = 21.5 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 143.5, 135.4, 129.6, 127.5, 95.7 (d, J = 164.4 Hz), 65.3, 60.5, 48.4, 41.3 (d, J = 22.9 Hz), 31.0, 28.5, 26.7 (d, J = 24.9 Hz), 26.1, 24.7, 23.6 (d, J = 5.1 Hz), 21.6.

^{19}F NMR (376 MHz, $CDCl_3$): –137.4 – –137.9 (m).

FT-IR (film): 2977, 2863, 1750, 1460, 1352, 1159, 1066, 907, 816, 709, 633, 592, 548 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $[C_{20}H_{30}NO_4FS]^+$: 400.1953, found: 400.1953.



6-Fluoro-6-methylheptyl *(S)*-2-(4-isobutylphenyl)propanoate (20^F). The title compound was synthesized from 6-chloro-6-methylheptyl *(S)*-2-(4-isobutylphenyl)propanoate **20** according to **GP–2**. The compound was purified by flash column chromatography on silica gel (3% → 6% Et_2O in pentane). Colorless oil.

Run 1: 212 mg, 79% yield. Run 2: 210 mg, 78%.

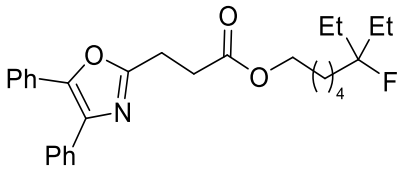
^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 8.1 Hz, 2H), 4.06 (td, J = 6.6, 1.1 Hz, 2H), 3.68 (q, J = 7.2 Hz, 1H), 2.44 (d, J = 7.2 Hz, 2H), 1.84 (dp, J = 13.5, 6.7 Hz, 1H), 1.65 – 1.50 (m, 4H), 1.48 (d, J = 7.1 Hz, 3H), 1.41 – 1.20 (m, 4H), 1.32 (d, J = 21.4 Hz, 6H), 0.90 (d, J = 6.6 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 140.5, 137.9, 129.3, 127.2, 95.6 (d, J = 164.6 Hz), 64.6, 45.2, 45.0, 41.3 (d, J = 22.9 Hz), 30.2, 28.5, 26.6 (d, J = 24.7 Hz), 26.1, 23.5 (d, J = 5.3 Hz), 22.4, 18.5.

$^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –137.5 (s).

FT-IR (film): 2950, 1732, 1512, 1464, 1373, 1319, 1201, 1163, 1070, 1022, 848, 759, 550 cm^{-1}.

HRMS (FD^+-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{21}H_{33}O_2F]^{+\bullet}$: 336.2465, found: 336.2465.



6-Ethyl-6-fluorooctyl 3-(4,5-diphenyloxazol-2-yl)propanoate (21^F). The title compound was synthesized from 6-ethyl-6-chlorooctyl 3-(4,5-diphenyloxazol-2-yl)propanoate **21** (0.60-mmol scale) according to **GP–2**. The compound was purified by flash column chromatography on silica gel (9% → 15% EtOAc in pentane). Colorless oil.

Run 1: 172 mg, 63% yield. Run 2: 171 mg, 63% yield.

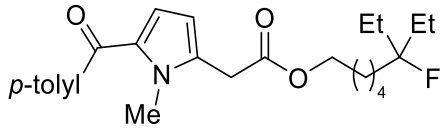
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.61 (m, 2H), 7.60 – 7.55 (m, 2H), 7.40 – 7.28 (m, 6H), 4.13 (t, J = 6.7 Hz, 2H), 3.19 (dd, J = 8.2, 6.8 Hz, 2H), 2.91 (dd, J = 8.2, 6.8 Hz, 2H), 1.70 – 1.48 (m, 8H), 1.41 – 1.29 (m, 4H), 0.87 (t, J = 7.5 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 161.8, 145.4, 135.1, 132.5, 129.0, 128.7, 128.6, 128.5, 128.1, 127.9, 126.5, 99.5 (d, J = 169.1 Hz), 64.8, 35.9 (d, J = 23.1 Hz), 31.2, 29.0 (d, J = 23.8 Hz), 28.6, 26.4, 23.6, 22.9 (d, J = 5.6 Hz), 7.7 (d, J = 7.0 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): –152.5 – –155.8 (m).

FT-IR (film): 2942, 1734, 1571, 1444, 1167, 1058, 1026, 962, 913, 763, 693, 674, 584, 523 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $[C_{28}H_{34}NO_3F]^+$: 432.2596, found: 432.2592.



6-Ethyl-6-fluorooctyl 2-(1-methyl-5-(4-methylbenzoyl)-1H-pyrrol-2-yl)acetate (22^{F}). The title compound was synthesized from 6-ethyl-6-chlorooctyl 2-(1-methyl-5-(4-methylbenzoyl)-1H-pyrrol-2-yl)acetate **22** (0.60-mmol scale) according to **GP–2**. The compound was purified by flash column chromatography on silica gel (9% → 15% EtOAc in pentane). Colorless oil.

Run 1: 173 mg, 69% yield. Run 2: 172 mg, 69% yield.

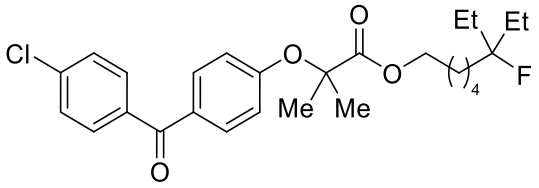
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.68 (m, 2H), 7.25 – 7.22 (m, 2H), 6.67 (d, J = 4.0 Hz, 1H), 6.11 (d, J = 4.0 Hz, 1H), 4.14 (t, J = 6.7 Hz, 2H), 3.95 (s, 3H), 3.71 (s, 2H), 2.42 (s, 3H), 1.71 – 1.49 (m, 8H), 1.38 – 1.30 (m, 4H), 0.88 (t, J = 7.5 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 185.9, 169.5, 141.9, 137.3, 134.6, 131.4, 129.5, 128.7, 122.3, 109.4, 99.5 (d, J = 169.1 Hz), 65.4, 35.9 (d, J = 23.1 Hz), 33.2, 33.0, 29.0 (d, J = 23.8 Hz), 28.5, 26.3, 22.9 (d, J = 5.5 Hz), 21.6, 7.7 (d, J = 7.0 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): –154.0 – –154.4 (m).

FT-IR (film): 2942, 1735, 1624, 1480, 1455, 1373, 1261, 1172, 1041, 975, 912, 882, 833, 790, 747, 705, 620, 480 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $[C_{25}H_{34}NO_3F]^+$: 416.2596, found: 416.2595.



6-Ethyl-6-fluorooctyl 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoate (23^F). The title compound was synthesized from 6-ethyl-6-chlorooctyl 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoate **23** (0.60-mmol scale) according to **GP–2**. The compound was purified by flash column chromatography on silica gel (8% → 12% Et_2O in pentane). Colorless oil.

Run 1: 203 mg, 71% yield. Run 2: 206 mg, 72% yield.

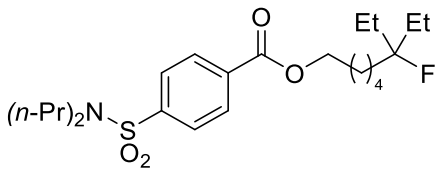
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, J = 13.8, 8.5 Hz, 4H), 7.44 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 4.16 (t, J = 6.6 Hz, 2H), 1.67 (s, 6H), 1.64 – 1.42 (m, 8H), 1.33 – 1.18 (m, 4H), 0.85 (t, J = 7.5 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2, 173.8, 159.7, 138.4, 136.4, 132.0, 131.2, 130.3, 128.6, 117.2, 99.4 (d, J = 169.3 Hz), 79.4, 65.7, 35.9 (d, J = 23.1 Hz), 28.9 (d, J = 23.8 Hz), 28.4, 26.2, 25.5, 22.8 (d, J = 5.5 Hz), 7.7 (d, J = 7.0 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): –153.6 – –154.9 (m).

FT-IR (film): 2942, 1732, 1654, 1597, 1505, 1462, 1385, 1284, 1249, 1171, 1137, 1089, 1014, 955, 926, 852, 762, 740, 680, 659, 577, 521, 479 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $[C_{27}H_{34}O_4ClFNa]^+$: 499.2021, found: 499.2022.



6-Ethyl-6-fluorooctyl 4-(*N,N*-dipropylsulfamoyl)benzoate (24^F). The title compound was synthesized from 6-ethyl-6-chlorooctyl 4-(*N,N*-dipropylsulfamoyl)benzoate

24 (0.60-mmol scale) according to **GP–2**. The compound was purified by flash column chromatography on silica gel (8% → 12% Et_2O in pentane). Viscous colorless oil.

Run 1: 195 mg, 73% yield. Run 2: 193 mg, 72% yield.

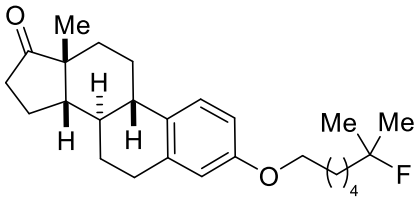
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H), 4.35 (t, J = 6.6 Hz, 2H), 3.11 – 3.06 (m, 4H), 1.83 – 1.76 (m, 2H), 1.69 – 1.50 (m, 10H), 1.48 – 1.38 (m, 4H), 0.90 – 0.84 (m, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3, 144.2, 133.7, 130.2, 127.0, 99.5 (d, J = 169.1 Hz), 65.7, 49.9, 36.0 (d, J = 23.1 Hz), 29.0 (d, J = 23.8 Hz), 28.6, 26.5, 22.9 (d, J = 5.5 Hz), 21.9, 11.2, 7.7 (d, J = 7.0 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): –154.0 – –154.4 (m).

FT-IR (film): 2968, 1722, 1461, 1344, 1271, 1107, 1087, 991, 912, 862, 797, 765, 740, 694, 602, 561, 456 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $[C_{23}H_{38}NO_4FS]^+$: 444.2579, found: 444.2569.



(8*R*,9*S*,13*S*,14*S*)-3-((6-Fluoro-6-methylheptyl)oxy)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[*a*]phenanthren-17-one (25^F). The title compound was synthesized from 8*R*,9*S*,13*S*,14*S*)-3-((6-chloro-6-methylheptyl)oxy)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[*a*]phenanthren-17-one **25** (0.60-mmol scale) according to **GP–2**. The compound was purified by flash column chromatography on silica gel (6% → 15% EtOAc in pentane). White solid.

Run 1: 193 mg, 80% yield. Run 2: 196 mg, 82% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (dd, J = 8.7, 1.1 Hz, 1H), 6.71 (dd, J = 8.6, 2.8 Hz, 1H), 6.64 (d, J = 2.7 Hz, 1H), 3.94 (t, J = 6.5 Hz, 2H), 2.98 – 2.83 (m, 2H), 2.50 (dd, J = 8.6 Hz, 1H), 2.42 – 2.35 (m, 1H), 2.30 – 2.21 (m, 1H), 2.20 – 2.11 (m, 1H), 2.10 – 1.92 (m, 3H),

1.84 – 1.74 (m, 2H), 1.70 – 1.56 (m, 4H), 1.56 – 1.40 (m, 8H), 1.34 (d, J = 21.5 Hz, 6H), 0.91 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 221.0, 157.1, 137.7, 131.9, 126.3, 114.5, 112.1, 95.7 (d, J = 164.3 Hz), 67.7, 50.4, 48.0, 44.0, 41.4 (d, J = 22.9 Hz), 38.4, 35.9, 31.6, 29.7, 29.3, 26.8, 26.6 (d, J = 4.1 Hz), 26.4, 25.9, 23.7 (d, J = 5.2 Hz), 21.6, 13.9.

^{19}F NMR (376 MHz, CDCl3): –135.7 – –139.5 (m).

FT-IR (film): 2935, 1733, 1607, 1498, 1471, 1373, 1310, 1281, 1233, 1161, 1053, 1027, 1005, 864, 846, 822, 787, 761, 647, 579, 461 cm^{-1}.

HRMS (FD^+-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{26}H_{37}O_2F]^{+\bullet}$: 400.2778, found: 400.2771.

m.p.: 95.0 °C.

The data are consistent with those reported in the literature.[20]

C. Effect of Reaction Parameters

General Procedure 3 (GP–3): In a nitrogen-filled glovebox, an oven-dried 4-mL vial that contained a PTFE stir bar was charged with PPh_3 (3.9 mg, 0.015 mmol) and AgF (19.0 mg, 0.15 mmol). Next, CH_2Cl_2 (0.7 mL) was added, and the vial was capped with a PTFE-septum cap. The mixture was stirred at r.t. for 10 min, and then a solution of 3-chloro-3-methylpentyl)benzene (**1^{Cl}**; 19.7 mg, 0.10 mmol), in CH_2Cl_2 (0.3 mL) was added. The vial was removed from the glovebox, the joint was wrapped with electrical tape, and the reaction mixture was allowed to stir at r.t. for 24 h, after which it was a dark gray slurry, which typically indicates the completion of the reaction. A solution of 4-fluorobiphenyl (17.2 mg, 0.10 mmol), an internal standard, in acetone (0.2 mL) was added. The mixture was then filtered through a plug of silica gel. The reaction flask and the plug of silica gel were washed with Et_2O, the combined organic solution was concentrated, and the yield was determined by single-pulse ^{19}F NMR spectroscopy.

The effects of reactions parameters were determined according to **GP–3** and reported in **Table 1** and **Table 2**.

D. Studies of Functional-Group Compatibility

GP–3 was followed, using electrophile $\mathbf{1^{Cl}}$ and the additives (0.10 mmol, 1.0 equiv) shown in **Figure 3**. The additive was added immediately before the solution of the electrophile was added; with polar additives, the reaction mixture was passed through a syringe filter rather than a plug of silica gel.

The yield of the fluorination product was determined through analysis via ^{19}F NMR spectroscopy, and the recovery of the additive was determined through analysis via GCMS, both using 4-fluorobiphenyl as the internal standard. Each entry represents an average of two experiments.

E. Mechanistic Studies

i. ^{31}P NMR Spectroscopy

In a nitrogen-filled glovebox, an oven-dried 4-mL vial that contained a PTFE stir bar was charged in turn with PPh_3 (3.9 mg, 0.015 mmol), AgF (19.0 mg, 0.15 mmol), dry CH_2Cl_2 (1.0 mL), and electrophile $\mathbf{1^{Cl}}$ (19.0 μL, 19.7 mg, 0.10 mmol). At specified time points, the reaction mixture was filtered by passage through a syringe filter in the glovebox, and the aliquots were analyzed via ^{31}P NMR spectroscopy.

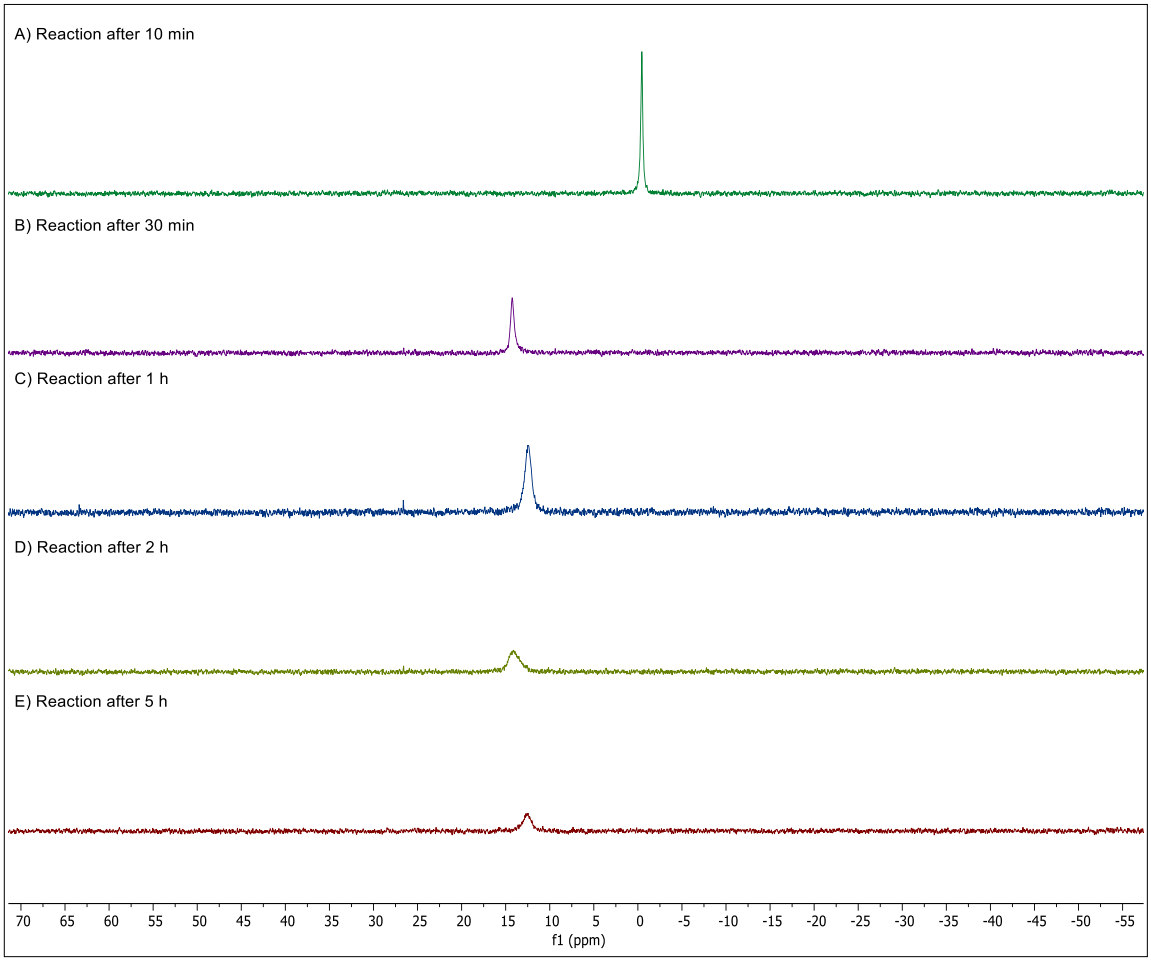


Figure 6. Study via ^{31}P NMR spectroscopy (162 MHz, CH_2Cl_2) of the time course of a fluorination at r.t. ^{31}P chemical shift of free PPh_3: δ –7.9.

A) δ –0.4 (s).

B) δ 14.3 (s, br).

C) δ 12.4 (s, br).

D) δ 14.1 (s, br).

E) δ 12.5 (s, br).

In order to examine whether the broad resonances are due to exchange processes, NMR spectra were obtained at –80 °C.

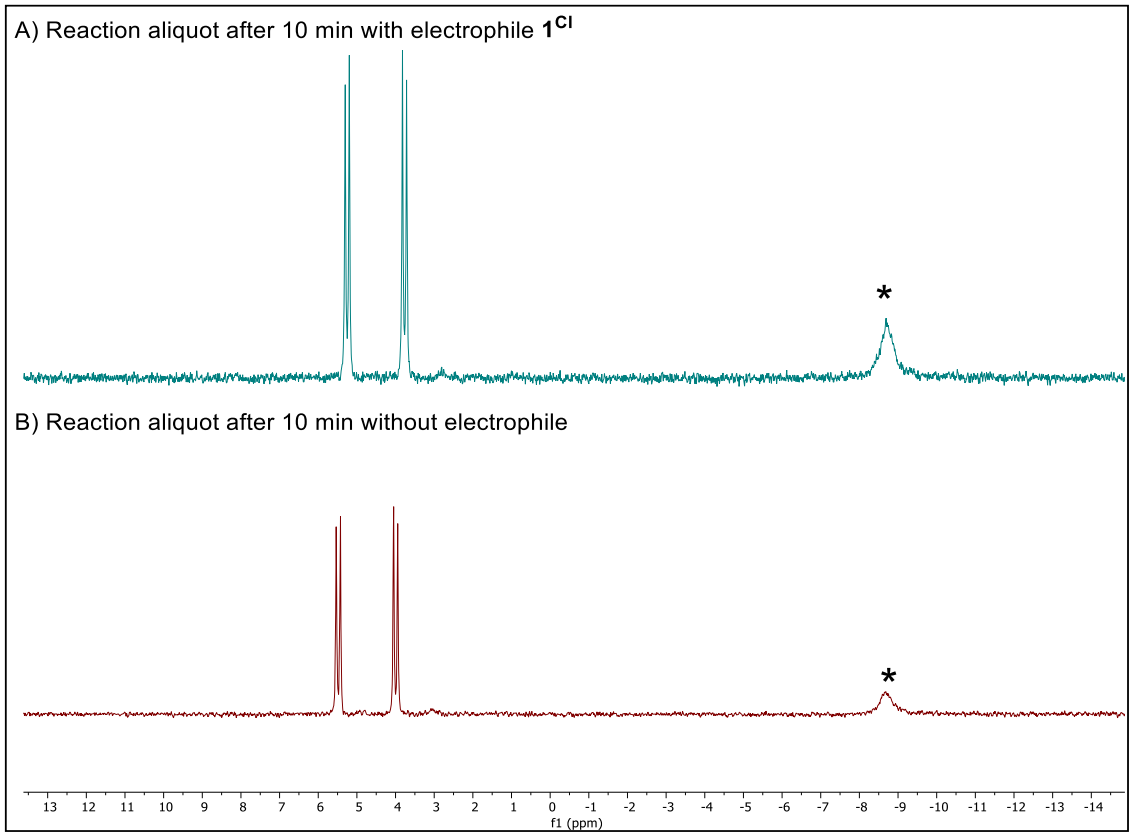


Figure 7. Low-temperature (–80 °C) ^{31}P NMR study of reaction aliquots after 10 min in CH_2Cl_2. A) Reaction aliquot without the tertiary alkyl chloride **1Cl**. B) Reaction aliquot with the tertiary alkyl chloride **1Cl**. * indicates unreacted free PPh_3, δ = –8.69 ppm.

A) ^{31}P NMR (162 MHz, CH_2Cl_2) δ 4.5 (dd, $^1J(^{107}Ag–^{31}P)$ = 223 Hz, $^1J(^{109}Ag–^{31}P)$ = 258 Hz).

B) ^{31}P NMR (162 MHz, CH_2Cl_2) δ 4.7 (dd, $^1J(^{107}Ag–^{31}P)$ = 223 Hz, $^1J(^{109}Ag–^{31}P)$ = 258 Hz).

The two species detected in A) and B) are most likely identical.

To determine the possible structure of the species detected in **Figure 7**, additional ^{31}P NMR experiments of the reaction aliquot with P(*p*-tolyl)$_3$ were performed.

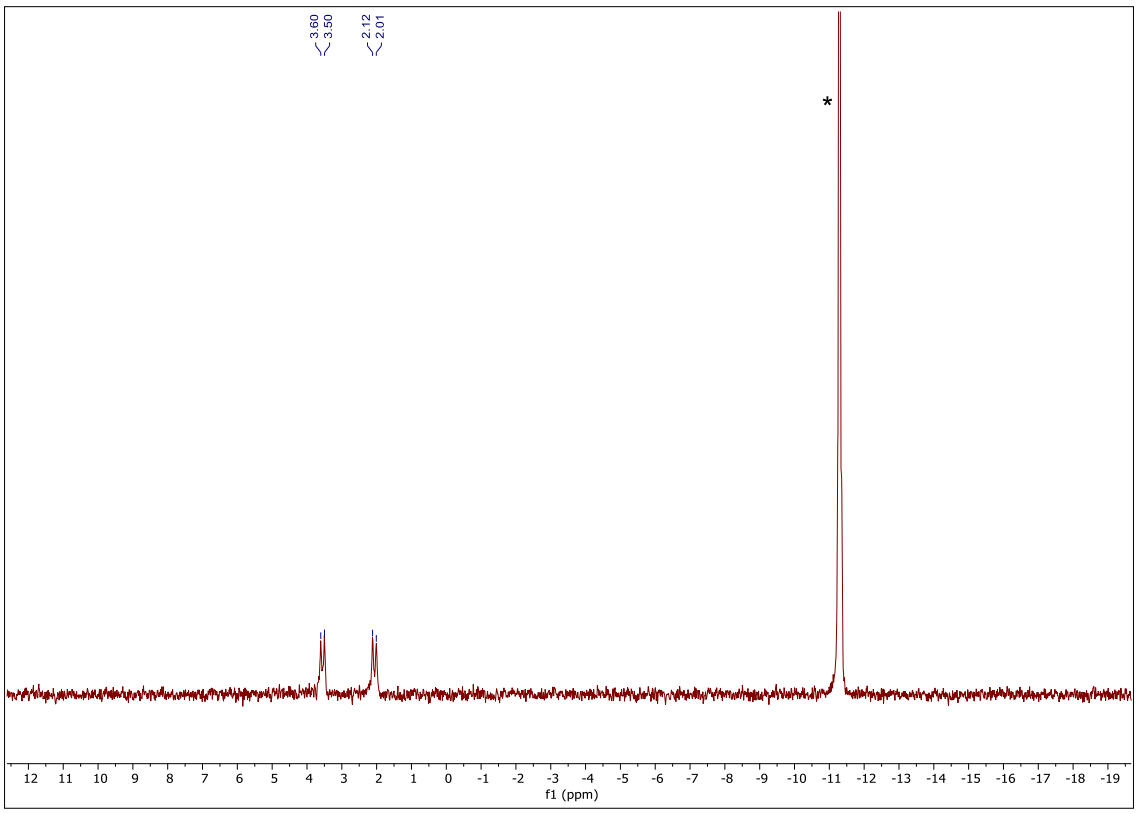
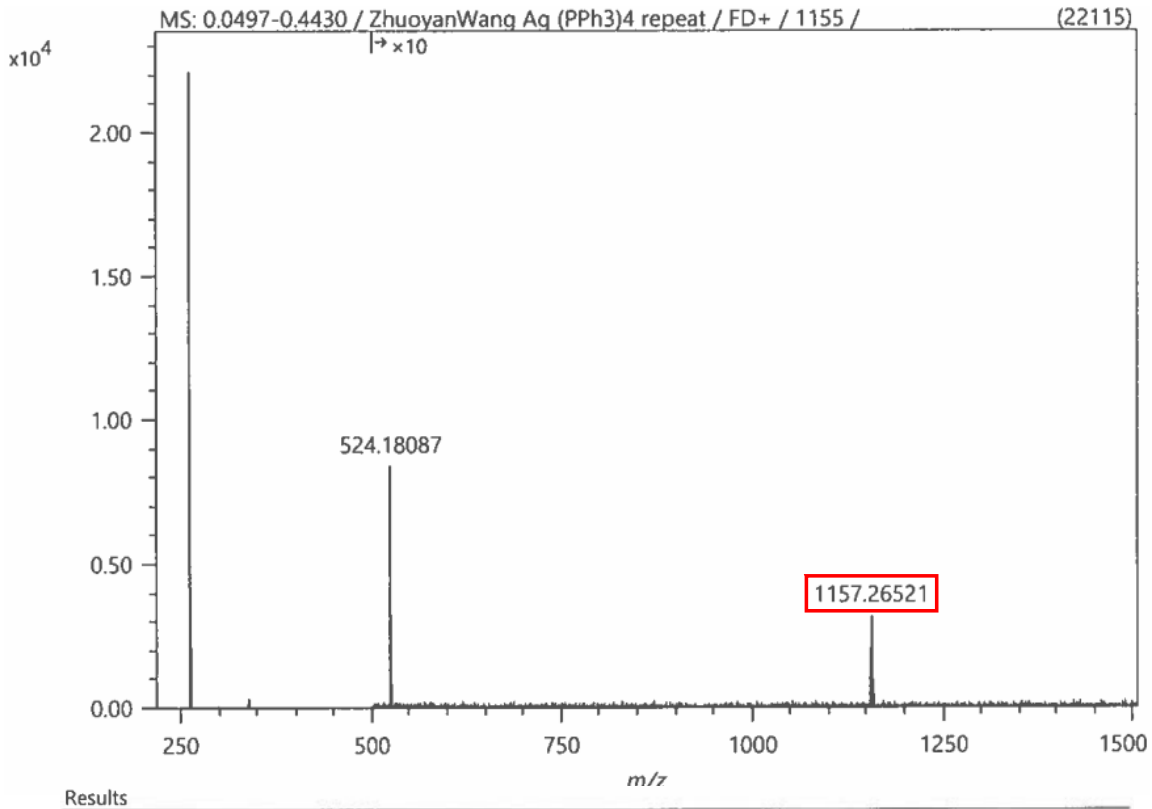


Figure 8. Low-temperature (–80 °C) ^{31}P NMR study of reaction aliquots after 5 min in CH_2Cl_2 with P(*p*-tolyl)$_3$ as the ligand. A) Reaction aliquot without the tertiary alkyl chloride **1^{Cl}**. B) Reaction aliquot with the tertiary alkyl chloride **1^{Cl}**. * indicates unreacted free P(p-tolyl)$_3$, δ = –11.3 ppm.

^{31}P NMR (162 MHz, CH_2Cl_2) δ 3.1 (dd, $^1J(^{107}Ag–^{31}P)$ = 224 Hz, $^1J(^{109}Ag–^{31}P)$ = 260 Hz). Both the chemical shift and the J-coupling matched with the report from literature[17]. Hence, this species can be assigned as $[Ag(P(p\text{-tolyl})_3)_4]^+$. Due to the approximate chemical shift and J-coupling value, the species in **Figure 7** (and in **Figure 5B**) can be assigned as $[Ag(PPh_3)_4]^+$.

The ^{31}P NMR experiments above are consistent with the formation of $[Ag(PPh_3)_4]^+$ at the initial stage (e.g., 10 min) of the fluorination reaction.

ii. Study of Ag–Phosphine Species via Mass Spectroscopy

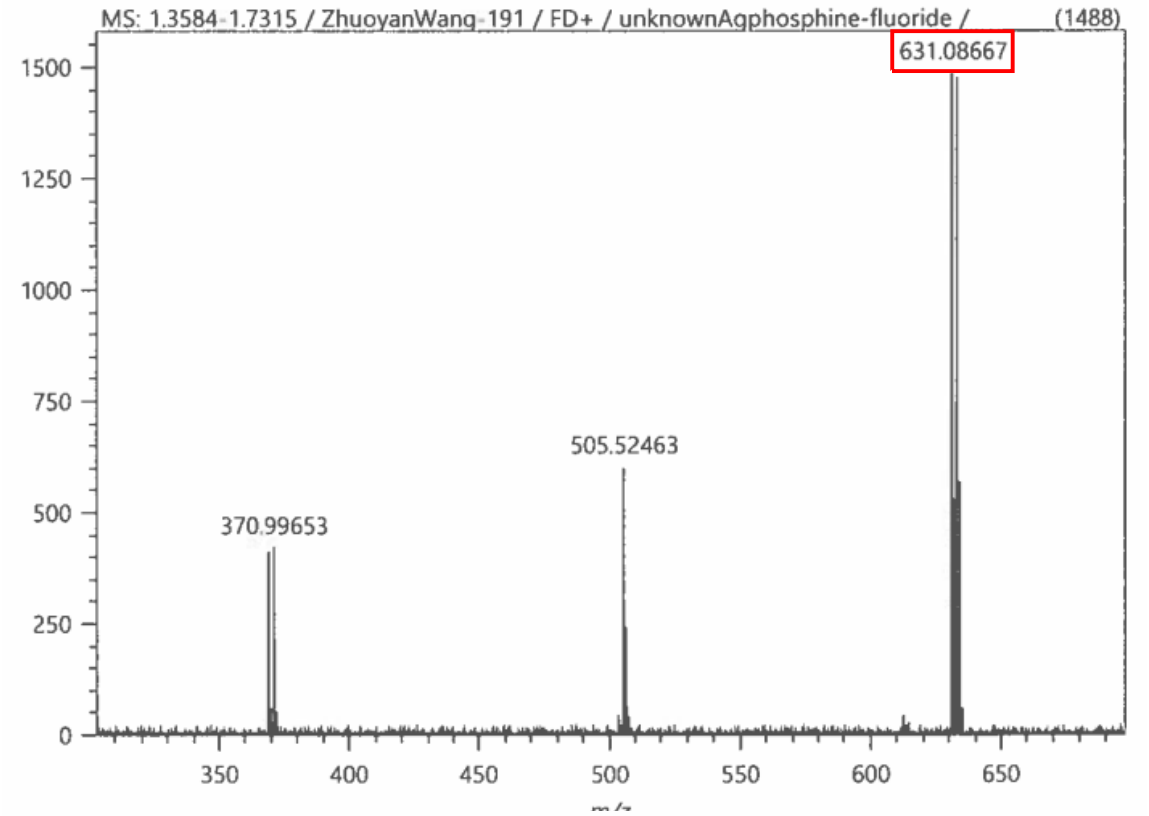


Results

Mass	Intensity	Formula	Calculated Mass	Mass Difference [mDa]	Mass Difference [ppm]	DBE
262.09085	22115.26	C18 H15 P	262.09114	-0.29	-1.11	12.0
524.18087	842.36	C36 H30 P2	524.18227	-1.41	-2.69	23.0
1155.26744	206.76	C72 H60 P4 Ag	1155.26964	-2.20	-1.91	44.5

Figure 9. Mass spectroscopic study of reaction aliquots after *10 min* in CH_2Cl_2 with PPh_3 as the ligand. The ^{31}P NMR data was collected simultaneously and reported in **Figure 7**.

HRMS (FD^+-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{72}H_{60}P_4Ag]^{+\bullet}$: 1155.2696, found: 1155.2674. The molecular mass is consistent with that of $[Ag(PPh_3)_4]^+$.



Results

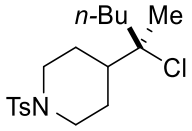
Mass	Intensity	Formula	Calculated Mass	Mass Difference [mDa]	Mass Difference [ppm]	DBE
368.99721	413.36	C18 H15 P Ag	368.99623	0.98	2.66	11.5
631.08667	1487.69	C36 H30 P2 Ag	631.08737	-0.70	-1.10	22.5

Figure 10. Mass spectroscopic study of reaction aliquots after *2 h* in CH_2Cl_2 with PPh_3 as the ligand. The ^{31}P NMR data was not available.

HRMS (FD^+-MS) *m/z* $[M]^{+\bullet}$ calcd for $[C_{36}H_{30}P_2Ag]^{+\bullet}$: 631.0874, found: 631.0867. The splitting pattern, i.e., approximate intensities for *m/z*($[M]^{+\bullet}$) and *m/z*($[M]^{+\bullet}$)+2, is consistent with a Ag–phosphine complex, because Ag has two isotopes (^{107}Ag and ^{109}Ag) with equal abundance. Hence, this species is most likely $[Ag(PPh_3)_2]^+$.

The HRMS data after *2 h* of reaction provide evidence consistent with the conversion from $[Ag(PPh_3)_4]^+$ to $[Ag(PPh_3)_2]^+$ over the course of the reaction. $[Ag(PPh_3)_2]^+$ is probably more relevant to the fluorination, as $[Ag(PPh_3)_4]^+$ is saturated in coordination.

iii. Stereochemical Studies



4-(2-Chlorohexan-2-yl)-1-tosylpiperidine (31^{Cl}). The title compound was synthesized according to **GP–1** and purified by flash column chromatography on silica gel using 10% EtOAc in hexanes. White solid. Yield: 1.72 g, 83%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H), 3.93 – 3.83 (m, 2H), 2.43 (s, 3H), 2.23 – 2.11 (m, 2H), 1.95 (dt, J = 12.7, 2.6 Hz, 1H), 1.79 (dt, J = 12.1, 2.6 Hz, 1H), 1.74 – 1.65 (m, 2H), 1.64 – 1.46 (m, 3H), 1.43 (s, 3H), 1.40 – 1.21 (m, 4H), 0.89 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5, 133.0, 129.6, 127.8, 76.9, 46.6 (d, J = 10.7 Hz), 46.2, 41.6, 26.9, 26.6 (d, J = 4.4 Hz), 26.4, 22.9, 21.5, 14.0.

FT-IR (film): 2956, 1598, 1467, 1448, 1338, 1253, 1164, 1094, 933, 816, 728, 652 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $[C_{18}H_{29}NO_2ClS]^+$: 358.1602, found: 358.1611.

m.p.: 93.5 °C.

Enantioenriched **31^{Cl}** was obtained using preparative SFC on a CHIRALPAK AD-H column with 12% EtOH in CO_2 as the eluent.

Fraction 1 (*R*)-**31^{Cl}**: retention time: 7.01 min; >99% ee. $[\alpha]^{24}_D$ = +1.5 (c 1.0, CHCl3).

Fraction 2 (*S*)-**31^{Cl}**: retention time: 7.84 min; –90% ee.

Determination of absolute configuration:

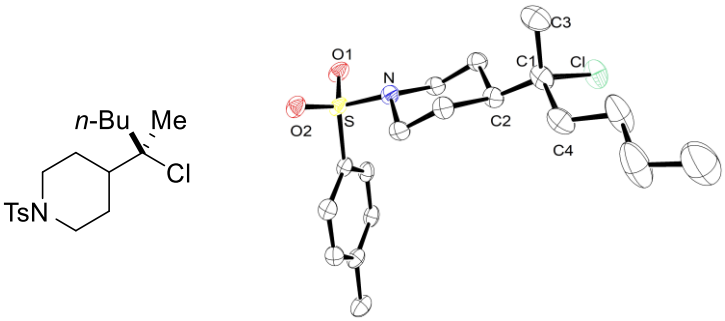


Figure 11. ORTEP drawing of (*R*)-**31**^{Cl} (CCDC 2294879). Thermal ellipsoid plot at 50% probability level. For clarity, the hydrogen atoms are not shown. A second molecule in the asymmetric unit has been omitted for clarity.

Crystal Structure Report for (*R*)-31^{Cl}

A colorless needle-like specimen of $C_{18}H_{28}ClNO_2S$, approximate dimensions 0.100 mm × 0.300 mm × 0.500 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured (λ = 1.54178 Å).

