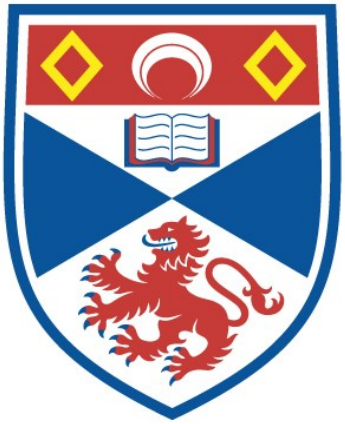
Chiral phosphoric acid-catalyzed asymmetric protonation reactions of vinylheteroaryls

Matthew Ashford

A thesis submitted for the degree of PhD
at the
University of St Andrews



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Abstract

This thesis describes investigations into the chiral phosphoric acid-catalyzed aza-Michael addition-asymmetric protonation between arylamines and various α-substituted vinylheterocycles.

Initially, research focused on the development of optimal reaction conditions for the aza-Michael addition-asymmetric protonation reaction of arylamines and fluorovinylheterocycles, furnishing heterocyclic phenethylamine products containing benzylic stereocentres with a carbon-fluorine bond in good yields (up to 95%) and enantioselectivity (up to >99:1 *e.r.*). Investigation into the asymmetric protonation step was carried out through DFT calculations and kinetic experiments, this provided evidence for a stereocontrolled proton transfer from catalyst to substrate. Additionally, the conformation of the heterocyclic phenethylamine products was explored through DFT calculations and XRD.

Chlorovinylheterocycles were also investigated within the aza-Michael addition-asymmetric protonation reaction, furnishing heterocyclic phenethylamine products containing benzylic stereocentres with a carbon-chlorine bond in good yields (up to 99%) and enantioselectivity (up to 99:1 *e.r.*). Development of a one-pot aza-Michael addition-asymmetric protonation-ring closure reaction was also carried out to furnish chiral heterocyclic aziridines in good yields (up to 81%) and enantioselectivity (up to 97:3 *e.r.*). Product derivatization of the chiral heterocyclic aziridines furnished chiral vicinal diamines in good yields (up to 84% yield) and enantioselectivity (up to 96:4 *e.r.*). Catalyst variation experiments showed the importance of steric interactions from the catalyst alkyl groups in enforcing high enantioselectivity.

General Acknowledgements

Firstly, I would like to thank my supervisor, Dr Allan Watson, for his support and guidance over the last four years. The development of my chemistry knowledge and soft skills have been invaluable and will continue to be invaluable for the rest of my life. For this, I cannot thank you enough.

A big thanks to everyone I have had a pleasure to work alongside, your help and discussions have been greatly appreciated. Especially Dr John Molloy, Dr Liam McLean, Dr Jamie Fyfe and Dr Chao Xu for showing me the ropes, along with their invaluable guidance and support. I am also grateful to Dr Andrew Leach in discussions and running the DFT calculations described in this thesis, and Prof. Alex Slawin and Dr Cameron Carpenter-Warren for their discussions and running the X-ray diffraction experiments described in this thesis.

Thanks to the current and previous members of the Watson group. Your friendships have made my last four years a very enjoyable experience. Finally, I would like to thank Dr Maria Oranges for your continued support and friendship through the final years of my PhD.

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Abbreviations

Å	Ångstrom
Ac	Acetate
acac	Acetylacetonate
Ad	Adamantyl
app.	Apparent
aq.	Aqueous
Ar	Aryl
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Boc	*N*-*tert*-Butoxycarbonyl
br	Broad
Bu	Butyl
C	Celsius
cal	Calorie(s)
cat.	Catalyst
cod	1,5-Cyclooctadiene
conc.	Concentrated
Conv.	Conversion
CPA	Chiral phosphoric acid
CPME	Cyclopentyl methyl ether
Cy	Cyclohexyl
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
d.r.	Diastereomeric ratio
DAP	Decarboxylative asymmetric protonation
DAST	Diethylaminosulfur trifluoride

dba	Dibenzylideneacetone
DCM	Dichloromethane
DEC	Diethyl carbonate
DFT	Density functional theory
DIPEA	*N*,*N*-Diisopropylethylamine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMI	1,3-Dimethyl-2-imidazolidinone
DPZ	5,6-Bis(5-methoxythiophen-2-yl)pyrazine-2,3-dicarbonitrile
e.r.	Enantiomeric ratio
equiv	Equivalent molar quantity
ESI	Electrospray ionisation
Et	Ethyl
g	Gram(s)
h	Hour(s)
h	Plank's constant
HMDS	Bis(trimethylsilyl)amine
HOBt	1-Hydroxybenzotriazole
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
I	iso
IPA	Isopropyl alcohol
k	Kilo
KIE	Kinetic isotope effect
L	Ligand
LDA	Lithium diisopropylamide
LED	Light emitting diode

m	Multiplet
M	Molar concentration
m	*meta*
*m*CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MEDAM	Bis(4-methoxy-3,5-dimethylphenyl)methyl
MEPO	*para*-Methoxypyridine *N*-oxide
Mes	Mesityl
mg	Milligram(s)
mL	Millilitres(s)
MHz	Megahertz
min	Minute(s)
mol	Mole(s)
MS	Molecular sieves
NHC	*N*-Heterocyclic Carbene
NMR	Nuclear magnetic resonance
Nuc	Nucleophile
o	*ortho*
p	*para*
PCCP	Pentacarboxylcyclopenatadiene
Ph	Phenyl
Phth	Phthalimide
Pin	Pinacol
Pr	Propyl
Py	Pyridine
q	Quartet
R	Alkyl

RDS	Rate determining step
rt	Ambient (room) temperature
s	Second(s)
sat.	Saturated
SET	Single electron transfer
t	Triplet
t	*tert*
TBA	*tert*-Butoxyphenyl
TBME	Methyl *tert*-butyl ether
TBS	*tert*-Butyldimethylsilyl
TCYP	3,3′-Bis(2,4,6-tricyclohexylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate
Temp	Temperature
TEA	Triethylamine
Tf	Triflate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
TRIP	3,3′-Bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate
Ts	Tosyl
VAPOL	2,2′-Diphenyl-(4-biphenanthrol)
W	Watt(s)
XRD	X-ray diffraction
v	Frequency
ϕ	Angle

Table of Contents

1 Introduction

1.1 Asymmetric Protonation

1.1.1 Concept

Two enantiomers of a chiral compound can exhibit different biological responses. One such example is the sedative thalidomide. It was identified that the (*R*)-enantiomer had the desired pharmacological effect, whereas the (*S*)-enantiomer was the cause of adverse biological effects.[1] Therefore, the development of enantioselective reactions has been of interest to many researchers. A widely explored area is asymmetric protonation; the enantiofacially selective protonation of a prochiral molecule to generate a chiral tertiary carbon center, which are present within many valuable pharmaceutical compounds.[2] There are inherent challenges associated with achieving enantioselectivity in the asymmetric protonation reaction. Fehr highlights these challenges within his review:[3]

- *"Proton exchange reactions between electronegative atoms are considered to be among the most rapid, often diffusion-controlled reactions, and thus it is difficult to discriminate efficiently between two diastereomeric transition states."*
- *"E- and Z-enolates exhibit different enantiofacial selectivities, because the two diastereomeric transition states for the protonation of the E-enolate are different from those for the Z-enolate."*

Despite these challenges, many asymmetric protonation reactions have been developed with excellent enantioselectivity. The research within this thesis will focus on applying asymmetric protonation to the aza-Michael reaction. This introduction broadly discusses reactions involving asymmetric protonation of prochiral enolates or enamines (Figure 1.1).

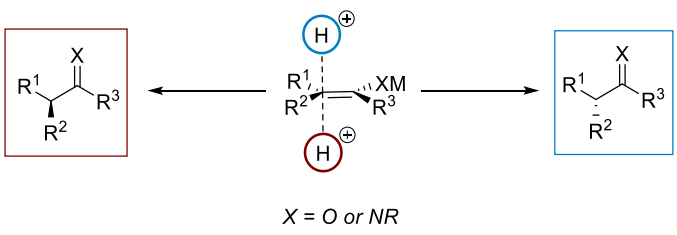
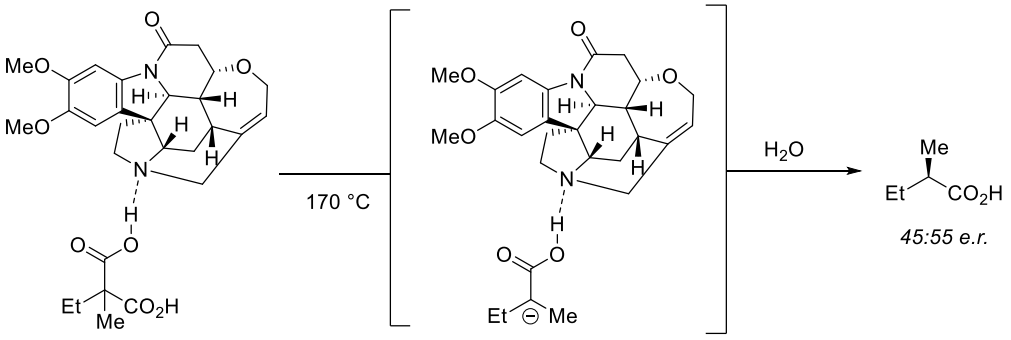


Figure 1.1: Asymmetric protonation of a prochiral enamine or enolate intermediate.

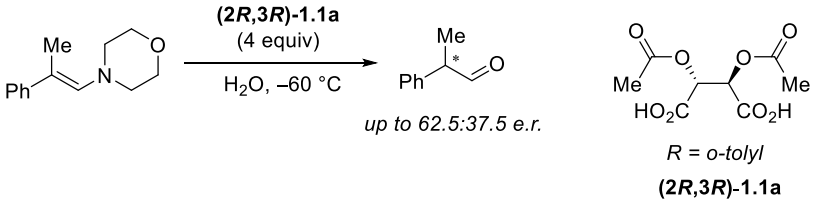
1.1.2 Frontier Work

The first example of an asymmetric protonation was in 1904 by Marckwald,[4] with the mechanism elucidated in 1952 by Kenyon and Ross.[5] The monobrucine salt of ethylmethylmalonic acid underwent thermal decarboxylation to provide a chiral proton acceptor, which reacted with water to provide a slightly enantiomerically enriched sample of 2-methylbutanoic acid (Scheme 1.1).



Scheme 1.1: Decarboxylative asymmetric protonation of ethylmethylmalonic acid with brucine.

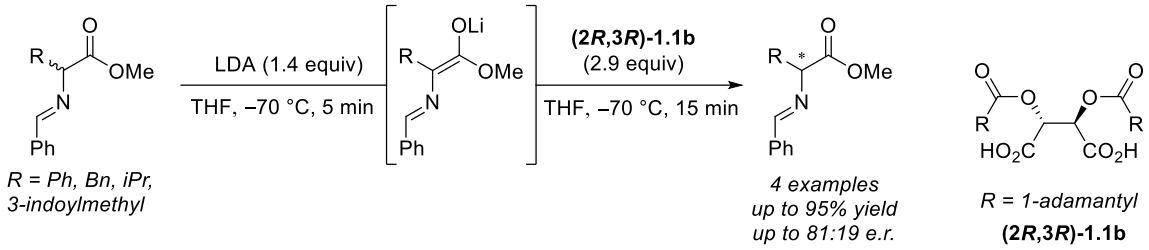
Duhamel and Plaquevent published a series of reports, between 1977 and 1983, on the asymmetric protonation of α-enolates and enamines *via* an asymmetric protonation protocol utilizing various diacyltartaric acids.[6-8] The first of these reports was the development of an enantionenriched synthesis for 2-phenylpropanal.[6] The morpholine enamine derivative of 2-phenylpropanal underwent an asymmetric protonation with **(2*R*,3*R*)-1.1a**, followed by hydrolysis of the resulting iminium ion with water to yield enantiomerically enriched 2-phenylpropanal (Scheme 1.2). Furthermore, applying the (*E*)- and (*Z*)-enamine yielded the (*S*)- and (*R*)-2-phenylpropanal, respectively.



Scheme 1.2: Enantioenriched synthesis of 2-phenylpropanal.

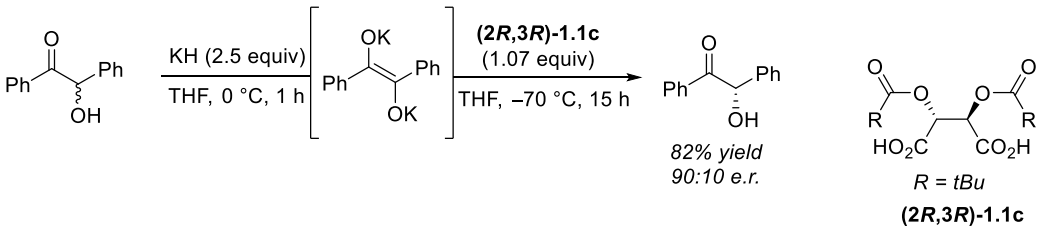
The following report focused on the asymmetric protonation of Schiff base methyl esters.[7] These products are of high synthetic value as they can be hydrolyzed to the corresponding amino acid. Schiff base methyl esters were deprotonated using LDA to

provide the corresponding lithium enolate, which, when treated with diacyl tartaric acids, yielded the desired enantiomerically enriched Schiff base methyl ester (Scheme 1.3). The authors demonstrated this methodology on various Schiff base methyl esters using various diacyltartaric acids, with the best example **(2*R*,3*R*)-1.1b** providing 81:19 *e.r.*



Scheme 1.3: Asymmetric protonation of Schiff base methyl esters via deprotonation/asymmetric protonation.

The final study of the series, conducted in 1983, focused on the deracemization of benzoin.[8] Benzoin was deprotonated with potassium hydride to form the corresponding benzoin potassium enediolate. Protonation of the potassium enediolate with **(2*R*,3*R*)-1.1c** afforded (*S*)-benzoin in 82% yield and 90:10 *e.r.* (Scheme 1.4). In addition, the authors explored the effect of quenching the reaction early. The yield of benzoin dramatically decreased as the unreacted potassium enediolate oxidized to benzil. Additionally, the potassium enediolate reacted with water, consequently decreasing the enantiomeric ratio.



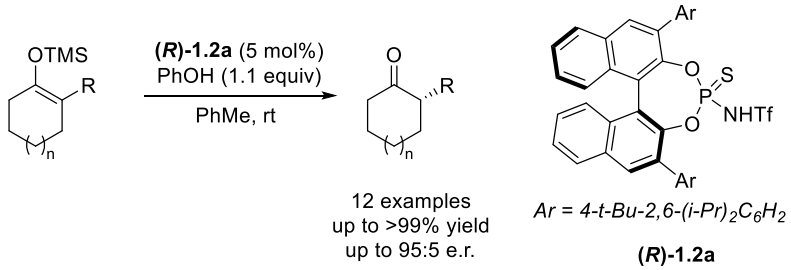
Scheme 1.4: Deracemization of benzoin.

1.2 Asymmetric Protonation Reactions

1.2.1 Asymmetric Protonation of α-Substituted Enolates

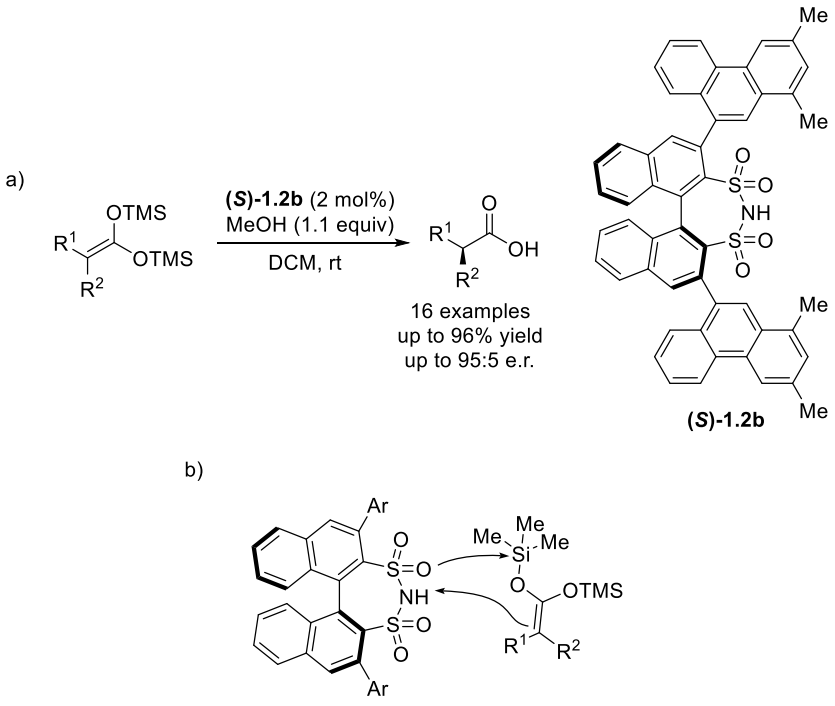
Since the seminal work of Duhamel and Plaquevent, there has been much interest in the asymmetric protonation of α-substituted enolates and enamines *via* asymmetric

protonation. In 2008, Yamamoto and co-workers reported the first metal-free Brønsted acid-catalyzed asymmetric protonation of silyl enol ethers using the CPA **(*R*)-1.2a** (Scheme 1.5).[9] Herein, the group were able to furnish α-substituted carbonyls in excellent yields and enantioselectivities.



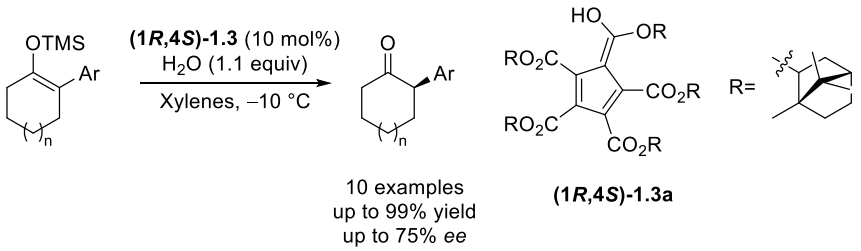
Scheme 1.5: Yamamoto's asymmetric protonation of silyl enol ethers using a CPA.

In 2019, List and co-workers developed an asymmetric protonation protocol for the synthesis of enantioenriched α-substituted carboxylic acids (Scheme 1.6a).[10] Treating bis-silyl ketene acetals with the chiral Brønsted acid catalyst **(*S*)-1.2b** in the presence of methanol the desired carboxylic acids were achieved in excellent yields and enantioselectivities. List proposed the bis silyl ketene acetal underwent protodesilylation *via* a bifunctional activation mode with **(*S*)-1.2b** (Scheme 1.6b).



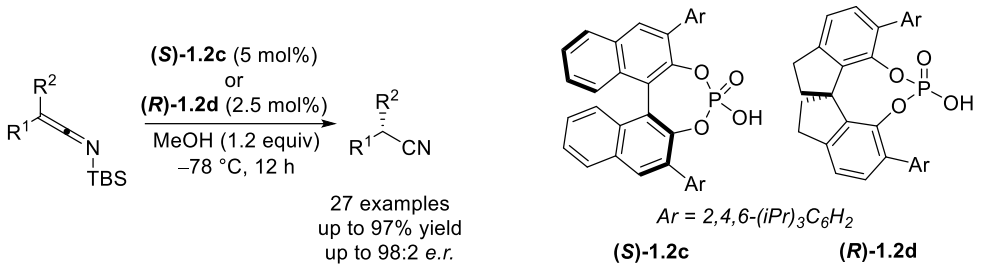
Scheme 1.6: List's asymmetric protonation of silyl ketene acetals using a CPA.

A recent example was by Li and co-workers in 2019.[11] The pentacarboxycyclopentadiene Brønsted acid **(1*S*,4*S*)-1.3** was utilized in the asymmetric protonation of silyl enol ethers to yield the desired enantiomerically enriched α-substituted cyclic ketone (Scheme 1.7).



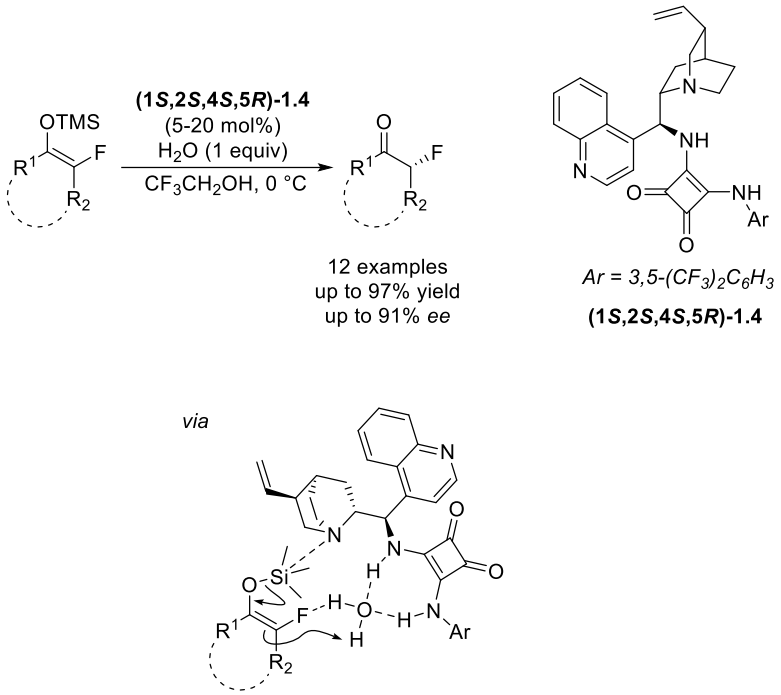
Scheme 1.7: Li's asymmetric protonation of silyl enol ethers using a PCCP Brønsted acid.

Although the research has primarily focused on carbonyls, there have been studies to develop protocols towards other functionalities.[12-14] Recently, List and co-workers developed an asymmetric protonation protocol for α-substituted nitriles (Scheme 1.8).[15] Silyl ketenimines treated with a catalytic amount of CPA **(*S*)-1.2c** or **(*R*)-1.2d** in the presence of methanol furnished the desired tertiary nitrile in excellent yields and enantioselectivities.



Scheme 1.8: List's asymmetric protonation of silyl ketenimine using a CPA.

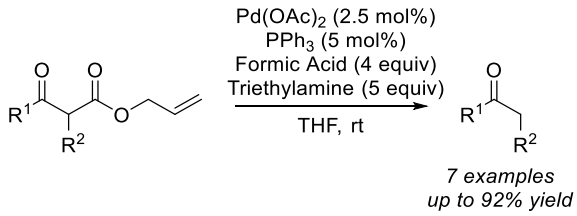
The α-substituent of the carbonyl is typically a sterically bulky group, attributable to providing a steric interaction with the catalyst to assist with stereocontrol. Though this steric interaction is not always necessary, as shown by Zhou and co-workers in 2019.[16] The group could use fluorine as the α-substituent and achieve excellent enantioselectivity despite its small atomic size (Scheme 1.9). α-Fluoro silyl enol ethers were treated with the squaramide cinchona alkaloid catalyst **(1*S*,2*S*,4*S*,5*R*)-1.4** to yield the enantiomerically enriched α-fluoroketone. They proposed that the enantioinduction was due to a dual activation from the catalyst, with tertiary amine coordination to the silyl group and a halogen-hydrogen bond between the fluorine and water bound to the squaramide functionality of **(1*S*,2*S*,4*S*,5*R*)-1.4**.



Scheme 1.9: Zhou's asymmetric protonation of α-fluoroketones.

1.2.1 Palladium-Catalyzed Decarboxylative Asymmetric Protonation

The decarboxylative asymmetric protonation (DAP) reaction typically requires a palladium-catalyzed system. Tsuji's decarboxylation inspired this in 1985.[17] Tsuji and co-workers showed decarboxylation of allylic β-keto esters in the presence of palladium at a catalyst loading as low as 2.5% and at room temperature to yield the desired ketone (Scheme 1.10).



Scheme 1.10: Tsuji's palladium-catalyzed decarboxylation of allylic β-keto esters.

The proposed mechanism proceeded through oxidative addition of palladium(0) with the allylic β-keto ester afforded the palladium(II) complex **1.5**. Next, triethylammonium formate reacted with **1.5** to yield the desired product and the palladium(II) species **1.6**, which released CO_2 to yield the palladium hydride species **1.7**. Finally, reductive elimination of **1.7** released propene, regenerating the catalyst and restarting the catalytic cycle (Figure 1.2).

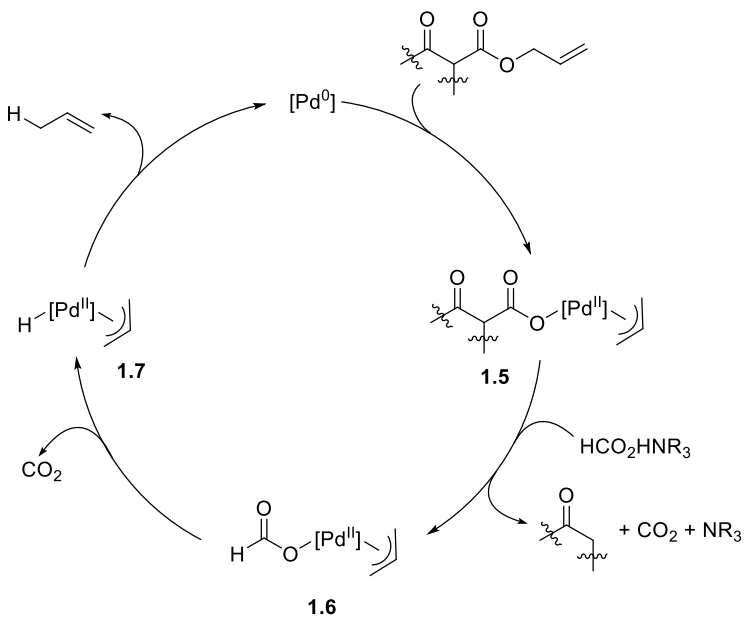
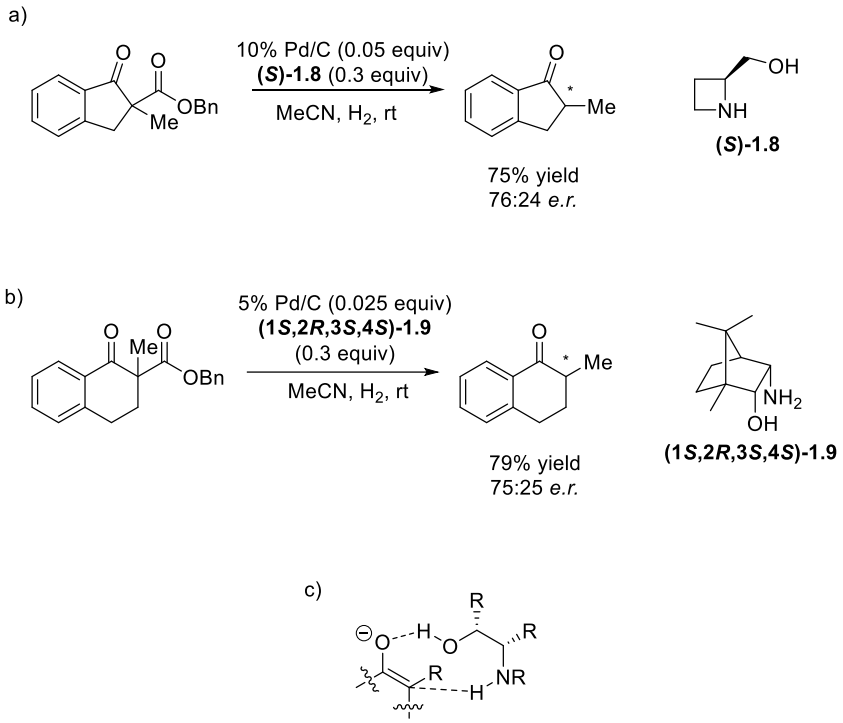


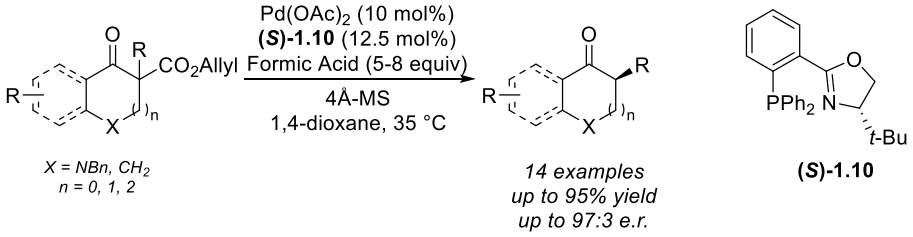
Figure 1.2: Tsuji's proposed mechanism for the palladium-catalyzed decarboxylation of allylic β-keto esters.