The total exposure time was 8.46 h. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 55642 reflections to a maximum θ angle of 70.08° (0.82 Å resolution), of which 7073 were independent (average redundancy 7.867, completeness = 99.9%, R_{int} = 8.43%, R_{sig} = 4.51%) and 6492 (91.79%) were greater than $2\sigma(F^2)$. The final cell constants of a = 10.0070(4) Å, b = 6.2510(2) Å, c = 29.7769(12) Å, β = 90.585(4)°, volume = 1862.56(12) Å^3, are based upon the refinement of the XYZ-centroids of 9874 reflections above 20 σ(I) with 5.935° < 2θ < 144.7°. Data were corrected for absorption effects using the Multi-Scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.671. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.3220 and 0.7580.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P 2_1, with Z = 4 for the formula unit, $C_{18}H_{28}ClNO_2S$. The final anisotropic full-matrix least-squares refinement on F^2 with 421 variables converged at R_1 = 4.50%, for the observed data and wR_2 = 11.84% for all data. The goodness-of-fit was 1.011.

The largest peak in the final difference electron density synthesis was 0.830 $e^-/Å^3$ and the largest hole was -0.454 $e^-/Å^3$ with an RMS deviation of 0.063 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.276 g/cm^3 and F(000), 768 e^-.

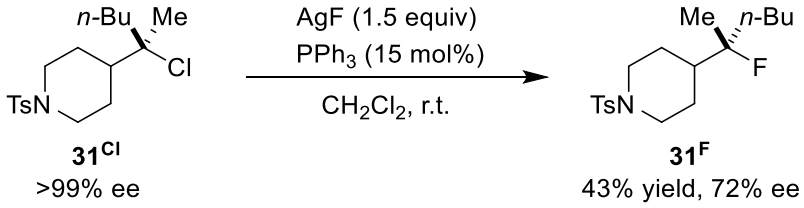
Sample and crystal data for (*R*)-31^{Cl}

Identification code	V23273	
Chemical formula	$C_{18}H_{28}ClNO_2S$	
Formula weight	357.92 g/mol	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal size	0.100 x 0.300 x 0.500 mm	
Crystal habit	colorless Needle	
Crystal system	monoclinic	
Space group	P 1 2_1 1	
Unit cell dimensions	a = 10.0070(4) Å	α = 90°
	b = 6.2510(2) Å	β = 90.585(4)°
	c = 29.7769(12) Å	γ = 90°
Volume	1862.56(12) $Å^3$	
Z	4	
Density (calculated)	1.276 g/cm^3	
Absorption coefficient	2.927 mm^{-1}	
F(000)	768	

Data collection and structure refinement for (*R*)-31^{Cl}

Theta range for data collection	2.97 to 70.08°
Index ranges	-12<=h<=12, -7<=k<=7, -36<=l<=36
Reflections collected	55642
Independent reflections	7073 [R(int) = 0.0843]
Coverage of independent reflections	99.9%
Absorption correction	Multi-Scan
Max. and min. transmission	0.7580 and 0.3220
Structure solution technique	direct methods

Structure solution program	SHELXT 2018/2 (Sheldrick, 2018)
Refinement method	Full-matrix least-squares on F^2
Refinement program	SHELXL-2018/3 (Sheldrick, 2018)
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	7073 / 1 / 421
Goodness-of-fit on F^2	1.011
Δ/σ_{max}	0.001
Final R indices	6492 data; I>2σ(I) $R_1 = 0.0450$, $wR_2 = 0.1120$
	all data $R_1 = 0.0514$, $wR_2 = 0.1184$
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0597P)^2+1.8399P]$ where $P=(F_o^2+2F_c^2)/3$
Absolute structure parameter	0.043(9)
Largest diff. peak and hole	0.830 and -0.454 eÅ^{-3}
R.M.S. deviation from mean	0.063 eÅ^{-3}



31^{Cl}
>99% ee

31^{F}
43% yield, 72% ee

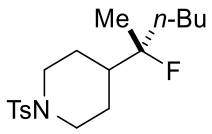
In a glovebox, PPh_3 (3.9 mg, 0.015 mmol), AgF (19.0 mg, 0.15 mmol), enantioenriched electrophile **31^{Cl}** (35.8 mg; 0.10 mmol), and CH_2Cl_2 (1.0 mL) were added in turn to a 4-mL vial equipped with a PTFE stir bar. The reaction mixture was stirred vigorously for 24 h, and then an internal standard (4-fluorobiphenyl; 17.2 mg, 0.10 mmol; in 0.2 mL of acetone) was added. The mixture was filtered through a pad of silica gel, using Et_2O as the eluent. The filtrate was concentrated, the residue was dissolved in $CDCl_3$, and the yield was determined via ^{19}F NMR spectroscopy. Pure alkyl fluoride **31^{F}** was obtained by preparative TLC on silica gel, using 16% EtOAc in hexanes as the eluent.

Crystals suitable for X-ray crystallography were obtained by diffusion of pentane into a solution of **31^{F}** in EtOAc.

The ee was determined via SFC analysis on a CHIRALPAK AD-3 column (10% EtOH in supercritical CO_2, 2.5 mL/min); retention time for (*R*)-**31^{F}**: 5.73 min; for (*S*)-**31^{F}**: 7.13 min.

From (*R*)-**31^{Cl}** (>99% ee): 43% yield, 72% ee.

[A second experiment was carried out with (*S*)-**31^{Cl}** (90% ee): 51% yield, 64% ee.]



(*S*)-4-(2-Fluorohexan-2-yl)-1-tosylpiperidine (31^{F}).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 3.96 – 3.80 (m, 2H), 2.43 (s, 3H), 2.25 – 2.06 (m, 2H), 1.78 (dt, *J* = 12.5, 2.4 Hz, 1H), 1.70 – 1.64 (m, 1H), 1.57 – 1.40 (m, 5H), 1.34 – 1.24 (m, 4H), 1.20 (d, *J* = 22.1 Hz, 3H), 0.92 – 0.86 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5, 133.1, 129.6, 127.8, 98.2 (d, *J* = 169.8 Hz), 46.6 (d, *J* = 4.3 Hz), 40.4 (dd, *J* = 647.4, 23.1 Hz), 26.2 (d, *J* = 7.0 Hz), 25.6 (d, *J* = 5.4 Hz), 25.1 (d, *J* = 4.3 Hz), 23.1, 21.5, 21.2 (d, *J* = 25.2 Hz), 14.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ –150.0 – –150.6 (m).

FT-IR (film): 2956, 1599, 1465, 1339, 1252, 1164, 1093, 934, 726, 651 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $[C_{18}H_{29}NO_2FS]^+$: 342.1898, found: 342.1907.

$[\alpha]^{24}_D$ = +2.5 (c 1.0, $CHCl_3$).

Determination of absolute configuration:

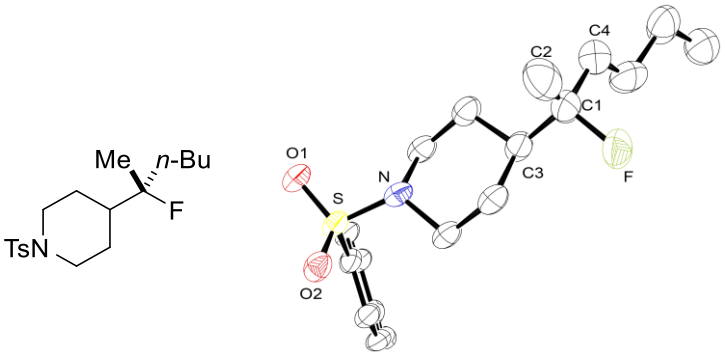


Figure 12. ORTEP drawing of (*R*)-**31^{F}** (CCDC 2294881). Thermal ellipsoid plot at 50% probability level. For clarity, the hydrogen atoms are not shown. A second molecule in the asymmetric unit has been omitted for clarity.

Crystal Structure Report for (*S*)-31^{F}

A colorless needle-like specimen of $C_{18}H_{28}FNO_2S$, approximate dimensions 0.050 mm × 0.050 mm × 0.300 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured (λ = 1.54178 Å).

The total exposure time was 11.47 h. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using

a monoclinic unit cell yielded a total of 31569 reflections to a maximum θ angle of 68.24° (0.83 Å resolution), of which 6445 were independent (average redundancy 4.898, completeness = 99.8%, R_{int} = 10.93%, R_{sig} = 8.22%) and 5303 (82.28%) were greater than $2\sigma(F^2)$. The final cell constants of a = 9.9158(11) Å, b = 6.1478(7) Å, c = 29.507(4) Å, β = 93.497(12)°, volume = 1795.4(4) Å^3, are based upon the refinement of the XYZ-centroids of 5783 reflections above 20 σ(I) with 6.001° < 2θ < 144.4°. Data were corrected for absorption effects using the Multi-Scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.643. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.6210 and 0.9170.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P 1 2_1 1, with Z = 4 for the formula unit, $C_{18}H_{28}FNO_2S$. The final anisotropic full-matrix least-squares refinement on F^2 with 421 variables converged at R_1 = 8.04% for the observed data and wR_2 = 21.27% for all data. The goodness-of-fit was 1.039.

The largest peak in the final difference electron density synthesis was 0.428 $e^-/Å^3$, and the largest hole was -0.522 $e^-/Å^3$ with an RMS deviation of 0.073 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.263 g/cm^3 and F(000), 736 e^-.

Sample and crystal data for (*S*)-31^F

Identification code	V23276	
Chemical formula	$C_{18}H_{28}FNO_2S$	
Formula weight	341.47 g/mol	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal size	0.050 x 0.050 x 0.300 mm	
Crystal habit	colorless Needle	
Crystal system	monoclinic	
Space group	P 1 2_1 1	
Unit cell dimensions	a = 9.9158(11) Å	α = 90°
	b = 6.1478(7) Å	β = 93.497(12)°
	c = 29.507(4) Å	γ = 90°
Volume	1795.4(4) $Å^3$	
Z	4	
Density (calculated)	1.263 g/cm^3	
Absorption coefficient	1.757 mm^{-1}	
F(000)	736	

Data collection and structure refinement for (*S*)-31^F

Theta range for data collection	3.00 to 68.24°
Index ranges	-11<=h<=11, -7<=k<=7, -35<=l<=35
Reflections collected	31569
Independent reflections	6445 [R(int) = 0.1093]
Coverage of independent reflections	99.8%
Absorption correction	Multi-Scan
Max. and min. transmission	0.9170 and 0.6210
Structure solution technique	direct methods
Structure solution program	XT, VERSION 2018/2

Refinement method	Full-matrix least-squares on F^2
Refinement program	SHELXL-2019/1 (Sheldrick, 2019)
Function minimized	$\Sigma\ w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	6445 / 1 / 421
Goodness-of-fit on F^2	1.039
Final R indices	5303 data; $I>2\sigma(I)$ $R_1 = 0.0804$, $wR_2 = 0.1869$
	all data $R_1 = 0.1165$, $wR_2 = 0.2127$
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0866P)^2+4.9502P]$ where $P=(F_o^2+2F_c^2)/3$
Absolute structure parameter	-0.05(4)
Largest diff. peak and hole	0.428 and -0.522 $eÅ^{-3}$
R.M.S. deviation from mean	0.073 $eÅ^{-3}$

7. Reference

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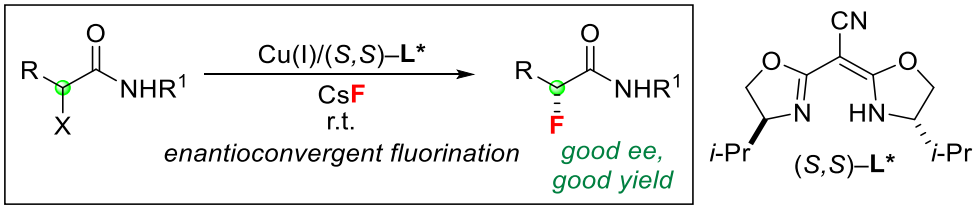
Chapter II

COPPER-CATALYZED ENANTIOCONVERGENT NUCLEOPHILIC FLUORINATION OF ALKYL ELECTROPHILES TO GENERATE α-FLUOROAMIDES



1. Introduction

In recent years, we and others have pursued the development of transition-metal catalysis that can broaden the scope of nucleophilic substitutions of alkyl electrophiles beyond classical S_N1 and S_N2 pathways, including enantioconvergent reactions.[1] One approach to realize enantioconvergence is the ablation and subsequent re-installation of chirality: the two enantiomers of the racemic starting material can be converted to a single, usually planarized intermediate to which the chirality is introduced by the chiral catalyst in subsequent transformations (Figure 1A).[2] Such "enantioconvergence" – conversion of both enantiomers of the starting material to a single enantioenriched product – maximizes the atomic efficiency of the transformation. In previous studies, we have established that transition metals, e.g., nickel and copper, can catalyze enantioconvergent substitutions of racemic alkyl electrophiles by carbon, boron, nitrogen and oxygen nucleophiles.[3] Naturally, we have been interested in expanding our investigations to new families of nucleophiles, including fluorides with poor nucleophilicity.

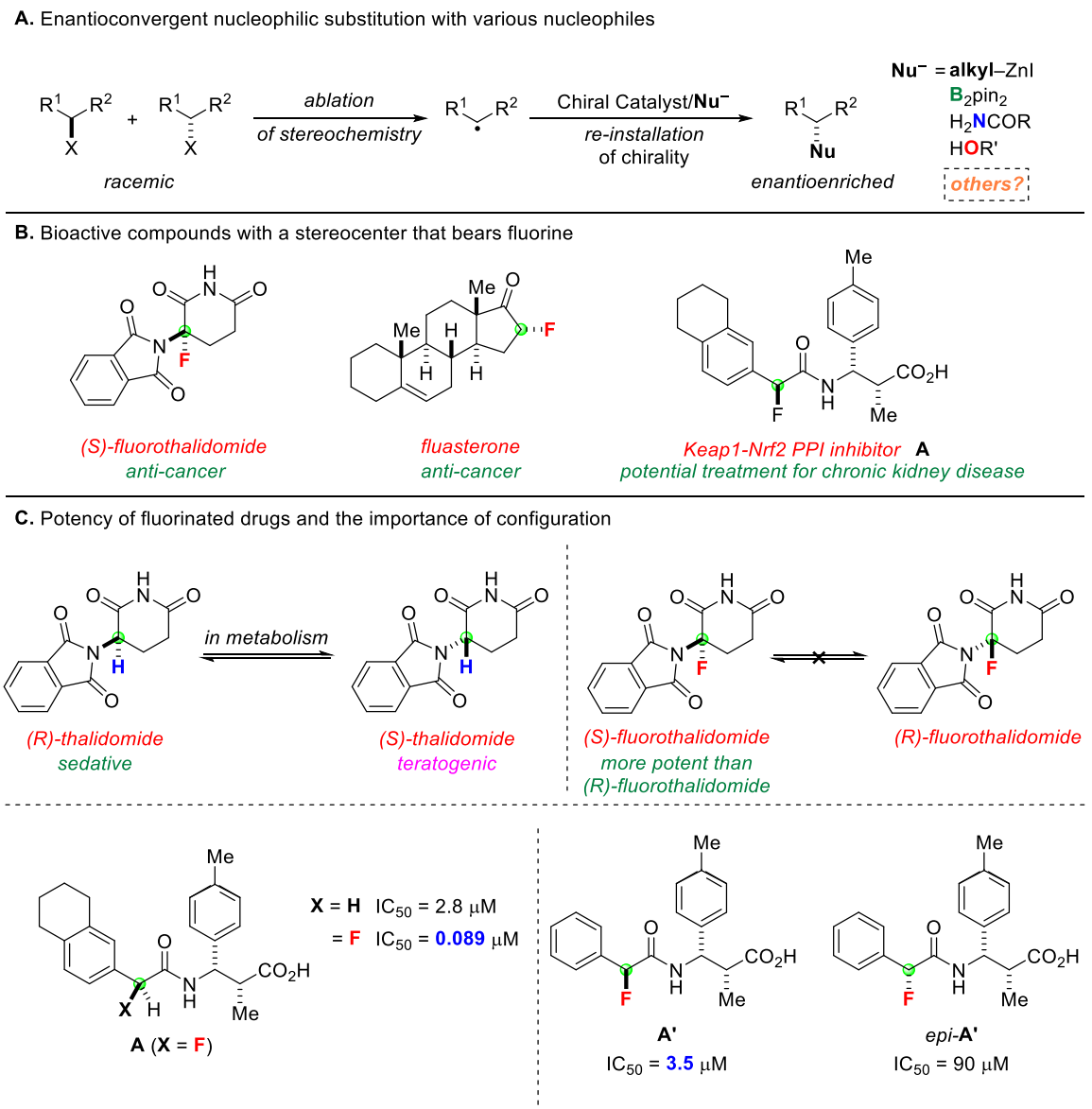


Figure 1. Background. (A) Enantioconvergent transformations represented by a chiral ablation–re-installation mechanism. (B) Bioactive compounds with a stereocenter that bears fluorine. (C) Potency of fluorinated drugs compared with their unfluorinated parents. Fluorinated drugs can exhibit superior activity to their unfluorinated analogues, but their efficacy is significantly influenced by the configuration of the stereocenter that bears fluorine.

As the incorporation of fluorine atoms in a molecule can lead to advantageous and versatile properties (discussed in Chapter 1), the development of efficient new methods to synthesize organofluorine compounds, in particular alkyl monofluorides, has therefore been the focus of significant and increasing effort.[4] Among alkyl fluorides, interesting bioactivity has been observed for alkyl fluorides wherein fluorine is attached to a stereogenic carbon

(Figure 1B). For example, (*R*)-thalidomide exhibits sedative effects, while (*S*)-enantiomer is teratogenic. The two enantiomers undergo *in situ* racemization during metabolism, such that teratogenic hazards are inevitable. Nevertheless, α-fluorination of thalidomides can maintain the desired stereochemical configuration without incurring racemization. Moreover, researches have established that (*S*)-fluorothalidomide possesses superior anti-cancer activity to the (*R*)-enantiomer and does not require P450-mediated metabolic activation as do unfluorinated analogues (Figure 1C, top panel).[5] In addition to the example of thalidomides, α-fluoroamide **A** has been reported by Otake and Harada to be a novel, orally bioavailable Keap1–Nrf2 PPI inhibitor that displayed the greatest inhibitory activity among a wide range of compounds that they examined, including the non-fluorinated compound (Figure 1C, bottom panel).[6] Interestingly, **A'** and *epi*-**A'** – the parent analogues of **A** – also exhibit starkly different activities, indicating the configuration of the fluorine-bearing carbon center is essential to the PPI inhibition efficiency. On the basis of crystallography, isothermal calorimetry and molecular simulations, the authors attribute the increased potency of **A** to fluorine serving both as a hydrogen-bond acceptor and as a steric impediment to a key serine/glutamine interaction in the binding site. These two examples highlight not only the potential utility of chiral alkyl monofluorides in pharmaceutical industry, but the importance of stereochemical control in the construction of carbon–fluorine bonds as well.

The significance of alkyl fluorides with fluorine-attached stereogenic center has stimulated various groups to pursue enantioselective C–F bond formation. Whereas most catalytic enantioselective processes (See Figure 2A left panel for asymmetric synthesis of α-fluorocarbonyl derivatives) have utilized electrophilic fluorinating reagents (e.g., NFSI and Selectfluor; oxidizing conditions),[7] only a few reports have employed mild, simple and relatively inexpensive nucleophile fluorinating reagents (e.g., KF and CsF). For example, CsF and HFIP, as a surrogate for HF, perform hydrofluorination of carbenes under mild and non-hazardous conditions with good enantioselectivity.[8]

In addition to methods described above, catalytic enantioconvergent substitution of a racemic alkyl halide (or pseudohalides such as sulfonates) by nucleophilic fluoride provides

a straightforward route to enantioenriched alkyl fluorides. Impediments to the development of such methods include weak nucleophilicity of fluorides, side reactions (e.g., elimination of HX to afford olefins rather than fluorinated product), a competing nonenantioselective background reaction and catalyst deactivation due to the basicity of the fluoride. When our study started in 2021, we had only noticed two families of substrates engaging in enantioselective nucleophilic fluorination: fluorination of racemic allylic halides [9] (transition-metal catalyst) and functionalized benzylic halides (organocatalyst) bearing innate symmetry that enables desymmetrization of prochiral intermediates (e.g., episulfonium or aziridinium, Figure 2A, right panel)[10].

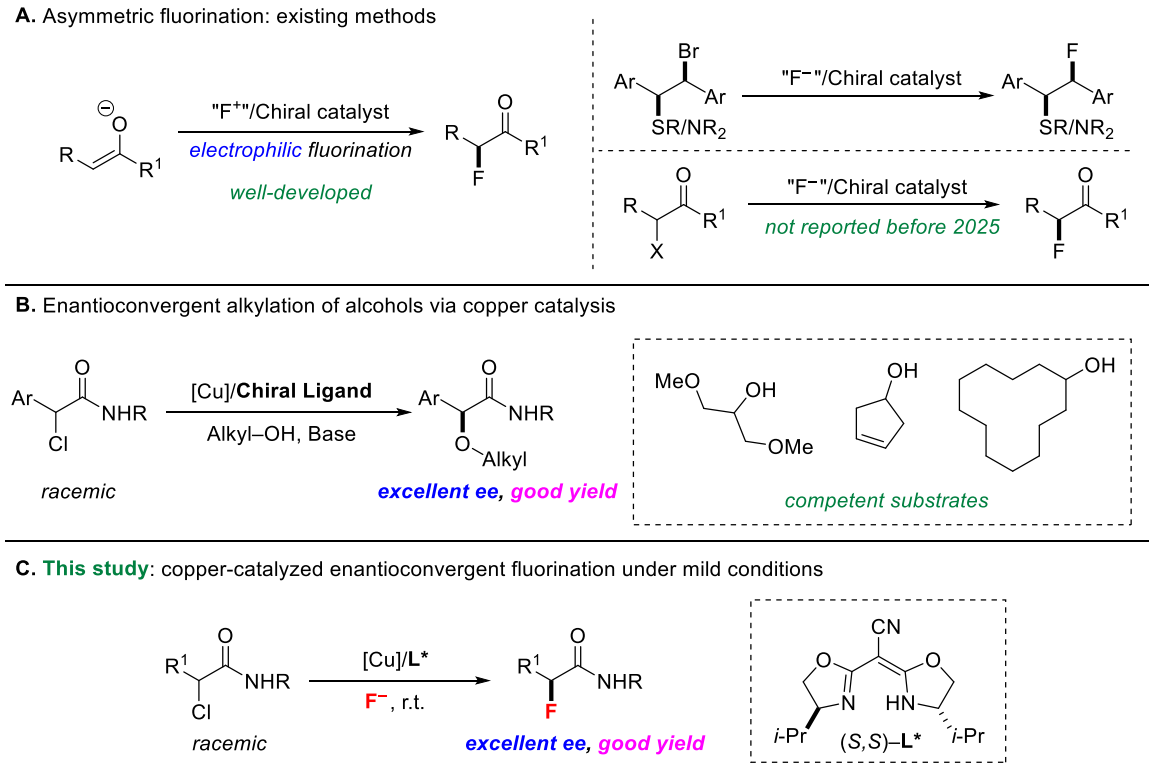


Figure 2. Existing methods for asymmetric fluorination and this study. (A) Existing methods for asymmetric fluorination. Nucleophilic approaches are rare (allylic fluorination not shown) and the enantioconvergent fluorination of α-halocarbonyl compounds has been reported only recently. (B) Seminal study in 2023: enantioconvergent alkylation of aliphatic alcohols. Secondary alcohols are competent nucleophiles. (C) This study: enantioconvergent fluorination via copper catalysis under mild conditions.

In view of the bioactivity of α-fluorocarbonyl compounds, we chose to explore metal-catalyzed enantioconvergent nucleophilic fluorinations of α-halocabonyl compounds. In

2023, we reported an example of copper-catalyzed enantioconvergent alkylation of alcohols (Figure 2B), in which poor nucleophiles such as secondary alcohols can afford the alkylated products with good enantioselecivity and yield.[11] In addition, kinetic studies reveal the reaction is first-order in the copper catalyst and zero-order in the nucleophile, implicating the nucleophile may not be involved in the rate-determining step. Both studies are consistent with a mechanism in which a transient intermediate generated from the starting material is rapidly trapped by a weak nucleophile. Hence, we envision alkali metal fluorides, as weak nucleophiles, can engage in similar transformations that afford alkyl fluorides enantioconvergently. In this chapter, we establish that a chiral copper catalyst can indeed achieve this objective, specifically, that racemic α-aryl-α-haloacetamides can undergo fluorination by CsF under simple and mild conditions with good enantioselectivity and in good yield (Figure 2C).[12] As this work was nearing completion, outstanding studies of enantioconvergent fluorination of racemic α-haloketones (aryl ketones) have been described by Gouverneur[13] and by Sun[14] (Figure 2A, right panel), exploiting organocatalysts inspired by the fluorinase.[15]

2. Optimization of Conditions

At the initial stage of reaction development, we employed α-alkyl-α-bromoacetamide **B** as a model electrophile and obtained the fluorinated product $\mathbf{B^F}$ with 97% ee and 20% yield. Further optimization of conditions, in particular of solvent systems, afforded a maximum yield of 40%. Interestingly, two enantiomers of **B'** exhibit different reactivity, which may indicate the fluorination of **B'** proceeds through kinetic resolution – leading to a maximum yield of 50% (based on electrophiles) – instead of enantioconvergence. We thus decided to change the model electrophile to α-phenyl-α-chloroacetamide **C**. While some attempts on condition optimization enhance the yield up to 70%, significant improvement of reactivity was observed with cyanobox-type (*S,S*)–**L*** as ligand, probably because the facile deprotonation of **L*** enables more efficient coordination with copper. Additionally, we realized this condition can be applied without modification on electrophiles derived from benzylamine, instead of aniline. We thus decided to use α-phenyl-α-chloroamide $\mathbf{1^{Cl}}$ as the

model electrophile, as alkylamine-derived electrophiles are representative of a broader class of substrates (Figure 3).[16]

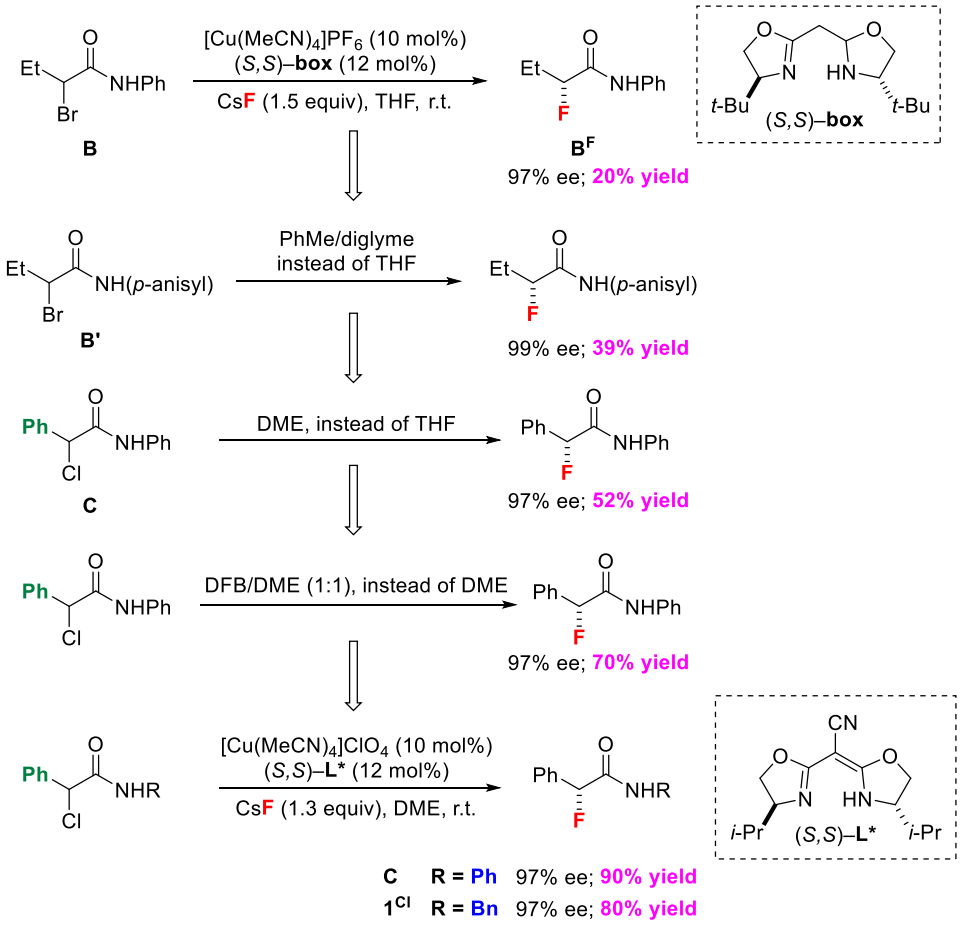
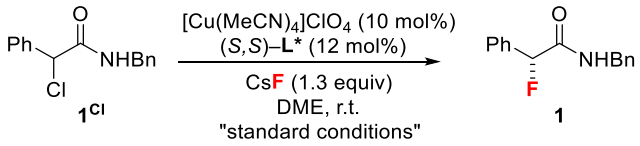


Figure 3. Evolution of conditions for the enantioconvergent fluorination. **1**^{Cl} was selected as the model substrate for further studies.

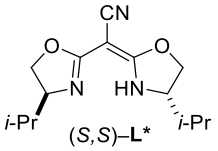
Upon exploring a variety of reaction conditions, we determined that, in the presence of a Cu(I) precatalyst ([Cu(MeCN)$_4$]ClO$_4$) and a readily available ligand (**L***, synthesized in one step from a commercially available precursor), enantioconvergent fluorination of racemic electrophile **1**^{Cl} proceeds in good yield and excellent ee with inexpensive CsF as the source of nucleophilic fluoride (80% yield and 97% ee; Table 1). No racemization of the product occurs under these mild conditions. Control experiments establish that alkyl fluoride **1** is not formed in the absence of the copper precatalyst or of ligand **L*** (entry 2). We have found that CsF is much more effective than KF and that, if the catalyst loading is reduced in half, only a small loss in yield and enantioselectivity is observed (entries 3–4). Trace amount

of moisture or air impacts the yield, but not the enantioselecitivity, of the enantioconvergent fluorination (entries 6–7).

Table 1. Optimized conditions for the enantioconvegent fluorination of α-haloamides[a]



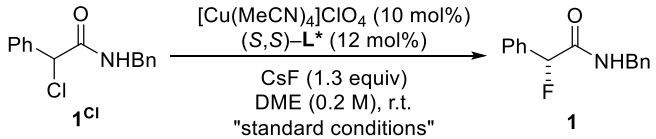
entry	variation from "standard conditions"	yield (%)	ee (%)
1	none	80	97
2	no $[Cu(MeCN)_4]ClO_4$ or no **L***	<1	<1
3	KF, instead of CsF	<1	<1
4	5.0 mol% [Cu] and 6.0 mol% **L***	75	95
5	DCE/DME = 4:1, instead of DME alone	81	97
6	0.2 equiv H_2O added	53	97
7	0.2 mL air added to the headspace	64	97



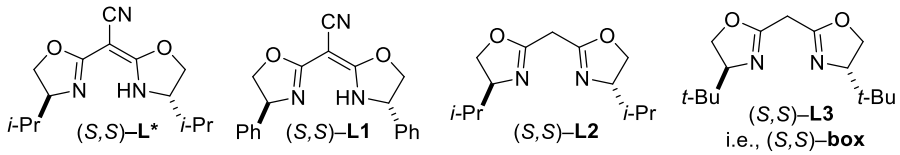
[a]Each entry represents the average yield of two runs (0.10-mmol scale). Yields were determined through analysis via ^{19}F NMR spectroscopy, with 4-fluorobiphenyl as the internal standard. ee values were determined via SFC analysis.

To examine the effects of various reaction parameters to the enantioconvergent fluorination, we tested other copper precatalysts including Cu(II) salts, different ligands and solvents other than DME (Table 2). From entries 5–6, reduced loading of CsF results in incomplete conversion of $\mathbf{1^{Cl}}$, suggesting **L*** may be deprotonated by CsF to be activated. The superior reactivity of CsF comparing to other alkali metal fluorides may be attributed to the high ionizability of CsF, as its solubility in organic solvents is not significant.[17] Elevated temperature compromises the enantioselectivity and the fluorination proceeds smoothly under lower temperature (entries 21–22).

Table 2. Effect of additional parameters for the enantioconvegent fluorination of α-haloamides[a]



entry	variation from the "standard conditions"	yield (%)	ee (%)
1	none	80	97
2	no $[Cu(MeCN)_4]ClO_4$	<1	–
3	no **L***	<1	–
4	no $[Cu(MeCN)_4]ClO_4$ and no **L***	<1	–
5	1.0 equiv, instead of 1.3 equiv, CsF	55	97
6	1.1 equiv, instead of 1.3 equiv, CsF	64	97
7	6, instead of 12, h	79	97
8	$[Cu(MeCN)_4]PF_6$, instead of $[Cu(MeCN)_4]ClO_4$	72	95
9	$[Cu(MeCN)_4]BF_4$, instead of $[Cu(MeCN)_4]ClO_4$	66	96
10	CuCl, instead of $[Cu(MeCN)_4]ClO_4$	70	96
11	$CuCl_2$, instead of $[Cu(MeCN)_4]ClO_4$	54	96
12	**L1**, instead of **L***	64	93
13	**L2**, instead of **L***	9	–
14	**L3** (**box**), instead of **L***	45	93
15	BINAP, instead of **L***	3	–
16	LiF, instead of CsF	<1	–
17	CsF, with 20 mol% 18-crown-6	48	93
18	DCE, instead of DME	46	98
19	THF, instead of DME	75	97
20	2-Me-THF, instead of DME	31	97
21	45 °C, instead of r.t.	76	79
22	0 °C, instead of r.t.	76	96



[a]Each entry represents the average yield of two runs (0.10-mmol scale). Yields were determined through analysis via ^{19}F NMR spectroscopy, with 4-fluorobiphenyl as the internal standard. ee values were determined via SFC analysis.

3. Scope of Substrates

Our standard conditions for the copper-catalyzed asymmetric nucleophilic fluorination of electrophile $\mathbf{1^{Cl}}$ can be applied to a wide array of α-aryl-α-chloroamides (Figure 4). Good enantioselectivity is observed regardless of whether the aromatic ring is electron-rich or electron-poor (entries 2−7), although DCE may sometimes be required as a co-solvent that probably inhibits decomposition of catalytically relevant species. Similarly, the aryl substituent may be para-substituted (entries 2−9), meta-substituted (entries 10−11), or ortho-

substituted (entries 12 and 13), and it may be an extended aromatic system (entry 15) or heteroaromatic (entry 16). A broad scope of functional groups including a thioester (entry 8)[18], boronate ester (entry 9) and nitrile (entry 11) are compatible with the enantioconvergent fluorination. Complex molecules such as the derivative of a drug molecule isoxepac can be fluorinated with good ee and good yield (entry 17). Carbon−fluorine bond formation proceeds with similar ee and yield on a 6.0 mmol scale (1.16 g of product; 5.0 mol% $[Cu(MeCN)_4]ClO_4$ and 6.0 mol% **L***) as on a 0.60 mmol scale (entry 1).

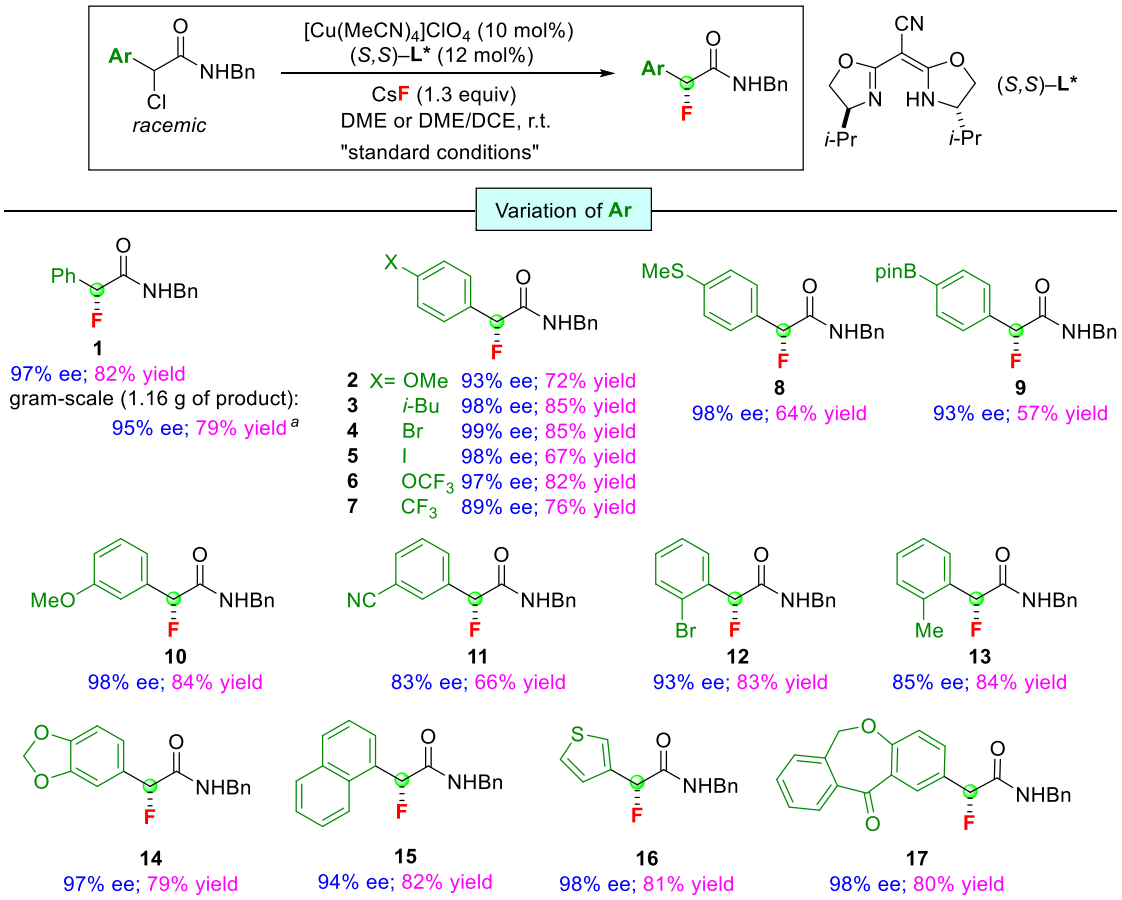
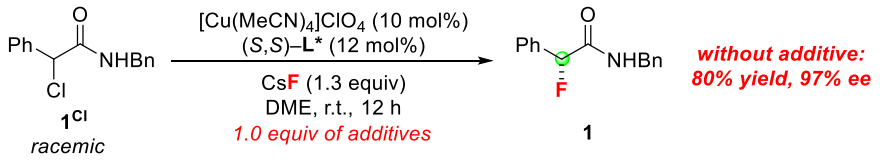
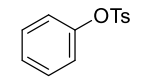
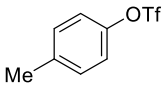
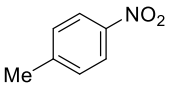
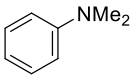
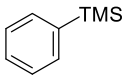
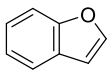
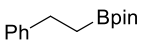
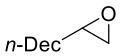


Figure 4. Copper-catalyzed enantioconvergent nucleophilic fluorination of α-chloroamides: variation of the arylacetyl groups. Reactions were conducted on a 0.60 mmol scale, unless otherwise noted. All ee values and yields are for purified products (average of two runs). Whether DCE is involved as a co-solvent is detailed in Section 6. [a] With 5.0 mol % $[Cu(MeCN)_4]ClO_4$ and 6.0 mol % **L***.

To further comprehend the functional-group compatibility of the nucleophilic fluorination, we included different additives under our standard conditions and investigated their recovery as well as their influence on reactivity (Figure 5). An internal alkyne, aniline,

aryl triflate, benzofuran, benzylic chloride, epoxide, nitroarene, and trialkyl phosphate are tolerated in the copper-catalyzed enantioconvergent fluorination. A pyridine, on the other hand, inhibits the reaction, probably due to competitive binding with copper.



additive; recovery (%)		yield (%)	ee (%)
	>95	82	97
	>95	81	96
	>95	80	96
	>95	74	90
	>95	82	97
	>95	81	96
	>95	83	97
	>95	81	97

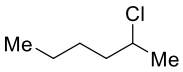
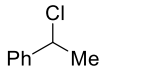
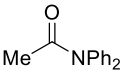
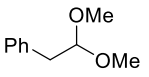
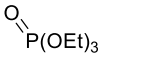
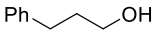
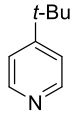
additive; recovery (%)		yield (%)	ee (%)
	>95	89	96
	>95	77	97
	>95	83	96
n-Oct-CN	>95	82	95
	>95	82	97
	>95	81	97
	>95	83	97
	56[a]	52	95
N(*n*-Bu)$_3$	93	58	79
	75	11	–

Figure 5. Effect of additives on the enantioconvergent fluorination of **1**^{Cl}. Each entry represents the average of two runs, one with each enantiomer of **L***. [a]Some C–O bond formation is observed.

In the past several years, a variety of copper-catalyzed enantioselective reactions of α-halo secondary amides have been reported, nearly all of which employ *N*-aryl, rather than *N*-alkyl, amides.[19] In this regard, our success with *N*-benzyl amides as electrophiles in these asymmetric fluorinations is anomalous (Figure 4, entries 1−17). It is noteworthy that *N*-benzyl amides are not unique – enantioconvergent fluorinations of other *N*-alkyl amides also proceed with high enantioselectivity. Thus, the alkyl substituent can vary in steric demand from linear to fully substituted (entries 18−21). Different functional groups can be tolerated,

including a protecting group which reveals a primary amide after protonolysis (entry 22),[20] and a primary alkyl chloride remaining completely intact during the catalysis. In the case of an *N*-alkyl substituent that includes a proximal stereocenter, the stereochemistry of the catalyst, rather than of the substituent, primarily determines the stereochemistry of the product (entry 26).

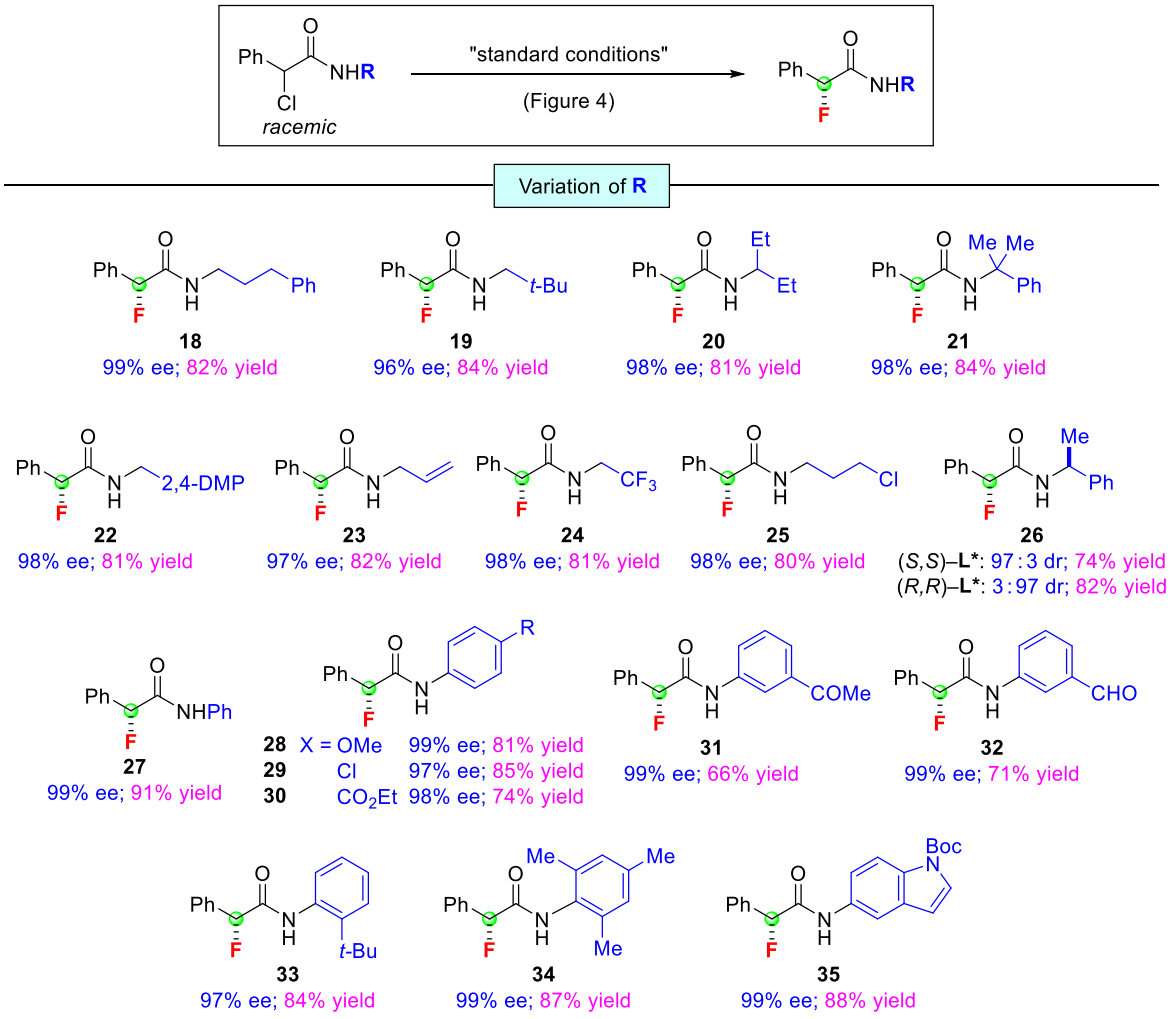


Figure 6. Copper-catalyzed enantioconvergent nucleophilic fluorination of α-chloroamides: variation of the *N*-substituents. Reactions were conducted on a 0.60 mmol scale, unless otherwise noted. All ee values and yields are for purified products (average of two runs). 2,4-DMP = 2,4-dimethoxyphenyl.

Although we have focused on the use of *N*-alkyl amides as electrophiles, we have also explored the application of our catalytic asymmetric fluorination to *N*-aryl amides. We were pleased to determine that the standard conditions that we developed for *N*-alkyl amides (Figure 4) can be applied directly to *N*-aryl amides. Excellent enantioselectivity is observed

not only for the parent substrate bearing a phenyl substituent (Figure 6, entry 27), but also for electron-rich or electron-poor aromatic rings (entries 28−30) and for ortho-, meta-, or para-substituted rings (entries 28−34); indeed, enantioconvergent carbon−fluorine bond formation proceeds in good yield and high ee even in the case of very hindered aromatic groups (entries 33 and 34). The *N*-substituent can be an extended heterocyclic aromatic ring (indole; entry 35), and functional groups such as an ester, aldehyde, and carbamate are compatible with the fluorination reaction.

With regard to scope, we have also explored other leaving groups. For example, we have determined that the standard conditions that we developed for asymmetric nucleophilic substitution of a chloride can be applied without modification to mesylates, providing the desired alkyl fluorides with excellent ee and good yield (Figure 7A). Whereas numerous studies of metal-catalyzed enantioconvergent substitution reactions of α-halocarbonyl compounds have been described, we are not aware of reports that employ sulfonates as leaving groups.[21] Interestingly, α-mesyloxyamide $\mathbf{1}^{\mathbf{OMs}}$ undergoes fluorination to **1** with 53% yield and 96% ee after 30 min (an average of two runs, 60% conversion), a timeframe suitable for ^{18}F labeling in the context of positron emission tomography (PET).

To approach α-fluoroamide **A**, the Keap1–Nrf2 PPI inhibitor reported by Otake and Harada (Figure 1C), we have applied our method to a streamlined route to alkyl fluoride **37**, the penultimate intermediate in the synthesis of **A** (Figure 7B). Compared to the original, chiral-auxiliary-based route requiring four steps, the copper catalyzed fluorination is more diastereoselective, more atom-economical, and requiring fewer steps. These advantages allow a more efficient synthesis of **38**, the epimer of **37**, as both diastereomers can be obtained from a common intermediate **36** instead of from a separate route employing another chiral auxiliary.

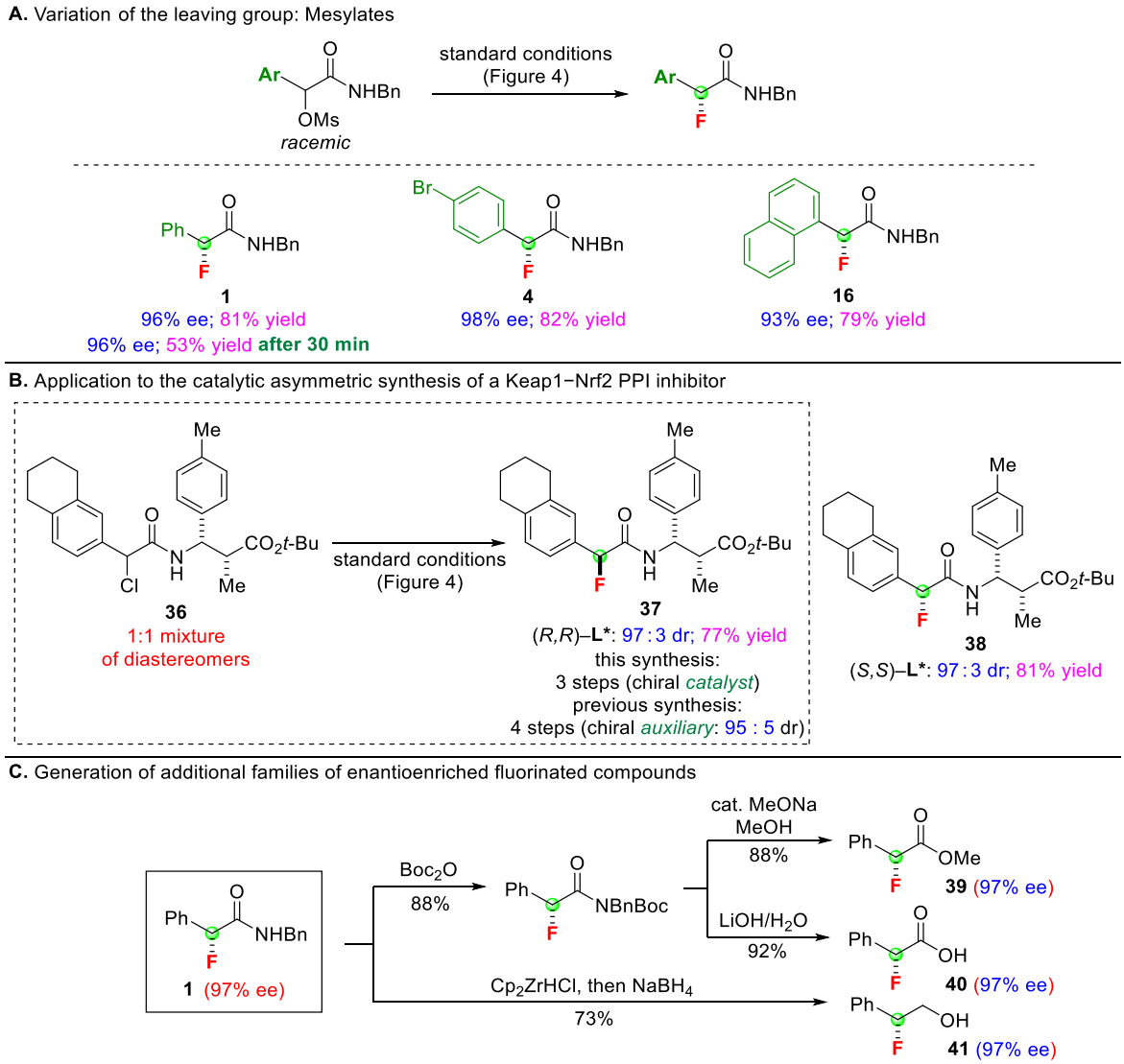


Figure 7. Copper-catalyzed enantioconvergent nucleophilic fluorination. (A) Variation of the leaving group: Mesylates. (B) Application to the catalytic asymmetric synthesis of a Keap1−Nrf2 PPI inhibitor. (C) Generation of additional families of enantioenriched fluorinated compounds. All ee (or dr) values and yields are for purified products (average of two runs).

In addition to being valuable organofluorine compounds in their own right, enantioenriched α-fluoroamides can be transformed into an array of useful derivatives. Thus, α-fluoroesters,[22] α-fluoroacids,[23] and β-fluoroalcohols[24] can be generated (Figure 7C) with essentially no racemization (<1% ee). However, we have not found a simple condition that reduces **1** to the β-fluoroamine, with defluorination as the major side product.

For α-alkylhaloamides, although we were not able to obtain any fluorinated product under the standard conditions, uncyanated bisoxazoline ligand **L3** can afford the α-fluoroamide **42** with good enantioselectivity yet with a modest yield (50%), due to the elimination to the unsaturated amide (Figure 8A). While the two enantiomers of **42** manifested different reactivity under the fluorination condition, suggesting a kinetic resolution pathway (Figure 8B), the mechanistic details for the fluorination of electrophiles such as **42** are currently unknown.

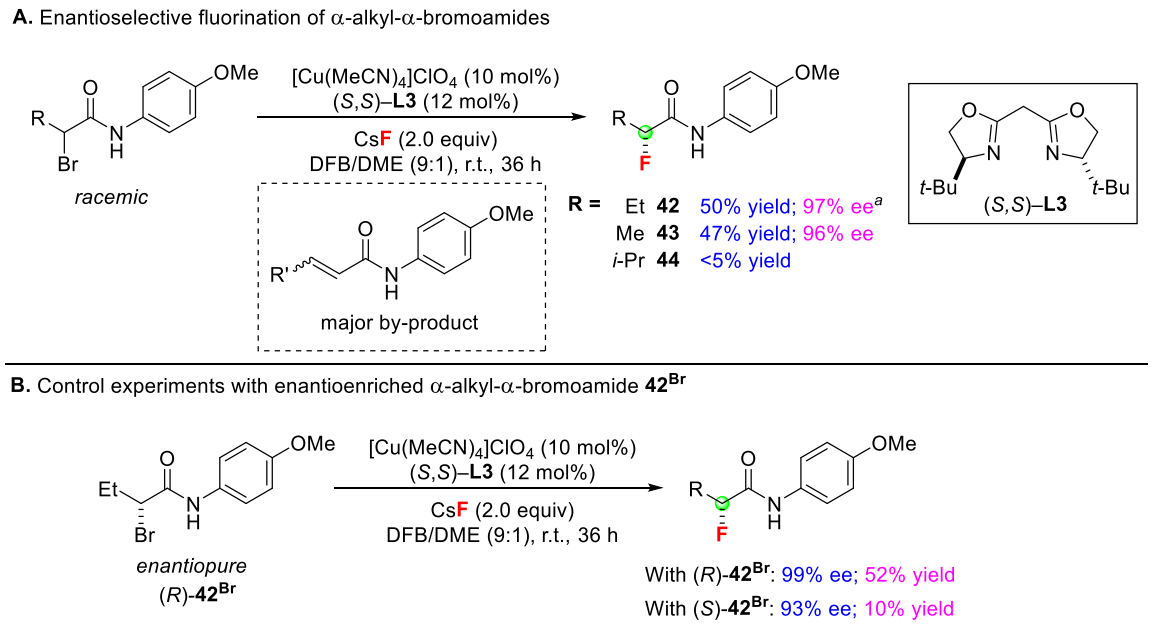


Figure 8. Copper-catalyzed fluorination of α-alkyl-α-bromoamides. (A) Enantioselective fluorination of α-alkyl-α-bromoamides. "Standard conditions" in Figure 3 result in complete conversion to the unsaturated amide (<1% fluorinated product). Reactions were conducted on a 1.0 mmol scale. All ee values and yields are for purified products (average of two runs). (B) Control experiments with enantioenriched **42**^{Br}. Elimination is the primary side-reaction for both enantiomers of **42**^{Br}.

4. Mechanistic Studies

We have begun to explore the mechanism of this new copper-catalyzed enantioconvergent fluorination. By subjecting the individual enantiomers of electrophile **1**^{Cl} to the reaction conditions, we have confirmed that the process is indeed enantioconvergent, with the two enantiomers undergoing fluorination with a relative rate of ~ 2:1 (Figure 9A). Moreover, enantiopure substrates do not undergo fast racemization under our reaction conditions through an S_N2 pathway. Racemization through enolization is also unlikely:

although the α-H of $\mathbf{1}^{Cl}$ can be deprotonated by CsF thus leading to racemization, the rate of such enolization is slower than that of nucleophilic fluorination, as no H/D exchange was observed under our standard conditions (Figure 9B). Overall, these data are consistent with a stereoablative pathway, in which both enantiomers of the substrate are likely converted to a common intermediate, instead of a dynamic kinetic resolution in which the two enantiomers should have exhibited drastically different rates under the fluorination condition.

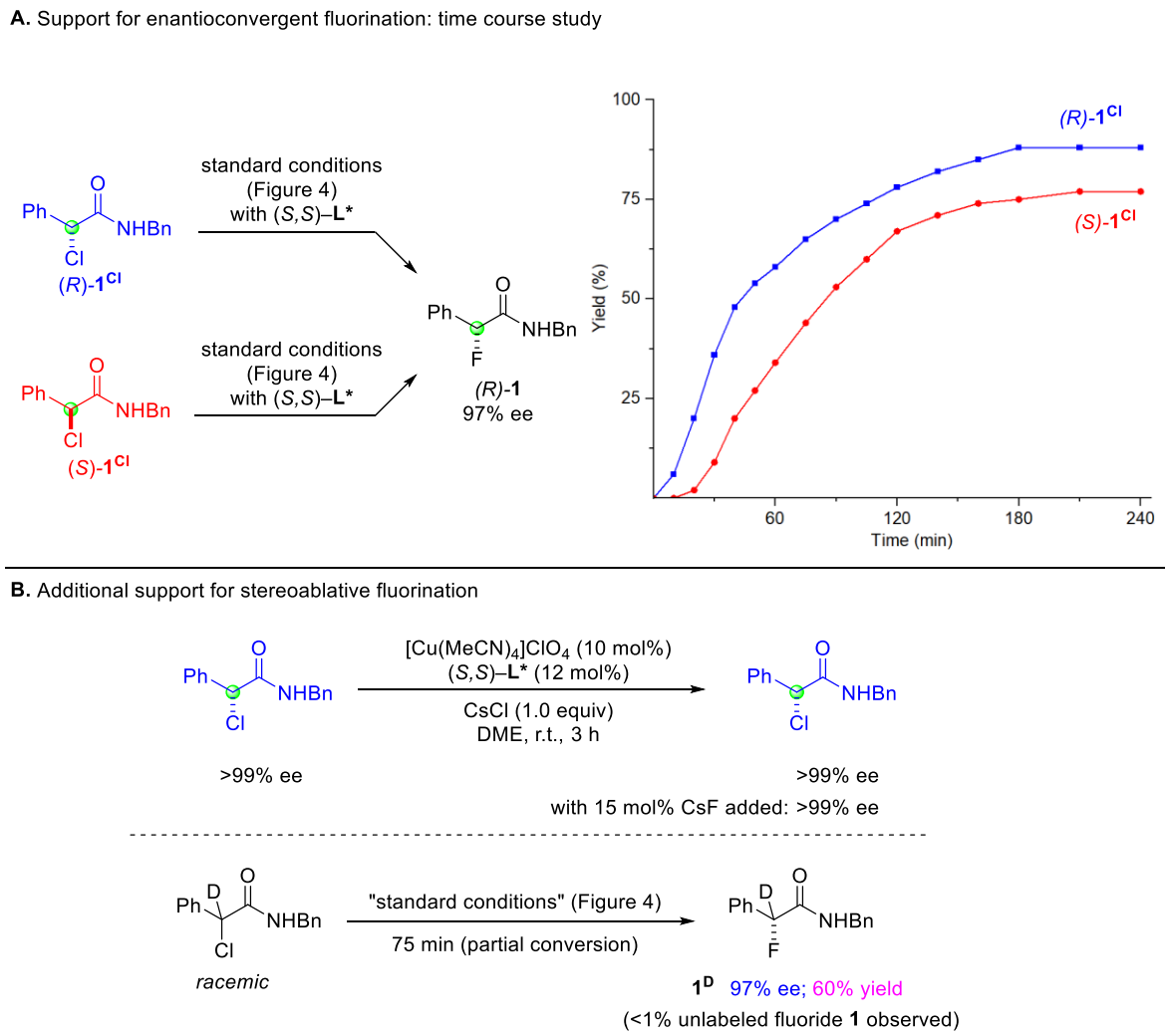


Figure 9. Evidence in support for enantioconvergence. (A) Time course study with two enantiomers of the electrophile $\mathbf{1}^{Cl}$. Estimated ratio of the initial rates is ~2:1. (B) Additional support for stereoablation. No racemization is observed either with or without catalytic amount of CsF capable of deprotonating the ligand (top panel). Enolization through deprotonation is also slower than fluorination, as no H/D exchange is observed during the fluorination to deliver $\mathbf{1}^{D}$.

As the stereoablative pathway suggests the formation of a planarized intermediate, we explored if a radical species can be involved in the enantioconvergent fluorination. In the presence of a radical trap TEMPO, the copper-catalyzed fluorination is inhibited, leading to reduced yield and the generation of a TEMPO adduct (Figure 10A). Interestingly, however, the fluorination can never be completely inhibited even with superstoichiometric amount of TEMPO, probably indicating the presence of a polar pathway unperturbed by radical traps. In addition, a DMPO (5,5-Dimethyl-1-pyrroline *N*-oxide) trapping experiment leads to similar results and the EPR simulation of the resulting radical adduct is consistent with the generation of the dechlorinated radical $\mathbf{1}^{\mathbf{rad}}$ (Figure 10B).

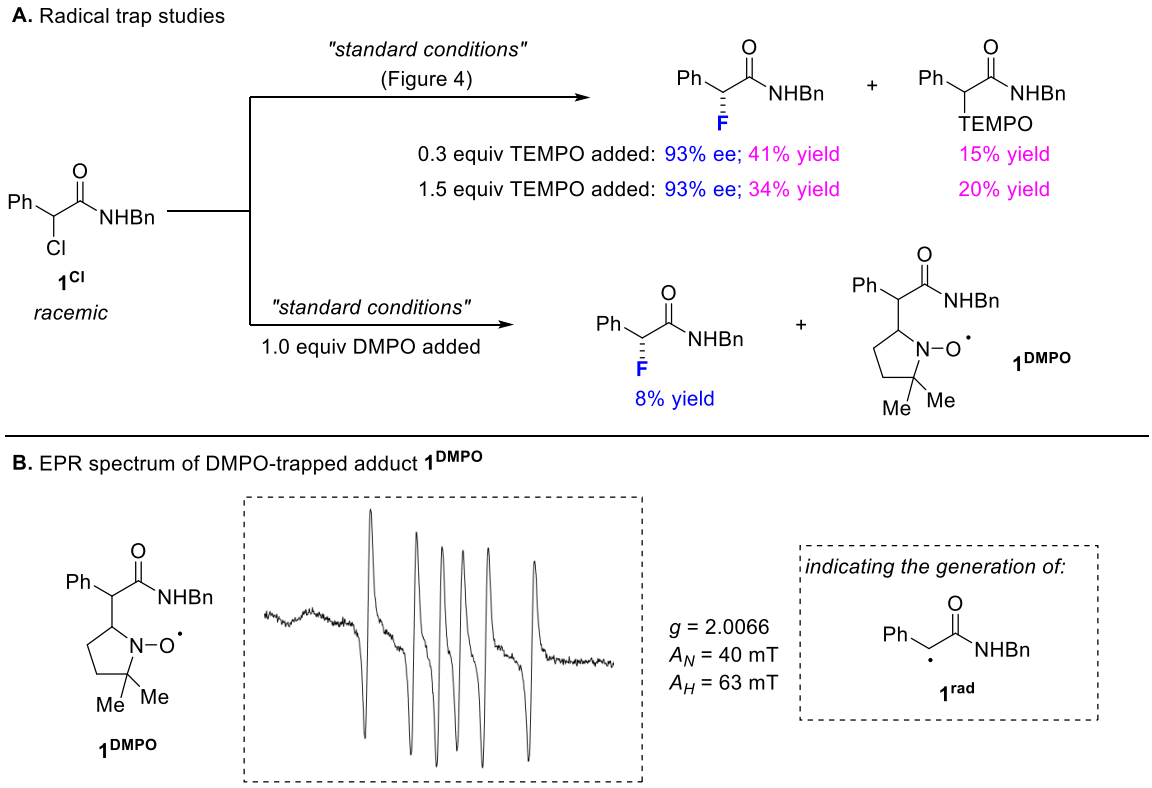


Figure 10. Evidence supporting the involvement of a radical intermediate. (A) Radical trap studies employing TEMPO and DMPO. Superstoichiometric amount of TEMPO (1.5 equiv) still cannot completely inhibit the fluorination. (B) EPR spectrum of the DMPO-adduct $\mathbf{1}^{\mathbf{DMPO}}$. CW X-band EPR: 9.8 GHz, 2 mW MW power, 298 K.

The reduction of **1** to generate radical $\mathbf{1}^{\mathbf{rad}}$ must be accompanied with a single-electron oxidation, e.g., oxidation of Cu(I) to Cu(II). Examination via EPR spectroscopy of a reaction in progress reveals an EPR-active species, which we have assigned to a Cu(II) complex that

bears two deprotonated **L*** ligands (~7% of total copper against external standard $CuSO_4$), based on independent synthesis and crystallographic characterization (Figure 11A).[25]

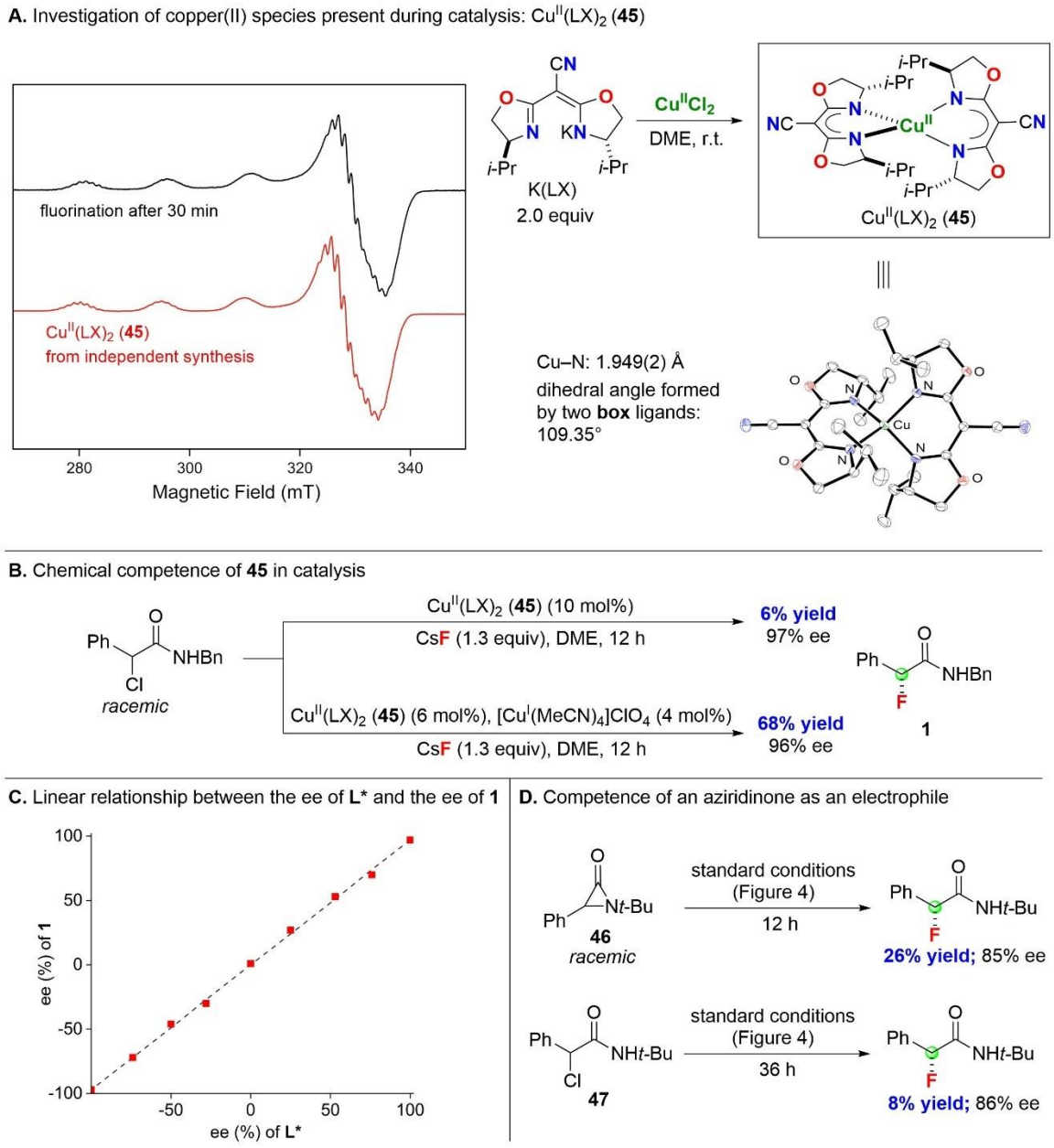


Figure 11. Evidence for Cu(II) species present during the catalysis. (A) EPR spectra of catalytic aliquots and independently synthesized copper complex **45**. CW X-band EPR: 9.4 GHz, 2 mW MW power, 77 K. ORTEP: thermal ellipsoids at 50% probability, hydrogen atoms omitted for clarity. (B) The competence of **45** during catalysis. (C) Linear relationship between the ee of ligand **L*** and the ee of the product **1**. (D) Competence of an aziridinone as an electrophile.

This Cu(II) complex **45** shows minimal activity as a fluorination catalyst, probably because it has been saturated in coordination. Nevertheless, the rate of fluorination greatly increases when $[Cu^{I}(MeCN)_4]ClO_4$ is added to the reaction mixture, consistent with a copper(I)/**L*** complex serving as the active catalyst under our optimized conditions (Figure 11B). Under these standard conditions, we observe a linear relationship between the ee of **L*** and the ee of product **1**, consistent with the involvement of an active catalyst bearing a single chiral ligand in the enantio-determining step (Figure 11C). In short, the copper(II) complex **45** is a catalytically latent species unable to directly catalyze the fluorination with high efficiency unless additional Cu(I) sources are provided.

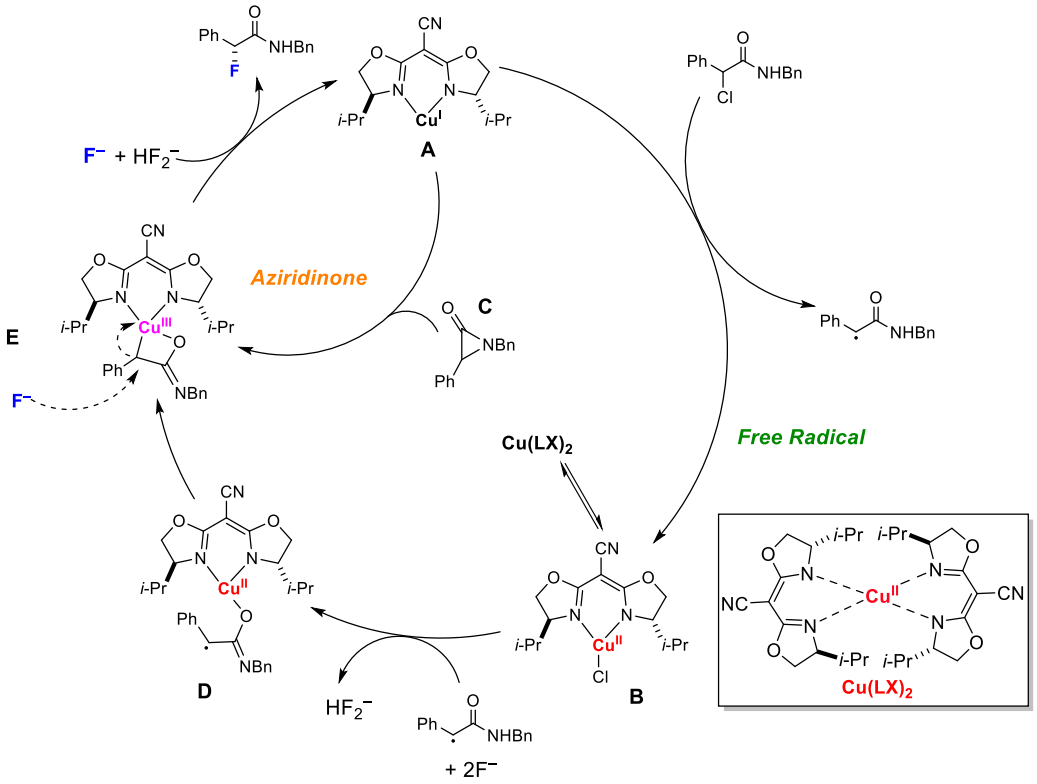


Figure 12. Proposed catalytic cycle of the enantioconvergent fluorination.

To account for the potential polar pathway that bypasses TEMPO inhibition, we hypothesize an aziridinone intermediate was also involved in the catalysis. The independently synthesized aziridinone **46** can undergo nucleophilic fluorination with modest yield but higher that of the corresponding chloride **47**. While the detailed mechanism of the pathway involving aziridinone intermediates is unknown, aziridinones such as **46** may be

chemically competent enough to remedy the fluorination if the radical pathway is compromised (Figure 11D). This hypothesis is also consistent with our observation that tertiary amide derived from $\mathbf{1}^{\mathbf{Cl}}$ does not undergo fluorination under our standard conditions.

To rationalize the mechanism of the enantioconvergent fluorination, we proposed the catalytic cycle in Figure 12. The free radical mechanism involves a single-electron reduction of $\mathbf{1}^{\mathbf{Cl}}$ to $\mathbf{1}^{\mathbf{rad}}$, accompanied by the oxidation of Cu(I) to Cu(II) (e.g., complex **B**). $\mathbf{1}^{\mathbf{rad}}$ may be added to **B** to generate **D** transiently. As anionic F^- may not engage radical reactions easily, we postulate the formation of a Cu(III) species **E** is necessary for the S_N2-type nucleophilic fluorination to deliver **1**. On the other hand, Cu(I) species can undergo direct oxidative addition of an aziridinone intermediate **C**, followed by reductive elimination to generate **1**. Nevertheless, most species except catalytically latent $\mathbf{Cu(LX)_2}$ have not been characterized and the heterogeneous nature of the reaction is impeding any investigation into rate laws.

5. Conclusion

We have developed a chiral transition-metal catalyst that achieves enantioconvergent nucleophilic fluorinations of racemic alkyl electrophiles, specifically, copper-catalyzed asymmetric substitutions of α-aryl-α-chloro (and α-mesyloxy) amides by CsF. The fluorinations proceed under simple and mild conditions, and they display excellent functional-group compatibility. We have applied the method to the streamlined catalytic asymmetric synthesis of a bioactive molecule and to the generation of other families of enantioenriched fluorinated compounds, such as α-fluoroacids and β-fluoroalcohols. While preliminary mechanistic investigations indicate the involvement of both a radical and a polar (aziridinone) pathway, additional studies are required to reach a more decisive conclusion that may inspire the enantioconvergent nucleophilic fluorination of other classes of electrophiles.