The development of an asymmetric variant of Tsuji's palladium-catalyzed decarboxylation protocol has fallen into two distinct methods. The first discussed being the utilization of a chiral proton donor. In 1992 and 1994, Muzart and co-workers investigated the palladium source and chiral proton donors within the DAP.[18,19] β-Keto benzyl esters underwent a palladium-catalyzed decarboxylation which, in the presence of an α,β-aminoalcohol, furnished the desired enantioenriched α-substituted ketones (Scheme 1.11a and 1.11b). Chiral proton donors **(*S*)-1.8** and **(1*S*,2*R*,3*S*,4*S*)-1.9** provided the best enantioselectivity. In addition, the authors proposed that the observed enantioselectivity was due to a dual interaction of the α,β-aminoalcohol with the enolate intermediate (Scheme 1.11c).



Scheme 1.11: Muzart's enantioselective DAP of β-Keto benzyl esters.

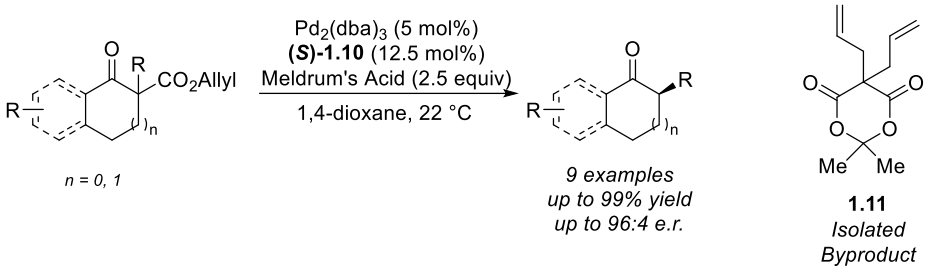
The alternative decarboxylative asymmetric protonation method utilized a chiral ligand for the palladium complex. The first example of this was in 2006 by Stoltz and co-workers.[20] The reaction of allylic β-ketoesters in the presence of palladium acetate, (*S*)-*t*-Bu-PHOX **(*S*)-1.10**, and formic acid, furnished the enantiomerically enriched α-substituted ketone (Scheme 1.12). The proposed mechanism was similar to Tsuji's proposal (Figure 1.2); however, the authors could not determine the mechanism of the enantioselective protonation step.



*Scheme 1.12: Stoltz's DAP using formic acid and the chiral ligand **(S)-1.10**.*

In 2008, Stoltz developed a homogenous DAP protocol which enabled further investigation of the mechanism.[21] The developed protocol treated allylic β-ketoesters in

the presence of $Pd_2(dba)_3$, **(*S*)-1.10**, and Meldrum's acid to yield the desired α-substituted ketone in good yields and enantiomeric ratios (Scheme 1.13).



Scheme 1.13: Stoltz's DAP using Meldrum's acid

During Stoltz and co-worker's development of this methodology, the diallyl Meldrum's acid by-product **1.11** was isolated.[21] With this, the group proposed a plausible mechanism (Figure 1.3). First, they postulated palladium(0) coordinated to the allylic group within the β-ketoester, followed by an oxidative addition to form the palladium (II) species **1.12**. Next, decarboxylation of **1.12** formed the chiral palladium(II) species **1.13,** which, in the presence of an achiral proton donor, yielded the enantiomerically enriched α-substituted ketone and palladium(II) species **1.14**. Finally, reductive elimination of **1.14** yielded the monoallylated achiral acid and the palladium(0) species, closing the catalytic cycle.

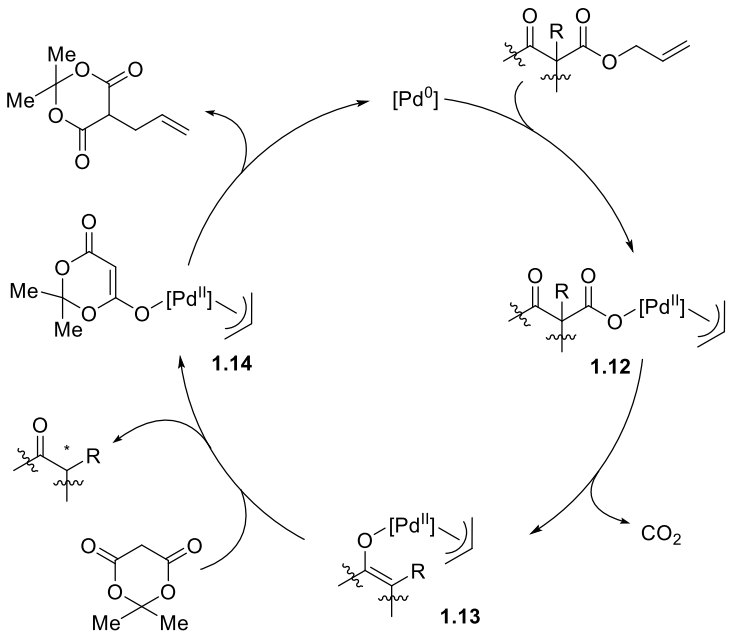
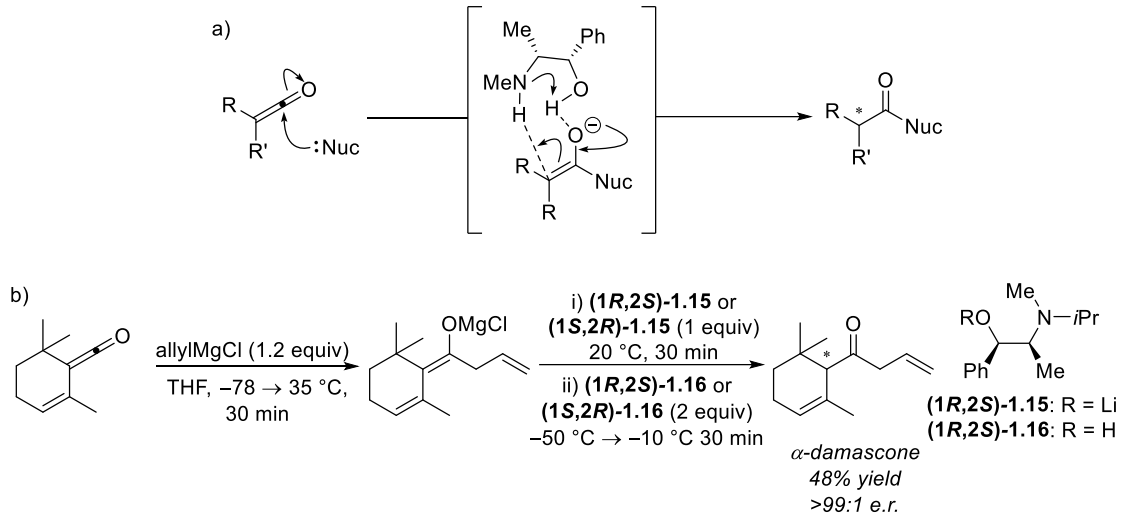


Figure 1.3: Stoltz's proposed mechanism for the DAP reaction.

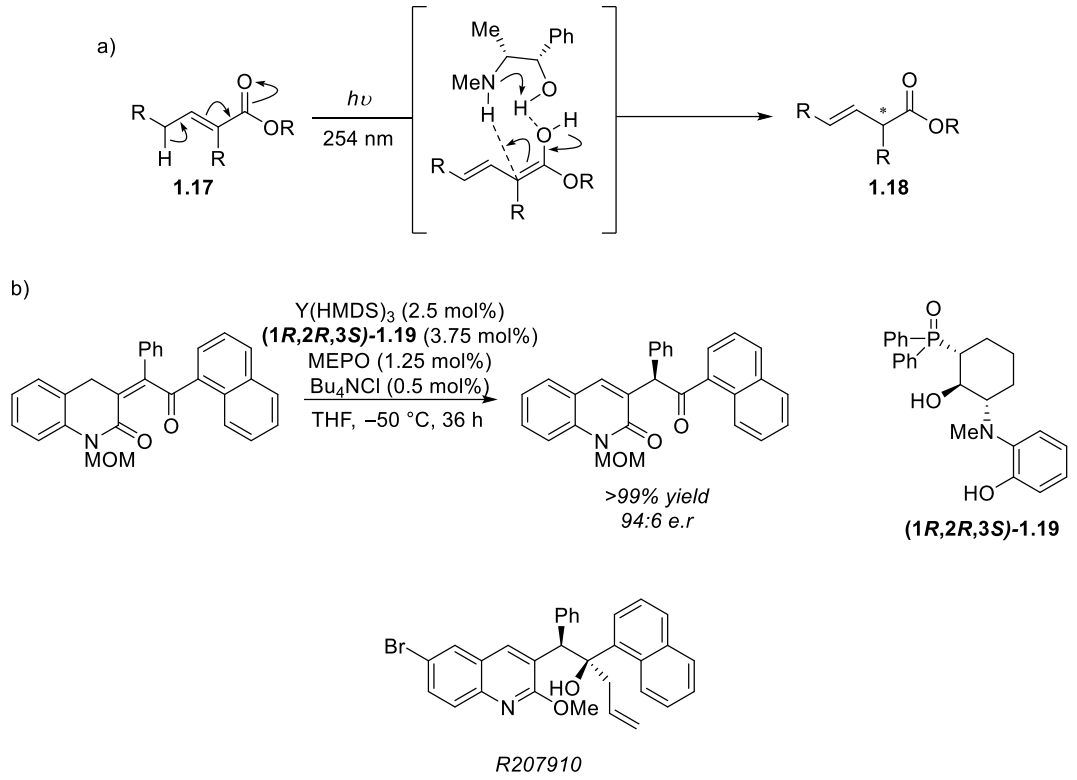
1.2.3 Miscellaneous Asymmetric Protonation Reactions

The addition of a nucleophile into a ketene proceeds through an enolate intermediate. The enolate can react with a chiral proton donor to yield enantiomerically enriched α-substituted carbonyl compounds (Scheme 1.14a). The first example of this was by Fehr and co-workers in 1988, during the synthesis of (*R*)- and (*S*)-α-damascone (Scheme 1.14b).[22]



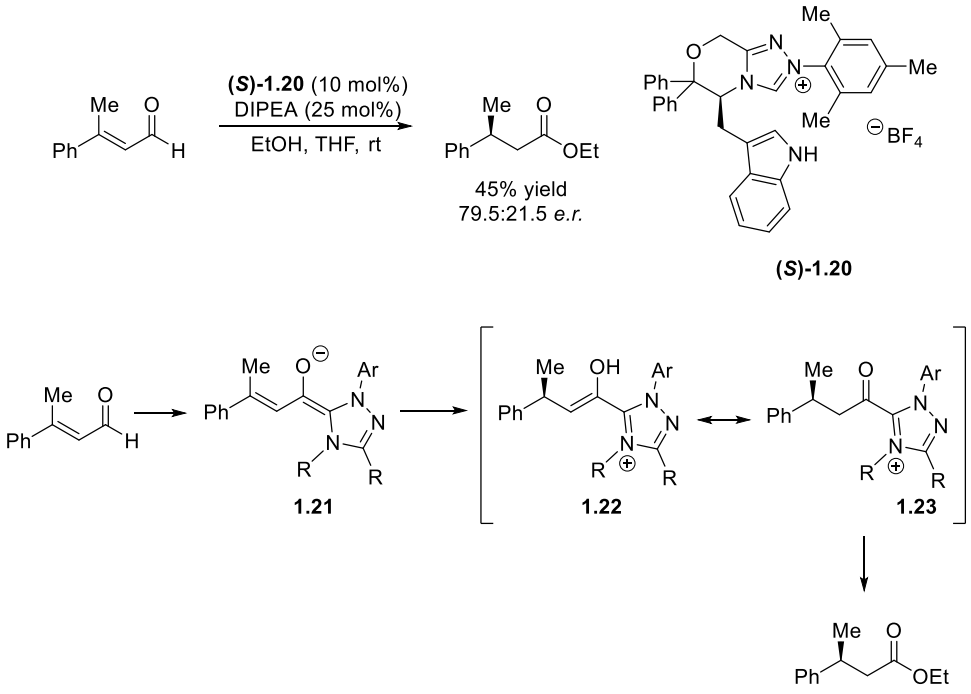
Scheme 1.14: Synthesis of (R)- and (S)-α-damascone using asymmetric protonation.

The isomerization of α-substituted α,β-unsaturated carbonyls can utilize an asymmetric protonation protocol. Muzart first showed this in 1993.[23] Light was utilized to tautomerize the α,β-unsaturated carbonyl **1.17** to **1.18**, as the strong base typically required would be incompatible with the chiral proton source (Scheme 1.15a). In 2010, Shibasaki and co-workers showcased their asymmetric protonation isomerization of α,β-unsaturated carbonyls in the synthesis of R207910, an antituberculosis drug candidate (Scheme 1.15b).[24]



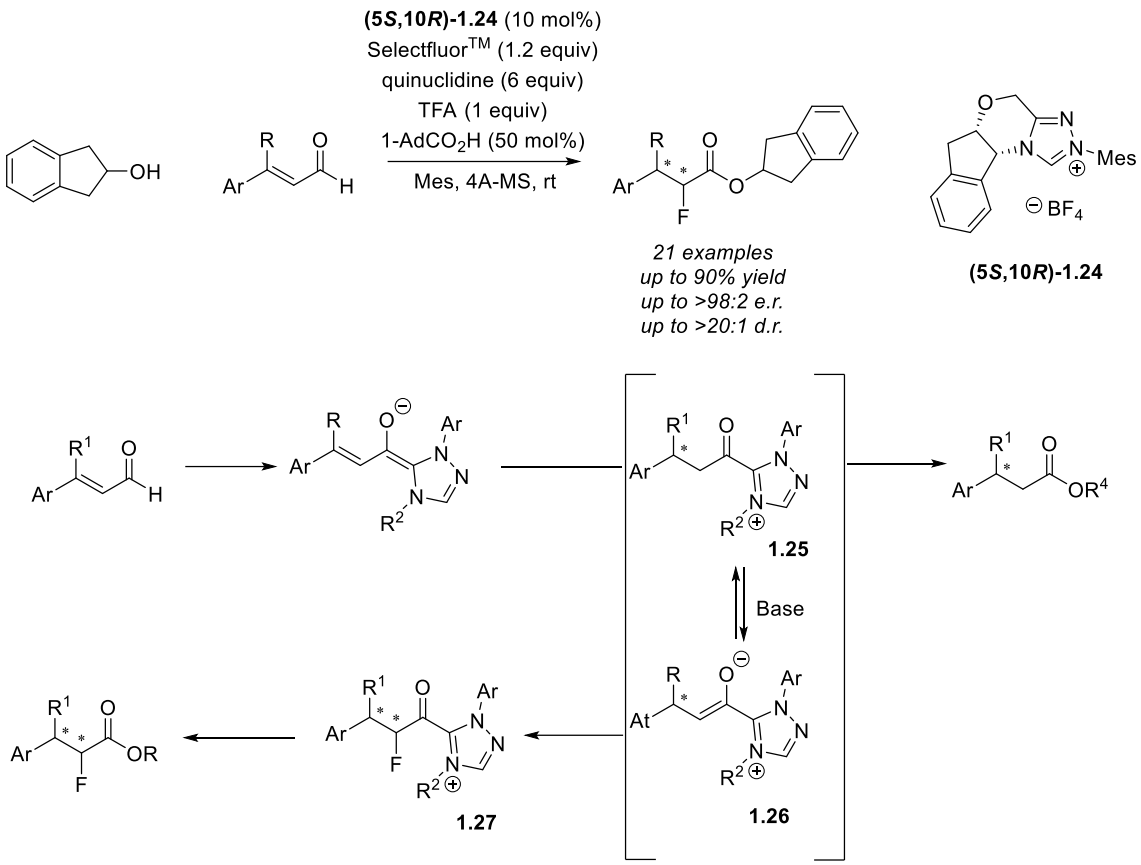
Scheme 1.15: a) Mechanism for the asymmetric protonation isomerization of α,β-unsaturated carbonyls. b) Shibasaki's asymmetric protonation isomerization of α,β-unsaturated carbonyls in the synthesis of R207910

Asymmetric protonation has been applied to the protonation of homoenolates. In 2008, Scheidt and co-workers (Scheme 1.16) demonstrated that the treatment of α,β-unsaturated aldehydes with NHC **(*S*)-1.20** furnished the homoenolate equivalent **1.21**. In the presence of an achiral proton source, **1.21** underwent asymmetric protonation to yield the enol **1.22**. Acyl azolium **1.23** was formed by tautomerization of enol **1.22**. Esterification of **1.23** yielded the desired enantiomerically enriched β-substituted esters.[25]



Scheme 1.16: Scheidt's asymmetric protonation of homoenolates.

Huang and co-workers, in 2019, developed an enantio- and diastereoselective hydrofluorination of α,β-unsaturated aldehydes by expanding upon the asymmetric homoenolate protonation methodology.[26] α,β-Unsaturated aldehydes were treated with NHC **(5*S*,10*R*)-1.24** to undergo the asymmetric homoenolate protonation. However, instead of esterification of intermediate **1.25** to yield the β-substituted esters, the corresponding enolate **1.26** was formed under basic conditions. Then, asymmetric fluorination of enolate **1.26** with Selectfluor™ furnished intermediate **1.27**, which was esterified to yield the desired enantiomerically enriched ester (Scheme 1.17).

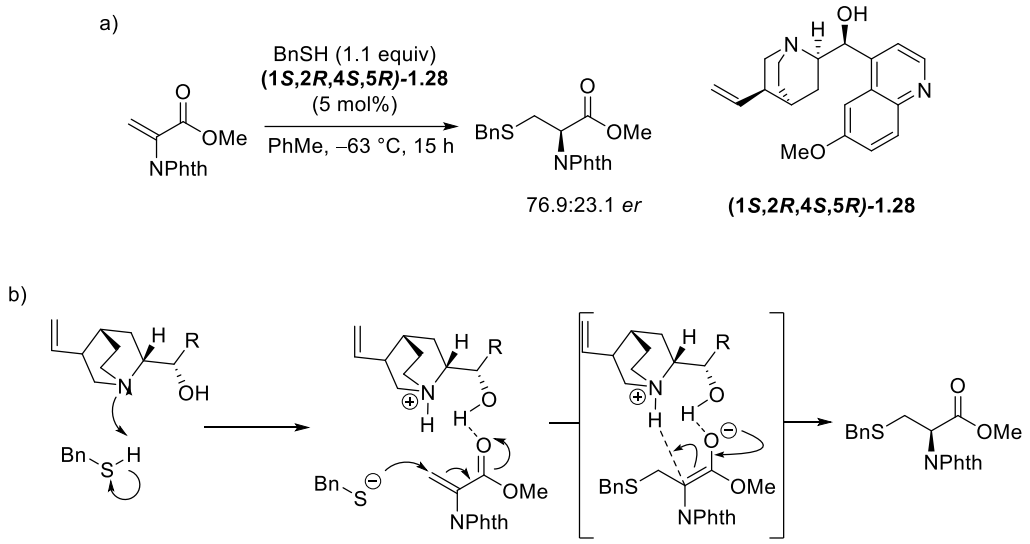


Scheme 1.17: Enantio- and diastereoselective hydrofluorination of α,β-unsaturated aldehydes.

1.3 Asymmetric Protonation in Conjugate Addition Reactions

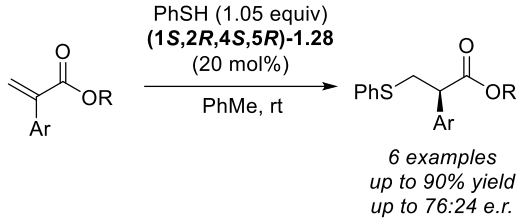
1.3.1 Frontier Work

In 1977, Pracejus and co-workers showed that the thio-Michael addition of benzylmercaptan and phthalimide protected α-aminoacrylates with the catalyst quinidine **(1*S*,2*R*,4*S*,5*R*)-1.28** provided enantiomerically enriched α-aminoesters (Scheme 1.18a).[27] Enantioinduction was due to the ability of **(1*S*,2*R*,4*S*,5*R*)-1.28** to asymmetrically protonate the corresponding enolate resulting from the Michael addition *via* the complex shown in Scheme 1.18b.



Scheme 1.18: Pracejus' thio-Michael addition-asymmetric protonation.

Kumar, Dike, and co-workers in 1991 demonstrated the synthesis of (*S*)-Naproxen by utilizing a conjugate addition-asymmetric protonation reaction.[28] They investigated the thio-Michael addition of thiophenol to α-arylacrylates in the presence of Cinchona alkaloids, with **(1*S*,2*R*,4*S*,5*R*)-1.28** providing the best results (Scheme 1.19). Therefore, the group proposed that the thiol protonates the tertiary amine on **(1*S*,2*R*,4*S*,5*R*)-1.28** before nucleophilic addition into the Michael acceptor to form an intermediate similar to the one shown in Scheme 1.18b.

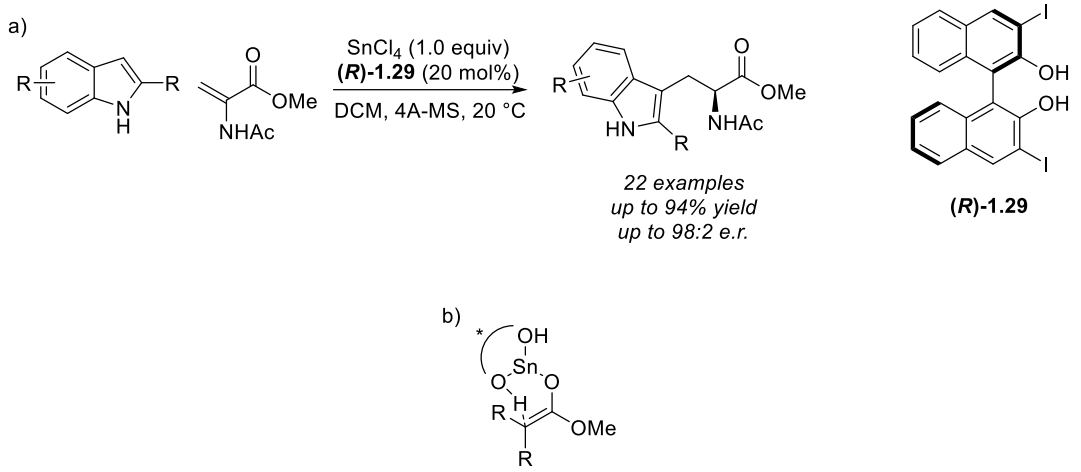


Scheme 1.19: Kumar and Dike's Michael addition-asymmetric protonation.

1.3.2 Lewis Acidic Metal-Ligand Complex Catalysis

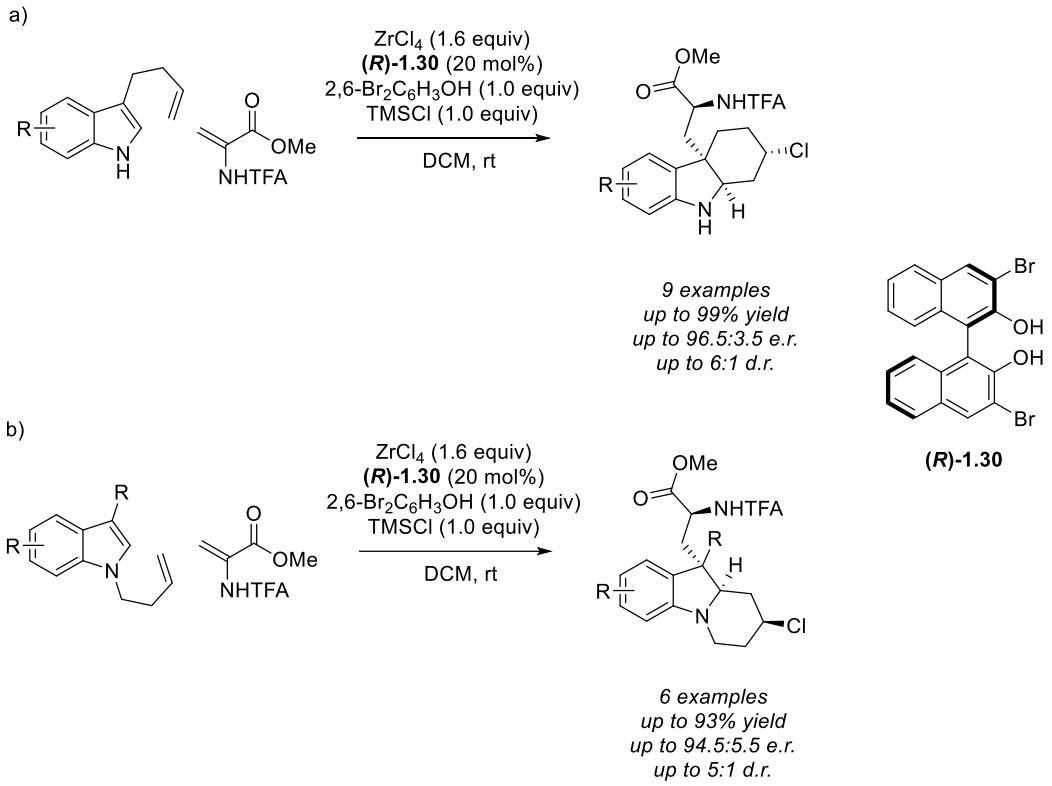
In 2012, Reisman and co-workers showcased the asymmetric protonation of the Michael addition between indoles and an α-amino methyl acrylate using tin (IV) chloride and the BINOL derivative **(*R*)-1.29**. This work furnished tryptophan derivatives in high yields and enantioselectivities (Scheme 1.20a).[29] Substitution upon the 2-position of the indole tolerated various aryl and alkyl motifs. However, the yield decreased while using the

bulky *t*Bu. Heteroatom substituents were explored at the 2-position of the indole. With iodine at the 2-position of the indole, the starting material underwent decomposition. Additionally, utilizing trimethylsilyl at the 2-position of the indole, no reaction occurred. Enantioinduction was achieved *via* the tin(IV)-**(*R*)-1.29** complex activating the Michael acceptor, creating a chiral proton donor (Scheme 1.20b).



Scheme 1.20: Reisman's Michael addition-asymmetric protonation.

In 2016, Reisman and co-workers developed a Michael addition-asymmetric protonation-aza-Prins cascade reaction (Scheme 1.21a and b).[30] Indoles containing a pendant vinyl motif were treated with an α-amino methyl acrylate, zirconium(IV) chloride, BINOL derivative **(*R*)-1.30**, 2,6-dibromophenol, and trimethylsilyl chloride to yield the desired hexahydrocarbazole. Indoles containing an electron-withdrawing group underwent this reaction with decreased yields. The decrease in yield was potentially due to the initial Michael addition step, as a decrease in yield was also observed within the previous study when electron-withdrawing groups were present upon the indole.