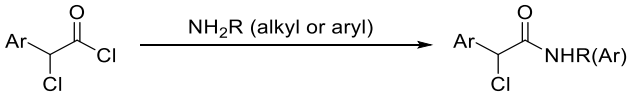
6. Experimental Session

To maintain reproducibility, CsF from Acros Organics™ is recommended. $[Cu(MeCN)_4]ClO_4$[26] and ligand **L***[27] were synthesized and purified according to previous reports.

A. Preparation of electrophiles

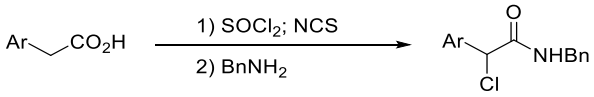
The yields have not been optimized.

General Procedure 1 (GP–1)



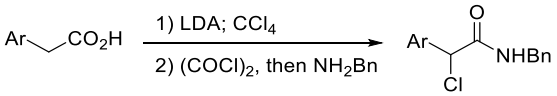
A solution of α-chloroarylacetyl chloride (10 mmol, neat or dissolved in a small amount of CH_2Cl_2) was added dropwise to a solution of the amine (20 mmol) or the aniline (11 mmol) and Et_3N (2.1 mL, 15 mmol) in Et_2O (75 mL) at 0 °C. The mixture was allowed to warm to r.t. and then stirred for 12 h. Next, the mixture was washed with water (50 mL), 1 N HCl (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated, yielding the crude product.

General Procedure 2 (GP–2)



The arylacetic acid (10 mmol) was dissolved in neat $SOCl_2$ (3.0 mL), and the solution was heated to 80 °C and stirred for 40 min (ventilated by a needle). The solution was allowed to cool to r.t., and then NCS (3.34 g, 25 mmol), additional $SOCl_2$ (2.0 mL), and 12 N HCl (4 drops) were added. The mixture was heated to 90 °C for 2 h (ventilated by a needle). Next, the mixture was allowed to cool to r.t., and then it was filtered through a pad of celite (flushing with 1:1 Et_2O/hexanes). The filtrate was concentrated to afford the α-chloroarylacetyl chloride, which was directly used according to **GP–1** with $BnNH_2$ as the amine.

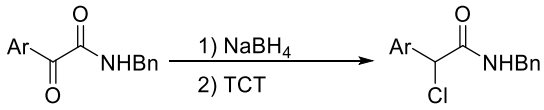
General Procedure 3 (GP–3)



This procedure is adapted from a literature report.[28] The arylacetic acid (10 mmol) and HMPA (3.4 mL, 20 mmol) were dissolved in THF (50 mL). The solution was cooled to –78 °C, and then LDA (11 mL, 2.0 M, 22 mmol) was added dropwise into the solution. The mixture was allowed to warm to 0 °C, and then it was stirred for 1 h. The resulting solution was cooled to –78 °C, and then a solution of CCl_4 (3.8 mL, 40 mmol) in THF (10 mL) was added dropwise. The reaction was allowed to warm to r.t., and then it was stirred for 12 h before it was quenched with brine (3 mL). Aqueous 1 N HCl (50 mL) was added, and then the aqueous layer was extracted with EtOAc (50 mL × 3). The combined organic layer was washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated to afford the corresponding α-chloroarylacetic acid, which was used directly in the next step without purification.

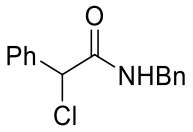
Oxalyl chloride (0.94 mL, 11 mmol) was added dropwise to a solution of the α-chloroarylacetic acid and DMF (4 drops) in CH_2Cl_2 (75 mL). The reaction mixture was stirred at r.t. for 1 h, and then it was concentrated to give the corresponding α-chloroarylacetyl chloride, which was reacted directly with $BnNH_2$ according to **GP–1**.

General Procedure 4 (GP–4)



NaOH (120 mg, 3.0 mmol) and $NaBH_4$ (760 mg, 20 mmol) were added in turn to a solution of the *N*-benzyl-2-oxo-2-arylacetamide in MeOH (50 mL) at 0 °C. The mixture was allowed to warm to r.t., and then it was stirred for 2 h. Next, the MeOH was evaporated, and the residue was dissolved in EtOAc (50 mL) and water (50 mL). The aqueous layer was extracted with EtOAc (50 mL × 3), and the combined organic layer was washed with brine (50 mL) and concentrated to give the *N*-benzyl-2-hydroxy-2-arylacetamide, which was used in the next step without further purification.

The following procedure is adapted from a literature report.[29] Trichlorotriazine (TCT, 15 mmol) was added to DMF (1.5 mL, 20 mmol). This mixture was stirred for 15 min, and then CH_2Cl_2 (75 mL) was added. After 5 min, the *N*-benzyl-2-hydroxy-2-arylacetamide was added, and the resulting mixture was stirred for 12 h. Next, the reaction mixture was washed sequentially with water (50 mL), sat. aqueous Na_2CO_3 (50 mL), and sat. aqueous LiCl (50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford the crude product.



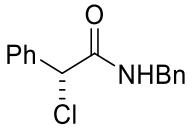
***N*-Benzyl-2-chloro-2-phenylacetamide (1^{Cl}) (CAS 27946-19-6).** The title compound was synthesized from 2-chloro-2-phenylacetyl chloride (12 mmol instead of 10 mmol) and $BnNH_2$ according to **GP–1**. It was purified by recrystallization from hot EtOAc/hexanes. White solid.

Yield: 2.50 g, 80%.

The spectroscopic data are consistent with those in the literature.[30]

(*R*)-*N*-Benzyl-2-chloro-2-phenylacetamide ((*R*)-1^{Cl}). The title compound was synthesized from enantiopure *(S)-N*-benzyl-2-hydroxy-2-phenylacetamide [31] (5.0 mmol instead of 10 mmol) according to **GP–4**. It was purified by flash column chromatography on silica (20→25% EtOAc/hexanes). White solid.

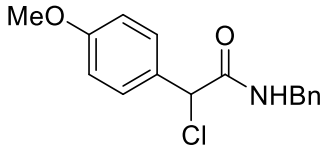
Yield: 675 mg, 52%, 99% ee.



(*S*)-*N*-Benzyl-2-chloro-2-phenylacetamide ((*S*)-1^{Cl}) was synthesized using the same procedure.

Yield: 753 mg, 58%, 99% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (20% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of (*S*)-$\mathbf{1^{Cl}}$: 6.00 min (major), 7.41 min (minor).



***N*-Benzyl-2-chloro-2-(4-methoxyphenyl)acetamide (2^{Cl}).** The title compound was synthesized from 2-(4-methoxyphenyl)acetic acid according to **GP–3**. It was purified by flash column chromatography on silica (30→35% EtOAc/hexanes). White solid.

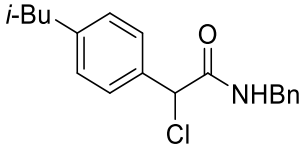
Yield: 1.88 g, 65%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.34 (m, 4H), 7.33 – 7.27 (m, 3H), 7.00 (s, br, 1H), 6.92 – 6.86 (m, 2H), 5.41 (s, 1H), 4.52 (dd, *J* = 5.8, 2.8 Hz, 2H), 3.81 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.6, 160.2, 137.5, 129.2, 128.9, 127.80, 127.78, 114.4, 61.8, 55.4, 44.1.

FT-IR (film): 3297, 3032, 1661, 1608, 1512, 1463, 1453, 1303, 1255, 1176, 1031, 737, 701 cm^{-1}.

HRMS (ESI^+-MS) *m/z* $[M+Na]^+$ calcd for $[C_{16}H_{16}ClNNaO_2]^+$: 312.0762, found: 312.0769.



***N*-Benzyl-2-chloro-2-(4-isobutylphenyl)acetamide (3^{Cl}).** The title compound was synthesized from ibufenac according to **GP–3**. It was purified by flash column chromatography on silica (15→25% EtOAc/hexanes). White solid.

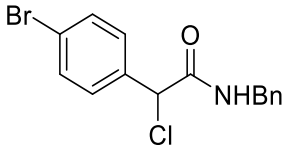
Yield: 1.70 g, 54%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.30 (m, 5H), 7.30 – 7.26 (m, 2H), 7.18 – 7.11 (m, 2H), 6.99 (s, br, 1H), 5.42 (s, 1H), 4.52 (d, *J* = 5.8 Hz, 2H), 2.47 (d, *J* = 7.2 Hz, 2H), 1.85 (hept, *J* = 6.8 Hz, 1H), 0.90 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.6, 143.0, 137.5, 134.3, 129.7, 128.9, 127.78, 127.75, 127.6, 61.9, 45.1, 44.1, 30.2, 22.4.

FT-IR (film): 3282, 3065, 2955, 1660, 1531, 1455, 1363, 1212, 1028, 730 cm^{-1}.

HRMS (ESI^+-MS) *m/z* $[M+H]^+$ calcd for $[C_{19}H_{23}ClNO]^+$: 316.1463, found: 316.1465.



***N*-Benzyl-2-(4-bromophenyl)-2-chloroacetamide (4^{Cl}).** The title compound was synthesized from 2-(4-bromophenyl)acetic acid according to **GP–3**. It was purified by flash column chromatography on silica (20→30% EtOAc/hexanes). White solid.

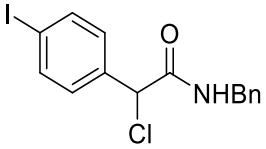
Yield: 1.96 g, 58%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 – 7.51 (m, 1H), 7.51 – 7.48 (m, 1H), 7.39 – 7.34 (m, 2H), 7.34 – 7.26 (m, 5H), 7.01 (s, br, 1H), 5.37 (s, 1H), 4.51 (d, J = 5.7 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.8, 137.2, 136.1, 132.1, 129.5, 128.9, 127.9, 127.8, 123.4, 60.9, 44.2.

FT-IR (film): 3295, 3067, 1661, 1540, 1488, 1211, 1072, 1011, 697 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{15}H_{14}BrClNO]^+$: 337.9946, found: 337.9942.



***N*-Benzyl-2-chloro-2-(4-iodophenyl)acetamide (5^{Cl}).** The title compound was synthesized from 2-(4-iodophenyl)acetic acid according to **GP–3**. It was purified by flash column chromatography on silica (20→30% EtOAc/hexanes). White solid.

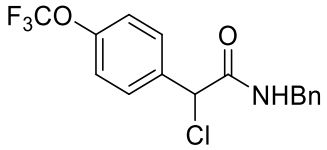
Yield: 1.90 g, 49%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8.4 Hz, 2H), 7.43 – 7.33 (m, 3H), 7.32 – 7.28 (m, 2H), 7.20 (d, J = 8.4 Hz, 2H), 7.04 (s, br, 1H), 5.37 (s, 1H), 4.58 – 4.49 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.8, 138.1, 137.3, 136.7, 129.6, 128.9, 127.9, 127.8, 95.1, 61.0, 44.2.

FT-IR (film): 3300, 2353, 1640, 1525, 1249, 1005, 739, 677 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{15}H_{14}ClINO]^+$: 385.9804, found: 385.9804.



***N*-Benzyl-2-chloro-2-(4-(trifluoromethoxy)phenyl)acetamide (6^{Cl}).** The title compound was synthesized from 2-(4-(trifluoromethoxy)phenyl)acetic acid according to **GP–2**. It was purified by flash column chromatography on silica (15→25% EtOAc/hexanes). White solid.

Yield: 2.32 g, 67%.

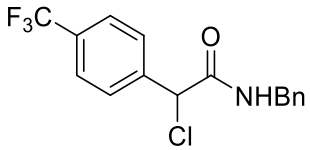
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.45 (m, 2H), 7.39 – 7.30 (m, 3H), 7.29 – 7.25 (m, 2H), 7.24 – 7.18 (m, 2H), 7.11 (s, br, 1H), 5.41 (s, 1H), 4.50 (d, J = 5.8 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.9, 149.6 (q, J = 1.9 Hz), 137.2, 135.7, 129.5, 128.9, 127.9, 127.8, 120.4 (q, J = 258.3 Hz), 121.3, 60.6, 44.2.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –57.8 (s).

FT-IR (film): 3265, 3088, 1660, 1651, 1554, 1217, 1022, 724, 671 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{16}H_{14}ClF_3NO_2]^+$: 344.0668, found: 344.0660.



***N*-Benzyl-2-chloro-2-(4-(trifluoromethyl)phenyl)acetamide (7^{Cl}).** The title compound was synthesized from 2-(4-(trifluoromethyl)phenyl)acetic acid according to **GP–2**. It was purified by flash column chromatography on silica (20→25% EtOAc/hexanes). White solid.

Yield: 2.32 g, 71%.

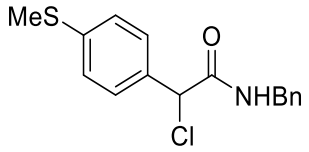
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 8.1 Hz, 2H), 7.57 (d, J = 8.0 Hz, 2H), 7.40 – 7.31 (m, 3H), 7.31 – 7.26 (m, 2H), 7.07 (s, br, 1H), 5.45 (s, 1H), 4.51 (d, J = 5.8 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.6, 140.8, 137.2, 131.3 (q, J = 32.8 Hz), 128.9, 128.3, 128.0, 127.8, 125.9 (q, J = 3.7 Hz), 123.8 (d, J = 272.4 Hz), 60.7, 44.2.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –62.8 (s).

FT-IR (film): 3270, 2340, 1665, 1538, 1331, 1217, 1164, 1112, 885, 744, 695, 642 cm^{-1}.

HRMS (ESI^+-MS) *m/z* $[M+H]^+$ calcd for $[C_{16}H_{14}ClF_3NO]^+$: 328.0711, found: 328.0715.



***N*-Benzyl-2-chloro-2-(4-(methylthio)phenyl)acetamide (8^{Cl}).** The title compound was synthesized from 2-(4-(methylthio)phenyl)acetic acid according to **GP–3**. It was purified by flash column chromatography on silica (20→25% EtOAc/hexanes). White solid.

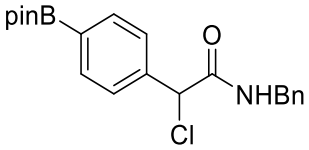
Yield: 1.35 g, 44%.

^1H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.32 (m, 5H), 7.31 – 7.27 (m, 2H), 7.25 – 7.20 (m, 2H), 6.99 (s, br, 1H), 5.39 (s, 1H), 4.51 (dd, *J* = 5.8, 2.0 Hz, 2H), 2.48 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.3, 140.2, 137.4, 133.6, 128.9, 128.2, 127.9, 127.8, 126.6, 61.5, 44.2, 15.5.

FT-IR (film): 3321, 1644, 1532, 1248, 1213, 889, 820, 736 cm^{-1}.

HRMS (ESI^+-MS) *m/z* $[M+Na]^+$ calcd for $[C_{16}H_{16}ClNNaOS]^+$: 328.0534, found: 328.0534.



***N*-Benzyl-2-chloro-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide (9^{Cl}).** The title compound was synthesized from 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetic acid according to **GP–3**. It was purified by flash column chromatography on silica (25→30% EtOAc/hexanes). White solid.

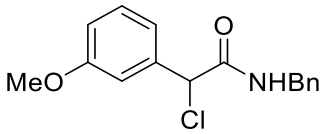
Yield: 1.51 g, 39%.

^1H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.1 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.38 – 7.33 (m, 2H), 7.33 – 7.25 (m, 3H), 6.95 (s, br, 1H), 5.42 (s, 1H), 4.50 (t, *J* = 5.2 Hz, 2H), 1.34 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.2, 139.7, 137.4, 135.4, 128.9, 127.80, 127.77, 127.0, 84.0, 61.7, 44.1, 24.9.

FT-IR (film): 3301, 2979, 1661, 1613, 1398, 1361, 1275, 1147, 1089, 1022, 962, 859, 730, 654 cm^{-1}.

HRMS (ESI^+-MS) *m/z* $[M+H]^+$ calcd for $[C_{21}H_{26}BClNO_3]^+$: 386.1689, found: 386.1694.



***N*-Benzyl-2-chloro-2-(3-methoxyphenyl)acetamide (10^{Cl}).** The title compound was synthesized from 2-(3-methoxyphenyl)acetic acid according to **GP–3**. It was purified by flash column chromatography on silica (20→30% EtOAc/hexanes). White solid.

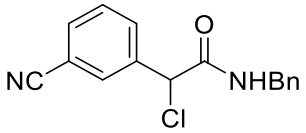
Yield: 1.71 g, 59%.

^1H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.33 (m, 2H), 7.33 – 7.26 (m, 4H), 7.05 – 7.00 (m, 1H), 7.00 – 6.94 (m, 2H), 6.91 – 6.86 (m, 1H), 5.39 (s, 1H), 4.51 (t, *J* = 5.6 Hz, 2H), 3.79 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.3, 159.9, 138.4, 137.4, 130.0, 128.9, 127.81, 127.78, 120.1, 114.9, 113.3, 61.7, 55.3, 44.1.

FT-IR (film): 3283, 2935, 1661, 1600, 1541, 1492, 1435, 1267, 1042, 725 cm^{-1}.

HRMS (ESI^+-MS) *m/z* $[M+H]^+$ calcd for $[C_{16}H_{17}ClNO_2]^+$: 290.0943, found: 290.0949.



***N*-Benzyl-2-chloro-2-(3-cyanophenyl)acetamide (11^{Cl}).** The title compound was synthesized from 2-(3-cyanophenyl)acetic acid according to **GP–2**. It was purified by flash column chromatography on silica (30→40% EtOAc/hexanes). White solid.

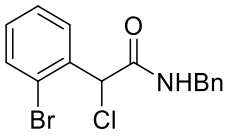
Yield: 1.25 g, 44%.

^1H NMR (400 MHz, $CDCl_3$): δ 7.74 (t, *J* = 1.8 Hz, 1H), 7.69 (dt, *J* = 7.9, 1.6 Hz, 1H), 7.64 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.41 – 7.32 (m, 3H), 7.31 – 7.27 (m, 2H), 7.09 (s, br, 1H), 5.41 (s, 1H), 4.51 (d, *J* = 5.8 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.2, 138.6, 137.0, 132.6, 132.4, 131.4, 129.7, 129.0, 128.1, 127.8, 118.1, 113.2, 60.1, 44.3.

FT-IR (film): 3299, 3064, 2232, 1667, 1537, 1434, 1362, 1334, 1211, 1028, 740, 714 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{16}H_{14}ClN_2O]^+$: 285.0790, found: 285.0794.



***N*-Benzyl-2-(2-bromophenyl)-2-chloroacetamide (12^{Cl}).** The title compound was synthesized from 2-(2-bromophenyl)acetic acid according to **GP–3**. It was purified by flash column chromatography on silica (20→25% EtOAc/hexanes). White solid.

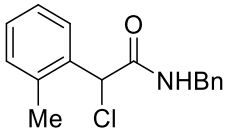
Yield: 2.03 g, 60%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.47 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.40 – 7.35 (m, 2H), 7.35 – 7.29 (m, 4H), 7.21 (td, *J* = 7.7, 1.6 Hz, 1H), 7.06 (s, br, 1H), 5.88 (s, 1H), 4.66 – 4.45 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.6, 137.3, 136.9, 133.3, 130.6, 129.7, 128.9, 128.2, 127.9, 124.4, 60.4, 44.3.

FT-IR (film): 3292, 3070, 1660, 1536, 1249, 1029, 1006, 693 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{15}H_{14}BrClNO]^+$: 337.9942, found: 337.9943.



***N*-Benzyl-2-chloro-2-(*o*-tolyl)acetamide (13^{Cl}).** The title compound was synthesized from 2-(*o*-tolyl)acetic acid according to **GP–2**. It was purified by flash column chromatography on silica (20→25% EtOAc/hexanes). White solid.

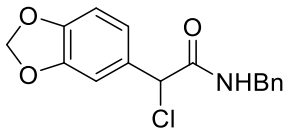
Yield: 1.97 g, 72%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.29 (m, 6H), 7.25 – 7.18 (m, 3H), 7.14 (s, br, 1H), 5.66 (s, 1H), 4.55 (dd, *J* = 5.8, 1.7 Hz, 2H), 2.45 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.6, 137.4, 136.9, 135.7, 131.1, 129.3, 128.9, 127.87, 127.85, 127.7, 126.7, 59.2, 44.2, 19.3.

FT-IR (film): 3295, 3029, 1660, 1523, 1455, 1350, 1221, 1028, 738 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{16}H_{17}ClNO]^+$: 274.0994, found: 274.0998.



2-(Benzo[*d*][1,3]dioxol-5-yl)-*N*-benzyl-2-chloroacetamide (14^{Cl}). The title compound was synthesized from 2-(benzo[*d*][1,3]dioxol-5-yl)-*N*-benzyl-2-oxoacetamide according to **GP–4**. It was purified by flash column chromatography on silica (20→30% EtOAc/hexanes). White solid.

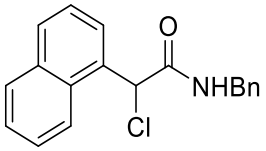
Yield: 1.92 g, 63%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.34 (m, 2H), 7.33 – 7.27 (m, 3H), 7.03 (s, br, 1H), 6.95 – 6.88 (m, 2H), 6.80 – 6.73 (m, 1H), 5.97 (s, 2H), 5.35 (s, 1H), 4.51 (d, *J* = 5.8 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.3, 148.4, 148.2, 137.4, 130.8, 128.9, 127.9, 127.8, 122.1, 108.4, 108.0, 101.5, 61.9, 44.2.

FT-IR (film): 3298, 3065, 2894, 1666, 1503, 1488, 1251, 1101, 1039, 930, 736 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{16}H_{15}ClNO_3]^+$: 304.0735, found: 304.0729.



***N*-Benzyl-2-chloro-2-(naphthalen-1-yl)acetamide (15^{Cl}).** The title compound was synthesized from *N*-benzyl-2-(naphthalen-1-yl)-2-oxoacetamide according to **GP–4** (6.5 mmol instead of 10 mmol). It was purified by flash column chromatography on silica (20→25% EtOAc/hexanes). White solid.

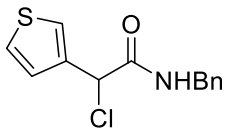
Yield: 1.48 g, 73%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 – 8.07 (m, 1H), 7.92 – 7.84 (m, 2H), 7.62 – 7.50 (m, 3H), 7.45 (t, *J* = 7.1 Hz, 1H), 7.40 – 7.28 (m, 5H), 7.13 (s, br, 1H), 6.13 (s, 1H), 4.66 – 4.43 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.6, 137.5, 134.1, 132.8, 130.7, 130.3, 129.1, 128.9, 127.9, 127.8, 127.0, 126.7, 126.3, 125.3, 123.3, 59.7, 44.3.

FT-IR (film): 3270, 3063, 1653, 1537, 1359, 1214, 1065, 1003, 881, 778, 667 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{19}H_{17}ClNO]^+$: 310.0993, found: 310.0994.



***N*-Benzyl-2-chloro-2-(thiophen-3-yl)acetamide (16^{Cl}).** The title compound was synthesized from *N*-benzyl-2-oxo-2-(thiophen-3-yl)acetamide according to **GP–4**. It was purified by flash column chromatography on silica (20→30% EtOAc/hexanes). White solid.

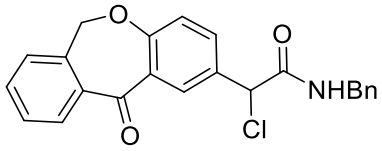
Yield: 1.73 g, 65%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.27 (m, 7H), 7.15 (dd, *J* = 5.0, 1.4 Hz, 1H), 6.92 (s, br, 1H), 5.52 (s, 1H), 4.52 (d, *J* = 5.8 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.1, 137.4, 137.1, 128.9, 127.8, 127.7, 127.0, 126.5, 124.9, 57.1, 44.1.

FT-IR (film): 3301, 2341, 1649, 1539, 1425, 1240, 1017, 751, 738 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{13}H_{13}ClNOS]^+$: 266.0401, found: 266.0399.



***N*-Benzyl-2-chloro-2-(11-oxo-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl)acetamide (17^{Cl})**. The title compound was synthesized from isoxepac and *N*-benzylhydroxylamine on a 5.0-mmol scale according to a procedure in the literature.[32] It was purified by flash column chromatography on silica (30→35% EtOAc/hexanes). White solid.

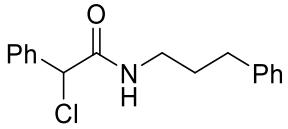
Yield: 979 mg, 50%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, *J* = 2.5 Hz, 1H), 7.88 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.48 (td, *J* = 7.6, 1.3 Hz, 1H), 7.40 – 7.34 (m, 3H), 7.34 – 7.27 (m, 3H), 7.14 (t, *J* = 6.0 Hz, 1H), 7.07 (d, *J* = 8.6 Hz, 1H), 5.45 (s, 1H), 5.20 (s, 2H), 4.53 (d, *J* = 5.7 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 190.4, 167.1, 161.7, 140.4, 137.3, 135.2, 134.6, 133.0, 131.7, 131.0, 129.52, 129.45, 128.9, 127.94, 127.85, 127.84, 125.1, 121.8, 73.6, 60.9, 44.2.

FT-IR (film): 3313, 3061, 1653, 1606, 1534, 1488, 1415, 1300, 1242, 1012, 753, 701, 635 cm^{-1}.

HRMS (ESI^+-MS) *m/z* $[M+H]^+$ calcd for $[C_{23}H_{19}ClNO_3]^+$: 392.1048, found: 392.1049.



2-Chloro-2-phenyl-*N*-(3-phenylpropyl)acetamide (18^{Cl}). The title compound was synthesized from 3-phenylpropan-1-amine according to **GP–1**. It was purified by recrystallization from hot EtOAc/hexanes. White solid.

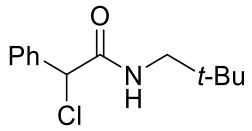
Yield: 2.39 g, 83%.

^1H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.39 (m, 2H), 7.39 – 7.34 (m, 3H), 7.30 (td, *J* = 7.2, 1.4 Hz, 2H), 7.24 – 7.14 (m, 3H), 6.72 (s, br, 1H), 5.35 (s, 1H), 3.36 (q, *J* = 7.0 Hz, 2H), 2.67 (t, *J* = 7.6 Hz, 2H), 1.91 (p, *J* = 7.3 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.3, 141.1, 137.2, 129.1, 128.9, 128.6, 128.4, 127.7, 126.2, 61.9, 39.7, 33.2, 30.9.

FT-IR (film): 3285, 3063, 2935, 2859, 1659, 1539, 1495, 1453, 1213, 856, 700 cm^{-1}.

HRMS (ESI^+-MS) *m/z* $[M+H]^+$ calcd for $[C_{17}H_{19}ClNO]^+$: 288.1150, found: 288.1157.



2-Chloro-*N*-neopentyl-2-phenylacetamide (19^{Cl}). The title compound was synthesized from neopentylamine according to **GP–1**. It was purified by recrystallization from hot EtOAc/hexanes. White solid.

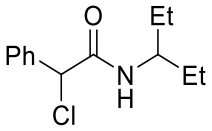
Yield: 2.06 g, 86%.

^1H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.43 (m, 2H), 7.41 – 7.30 (m, 3H), 6.77 (s, br, 1H), 5.41 (s, 1H), 3.21 – 3.07 (m, 2H), 0.93 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.4, 137.2, 129.1, 128.9, 127.7, 62.3, 51.1, 32.1, 27.2.

FT-IR (film): 3302, 2959, 1661, 1556, 1364, 1244, 1209, 1070, 703 cm^{-1}.

HRMS (ESI^+-MS) *m/z* $[M+H]^+$ calcd for $[C_{13}H_{19}ClNO]^+$: 240.1150, found: 240.1155.



2-Chloro-*N*-(pentan-3-yl)-2-phenylacetamide (20^{Cl}). The title compound was synthesized from 3-aminopentane according to **GP–1**. It was purified by recrystallization from hot EtOAc/hexanes. White solid.

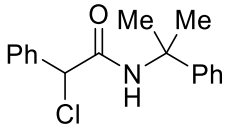
Yield: 1.92 g, 80%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 – 7.41 (m, 2H), 7.41 – 7.30 (m, 3H), 6.41 (s, br, 1H), 5.39 (s, 1H), 3.88 – 3.72 (m, 1H), 1.70 – 1.53 (m, 2H), 1.52 – 1.37 (m, 2H), 0.91 (dt, *J* = 17.2, 7.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.0, 137.4, 129.0, 128.9, 127.7, 62.2, 52.8, 27.3 (d, *J* = 8.4 Hz), 10.2 (d, *J* = 8.8 Hz).

FT-IR (film): 3277, 3079, 2964, 1650, 1552, 1455, 1343, 1213, 950, 691 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{13}H_{19}ClNO]^+$: 240.1150, found: 240.1155.



2-Chloro-2-phenyl-*N*-(2-phenylpropan-2-yl)acetamide (21^{Cl}). The title compound was synthesized from 2-phenylpropan-2-amine according to **GP–1**. It was purified by recrystallization from hot EtOAc/hexanes. White solid.

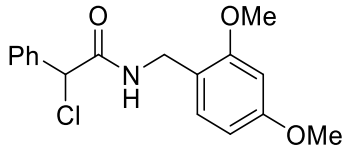
Yield: 2.14 g, 74%.

^{1}H NMR (400 MHz, $CDCl_3$) 7.46 – 7.41 (m, 2H), 7.41 – 7.35 (m, 5H), 7.35 – 7.30 (m, 2H), 7.26 – 7.21 (m, 1H), 6.98 (s, br, 1H), 5.29 (s, 1H), 1.75 (d, *J* = 1.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.2, 146.2, 137.2, 129.0, 128.9, 128.5, 127.7, 127.0, 124.6, 62.1, 56.5, 28.8, 28.5.

FT-IR (film): 3285. 3063, 2978, 1663, 1547, 1449, 1361, 1256, 1212, 760, 684 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{17}H_{19}ClNO]^+$: 288.1150, found: 288.1156.



2-Chloro-*N*-(2,4-dimethoxybenzyl)-2-phenylacetamide (22^{Cl}). The title compound was synthesized from (2,4-dimethoxyphenyl)methanamine according to **GP–1**. It was purified by recrystallization from hot EtOAc/hexanes. White solid.

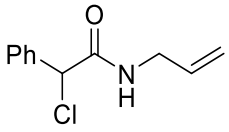
Yield: 2.46 g, 77%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.38 (m, 2H), 7.37 – 7.31 (m, 3H), 7.21 (s, br, 1H), 7.17 (d, *J* = 8.2 Hz, 1H), 6.48 (d, *J* = 2.4 Hz, 1H), 6.44 (dd, *J* = 8.2, 2.4 Hz, 1H), 5.35 (s, 1H), 4.43 (t, *J* = 6.0 Hz, 2H), 3.82 (s, 3H), 3.81 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.8, 160.8, 158.7, 137.4, 130.6, 129.0, 128.8, 127.9, 118.0, 104.0, 98.7, 61.9, 55.5, 55.4, 40.0.

FT-IR (film): 3295, 2958, 2836, 1651, 1614, 1589, 1506, 1435, 1290, 1267, 1209, 1129, 1036, 935, 703 cm^{-1}.

HRMS (ESI+-MS) *m/z* $[M+Na]^+$ calcd for $[C_{17}H_{18}ClNNaO_3]^+$: 342.0868, found: 342.0876.



***N*-Allyl-2-chloro-2-phenylacetamide (23^{Cl}).** The title compound was synthesized from allylamine according to **GP–1**. It was purified by flash column chromatography on silica (20→30% EtOAc in hexanes). White solid.

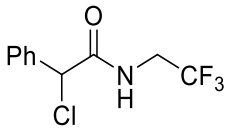
Yield: 1.60 g, 76%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.42 (m, 2H), 7.42 – 7.31 (m, 3H), 6.79 (s, br, 1H), 5.87 (ddt, *J* = 17.1, 10.2, 5.6 Hz, 1H), 5.40 (s, 1H), 5.29 – 5.15 (m, 2H), 4.01 – 3.89 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.3, 137.0, 133.3, 129.1, 128.9, 127.8, 117.0, 61.8, 42.4.

FT-IR (film): 3283, 3067, 1661, 1540, 1420, 1244, 1211, 989, 922, 726, 707 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{11}H_{13}ClNO]^+$: 210.0681, found: 210.0683.



2-Chloro-2-phenyl-*N*-(2,2,2-trifluoroethyl)acetamide (24^{Cl}). The title compound was synthesized from 2,2,2-trifluoroethylamine according to **GP–1**. It was purified by flash column chromatography on silica (20→30% EtOAc in hexanes). White solid.

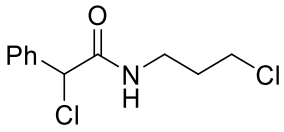
Yield: 1.94 g, 77%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.35 (m, 5H), 7.01 (s, br, 1H), 5.44 (s, 1H), 4.20 – 3.81 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9, 136.3, 129.4, 129.1, 127.7, 123.8 (d, J = 278.1 Hz), 61.5, 41.2 (q, J = 35.0 Hz).

FT-IR (film): 3302, 3069, 2967, 1681, 1538, 1398, 1269, 1178, 993, 834, 727, 697 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{10}H_{10}ClF_3NO]^+$: 252.0398, found: 252.0396.



2-Chloro-*N*-(3-chloropropyl)-2-phenylacetamide (25^{Cl}). The title compound was synthesized according to the following procedure: 2-Chloro-2-phenylacetyl chloride was added to a solution of 3-chloropropan-1-amine hydrochloride (1.43 g, 11 mmol) and Et_3N (3.5 mL, 25 mmol) in CH_2Cl_2 (60 mL). The mixture was stirred for 12 h, and then it was quenched by the addition of water. The organic layer was washed with water (50 mL), 1 N HCl (50 mL), and brine (50 mL), and then it was dried over Na_2SO_4, filtered, and concentrated. The product was purified by flash column chromatography on silica (20→30% EtOAc in hexanes). White solid.

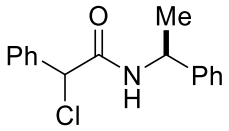
Yield: 2.39 g, 83%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.41 (m, 2H), 7.40 – 7.33 (m, 3H), 6.91 (s, br, 1H), 5.36 (s, 1H), 3.57 (t, J = 6.3 Hz, 2H), 3.49 (q, J = 6.5 Hz, 2H), 2.04 (p, J = 6.5 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.8, 137.0, 129.2, 129.0, 127.7, 61.8, 42.4, 37.7, 31.7.

FT-IR (film): 3291, 3068, 2956, 1659, 1539, 1454, 1291, 1212, 1076, 856, 727 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{11}H_{14}Cl_2NO]^+$: 246.0447, found: 246.0448.



2-Chloro-2-phenyl-*N*-((*S*)-1-phenylethyl)acetamide (26^{Cl}). The title compound was synthesized from (*S*)-1-phenylethan-1-amine according to **GP–1**. It was purified by flash column chromatography on silica (20→25% EtOAc in hexanes), isolated as a 1:1 mixture of diastereomers. White solid.

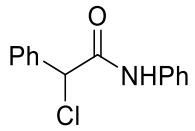
Yield: 2.06 g, 73%.

^{1}H NMR (400 MHz, $CDCl_3$): (1:1 mixture of diastereomers) δ 7.47 – 7.42 (m, 1H), 7.42 – 7.32 (m, 7H), 7.32 – 7.27 (m, 2H), 6.96 (s, br, 1H), 5.38 (d, 1H), 5.21 – 5.08 (m, 1H), 1.56 (t, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (mixture of diastereomers) 166.4, 142.4 (2), 137.1 (2), 129.1 (2), 128.9 (2), 128.8 (2), 127.8 (2), 127.7 (2), 126.1 (2), 61.8, 49.5 (2), 21.6 (2).

FT-IR (film): 3327, 2973, 1650, 1537, 1495, 1215, 1125, 1020, 737, 693 cm^{-1}.

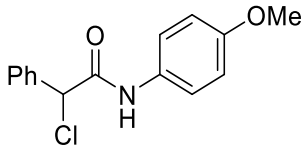
HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{16}H_{17}ClNO]^+$: 274.0994, found: 274.0998.



***2*-Chloro-*N*,2-diphenylacetamide (27^{Cl}).** The title compound was synthesized from aniline according to **GP–1**. It was purified by recrystallization from EtOAc/hexanes. White solid.

Yield: 2.17 g, 88%.

The spectroscopic data are consistent with those in the literature.[33]



2-Chloro-*N*-(4-methoxyphenyl)-2-phenylacetamide (28^{Cl}). The title compound was synthesized from *p*-anisidine according to **GP–1**. It was purified by flash column chromatography on silica (25→35% EtOAc in hexanes). White solid.

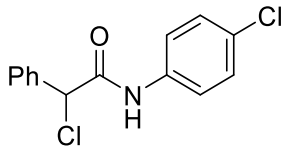
Yield: 2.29 g, 83%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, br, 1H), 7.54 – 7.43 (m, 4H), 7.42 – 7.34 (m, 3H), 6.95 – 6.83 (m, 2H), 5.48 (s, 1H), 3.79 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.2, 157.0, 136.9, 129.9, 129.3, 129.0, 127.8, 121.9, 114.3, 62.1, 55.5.

FT-IR (film): 3270, 2554, 1643, 1503, 1301, 1242, 1033, 970, 830, 716 cm^{-1}.

HRMS (ESI^+-MS) *m/z* $[M+H]^+$ calcd for $[C_{15}H_{15}ClNO_2]^+$: 274.0786, found: 274.0788.



2-Chloro-*N*-(4-chlorophenyl)-2-phenylacetamide (29^{Cl}). The title compound was synthesized from 4-chloroaniline according to **GP–1**. It was purified by recrystallization from hot EtOAc/hexanes. White solid.

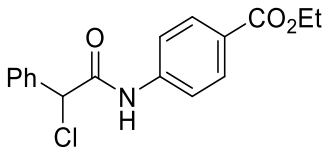
Yield: 2.48 g, 88%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (s, br, 1H), 7.57 – 7.45 (m, 4H), 7.45 – 7.37 (m, 3H), 7.34 – 7.29 (m, 2H), 5.50 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.5, 136.5, 135.4, 130.3, 129.4, 129.2, 129.1, 127.8, 121.3, 62.0.

FT-IR (film): 3720, 3232, 2552, 1659, 1486, 1168, 1089, 814, 721 cm^{-1}.

HRMS (ESI^+-MS) *m/z* $[M+H]^+$ calcd for $[C_{14}H_{12}Cl_2NO]^+$: 280.0291, found: 280.0293.



Ethyl 4-(2-chloro-2-phenylacetamido)benzoate (30^{Cl}). The title compound was synthesized from ethyl 4-aminobenzoate according to **GP–1**. It was purified by recrystallization from hot EtOAc/hexanes. White solid.

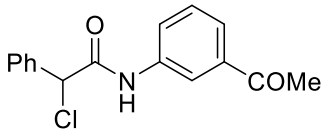
Yield: 2.39 g, 75%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (s, br, 1H), 8.03 (d, *J* = 8.7 Hz, 2H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.50 (dd, *J* = 7.8, 1.9 Hz, 2H), 7.45 – 7.35 (m, 3H), 5.51 (s, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.0, 165.6, 140.8, 136.3, 130.9, 129.5, 129.1, 127.8, 127.0, 119.2, 62.0, 61.0, 14.4.

FT-IR (film): 3309, 2981, 1713, 1697, 1601, 1538, 1409, 1364, 1260, 1170, 1109, 1020, 858, 770, 729 cm^{-1}.

HRMS (ESI^{+}-MS) *m/z* $[M+H]^{+}$ calcd for $[C_{17}H_{17}ClNO_3]^{+}$: 318.0892, found: 318.0898.



***N*-(3-Acetylphenyl)-2-chloro-2-phenylacetamide (31^{Cl}).** The title compound was synthesized from 1-(3-aminophenyl)ethan-1-one according to **GP–1**. It was purified by recrystallization from EtOAc/hexanes. White solid.

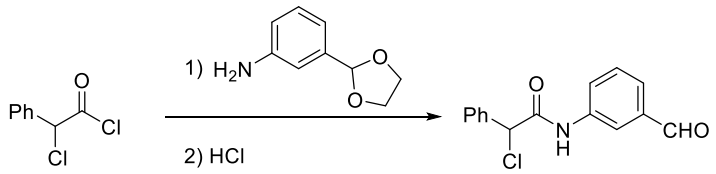
Yield: 2.07 g, 72%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (s, br, 1H), 8.11 – 8.05 (m, 1H), 7.93 – 7.85 (m, 1H), 7.79 – 7.64 (m, 1H), 7.54 – 7.48 (m, 2H), 7.48 – 7.32 (m, 4H), 5.52 (s, 1H), 2.60 (s, 3H).

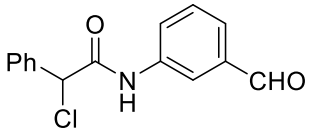
^{13}C NMR (101 MHz, $CDCl_3$): δ 197.7, 165.7, 137.9, 137.4, 136.4, 129.52, 129.45, 129.1, 127.8, 125.0, 124.5, 119.5, 62.0, 26.7.

FT-IR (film): 3314, 3064, 1681, 1593, 1556, 1487, 1455, 1434, 1356, 1272, 1171, 790, 737, 694 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{16}H_{15}ClNO_2]^+$: 288.0786, found: 288.0791.



2-Chloro-*N*-(3-formylphenyl)-2-phenylacetamide (32^{Cl}). The title compound was synthesized according to the following procedure: The secondary amide was synthesized from 3-(1,3-dioxolan-2-yl)aniline according to **GP–1**. The crude product was dissolved in 1:1 THF/3 N HCl and heated at 65 °C for 3 h. The mixture was then cooled to r.t., diluted with water, and extracted with Et_2O three times. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated to afford **32^{Cl}**, which was purified by flash column chromatography on silica (25% EtOAc/hexanes). White solid.



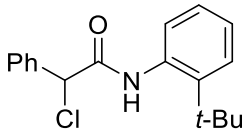
Yield: 1.66 g, 60%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (s, 1H), 8.54 (s, br, 1H), 8.06 (t, *J* = 1.9 Hz, 1H), 7.90 (ddd, *J* = 8.0, 2.3, 1.1 Hz, 1H), 7.69 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.57 – 7.47 (m, 3H), 7.45 – 7.35 (m, 3H), 5.53 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 191.7, 165.8, 137.8, 137.2, 136.3, 129.9, 129.5, 129.1, 127.8, 126.4, 125.8, 120.7, 62.0.

FT-IR (film): 3734, 3314, 2836, 1697, 1662, 1594, 1555, 1539, 1262, 729 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{15}H_{13}ClNO_2]^+$: 274.0630, found: 274.0630.



***N*-(2-(*t*-Butyl)phenyl)-2-chloro-2-phenylacetamide (33^{Cl}).** The title compound was synthesized from 2-(*t*-butyl)aniline according to **GP–1**. It was purified by recrystallization from EtOAc/hexanes. White solid.

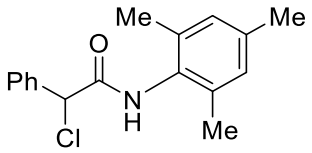
Yield: 2.32 g, 77%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (s, br, 1H), 7.70 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.59 – 7.51 (m, 2H), 7.48 – 7.36 (m, 4H), 7.26 – 7.20 (m, 1H), 7.20 – 7.13 (m, 1H), 5.57 (s, 1H), 1.40 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.3, 142.0, 136.7, 134.5, 129.3, 129.1, 127.8, 126.9, 126.7, 126.4, 126.3, 62.5, 34.5, 30.5.

FT-IR (film): 3234, 2967, 1651, 1515, 1335, 1167, 769, 749, 680 cm^{-1}.

HRMS (ESI^+-MS) *m/z* $[M+H]^+$ calcd for $[C_{18}H_{21}ClNO]^+$: 302.1307, found: 302.1315.



2-Chloro-*N*-mesityl-2-phenylacetamide (34^{Cl}). The title compound was synthesized from 2,4,6-trimethylaniline (6.0 mmol instead of 10 mmol) according to **GP–1**. It was purified by flash column chromatography on silica (15→25% EtOAc/hexanes). White solid.

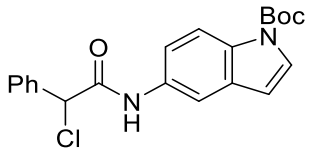
Yield: 1.43 g, 83%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (s, br, 1H), 7.63 – 7.54 (m, 2H), 7.48 – 7.35 (m, 3H), 6.88 (s, 2H), 5.55 (s, 1H), 2.26 (s, 3H), 2.12 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.9, 137.5, 136.8, 135.1, 130.1, 129.2, 129.1, 129.0, 127.7, 62.3, 20.9, 18.2.

FT-IR (film): 3235, 3030, 1660, 1537, 1332, 1224, 1033, 848, 698 cm^{-1}.

HRMS (ESI^+-MS) *m/z* $[M+H]^+$ calcd for $[C_{17}H_{19}ClNO]^+$: 288.1150, found: 288.1154.



***t*-Butyl 5-(2-chloro-2-phenylacetamido)-1*H*-indole-1-carboxylate (35^{Cl}).** The title compound was synthesized from *t*-butyl 5-amino-1*H*-indole-1-carboxylate according to **GP–1**. It was purified by flash column chromatography on silica (10→15% EtOAc in hexanes). White solid.

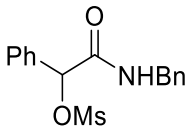
Yield: 2.72 g, 71%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (s, br, 1H), 8.10 (d, *J* = 8.9 Hz, 1H), 7.96 (d, *J* = 2.0 Hz, 1H), 7.59 (d, *J* = 3.7 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.44 – 7.35 (m, 3H), 7.30 (dd, *J* = 8.9, 2.2 Hz, 1H), 6.52 (d, *J* = 3.8 Hz, 1H), 5.53 (s, 1H), 1.67 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.3, 149.6, 136.9, 132.6, 132.0, 131.0, 129.3, 129.0, 127.9, 126.9, 117.2, 115.5, 112.6, 107.4, 83.9, 62.2, 28.2.

FT-IR (film): 3286, 2980, 1731, 1666, 1598, 1555, 1472, 1350, 1291, 1265, 1161, 1083, 1024, 855, 764, 724 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{21}H_{22}ClN_2O_3]^+$: 385.1314, found: 385.1319.



2-(Benzylamino)-2-oxo-1-phenylethyl methanesulfonate (1^{OMs}) (CAS 188025-29-8). The compound was synthesized according to a procedure in the literature on a 3.0-mmol scale.[34]

Yield: 813 mg, 85%.

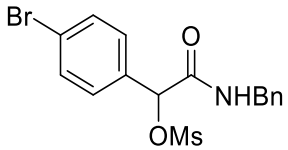
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.40 (m, 5H), 7.38 – 7.33 (m, 2H), 7.32 – 7.26 (m, 3H), 6.75 (s, br, 1H), 5.93 (s, 1H), 4.63 – 4.38 (m, 2H), 2.81 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.7, 137.3, 134.0, 130.1, 129.2, 128.9, 127.9, 127.8, 81.6, 43.7, 39.4.

FT-IR (film): 3303, 3033, 2934, 1681, 1667, 1537, 1455, 1354, 1170, 959, 840, 700 cm^{-1}.

HRMS (ESI+-MS) *m/z* $[M+Na]^+$ calcd for $[C_{16}H_{17}NNaO_4S]^+$: 342.0771, found: 342.0772.

The spectroscopic data are consistent with those in the literature.[32]



2-(Benzylamino)-1-(4-bromophenyl)-2-oxoethyl methanesulfonate (4^{OMs}). MsCl (0.51 mL, 6.6 mmol) was added to a solution of *N*-benzyl-2-(4-bromophenyl)-2-hydroxyacetamide (1.92 g, 6.0 mmol, obtained according to **GP–4**) and Et_3N (1.25 mL, 9.0

mmol) in CH_2Cl_2 at 0 °C. The solution was warmed to r.t. and stirred for 2 h. Next, the reaction was quenched by the addition of water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (25 mL × 2), and the combined organic layer was dried over Na_2SO_4, filtered, and concentrated to yield the crude product. Pure **4**^{OMs} was obtained by flash chromatography on silica (40→50% EtOAc in hexanes).

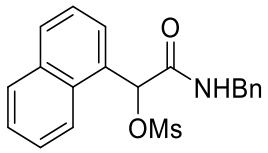
Yield: 2.00 g, 84%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.5 Hz, 2H), 7.41 – 7.30 (m, 5H), 7.28 – 7.22 (m, 2H), 6.77 (t, br, *J* = 5.9 Hz, 1H), 5.88 (s, 1H), 4.65 – 4.35 (m, 2H), 2.87 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.3, 137.1, 133.0, 132.4, 129.3, 128.9, 127.9, 127.8, 124.4, 80.5, 43.7, 39.5.

FT-IR (film): 3305, 1667, 1531, 1351, 1174, 1071, 957, 849 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+Na]^+$ calcd for $[C_{16}H_{16}BrNNaO_4S]^+$: 419.9876, found: 419.9884.



2-(Benzylamino)-1-(naphthalen-1-yl)-2-oxoethyl methanesulfonate (15^{OMs}**).** The synthetic procedure for the title compound follows that for **4**^{OMs}, from *N*-benzyl-2-hydroxy-2-(naphthalen-1-yl)acetamide (7.0-mmol, instead of 6.0-mmol, scale).

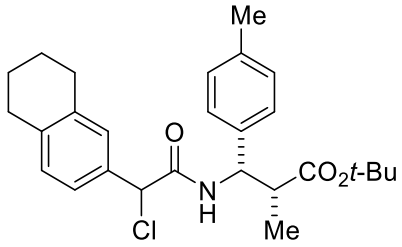
Yield: 1.70 g, 77%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 – 8.04 (m, 1H), 7.98 – 7.85 (m, 2H), 7.63 (dd, *J* = 7.1, 1.3 Hz, 1H), 7.58 – 7.44 (m, 3H), 7.38 – 7.28 (m, 3H), 7.26 – 7.21 (m, 2H), 6.78 (s, br, 1H), 6.49 (s, 1H), 4.53 (ddd, *J* = 73.2, 14.8, 6.0 Hz, 2H), 2.71 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.0, 137.3, 134.2, 131.2, 130.7, 129.6, 129.1, 128.85, 128.82, 127.9, 127.8, 127.4, 126.5, 125.2, 123.5, 81.0, 43.8, 39.4.

FT-IR (film): 3308, 3030, 2935, 1667, 1531, 1359, 1176, 952, 847, 776, 736 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+Na]^+$ calcd for $[C_{20}H_{19}NNaO_4S]^+$: 392.0927, found: 392.0927.



***t*-Butyl (2*R*,3*S*)-3-(2-chloro-2-(5,6,7,8-tetrahydronaphthalen-2-yl)acetamido)-2-methyl-3-(*p*-tolyl)propanoate (36).** The title compound was synthesized according to the following procedure:

2-Chloro-2-(5,6,7,8-tetrahydronaphthalen-2-yl)acetic acid was synthesized from 2-(5,6,7,8-tetrahydronaphthalen-2-yl)acetic acid[35] (4.0-mmol scale) according to **GP–3**. The crude product was used directly without purification.

tert-Butyl (2*R*,3*S*)-3-amino-2-methyl-3-(*p*-tolyl)propanoate (1.17 g, 4.7 mmol) was synthesized according to a report by Otake and Harada.[36]

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.00 g, 5.2 mmol) and 4-dimethylaminopyridine (60 mg, 0.50 mmol) were added into a solution that contained both the acid and the amine in CH_2Cl_2 (50 mL) at 0 °C. The reaction mixture was allowed to warm to r.t., and then it was stirred for 12 h. Next, the reaction was quenched by the addition of H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (25 mL × 2), and the combined organic layer was dried over Na_2SO_4, filtered and concentrated to afford crude product **36**. Purification by flash chromatography on silica (15%→18% EtOAc in hexanes) provided **36** as a 1:1 mixture of diastereomers. Yellow viscous oil.

Yield: 1.34 g, 73%.

^{1}H NMR (400 MHz, $CDCl_3$): (1:1 mixture of diastereomers) δ 8.36 – 8.08 (m, br, 1H), 7.23 – 7.11 (m, 6H), 7.11 – 6.98 (m, 2H), 5.36 (d, 1H), 5.17 – 5.01 (m, 1H), 2.98 – 2.87 (m, 1H), 2.83 – 2.62 (m, 4H), 2.32 (s, 2H), 1.89 – 1.71 (m, 4H), 1.35 (d, 9H), 1.25 (dd, 3H).

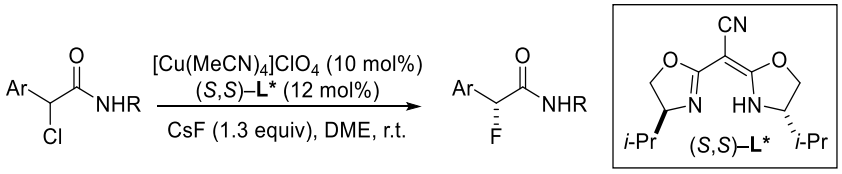
^{13}C NMR (101 MHz, $CDCl_3$): (mixture of diastereomers) δ 174.3 (2), 167.5, 138.3 (2), 137.7, 137.2 (2), 137.0 (2), 134.3 (2), 129.7 (2), 129.1 (2), 128.5 (2), 126.2 (2), 124.9 (2), 81.5, 62.1 (2), 55.3 (2), 45.5 (2), 29.3 (2), 29.2 (2), 27.9, 23.04, 23.01 (2), 21.1, 15.8 (2).

FT-IR (film): 3320, 2932, 2838, 1713, 1684, 1514, 1454, 1366, 1289, 1154, 1058, 910, 728, 645 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{27}H_{35}ClNO_3]^+$: 456.2300, found: 456.2300.

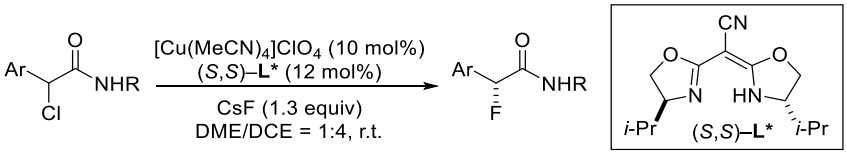
B. Enantioconvergent Fluorination of Alkyl Electrophiles

General Procedure 5 (GP–5: DME as the solvent)



In a glovebox, an oven-dried 7-mL glass vial equipped with a PTFE-coated stir bar was charged in turn with $[Cu(MeCN)_4]ClO_4$ (19.6 mg, 0.060 mmol), **L*** (19.0 mg, 0.072 mmol), CsF (119 mg, 0.78 mmol), and DME (1.5 mL). The mixture was stirred at r.t. for 20 min, and then the electrophile (0.60 mmol), dissolved (or suspended) in DME (1.0 mL), was transferred into the vial. DME (0.5 mL) was used to rinse the flask that had previously contained the electrophile, and the rinse was transferred into the 7-mL vial. The vial was capped with a PTFE cap and then taken out of the glovebox. The reaction mixture was stirred at r.t. for 12 h. Next, the reaction mixture was passed through a pad of silica gel. The reaction vial and cap were washed with Et_2O, and the washings were passed through the pad of silica gel. The silica gel was flushed with Et_2O, and the combined organic layer was concentrated. The residue was purified by flash column chromatography on silica to afford the product.

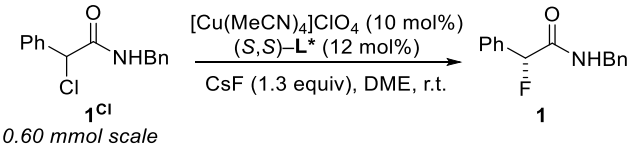
General Procedure 5–1 (GP–5–1: 1:4 DME/DCE as the solvent)



In a glovebox, an oven-dried 7-mL glass vial equipped with a PTFE-coated stir bar was charged in turn with $[Cu(MeCN)_4]ClO_4$ (19.6 mg, 0.060 mmol), **L*** (19.0 mg, 0.072 mmol), CsF (119 mg, 0.78 mmol), DME (0.6 mL), and DCE (0.9 mL). The mixture was stirred at r.t. for 20 min, and then the electrophile (0.60 mmol), dissolved (or suspended) in DCE (1.0 mL), was transferred into the vial. DCE (0.5 mL) was used to rinse the flask that had

previously contained the electrophile, and the rinse was transferred into the 7-mL vial. The vial was capped with a PTFE cap and then taken out of the glovebox. The reaction mixture was stirred at r.t. for 12 h. Next, the reaction mixture was passed through a pad of silica gel. The reaction vial and cap were washed with Et_2O, and the washings were passed through the pad of silica gel. The silica gel was flushed with Et_2O, and the combined organic layer was concentrated.

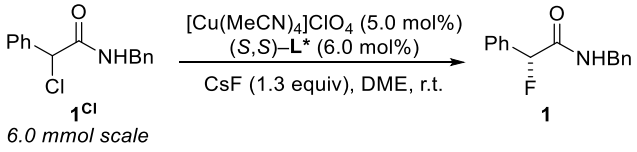
The residue was purified by flash column chromatography on silica to afford the product.



$\mathbf{1^{Cl}}$ *0.60 mmol scale* **1**

***N*-Benzyl-2-fluoro-2-phenylacetamide (1).** The title compound was synthesized from $\mathbf{1^{Cl}}$ according to **GP–5**. The compound was purified by flash column chromatography on silica (20→25% EtOAc in hexanes). White solid.

With (*S*,*S*)–**L***: 118 mg, 81% yield; 97% ee. With (*R*,*R*)–**L***: 120 mg, 82% yield; 97% ee.



$\mathbf{1^{Cl}}$ *6.0 mmol scale* **1**

Gram-scale synthesis of 1: In a glovebox, an oven-dried round-bottom flask equipped with a PTFE-coated stir bar was charged in turn with $[Cu(MeCN)_4]ClO_4$ (98.2 mg, 0.30 mmol), **L*** (94.8 mg, 0.36 mmol), CsF (1.19 g, 7.8 mmol), and DME (30 mL). The mixture was stirred at r.t. for 20 min, and then $\mathbf{1^{Cl}}$ (1.56 g, 6.0 mmol) was added in one portion. The flask was then closed with a septum, with the joint wrapped with electrical tape, and moved out of the glovebox.

The mixture was stirred at r.t. for 12 h, and then it was filtered by passing it through a pad of silica gel, flushing with Et_2O. The flask, septum, and silica gel were washed with Et_2O, and the combined solution was concentrated to afford the crude product, which was purified by flash column chromatography on silica (20→25% EtOAc/hexanes).

With (*S*,*S*)–**L***: 1.16 g, 79% yield; 94% ee. With (*R*,*R*)–**L***: 1.14 g, 78% yield; 95% ee.

The gram-scale reaction was also conducted with 2.0 mol% $[Cu(MeCN)_4]ClO_4$ (49.1 mg, 0.15 mmol), 2.5 mol% **L*** (47.4 mg, 0.18 mmol), and 7.0 mmol (1.82 g) $\mathbf{1}^{Cl}$: (*S,S*)–**L*** as ligand: 1.17 g, 68% yield; 90% ee. (*R,R*)–**L*** as ligand: 1.15 g, 67% yield; 91% ee.

Analysis and characterization of **1**:

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (15% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **1** obtained from (*S,S*)–**L***: 5.43 min (major), 7.02 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.43 (m, 2H), 7.44 – 7.38 (m, 3H), 7.38 – 7.27 (m, 5H), 6.80 (s, br, 1H), 5.83 (d, J = 48.3 Hz, 1H), 4.60 – 4.47 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.6 (d, J = 21.7 Hz), 137.6, 135.0 (d, J = 19.2 Hz), 129.6 (d, J = 2.5 Hz), 129.0, 128.9, 128.1, 128.0, 126.8, 126.7, 92.1 (d, J = 187.8 Hz).

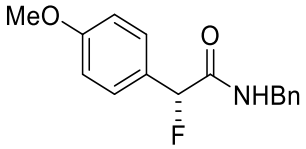
^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –177.8 (s).

FT-IR (film): 3290, 2356, 1656, 1549, 1453, 1041, 837 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{15}H_{15}FNO]^+$: 244.1133, found: 244.1134.

$[\alpha]^{23}_D$: –44 (*c* 1.0, $CHCl_3$); 97% ee, from (*S,S*)–**L***.

All data are consistent with those reported in the literature.[37]



***N*-Benzyl-2-fluoro-2-(4-methoxyphenyl)acetamide (2).** The title compound was synthesized from $\mathbf{2}^{Cl}$ according to **GP–5**. The compound was purified by flash column chromatography on silica (25→35% EtOAc in hexanes). Pale-yellow solid.

With (*S,S*)–**L***: 117 mg, 71% yield; 93% ee. With (*R,R*)–**L***: 120 mg, 73% yield; 92% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (25% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **2** obtained from (*S,S*)–**L***: 4.71 min (major), 6.73 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.34 (m, 4H), 7.34 – 7.29 (m, 3H), 6.95 – 6.86 (m, 2H), 6.80 (s, br, 1H), 5.78 (d, J = 48.7 Hz, 1H), 4.54 (d, J = 5.8 Hz, 2H), 3.82 (s, 3H).

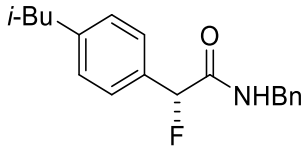
^{13}C NMR (101 MHz, $CDCl_3$): δ 168.7 (d, *J* = 22.6 Hz), 160.6 (d, *J* = 2.7 Hz), 137.5, 128.9, 128.6 (d, *J* = 5.7 Hz), 127.9, 127.8, 127.0 (d, *J* = 19.7 Hz), 114.2, 91.8 (d, *J* = 186.5 Hz), 55.4, 43.2.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –172.0 (s).

FT-IR (film): 3281, 2934, 2337, 1651, 1537, 1236, 1032, 822, 695 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* [M+Na]$^+$ calcd for $[C_{16}H_{16}FNNaO_2]^+$: 296.1058, found: 296.1062.

$[\alpha]^{23}_D$: –66 (*c* 1.0, $CHCl_3$); 93% ee, from (*S,S*)–**L***.



***N*-Benzyl-2-fluoro-2-(4-isobutylphenyl)acetamide** (**3**). The title compound was synthesized from **3^{Cl}** according to **GP–5**. The compound was purified by flash column chromatography on silica (15→20% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 150 mg, 85% yield; 97% ee. With (*R,R*)–**L***: 152 mg, 85% yield; 98% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (15% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **3** obtained from (*S,S*)–**L***: 7.55 min (major), 9.78 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.36 (m, 4H), 7.35 – 7.30 (m, 3H), 7.21 (d, *J* = 7.8 Hz, 2H), 6.83 (s, br, 1H), 5.83 (d, *J* = 48.5 Hz, 1H), 4.56 (dd, *J* = 5.9, 2.3 Hz, 2H), 2.51 (dd, *J* = 7.2, 1.2 Hz, 2H), 1.89 (hept, *J* = 6.8 Hz, 1H), 0.93 (d, *J* = 6.6 Hz, 6H).

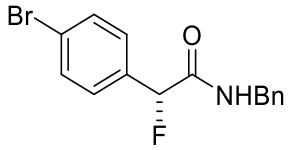
^{13}C NMR (101 MHz, $CDCl_3$): δ 168.6 (d, *J* = 22.2 Hz), 143.3 (d, *J* = 2.7 Hz), 137.5, 132.1 (d, *J* = 19.3 Hz), 129.5, 128.8, 127.9, 127.8, 126.6 (d, *J* = 6.2 Hz), 92.0 (d, *J* = 186.9 Hz), 45.2, 43.2, 30.2 (d, *J* = 1.3 Hz), 22.4 (d, *J* = 1.4 Hz).

^{19}F{^{1}H} NMR (376 MHz, CDCl3): δ –175.3 (s).

FT-IR (film): 3304, 2949, 1650, 1540, 1460, 1039, 704 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* [M+H]$^+$ calcd for $[C_{19}H_{23}FNO]^+$: 300.1759, found: 300.1749.

$[\alpha]^{23}_D$: –86 (*c* 1.0, $CHCl_3$); 97% ee, from (*S,S*)–**L***.



***N*-Benzyl-2-(4-bromophenyl)-2-fluoroacetamide** (**4**). The title compound was synthesized from **4**$^{\mathbf{Cl}}$ according to **GP–5–1**. The compound was purified by flash column chromatography on silica (15→25% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 164 mg, 85% yield; 98% ee. With (*R,R*)–**L***: 164 mg, 85% yield; 99% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (15% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **4** obtained from (*S,S*)–**L***: 5.89 min (major), 8.27 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 – 7.51 (m, 2H), 7.40 – 7.26 (m, 7H), 6.76 (s, br, 1H), 5.79 (d, J = 48.2 Hz, 1H), 4.57 – 4.46 (m, 2H).

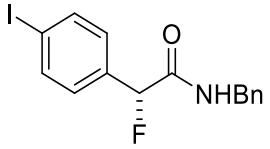
^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9 (d, J = 21.4 Hz), 137.3, 133.8 (d, J = 19.7 Hz), 131.9, 128.9, 128.1 (d, J = 6.9 Hz), 127.90, 127.88, 123.7 (d, J = 2.8 Hz), 91.1 (d, J = 189.2 Hz), 43.3.

^{19}F{^{1}H} NMR (376 MHz, CDCl3): δ –180.0 (s).

FT-IR (film): 3278, 1650, 1538, 1421, 1029, 825, 734 cm^{-1}.

HRMS (ESI^{+}-MS) *m/z* [M+H]$^{+}$ calcd for [$C_{15}H_{14}BrFNO$]$^{+}$: 322.0238, found: 322.0242.

[α]$^{23}_{D}$: –69 (*c* 1.0, $CHCl_3$); 98% ee, from (*S,S*)–**L***.



***N*-Benzyl-2-fluoro-2-(4-iodophenyl)acetamide** (**5**). The title compound was synthesized from **5**$^{\mathbf{Cl}}$ according to **GP–5–1**. The compound was purified by flash column chromatography on silica (15→25% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 148 mg, 67% yield; 98% ee. With (*R,R*)–**L***: 149 mg, 67% yield; 98% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (20% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **5** obtained from (*S,S*)–**L***: 5.48 min (major), 7.70 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 – 7.64 (m, 2H), 7.41 – 7.30 (m, 3H), 7.30 – 7.26 (m, 2H), 7.24 – 7.19 (m, 2H), 6.76 (s, br, 1H), 5.77 (d, J = 48.2 Hz, 1H), 4.59 – 4.44 (m, 2H).

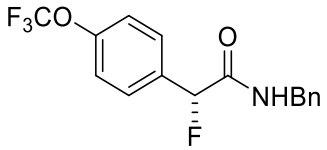
^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9 (d, J = 21.5 Hz), 137.8, 137.3, 134.4 (d, J = 19.6 Hz), 128.9, 128.2 (d, J = 6.9 Hz), 127.90, 127.88, 95.5 (d, J = 2.9 Hz), 91.2 (d, J = 189.2 Hz), 43.3.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –180.6 (s).

FT-IR (film): 3278, 2978, 1651, 1549, 1043, 818, 695 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{15}H_{14}FINO]^+$: 370.0099, found: 370.0092.

$[\alpha]^{23}_D$: –106 (*c* 1.0, $CHCl_3$); 98% ee, from (*S,S*)–**L***.



***N*-Benzyl-2-fluoro-2-(4-(trifluoromethoxy)phenyl)acetamide (6)**. The title compound was synthesized from **6^{Cl}** according to **GP–5–1**. The compound was purified by flash column chromatography on silica (15→25% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 159 mg, 81% yield; 97% ee. With (*R,R*)–**L***: 161 mg, 82% yield; 96% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (7% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **6** obtained from (*S,S*)–**L***: 3.71 min (major), 4.92 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, J = 8.3 Hz, 2H), 7.42 – 7.21 (m, 7H), 6.80 (s, br, 1H), 5.86 (d, J = 48.1 Hz, 1H), 4.62 – 4.45 (m, 2H).

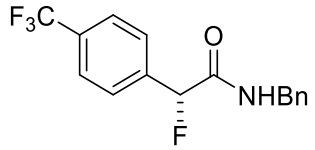
^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9 (d, J = 21.6 Hz), 149.9 (d, J = 2.1 Hz), 137.3, 133.4 (d, J = 19.7 Hz), 128.9, 128.1 (d, J = 6.9 Hz), 127.92, 127.88, 121.1, 120.4 (q, J = 257.9 Hz), 91.0 (d, J = 189.2 Hz), 43.3.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –57.8 (s, 3F), –179.7 (s, 1F).

FT-IR (film): 3311, 2350, 1652, 1291, 1170, 1041, 997, 842, 697 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{16}H_{14}F_4NO_2]^+$: 328.0956, found: 328.0960.

$[\alpha]^{23}_D$: –48 (*c* 1.0, $CHCl_3$); 97% ee, from (*S,S*)–**L***.



***N*-Benzyl-2-fluoro-2-(4-(trifluoromethyl)phenyl)acetamide** (**7**). The title compound was synthesized from **7^{Cl}** according to **GP–5–1**. The compound was purified by flash column chromatography on silica (15→25% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 142 mg, 76% yield; 89% ee. With (*R,R*)–**L***: 141 mg, 76% yield; 89% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (7% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **7** obtained from (*S,S*)–**L***: 3.91 min (major), 5.24 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.39 – 7.32 (m, 3H), 7.32 – 7.26 (m, 2H), 6.79 (s, br, 1H), 5.89 (d, *J* = 48.0 Hz, 1H), 4.61 – 4.39 (m, 2H).

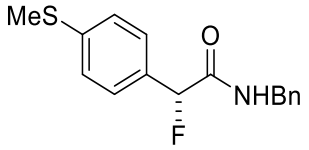
^{13}C NMR (101 MHz, $CDCl_3$): δ 167.6 (d, *J* = 21.1 Hz), 138.5 (d, *J* = 20.0 Hz), 137.2, 131.4 (d, *J* = 31.4 Hz), 128.9, 128.0, 127.9, 126.5 (d, *J* = 7.4 Hz), 125.6 (q, *J* = 3.8 Hz), 123.9 (d, *J* = 272.4 Hz), 90.9 (d, *J* = 190.1 Hz), 43.3.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –62.8 (s, 3F), –183.4 (s, 1F).

FT-IR (film): 3304, 1659, 1561, 1336, 1119, 837, 737 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{16}H_{14}F_4NO]^+$: 312.1007, found: 312.1000.

$[\alpha]^{23}_D$: –38 (*c* 1.0, $CHCl_3$); 89% ee, from (*S,S*)–**L***.



***N*-Benzyl-2-fluoro-2-(4-(methylthio)phenyl)acetamide** (**8**). The title compound was synthesized from **8**$^{\mathbf{Cl}}$ according to **GP–5**. The compound was purified by flash column chromatography on silica (15→30% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 109 mg, 63% yield; 97% ee. With (*R,R*)–**L***: 112 mg, 65% yield; 97% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (20% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **8** obtained from (*S,S*)–**L***: 7.40 min (major), 10.73 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.34 (m, 4H), 7.34 – 7.23 (m, 5H), 6.83 (s, br, 1H), 5.81 (d, J = 48.4 Hz, 1H), 4.55 (d, J = 5.8 Hz, 2H), 2.51 (s, 3H).

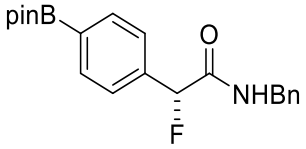
^{13}C NMR (101 MHz, $CDCl_3$): δ 168.4 (d, J = 22.1 Hz), 140.6 (d, J = 2.8 Hz), 137.5, 131.4 (d, J = 19.4 Hz), 128.9, 127.9, 127.8, 127.2 (d, J = 6.3 Hz), 126.4, 91.6 (d, J = 187.7 Hz), 43.2, 15.5.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –176.5 (s).

FT-IR (film): 3277, 1648, 1537, 1042, 812, 695, 953 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+Na]^+$ calcd for $[C_{16}H_{16}FNNaOS]^+$ 312.0829, found: 312.0831.

$[\alpha]^{23}_D$: –81 (*c* 1.0, $CHCl_3$); 97% ee, from (*S,S*)–**L***.



***N*-Benzyl-2-fluoro-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide** (**9**). The title compound was synthesized from **9**$^{\mathbf{Cl}}$ according to **GP–5**, with 12 mL DME (0.05 M) and a reaction time of 36 h (Note: a cross-shaped stir bar is recommended for efficient stirring). The compound was purified by flash column chromatography on silica (15→25% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 125 mg, 56% yield; 92% ee. With (*R,R*)–**L***: 127 mg, 57% yield; 93% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (20% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **9** obtained from (*S,S*)–**L***: 4.45 min (major), 4.97 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 – 7.81 (m, 2H), 7.60 – 7.45 (m, 2H), 7.38 – 7.32 (m, 2H), 7.32 – 7.25 (m, 3H), 6.75 (s, br, 1H), 5.84 (d, J = 48.3 Hz, 1H), 4.51 (d, J = 5.9 Hz, 2H), 1.35 (s, 12H).

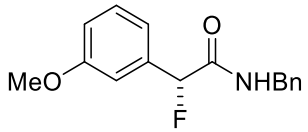
^{13}C NMR (101 MHz, $CDCl_3$): δ 168.2 (d, J = 21.6 Hz), 137.6, 137.5, 135.1, 128.9, 127.9, 127.8, 125.6, 125.5, 91.8 (d, J = 188.5 Hz), 84.3, 43.2, 24.9 (d, J = 2.2 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –180.2 (s).

FT-IR (film): 3323, 2979, 1667, 1614, 1537, 1359, 1272, 1144, 1089, 1021, 859, 732, 698, 657 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* [M+H]$^+$ calcd for $[C_{21}H_{26}BFNO_3]^+$: 320.1985, found: 320.1996.

$[\alpha]^{23}_D$: –52 (*c* 1.0, $CHCl_3$); 92% ee, from (*S,S*)–**L***.



***N*-Benzyl-2-fluoro-2-(3-methoxyphenyl)acetamide** (**10**). The title compound was synthesized from **10^{Cl}** according to **GP–5–1**. The compound was purified by flash column chromatography on silica (20→30% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 137 mg, 84% yield; 98% ee. With (*R,R*)–**L***: 138 mg, 84% yield; 98% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (20% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **10** obtained from (*S,S*)–**L***: 6.04 min (major), 6.90 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.27 (m, 6H), 7.06 (d, J = 7.5 Hz, 1H), 6.99 (s, br, 1H), 6.97 – 6.89 (m, 1H), 6.80 (s, br, 1H), 5.80 (d, J = 48.3 Hz, 1H), 4.52 (d, J = 5.8 Hz, 2H), 3.80 (s, 3H).

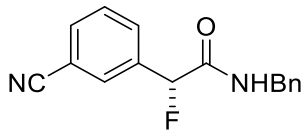
^{13}C NMR (101 MHz, $CDCl_3$): δ 168.3 (d, *J* = 21.9 Hz), 159.8, 137.5, 136.2 (d, *J* = 19.2 Hz), 129.8, 128.9, 127.9, 127.8, 118.8 (d, *J* = 6.8 Hz), 115.3 (d, *J* = 2.3 Hz), 111.9 (d, *J* = 6.9 Hz), 91.8 (d, *J* = 188.5 Hz), 55.3, 43.2.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –178.2 (s).

FT-IR (film): 3309, 2936, 1669, 1601, 1537, 1493, 1453, 1266, 1158, 1037 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{16}H_{17}FNO_2]^+$: 274.1238, found: 274.1245.

$[\alpha]^{23}_D$: –49 (*c* 1.0, $CHCl_3$); 98% ee, from (*S,S*)–**L***.