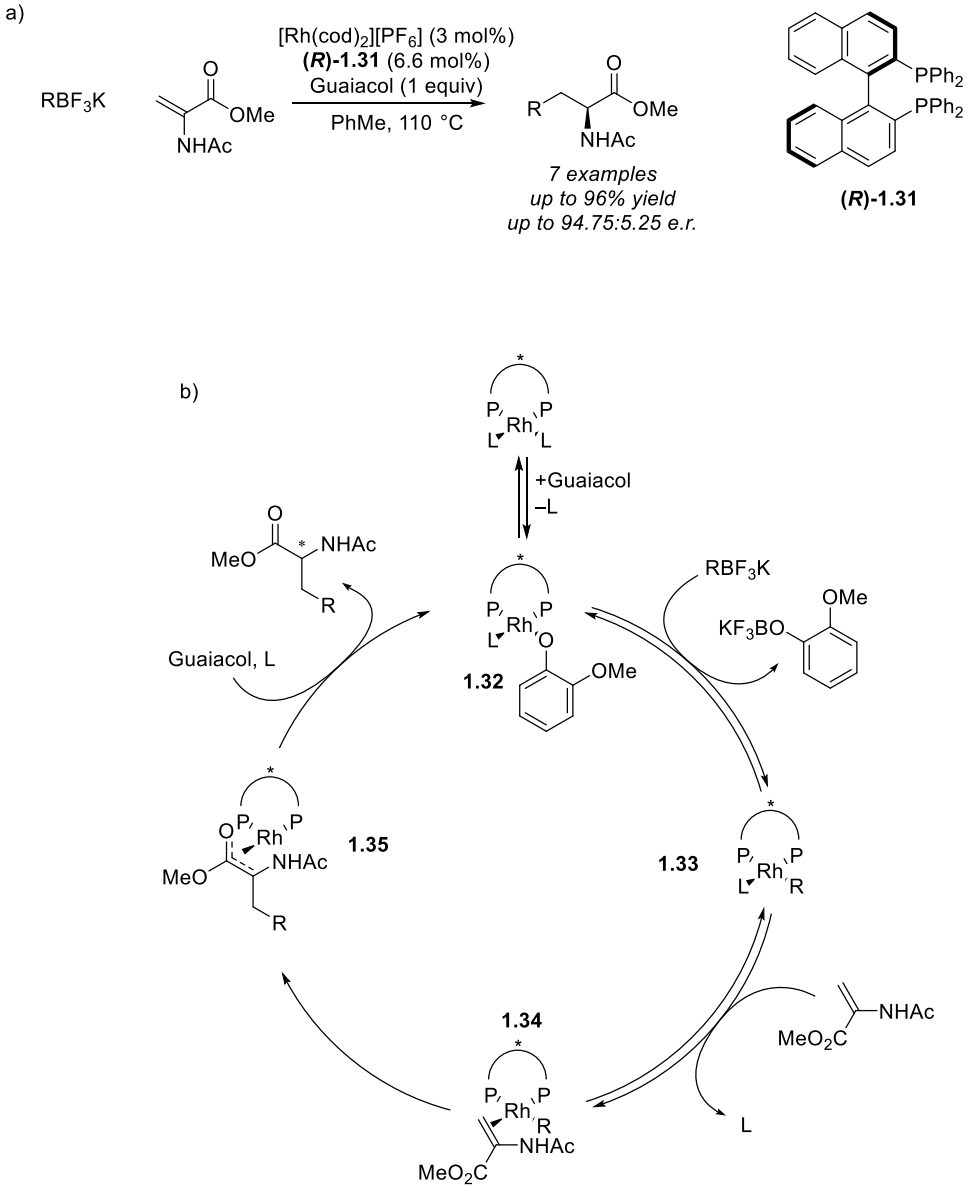


Scheme 1.21: Reisman's Michael addition-asymmetric protonation-aza Prinz cascade reaction.

1.3.3 Transition Metal-Ligand Complex Catalysis

In 2004, Genet and co-workers investigated asymmetric protonation in a rhodium-catalyzed Michael addition using methyl acrylates, aryl potassium trifluoroborate salts, a rhodium(I) catalyst in combination with bidentate phosphine ligand **(*R*)-1.31**, and the achiral proton donor guaiacol to yield enantiomerically enriched amino acid derivatives (Scheme 1.22a).[31] This methodology also tolerated alkenyl potassium trifluoroborate salts; however, due to rhodium-catalyzed double-bond migration, the products were inseparable mixtures of alkene isomers. Therefore, the group proposed that the reaction proceeded *via* the active catalyst **1.32**, which was formed by adding guaiacol to the rhodium (0) species. The rhodium(II) species **1.32** then underwent a transmetallation with the potassium trifluoroborate salt to form the rhodium(II) species **1.33**, which then coordinated to the Michael acceptor to form the rhodium(II) species **1.34**. Next, migratory insertion of an alkenyl/aryl group from **1.34** provided the rhodium(II) enolate species **1.35**. Finally, asymmetric protonation of the enolate species from guaiacol

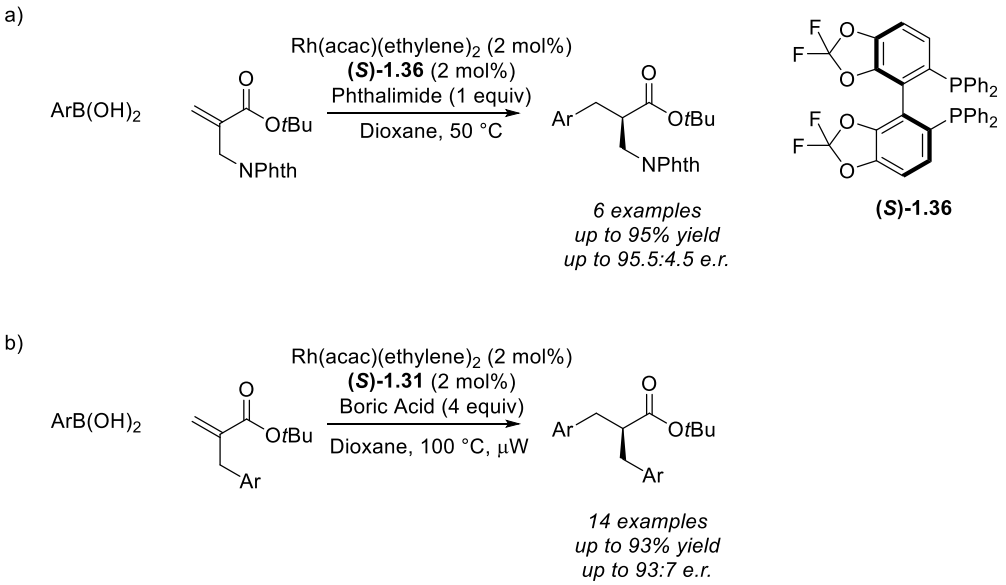
yielded the desired product and the rhodium(II) species **1.32**, closing the cycle (Scheme 1.20b).



Scheme 1.22: Rhodium-catalyzed Michael addition-asymmetric protonation of aminoacrylate.

This procedure was further developed in 2005 by Patil and co-workers. This reaction was able to utilize the widely available boronic acid, which provided access to a broader range of starting materials compared to the potassium trifluoroborates.[32] *t*Bu-Acrylates, boronic acids, rhodium, difluorophos **(*S*)-1.36**, and phthalimide were used to furnish the enantiomerically enriched β-amino acids (Scheme 1.23a), proceeding through a similar mechanism to Scheme 1.22b.[31] In 2007, Gleave and co-workers developed a method for

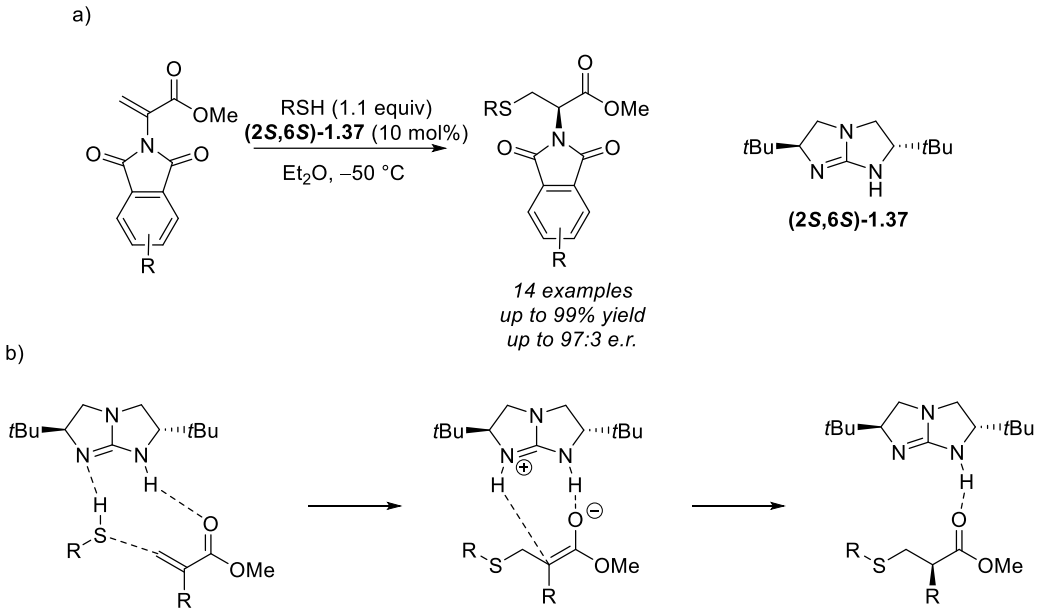
the rhodium-catalyzed Michael addition-asymmetric protonation of α-benzyl *t*-butylacrylates arylboronic acids using **(*S*)-1.31**, to furnish the desired enantiomerically enriched products (Scheme 1.23b).[33]



Scheme 1.23: Rhodium-catalyzed Michael addition-asymmetric protonation.

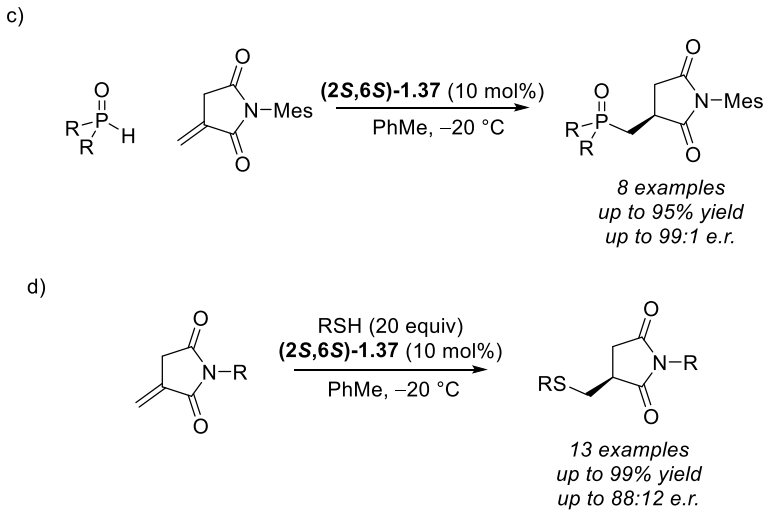
1.3.4 Organocatalysis

The development of organocatalysts has been of interest to many researchers in chemistry. Organocatalysts offers ease and low costs compared to organometallic catalytic systems, which can be expensive, toxic, or not bench stable.[34] In 2008, Tan and co-workers investigated the use of the bicyclic guanidine **(2*S*,6*S*)-1.37** as a chiral Brønsted base in the Michael addition-asymmetric protonation of phthalimide protected α-amino methyl acrylates with thiols, to yield the desired products in excellent yields and enantioselectivities (Scheme 1.24a).[35] This organocatalysis variant allowed for a much simpler procedure due to only requiring a single additive. Furthermore, this enantioselectivity was due to the basic nature of **(2*S*,6*S*)-1.37**, yielding a chiral conjugate acid to react with the enolate (Scheme 1.24b).



Scheme 1.24: Guanidine catalyzed Michael addition-asymmetric protonation.

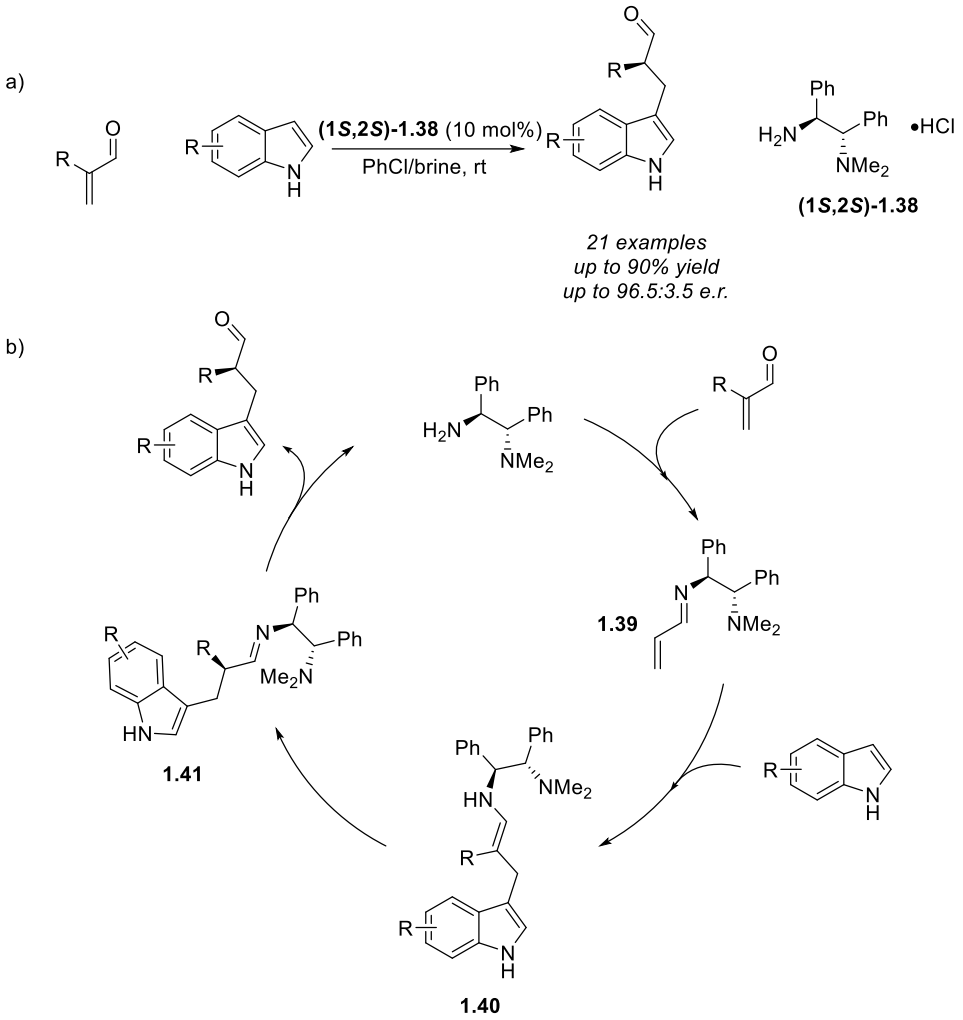
Tan and co-workers also demonstrated the tolerance of phosphine (Scheme 1.25a) and thiol nucleophiles (Scheme 1.25b) in the Michael addition-asymmetric protonation reaction with vinyl succinimides utilizing guanidine catalyst **(2*S*,6*S*)-1.37**.[36]



Scheme 1.25: Guanidine catalyzed Michael addition-asymmetric protonation of vinyl succinimides.

Activation of α,β-unsaturated aldehydes in the Michael addition-asymmetric protonation typically employs a diamine salt. In 2013, Cheng and co-workers developed a procedure using α,β-unsaturated aldehydes with indoles employing the diamine salt catalyst **(1*S*,2*S*)-1.38** to yield the enantiomerically enriched products (Scheme 1.26a).[37]

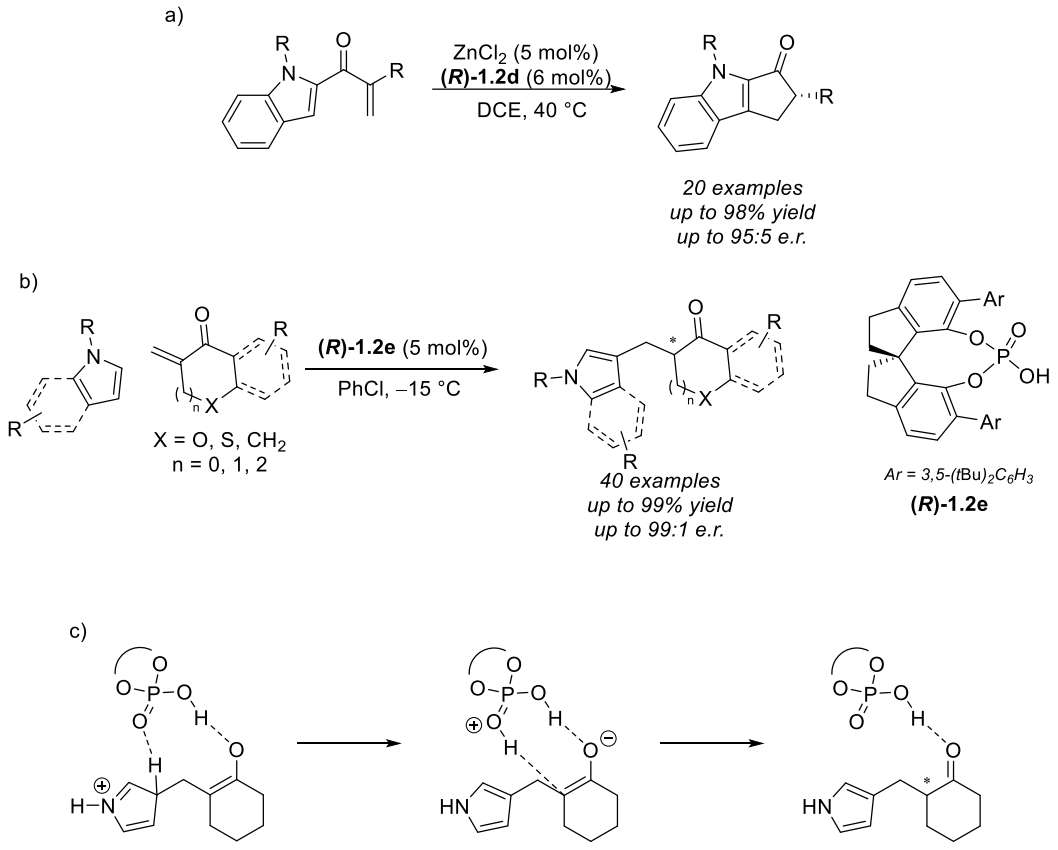
The mechanism followed the formation of an imine **1.39** from **1.38** and an α,β-unsaturated aldehyde. First, **1.39** underwent the Michael addition with an indole to form the enamine intermediate **1.40**, followed by an asymmetric protonation and reformation of the imine functionality **1.41**. Next, the imine underwent hydrolysis, releasing the desired product and catalyst, restarting the catalytic cycle (Scheme 1.26b).



Scheme 1.26: Michael addition-asymmetric protonation of α,β-unsaturated aldehydes

In 2017, Zhou and co-workers developed a Nazarov cyclization-asymmetric protonation reaction using an indole-based α,β-unsaturated ketone in the co-catalyzed system of zinc(II) chloride and SPINOL-based chiral phosphoric acid **(*R*)-1.2d** to yield the desired products in excellent yields and enantioselectivity (Scheme 1.27a).[38] In 2019, Zhou also utilized the SPINOL-based chiral phosphoric acid **(*R*)-1.2e** in the Michael addition of pyrroles and indoles with the α,β-unsaturated ketones to yield the desired

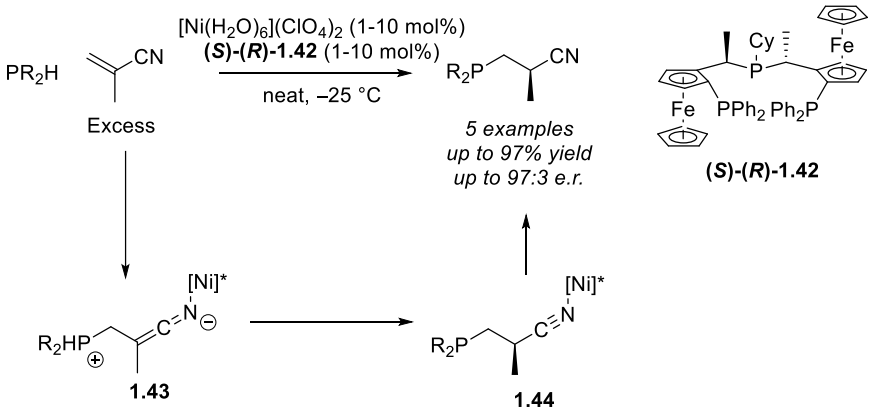
enantiomerically enriched products (Scheme 1.27b).[39] Zhou proposed that the Lewis basic site of the CPA shuttled the proton from the nucleophile to the enolate site (Scheme 1.27c).



Scheme 1.27: CPA catalyzed asymmetric protonation reactions of vinyl ketones.

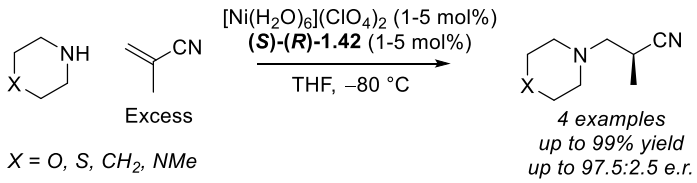
1.4 Alternative Michael Acceptors

The Togni group demonstrated the use of methylacrylonitriles as a Michael acceptor in the Michael addition-asymmetric protonation reaction.[40] The reaction of phosphine nucleophiles with an excess of methylacrylonitrile in the presence of nickel-(II) and triphosphine ligand **(*S*)-(*R*)-1.42** yielded the desired enantiomerically enriched nitrile product (Scheme 1.28). Activation of the vinylnitrile with the nickel-(II) catalyst facilitated the Michael addition to yield the intermediate **1.43**. Next, asymmetric protonation of **1.43** formed the intermediate **1.44**. Finally, the nickel catalyst released the product and re-entered the catalytic cycle.



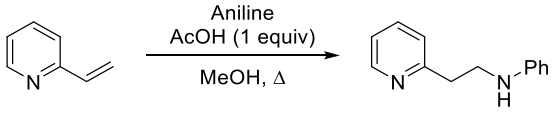
Scheme 1.28: Nickel catalyzed Michael addition-asymmetric protonation of acrylonitriles.

In 2008, the same group investigated the use of cyclic secondary amines in this reaction. Using the same conditions as Scheme 1.28, they achieved excellent yields and enantioselectivities using amine nucleophiles to generate chiral nitrile products (Scheme 1.29).[41]



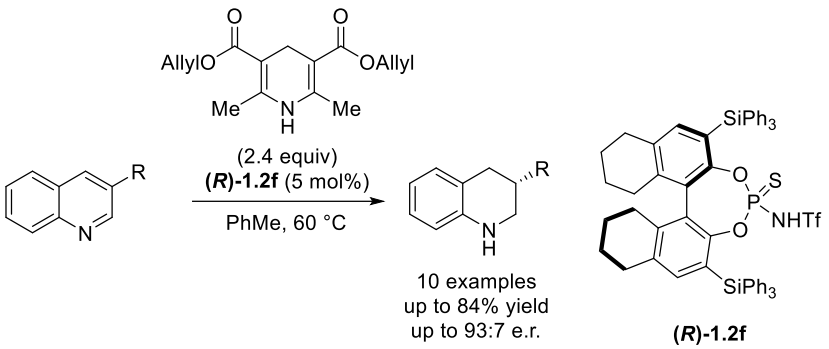
Scheme 1.29: Nickel catalyzed Michael addition-asymmetric protonation of acrylonitriles.

The first use of vinylheterocycles as Michael acceptors was in 1955, where Levine and co-workers employed vinyl pyridine and aniline in the presence of acetic acid to yield the desired Michael addition products (Scheme 1.30).[42]



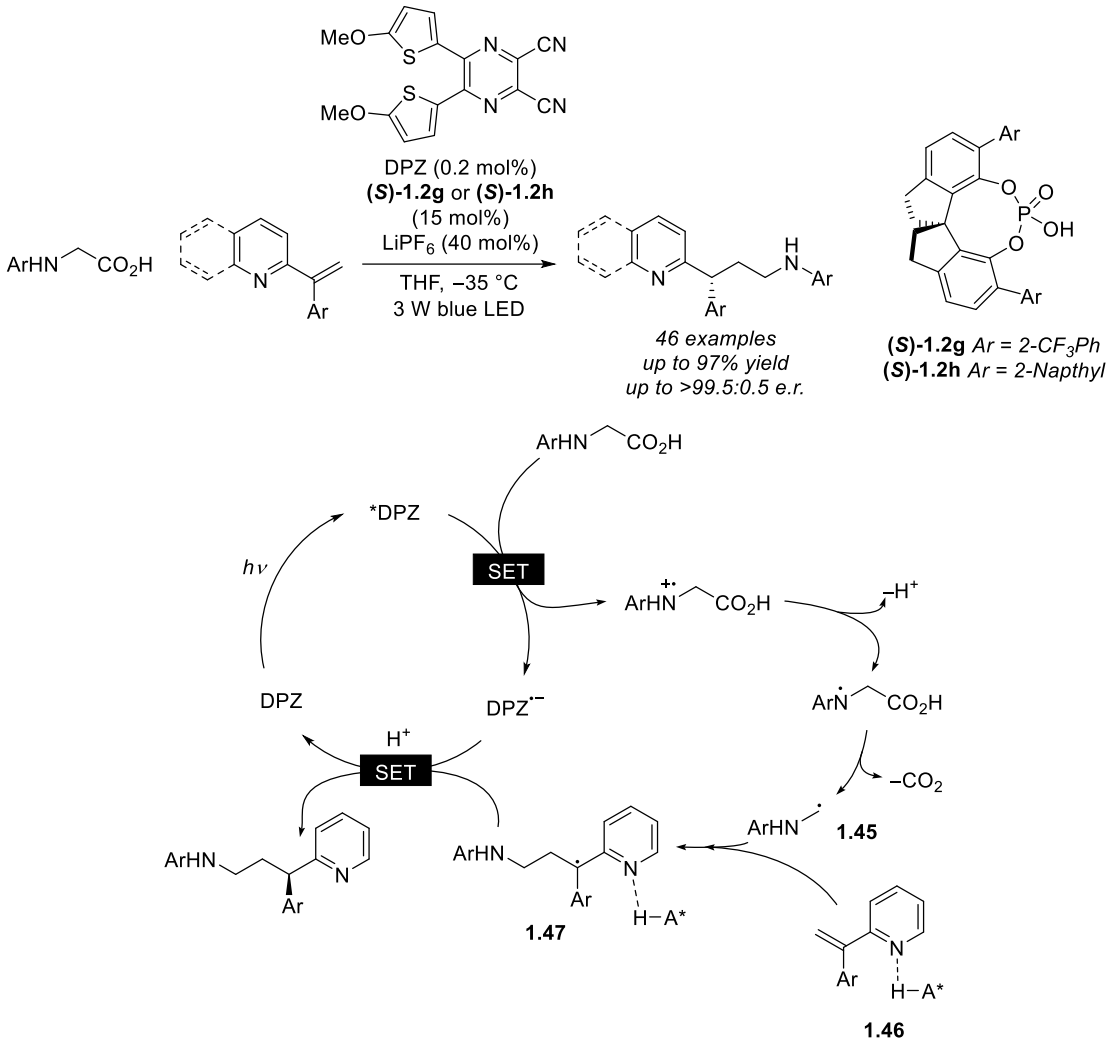
Scheme 1.30: Michael addition of vinylpyridine.

In 2008, Rueping and co-workers reported a 1,4-addition-asymmetric protonation-1,2-addition (Scheme 1.31).[43] Herein, 3-substituted quinolines in the presence of CPA **(*R*)-1.2f** and a Hantzsch dihydropyridine 3-substituted tetrahydroquinolines were furnished in up to excellent yields and excellent enantioselectivities.



Scheme 1.31: Rueping's CPA catalyzed 1,4-addition-asymmetric protonation-1,2-addition of 3-substituted quinolines.

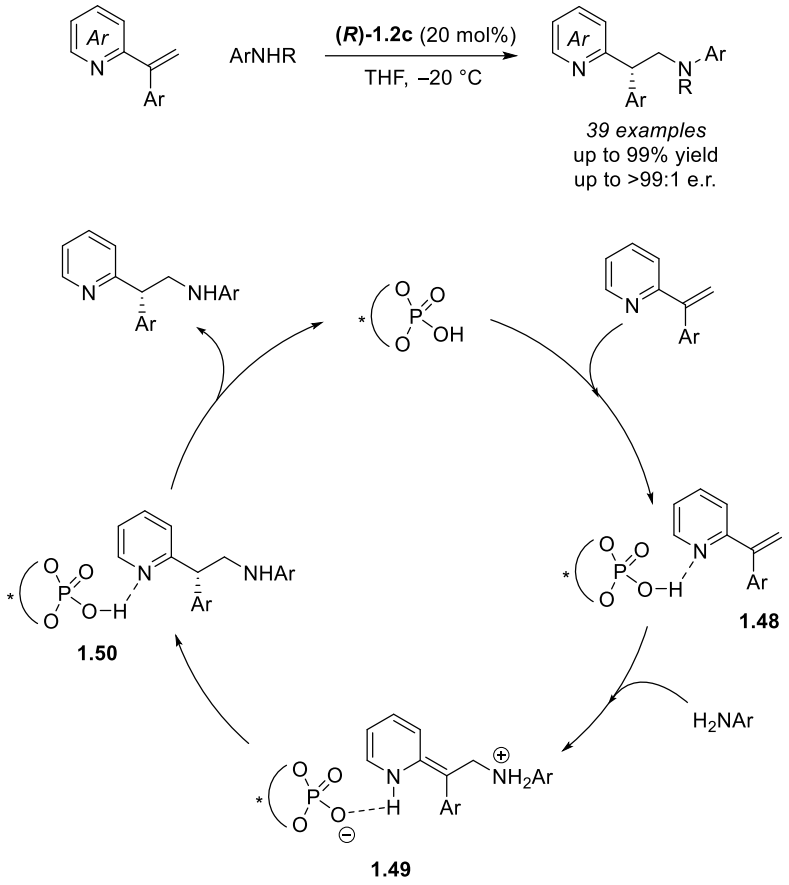
In 2018, Jiang and co-workers developed an enantioselective protonation approach to the Michael addition reaction of vinylheterocycles.[44] Treating α-substituted 2-vinylpyridine and 2-vinylquinolines with the photocatalyst DPZ, SPINOL-based CPA **(*S*)-1.2g** or **(*S*)-1.2h**, $LiPF_6$, and α-amino carboxylic acids, to yield the desired enantiomerically enriched α,γ-arylamino products (Scheme 1.32). The reaction proceeded through the generation of the radical **1.45** *via* a single electron transfer (SET) and decarboxylation of the α-amino carboxylic acid, which underwent the radical Giese addition with a chiral phosphoric acid activated vinyl heterocycle **1.46**. Finally, tertiary radical intermediate **1.47** underwent a SET and asymmetric protonation to regenerate the photocatalyst and yield the desired product.



Scheme 1.32: CPA catalyzed Michael addition-asymmetric protonation of vinylheterocycles.

In the same year, Watson and co-workers developed their reaction using vinylheterocycles as Michael acceptors (Scheme 1.33).[45] Arylamine nucleophiles, vinylheterocycles, and **(*R*)-1.2c** generated the desired chiral phenethylamine compounds in excellent yields and enantioselectivity. This procedure highlighted the use of many alternative nitrogen-based heterocycles and was compatible with benzothiazole, benzoxazole, quinoxaline, and 1,8-napthyridine. This reaction followed a similar pathway, where the chiral phosphoric acid activates the vinylheterocycle to form the bound complex **1.48**, followed by an aza-Michael addition to form the enamine intermediate **1.49**. Next, the enamine intermediate underwent an asymmetric protonation to yield the bound complex **1.50**. Finally, the product was released and the catalyst regenerated. Compared to the system developed by Jiang and co-workers, this

is simpler due to not requiring a photocatalyst and an additive. Additionally, both systems utilized different nucleophiles, Jiang's methodology utilized nucleophilic carbon radicals, and the Watson methodology utilized arylamines. In both systems, the scope of the Michael addition-asymmetric protonation reaction only included vinylheterocycles with aryl and alkyl substituents in the α-position.



Scheme 1.33: CPA catalyzed Michael addition-asymmetric protonation of vinylheterocycles.

1.4 Proposed Work

Based on the Watson group's work regarding applying an aza-Michael addition-asymmetric protonation to vinylheterocycles (Scheme 1.30),[45] this project aimed to investigate the ability to alter the functionality at the α-position of the vinylheterocycle. The proposal was to use fluorovinylheterocycles, allowing access to valuable chiral benzylic fluorine compounds by introducing chirality to an already established C–F bond, obviating the use of reactive F^+ and F^- reagents. The reaction would be mechanistically similar to the previous work done by the Watson group. However, when previously the

control of enamine geometry was assisted by a steric interaction of the catalyst with the bulky aryl group, this will no longer be possible with fluorine due to its small atomic size. It was hypothesized that enamine geometry would instead be controlled using fluorine's intrinsic polarity, dipole-dipole minimization between the C–F bond and heterocycle core will expectantly cause a favored enamine geometry (Figure 1.4).[43]

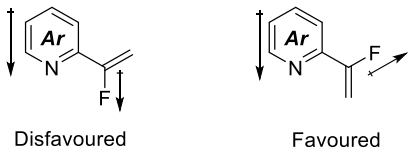
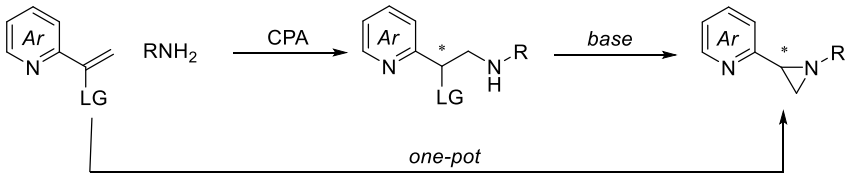


Figure 1.4: Dipole-dipole minimization of fluorovinylheterocycles.

Succeeding this, we envisioned that utilizing an aza-Michael-asymmetric protonation reaction upon vinylheterocycles with a leaving group at the α-position would yield a suitable precursor for enantioenriched heterocyclic aziridines. This was followed by investigating the viability for a one-pot procedure, allowing for the direct synthesis of enantioenriched aziridines from a vinylheterocycle, amine, and CPA (Scheme 1.31).



Scheme 1.31: Proposed one-pot procedure to chiral aziridines from vinylheterocycles.

Furthermore, during the development of these methodologies, an additional aim of elucidating the nature of the asymmetric protonation step through both kinetic and computational analysis was explored.

1.5 References

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Chapter 2

Investigation of Fluorovinylheterocycles in the Aza-Michael Addition-Asymmetric Protonation Reaction

This chapter is based upon the following publication: *Chem. Eur. J.* **2020**, *26*, 12249 – 12255.[47]

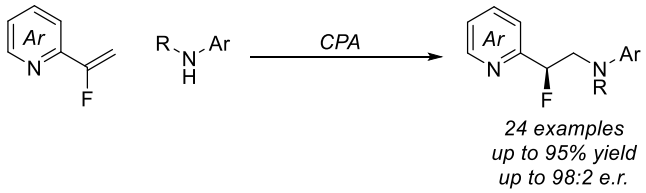
The chapter has the following contributions: I synthesized the required starting materials and catalysts. Dr Chao Xu and I prepared the racemic HPLC references. Dr Chao Xu and I performed the optimization reactions. Dr Chao Xu, Dr John J. Molloy, and I performed substrate screening reactions. Dr Andrew Leach performed the DFT calculations. I prepared the XRD samples and Prof. Alexandra Slawin and Cameron Carpenter-Warren collected the XRD data. I performed the KIE experiments.

Numbered compounds in chapter 2 will follow the order 2.1, 2.2, 2.3,…etc.

2 Investigation of Fluorovinylheterocycles in the Aza-Michael Addition-Asymmetric Protonation Reaction

2.1 Synopsis

This chapter discusses the development of the CPA-catalyzed dearomatizing aza-Michael addition-rearomatizing asymmetric protonation of fluorovinylheterocycles. The reaction was able to afford heterocyclic phenethylamine products containing a benzylic stereocentre with a carbon-fluorine bond, with excellent yields and levels of enantioselectivity (Scheme 2.1). Computational and kinetic experiments were conducted to investigate the mechanism of the reaction. The conformational bias of the products was explored *via* XRD and computational data. Finally, the utility of the products in medicinal chemistry was discussed.



Scheme 2.1: Fluorovinylheterocycles as Michael acceptors in the dearomatizing Michael addition-rearomatizing asymmetric protonation reaction.

2.2 Background

It has been reported that 20% of pharmaceutical and 35% of agricultural compounds contain a fluorine atom.[48] Amongst these compounds a chiral C–F bond is present. For example, MK-0731 is a kinesin spindle protein inhibitor,[49] 7-F-PGI$_2$ has potent anti-anginal activity,[50] and Fludrocortisone used to treat adrenogenital syndrome, postural hypotension, and adrenal insufficiency (Figure 2.1).[51]

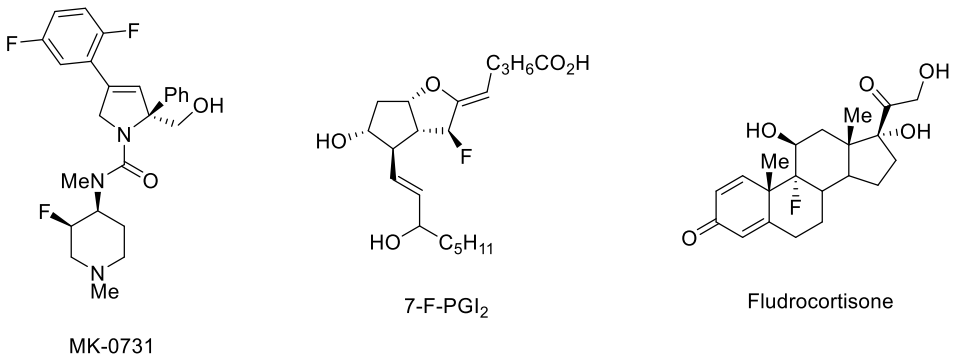
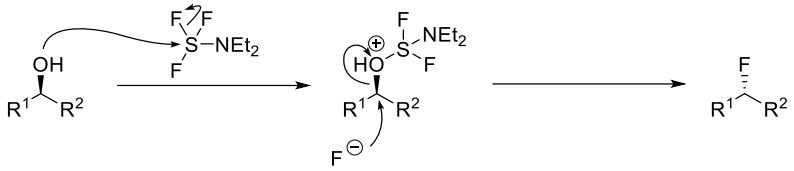


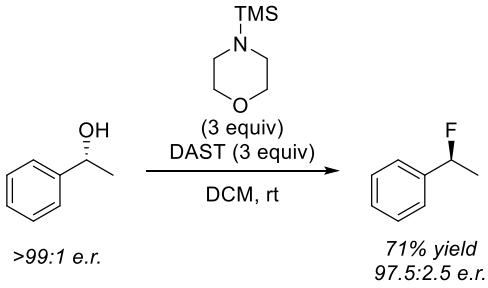
Figure 2.1: Examples of biologically active compounds containing carbon stereocentres with a carbon-fluorine bond.

Synthesis of enantioenriched compounds containing carbon stereocentres with a carbon-fluorine bond is commonly achieved *via* deoxyfluorination of an already established chiral precursor (Scheme 2.2).[52]



Scheme 2.2: Deoxyfluorination example using DAST

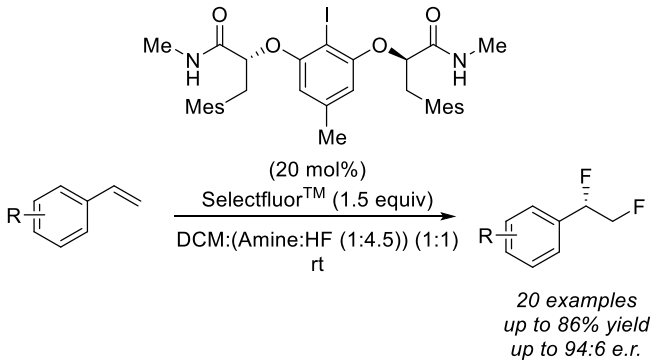
Stereospecificity is often diminished in benzylic substrates due to a competing S_N1 pathway. In 2010, O'Hagan and co-workers developed a methodology to allow for a stereospecific deoxyfluorination of benzylic alcohols.[53] Using the additive TMS-morpholine and DAST, the dissociative pathway was hindered and furnished the benzyl fluoride with an excellent enantiomeric ratio (Scheme 2.3).



Scheme 2.3: Dehydroxyfluorination of Benzylic Alcohols.

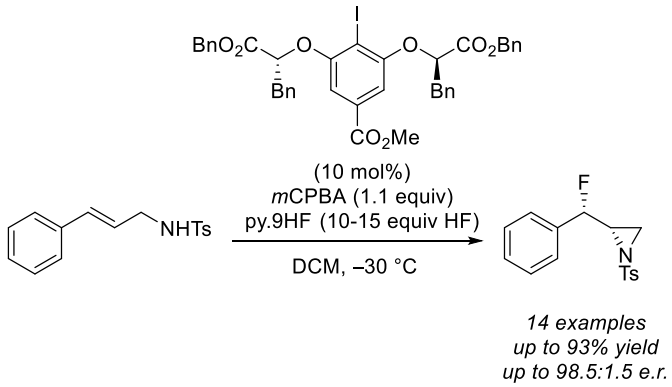
Hypervalent iodine catalysis has been used to generate highly enantioenriched benzylic fluorides. For example, in 2018, Gilmour and co-workers developed a difluorination

protocol to generate benzylic fluorides with excellent yields and enantioselectivity (Scheme 2.5).[54]



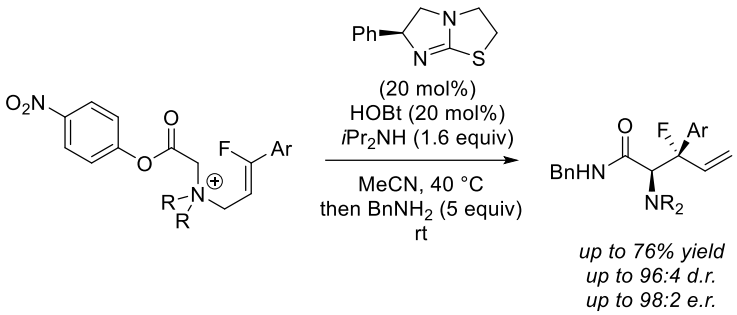
Scheme 2.4: Enantioselective difluorination of styrenes.

Another example was by Jacobsen and co-workers in 2018. A hypervalent iodine catalyst was used to furnish *syn*-β-fluoroaziridine compounds in excellent yields and enantioselectivity (Scheme 2.5).[55]



Scheme 2.5: Stereoselective synthesis of syn*-β-fluoroaziridine compounds.*

In these cases, highly reactive selectfluor™ is required. However, it is possible to introduce chirality into an already established C–F bond, this alleviates the use of reactive fluorinating reagents. For example, in 2017, Smith and co-workers reported an isothiourea-catalyzed process to generate β-fluoro-β-aryl-α-aminopentenamides in good yields and excellent enantioselectivities (Scheme 2.6). [56]

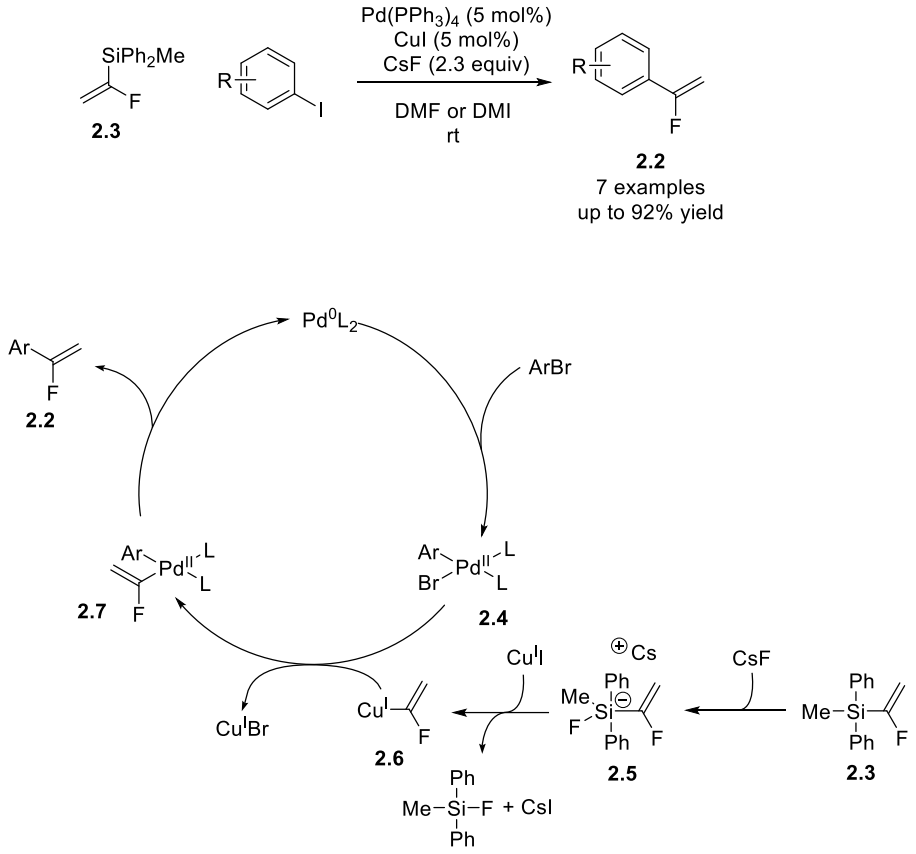


Scheme 2.6: Stereoselective synthesis of β-fluoro-β-aryl-α-aminopentenamides.

2.3 Preliminary Work

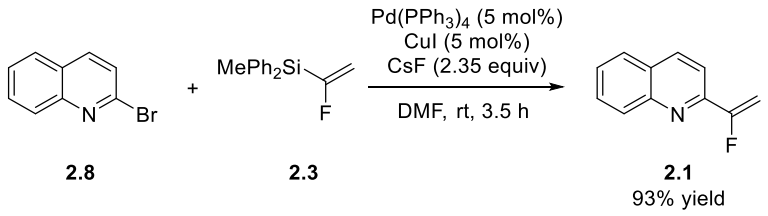
2.3.1 The Synthesis of 2-(1-Fluorovinyl)heterocycles

A synthetic route to the desired benchmark substrate, 2-(1-fluorovinyl)quinoline **2.1**, was sought to begin the investigation. The work of Hanamoto and co-workers, where compound **2.2** was synthesized *via* a Hiyama coupling between compound **2.3** and an aryl iodide (Scheme 2.7a), appeared promising.[57] The mechanism proceeded through an oxidative addition between an aryl halide and palladium(0) to yield the palladium(II) complex **2.4**. Next, using cesium fluoride to form the reactive pentavalent silyl species **2.5** drove the transmetallation of compound **2.3** with copper(I) to yield the copper(I) species **2.6**. Next, compound **2.6** underwent transmetallation with **2.4** to yield the palladium(II) species **2.7**. Finally, compound **2.7** underwent reductive elimination to regenerate the palladium(0) and yielded the desired product (Scheme 2.7b). The authors explored using their methodology on heterocycles by using 2-bromo-5-nitropyridine, although this achieved a yield of 29%.



*Scheme 2.7: a) Synthesis of **2.2**. b) Mechanism of the Hiyama coupling.*

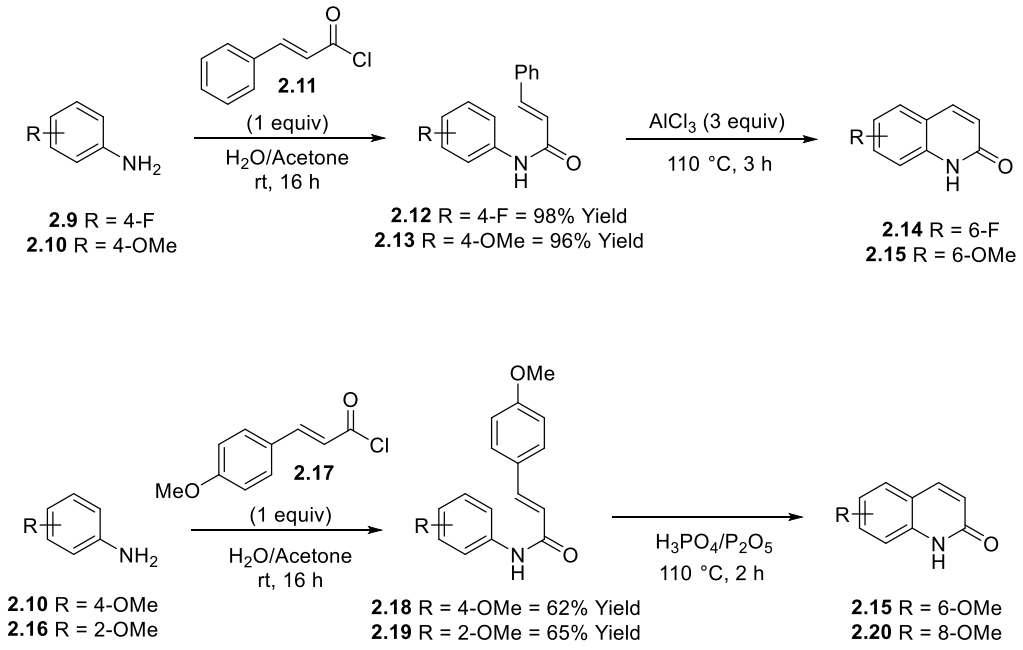
Utilizing the procedure of Hanamoto and co-workers, **2.1** was prepared in excellent yield from **2.8** and **2.3** (Scheme 2.8). Despite the low yield for the pyridine substrate Hanamoto and co-workers achieved, this result demonstrated that the poor tolerance of the Hiyama coupling was not a characteristic of nitrogen-based heterocycles.



*Scheme 2.8: Synthesis of **2.1**.*

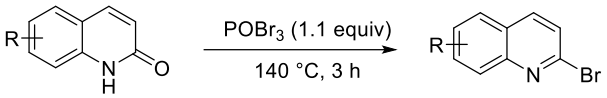
It was necessary to synthesize a variety of heterocycles to explore the substrate scope of the reaction fully. The synthesis of some of the desired bromoheterocycles was required as they were not readily available. The amide couplings of anilines **2.9** and **2.10** with the acyl chloride **2.11** furnished the desired amides **2.12** and **2.13** (Scheme 2.9).[58]

The corresponding Friedel-Crafts reaction of **2.12** with aluminium trichloride furnished the desired crude carbostyril **2.14**, though this product was insoluble in most solvents. As a result, the crude carbostyril was used directly in the next step.[59] The Friedel-Crafts reaction of amide **2.13** with aluminum trichloride yielded a complex crude mixture with no desired carbostyril **2.15**. Therefore the synthesis of compound **2.15** was revised. Amides **2.18** and **2.19** were prepared *via* the coupling of **2.10** and **2.16** with the acyl chloride **2.17**.[58] The Friedel-Crafts reaction of **2.18** and **2.19** with phosphoric acid and P_2O_5 achieved the desired crude carbostyrils **2.15** and **2.20**.[59]



Scheme 2.9: Synthesis of desired carbostyrils

Deoxybromination of the crude carbostyril **2.14** and the commercially available carbostyril **2.21** yielded the desired bromoheterocycles **2.22** and **2.23** in moderate yields (Scheme 2.10).[60] However, the deoxybromination of crude carbostyrils **2.15** and **2.20** only provided trace quantities of the desired products; therefore, these substrates were not pursued further.

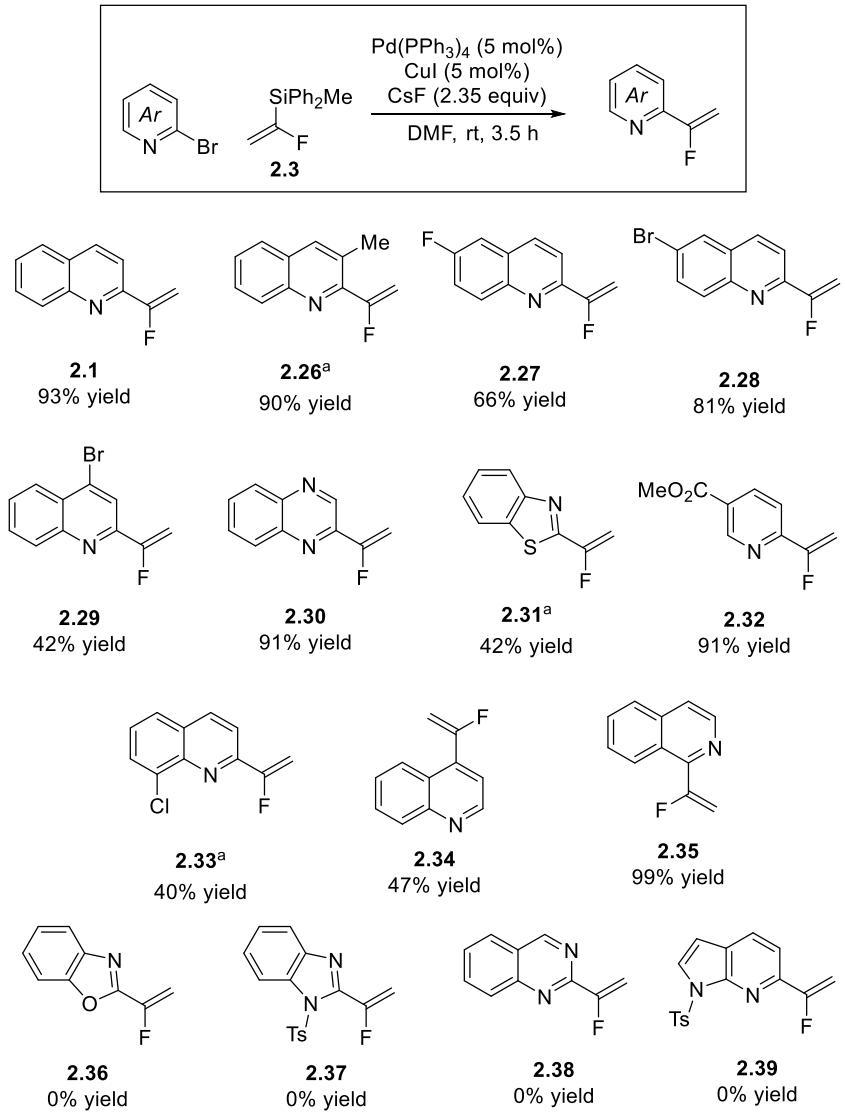


2.14 R = 6-F
2.15 R = 6-OMe
2.20 R = 8-OMe
2.21 R = 6-Br

2.22 R = 6-F = 50% Yield (2 steps)
2.23 R = 6-Br = 62% Yield (2 steps)
2.24 R = 6-OMe = trace
2.25 R = 8-OMe = trace

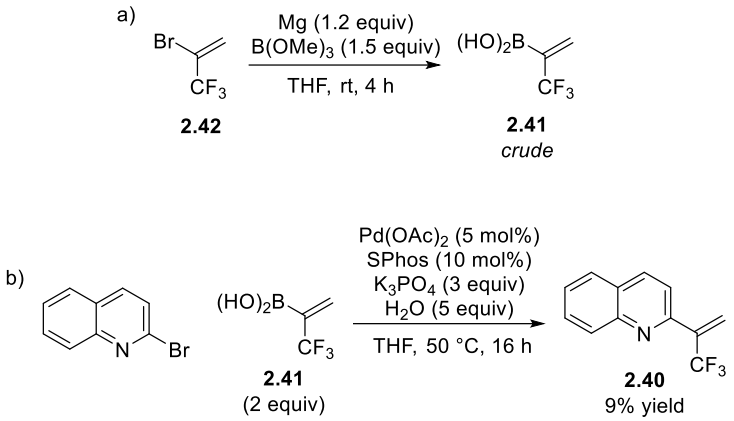
Scheme 2.10: Synthesis of bromoheterocycles.

By utilizing the Hiyama coupling developed by Hanamota and co-workers to synthesize the model substrate **2.1**, access to the heterocycles **2.26**-**2.35** was achieved (Scheme 2.11).[57] Heterocycles **2.26**, **2.31**, and **2.33** were achieved with a conversion of 5% under the standard conditions. The palladium catalyst did not turnover during the cycle, and increasing the stoichiometry of palladium and copper catalysts to one equivalent provided much higher conversions. The preparation of compounds **2.36**-**2.39** was unsuccessful and only returned the intact starting materials.