***N*-Benzyl-2-(3-cyanophenyl)-2-fluoroacetamide** (**11**). The title compound was synthesized from **11^{Cl}** according to **GP–5–1**. The compound was purified by flash column chromatography on silica (30→35% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 106 mg, 66% yield; 82% ee. With (*R,R*)–**L***: 104 mg, 65% yield; 84% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (25% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **11** obtained from (*S,S*)–**L***: 4.10 min (major), 4.89 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 – 7.77 (m, 1H), 7.78 – 7.73 (m, 1H), 7.71 – 7.64 (m, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.41 – 7.31 (m, 3H), 7.30 – 7.26 (m, 2H), 6.80 (s, br, 1H), 5.86 (d, *J* = 47.9 Hz, 1H), 4.65 – 4.34 (m, 2H).

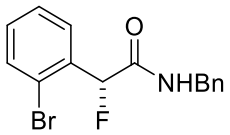
^{13}C NMR (101 MHz, $CDCl_3$): δ 167.3 (d, *J* = 21.0 Hz), 137.1, 136.3 (d, *J* = 19.9 Hz), 132.8 (d, *J* = 1.7 Hz), 130.6 (d, *J* = 7.0 Hz), 129.6, 129.5, 129.0, 128.0, 127.9, 118.2, 113.0, 90.4 (d, *J* = 191.3 Hz), 43.4.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –183.9 (s).

FT-IR (film): 3317, 3063, 2232, 1667, 1537, 1454, 1271, 1046, 791, 693 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{16}H_{14}FN_2O]^+$: 269.1085, found: 269.1089.

$[\alpha]^{23}_D$: +31 (*c* 1.0, $CHCl_3$); 82% ee, from (*S,S*)–**L***.



***N*-Benzyl-2-(2-bromophenyl)-2-fluoroacetamide (12)**. The title compound was synthesized from **12^{Cl}** according to **GP–5–1**. The compound was purified by flash column chromatography on silica (15→20% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 161 mg, 83% yield; 92% ee. With (*R,R*)–**L***: 161 mg, 83% yield; 93% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (20% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **12** obtained from (*S,S*)–**L***: 6.26 min (major), 6.94 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 – 7.60 (m, 1H), 7.41 – 7.31 (m, 7H), 7.31 – 7.24 (m, 1H), 6.87 (s, br, 1H), 6.24 (d, J = 47.4 Hz, 1H), 4.57 (dd, J = 6.0, 1.7 Hz, 2H).

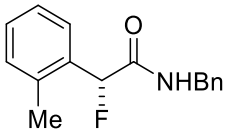
^{13}C NMR (101 MHz, $CDCl_3$): δ 167.7 (d, J = 22.2 Hz), 137.4, 134.4 (d, J = 18.5 Hz), 133.4 (d, J = 1.8 Hz), 131.3 (d, J = 3.1 Hz), 129.2 (d, J = 5.4 Hz), 128.9, 128.0, 127.88, 127.86, 124.6 (d, J = 4.6 Hz), 90.8 (d, J = 187.6 Hz), 43.4.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –175.0 (s).

FT-IR (film): 3318, 1668, 1539, 1285, 1197, 1028, 753, 706 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{15}H_{14}BrFNO]^+$: 322.0238, found: 322.0236.

$[\alpha]^{23}_D$: –86 (*c* 1.0, $CHCl_3$); 92% ee, from (*S,S*)–**L***.



***N*-Benzyl-2-fluoro-2-(*o*-tolyl)acetamide (13).** The title compound was synthesized from **13^{Cl}** according to **GP–5**. The compound was purified by flash column chromatography on silica (15→20% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 129 mg, 84% yield; 85% ee. With (*R,R*)–**L***: 129 mg, 84% yield; 84% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (15% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **13** obtained from (*S,S*)–**L***: 5.64 min (major), 6.42 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.27 (m, 7H), 7.25 – 7.19 (m, 2H), 6.88 (s, br, 1H), 6.05 (d, J = 48.0 Hz, 1H), 4.56 (d, J = 5.9 Hz, 2H), 2.47 (s, 3H).

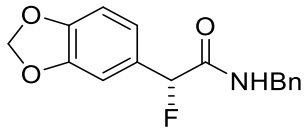
^{13}C NMR (101 MHz, $CDCl_3$): δ 168.8 (d, J = 22.2 Hz), 137.6, 137.5 (d, J = 4.0 Hz), 133.3 (d, J = 17.6 Hz), 131.0 (d, J = 1.6 Hz), 129.7 (d, J = 3.1 Hz), 128.9, 127.9, 127.8, 127.2 (d, J = 6.5 Hz), 126.2 (d, J = 1.6 Hz), 89.9 (d, J = 185.6 Hz), 43.2, 19.3.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –175.5 (s).

FT-IR (film): 3315, 3029, 2932, 1671, 1535, 1454, 1289, 1030, 749, 703 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{16}H_{17}FNO]^+$: 258.1289, found: 258.1276.

$[\alpha]^{23}_D$: –70 (*c* 1.0, $CHCl_3$); 85% ee, from (*S,S*)–**L***.



2-(Benzo[*d*][1,3]dioxol-5-yl)-*N*-benzyl-2-fluoroacetamide (14). The title compound was synthesized from **14^{Cl}** according to **GP–5**. The compound was purified by flash column chromatography on silica (25→30% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 135 mg, 78% yield; 97% ee. With (*R,R*)–**L***: 136 mg, 79% yield; 97% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (25% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **14** obtained from (*S,S*)–**L***: 4.50 min (major), 6.59 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.33 (m, 2H), 7.34 – 7.27 (m, 3H), 6.94 (dt, J = 8.0, 1.9 Hz, 1H), 6.90 (s, 1H), 6.82 (d, J = 8.0 Hz, 2H), 5.98 (s, 2H), 5.72 (d, J = 48.4 Hz, 1H), 4.53 (d, J = 5.9 Hz, 2H).

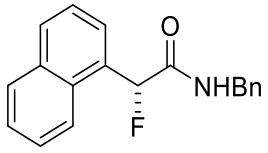
^{13}C NMR (101 MHz, $CDCl_3$): δ 168.5 (d, J = 22.6 Hz), 148.7 (d, J = 2.8 Hz), 148.0, 137.5, 128.9, 128.5 (d, J = 19.6 Hz), 127.9, 127.8, 121.4 (d, J = 7.0 Hz), 108.5 (d, J = 1.3 Hz), 107.3 (d, J = 5.7 Hz), 101.4, 91.9 (d, J = 187.8 Hz), 43.3.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –172.5 (s).

FT-IR (film): 3284, 2916, 1656, 1494, 1452, 1251, 1100, 1041, 933, 810, 754, 737 cm^{-1}.

HRMS (ESI^+-MS) *m/z* $[M+Na]^+$ calcd for $[C_{16}H_{14}FNNaO_3]^+$: 310.0850, found: 310.0849.

$[\alpha]^{23}_D$: –50 (*c* 1.0, $CHCl_3$); 97% ee, from (*S,S*)–**L***.



***N*-Benzyl-2-fluoro-2-(naphthalen-1-yl)acetamide (15)**. The title compound was synthesized from **15^{Cl}** according to **GP–5**. The compound was purified by flash column chromatography on silica (15→20% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 146 mg, 83% yield; 94% ee. With (*R,R*)–**L***: 141 mg, 80% yield; 93% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (25% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **15** obtained from (*S,S*)–**L***: 7.85 min (major), 8.98 min (minor).

^1H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 7.3 Hz, 1H), 7.94 – 7.85 (m, 2H), 7.60 – 7.51 (m, 3H), 7.50 – 7.44 (m, 1H), 7.41 – 7.29 (m, 5H), 6.95 (s, br, 1H), 6.50 (d, *J* = 48.0 Hz, 1H), 4.67 – 4.51 (m, 2H).

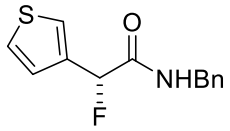
^{13}C NMR (101 MHz, $CDCl_3$): δ 168.6 (d, *J* = 21.8 Hz), 137.5, 133.9 (d, *J* = 1.3 Hz), 131.2 (d, *J* = 2.2 Hz), 130.61 (d, *J* = 3.0 Hz), 130.58 (d, *J* = 17.2 Hz), 128.9, 128.8, 128.0, 127.8, 127.0, 126.3 (d, *J* = 8.2 Hz), 126.2, 125.0 (d, *J* = 1.6 Hz), 123.7, 90.5 (d, *J* = 186.4 Hz), 43.4.

$^{19}F\{^1H\}$ NMR (376 MHz, CDCl3): δ –174.2 (s).

FT-IR (film): 3293, 1667, 1531, 1255, 1028, 782, 695 cm^{-1}.

HRMS (ESI^+-MS) *m/z* $[M+H]^+$ calcd for $[C_{19}H_{17}FNO]^+$: 294.1289, found: 294.1282.

$[\alpha]^{23}_D$: –83 (*c* 1.0, $CHCl_3$); 94% ee, from (*S,S*)–**L***.



***N*-Benzyl-2-fluoro-2-(thiophen-3-yl)acetamide (16).** The title compound was synthesized from **16^{Cl}** according to **GP–5**. The compound was purified by flash column chromatography on silica (18→25% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 122 mg, 82% yield; 97% ee. With (*R,R*)–**L***: 120 mg, 80% yield; 98% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (15% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **16** obtained from (*S,S*)–**L***: 5.89 min (major), 7.10 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 – 7.44 (m, 1H), 7.39 – 7.27 (m, 6H), 7.17 (d, *J* = 5.1 Hz, 1H), 6.77 (s, br, 1H), 5.92 (d, *J* = 49.0 Hz, 1H), 4.54 (d, *J* = 5.8 Hz, 2H).

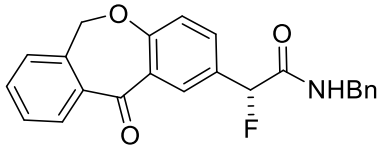
^{13}C NMR (101 MHz, $CDCl_3$): δ 168.0 (d, *J* = 21.1 Hz), 137.4, 135.5 (d, *J* = 21.1 Hz), 128.9, 127.9, 127.8, 126.8, 125.7 (d, *J* = 3.8 Hz), 124.5 (d, *J* = 7.9 Hz), 88.3 (d, *J* = 186.3 Hz), 43.2.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –174.2 (s).

FT-IR (film): 3307, 3093, 1659, 1543, 1454, 1173, 1080, 1024, 988, 792, 734, 699 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+Na]^+$ calcd for $[C_{13}H_{12}FNNaOS]^+$: 272.0516, found: 272.0508.

$[\alpha]^{23}_D$: –57 (*c* 1.0, $CHCl_3$); 97% ee, from (*S,S*)–**L***.



***N*-Benzyl-2-fluoro-2-(11-oxo-6,11-dihydrodibenzo[*b,e*]oxepin-2-yl)acetamide (17).** The title compound was synthesized from **17^{Cl}** according to **GP–5**. The compound was purified by flash column chromatography on silica (35→40% EtOAc in hexanes). Pale-yellow solid.

With (*S,S*)–**L***: 182 mg, 80% yield; 98% ee. With (*R,R*)–**L***: 180 mg, 80% yield; 98% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK AD column (35% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **17** obtained from (*S,S*)–**L***: 5.67 min (major), 7.00 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (t, *J* = 2.0 Hz, 1H), 7.89 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.63 – 7.53 (m, 2H), 7.49 (td, *J* = 7.6, 1.3 Hz, 1H), 7.41 – 7.35 (m, 3H), 7.35 – 7.28 (m, 3H), 7.10 (dd, *J* = 8.5, 1.0 Hz, 1H), 6.85 (s, br, 1H), 5.84 (d, *J* = 48.2 Hz, 1H), 5.21 (s, 2H), 4.65 – 4.47 (m, 2H).

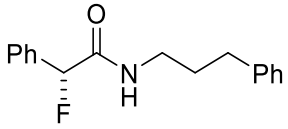
^{13}C NMR (101 MHz, $CDCl_3$): δ 190.5, 168.2 (d, *J* = 22.2 Hz), 162.1 (d, *J* = 2.3 Hz), 140.4, 137.4, 135.3, 133.7 (d, *J* = 4.8 Hz), 132.9, 131.0 (d, *J* = 6.9 Hz), 129.5, 129.4, 128.9, 128.7 (d, *J* = 19.9 Hz), 127.94, 127.91, 127.86, 125.2, 121.5, 91.2 (d, *J* = 188.5 Hz), 73.6, 43.3.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –175.2 (s).

FT-IR (film): 3320, 3062, 2926, 1659, 1609, 1536, 1490, 1301, 1265, 1141, 1120, 1011, 921, 835, 759, 734, 701, 640 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{23}H_{19}FNO_3]^+$: 376.1344, found: 376.1352.

$[\alpha]^{23}_D$: +29 (*c* 1.0, $CHCl_3$); 98% ee, from (*S,S*)–**L***.



1-Fluoro-2-phenyl-*N*-(3-phenylpropyl)acetamide (18). The title compound was synthesized from **18^{Cl}** according to **GP–5**. The compound was purified by flash column chromatography on silica (15→25% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 134 mg, 82% yield; 99% ee. With (*R,R*)–**L***: 134 mg, 82% yield; 98% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK OJ column (15% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **18** obtained from (*S,S*)–**L***: 7.11 min (minor), 8.28 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 – 7.42 (m, 2H), 7.42 – 7.36 (m, 3H), 7.32 – 7.26 (m, 2H), 7.24 – 7.13 (m, 3H), 6.48 (s, br, 1H), 5.75 (d, *J* = 48.5 Hz, 1H), 3.38 (q, *J* = 7.0 Hz, 2H), 2.67 (t, *J* = 7.9 Hz, 2H), 1.91 (tt, *J* = 7.6, 6.5 Hz, 2H).

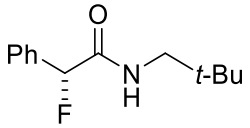
^{13}C NMR (101 MHz, $CDCl_3$): δ 168.5 (d, *J* = 21.6 Hz), 141.1, 134.9 (d, *J* = 19.1 Hz), 129.4 (d, *J* = 2.4 Hz), 128.7, 128.6, 128.4, 126.6 (d, *J* = 6.6 Hz), 126.1, 91.9 (d, *J* = 187.7 Hz), 38.8, 33.2, 31.1.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –177.3 (s).

FT-IR (film): 3294, 2934, 1462, 1538, 1453, 1267, 1197, 1089, 1012, 916, 731 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{17}H_{19}FNO]^+$: 272.1446, found: 272.1453.

$[\alpha]^{23}_D$: –23 (*c* 1.0, $CHCl_3$); 99% ee, from (*S,S*)–**L***.



2-Fluoro-*N*-neopentyl-2-phenylacetamide (**19**). The title compound was synthesized from **19^{Cl}** according to **GP–5**. The compound was purified by flash column chromatography on silica (12→20% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 112 mg, 84% yield; 96% ee. With (*R,R*)–**L***: 113 mg, 84% yield; 96% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IE column (7% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **19** obtained from (*S,S*)–**L***: 4.23 min (major), 4.84 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.44 (m, 2H), 7.44 – 7.34 (m, 3H), 6.54 (s, br, 1H), 5.80 (d, *J* = 48.5 Hz, 1H), 3.26 – 3.03 (m, 2H), 0.93 (s, 9H).

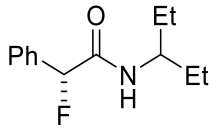
^{13}C NMR (101 MHz, $CDCl_3$): δ 168.5 (d, *J* = 21.3 Hz), 135.0 (d, *J* = 19.3 Hz), 129.4 (d, *J* = 2.6 Hz), 128.7, 126.6 (d, *J* = 6.5 Hz), 92.1 (d, *J* = 187.4 Hz), 50.1, 32.0, 27.2.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –177.1 (s).

FT-IR (film): 3316, 2960, 1667, 1537, 1475, 1397, 1211, 1015, 732, 696 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{13}H_{19}FNO]^+$: 224.1446, found: 224.1448.

$[\alpha]^{23}_D$: –15 (*c* 1.0, $CHCl_3$); 96% ee, from (*S,S*)–**L***.



2-Fluoro-*N*-(pentan-3-yl)-2-phenylacetamide (20). The title compound was synthesized from **20^{Cl}** according to **GP–5**, with [electrophile] = 0.4 M instead of 0.2 M (Note: use of a 4-mL vial is recommended for efficient stirring). The compound was purified by flash column chromatography on silica (10→15% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 109 mg, 81% yield; 98% ee. With (*R,R*)–**L***: 108 mg, 81% yield; 98% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK OJ column (3% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **20** obtained from (*S,S*)–**L***: 3.04 min (major), 3.90 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.46 (m, 2H), 7.45 – 7.38 (m, 3H), 6.22 (s, br, 1H), 5.80 (d, *J* = 48.2 Hz, 1H), 3.96 – 3.76 (m, 1H), 1.73 – 1.55 (m, 2H), 1.55 – 1.37 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H).

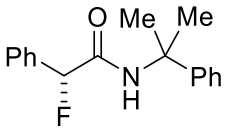
^{13}C NMR (101 MHz, $CDCl_3$): δ 168.2 (d, *J* = 21.4 Hz), 135.1 (d, *J* = 18.9 Hz), 129.4, 128.7, 126.7 (d, *J* = 6.3 Hz), 92.0 (d, *J* = 187.5 Hz), 51.9, 27.5 (d, *J* = 3.9 Hz), 10.2.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –176.1 (s).

FT-IR (film): 3306, 2961, 1658, 1548, 1453, 1293, 1015, 936, 856, 697 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{13}H_{19}FNO]^+$: 224.1446, found: 224.1450.

$[\alpha]^{23}_D$: –13 (*c* 1.0, $CHCl_3$); 98% ee, from (*S,S*)–**L***.



2-Fluoro-2-phenyl-*N*-(2-phenylpropan-2-yl)acetamide (21). The title compound was synthesized from **21^{Cl}** according to **GP–5**, with [electrophile] = 0.4 M instead of 0.2 M (Note: use of a 4-mL vial is recommended for efficient stirring). The compound was purified by flash column chromatography on silica (15→20% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 135 mg, 83% yield; 98% ee. With (*R,R*)–**L***: 137 mg, 84% yield; 97% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (20% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **21** obtained from (*S,S*)–**L***: 3.86 min (major), 6.23 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.45 (m, 2H), 7.44 – 7.38 (m, 5H), 7.38 – 7.32 (m, 2H), 7.31 – 7.23 (m, 1H), 6.78 (s, br, 1H), 5.72 (d, J = 48.8 Hz, 1H), 1.79 (d, J = 2.9 Hz, 6H).

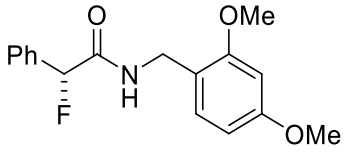
^{13}C NMR (101 MHz, $CDCl_3$): δ 167.3 (d, J = 20.3 Hz), 146.3, 135.0 (d, J = 19.2 Hz), 129.3 (d, J = 2.5 Hz), 128.7, 128.5, 127.0, 126.5 (d, J = 6.6 Hz), 124.7, 91.9 (d, J = 188.8 Hz), 56.1, 28.9 (d, J = 11.0 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –175.1 (s).

FT-IR (film): 3423, 3305, 3062, 2977, 1672, 1538, 1450, 1383, 1258, 1193, 1080, 1034, 919, 759, 685 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{17}H_{19}FNO]^+$: 272.1446, found: 272.1445.

$[\alpha]^{23}_D$: +74 (*c* 1.0, $CHCl_3$); 98% ee, from (*S,S*)–**L***.



***N*-(2,4-Dimethoxybenzyl)-2-fluoro-2-phenylacetamide (22)**. The title compound was synthesized from **22^{Cl}** according to **GP–5**. The compound was purified by flash column chromatography on silica (25→30% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 150 mg, 82% yield; 97% ee. With (*R,R*)–**L***: 144 mg, 79% yield; 98% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (20% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **22** obtained from (*S,S*)–**L***: 7.67 min (minor), 9.48 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 – 7.41 (m, 2H), 7.40 – 7.34 (m, 3H), 7.18 (d, J = 8.2 Hz, 1H), 6.93 (s, br, 1H), 6.48 (d, J = 2.4 Hz, 1H), 6.44 (dd, J = 8.2, 2.4 Hz, 1H), 5.75 (d, J = 48.5 Hz, 1H), 4.45 (d, J = 5.8 Hz, 2H), 3.83 (s, 3H), 3.81 (s, 3H).

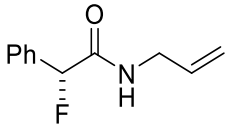
^{13}C NMR (101 MHz, $CDCl_3$): δ 168.0 (d, *J* = 21.6 Hz), 160.8, 158.7, 135.1 (d, *J* = 19.1 Hz), 130.7, 129.3 (d, *J* = 2.5 Hz), 128.6, 126.7 (d, *J* = 6.5 Hz), 118.1, 104.0, 98.7, 91.9 (d, *J* = 187.6 Hz), 55.44, 55.37, 38.8.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –177.1 (s).

FT-IR (film): 3318, 2935, 1681, 1614, 1589, 1508, 1454, 1291, 1260, 1208, 1157, 1131, 1036, 924, 697, 680 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+Na]^+$ calcd for $[C_{17}H_{18}FNNaO_3]^+$: 326.1163, found: 326.1172.

$[\alpha]^{23}_D$: –63 (*c* 1.0, $CHCl_3$); 97% ee, from (*S,S*)–**L***.



***N*-Allyl-2-fluoro-2-phenylacetamide (23)**. The title compound was synthesized from **23^{Cl}** according to **GP–5**. The compound was purified by flash column chromatography on silica (20→25% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 95.0 mg, 82% yield; 97% ee. With (*R,R*)–**L***: 95.2 mg, 82% yield; 97% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IF column (7% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **23** obtained from (*S,S*)–**L***: 5.09 min (major), 5.65 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 – 7.43 (m, 2H), 7.43 – 7.36 (m, 3H), 6.57 (s, br, 1H), 5.93 – 5.81 (m, 1H), 5.82 (d, *J* = 48.3 Hz, 1H), 5.31 – 5.10 (m, 2H), 4.04 – 3.90 (m, 2H).

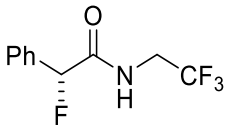
^{13}C NMR (101 MHz, $CDCl_3$): δ 168.4 (d, *J* = 21.6 Hz), 134.8 (d, *J* = 19.3 Hz), 133.4, 129.4 (d, *J* = 2.5 Hz), 128.7, 126.5 (d, *J* = 6.7 Hz), 117.1, 91.9 (d, *J* = 187.8 Hz), 41.5.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –178.0 (s).

FT-IR (film): 3292, 3069, 1659, 1538, 1454, 1427, 1257, 1026, 1000, 920, 733, 693 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+Na]^+$ calcd for $[C_{11}H_{12}FNNaO]^+$: 216.0796, found: 216.0796.

$[\alpha]^{23}_{D}$: +56 (*c* 1.0, $CHCl_3$); 97% ee, from (*S,S*)–**L***.



2-Fluoro-2-phenyl-*N*-(2,2,2-trifluoroethyl)acetamide (24). The title compound was synthesized from **24^{Cl}** according to **GP–5–1**. The compound was purified by flash column chromatography on silica (20→25% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 114 mg, 81% yield; 98% ee. With (*R,R*)–**L***: 115 mg, 81% yield; 98% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK AD column (3% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **24** obtained from (*S,S*)–**L***: 3.06 min (major), 4.15 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 – 7.38 (m, 5H), 6.83 (s, br, 1H), 5.88 (d, *J* = 48.4 Hz, 1H), 4.27 – 3.82 (m, 2H).

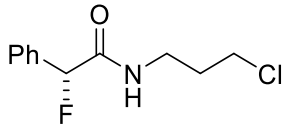
^{13}C NMR (101 MHz, $CDCl_3$): δ 169.0 (d, *J* = 22.8 Hz), 134.0 (d, *J* = 19.0 Hz), 129.8 (d, *J* = 2.7 Hz), 128.9, 126.7 (d, *J* = 6.3 Hz), 122.4 (q, *J* = 278.8 Hz), 91.8 (d, *J* = 187.9 Hz), 40.3 (q, *J* = 35.2 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –57.8 (s, 3F), –179.7 (s, 1F).

FT-IR (film): 3290, 1667, 1544, 1262, 1173, 1152, 980, 753, 680 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{10}H_{10}ClF_3NO]^+$: 236.0694, found: 236.0699.

$[\alpha]^{23}_{D}$: +29 (*c* 1.0, $CHCl_3$); 98% ee, from (*S,S*)–**L***.



***N*-(3-Chloropropyl)-2-fluoro-2-phenylacetamide (25)**. The title compound was synthesized from **25^{Cl}** according to **GP–5**. The compound was purified by flash column chromatography on silica (22→30% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 108 mg, 78% yield; 98% ee. With (*R,R*)–**L***: 113 mg, 82% yield; 98% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IE column (7% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **25** obtained from (*S,S*)–**L***: 7.06 min (minor), 8.04 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 – 7.42 (m, 2H), 7.42 – 7.36 (m, 3H), 6.51 (s, br, 1H), 5.77 (d, *J* = 48.3 Hz, 1H), 3.58 (td, *J* = 6.4, 1.6 Hz, 2H), 3.51 (q, *J* = 6.4 Hz, 2H), 2.04 (p, *J* = 6.5 Hz, 2H).

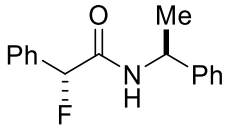
^{13}C NMR (101 MHz, $CDCl_3$): δ 168.8 (d, *J* = 21.6 Hz), 134.8 (d, *J* = 19.1 Hz), 129.5 (d, *J* = 2.6 Hz), 128.7, 126.5 (d, *J* = 6.6 Hz), 91.9 (d, *J* = 187.6 Hz), 42.3, 36.8, 31.9.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –177.9 (s).

FT-IR (film): 3300, 2970, 1662, 1546, 1454, 1378, 1289, 1197, 1077, 1009, 919, 858, 695 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{11}H_{14}ClFNO]^+$: 230.0743, found: 230.0748.

$[\alpha]^{23}_D$: –7.6 (*c* 1.0, $CHCl_3$); 98% ee, from (*S,S*)–**L***.



(*R*)-2-Fluoro-2-phenyl-*N*-((*S*)-1-phenylethyl)acetamide ((*R*)-26). The title compound was synthesized from **26^{Cl}** according to **GP–5**. The compound was purified by flash column chromatography on silica (15→25% EtOAc in hexanes). White solid.

The diastereomer above was synthesized with (*S,S*)–**L***. Diastereoselectivity was determined by quantitative ^{19}F NMR of the crude mixture before column chromatography. Only the major diastereomer was isolated and characterized.

Run 1: 97:3 dr. 113 mg isolated as a single diastereomer, 73% yield.

Run 2: 97:3 dr. 116 mg isolated as a single diastereomer, 75% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.35 (m, 5H), 7.35 – 7.25 (m, 5H), 6.73 (s, br, 1H), 5.79 (d, *J* = 48.6 Hz, 1H), 5.26 – 5.15 (m, 1H), 1.59 (d, *J* = 6.9 Hz, 3H).

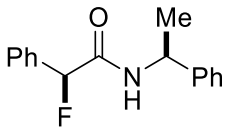
^{13}C NMR (101 MHz, $CDCl_3$): δ 167.5 (d, *J* = 21.6 Hz), 142.5, 134.8 (d, *J* = 19.1 Hz), 129.4 (d, *J* = 2.6 Hz), 128.8, 128.7, 127.6, 126.8 (d, *J* = 6.4 Hz), 126.1, 91.9 (d, *J* = 187.5 Hz), 48.5, 21.7.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –176.1 (s).

FT-IR (film): 3298, 3064, 2933, 1647, 1537, 1454, 1378, 1236, 1020, 758, 698 cm^{-1}.

HRMS (ESI^+-MS) *m/z* $[M+H]^+$ calcd for $[C_{16}H_{17}FNO]^+$: 258.1289, found: 258.1293.

$[\alpha]^{23}_D$: –141 (*c* 1.0, $CHCl_3$).



(*S*)-2-Fluoro-2-phenyl-*N*-((*S*)-1-phenylethyl)acetamide ((*S*)-26). The title compound was synthesized from **26^{Cl}** according to **GP–5**. The compound was purified by flash column chromatography on silica (15→25% EtOAc in hexanes). White solid.

The diastereomer above was synthesized with (*R,R*)–**L***. Diastereoselectivity was determined by quantitative ^{19}F NMR of the crude mixture before column chromatography. Only the major diastereomer was isolated and characterized.

Run 1: 3:97 dr. 125 mg isolated as a single diastereomer, 81% yield.

Run 2: 3:97 dr. 127 mg isolated as a single diastereomer, 82% yield.

^1H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.45 (m, 2H), 7.44 – 7.40 (m, 3H), 7.40 – 7.35 (m, 4H), 7.34 – 7.28 (m, 1H), 6.75 (s, br, 1H), 5.76 (d, *J* = 48.5 Hz, 1H), 5.24 – 5.14 (m, 1H), 1.54 (d, *J* = 6.9 Hz, 3H).

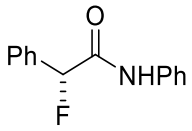
^{13}C NMR (101 MHz, $CDCl_3$): δ 167.6 (d, *J* = 21.8 Hz), 142.4, 134.9 (d, *J* = 19.1 Hz), 129.4 (d, *J* = 2.5 Hz), 128.8, 128.7, 127.7, 126.6 (d, *J* = 6.5 Hz), 126.3, 91.8 (d, *J* = 187.7 Hz), 48.7, 21.7.

$^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ –177.3 (s).

FT-IR (film): 3298, 2976, 1651, 1537, 1454, 1256, 1129, 1020, 758, 698 cm^{-1}.

HRMS (ESI^+-MS) *m/z* $[M+H]^+$ calcd for $[C_{16}H_{17}FNO]^+$: 258.1289, found: 258.1292.

$[\alpha]^{23}_D$: –47 (*c* 1.0, $CHCl_3$).



***2*-Fluoro-*N*,2-diphenylacetamide (27).** The title compound was synthesized from **27^{Cl}** according to **GP–5–1**. The compound was purified by flash column chromatography on silica (10→15% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 124 mg, 90% yield; 99% ee. With (*R,R*)–**L***: 126 mg, 91% yield; 99% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK OD column (15% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **27** obtained from (*S,S*)–**L***: 4.20 min (major), 7.03 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (s, br, 1H), 7.60 (d, *J* = 8.6 Hz, 2H), 7.55 – 7.48 (m, 2H), 7.45 – 7.40 (m, 3H), 7.39 – 7.31 (m, 2H), 7.22 – 7.11 (m, 1H), 5.90 (d, *J* = 48.5 Hz, 1H).

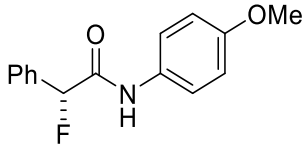
^{13}C NMR (101 MHz, $CDCl_3$): δ 166.4 (d, *J* = 20.5 Hz), 136.6, 134.5 (d, *J* = 19.1 Hz), 129.6 (d, *J* = 2.5 Hz), 129.2, 128.8, 126.7 (d, *J* = 6.6 Hz), 125.1, 120.0, 91.9 (d, *J* = 189.5 Hz).

^{1}9F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –175.4 (s).

FT-IR (film): 3312, 1672, 1598, 1529, 1442, 1015, 739 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{14}H_{13}FNO]^+$: 230.0976, found: 230.0976.

$[\alpha]^{23}_D$: +13 (*c* 1.0, $CHCl_3$); 99% ee, from (*S,S*)–**L***.



2-Fluoro-*N*-(4-methoxyphenyl)-2-phenylacetamide (**28**). The title compound was synthesized from 2-chloro-*N*-(4-methoxyphenyl)-2-phenylacetamide **28^{Cl}** according to **GP–5–1**. The compound was purified by flash column chromatography on silica (20→25% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 123 mg, 79% yield; 99% ee. With (*R,R*)–**L***: 128 mg, 82% yield; 99% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK OJ column (15% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **28** obtained from (*S,S*)–**L***: 7.82 min (minor), 9.94 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (s, br, 1H), 7.57 – 7.46 (m, 4H), 7.44 – 7.35 (m, 3H), 6.93 – 6.80 (m, 2H), 5.89 (d, J = 48.5 Hz, 1H), 3.80 (s, 3H).

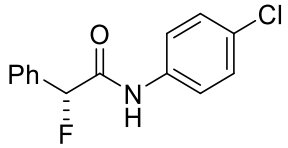
^{13}C NMR (101 MHz, $CDCl_3$): δ 166.2 (d, J = 20.7 Hz), 156.9, 134.6 (d, J = 19.1 Hz), 129.7, 129.6, 128.8, 126.7 (d, J = 6.6 Hz), 121.8, 114.3, 91.9 (d, J = 189.3 Hz), 55.5.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –175.5 (s).

FT-IR (film): 3302, 1661, 1523, 1243, 1018, 824, 693 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{15}H_{15}FNO_2]^+$: 260.1082, found: 260.1071.

$[\alpha]^{23}_D$: +42 (*c* 1.0, $CHCl_3$); 99% ee, from (*S,S*)–**L***.



***N*-(4-Chlorophenyl)-2-fluoro-2-phenylacetamide (29)**. The title compound was synthesized from **29^{Cl}** according to **GP–5–1**. The compound was purified by flash column chromatography on silica (12→15% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 134 mg, 85% yield; 96% ee. With (*R,R*)–**L***: 132 mg, 84% yield; 97% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (10% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **29** obtained from (*S,S*)–**L***: 5.18 min (minor), 5.70 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (s, br, 1H), 7.59 – 7.53 (m, 2H), 7.53 – 7.48 (m, 2H), 7.46 – 7.40 (m, 3H), 7.34 – 7.29 (m, 2H), 5.90 (d, J = 48.4 Hz, 1H).

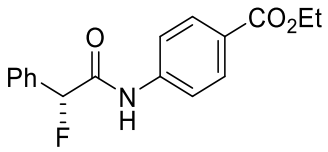
^{13}C NMR (101 MHz, $CDCl_3$): δ 166.5 (d, J = 20.8 Hz), 135.2, 134.2 (d, J = 19.1 Hz), 130.2, 129.7 (d, J = 2.5 Hz), 129.2, 128.9, 126.6 (d, J = 6.6 Hz), 121.3, 91.9 (d, J = 189.6 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –176.0 (s)

FT-IR (film): 3323, 1677, 1519, 1400, 1019, 818, 737 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{14}H_{12}ClFNO]^+$: 264.0586, found: 264.0586.

$[\alpha]^{23}_{D}$: +21 (*c* 1.0, $CHCl_3$); 96% ee, from (*S,S*)–**L***.



Ethyl 4-(2-fluoro-2-phenylacetamido)benzoate (30). The title compound was synthesized from **30^{Cl}** according to **GP–5–1**. The compound was purified by flash column chromatography on silica (20→25% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 134 mg, 74% yield; 98% ee. With (*R,R*)–**L***: 133 mg, 74% yield; 97% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (20% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **30** obtained from (*S,S*)–**L***: 3.95 min (minor), 5.06 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, br, *J* = 6.4 Hz, 1H), 8.04 (d, *J* = 8.7 Hz, 2H), 7.69 (d, *J* = 8.7 Hz, 2H), 7.51 (dt, *J* = 6.0, 1.9 Hz, 2H), 7.43 (dd, *J* = 5.0, 1.9 Hz, 3H), 5.91 (d, *J* = 48.4 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H).

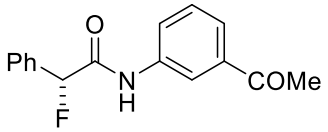
^{13}C NMR (101 MHz, $CDCl_3$): δ 166.7 (d, *J* = 20.9 Hz), 166.0, 140.6, 134.1 (d, *J* = 19.3 Hz), 130.9, 129.8 (d, *J* = 2.5 Hz), 128.9, 126.9, 126.6 (d, *J* = 6.7 Hz), 119.2, 91.9 (d, *J* = 189.9 Hz), 61.0, 14.4.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –176.1 (s).

FT-IR (film): 3323, 1703, 1599, 1529, 1408, 1278, 1106, 1019, 852, 697 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{17}H_{17}FNO_3]^+$: 302.1187, found: 302.1187.

$[\alpha]^{23}_{D}$: +71 (*c* 1.0, $CHCl_3$); 98% ee, from (*S,S*)–**L***.



***N*-(3-Acetylphenyl)-2-fluoro-2-phenylacetamide (31)**. The title compound was synthesized from **31^{Cl}** according to **GP–5–1**. The compound was purified by flash column chromatography on silica (15→20% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 107 mg, 66% yield; 99% ee. With (*R,R*)–**L***: 108 mg, 66% yield; 98% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IE column (20% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **31** obtained from (*S,S*)–**L***: 6.86 min (major), 8.37 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, br, 1H), 8.14 (t, *J* = 1.9 Hz, 1H), 7.98 – 7.88 (m, 1H), 7.78 – 7.69 (m, 1H), 7.55 – 7.49 (m, 2H), 7.48 – 7.40 (m, 4H), 5.92 (d, *J* = 48.4 Hz, 1H), 2.61 (s, 3H).

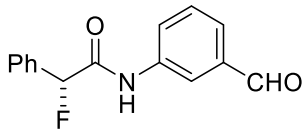
^{13}C NMR (101 MHz, $CDCl_3$): δ 197.6, 166.8 (d, *J* = 21.1 Hz), 138.0, 137.2, 134.2 (d, *J* = 19.1 Hz), 129.8 (d, *J* = 2.4 Hz), 129.5, 128.9, 126.6 (d, *J* = 6.6 Hz), 124.9, 124.5, 119.6, 91.9 (d, *J* = 189.7 Hz), 26.7.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –176.3 (s).