*Scheme 2.11: Synthesis of vinylheteroaryls **2.6**, **2.26**-**2.39**. [a]Pd(PPh3)4 (1 equiv), CuI (1 equiv).*

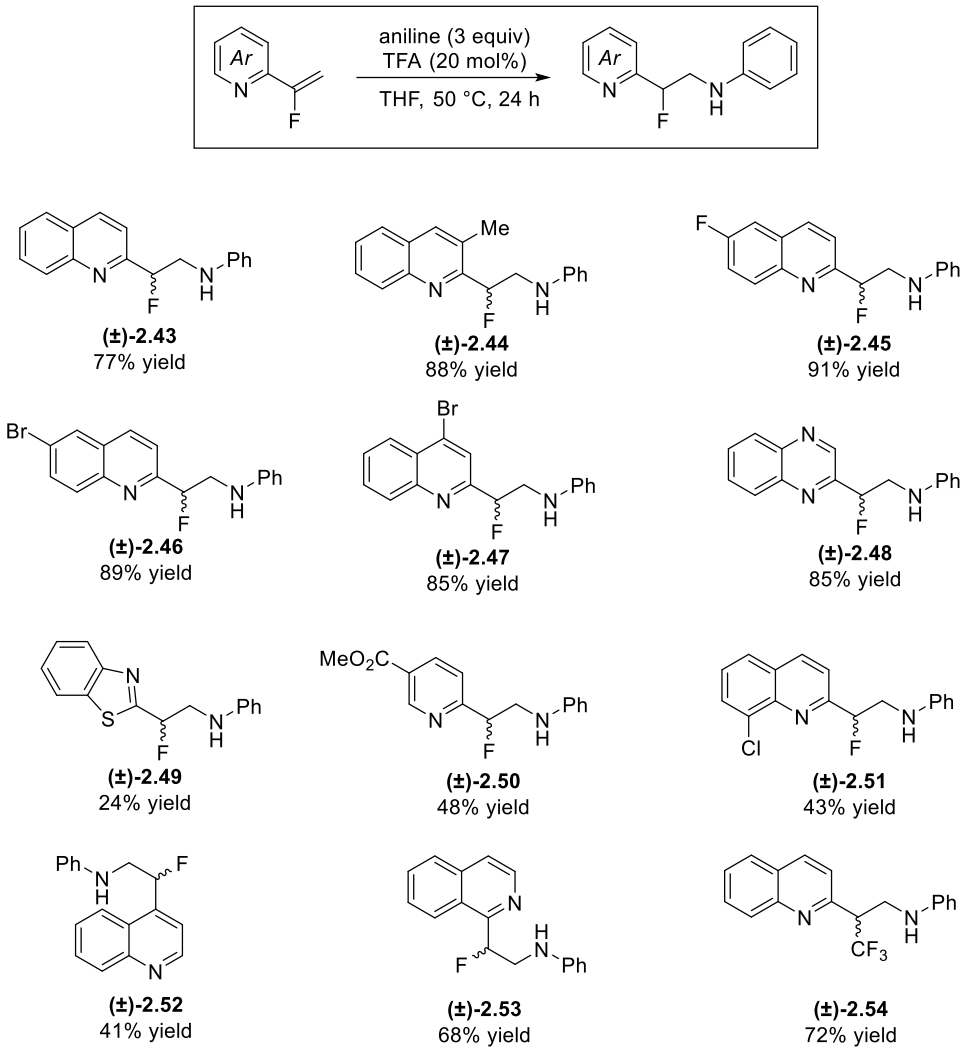
Due to the trifluoromethyl analog of **2.3** not being commercially available, an alternative route to furnish compound **2.40** was sought. The Suzuki-Miyaura coupling was appealing, as there was precedent for synthesizing the desired boronic acid starting material **2.41**.[61] Forming the Grignard reagent of **2.42**, followed by a reaction with trimethylborate and aqueous workup, **2.41** was furnished (Scheme 2.12a). Finally, **2.41** was used directly in a Suzuki-Miyaura coupling with 2-bromoquinoline to furnish the desired product **2.40** (Scheme 2.12b).[62] The low yield was attributed to the stability of **2.40**, which was required to be used directly after purification.



*Scheme 2.12: Synthesis of **2.40**.*

2.3.2 Preparation of Racemic Substrates (Heteroaryl Scope)

Following the synthesis of the desired heterocycle starting materials, it was essential to utilize the achiral acid-catalyzed conjugate addition to provide the achiral products used as HPLC references. Thus, the reaction of heterocycles **2.1**, **2.26**-**2.35**, **2.40**, and aniline were catalyzed by trifluoroacetic acid (TFA) at 50 °C for 24 h to furnish the achiral products **(±)**-**2.43**-**2.54** (Scheme 2.13).



*Scheme 2.13: Synthesis of racemic compounds **(±)-2.48-2.59**.*

The mechanism of this reaction proceeded in the same fashion as the chiral acid-catalyzed reaction (Figure 2.2): activation of the vinyl heterocycle **2.55** with TFA formed the bound complex **2.56**; this underwent an aza-Michael addition forming the enamine intermediate **2.57**. Finally, a rearomatizing protonation of intermediate **2.57** formed the TFA-bound product **2.58**. The product **2.59** was then released, turning over TFA to begin the next cycle.

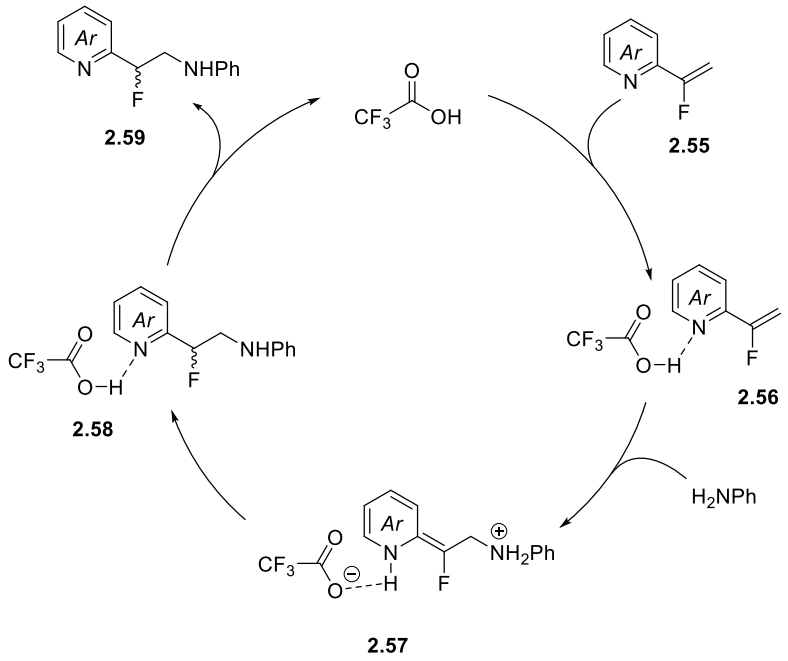


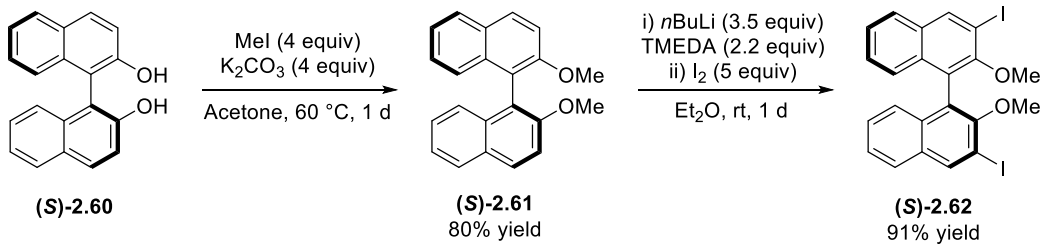
Figure 2.2: Catalytic cycle for the racemic dearomatizing Michael addition-rearomatizing protonation reaction.

The use of alternative nucleophiles was also explored. However, the increased basicity of alkylamines form an acid-base salt with TFA and removed the catalyst out of the reaction. Alkyl alcohols and aryl alcohols provided no reaction, presumably due to their lower nucleophilicity. Alkylthiols and arylthiols underwent a Michael-addition with **2.1**. However, owing to the presence of a significant background reaction, these substrates were not pursued further.

2.3.3 Catalyst Synthesis

With the synthesis of the fluorovinylheterocycle starting materials and the validation and scope of the achiral acid-catalyzed conjugate addition complete, attention turned towards the enantioselective reaction. Based on the Watson group's previous work,[45] chiral phosphoric acid **1.2c** was proposed to be an ideal catalyst to begin this investigation.

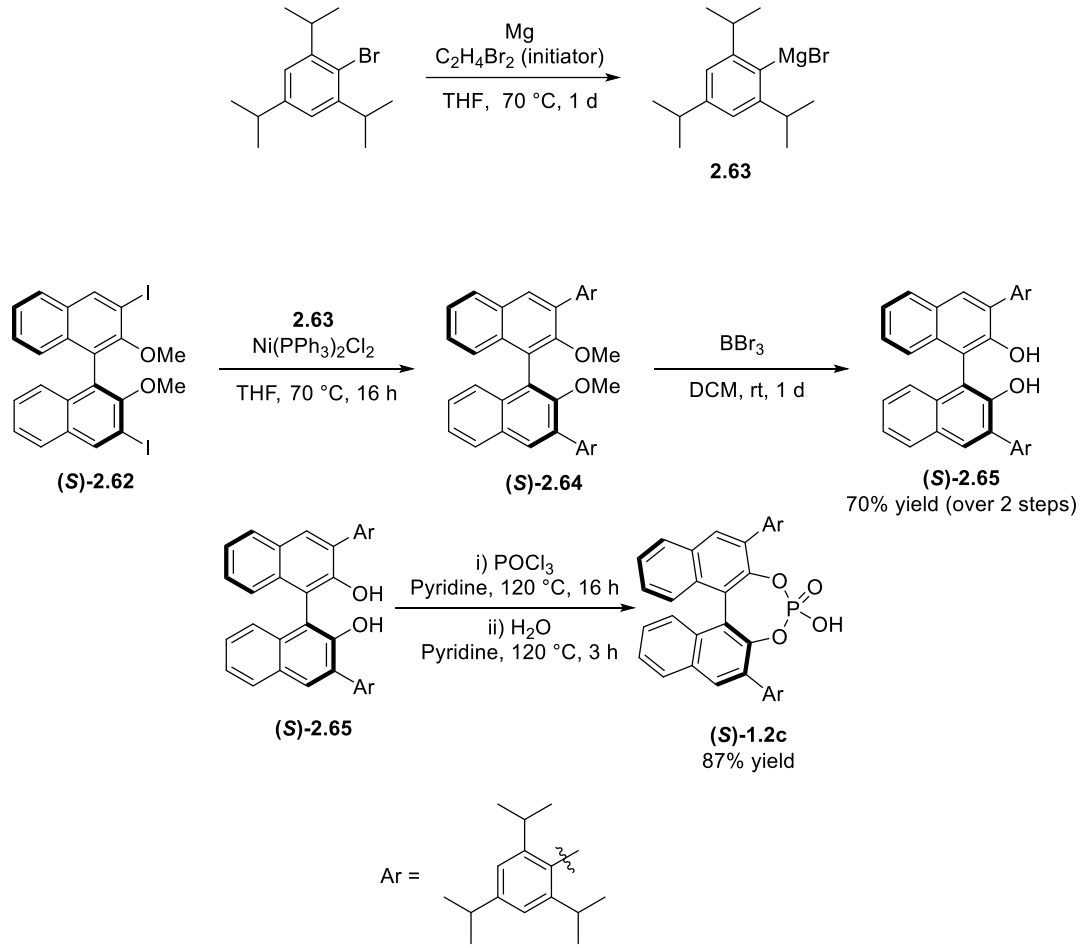
The CPA **(*S*)-1.2c** was prepared *via* the synthetic route shown below (Scheme 2.14 and 2.15). Initially, BINOL **(*S*)-2.60** was reacted with methyl iodide to provide the dimethyl protected BINOL **(*S*)-2.61**.[63] The methylated BINOL **(*S*)-2.61** was then iodinated in the 3,3'-position, *via* directed *ortho*-metalation, furnished **(*S*)-2.62** in an excellent yield.[64]



*Scheme 2.14: Synthesis of **2.62**.*

The Grignard reagent **2.63** was prepared by reacting the parent arylbromide with magnesium, using 1,2-dibromoethane as an activator. The Grignard solution of **2.63** (0.4 M) was then used in the Kumada coupling with compound **(*S*)-2.62** using $Ni(PPh_3)_2Cl_2$ as the catalyst to yield compound **(*S*)-2.64**; however, this reaction provided little conversion to the product in the first instance. Investigating the Kumada coupling led to two discoveries. Higher conversions were achieved by storing freshly synthesized $Ni(PPh_3)_2Cl_2$ in a vacuum desiccator. The nickel catalyst would become wet with water over time in the fridge, making it incompatible with the Kumada coupling. Secondly, degassing THF by the freeze-pump-thaw method gave a slight increase in conversion.

Compound **(*S*)-2.64** was brought into the following step crude due to inadequate separation with the undesired mono coupled product. Intermediate **(*S*)-2.64** was then deprotected using boron tribromide to provide diol compound **(*S*)-2.65.** Purification was trivial following deprotection owing to the significant polarity shift caused by the newly formed diol. Compound **(*S*)-2.65** was treated with $POCl_3$, then hydrolyzed to yield the desired CPA catalyst **(*S*)-1.2c**.[63]

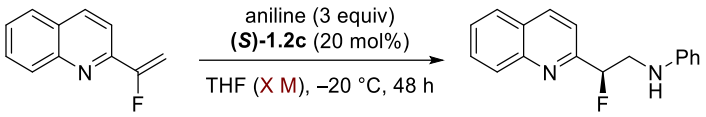


*Scheme 2.15: Synthesis of **2.60***

2.4 Reaction Discussion

2.4.1 Reaction Optimization

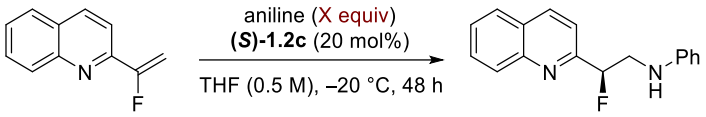
The optimization began by probing the concentration of the reaction. Decreasing the reaction concentration decreased the conversion to product, with comparable enantioselectivity (Table 2.1, Entry 1 vs. Entry 3). This trend in concentration is similar to the trend published within the Watson group's previous work,[45] where decreasing the concentration decreases the conversion to the product with similar enantiomeric ratios.



Entry	*Concentration (M)*	*Conversion (%)*	*e.r.*
1	0.5	40	96:4
2	0.25	28	97:3
3	0.1	15	98:2

Table 2.1: Concentration study performed by Dr Xu. Conversion and e.r. were determined by HPLC analysis with an internal standard.

Investigating the effects of the stoichiometry of the nucleophile in the reaction showed that increasing the stoichiometry of aniline gave an increase in conversion; this provided comparable enantioselectivity (Table 2.2, Entry 1 vs. Entries 2 and 3). Due to the similarities in the polarity of aniline and the product, increased aniline equivalents made purification by flash column chromatography difficult. Therefore, for ease of purification, three equivalents of aniline appeared optimal. The trend in aniline is similar to the previously published study, where increasing the stoichiometry provided a slight increase in conversion, with little to no effect on the enantioselectivity.[45]

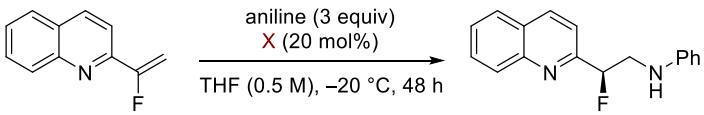


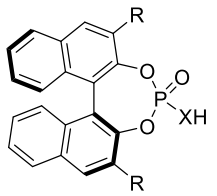
Entry	*Aniline (equiv)*	*Conversion (%)*	*e.r.*
1	3	40	96:4
2	5	48	95:5
3	10	58	95:5

Table 2.2: Concentration study performed by Dr Xu. Conversion and e.r. were Determined by HPLC analysis with an internal standard.

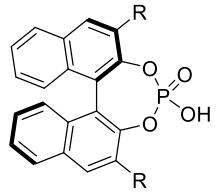
Examination of modified catalyst structures using commercially available CPAs **1.2i**-**1.2o** showed that alternative stereodirecting **(*S*)-1.2i**, **(*S*)-1.2j**, **(*R*)-1.2l**, and **(*R*)-1.2m** groups provided less enantioselectivity and conversions in comparison to **1.2c**. There appears to be no real trend observed with altering the groups. Changing the phosphoric acid to a phosphoramide **(*S*)-1.2k** yielded no conversion to the product. Modifying the catalyst

backbone lead to no improvements to enantioselectivity or yield: H^8-TRIP catalyst **(*S*)-1.2n** slightly reduced both enantioselectivity and conversion, whereas the SPINOL-based CPA **(*S*)-1.2o** yielded no product.

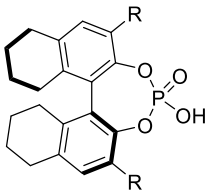




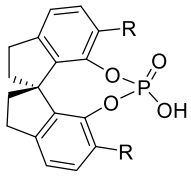
R = 2,4,6-triisopropylphenyl, X = O (**(*S*)-1.2c**)
R = 3,5-di(trifluoromethyl)phenyl, X = O (**(*S*)-1.2i**)
R = Iodine, X = O (**(*S*)-1.2j**)
R = 2,4,6-triisopropylphenyl, X = NTf (**(*S*)-1.2k**)



R = triphenylsilyl (**(*R*)-1.2l**)
R = 9-anthryl (**(*R*)-1.2m**)



R = 2,4,6-triisopropylphenyl (**(*S*)-1.2n**)



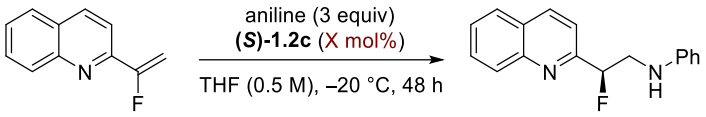
R = 2,4,6-triisopropylphenyl (**(*S*)-1.2o**)

Entry	*Catalyst*	*Conversion (%)*	*e.r.*
1[a]	**(*S*)-1.2c**	40	96:4
2[a]	**(*S*)-1.2i**	--	--
3[a]	**(*S*)-1.2j**	6	55:45
4[a]	**(*S*)-1.2k**	--	--
5[a]	**(*R*)-1.2l**	10	62:38
6[a]	**(*R*)-1.2m**	25	25:75
7	**(*S*)-1.2n**	28	89:11
8	**(*S*)-1.2o**	--	--

Table 2.3: Catalyst study [a]performed by Dr Xu. Conversion and e.r. were Determined by HPLC analysis with an internal standard.

In the absence of catalyst, no conversion to the product was observed (Table 2.4, Entry 3); this suggests no background reaction was present within this system. Attempts to

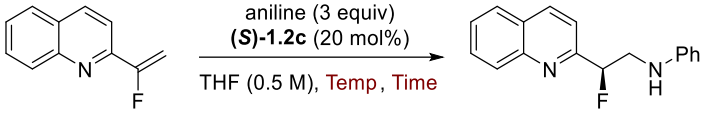
lower the catalyst loading to 10% resulted in a slight decrease in conversion and the enantiomeric ratio (Table 2.4, Entry 2).



Entry	*Cat. Loading (mol%)*	*Conversion (%)*	*e.r.*
1	20	40	96:4
2	10	37	95:5
3	0	--	--

Table 2.4: Catalyst loading study performed by Dr Xu. Conversion and e.r. were Determined by HPLC analysis with an internal standard.

Investigating the temperature showed that increasing to –10 °C from –20 °C provided an increase in conversion without compromising the enantioselectivity of the reaction (Table 2.5, Entry 1 vs. Entry 2). Following this, increasing the reaction duration, a higher conversion was achieved (Table 2.5, Entry 3).

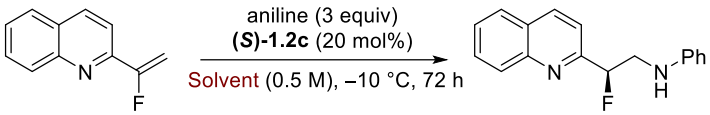


Entry	*Temperature (°C)*	*Time (h)*	*Conversion (%)*	*e.r.*
1	–20	48	40	96:4
2	–10	48	68	96:4
3	–10	72	82	96:4

Table 2.5: Temperature and time study performed by Dr Xu. Conversion and e.r. were Determined by HPLC analysis with an internal standard.

The last parameter to be studied was the choice of solvent. Ethereal solvents, including THF, CPME, and Et_2O, provided high yields and enantiomeric ratios (Table 2.6, Entries 1, 2, and 5). Non-polar solvents, hexane and toluene, provided excellent conversions; however, the enantiomeric ratio decreased (Table 2.6, Entries 3 and 4). CPME was selected as optimal because it possessed a combination of excellent reaction performance (conversion, enantioselectivity) with solvent properties that are desirable in industry (narrow explosivity, sustainable synthesis, low formation of peroxides). THF

was utilized in the cases where the reaction mixture was heterogeneous in CPME. Insoluble reactions often required a higher temperature, which was detrimental to the enantioselectivity.

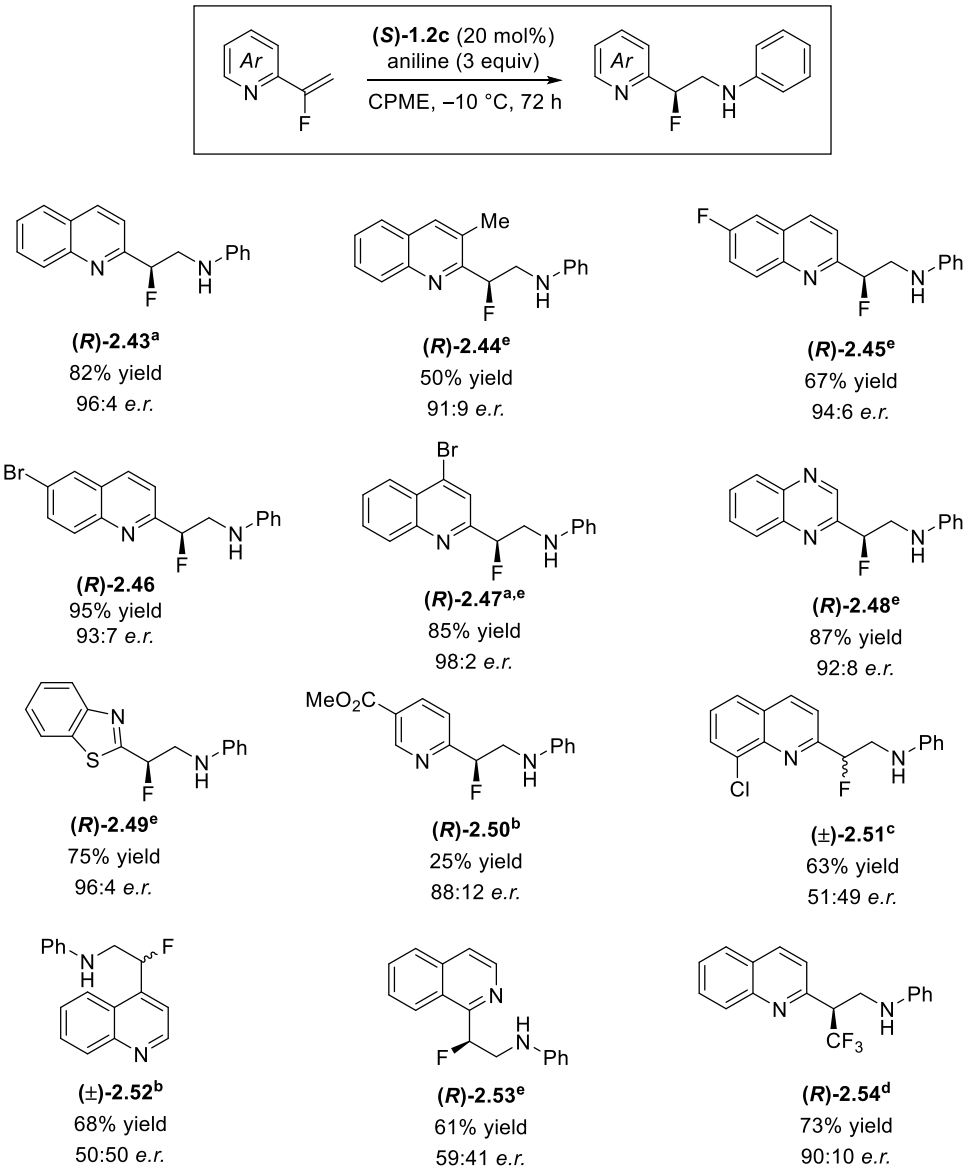


Entry	*Solvent*	*Conversion*	*e.r.*
1	THF	82	96:4
2	CPME	89	95:5
3	Hexane	98	71:29
4	Toluene	95	89:11
5	Et_2O	94	94:6
6	CH_2Cl_2	70	75:25

Table 2.6: Solvent study performed by Dr Xu. Conversion and e.r. were Determined by HPLC analysis with an internal standard.

2.4.2 Substrate Scope

With the proposed aza-Michael addition-asymmetric protonation reaction having undergone reaction optimization, the substrate scope was explored (Scheme 2.16).



*Scheme 2.16: Heterocycle scope. [a]Reaction carried out in THF, [b]Reaction carried out at room temperature, [c]Reaction carried out at 40 °C, [d]Reaction carried out at –50 °C with 1 equiv of **2.60**, [e]Reaction carried out by Dr Molloy*

Utilization of this methodology upon altering the core heterocycle showed the reaction could tolerate a variety of changes. The addition of a methyl group at the 3-position of the quinoline **(*R*)-2.44** and a fluorine atom at the 6-position **(*R*)-2.45** significantly decreased the yield with a slight decrease in the enantioselectivity. The addition of a bromine atom in the 6- and 4-positions of the quinoline ring, **(*R*)-2.46** and **(*R*)-2.47**, provided a comparable yield and enantioselectivity to the model substrate. However, substitution at the 8-position of the quinoline, in the case of **(±)-2.51**, provided no enantioselectivity. The chlorine atom blocking the CPA from effectively binding may

have caused the lack of enantioselectivity. Additionally, the previous study showed that the proton at the 8-position provided a further interaction with the catalyst *via* hydrogen bonding,[45] which is no longer possible within 8-chloroquinoline **2.33** (Figure 2.3).

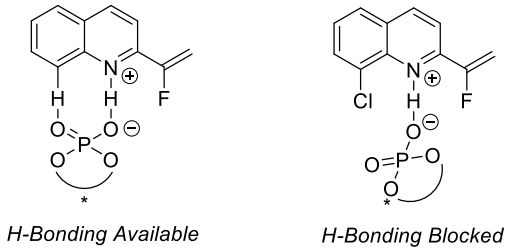


*Figure 2.3: H-Bonding of the catalyst **1.2c** with **2.1** and **2.33.***

Other nitrogen-based heterocycles were also well-tolerated; quinoxaline **(*R*)-2.48** and benzothiazole **(*R*)-2.49** gave comparable results to the model substrate **(*R*)-2.43**. Pyridine **2.80** was an exception as the loss of enantioselectivity was due to higher temperatures required to enable the reaction to proceed. As pyridine required full dearomatization compared to quinolines partial dearomatization during the Michael addition step of the reaction, an increase in the activation energy barrier was incurred (Figure 2.4).

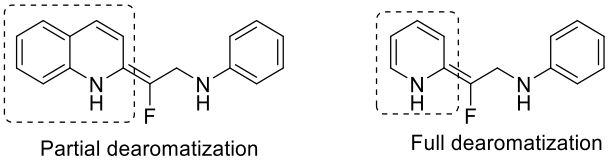


Figure 2.4: Partial vs. full dearomatization.

Positioning the fluorovinyl group at the 4-position, as in the example of **(±)-2.52,** showed no enantioselectivity under the optimized conditions. This erosion in enantioselectivity was potentially due to loss of enamine control, as there was no favorable geometry *via* dipole-dipole minimization (Figure 2.5a). Additionally, the catalyst is unable to interact with the ammonium proton from the nucleophile in the transition state, which could additionally cause the erosion in enantioselectivity (Figure 2.5b).

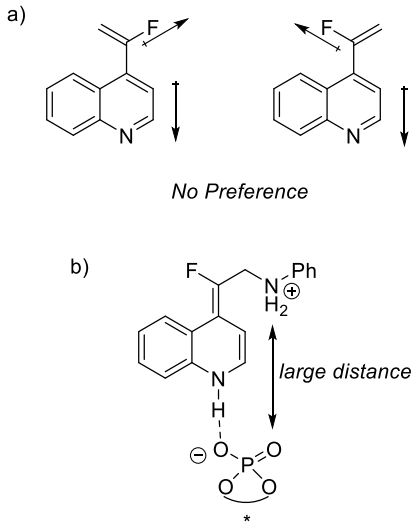
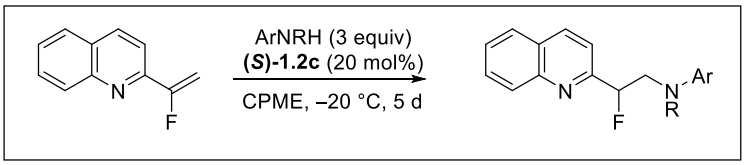
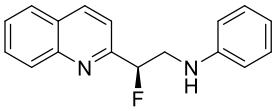


*Figure 2.5: a) Dipole-dipole minimization of **2.52**. b) CPA-ammonium proton distance in TS.*

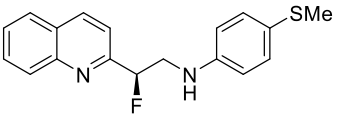
The standard conditions for the synthesis of **(*R*)-2.54** achieved an enantiomeric ratio of 76:24. However, further investigation into this showed there was a significant background reaction. Utilizing a stoichiometric amount of **(*S*)-1.2c** at –50 °C achieved excellent enantioselectivity (90:10).