FT-IR (film): 3322, 3036, 1681, 1592, 1547, 1488, 1434, 1359, 1302, 1278, 1198, 1083, 1025, 958, 904, 793, 738, 698 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{16}H_{15}FNO_2]^+$: 272.1082, found: 272.1088.

$[\alpha]^{23}_D$: –14 (*c* 1.0, $CHCl_3$); 99% ee, from (*S,S*)–**L***.



2-Fluoro-*N*-(3-formylphenyl)-2-phenylacetamide (32). The title compound was synthesized from **32^{Cl}** according to **GP–5–1**. The compound was purified by flash column chromatography on silica (15→20% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 109 mg, 71% yield; 99% ee. With (*R,R*)–**L***: 110 mg, 71% yield; 99% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IE column (20% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **32** obtained from (*S,S*)–**L***: 5.03 min (major), 5.68 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.00 (d, *J* = 1.1 Hz, 1H), 8.32 (s, br, 1H), 8.12 (t, *J* = 1.9 Hz, 1H), 7.95 – 7.86 (m, 1H), 7.69 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.58 – 7.47 (m, 3H), 7.46 – 7.37 (m, 3H), 5.93 (d, *J* = 48.4 Hz, 1H).

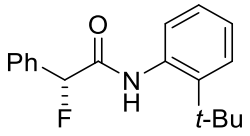
^{13}C NMR (101 MHz, $CDCl_3$): δ 191.7, 166.8 (d, *J* = 21.1 Hz), 137.4 (d, *J* = 32.3 Hz), 134.1 (d, *J* = 19.3 Hz), 129.9, 129.8 (d, *J* = 2.4 Hz), 128.9, 126.6, 126.5, 126.1, 125.7, 120.8, 91.8 (d, *J* = 189.7 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –176.5 (s).

FT-IR (film): 3314, 1692, 1594, 1544, 1486, 1445, 1306, 1026, 2694 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* [M+H]$^+$ calcd for $[C_{15}H_{13}FNO_2]^+$: 258.0925, found: 258.0925.

$[\alpha]^{23}_D$: +72 (*c* 1.0, $CHCl_3$); 99% ee, from (*S,S*)–**L***.



***N*-(2-(*t*-Butyl)phenyl)-2-fluoro-2-phenylacetamide (33)**. The title compound was synthesized from **33^{Cl}** according to **GP–5–1**. The compound was purified by flash column chromatography on silica (8→12% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 144 mg, 84% yield; 97% ee. With (*R,R*)–**L***: 142 mg, 83% yield; 97% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (10% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **33** obtained from (*S,S*)–**L***: 6.38 min (major), 7.58 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (s, br, 1H), 7.81 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.60 – 7.51 (m, 2H), 7.48 – 7.35 (m, 4H), 7.26 – 7.21 (m, 1H), 7.17 (td, *J* = 7.6, 1.6 Hz, 1H), 5.97 (d, *J* = 48.5 Hz, 1H), 1.44 (s, 9H).

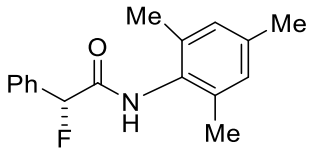
^{13}C NMR (101 MHz, $CDCl_3$): δ 166.2 (d, *J* = 20.5 Hz), 141.6, 134.5 (d, *J* = 19.3 Hz), 134.1, 129.5 (d, *J* = 2.3 Hz), 128.8, 126.9, 126.7, 126.5 (d, *J* = 6.9 Hz), 126.2, 126.0, 92.2 (d, *J* = 189.2 Hz), 34.5, 30.6.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –177.2 (s).

FT-IR (film): 3246, 2953, 1667, 1523, 1235, 1044, 754 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* [M+H]$^+$ calcd for $[C_{18}H_{21}FNO]^+$: 286.1602, found: 286.1605.

$[\alpha]^{23}_D$: +23 (*c* 1.0, $CHCl_3$); 97% ee, from (*S,S*)–**L***.



2-Fluoro-*N*-mesityl-2-phenylacetamide (34). The title compound was synthesized from **34^{Cl}** according to **GP–5–1**. The compound was purified by flash column chromatography on silica (8→12% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 141 mg, 87% yield; 98% ee. With (*R,R*)–**L***: 142 mg, 87% yield; 99% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK AD column (20% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **34** obtained from (*S,S*)–**L***: 4.51 min (major), 7.59 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (s, br, 1H), 7.61 – 7.55 (m, 2H), 7.48 – 7.38 (m, 3H), 6.90 (s, 2H), 5.97 (d, J = 48.5 Hz, 1H), 2.27 (s, 3H), 2.15 (s, 6H).

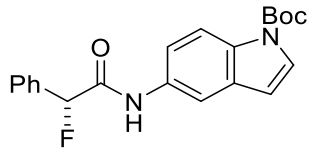
^{13}C NMR (101 MHz, $CDCl_3$): δ 166.9 (d, J = 21.3 Hz), 137.4, 135.1, 134.8 (d, J = 19.3 Hz), 129.48, 129.46 (d, J = 2.4 Hz), 129.1, 128.8, 126.4 (d, J = 6.7 Hz), 92.4 (d, J = 188.3 Hz), 20.9, 18.2.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –176.8 (s).

FT-IR (film): 3241, 2997, 1660, 1529, 1040, 844, 707 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* [M+H]$^+$ calcd for [$C_{17}H_{19}FNO$]$^+$: 272.1446, found: 272.1446.

[α]$^{23}_D$: +57 (*c* 1.0, $CHCl_3$); 98% ee, from (*S,S*)–**L***.



***t*-Butyl 5-(2-fluoro-2-phenylacetamido)-1*H*-indole-1-carboxylate (35).** The title compound was synthesized from **35^{Cl}** according to **GP–5–1**. The compound was purified by flash column chromatography on silica (12→15% EtOAc in hexanes). White solid.

With (*S,S*)–**L***: 195 mg, 88% yield; 99% ee. With (*R,R*)–**L***: 194 mg, 88% yield; 99% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (20% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of **35** obtained from (*S,S*)–**L***: 7.49 min (major), 8.59 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, br, 1H), 8.10 (d, *J* = 8.9 Hz, 1H), 8.00 (d, *J* = 2.2 Hz, 1H), 7.59 (d, *J* = 3.7 Hz, 1H), 7.57 – 7.51 (m, 2H), 7.46 – 7.39 (m, 3H), 7.34 (dd, *J* = 8.9, 2.2 Hz, 1H), 6.53 (d, *J* = 3.7 Hz, 1H), 5.93 (d, *J* = 48.5 Hz, 1H), 1.67 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.3 (d, *J* = 20.6 Hz), 149.6, 134.6 (d, *J* = 19.2 Hz), 132.5, 131.7, 131.0, 129.6 (d, *J* = 2.4 Hz), 128.8, 126.9, 126.7 (d, *J* = 6.6 Hz), 117.1, 115.5, 112.5, 107.3, 92.0 (d, *J* = 189.4 Hz), 83.9, 28.2.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –175.5 (s).

FT-IR (film): 3306, 2981, 1729, 1664, 1595, 1537, 1469, 1372, 1130, 1083, 1025, 848, 734 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{21}H_{22}FN_2O_3]^+$: 369.1609, found: 369.1616.

$[\alpha]^{23}_D$: +71 (*c* 1.0, $CHCl_3$); 99% ee, from (*S,S*)–**L***.

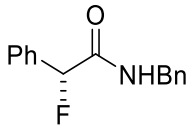
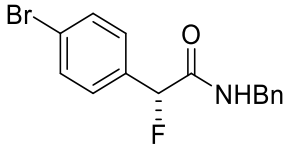


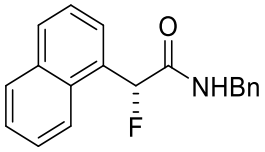
Figure 7A: *N*-Benzyl-2-fluoro-2-phenylacetamide (1). Compound **1** was also synthesized from $\mathbf{1^{OMs}}$ according to **GP–5**.

With (*S,S*)–**L***: 118 mg, 81% yield; 96% ee. With (*R,R*)–**L***: 117 mg, 80% yield; 96% ee.



***N*-Benzyl-2-(4-bromophenyl)-2-fluoroacetamide (4)**. Compound **4** was also synthesized from $\mathbf{4^{OMs}}$ according to **GP–5–1**.

With (*S,S*)–**L***: 160 mg, 83% yield; 98% ee. With (*R,R*)–**L***: 154 mg, 80% yield; 98% ee.



***N*-Benzyl-2-fluoro-2-(naphthalen-1-yl)acetamide (15)**. Compound **15** was also synthesized from **15^{OMs}** according to **GP–5**.

With (*S,S*)–**L***: 137 mg, 78% yield; 93% ee. With (*R,R*)–**L***: 141 mg, 80% yield; 92% ee.

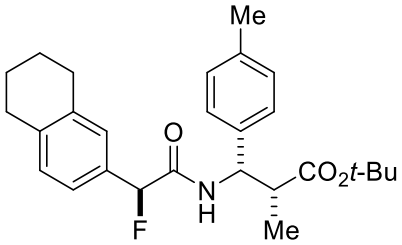


Figure 7B: *t*-Butyl (2*R*,3*S*)-3-((*S*)-2-fluoro-2-(5,6,7,8-tetrahydronaphthalen-2-yl)acetamido)-2-methyl-3-(p-tolyl)propanoate (37). The title compound was synthesized from **36** (0.30 mmol) according to **GP–5–1**, with [electrophile] = 0.4 M instead of 0.2 M (Note: use of a 4-mL vial is recommended for efficient stirring). The compound was purified by flash column chromatography on silica (20→30% Et_2O in hexanes). Colorless viscous oil.

The diastereomer shown above was synthesized with (*R,R*)–**L***. The diastereoselectivity was determined by quantitative ^{19}F NMR spectroscopy of the crude mixture before column chromatography. Only the major diastereomer was isolated and characterized.

Run 1: 97:3 dr. 100 mg isolated as a single diastereomer, 76% yield.

Run 2: 97:3 dr. 102 mg isolated as a single diastereomer, 77% yield.

^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (dd, *J* = 9.3, 3.9 Hz, 1H), 7.21 – 7.16 (m, 4H), 7.16 – 7.11 (m, 2H), 7.08 (d, *J* = 7.8 Hz, 1H), 5.70 (d, *J* = 48.5 Hz, 1H), 5.10 (ddd, *J* = 9.2, 5.6, 1.7 Hz, 1H), 2.89 (qd, *J* = 7.1, 5.5 Hz, 1H), 2.76 (t, *J* = 3.3 Hz, 4H), 2.32 (s, 3H), 1.86 – 1.72 (m, 4H), 1.33 (s, 9H), 1.19 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.1, 168.4 (d, J = 22.4 Hz), 138.6 (d, J = 2.7 Hz), 137.5, 137.14, 137.12, 132.1 (d, J = 19.2 Hz), 129.4, 129.2, 127.8, 127.7, 126.4, 123.8 (d, J = 6.0 Hz), 92.2 (d, J = 187.1 Hz), 81.5, 54.5, 45.6, 29.4, 29.3, 27.9, 23.0, 21.1, 15.8.

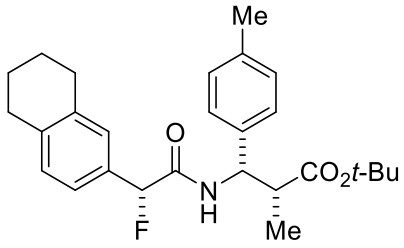
^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –175.4 (s).

FT-IR (film): 3339, 2930, 1693, 1514, 1383, 1366, 1150, 1022 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{27}H_{35}FNO_3]^+$: 440.2596, found: 440.2504.

$[\alpha]^{23}_D$: –40 (*c* 1.0, $CHCl_3$).

The ^{1}H NMR data (DMSO-*d6*) are consistent with the report of Otake and Harada.



***t*-Butyl (2*R*,3*S*)-3-((*R*)-2-fluoro-2-(5,6,7,8-tetrahydronaphthalen-2-yl)acetamido)-2-methyl-3-(*p*-tolyl)propanoate (38).** The title compound was synthesized from **36** (0.30 mmol) according to **GP–5–1**, with [electrophile] = 0.4 M instead of 0.2 M (Note: use of a 4-mL vial is recommended for efficient stirring). The compound was purified by flash column chromatography on silica (20→30% Et_2O in hexanes). Colorless viscous oil.

The diastereomer shown above was synthesized with (*S,S*)–**L***. The diastereoselectivity was determined by quantitative ^{19}F NMR spectroscopy of the crude mixture before column chromatography. Only the major diastereomer was isolated and characterized.

Run 1: 97:3 dr. 108 mg isolated as a single diastereomer, 82% yield.

Run 2: 97:3 dr. 104 mg isolated as a single diastereomer, 79% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 – 7.92 (m, 1H), 7.15 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 8.0 Hz, 3H), 7.03 (d, J = 9.2 Hz, 2H), 5.74 (d, J = 49.0 Hz, 1H), 5.14 (dd, J = 9.0, 5.7 Hz, 1H), 2.89 (td, J = 7.1, 5.7 Hz, 1H), 2.78 – 2.60 (m, 4H), 2.31 (s, 3H), 1.84 – 1.67 (m, 4H), 1.36 (s, 9H), 1.26 (d, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.2, 168.4 (d, J = 22.2 Hz), 138.7 (d, J = 2.9 Hz), 137.5, 137.2, 137.0, 132.0 (d, J = 19.1 Hz), 129.47, 129.45, 129.1, 127.9 (d, J = 5.6 Hz),

126.3, 124.1 (d, J = 5.7 Hz), 92.0 (d, J = 186.7 Hz), 81.5, 54.5, 45.5, 29.3, 29.2, 27.9, 23.0, 21.1, 15.7.

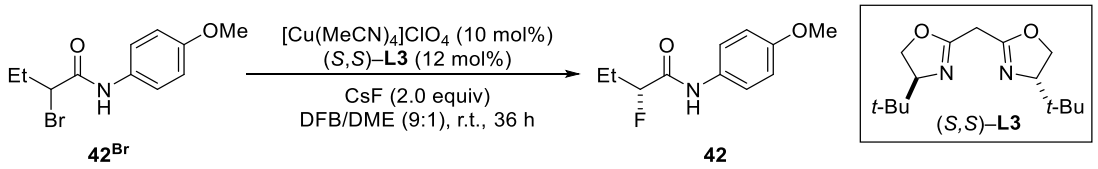
$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ –172.8 (s).

FT-IR (film): 3317, 2975, 2931, 1726, 1681, 1514, 1456, 1366, 1152, 1050, 816, 727 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{27}H_{35}FNO_3]^+$: 440.2596, found: 440.2589.

$[\alpha]^{23}_D$: –87 (*c* 1.0, $CHCl_3$).

Reactivity of an α-*alkyl*-α-haloamide (Figure 8A):



2-Fluoro-*N*-(4-methoxyphenyl)butanamide (42). In a glovebox, an oven-dried 20-mL glass vial equipped with a cross-shaped PTFE-coated stir bar was charged in turn with $[Cu(MeCN)_4]ClO_4$ (32.7 mg, 0.10 mmol), **L3** (32.0 mg, 0.12 mmol), CsF (304 mg, 2.0 mmol), and DME/1,2-DFB (7.5 mL, pre-mixed as a 1:9 solution). The mixture was stirred at r.t. for 20 min, and then a solution of the electrophile (272 mg, 1.0 mmol) in DME/1,2-DFB (2.0 mL) was transferred into the 20-mL vial. Additional DME/1,2-DFB (0.5 mL) was used to rinse the flask that previously contained the electrophile, and the rinse was transferred into the vial. The 20-mL vial was capped with a PTFE cap and then taken out of the glovebox. The reaction mixture was stirred at r.t. for 36 h. Next, the reaction mixture was passed through a pad of silica gel.

The reaction vial and cap were washed with Et_2O, and the washings were passed through the pad of silica gel. The silica gel was flushed with Et_2O, and the combined organic layer was concentrated. The residue was purified by flash column chromatography on silica (15%→20% EtOAc in hexanes). White solid.

With (*S,S*)–**L3**: 108 mg, 51% yield, 97% ee. With (*R,R*)–**L3**: 106 mg, 50% yield, 96% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (10% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention time for this compound obtained from (*S,S*)–**L3**: 4.49 min (minor), 5.28 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (s, br, 1H), 7.47 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 4.97 (ddd, *J* = 49.8, 7.0, 3.9 Hz, 1H), 3.80 (s, 3H), 2.23 – 1.79 (m, 2H), 1.07 (t, *J* = 7.4 Hz, 3H).

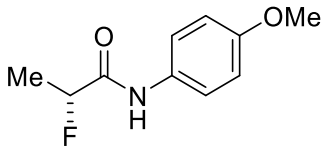
^{13}C NMR (101 MHz, $CDCl_3$): δ 167.8 (d, *J* = 18.2 Hz), 156.8, 129.8, 121.8, 114.3, 93.1 (d, *J* = 187.2 Hz), 55.5, 25.7 (d, *J* = 20.5 Hz), 8.6 (d, *J* = 3.8 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –190.1 (s).

FT-IR (film): 3321, 2961, 1661, 1542, 1518, 1029, 820, 681 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $[C_{11}H_{15}NO_2F]^+$: 212.1082, found: 212.1087.

$[\alpha]^{23}_D$: +108 (*c* 1.0, $CHCl_3$); 97% ee, from (*S,S*)–**L3**.



2-Fluoro-*N*-(4-methoxyphenyl)propanamide (43). The title compound was synthesized from 2-bromo-*N*-(4-methoxyphenyl)propanamide **43^{Br}** according to the procedure for synthesizing **42**. The compound was purified by flash column chromatography on silica (20% – 25% EtOAc in hexanes). White solid.

With (*S,S*)–**L3**: 93 mg, 47% yield, 95% ee. With (*R,R*)–**L3**: 89 mg, 46% yield, 96% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (10% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention time for **43** obtained from (*S,S*)–**L3**: 4.39 min (minor), 5.56 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (s, br, 1H), 7.47 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 5.11 (dq, *J* = 49.5, 6.8 Hz, 1H), 3.80 (s, 3H), 1.67 (dd, *J* = 24.9, 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.4 (d, *J* = 17.9 Hz), 156.8, 129.8, 121.8, 114.3, 89.0 (d, *J* = 184.4 Hz), 55.5, 18.5 (d, *J* = 21.4 Hz).

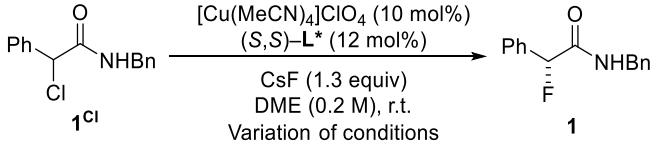
^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –180.2 (s).

FT-IR (film): 3329, 2951, 1662, 1541, 1411, 1248, 1174, 1093, 1033, 820, 684 cm^{-1}.

HRMS (ESI$^+$-MS) *m/z* $[M+H]^+$ calcd for $C_{10}H_{12}NO_2F$: 198.0925, found: 198.0926.

$[\alpha]^{23}_{D}$: +85.5 (*c* 1.0, $CHCl_3$); 95% ee, from (*S,S*)–**L3**.

C. Effect of Reaction Parameters



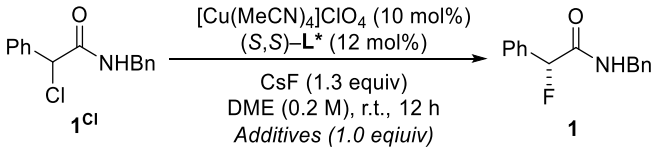
General Procedure 6 (GP–6)

In a glovebox, an oven-dried 4-mL vial that contained a PTFE-coated stir bar was charged with $[Cu(MeCN)_4]ClO_4$ (3.3 mg, 0.010 mmol), **L*** (3.2 mg, 0.012 mmol), and CsF (19.7 mg, 0.13 mmol). Next, DME (0.2 mL) was added, and the vial was capped with a PTFE-septum cap. The mixture was stirred at r.t. for 5 min, and then a solution of $\mathbf{1^{Cl}}$ (26.0 mg, 0.10 mmol) in DME (0.3 mL) was added. The vial was removed from the glovebox, and the reaction mixture was stirred at r.t. for 12 h. A solution of 4-fluorobiphenyl (17.2 mg, 0.10 mmol), an internal standard, in acetone (0.2 mL) was added. The mixture was then filtered through a plug of silica gel with the aid of Et_2O washings. The reaction flask and the plug of silica gel were washed with Et_2O, the combined organic solution was concentrated, and the yield was determined by ^{19}F NMR spectroscopy.

Pure product was obtained by preparative TLC (30% EtOAc/hexanes), which was analyzed by SFC for the ee.

The effects of reaction parameters are recorded in Table 1 and Table 2.

D. Investigation of Functional-Group Compatibility: Additive Studies



General Procedure 7 (GP–7)

In a glovebox, an oven-dried 4-mL vial that contained a PTFE-coated stir bar was charged with $[Cu(MeCN)_4]ClO_4$ (3.3 mg, 0.010 mmol), **L*** (3.2 mg, 0.012 mmol), and CsF (19.7 mg, 0.13 mmol). Next, DME (0.1 mL) was added, and the vial was capped with a

PTFE-septum cap. The mixture was stirred at r.t. for 5 min, and then a solution of $\mathbf{1}^{Cl}$ (26.0 mg, 0.10 mmol) in DME (0.2 mL) and a solution of the additive (0.10 mmol) and 4-fluorobiphenyl (17.2 mg, 0.10 mmol) in DME (0.2 mL) were added. The vial was removed from the glovebox, and the reaction mixture was stirred at r.t. for 12 h.

Next, an aliquot (~0.05 mL) was withdrawn, diluted with Et_2O, and filtered through a syringe filter. The resulting solution was subjected to GC analysis to quantify the recovery of the additive, using 4-fluorobiphenyl as the calibration standard.

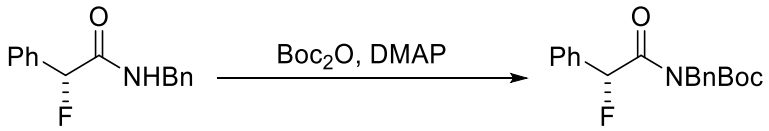
The mixture was then filtered through a plug of silica gel with the aid of Et_2O washings. The reaction flask and the plug of silica gel were washed with Et_2O, the combined organic solution was concentrated, and the yield was determined by ^{19}F NMR spectroscopy.

Pure product was obtained by preparative TLC (30% EtOAc/hexanes), which was analyzed by SFC for the ee.

The effects of additives are recorded in Figure 5.

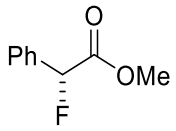
*E. Derivatization of the fluorinated product **1***

Each enantiomer of *N*-benzyl-2-fluoro-2-phenylacetamide (**1**) used in this section was 97% ee.



***tert*-Butyl (*R*)-benzyl(2-fluoro-2-phenylacetyl)carbamate.** DMAP (36 mg, 0.30 mmol) and Boc_2O (687 mg, 3.15 mmol) were added to a solution of (*R*)-**1** (730 mg, 3.0 mmol) in CH_2Cl_2 (6 mL) in an oven-dried 20-mL vial equipped with a cross-shaped stir bar. The mixture was stirred for 12 h, and then the reaction was quenched by the addition of water. The aqueous layer was extracted with CH_2Cl_2 (10 mL × 3), and the combined organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (6→8% EtOAc/hexanes) on silica to afford the title compound (907 mg, 88% yield).

The same procedure was applied to (*S*)-**1** (730 mg, 3.0 mmol): 903 mg, 88% yield.

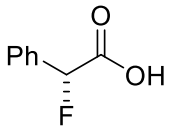


Methyl (*R*)-2-fluoro-2-phenylacetate (**39**). A solution of *tert*-butyl (*R*)-benzyl(2-fluoro-2-phenylacetyl)carbamate (343 mg, 1.00 mmol) in MeOH (8 mL) in an oven-dried 20-mL vial equipped with a cross-shaped stir bar was cooled to 0 °C. A solution of MeONa (5.4 mg, 0.10 mmol) in MeOH (2 mL) was added in one portion, and after 3 min the combined solution was filtered by passage through a pad of silica (Note: racemization may occur if the reaction time is too long). The resulting solution was concentrated, and the residue was purified by flash column chromatography (3→6% EtOAc/hexanes) to afford methyl 2-fluoro-2-phenylacetate.

With (*R*)-benzyl(2-fluoro-2-phenylacetyl)carbamate: 151 mg, 90% yield, 96% ee.

With (*S*)-benzyl(2-fluoro-2-phenylacetyl)carbamate: 144 mg, 86% yield, 97% ee. All spectroscopic data are consistent with those in the literature.[38]

Analysis of ee: The ee was determined via chiral GC on a CP-Chirasil-Dex CB column (70→110 °C at 0.4 °C/min, flow rate 1.3 mL/min); retention times for (*R*)-**39**: 63.1 min (major), 64.9 min (minor).

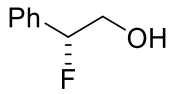


(*R*)-2-Fluoro-2-phenylacetic acid (**40**). A solution of LiOH•H_2O (134 mg, 3.2 mmol), dissolved in a minimal amount of water, was added dropwise to a 0 °C solution of (*R*)-benzyl(2-fluoro-2-phenylacetyl)carbamate (343 mg, 1.0 mmol) in 1:1 THF/H_2O (10 mL) in a 20-mL vial equipped with a stir bar. The reaction mixture was stirred for 3 h, during which time the temperature of the mixture warmed to r.t. Next, Et_2O was added, and the layers were separated. The organic layer was discarded, and the aqueous layer was washed with Et_2O (5 mL × 2), acidified with 3N HCl until pH=1, and extracted with Et_2O (5 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated to afford pure **40**.

With (*R*)-substrate: 142 mg, 92% yield; 97% ee.

With (*S*)-substrate: 140 mg, 92% yield; 97% ee.

Analysis of ee: A solution of $TMSCHN_2$ (0.1 mL, 2.0 M in Et_2O) was added to a solution of acid **40** (15.4 mg, 0.10 mmol) in MeOH (0.5 mL). After 1 min, the solution of methyl ester **39** was diluted with MeOH and subjected to ee analysis by chiral GC according to the conditions described for methyl ester **39** above.



(*R*)-2-Fluoro-2-phenylethan-1-ol (**41**). In a glovebox, **1** (243 mg, 1.0 mmol) was added in one portion to Cp_2ZrHCl (309 mg, 1.2 mmol) suspended in DME (10 mL) in an oven-dried 20-mL scintillation vial equipped with a cross-shaped stir bar. The mixture was stirred at r.t. for 1 h, during which time the mixture became homogeneous. The reaction was quenched by the addition of aqueous citric acid (0.5 mL; 2.0 M). The reaction mixture was poured into water (25 mL), and the aqueous layer was extracted with Et_2O (15 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated, affording 2-fluoro-2-phenylacetaldehyde as a crude product.

2-Fluoro-2-phenylacetaldehyde was dissolved in MeOH (10 mL) and cooled to 0 °C. Approximately 100 mg $NaBH_4$ (excess, >2.5 equiv) was added to the solution with venting. After 10 min, the MeOH was evaporated, and the residue was redissolved in Et_2O (15 mL). The mixture was filtered through a pad of celite, flushing with Et_2O, and concentrated. The residue was purified by flash chromatography on silica (20→25% EtOAc/hexanes) to afford pure **41** as a colorless oil.

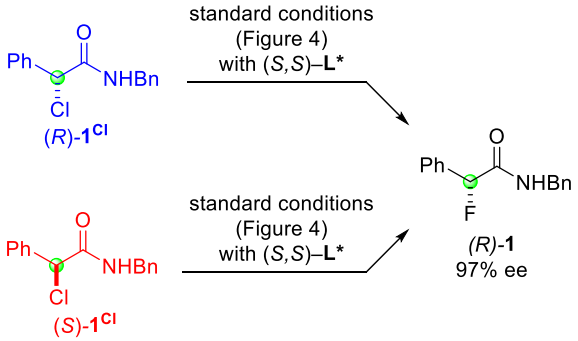
With (*R*)-**1** as starting material: 102 mg, 73% yield; 97% ee. With (*S*)-**1** as starting material: 102 mg, 73% yield; 98% ee.

All spectroscopic data are consistent with those in the literature.[39]

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (5% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times of (*R*)-**41**: 4.10 min (minor), 4.98 min (major).

F. Mechanistic studies

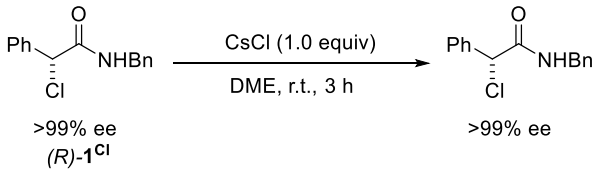
i. Support for enantioconvergent fluorination (Figure 9A)



GP–5 was followed, with $\mathbf{1}^{Cl}$ (each enantiomer, separately) as the electrophile (0.60 mmol) and an internal standard, 4-fluorobiphenyl (103 mg, 0.60 mmol, 1.0 equiv), added to the reaction mixture. At the indicated times, an aliquot (100 μL) was removed from the reaction under vigorous stirring. The aliquot was filtered through a pad of silica, flushing with Et_2O. The filtrate was concentrated, and the residue was subjected to analysis by 19F NMR spectroscopy (yield) and SFC (ee; after purification by preparative TLC).

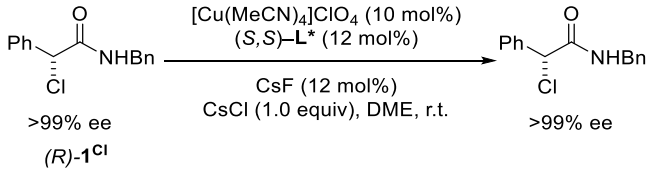
The yield of **1** as a function of time was recorded in Figure 9A.

ii. Investigation of potential racemization pathways of substrates (Figure 9B)



In a nitrogen-filled glovebox, an oven-dried 4 mL vial equipped with a PTFE-coated stir bar was charged (*R*)-**1** (26.0 mg, 0.10 mmol) and CsCl (16.8 mg, 0.10 mmol), before 0.5 mL DME was added. The mixture was allowed to stir under r.t. for 3 h, before filtered passing through a pad of silica gel with the help of Et_2O. The solution was concentrated and the residue was purified by preparative TLC (30% EtOAc/hexanes) to afford the pure product subjected to SFC analysis.

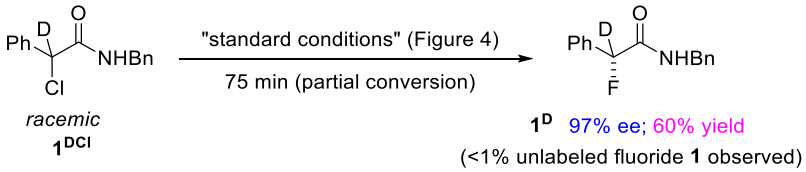
Product ee: >99%. No racemization observed.



In a nitrogen-filled glovebox, an oven-dried 4 mL vial equipped with a PTFE-coated stir bar was charged $[Cu(MeCN)_4]ClO_4$ (3.3 mg, 0.010 mmol), **L*** (3.2 mg, 0.012 mmol), CsF (1.8 mg, 0.012 mmol) and CsCl (16.8 mg, 0.10 mmol), before 0.2 mL DME was added. After 10 min, (*R*)-$\mathbf{1^{Cl}}$ (26.0 mg, 0.10 mmol) dissolved in 0.3 mL DME was added into the vial. The mixture was allowed to stir under r.t. for 3 h, before filtered passing through a pad of silica gel with the help of Et_2O. The solution was concentrated and the residue was purified by preparative TLC (30% EtOAc/hexanes) to afford the pure product subjected to SFC analysis.

Product ee: >99%. No racemization observed.

The above two experiments support that electrophile $\mathbf{1^{Cl}}$ does not racemize under an S_N2 pathway, with the help of CsCl, regardless whether Cu-catalyst is involved.



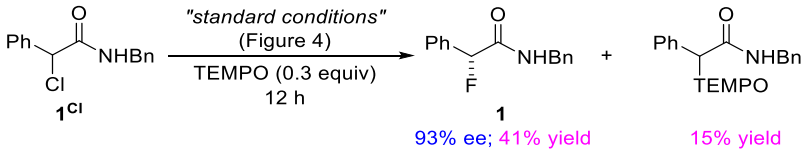
The starting material $\mathbf{1^{DCl}}$ was synthesized according to **GP–4**, with $NaBD_4$ replacing $NaBH_4$.

GP–6 was followed, with $\mathbf{1^{DCl}}$ as electrophile instead of $\mathbf{1^{Cl}}$. The reaction was terminated after 75 min; the yields of $\mathbf{1^{D}}$ and $\mathbf{1^{DCl}}$ were determined by ^{1}H NMR with 1,3,5-trimethoxybenzene.

Yield of $\mathbf{1^{DF}}$: 60%; 97% ee. Yield of $\mathbf{1^{D}}$: 20%. In both compounds, <1% H/D exchange (replacing α-H by α-D) was observed.

This experiment supports no racemization happens via enolization pathway (i.e., by abstraction of α-H).

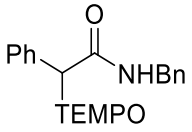
iii. Reaction in the presence of radical traps (Figure 10)



GP–6 was followed, with (*S,S*)–**L*** as the ligand and the TEMPO (4.7 mg, 0.030 mmol) added immediately after the electrophile. The yield of **1** was determined by quantitative 19F NMR spectroscopy; the yield of $\mathbf{1}^{\mathbf{TEMPO}}$ was determined by ^{1}H NMR spectroscopy (1,3,5-trimethoxybenzene (5.6 mg, 0.033 mmol) dissolved in acetone (0.2 mL) was added as an internal standard at the end of the reaction). Pure **1** and $\mathbf{1}^{\mathbf{TEMPO}}$ were obtained by preparative TLC (30% EtOAc/hexanes), and the ee values were determined by SFC.

1: 41% yield; 93% ee; $\mathbf{1}^{\mathbf{TEMPO}}$: 15% yield; 7% ee.

With 1.5 equiv, instead of 0.3 equiv, of TEMPO: 34% yield of **1**, 93% ee; $\mathbf{1}^{\mathbf{TEMPO}}$: 20% yield, 7% ee.



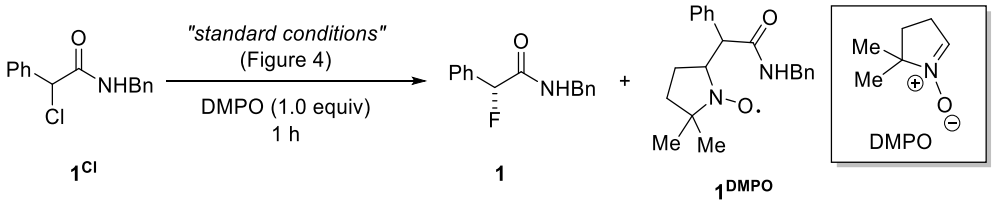
***N*-Benzyl-2-phenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetamide ($\mathbf{1}^{\mathbf{TEMPO}}$).**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.36 (m, 2H), 7.36 – 7.28 (m, 6H), 7.28 – 7.22 (m, 2H), 6.81 (s, br, 1H), 5.12 (s, 1H), 4.59 – 4.31 (m, 2H), 1.50 – 0.84 (m, br, 18H), 0.54 (s, br, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8, 139.6, 138.1, 128.7, 128.4, 128.0, 127.9, 127.6, 127.1, 90.4, 60.3, 43.2, 40.4, 33.0, 20.4, 16.9.

FT-IR (film): 3297, 2931, 1659, 1529, 1453, 1360, 1258, 1133, 1030, 919, 732, 684 cm^{-1}.

HRMS (ESI^{+}-MS) *m/z* $[M+H]^{+}$ calcd for $[C_{24}H_{33}N_2O_2]^{+}$: 381.2537, found: 381.2541.



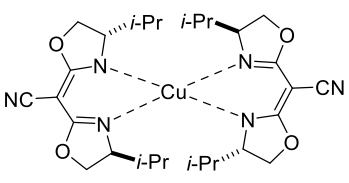
$\mathbf{1}^{Cl}$ $\mathbf{1}$ $\mathbf{1}^{DMPO}$

GP–6 was followed ((*S,S*)–**L*** as ligand), with 5,5-Dimethyl-1-pyrroline *N*-oxide (DMPO, 11.3 mg, 0.10 mmol) added as an additive. After 1 h of reaction, approximately 0.2 mL of aliquot was taken, filtered passing through a syringe filter and injected into a clear fused-quartz (CFQ) Q-band EPR tube (1.6 mm OD, 1.1 mm ID; 70 mm sample height). The Q-band tube was inserted into an X-band EPR tube (4.0 mm OD) which was subsequently sealed with a cap. EPR experiments were conducted with the X-band EPR tube carrying sample at 298 K.

Yield of **1**: 8% yield. The EPR spectrum for $\mathbf{1}^{DMPO}$ and simulation parameters are recorded in Figure 10B.

*iv. Investigation of copper(II) species during catalysis: $Cu^{II}(LX)_2$ (**45**) (Figure 11A)*

$Cu^{II}(LX)_2$ (45). In a glovebox, a 7-mL vial equipped with a stir bar was charged in turn with $CuCl_2$ (34 mg, 0.25 mmol), potassium 2-(cyano((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)methylene)-4-isopropyloxazolidin-3-ide[40] (K(LX), 151 mg, 0.50 mmol), and DME (3.0 mL). The mixture was stirred at r.t. for 2 h. Next, the dark purple slurry was filtered through a syringe filter. The resulting solution was layered with Et_2O and then cooled to –40 °C. After 3 days, dark purple crystals of $Cu^{II}(LX)_2$ formed and were collected (75 mg, 51%).