The arylamine scope was then explored (Scheme 2.17). The arylamines containing a thioether group **(*R*)-2.66**, halogen atoms **(*R*)-2.68** and **(*R*)-2.71**, a trifluoromethyl group **(*R*)-2.69**, and the boronic ester group **(*R*)-2.70** achieved high yields and enantioselectivities comparable to that of the model substrate **(*R*)-2.43**. A fluorine atom in the *ortho*-position in the example of **(*R*)-2.72** was achieved with a lower yield compared to the model substrate **(*R*)-2.43**. Arylamines with multiple substitutions, as in the examples of **(*R*)-2.73** and **(*R*)-2.74**, were achieved with high yields and enantioselectivity. Heterocyclic arylamines furnished the products **(*R*)-2.75** and **(*R*)-2.76** in lower yields compared to the model substrate. Heterocyclic arylamine **(*R*)-2.77**, an example of a secondary amine, was furnished with a comparable yield and enantioselectivity to the model substrate **(*R*)-2.43**.

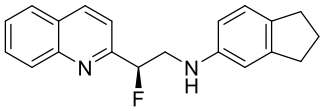




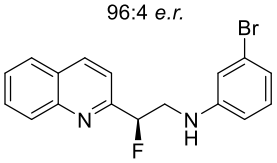
(*R*)-2.43[a,b]
82% yield
96:4 *e.r.*



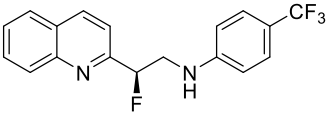
(*R*)-2.66[c]
93% yield
97:3 *e.r.*



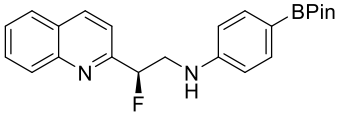
(*R*)-2.67[c]
74% yield
91:9 *e.r.*



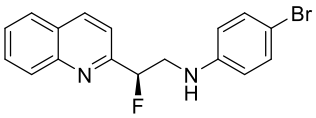
(*R*)-2.68[c]
88% yield
94:6 *e.r.*



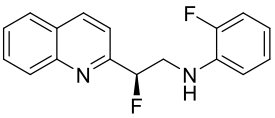
(*R*)-2.69[c]
93% yield
97:3 *e.r.*



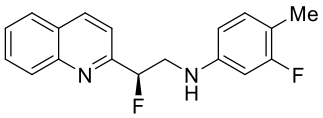
(*R*)-2.70[b,c]
79% yield
93:7 *e.r.*



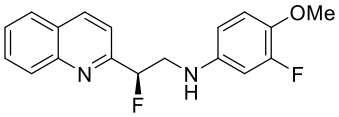
(*R*)-2.71[a,c]
71% yield
90:10 *e.r.*



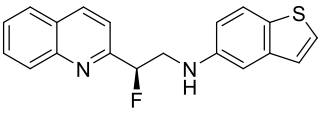
(*R*)-2.72[c]
46% yield
89:11 *e.r.*



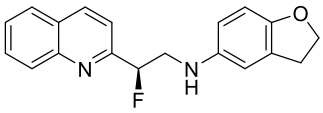
(*R*)-2.73[c]
94% yield
98:2 *e.r.*



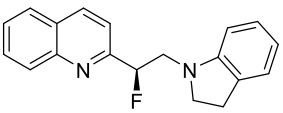
(*R*)-2.74[a,b,c]
72% yield
93:7 *e.r.*



(*R*)-2.75[a,c]
58% yield
94:6 *e.r.*



(*R*)-2.76[a,c]
37% yield
89:11 *e.r.*



(*R*)-2.77[c]
88% yield
92:8 *e.r.*

Scheme 2.17: Arylamine scope. [a]Reaction carried out THF. [b]Reaction carried out at −10 °C for 3 d. [c] Reactions performed by Dr Xu.

2.4.3 Mechanistic Insight

The previously proposed mechanism proceeded through an asymmetric protonation, with an energy barrier of 32.7 kcal mol^{-1} for the RDS.[45] It is unlikely the reaction would proceed at low temperatures, which the experimental data disagrees with (Figure 2.6, Pathway 1). The proposed mechanism proceeded through initial coordination of the **2.1** with the CPA **(*S*)-1.2c** to form the complex **2.78**. Conjugate addition of **2.78** with aniline formed the enamine intermediate **2.79**. The proposed RDS proceeded through the four-membered transition state **2.80** to form **2.81**, with protonation occurring directly from the aniline nitrogen proton to the electrophilic site. CPA **(*S*)-1.2c** can then dissociate from **2.81** to regenerate the catalyst and furnish **2.43**. An alternative pathway, inspired by proposed mechanisms of other CPA-catalyzed conjugate addition reactions (as seen in Scheme 1.25),[38,39] was computationally modeled (Figure 2.6, Pathway 2). The data showed that the nucleophilic center was protonated indirectly *via* the CPA acting as a shuttle rather than the ammonium proton directly. The calculated energy barrier for Pathway 2 was 15.4 kcal mol^{-1}.

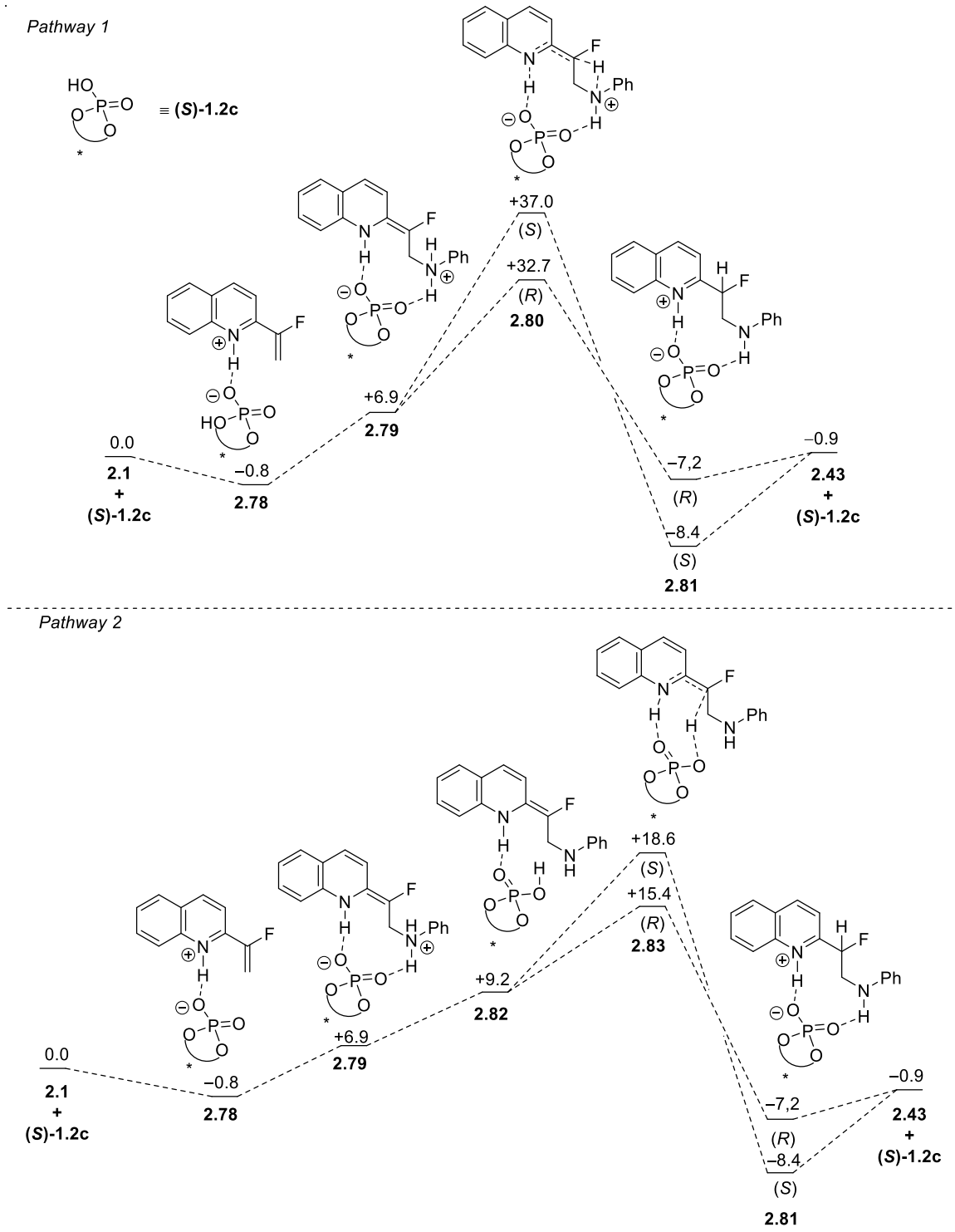
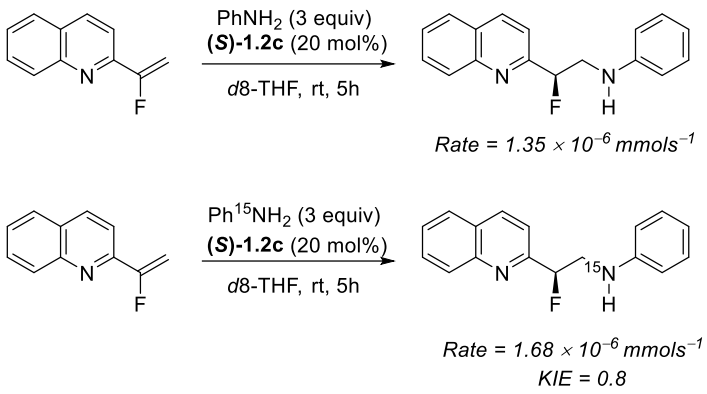


*Figure 2.6: Computation conducted by Dr Leach. Proposed pathways for the asymmetric protonation step. Free energy profile comparison (ONIOM (B3LYP/6-31G**:UFF), All calculations were performed in Gaussian09, and free energies at −20 °C and 1 M concentration were obtained using goodvibes.*

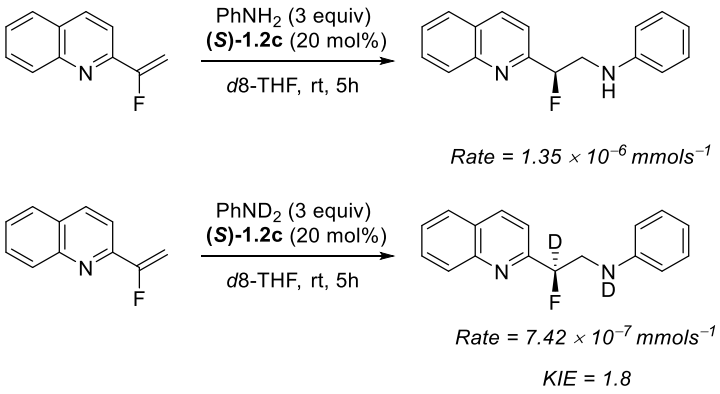
A series of KIE experiments were performed to distinguish between the two proposed RDSs (Figure 2.6, Pathway 1 vs. Pathway 2). Using aniline, ^{15}N-aniline, and d_2-aniline

initial reaction rates were calculated (Scheme 2.18 and 2.19). Firstly, with the nitrogen KIE, it was expected that a slight increase in the rate of reaction for Pathway 1 would be observed, as breaking the N-H bond is included in the rate-determining step. On the other hand, Pathway 2 does not include the aniline nitrogen within the RDS; therefore, it was expected not to observe a difference in reaction rate. The observed KIE was 0.8, which did not support either mechanism (Scheme 2.18).



Scheme 2.18: Nitrogen KIE experiment.

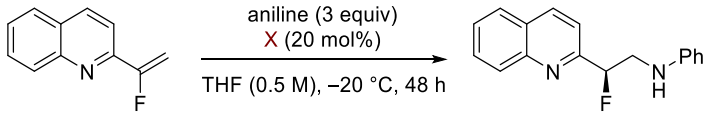
A proposal for overcoming such a significant energy barrier would be through quantum tunneling.[65] If this were the case, we would expect a relatively large KIE. Instead, we observed a KIE of 1.8 (Scheme 2.19). Reflecting upon this result, the experiment was believed to be flawed as the amine protons of aniline could exchange in solution with the CPA, consequently affecting the observed KIE.

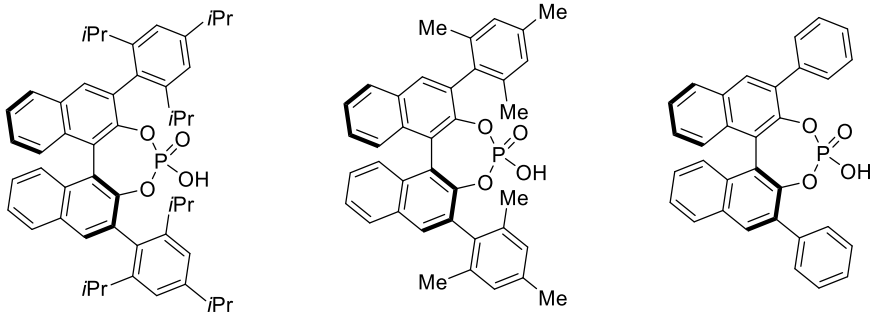


Scheme 2.19: Deuterium KIE experiment.

Finally, the cause of the observed enantioselectivity was explored. Here, catalysts **(*S*)-1.2c**, **(*S*)-1.2p**, and **(*S*)-1.2q** were investigated within the reaction. The choice of these

catalysts was due to the variation of steric interactions available from the aryl group (Table 2.7).





(*S*)-1.2c **(*S*)-1.2p** **(*S*)-1.2q**

Entry	*Catalyst*	*Conversion*	e.r.
1	**(*S*)-1.2c**	40	96:4
2	**(*S*)-1.2p**	25	88:12
3	**(*S*)-1.2q**	11	58:42

Table 2.7: Enantioselectivity study.

Catalyst **(*S*)-1.2c** affords the greatest enantioselectivity (Table 2.7, Entry 1), with **(*S*)-1.2p** and **(*S*)-1.2q** providing reduced enantioselectivity (Table 2.7, Entries 2 and 3). DFT calculations were conducted to help elucidate this phenomenon. The difference in energy between the two diastereomeric transition states was in the order of **(*S*)-1.2c** > **(*S*)-1.2p** > **(*S*)-1.2q** (Figure 2.7). This increase in energy was due to an interaction of the alkyl groups with the substrate in the minor transition state (Figure 2.6, (*R*)- **(*S*)-1.2p**). This strain disrupts the hydrogen bonding present within the transition state, causing the energy barrier of the transition state to increase.

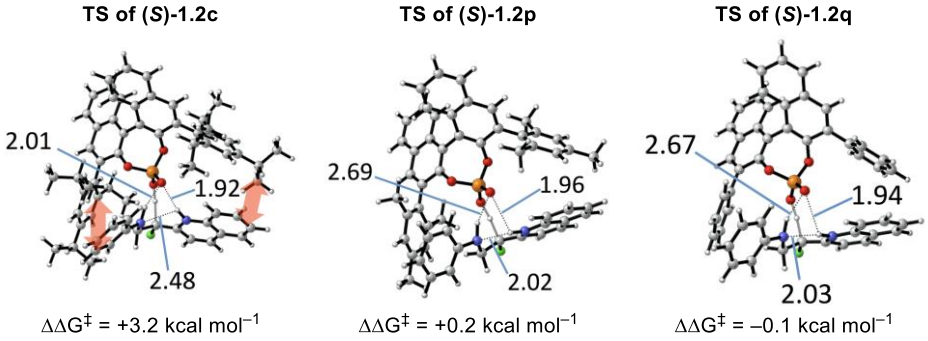


Figure 2.7: Comparison of TS of catalysts ***(S)-1.2c****,* ***(S)-1.2p****, and* ***(S)-1.2q****.*

2.4.4 Conformational Analysis

The conformation of **(*R*)-2.43** was examined by XRD crystallography (Figure 2.8). The C–F bond and the aniline nitrogen exhibit an *anti*-relationship through ϕ_2, potentially due to favorable interaction of the lone pair upon the nitrogen with the C–F σ* orbital. Additionally, the heterocyclic ring has a ϕ_1 of 110° with the C–F bond. The observed dihedral angle arises due to two effects: firstly, a dipole-dipole minimization that prefers the fluorine to be 180° to the heterocycle nitrogen, whereas the π orbital of the aromatic ring can interact with the C–F σ* orbital preferring the fluorine to be orthogonal to the heterocyclic nitrogen.

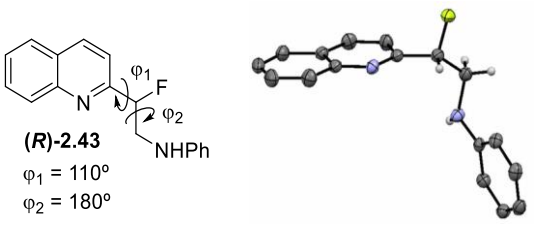


Figure 2.8: Crystal structure of ***(R)-2.43****.*

The aniline nitrogen was acylated to investigate the interaction between the nitrogen lone-pair and the C–F σ* orbital further (compound **2.84**, Figure 2.9).[66] In the crystal structure of this compound, a gauche conformation was observed between the aniline nitrogen and the C–F bond, showing that the preference towards the anti-conformation diminished. The observation was due to the reduction in the electron density of the lone pair of the nitrogen, consequently reducing the donation of electron density to the C–F σ* orbital. Additionally, the dihedral angle between the C–F bond and the aromatic ring

is 180°, showing exclusive dipole-dipole minimization and no donation of the aromatic π orbital into the C–F σ* orbital.

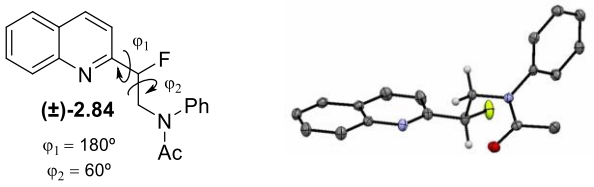


*Figure 2.9: Crystal structure of **(±)-2.84**.*

The possible conformations of **(*R*)-2.43** and **(*R*)-2.84** were explored by DFT and depicted in Ramachandran plots (Figure 2.10). As a result, it was shown that the preference for the anti-conformation for the model compound **(*R*)-2.43** was 1.8 kcal mol^{-1} and the acylated compound **(*R*)-2.84** had a diminished preference of 0.9 kcal mol^{-1}. Thus, the data agrees with the hypothesis that reducing the electron density of the lone pair of the nitrogen by adding an acyl group reduces the preference for the anti-conformation.

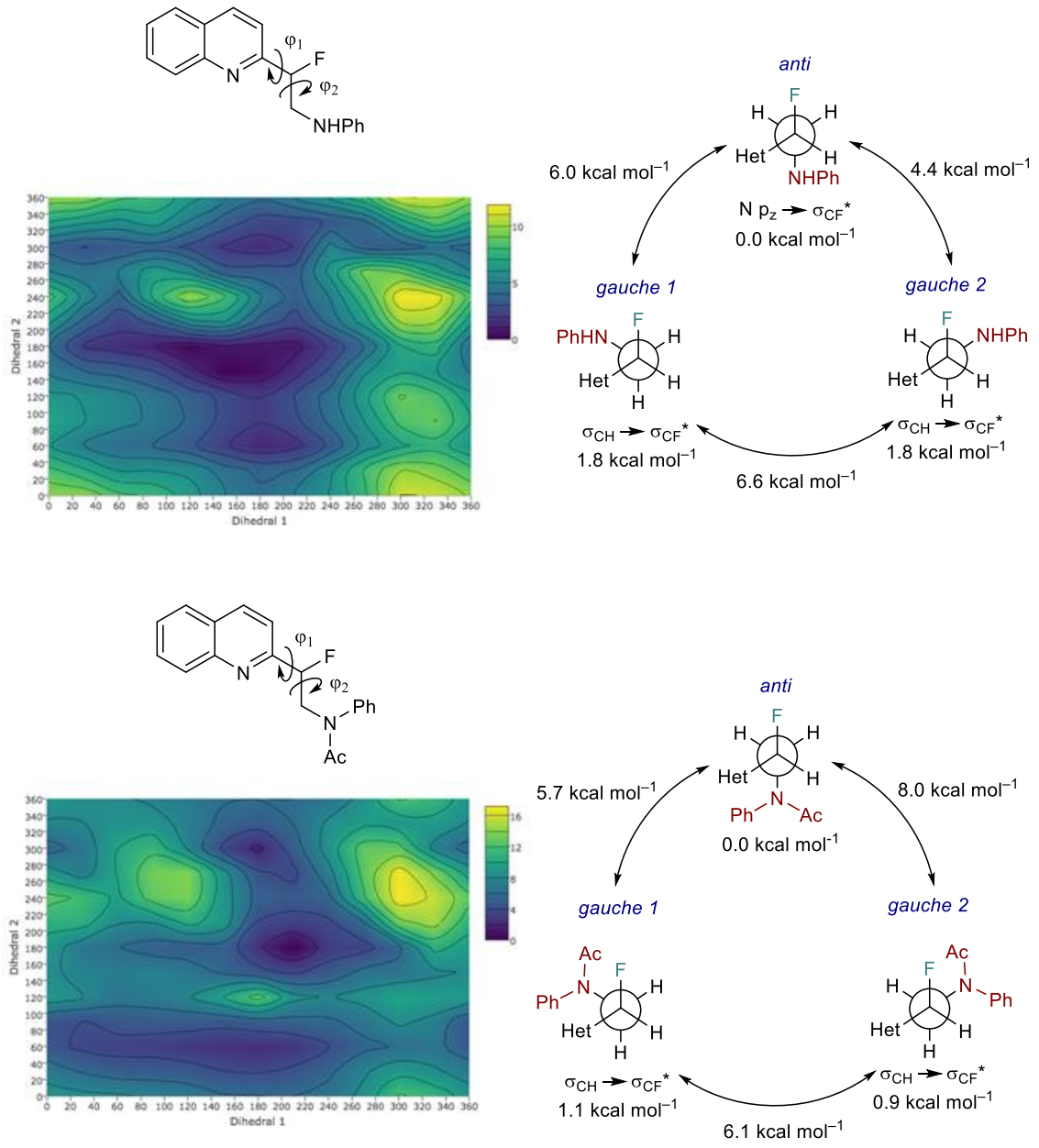


Figure 2.10: Conformational analysis of ***(R)-2.43*** *and the acylated analog* ***(R)-2.84****.*

The protein databank was searched for ligands that contain the 2-pyridylethylamine substructure. Five compounds were found to adopt the conformation exhibited by **(*R*)-2.43**. Inhibitors identified bound to targets were compounds **2.85**, **2.86**, and **2.87** (HIV reverse transcriptase),[67-69] **2.88** (cathepsin L),[70] and **2.89** (purine nucleoside phosphorylase)(Figure 2.11).[71] It was believed that the addition of a carbon-fluorine bond at the benzylic center of the phenethylamine functionality of these compounds would provide beneficial conformational control for protein inhibition.

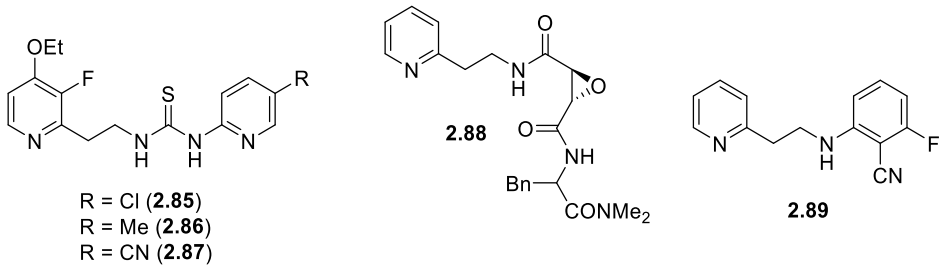


Figure 2.11: Drug-like molecules in PDB that may benefit from conformational control induced by benzylic fluorination.

2.5 Conclusions

In conclusion, a synthetic route for fluorovinylheterocycles was established by utilizing bromoheterocycles with a fluorovinyl silyl species in a Hiyama reaction. The racemic reaction of these fluorovinylheteroaryls was investigated with aniline and alternative nucleophiles, with only arylamines yielding promising results. The enantioselective reaction of arylamines with fluorovinylheterocycles was then investigated, and their enantiomeric ratios were directly compared to the racemic samples previously prepared. The reaction provided high yields and enantioselectivities, and rationalization was given to substrates that provided diminished enantioselectivity. DFT calculations provided insight into the reaction mechanism and the rise of enantioselectivity imposed by the catalyst (Figure 2.12). These hypotheses generated from DFT calculations were further investigated using KIE and catalyst variation experiments. Additionally, crystal structure data has highlighted the dominance of non-covalent interactions in core structure conformation, with subtle manipulation of the terminal nitrogen substituent enabling modulation of the phenethylamine acyclic topology.

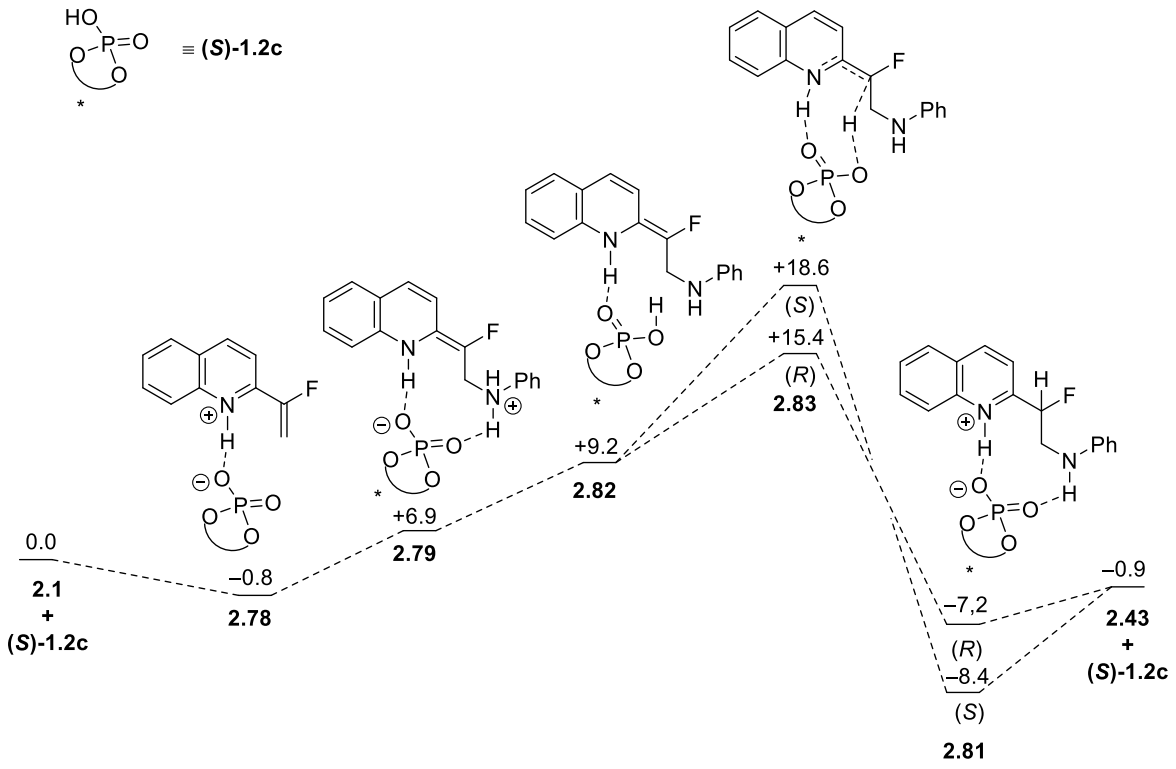


*Figure 2.12: Computation conducted by Dr Leach. Proposed pathways for the asymmetric protonation step. Free energy profile comparison (ONIOM (B3LYP/6-31G**:UFF), All calculations were performed in Gaussian09, and free energies at −20 °C and 1 M concentration were obtained using goodvibes.*

2.6 Experimental

2.6.1 General Information

All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods.[72]

Purification of Solvents

Dry THF for reactions was obtained from a PureSolv SPS-400-5 solvent purification system. Et_2O, EtOAc, and petroleum ether 40-60 °C for purification purposes were used as obtained from suppliers without further purification.

Experimental Details

Reactions were carried out using conventional glassware (preparation of intermediates), 2 mL HPLC vials, or in capped 5, 10, and 20 mL microwave vials. The glassware was oven-dried (150 °C) and purged with N_2 before use. Purging refers to a vacuum/nitrogen-refilling procedure. Prior to use, Mg turnings were oven-dried at 150 °C overnight. Room temperature (rt) was generally *ca.* 18 °C. Reactions were carried out at elevated temperatures using a temperature-regulated hotplate/stirrer with a sand bath. Reactions were carried out at −10, −20, and −50 °C using an isopropanol bath cooled by a Thermo Haake EK90 cryocooler. Reactions were carried out at 0 °C using an ice/water bath.

Purification of Products

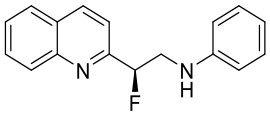
Thin layer chromatography was carried out using Merck silica plates coated with fluorescent indicator UV254. These were analyzed under 254 nm UV light, developed using potassium permanganate or vanillin solutions. Normal phase flash chromatography was carried out using ZEOprep 60 HYD 40-63 µm silica gel.

Analysis of Products

Fourier Transformed Infra-Red (FTIR) spectra were obtained on a Shimadzu IRAffinity-1 machine. ^{13}C and ^{19}F NMR spectra were obtained using a proton decoupled method. ^{19}F NMR spectra were obtained on either a Bruker AV 400 spectrometer at 376 or 377 MHz, or a Bruker AV 500 spectrometer at 470 MHz, respectively. ^{11}B NMR spectra were obtained on a Bruker AV 400 spectrometer at 128 MHz. ^{1}H and ^{13}C NMR spectra were obtained on either a Bruker AV 400 at 400 MHz and 101 MHz, respectively, or Bruker DRX 500 at 500 MHz and 126 MHz, respectively. Chemical shifts are reported in ppm and coupling constants are reported in Hz with $CDCl_3$ referenced at 7.26 (^{1}H) and 77.0 ppm (^{13}C) and DMSO-d_6 referenced at 2.50 (^{1}H) and 39.5 (^{13}C). ^{11}B NMR spectra are referenced to $BF_3{\cdot}Et_2O$. Unless otherwise stated, J refers to $^{3}J_{HH}$ and J_{CF} in ^{1}H and ^{13}C NMR, respectively. High-resolution mass spectra were obtained either through analysis at the EPSRC UK National Mass Spectrometry Facility at Swansea University, or through analysis at the University of St Andrews. High performance liquid chromatography (HPLC) was performed on an Agilent 1200 series HPLC using a chiral stationary phase column (column, Daicel Co. CHIRALCEL OJ-H, or CHIRALPAK IA; eluent: *n*-hexane/*i*-PrOH). All solvents used were HPLC-grade solvents purchased from Fisher. The column employed and the respective solvent mixture are indicated for each experiment. Optical rotations were obtained on a Perkin Elmer Model 341 polarimeter.

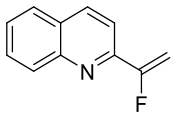
2.6.2 General Experimental Procedures

General Procedure A: Kinetic isotope effect



A 2 mL HPLC vial was charged with 2-(1-fluorovinyl)quinoline (17.3 mg, 0.10 mmol, 1.0 equiv), (*S*)-TRIP catalyst (15.1 mg, 0.02 mmol, 20 mol%), and aniline (27 µL, 0.30 mmol, 3.0 equiv). The vial was then capped and purged with N_2 before adding d_8-THF (400 µL, 0.25 M). The resulting mixture was then transferred into a 0.5 mm NMR tubes (7 inch) and ^{19}F NMR was taken every 6 min for a period of 5 h to allow the determination of the conversion.

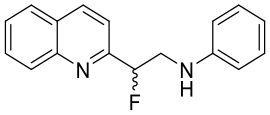
General Procedure B: Hiyama coupling.



Prepared according to adapted literature procedure.[57]

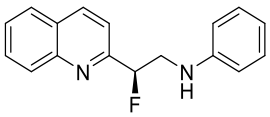
An oven dried, 20 mL microwave vial was charged with 2-bromoquinoline (207 mg, 1.00 mmol, 1.0 equiv), (1-fluorovinyl)(methyl)diphenylsilane (356 mg, 1.5 mmol, 1.5 equiv), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol, 5 mol%), CuI (9.7 mg, 0.05 mmol, 5 mol%) and CsF (357 mg, 2.35 mmol, 2.35 equiv). The microwave vial was then capped and purged with N_2 before addition of DMF (10 mL, 0.1 M). The reaction mixture was then allowed to stir at rt for 3.5 h. The reaction was quenched with water (20 mL) and diluted with Et_2O (20 mL). The organic phase was separated, washed with water (2 × 10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the crude reaction mixture *via* flash chromatography (silica gel, Et_2O:petroleum ether, 1:99) gave the desired product as a pale yellow oil (161 mg, 93%).

General Procedure C: Aza-Michael reaction catalyzed using an achiral acid (THF as solvent).



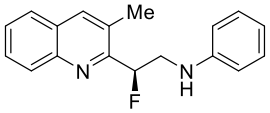
A 2 mL HPLC vial was charged with 2-(1-fluorovinyl)quinoline (17.3 mg, 0.10 mmol, 1.0 equiv). The vial was then capped and purged with N_2 before adding THF (200 µL, 0.5 M), and TFA (1.5 µL, 0.02 mmol, 20 mol%). The reaction mixture was cooled to −10 °C for 15 min before the addition of aniline (27 µL, 0.30 mmol, 3.0 equiv). The resulting mixture was then allowed to stir at −10 °C for 3 d before being quenched by sat. aq. K_2CO_3 solution (2 mL). The phases were separated and the aqueous phase extracted with EtOAc (5 mL × 3). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the crude reaction mixture *via* flash chromatography (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) gave the desired product as a pale yellow oil (20.6 mg, 77%)

General Procedure D: Aza-Michael reaction catalyzed using a chiral acid (THF as solvent).



A 2 mL HPLC vial was charged with 2-(1-fluorovinyl)quinoline (17.3 mg, 0.10 mmol, 1.0 equiv), and (*S*)-TRIP catalyst (15.1 mg, 0.02 mmol, 20 mol%). The vial was then capped and purged with N_2 before adding THF (200 µL, 0.5 M). The reaction mixture was cooled to −10 °C for 15 min before the addition of aniline (27 µL, 0.30 mmol, 3.0 equiv). The resulting mixture was then allowed to stir at −10 °C for 3 d before being quenched by sat. aq. K_2CO_3 solution (2 mL). The phases were separated, and the aqueous phase extracted with EtOAc (5 mL × 3). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the crude reaction mixture *via* flash chromatography (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) gave the desired product as a pale yellow oil (21.8 mg, 82%, 96:4 e.r.).

General Procedure E: Aza-Michael reaction catalyzed using a chiral acid (CPME as solvent).

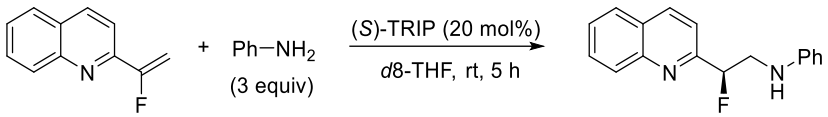


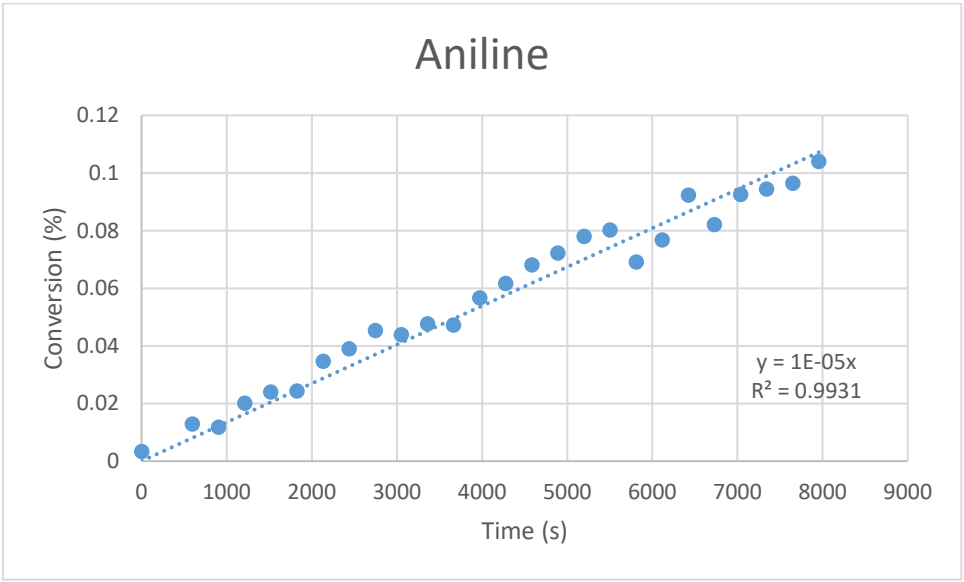
A 2 mL HPLC vial was charged with 3-methyl-2-(1-fluorovinyl)quinoline (18.8 mg. 0.10 mmol, 1.0 equiv), and (*S*)-TRIP catalyst (15.1 mg, 0.02 mmol, 20 mol%). The vial was then capped and purged with N_2 before adding CPME (200 µL, 0.5 M). The reaction mixture was cooled to −20 °C for 15 min before the addition of aniline (27 µL, 0.3 mmol, 3.0 equiv). The resulting mixture was then allowed to stir at −10 °C for 3 d before being quenched by sat. aq. K_2CO_3 solution (2 mL). The phases were separated, and the aqueous phase extracted with EtOAc (5 mL × 3). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the crude reaction mixture *via* flash chromatography (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) gave the desired product as a pale yellow oil (13.8 mg, 50%, 91:9 e.r.).

2.6.2 Kinetic Isotope Effect

Kinetic Isotope Effect of Aniline

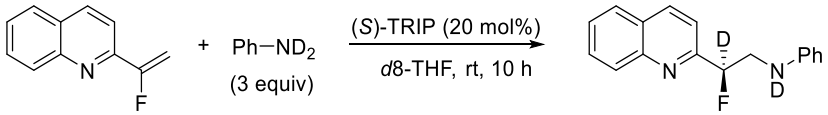
Data was obtained according to General Procedure A using aniline.

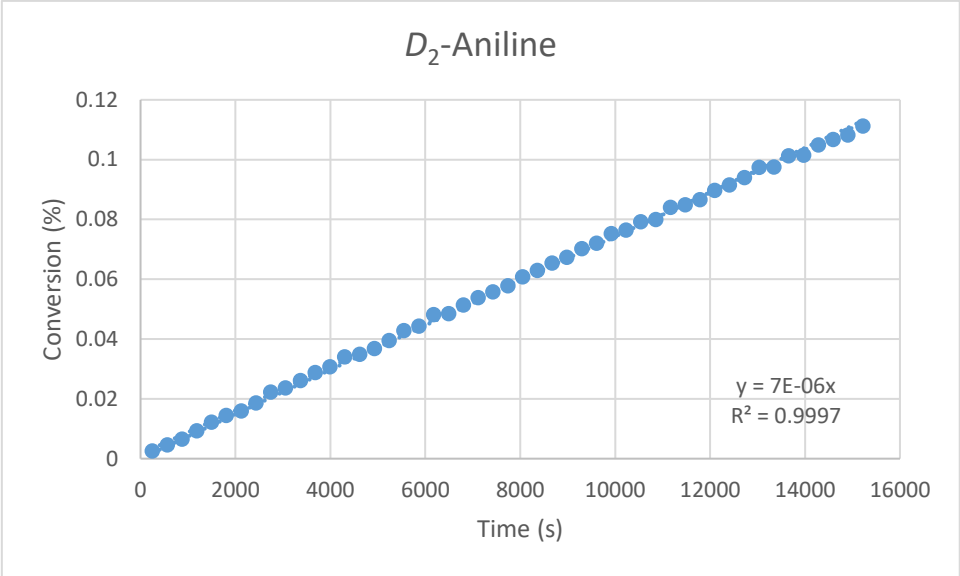




Kinetic Isotope Effect of D_2-Aniline

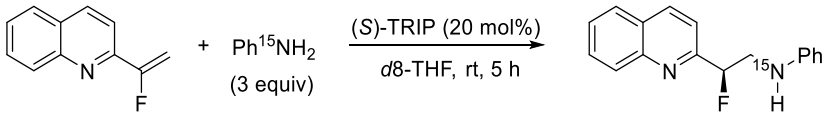
Data was obtained according to General Procedure A using D_2-aniline for 10 h.

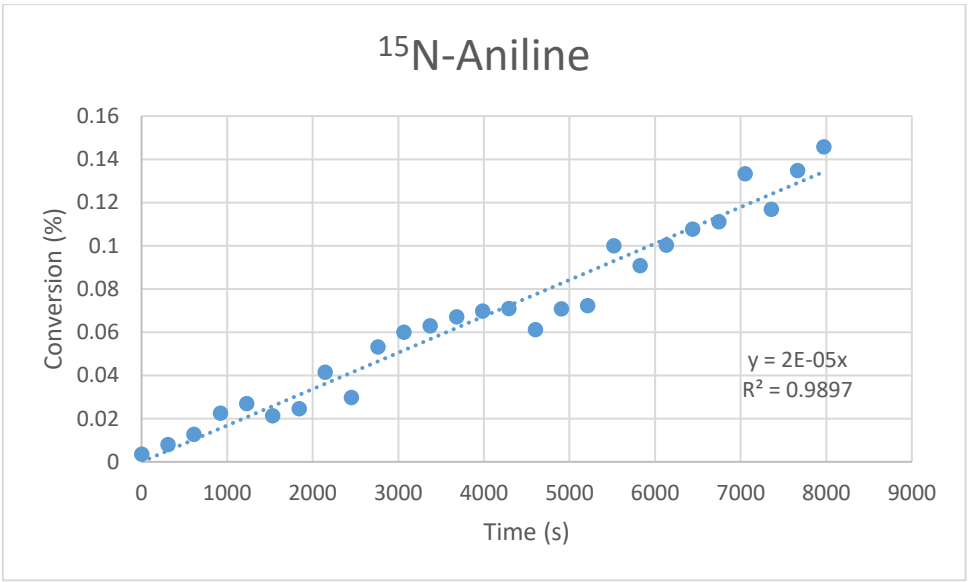




Kinetic Isotope Effect of ^{15}*N*-Aniline

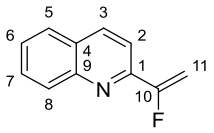
Data was obtained according to General Procedure A using ^{15}*N*-aniline.





2.6.3 Characterization Data for Compounds

2-(1-Fluorovinyl)quinoline 2.1



Chemical Formula: $C_{11}H_8FN$
Exact Mass: 173.0641
Molecular Weight: 173.1904

Prepared according to General Procedure B using 2-bromoquinoline (207 mg, 1.00 mmol, 1.0 equiv), (1-fluorovinyl)(methyl)diphenylsilane (356 mg, 1.50 mmol, 1.5 equiv), $Pd(PPh_3)_4$ (59.0 mg, 0.05 mmol, 5 mol%), CuI (9.7 mg, 0.05 mmol, 5 mol%), CsF (364 mg, 2.35 mmol, 2.35 equiv), and DMF (10 mL, 0.1 M). The reaction mixture was subjected to the purification outlined in the General Procedure B (silica gel, Et_2O:petroleum ether, 1:99) to afford the desired product as a pale yellow oil (161 mg, 93%).

υ_{max} (film): 1654, 1504, 1284 cm^{-1}.

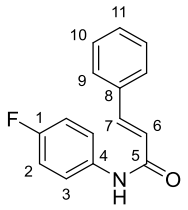
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.6 Hz, 1H, C(3)*H*), 8.10 (d, *J* = 8.5 Hz, 1H, C(8)*H*), 7.81 (dd, *J* = 8.1, 0.9 Hz, 1H, C(5)*H*), 7.73 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H, C(7)*H*), 7.69 (dd, *J* = 8.6, 1.2 Hz, 1H, C(2)*H*), 7.54 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H, C(6)*H*), 5.87 (dd, $^3J_{HF}$ = 48.6 Hz, $^2J_{HH}$ = 2.9 Hz, 1H, C(11)H_{trans}), 5.14 (dd, $^3J_{HF}$ = 16.4 Hz, $^2J_{HH}$ = 2.9 Hz, 1H, C(11)H_{cis}).

^{13}C NMR (126 MHz, $CDCl_3$): δ 162.3 (d, ^1J = 251.2 Hz, *C*(10)), 150.1 (d, ^2J = 35.4 Hz, *C*(1)), 147.9 (d, ^4J = 3.8 Hz, *C*(9)), 136.9 (*C*(3)), 130.0 (*C*(7)), 129.8 (*C*(8)), 128.0 (*C*(4)), 127.6 (*C*(5)), 127.1 (*C*(6)), 116.8 (d, ^3J = 4.7 Hz, *C*(2)), 93.8 (d, ^2J = 18.4 Hz, *C*(11)).

^{19}F NMR (376 MHz, $CDCl_3$): δ −114.28.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{11}H_9NF$) requires *m/z* 174.0714, found *m/z* 174.0712.

***N*-(4-Fluorophenyl)cinnamamide 2.12**



Chemical Formula: $C_{15}H_{12}FNO$
Exact Mass: 241.0903
Molecular Weight: 241.2654

Prepared according to literature procedure.[58]

A 100 mL round bottom flask was charged with 4-fluoroaniline (142 µL, 1.50 mmol, 1.0 equiv) and K_2CO_3 (311 mg, 2.25 mmol, 1.5 equiv). Water (0.75 mL) and acetone (0.75 mL) was added. The mixture was cooled to 0 °C and cinnamoyl chloride (251 mg, 1.50 mmol, 1.0 equiv) was added. The reaction was then stirred for 2 h at 0 °C and then poured over ice water (5 mL). The resulting precipitate was collected, washed with water and dried *in vacuo* to give the desired product as a slight brown solid (174 mg, 96%).

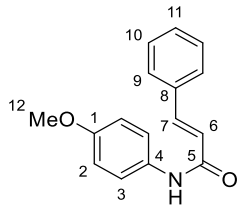
^{1}H NMR (500 MHz, DMSO-d_6): δ 10.35 (s, 1H, N*H*), 7.75 – 7.70 (m, 2H, C(2)*H*), 7.65 – 7.60 (m, 3H, C(7)*H* & C(10)*H*), 7.52 – 7.35 (m, 3H, C(9)*H* & C(11)*H*), 7.18 (t, *J* = 8.9 Hz, 2H, C(3)*H*), 6.83 (d, *J* = 15.7 Hz, 1H, C(6)*H*).

^{13}C NMR (126 MHz, DMSO-d_6): δ 163.5, 158.1 (d, ^1J = 239.7 Hz), 140.2, 135.8, 134.7, 129.9, 129.1, 127.8, 122.1, 120.9 (d, ^3J = 7.9 Hz), 115.4 (d, ^2J = 22.2 Hz).

^{19}F NMR (470 MHz, DMSO-d_6): δ −119.17.

Spectroscopic data in agreement with literature values.[59]

***N*-(4-Fluorophenyl)cinnamamide 2.13**



Chemical Formula: $C_{16}H_{15}NO_2$
Exact Mass: 253.1103
Molecular Weight: 253.3010

Prepared according to literature procedure.[58]

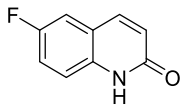
A 100 mL round bottom flask was charged with *p*-anisidine (185 mg, 1.50 mmol, 1.0 equiv) and K_2CO_3 (311 mg, 2.25 mmol, 1.5 equiv). Water (0.75 mL) and acetone (0.75 mL) was added. The mixture was cooled to 0 °C and cinnamoyl chloride (251 mg, 1.50 mmol, 1.0 equiv) was added. The reaction was then stirred for 2 h at 0 °C and then poured over ice water (5 mL). The resulting precipitate was collected, washed with water and dried *in vacuo* to give the desired product as a slight brown solid (306 mg, 85%).

^{1}H NMR (500 MHz, DMSO-d_6): δ 7.73 (d, *J* = 15.6 Hz, 1H, C(7)*H*), 7.67 (s, 1H, NH), 7.54 (d, *J* = 8.9 Hz, 2H, C(3)*H*), 7.50 – 7.45 (m, 2H, C(10)*H*), 7.35 – 7.33 (m, 3H, C(9)*H*, C(11)*H*), 6.86 (d, *J* = 8.9 Hz, 2H, C(2)*H*), 6.57 (d, *J* = 15.6 Hz, 1H, C(6)*H*), 3.78 (s, 3H, C(12)*H*).

^{13}C NMR (126 MHz, DMSO-d_6): δ 164.0, 156.6, 141.9, 134.8, 131.2, 129.9, 128.9, 127.9, 121.8, 121.0, 114.2, 55.4.

Spectroscopic data in agreement with literature values.[73]

6-Fluoroquinolin-2(1*H*)-one 2.14

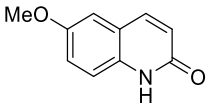


Chemical Formula: C_9H_6FNO
Exact Mass: 163.0433
Molecular Weight: 163.1514

Prepared according to literature procedure.[59]

An oven-dried 20 mL microwave vial was charged with *N*-(4-fluorophenyl)cinnamamide (253 mg, 1.00 mmol, 1.0 equiv) and aluminium chloride (400 mg, 3.00 mmol, 3.0 equiv). The vial was capped and purged with N_2. The mixture was then stirred at 100 °C for 3 h. Water (10 mL) was added and the resulting precipitate was collected, washed with water and dried *in vacuo*. The resulting crude material was subjected to the next step without further purification.

6-Fluoroquinolin-2(1*H*)-one 2.15

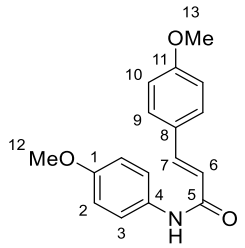


Chemical Formula: $C_{10}H_9NO_2$
Exact Mass: 175.0633
Molecular Weight: 175.1870

Prepared according to literature procedure.[59]

An oven-dried 20 mL microwave vial was charged with phosphoric acid (2.60 mL, 50.0 mmol, 50 equiv) and phosphorus pentoxide (2.84 g, 20.0 mmol, 20 equiv). The vial was capped and purged with N_2. The mixture was then stirred at 80 °C for 2 h**. 1.18** (283 mg, 1.00 mmol, 1.0 equiv) was added and the reaction was left to stir for an additional 2 h at 110 °C. Water was added and the resulting precipitate was collected, washed with water and dried *in vacuo*. The resulting crude was subjected to the next step without further purification.

(*E*)-*N*,3-bis(4-methoxyphenyl)acrylamide 2.18



Chemical Formula: $C_{17}H_{17}NO_3$
Exact Mass: 283.1208
Molecular Weight: 283.3270

Prepared according to literature procedure.[58]

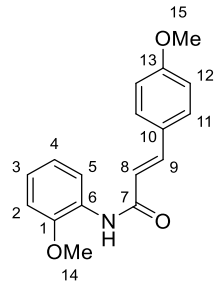
A 100 mL round bottom flask was charged with *p*-anisidine (246 mg, 2.00 mmol, 1.0 equiv) and K_2CO_3 (622 mg, 4.5 mmol, 2.25 equiv). Water (1 mL) and acetone (1 mL) was added. The mixture was cooled to 0 °C and (*E*)-3-(4-methoxyphenyl)acryloyl chloride (393 mg, 2.00 mmol, 1.0 equiv) was added. The reaction was then stirred for 2 h at 0 °C and then poured over ice water (5 mL). The resulting precipitate was collected, washed with water and dried *in vacuo* to give the desired product as a slight brown solid (701 mg, 62%).

^{1}H NMR (500 MHz, DMSO-d_6): δ 7.69 (d, *J* = 15.5 Hz, 1H, C(7)*H*), 7.53 (d, *J* = 8.2 Hz, 2H, C(3)*H* or C(9)*H*), 7.47 (d, *J* = 8.5 Hz, 2H, C(3)*H* or C(9)*H*), 7.32 (s, 1H, N*H*), 6.89 (d, *J* = 8.5 Hz, 2H, C(2)*H* or C(10)*H*), 6.88 (d, *J* = 8.8 Hz, 2H, C(2)*H* or C(10)*H*), 6.40 (d, *J* = 15.5 Hz, 1H, C(6)*H*), 3.83 (s, 3H, C(12)*H* or C(13)*H*), 3.80 (s, 3H, C(12)*H* or C(13)*H*).

^{13}C NMR (126 MHz, DMSO-d_6): δ 163.1, 160.0, 155.4, 140.6, 130.2, 128.5, 126.4, 120.6, 117.4, 113.3, 113.2, 54.5, 54.3.

Spectroscopic data in agreement with literature values.[58]

(*E*)-*N*-(2-methoxyphenyl)-3-(4-methoxyphenyl)acrylamide 2.19



Chemical Formula: $C_{17}H_{17}NO_3$
Exact Mass: 283.1208
Molecular Weight: 283.3270

Prepared according to literature procedure.[58]

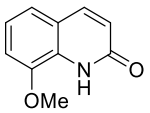
A 100 mL round bottom flask was charged with *o*-anisidine (0.225 mL, 2.00 mmol, 1.0 equiv) and K_2CO_3 (622 mg, 4.5 mmol, 2.25 equiv). Water (1 mL) and acetone (1 mL) was added. The mixture was cooled to 0 °C and (*E*)-3-(4-methoxyphenyl)acryloyl chloride (393 mg, 2.00 mmol, 1.0 equiv) was added. The reaction was then stirred for 2 h at 0 °C and then poured over ice water (5 mL). The resulting precipitate was collected, washed with water and dried *in vacuo* to give the desired product as a slight brown solid (735 mg, 65%).

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.52 (d, *J* = 6.4 Hz, 1H, C(5)*H*), 7.92 (s, 1H, N*H*), 7.70 (d, *J* = 15.5 Hz, 1H, C(9)*H*), 7.52 (d, *J* = 8.8 Hz, 2H, C(11)*H*), 7.06 (td, J = 7.9, 1.8 Hz, 1H, C(4)*H*), 7.00 (td, *J* = 7.6, 1.5 Hz, 1H, C(3)*H*), 6.92 (d, *J* = 8.8 Hz, 2H, C(12)*H*), 6.90 (dd, *J* = 6.4, 1.5 Hz, 1H, C(4)*H*)), 6.46 (d, *J* = 15.5 Hz, C(8)*H*), 3.92 (s, 3H, C(14)*H* or C(15)*H*), 3.85 (s, 3H, C(14)*H* or C(15)*H*).

^{13}C NMR (126 MHz, DMSO-d_6): δ 164.0, 160.9, 147.7, 141.4, 129.4, 127.8, 127.3, 123.5, 120.9, 119.8, 118.7, 114.1, 109.7, 55.5, 55.2.

Spectroscopic data in agreement with literature values.[74]

6-Fluoroquinolin-2(1*H*)-one 2.20

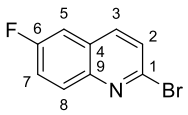


Chemical Formula: $C_{10}H_9NO_2$
Exact Mass: 175.0633
Molecular Weight: 175.1870

Prepared according to literature procedure.[59]

An oven-dried 20 mL microwave vial was charged with phosphoric acid (2.60 mL, 50.0 mmol, 50 equiv) and phosphorus pentoxide (2.84 g, 20.0 mmol, 20 equiv). The vial was capped and purged with N_2. The mixture was then stirred at 80 °C for 2 h**. 1.19** (283 mg, 1.00 mmol, 1.0 equiv) was added and the reaction was left to stir for an additional 2 h at 110 °C. Water was added and the resulting precipitate was collected, washed with water and dried *in vacuo*. The resulting crude was subjected to the next step without further purification.

2-Bromo-6-fluoroquinoline 2.22



Chemical Formula: C_9H_5BrFN
Exact Mass: 224.9589
Molecular Weight: 226.0484

Prepared according to a literature procedure.[60]

An oven-dried, 10 mL microwave vial was charged with 6-fluoroquinolin-2(1*H*)-one (226 mg, 1.00 mmol, 1.0 equiv) and $POBr_3$ (56.2 mg, 1.10 mmol, 1.1 equiv). The vessel was capped and purged with N_2. The mixture was stirred at 140 °C for 3 h, then cooled to rt and poured over ice. The resulting precipitate was collected, washed with petroleum ether and dried *in vacuo* to give the desired product as a pale brown solid (114 mg, 50%).

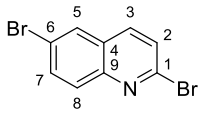
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (dd, *J* = 9.2, 5.2 Hz, 1H, C(8)*H*), 7.96 (d, *J* = 8.6 Hz, 1H, C(3)*H*), 7.54 (d, *J* = 8.6 Hz, 1H, C(2)*H*), 7.50 (td, *J* = 8.8, 2.8 Hz, 1H, C(7)*H*), 7.43 (dd, *J* = 8.6, 2.8 Hz, 1H, C(5)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 160.7 (d, ^1J = 249.5 Hz), 145.7, 141.1, 137.8 (d, ^4J = 5.2 Hz), 131.3 (d, ^3J = 9.3 Hz), 127.8 (d, ^3J = 10.3 Hz), 126.7, 120.9 (d, ^2J = 25.5 Hz), 111.2 (d, ^2J = 22.2 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ −111.94.