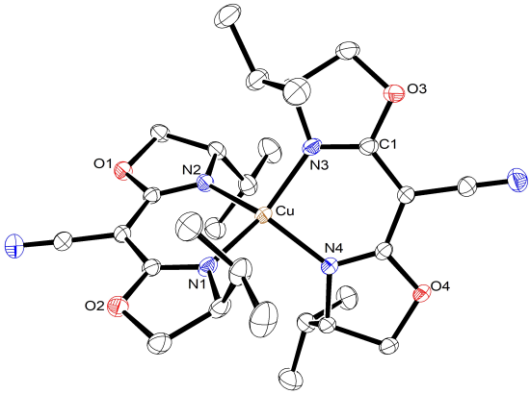


Figure 13. ORTEP drawing of **45** (CCDC 2520881). The compound was synthesized from (*S,S*)–**L***. Thermal ellipsoids are plotted at 50% probability. Hydrogen atoms are omitted for clarity.

Crystal Structure Report for $Cu^{II}(LX)_2$

A purple block-like specimen of $C_{28}H_{40}CuN_6O_4$, approximate dimensions 0.150 mm × 0.300 mm × 0.300 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured (λ = 0.71073 Å).

The total exposure time was 1.49 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a trigonal unit cell yielded a total of 66616 reflections to a maximum θ angle of 36.31° (0.60 Å resolution), of which 7690 were independent (average redundancy 8.663, completeness = 100.0%, R_{int} = 7.49%, R_{sig} = 4.09%) and 6726 (87.46%) were greater than $2\sigma(F^2)$. The final cell constants of a = 12.0088(16) Å, b = 12.0088(16) Å, c = 19.070(3) Å, volume = 2381.7(8) $Å^3$, are based upon the refinement of the XYZ-centroids of 9914 reflections above 20 σ(I) with 4.461° < 2θ < 72.16°. Data were corrected for absorption effects using the Multi-Scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.893. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.8110 and 0.8990.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group $P3_121$, with Z = 3 for the formula unit, $C_{28}H_{40}CuN_6O_4$. The final anisotropic full-matrix least-squares refinement on F^2 with 181 variables converged at R_1 = 2.95% for the observed data and wR_2 = 9.87% for all data. The goodness-of-fit was 0.717. The largest peak in the final difference electron density synthesis was 0.598 $e^-/Å^3$ and the largest hole was -0.337 $e^-/Å^3$ with an RMS deviation of 0.052 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.230 g/cm^3 and F(000), 933 e^-.

Sample and crystal data for $Cu(LX)_2$.

Identification code	V25064

Chemical formula	$C_{28}H_{40}CuN_6O_4$
Formula weight	588.20 g/mol
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal size	0.150 × 0.300 × 0.300 mm
Crystal habit	purple Block
Crystal system	trigonal
Space group	P 31 2 1
Unit cell dimensions	a = 12.0088(16) Å α = 90°
	b = 12.0088(16) Å β = 90°
	c = 19.070(3) Å γ = 120°
Volume	2381.7(8) $Å^3$
Z	3
Density (calculated)	1.230 g/cm3
Absorption coefficient	0.727 mm^{-1}
F(000)	933

Data collection and structure refinement for $Cu(LX)_2$

Theta range for data collection	2.23 to 36.31°	
Index ranges	-19<=h<=20, -20<=k<=20, -31<=l<=31	
Reflections collected	66616	
Independent reflections	7690 [R(int) = 0.0749]	
Coverage of independent reflections	100.0%	
Absorption correction	Multi-Scan	
Max. and min. transmission	0.8990 and 0.8110	
Structure solution technique	direct methods	
Structure solution program	SHELXT 2018/2 (Sheldrick, 2018)	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2018/3 (Sheldrick, 2018)	
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	7690 / 0 / 181	
Goodness-of-fit on F^2	0.717	
Δ/σ_{max}	0.001	
Final R indices	6726 data; I>2σ(I)	R1 = 0.0295, wR2 = 0.0911
	all data	R1 = 0.0370, wR2 = 0.0987

Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.1000P)^2]$ where $P=(F_o^2+2F_c^2)/3$
Absolute structure parameter	0.015(4)
Largest diff. peak and hole	0.598 and -0.337 eÅ^{-3}
R.M.S. deviation from mean	0.052 eÅ^{-3}

EPR spectrum of 45 and its simulation:

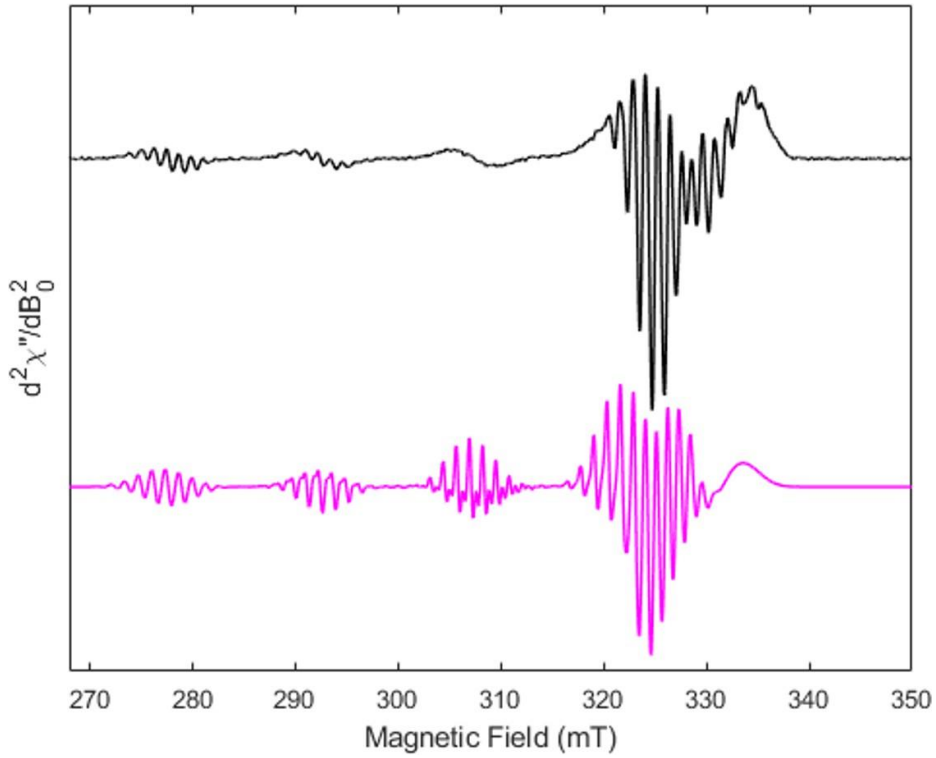
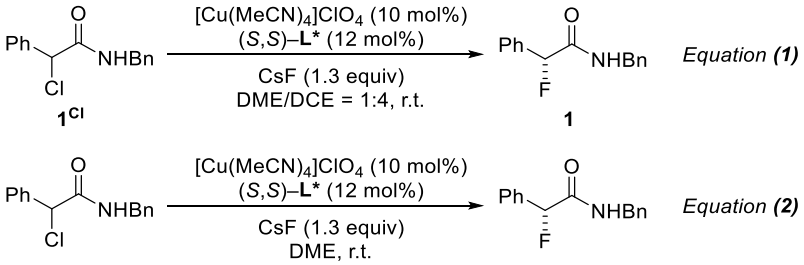


Figure 14. Simulation of the EPR spectrum (second-order derivative) of **45**. Black trace: spectrum of **45** from an EPR experiment (in 4:1 DCE/DME, 9.4 GHz, 2 mW MW power, 77 K). Magenta trace: simulated spectrum. Parameters for simulation: g = [2.0625, 2.0625, 2.2370]; A_{Cu} = [10, 10, 460] mT; A_N = [31, 31, 40] mT (identical for 4 *N*-atoms).

v. The major Cu(II) species in catalytic reaction



Equation **(1)**: **GP–6** was followed, with 1:4 DME/DCE instead of DME. After 30 min, an aliquot (0.3 mL) was removed by syringe, passed through a syringe filter, and injected into an X-band EPR tube (4.0 mm OD). The sample was immediately frozen at 77 K, and then an EPR spectrum was taken.

Equation **(2)**: **GP–6** was followed. After 40 min, an EPR sample was prepared according to the procedure above.

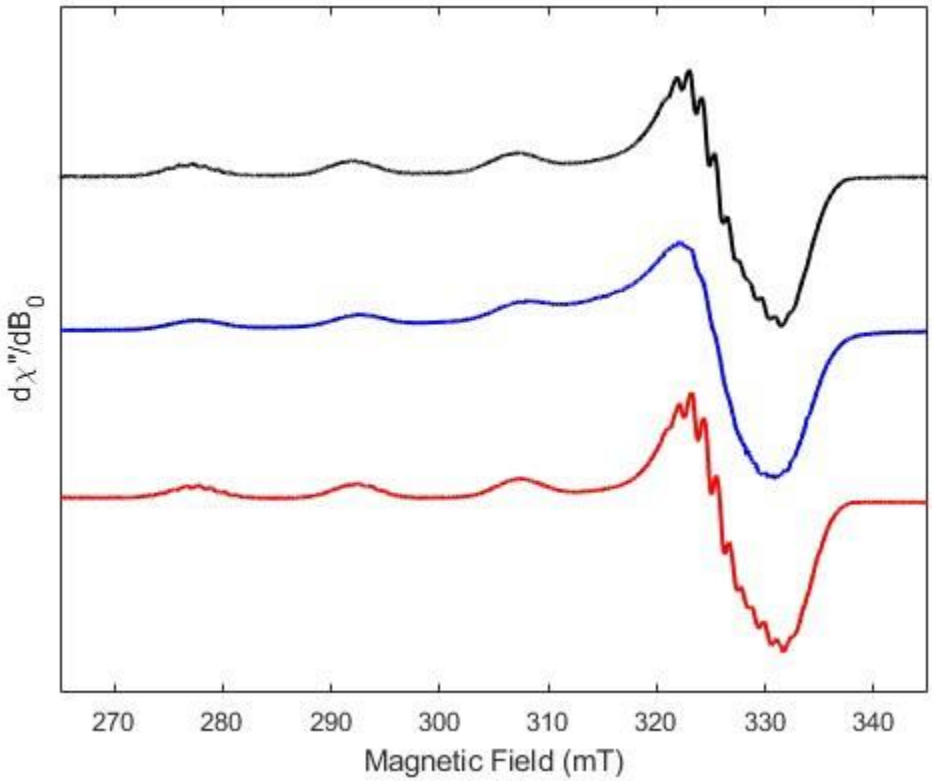


Figure 15. First-order derivatives of X-band EPR spectra (9.4 GHz, 2 mW MW power, 77 K) of aliquots from catalytic reactions and of copper(II) complex **45**. Black trace: Reaction aliquot from Equation **(1)**. EPR-active copper(II) constitutes 7% of all copper species. Blue trace: Reaction aliquot from Equation **(2)**: EPR-active copper(II) constitutes 45% of all copper species. Red trace: Copper(II) complex **45** in

1:4 DME/DCE. Quantification was conducted with respect to equimolar $CuSO_4•5H_2O$ (aq., 77 K) as an external standard.

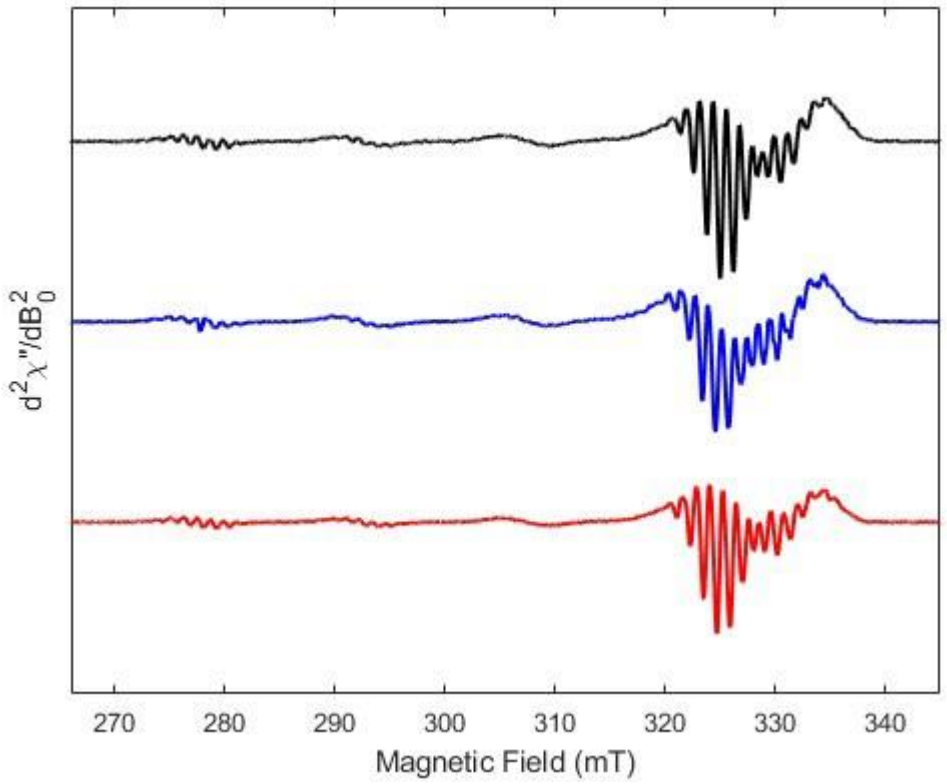
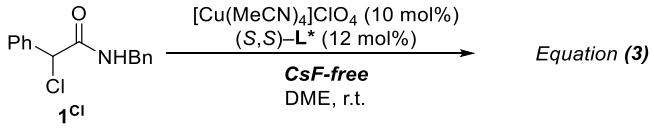


Figure 16. Second-order derivatives of X-band EPR spectra (9.39 GHz, 77K) of aliquots from catalytic reactions and **Cu(LX)$_2$** solution. Black trace: Reaction aliquot from Equation **(1)**. Blue trace: Reaction aliquot from Equation **(2)**. Red trace: Copper(II) complex **45** in 1:4 DCE/DME.



Equation **(3)**: In a glovebox, an oven-dried 4-mL vial equipped with a PTFE-coated stir bar was charged in turn with [Cu(MeCN)$_4$]ClO$_4$ (3.3 mg, 0.010 mmol), K(LX) (3.0 mg, 0.010 mmol), and DME (0.2 mL). The mixture was stirred at r.t. for 10 min, and then a solution of $\mathbf{1^{Cl}}$ in DME (0.3 mL) was added. After 45 min, an aliquot (0.3 mL) was removed by syringe, passed through a syringe filter, and injected into an X-band EPR tube (4.0 mm OD). The sample was immediately frozen at 77 K, and then an EPR spectrum was taken.

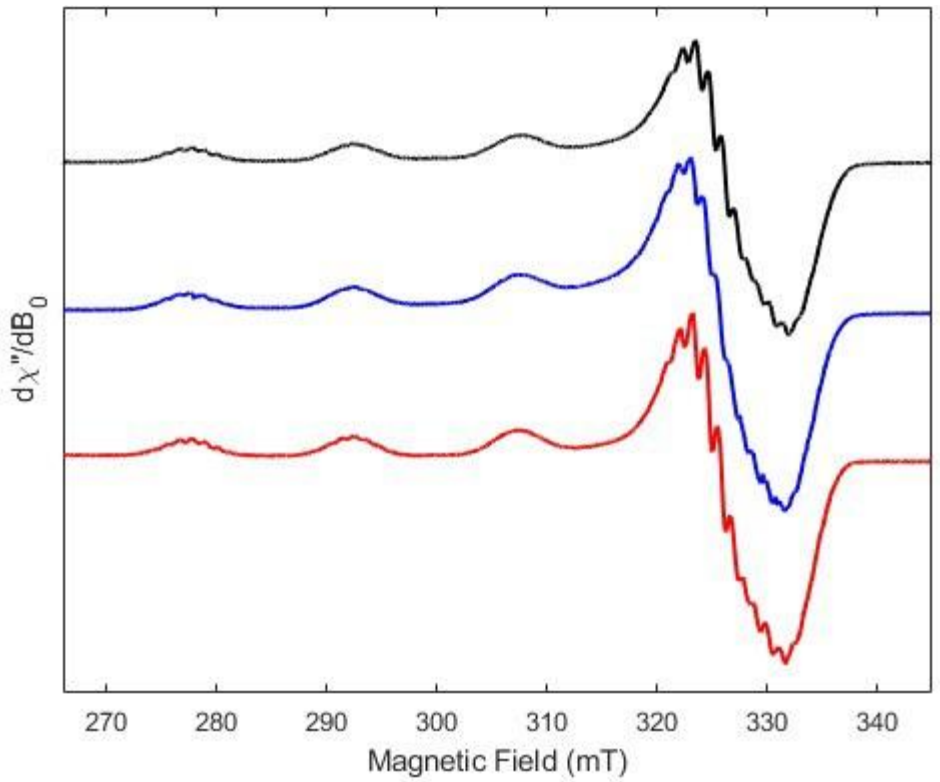
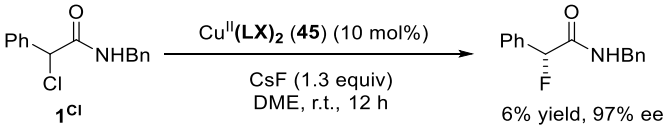


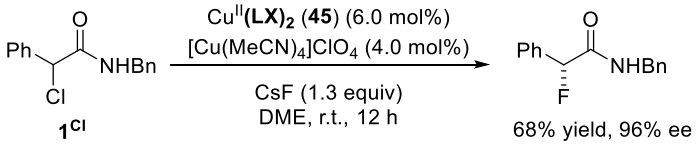
Figure 17. First-order derivatives of X-band EPR spectra (9.4 GHz, 2 mW MW power, 77 K) of aliquots from a catalytic reaction and of copper(II) complex **45**. Black trace: Reaction aliquot from Equation **(1)**. Blue trace: Reaction aliquot from Equation **(3)** (generation of **45** under fluoride-free conditions). Red trace: Copper(II) complex **45** in 4:1 DCE/DME.

These EPR data are consistent with the assignment of copper(II) complex **45** as the major EPR-active copper(II) species present in the catalytic reaction, in DME or DME/DCE alike.

vi. Chemical Competence of ***Cu(LX)$_2$*** *(Figure 11B)*

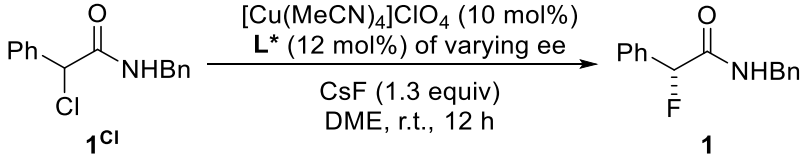


GP–6 was followed, with **45** (5.9 mg, 0.010 mmol) replacing [Cu(MeCN)$_4$]ClO$_4$/**L*** as catalyst. 6% yield; 97% ee.



GP–6 was followed, with **45** (3.5 mg, 0.0060 mmol) and $[Cu(MeCN)_4]ClO_4$ (1.3 mg, 0.0040 mmol) replacing $[Cu(MeCN)_4]ClO_4$/**L*** as catalyst. 68% yield; 96% ee.

*vii. Relationship between the ee of **L*** and the ee of the product: Linear. (Figure 11C)*



In a glovebox, (*S,S*)–**L*** and (*R,R*)–**L*** (23.7 mg, 0.090 mmol) were dissolved in DME (1.5 mL) in two separate 4-mL vials. Solutions with different ratios of (*S,S*)–**L*** and (*R,R*)–**L***, adding up to 400 μL, were transferred to 2-mL GC vials (e.g., 350 μL of (*S,S*)–**L*** and 50 μL of (*R,R*)–**L*** to make **L*** ~75% ee). $[Cu(MeCN)_4]ClO_4$ (3.3 mg, 0.010 mmol) and CsF (19.7 mg, 0.13 mmol) were charged in a separate 4-mL vial equipped with a PTFE-coated stir bar. Part of the ligand solution (200 μL) was transferred from each GC vial into the 4-mL vial, and the mixture was stirred at r.t. for 10 min. Next, a solution of $\mathbf{1^{Cl}}$ (26.0 mg, 0.10 mmol) in DME (0.3 mL) was added in one portion. After 12 h, an internal standard (4-fluorobiphenyl; 17.2 mg, 0.10 mmol) was added, and the mixture was filtered by passing it through a pad of silica gel, flushing with Et_2O. The solvent was removed, and the residue was dissolved in $CDCl_3$ to determine the yield by ^{19}F NMR spectroscopy.

Pure product was obtained by preparative TLC (30% EtOAc/hexanes), and the ee of this material was determined by SFC analysis.

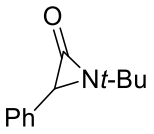
The ee of the enantiomeric mixture of ligands was determined by SFC analysis on a CHIRALPAK IC column (35% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention time of (*rac*)–**L***: 14.34 min, 15.38 min.

Table 3. Relationship between the ee of **L*** and the ee of product **1**.

ee (%) of **L***	predicted ee (%) of **1** for a linear relationship	experimental ee (%) of **1**
100	97	97
76	74	70
53	51	53
25	24	27
0	0	1
–28	–27	–30
–50	–49	–46
–74	–72	–72
–100	–97	–97

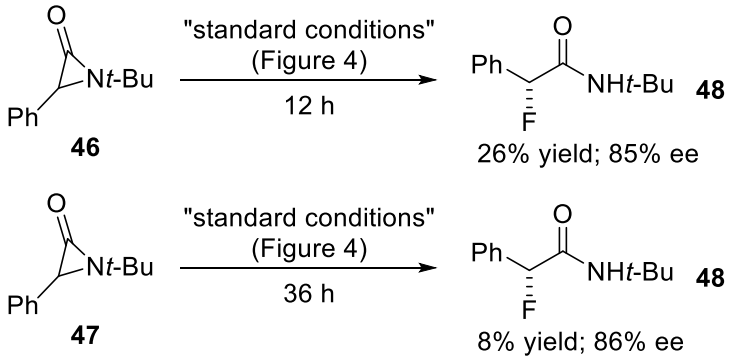
The ee of (*S,S*)–**L*** and of (*R*)-**1** are assigned as positive ee values. The graphic representation of Table 3 is Figure 11C.

viii. Competence of an aziridinone as an electrophile. (Figure 11D)



1-(*tert*-Butyl)-3-phenylaziridin-2-one (**46**). In a glovebox, an oven-dried 40-mL vial equipped with a cross-shaped stir bar was charged with 15-crown-5 (220 mg, 1.0 mmol), NaH (48 mg, 2.0 mmol; >95%, washed with hexanes), and CH_2Cl_2 (10 mL). The mixture was stirred at r.t. for 30 min, and then 2-bromo-*N*-(*t*-butyl)-2-phenylacetamide (270 mg, 1.0 mmol) was added in one portion. The reaction vessel was capped and ventilated with a needle. After vigorous stirring at r.t. for 3 h, the reaction mixture was moved out of the glovebox, diluted with CH_2Cl_2 (10 mL), and quenched carefully with water. The biphasic mixture was transferred into a separation funnel that contained sat. brine (20 mL), with the help of CH_2Cl_2 rinses. The organic layer was washed with sat. brine (20 mL × 4), dried over Na_2SO_4, and concentrated to afford 1-(*t*-butyl)-3-phenylaziridin-2-one **46**.

Yield: 104 mg, 55%. The spectroscopic data are consistent with that reported in the literature.[41]



GP–6 was followed, with either **46** or **47** as the electrophile. The yield was determined by quantitative ^{19}F NMR spectroscopy. Pure product was obtained by preparative TLC (15% EtOAc/hexanes), and the ee was determined by SFC analysis.

For **46**: (*S,S*)–**L***: 22% yield; 85% ee; (*R,R*)–**L***: 29% yield; 85% ee; <5% yield in the absence of copper.

For **47**: (*S,S*)–**L***: 8% yield; 85% ee; (*R,R*)–**L***: 8% yield; 87% ee.

All spectroscopic data for **48** are consistent with those in the literature.[42]

ix. Assignment of absolute configuration

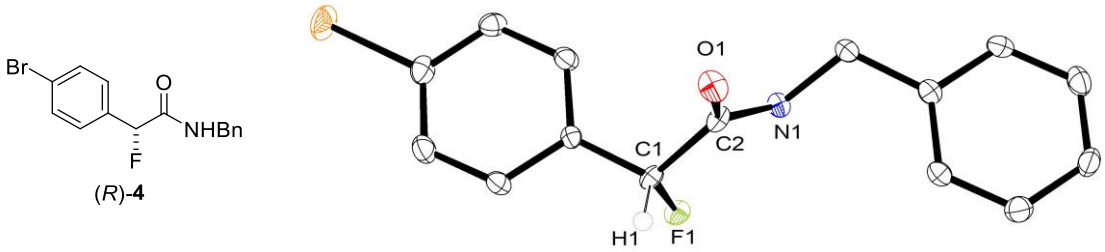


Figure 18. ORTEP drawing of (*R*)-*N*-benzyl-2-(4-bromophenyl)-2-fluoroacetamide (*R*)-**4** (CCDC 2520882). The compound was synthesized using (*S,S*)–**L***. Thermal ellipsoids are plotted at 50% probability. Most of the hydrogen atoms are omitted for clarity.

Crystal Structure Report for (*R*)-4

A colorless needle-like specimen of $C_{15}H_{13}BrFNO$, approximate dimensions 0.100 mm × 0.200 mm × 0.400 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured (λ = 1.54178 Å).

The total exposure time was 3.25 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 26084 reflections to a maximum θ angle of 70.07° (0.82 Å resolution), of which 5128 were independent (average redundancy 5.087, completeness = 100.0%, R_{int} = 4.41%, R_{sig} = 3.41%) and 5064 (98.75%) were greater than 2σ(F2). The final cell constants of a = 5.7913(7) Å, b = 29.803(3) Å, c = 7.8636(6) Å, β = 92.048(8)°, volume = 1356.4(2) Å3, are based upon the refinement of the XYZ-centroids of 9740 reflections above 20 σ(I) with 5.931° < 2θ < 144.3°. Data were corrected for absorption effects using the Multi-Scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.386. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.2860 and 0.6810.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group $P2_1$, with Z = 4 for the formula unit, $C_{15}H_{13}BrFNO$. The final anisotropic full-matrix least-squares refinement on F^2 with 349 variables converged at R_1 = 6.29% for the observed data and wR_2 = 16.51% for all data. The goodness-of-fit was 1.056. The largest peak in the final difference electron density synthesis was 0.430 $e^-/Å^3$ and the largest hole was –0.947 $e^-/Å^3$ with an RMS deviation of 0.080 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.578 g/cm^3 and F(000), 648 e^-.

Sample and crystal data for (*R*)-4

Identification code	V24220	
Chemical formula	$C_{15}H_{13}BrFNO$	
Formula weight	322.17 g/mol	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal size	0.100 x 0.200 x 0.400 mm	
Crystal habit	colorless Needle	
Crystal system	monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 5.7913(7) Å	α = 90°
	b = 29.803(3) Å	β = 92.048(8)°
	c = 7.8636(6) Å	γ = 90°

Volume	1356.4(2) $Å^3$
Z	4
Density (calculated)	1.578 g/cm^3
Absorption coefficient	4.168 mm^{-1}
F(000)	648

Data collection and structure refinement for (*R*)-4

Theta range for data collection	2.96 to 70.07°
Index ranges	-6<=h<=7, -35<=k<=36, -9<=l<=9
Reflections collected	26084
Independent reflections	5128 [R(int) = 0.0441]
Coverage of independent reflections	100.0%
Absorption correction	Multi-Scan
Max. and min. transmission	0.6810 and 0.2860
Structure solution technique	direct methods
Structure solution program	SHELXT 2018/2 (Sheldrick, 2018)
Refinement method	Full-matrix least-squares on F^2
Refinement program	SHELXL-2018/3 (Sheldrick, 2018)
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	5128 / 3 / 349
Goodness-of-fit on F^2	1.056
Δ/σ_{max}	0.001
Final R indices	5064 data; I>2σ(I) R1 = 0.0629, wR2 = 0.1647
	all data R1 = 0.0636, wR2 = 0.1651
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.1298P)^2+0.9824P]$ where $P=(F_o^2+2F_c^2)/3$
Absolute structure parameter	0.05(3)
Largest diff. peak and hole	0.430 and –0.947 $eÅ^{-3}$
R.M.S. deviation from mean	0.080 $eÅ^{-3}$

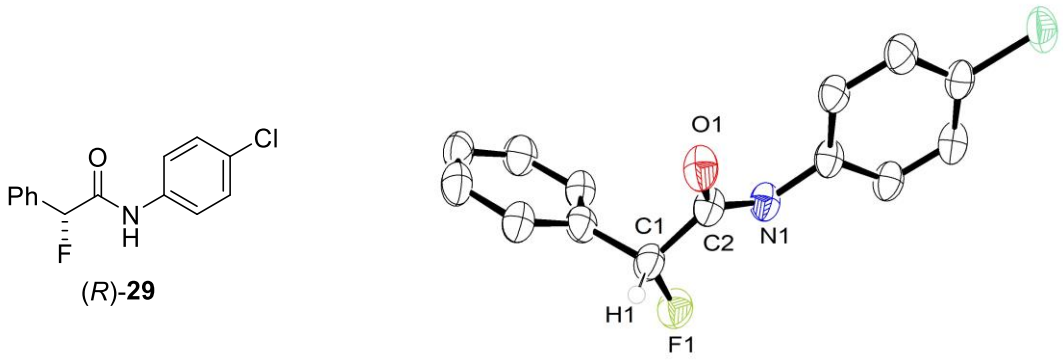


Figure 19. ORTEP drawing of (*R*)-*N*-(4-chlorophenyl)-2-fluoro-2-phenylacetamide (*R*)-**29** (CCDC 2520883). The compound was synthesized using (*S*,*S*)–**L***. Thermal ellipsoids are plotted at 50% probability. Most of the hydrogen atoms are omitted for clarity.

Crystal Structure Report for CCDC (*R*)-29

A colorless needle-like specimen of $C_{14}H_{11}ClFNO$, approximate dimensions 0.050 mm × 0.050 mm × 0.200 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured (λ = 1.54178 Å).

The total exposure time was 7.50 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using an orthorhombic unit cell yielded a total of 29722 reflections to a maximum θ angle of 74.72° (0.80 Å resolution), of which 2490 were independent (average redundancy 11.937, completeness = 100.0%, Rint = 17.25%, Rsig = 6.07%) and 2042 (82.01%) were greater than 2σ(F2). The final cell constants of a = 10.0891(10) Å, b = 25.693(4) Å, c = 4.6970(6) Å, volume = 1217.6(3) Å3, are based upon the refinement of the XYZ-centroids of 8404 reflections above 20 σ(I) with 9.417° < 2θ < 149.3°. Data were corrected for absorption effects using the Multi-Scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.720. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.6060 and 0.8730.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group $Pna2_1$, with Z = 4 for the formula unit, $C_{14}H_{11}ClFNO$. The final anisotropic full-matrix least-squares refinement on F^2 with 167 variables converged at R_1 = 6.35% for the observed data and wR_2 = 18.11% for all data. The goodness-of-fit was 1.054.

The largest peak in the final difference electron density synthesis was 0.716 $e^-/Å^3$ and the largest hole was -0.393 $e^-/Å^3$ with an RMS deviation of 0.071 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.438 g/cm^3 and F(000), 544 e^-.

Sample and crystal data for (*R*)-29

Identification code	V24259	
Chemical formula	$C_{14}H_{11}ClFNO$	
Formula weight	263.69 g/mol	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal size	0.050 x 0.050 x 0.200 mm	
Crystal habit	colorless Needle	
Crystal system	orthorhombic	
Space group	$Pna2_1$	
Unit cell dimensions	a = 10.0891(10) Å	α = 90°
	b = 25.693(4) Å	β = 90°
	c = 4.6970(6) Å	γ = 90°
Volume	1217.6(3) $Å^3$	
Z	4	
Density (calculated)	1.438 g/cm^3	
Absorption coefficient	2.786 m^{m-1}	
F(000)	544	

Data collection and structure refinement for (*R*)-29

Theta range for data collection	3.44 to 74.72°
Index ranges	-12<=h<=12, -31<=k<=32, -5<=l<=5
Reflections collected	29722
Independent reflections	2490 [R(int) = 0.1725]
Coverage of independent reflections	100.0%
Absorption correction	Multi-Scan
Max. and min. transmission	0.8730 and 0.6060
Structure solution technique	direct methods
Structure solution program	XT, VERSION 2018/2

Refinement method		Full-matrix least-squares on F^2
Refinement program		SHELXL-2019/1 (Sheldrick, 2019)
Function minimized		$\Sigma\, w(F_o^2 - F_c^2)^2$
Data / restraints / parameters		2490 / 2 / 167
Goodness-of-fit on F^2		1.054
Final R indices	2042 data; I>2σ(I)	R1 = 0.0635, wR2 = 0.1641
	all data	R1 = 0.0793, wR2 = 0.1811
Weighting scheme		$w=1/[\sigma^2(F_o^2)+(0.0830P)^2+1.4440P]$ where $P=(F_o^2+2F_c^2)/3$
Absolute structure parameter		0.11(3)
Largest diff. peak and hole		0.716 and -0.393 eÅ^{-3}
R.M.S. deviation from mean		0.071 eÅ^{-3}

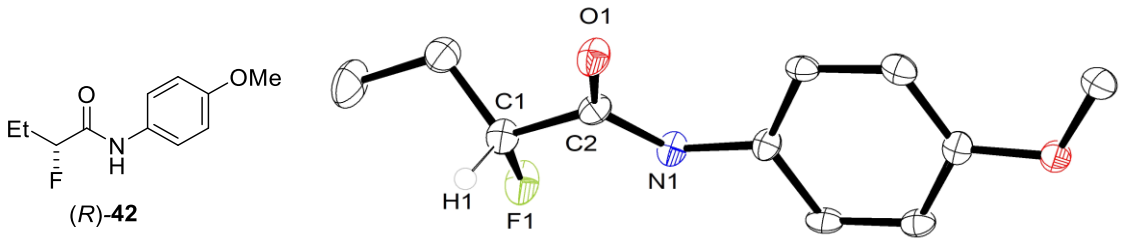


Figure 20. ORTEP drawing of (*R*)-2-fluoro-*N*-(4-methoxyphenyl)butanamide (*R*)-**42**. The compound was synthesized from (*S,S*)–**L3**. Thermal ellipsoids are plotted at 50% probability. Most of the hydrogen atoms are omitted for clarity.

Crystal Structure Report for (*R*)-42

A colorless Block-like specimen of $C_{11}H_{14}FNO_2$, approximate dimensions 0.100 mm × 0.200 mm × 0.250 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured (λ = 1.54178 Å).

The total exposure time was 2.25 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 24906 reflections to a maximum θ angle of 70.05° (0.82 Å resolution), of which 3917 were independent (average redundancy 6.358, completeness = 99.4%, R_{int} = 7.36%, R_{sig} = 4.24%) and 3184 (81.29%) were greater than $2\sigma(F^2)$. The final cell constants of a = 25.895(3) Å, b = 5.2417(6) Å, c = 7.7518(10) Å, β

= 93.196(8)°, volume = 1050.5(2) Å^3, are based upon the refinement of the XYZ-centroids of 9957 reflections above 20 σ(I) with 6.837° < 2θ < 149.1°. Data were corrected for absorption effects using the Multi-Scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.733. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.8120 and 0.9180.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group $P2_1$, with Z = 4 for the formula unit, $C_{11}H_{14}FNO_2$. The final anisotropic full-matrix least-squares refinement on F^2 with 281 variables converged at R1 = 6.27%, for the observed data and wR2 = 19.59% for all data. The goodness-of-fit was 1.111. The largest peak in the final difference electron density synthesis was 0.445 e^-/Å^3 and the largest hole was -0.340 e^-/Å^3 with an RMS deviation of 0.074 e^-/Å^3. On the basis of the final model, the calculated density was 1.336 g/cm^3 and F(000), 448 e^-.

Sample and crystal data for (*R*)-42

Identification code	V25015	
Chemical formula	$C_{11}H_{14}FNO_2$	
Formula weight	211.23 g/mol	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal size	0.100 × 0.200 × 0.250 mm	
Crystal habit	colorless Block	
Crystal system	monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 25.895(3) Å	α = 90°
	b = 5.2417(6) Å	β = 93.196(8)°
	c = 7.7518(10) Å	γ = 90°
Volume	1050.5(2) Å^3	
Z	4	
Density (calculated)	1.336 g/cm^3	
Absorption coefficient	0.867 mm^{-1}	
F(000)	448	

Data collection and structure refinement for (*R*)-42

Theta range for data collection	3.42 to 70.05°
Index ranges	-31<=h<=31, -6<=k<=6, -9<=l<=9
Reflections collected	24906
Independent reflections	3917 [R(int) = 0.0736]
Coverage of independent reflections	99.4%
Absorption correction	Multi-Scan
Max. and min. transmission	0.9180 and 0.8120
Structure solution technique	direct methods
Structure solution program	SHELXT 2018/2 (Sheldrick, 2018)
Refinement method	Full-matrix least-squares on F^2
Refinement program	SHELXL-2018/3 (Sheldrick, 2018)
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	3917 / 3 / 281
Goodness-of-fit on F^2	1.111
Δ/σ_{max}	0.001
Final R indices	3184 data; I>2σ(I) R1 = 0.0627, wR2 = 0.1882
	all data R1 = 0.0751, wR2 = 0.1959
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0949P)^2+1.4436P]$ where $P=(F_o^2+2F_c^2)/3$
Absolute structure parameter	0.19(14)
Largest diff. peak and hole	0.445 and -0.340 eÅ^{-3}
R.M.S. deviation from mean	0.074 eÅ^{-3}

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Chapter III

SYNTHESIS OF AXIALLY CHIRAL COMPOUNDS VIA NICKEL-CATALYZED CROSS-COUPLING

This chapter is temporarily embargoed.