Spectroscopic data in agreement with literature values.[75]

2,6-Dibromoquinoline 2.23



Chemical Formula: $C_9H_5Br_2N$
Exact Mass: 284.8789
Molecular Weight: 286.9540

Prepared according to a literature procedure.[60]

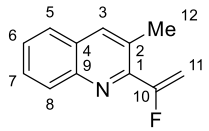
An oven-dried, 10 mL microwave vial was charged with 6-bromoquinolin-2(1*H*)-one (251 mg, 1.13 mmol, 1.13 equiv) and $POBr_3$ (287 mg, 1.00 mmol, 1.0 equiv). The vessel was capped and purged with N_2. The mixture was stirred at 140 °C for 3 h, then cooled to rt and poured over ice. The resulting precipitate was collected, washed with petroleum ether and dried *in vacuo* to give the desired product as a brown solid (178 mg, 62%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, *J* = 2.2 Hz, 1H, C(5)*H*), 7.91 (dd, *J* = 8.7, 2.0 Hz, 2H, C(3)*H*, C(8)*H*), 7.80 (dd, *J* = 8.9, 2.2 Hz, 1H, C(7)*H*), 7.55 (d, *J* = 8.6 Hz, 1H, C(2)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 147.3, 142.4, 137.4, 134.2, 130.5, 129.9, 128.2, 126.9, 121.2.

Spectroscopic data in agreement with literature values.[75]

2-(1-Fluorovinyl)-3-methylquinoline 2.26



Chemical Formula: $C_{12}H_{10}FN$
Exact Mass: 187.0797
Molecular Weight: 187.2174

Prepared according to General Procedure B using 2-bromo-3-methylquinoline (99.5 mg, 0.45 mmol, 1.0 equiv), (1-fluorovinyl)(methyl)diphenylsilane (164 mg, 0.675 mmol, 1.5 equiv), $Pd(PPh_3)_4$ (520 mg, 0.45 mmol, 1.0 equiv), CuI (85.7 mg, 0.45 mmol, 1.0 equiv), CsF (161 mg, 1.06 mmol, 2.35 equiv), and DMF (4.5 mL, 0.1 M). The reaction mixture was subjected to the purification outlined in General Procedure B (silica gel, Et_2O:petroleum ether, 1:99) to afford the desired product as a pale yellow oil (75.4 mg, 90%).

υ_{max} (film): 1655, 1493, 1273 cm^{-1}.

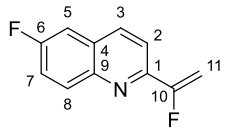
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08 (dd, *J* = 8.4, 1.3 Hz, 1H, C(8)*H*), 7.97 (s, 1H, C(3)*H*), 7.75 (dd, *J* = 8.2, 1.5 Hz, 1H, C(5)*H*), 7.67 (ddd, *J* = 8.4, 6.8, 1.5 Hz, 1H, C(6)*H*), 7.53 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H, C(7)*H*), 5.37 (dd, $^3J_{HF}$ = 48.2 Hz, $^2J_{HH}$ = 3.0 Hz, 1H, C(11)H_{trans}), 5.19 (dd, $^3J_{HF}$ = 16.8 Hz, $^2J_{HH}$ = 3.0 Hz, 1H, C(11)H_{cis}), 2.60 (d, *J* = 4.9 Hz, 3H, C(12)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 163.9 (d, ^1J = 256.3 Hz, *C*(10)), 151.2 (d, ^2J = 32.3 Hz, *C*(1)), 146.2 (*C*(9)), 146.2 (*C*(2)), 137.6 (*C*(3)), 129.6 (*C*(7)), 129.2 (*C*(8)), 128.4 (*C*(4)), 127.5 (*C*(5)), 126.8 (*C*(6)), 96.3 (d, ^2J = 19.2 Hz, *C*(11)), 20.0 (d, ^4J = 7.6 Hz, *C*(12)).

^{19}F NMR (470 MHz, $CDCl_3$): δ −99.90.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{12}H_{11}FN$) requires *m/z* 188.0870, found *m/z* 188.0866.

6-Fluoro-2-(1-fluorovinyl)quinoline 2.27



Chemical Formula: $C_{11}H_7F_2N$
Exact Mass: 191.0547
Molecular Weight: 191.1808

Prepared according to General Procedure B using 6-fluoro-2-bromoquinoline (150 mg, 0.664 mmol, 1.0 equiv), (1-fluorovinyl)(methyl)diphenylsilane (241 mg, 0.995 mmol, 1.5 equiv), $Pd(PPh_3)_4$ (38.3 mg, 0.033 mmol, 5 mol%), CuI (6.3 mg, 0.033 mmol, 5 mol%), CsF (237 mg, 1.56 mmol, 2.35 equiv), and DMF (6.6 mL, 0.1 M). The reaction mixture was subjected to the purification outlined in General Procedure B (silica gel, Et_2O:petroleum ether, 1:99) to afford the desired product as a pale yellow oil (84.0 mg, 66%).

υ_{max} (film): 1657, 1501, 1285, 1221 cm^{-1}.

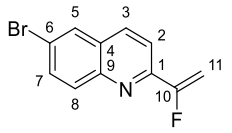
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.7 Hz, 1H, C(3)*H*), 8.08 (dd, *J* = 9.3, 5.3 Hz, 1H, C(8)*H*), 7.68 (d, *J* = 8.7 Hz, 1H, C(2)*H*), 7.49 (td, *J* = 8.9, 2.8 Hz, 1H, C(7)*H*), 7.40 (dd, *J* = 8.7, 2.9 Hz, 1H, C(5)*H*), 5.84 (dd, $^3J_{HF}$ = 48.6 Hz, $^2J_{HH}$ = 3.0 Hz, 1H, C(11)H_{trans}), 5.13, (dd, $^3J_{HF}$ = 16.4 Hz, $^2J_{HH}$ = 3.1 Hz, 1H, C(11)H_{cis}).

^{13}C NMR (126 MHz, $CDCl_3$): δ 162.0 (d, ^1J = 251.0 Hz, *C*(10)), 160.8 (d, ^1J = 249.4 Hz, C(6)*H*), 149.6, (dd, ^2J = 35.8, 3.1 Hz, *C*(1)), 145.0 (d, ^4J = 4.0 Hz, *C*(9)), 136.4 (d, ^4J = 6.6 Hz, *C*(3)), 132.3 (d, ^3J = 9.1 Hz, *C*(8)), 128.6 (d, ^3J = 10.1 Hz, *C*(4)), 120.5 (d, ^2J = 26.0 Hz, *C*(7)), 117.6 (d, ^3J = 4.7 Hz, *C*(2)), 110.6 (d, ^2J = 21.8 Hz, *C*(5)), 93.8 (d, ^2J = 18.5 Hz, *C*(11)).

^{19}F NMR (376 MHz, $CDCl_3$): δ −112.23, −114.42.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{11}H_8F_2N$) requires *m/z* 192.0619, found *m/z* 192.0618.

6-Bromo-2-(1-fluorovinyl)quinoline 2.28



Chemical Formula: $C_{11}H_7BrFN$
Exact Mass: 250.9746
Molecular Weight: 252.0864

Prepared according to General Procedure B using 2,6-dibromoquinoline (259 mg, 0.90 mmol, 1.0 equiv), (1-fluorovinyl)(methyl)diphenylsilane (328 mg, 1.38 mmol, 1.5 equiv), $Pd(PPh_3)_4$ (52.0 mg, 0.045 mmol, 5 mol%), CuI (8.6 mg, 0.045 mmol, 5 mol%), CsF (322 mg, 2.12 mmol, 2.35 equiv), and DMF (9 mL, 0.1 M). The reaction mixture was subjected to the purification outlined in General Procedure B (silica gel, Et_2O:petroleum ether, 1:99) to afford the desired product as a pale yellow solid (183 mg, 81%).

υ_{max} (film): 1659, 1489, 1283 cm^{-1}.

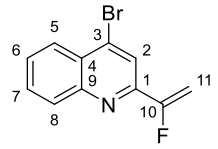
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, *J* = 8.6 Hz, 1H, C(3)*H*), 7.97 (d, *J* = 2.2 Hz, 1H, C(5)*H*), 7.95 (d, *J* = 9.0 Hz, 1H, C(8)*H*), 7.78 (dd, *J* = 9.0, 2.2 Hz, 1H, C(7)*H*), 7.70 (dd, *J* = 8.7, 1.3 Hz, 1H, C(2)*H*), 5.87 (dd, $^3J_{HF}$ = 48.5 Hz, $^2J_{HH}$ = 3.1 Hz, 1H, C(11)H_{trans}), 5.16 (dd, $^3J_{HF}$ = 16.3 Hz, $^2J_{HH}$ = 3.1 Hz, 1H, C(11)H_{cis}).

^{13}C NMR (126 MHz, $CDCl_3$): δ 161.9 (d, ^1J = 251.1 Hz, *C*(10)), 150.5 (d, ^2J = 35.6 Hz, *C*(1)), 146.5 (d, ^4J = 4.0 Hz, *C*(9)), 136.1 (*C*(3)), 133.7 (*C*(7)), 131.5 (*C*(5)), 129.7 (*C*(8)), 129.1 (*C*(4)), 121.2 (*C*(6)), 117.8 (d, ^3J = 4.6 Hz, *C*(2)), 94.4 (d, ^2J = 18.3 Hz, *C*(11)).

^{19}F NMR (376 MHz, $CDCl_3$): δ −114.60.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{11}H_8{}^{79}BrFN$) requires *m/z* 251.9819, found *m/z* 251.9816.

4-Bromo-2-(1-fluorovinyl)quinoline 2.29



Chemical Formula: $C_{11}H_7BrFN$
Exact Mass: 250.9746
Molecular Weight: 252.0864

Prepared according to General Procedure B using 2,4-dibromoquinoline (259 mg, 0.90 mmol, 1.0 equiv), (1-fluorovinyl)(methyl)diphenylsilane (328 mg, 1.35 mmol, 1.5 equiv), $Pd(PPh_3)_4$ (52.0 mg, 0.045 mmol, 5 mol%), CuI (8.6 mg, 0.045 mmol, 5 mol%), CsF (322mg, 2.12 mmol, 2.35 equiv), and DMF (9 mL, 0.1 M). The reaction mixture was subjected to the purification outlined in General Procedure B (silica gel, Et_2O:petroleum ether, 1:99) to afford the desired product as a pale yellow solid (105 mg, 42%).

υ_{max} (film): 1491, 1265 cm^{-1}.

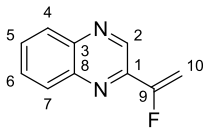
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 8.5, 1.4 Hz, 1H, C(5)*H*), 8.05 (dd, *J* = 8.5, 1.2 Hz, 1H, C(8)*H*), 7.94 (d, *J* = 1.2 Hz, 1H, C(2)*H*), 7.74 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H, C(6)*H*), 7.60 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H, C(7)*H*), 5.89 (dd, $^3J_{HF}$ = 48.4 Hz, $^2J_{HH}$ = 3.1 Hz, 1H, C(11)H_{trans}), 5.16 (dd, $^3J_{HF}$ = 16.2 Hz, $^2J_{HH}$ = 3.1 Hz, 1H, C(11)H_{cis}).

^{13}C NMR (126 MHz, $CDCl_3$): δ 161.0 (d, ^1J = 251.5 Hz, *C*(10)), 149.8 (d, ^2J = 36.1 Hz, *C*(1)), 148.3 (d, ^4J = 4.0 Hz, *C*(9)), 135.0 (d, ^4J = 1.7 Hz, *C*(3)), 130.9 (*C*(7)), 130.2 (*C*(8)), 128.3 (*C*(5)), 127.5 (*C*(4)), 126.7 (*C*(6)), 120.9 (d, ^3J = 5.1 Hz, *C*(2)), 94.7 (d, ^2J = 17.9 Hz, *C*(11)).

^{19}F NMR (470 MHz, $CDCl_3$): δ −114.71.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{11}H_8{}^{79}BrFN$) requires *m/z* 251.9819, found *m/z* 251.9817.

2-(1-Fluorovinyl)quinoxaline 2.30



Chemical Formula: $C_{10}H_7FN_2$
Exact Mass: 174.0593
Molecular Weight: 174.1784

Prepared according to General Procedure B using 2-bromoquinoxaline (174 mg, 1.00 mmol, 1.0 equiv), (1-fluorovinyl)(methyl)diphenylsilane (363 mg, 1.50 mmol, 1.5 equiv), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol, 5 mol%), CuI (6.6 mg, 0.05 mmol, 5 mol%), CsF (448 mg, 2.35 mmol, 2.35 equiv), and DMF (10 mL, 0.1 M). The reaction mixture was subjected to the purification outlined in General Procedure B (silica gel, Et_2O:petroleum ether, 1:99) to afford the desired product as a pale yellow solid (158 mg, 91%).

υ_{max} (film): 1655, 1506, 1105 cm^{-1}.

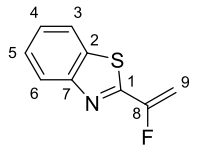
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.13 (s, 1H, C(2)*H*), 8.16 – 8.07 (m, 2H, C(4)*H*, C(7)*H*), 7.87 – 7.74 (m, 2H, C(5)*H*, C(6)*H*), 5.92 (dd, $^3J_{HF}$ = 48.2 Hz, $^2J_{HH}$ = 3.4 Hz, 1H, C(10)H_{trans}), 5.27 (dd, $^3J_{HF}$ = 16.5 Hz, $^2J_{HH}$ = 3.4 Hz, 1H, C(10)H_{cis}).

^{13}C NMR (126 MHz, $CDCl_3$): δ 160.7 (d, ^1J = 250.8 Hz, *C*(9)), 145.0 (d, ^2J = 34.0 Hz, *C*(1)), 142.6 (*C*(3)), 141.9 (*C*(8)), 141.3 (d, ^3J = 5.3 Hz, *C*(2)), 130.9 (*C*(4)), 130.7 (*C*(6)), 129.8 (*C*(5)), 129.4 (*C*(7)), 95.9 (d, ^2J = 17.3 Hz, *C*(10)).

^{19}F NMR (376 MHz, $CDCl_3$): δ −116.24.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{10}H_8FN_2$) requires *m/z* 175.0666, found *m/z* 175.0665.

2-(1-Fluorovinyl)benzo[*d*]thiazole 2.31



Chemical Formula: C_9H_6FNS
Exact Mass: 179.0205
Molecular Weight: 179.2124

Prepared according to General Procedure B using 2-Bromobenzothiazole (214 mg, 1.00 mmol, 1.0 equiv), (1-fluorovinyl)(methyl)diphenylsilane (356 mg, 1.50 mmol, 1.5 equiv), $Pd(PPh_3)_4$ (1.16 g, 1.00 mmol, 1.0 equiv), CuI (132 mg, 1.00 mmol, 1.0 equiv), CsF (364 mg, 2.40 mmol, 2.4 equiv), and DMF (10 mL, 0.1 M). The reaction mixture was subjected to the purification outlined in General Procedure B (silica gel, Et_2O:petroleum ether, 1:99) to afford the desired product as a pale yellow solid (73.8 mg, 42%).

υ_{max} (film): 1647, 1558, 1290 cm^{-1}.

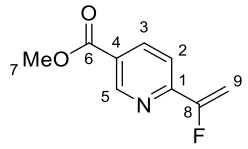
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.2 Hz, 1H, C(6)*H*), 7.92 (d, *J* = 8.0 Hz, 1H, C(3)*H*), 7.64 – 7.36 (m, 2H, C(4)*H*, C(5)*H*), 5.74 (dd, $^3J_{HF}$ = 47.1 Hz, $^2J_{HH}$ = 3.7 Hz, 1H, C(9)H_{trans}), 5.21 (dd, $^3J_{HF}$ = 15.5 Hz, $^2J_{HH}$ = 3.8 Hz, 1H, C(9)H_{cis}).

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.9 (d, ^2J = 39.3 Hz, *C*(1)), 157.3 (d, ^1J = 247.7 Hz, *C*(8)), 153.5 (d, ^4J = 2.0 Hz, *C*(7)), 135.0 (*C*(2)), 126.8 (*C*(5)), 126.1 (*C*(3)), 123.8 (*C*(4)), 121.9 (*C*(6)), 95.5 (d, ^2J = 17.2 Hz, *C*(9)).

^{19}F NMR (470 MHz, $CDCl_3$): δ −106.57.

HRMS (ESI): exact mass calculated for $[M+H]^+$ (C_9H_7FNS) requires *m/z* 180.0278, found *m/z* 180.0277.

Methyl 6-(1-fluorovinyl)nicotinate 2.32



Chemical Formula: $C_9H_8FNO_2$
Exact Mass: 181.0539
Molecular Weight: 181.1664

Prepared according to General Procedure B using 6-bromonicotinate (216 mg, 1.00 mmol, 1.0 equiv), (1-fluorovinyl)(methyl)diphenylsilane (356 mg, 1.50 mmol, 1.5 equiv), $Pd(PPh_3)_4$ (59.0 mg, 0.05 mmol, 5 mol%), CuI (9.7 mg, 0.05 mmol, 5 mol%), CsF (364 mg, 2.40 mmol, 2.4 equiv), and DMF (10 mL, 0.1 M). The reaction mixture was subjected to the purification outlined in General Procedure B (silica gel, Et_2O:petroleum ether, 1:99) to afford the desired product as a pale yellow solid (164 mg, 91%).

υ_{max} (film): 1722, 1655, 1593, 1287, 1273, 1130, 1101 cm^{-1}.

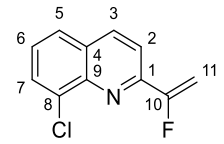
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.14 – 9.13 (m, 1H, C(5)*H*), 8.31 (dd, *J* = 8.2, 2.1 Hz, 1H, C(3)*H*), 7.59 (d, *J* = 7.9 Hz, 1H, C(2)*H*), 5.84 (dd, $^3J_{HF}$ = 48.5 Hz, $^2J_{HH}$ = 2.9 Hz, 1H, C(9)H_{trans}), 5.11 (dd, $^3J_{HF}$ = 16.3 Hz, $^2J_{HH}$ = 2.9 Hz, 1H, C(9)H_{cis}), 3.94 (s, 3H, C(7)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 165.4 (*C*(6)), 161.3 (d, ^1J = 249.3 Hz, *C*(8)), 153.3 (d, ^2J = 36.8 Hz, *C*(1)), 150.8 (d, ^4J = 4.5 Hz, *C*(5)), 138.2 (d, ^4J = 1.8 Hz, *C*(3)), 125.8 (*C*(4)), 118.2 (d, ^3J = 4.5 Hz, *C*(2)), 95.2 (d, ^2J = 17.6 Hz, *C*(9)), 52.6 (*C*(7)).

^{19}F NMR (376 MHz, $CDCl_3$): δ −115.94.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_9H_9FNO_2$) requires *m/z* 182.0612, found *m/z* 182.0610.

8-Chloro-2-(1-fluorovinyl)quinoline 2.33



Chemical Formula: $C_{11}H_7ClFN$
Exact Mass: 207.0251
Molecular Weight: 207.6324

Prepared according to General Procedure B using 2-bromo-8-chloroquinoline (121 mg, 0.50 mmol, 1.0 equiv), (1-fluorovinyl)(methyl)diphenylsilane (182 mg, 0.75 mmol, 1.5 equiv), $Pd(PPh_3)_4$ (57.8 mg, 0.50 mmol, 1.0 equiv), CuI (6.6 mg, 0.50 mmol, 1.0 equiv), CsF (224 mg, 1.18 mmol, 2.35 equiv), and DMF (10 mL, 0.1 M). The reaction mixture was subjected to the purification outlined in General Procedure B (silica gel, Et_2O:petroleum ether, 1:99) to afford the desired product as a white solid (42.0 mg, 40%).

υ_{max} (film): 1601, 1501, 1261, 752 cm^{-1}.

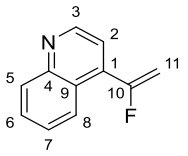
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.6 Hz, 1H, C(3)*H*), 7.82 (dd, *J* = 7.5, 1.3 Hz, 1H, C(5)*H*), 7.72 (ddd, *J* = 8.1, 6.8, 1.4 Hz, 2H, C(2)*H*, C(7)*H*), 7.43 (dd, *J* = 8.2, 7.4 Hz, 1H, C(6)*H*), 6.06 (dd, $^3J_{HF}$ = 48.5 Hz, $^2J_{HH}$ = 2.9 Hz, 1H, C(11)H_{trans}), 5.17 (dd, $^3J_{HF}$ = 16.0 Hz, $^2J_{HH}$ = 2.9 Hz, 1H, C(11)H_{cis}).

^{13}C NMR (126 MHz, $CDCl_3$): δ 161.9 (d, ^1J = 250.7 Hz, *C*(10)), 150.60 (d, ^2J = 37.5 Hz, *C*(1)), 144.1 (d, ^4J = 4.5 Hz, *C*(9)), 137.6 (*C*(3)), 133.9 (*C*(8)), 130.2 (*C*(7)), 129.2 (*C*(4)), 126.9 (*C*(5)), 126.7 (*C*(6)), 117.5 (d, ^3J = 4.4 Hz, *C*(2)), 94.7 (d, ^2J = 17.6 Hz, *C*(11)).

^{19}F NMR (376 MHz, $CDCl_3$): δ −115.61.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{11}H_8ClFN$) requires *m/z* 208.0324, found *m/z* 208.0320.

4-(1-Fluorovinyl)quinoline 2.34



Chemical Formula: $C_{11}H_8FN$
Exact Mass: 173.0641
Molecular Weight: 173.1904

Prepared according to General Procedure B using 4-bromoquinoline (208 mg, 1.00 mmol, 1.0 equiv), (1-fluorovinyl)(methyl)diphenylsilane (356 mg, 1.50 mmol, 1.5 equiv), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol, 5 mol%), CuI (9.7 mg, 0.05 mmol, 5 mol%), CsF (364 mg, 2.40 mmol, 2.4 equiv), and DMF (10 mL, 0.1 M). The reaction mixture was subjected to the purification outlined in General Procedure B (silica gel, Et_2O:petroleum ether, 1:99) to afford the desired product as a pale yellow oil (82.1 mg, 47%).

NB. Due to the reactive nature of this compound, an analytically pure sample was not obtained, data reported as observed. The compound, which contained impurities, was used directly in the next step.

υ_{max} (film): 1659, 1508, 1282 cm^{-1}.

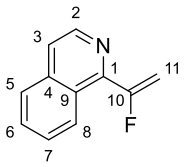
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.93 (d, *J* = 4.5 Hz, 1H, C(3)*H*), 8.23 – 8.15 (m, 2H, C(5)*H*, C(8)*H*), 7.79 – 7.73 (m, 1H, C(6)*H*), 7.67 – 7.58 (m, 1H, C(7)*H*), 7.49 (dd, *J* = 4.4, 1.1 Hz, 1H, C(2)*H*), 5.30 (dd, $^3J_{HF}$ = 16.7 Hz, $^2J_{HH}$ = 3.4 Hz, 1H, C(11)H_{cis}), 5.09 (dd, $^3J_{HF}$ = 47.9 Hz, $^2J_{HH}$ = 3.4 Hz, 1H C(11)H_{trans}).

^{13}C NMR (126 MHz, $CDCl_3$): δ 162.5, 160.5, 149.9, 149.9, 148.9, 148.7, 138.5, 138.3, 134.5, 134.1, 130.6, 130.1, 129.9, 128.1, 127.6, 127.0, 125.4, 125.4, 125.3, 125.1, 120.4, 97.7, 97.5, 85.5, 85.1, 82.9. *NB.* J_{CF} not indicated due to overlap of impurities.

^{19}F NMR (376 MHz, $CDCl_3$): δ −92.69.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{11}H_9FN$) requires *m/z* 174.0714, found *m/z* 174.0709.

1-(1-Fluorovinyl)isoquinoline 2.35



Chemical Formula: $C_{11}H_8FN$
Exact Mass: 173.0641
Molecular Weight: 173.1904

Prepared according to General Procedure B using 1-bromoisoquinoline (207 mg, 1.00 mmol, 1.0 equiv), (1-fluorovinyl)(methyl)diphenylsilane (356 mg, 1.50 mmol, 1.5 equiv), $Pd(PPh_3)_4$ (59.0 mg, 0.05 mmol, 5 mol%), CuI (9.7 mg, 0.05 mmol, 5 mol%), CsF (364 mg, 2.40 mmol, 2.4 equiv), and DMF (10 mL, 0.1 M). The reaction mixture was subjected to the purification outlined in General Procedure B (silica gel, Et_2O:petroleum ether, 1:99) to afford the desired product as a pale yellow oil (171 mg, 99%).

υ_{max} (film): 1657, 1557, 1298 cm^{-1}.

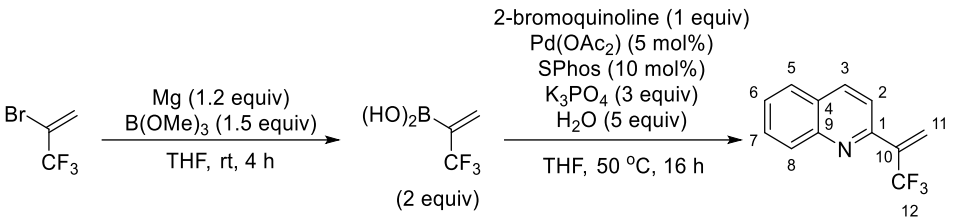
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, *J* = 5.6 Hz, 1H, C(2)*H*), 8.37 (d, *J* = 8.6 Hz, 1H, C(8)*H*), 7.83 (d, *J* = 8.2 Hz, 1H, C(5)*H*), 7.76 – 7.65 (m, 2H, C(3)*H*, C(7)*H*), 7.61 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H, C(6)*H*), 5.50 – 5.19 (m, 2H, C(11)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 163.0 (d, ^1J = 256.4 Hz, *C*(10)), 151.0 (d, ^2J = 31.1 Hz, *C*(1)), 141.9 (*C*(6)), 136.9 (*C*(5)), 130.5 (*C*(7)), 128.0 (d, ^4J = 1.9 Hz, *C*(2)), 127.2 (*C*(8)), 126.3 (d, ^3J = 9.7 Hz, *C*(9)), 126.0 (d, ^4J = 2.3 Hz, *C*(4)), 122.2 (*C*(3)), 97.3 (d, ^2J = 19.2 Hz, *C*(11)).

^{19}F NMR (376 MHz, $CDCl_3$): δ −97.19.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{11}H_9FN$) requires *m/z* 174.0714, found *m/z* 174.0710.

2-(3,3,3-Trifluoroprop-1-en-2-yl)quinoline 2.40



Chemical Formula: $C_{12}H_8F_3N$
Exact Mass: 223.0609
Molecular Weight: 223.1982

This compound was prepared according to an adapted literature procedure.[61,62]

An oven-dried 100 mL round bottom flask was charged with Mg turnings (262 mg, 10.8 mmol, 1.2 equiv), capped and purged with N_2. Then THF (18 mL, 0.5 M) and freshly distilled trimethylborate (1.50 mL, 13.5 mmol, 1.5 equiv) were added sequentially and the mixture was allowed to stir at rt for 5 min. 2-Bromo-1,1,1-trifluoropropene (0.96 mL, 9.00 mmol, 1.0 equiv) was then added dropwise over 5 min, then the reaction was stirred for 4 h at rt. The reaction was quenched using 6 M HCl (50 mL) and the solution was left to stir for 5 min. The organic layer was then separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Formation of the boronic acid was confirmed *via* ^{11}B NMR, then the crude material was used directly in the next step.

NB. Calculations based upon quantitative conversion to boronic acid in the previous step. An oven-dried 2-necked 100 mL round bottomed flask equipped with a reflux condenser was charged with $Pd(OAc)_2$ (50.5 mg, 0.225 mmol, 5 mol%), SPhos (185 mg, 0.45 mmol, 10 mol%), 2-bromoquinoline (936 mg, 4.50 mmol, 1.0 equiv), the crude boronic acid (9.00 mmol, 2.0 equiv), and K_3PO_4 (2.87 g, 13.5 mmol, 3.00 equiv). The vessel was capped and purged with N_2. THF (22.5 mL, 0.2 M) and water (405 µL, 22.5 mmol, 5.0 equiv) were then added to the mixture sequentially. The reaction was then heated to 50 °C for 16 h. The reaction mixture was then cooled to rt, filtered through Celite, eluting with EtOAc and concentrated *in vacuo*. Purification of the crude *via* flash

chromatography (silica gel, EtOAc:petroleum ether, 10:90) gave the desired product as a pale yellow oil (102 mg, 9%).

NB. Due to the reactive nature of this compound, an analytically pure sample was not obtained, data reported as observed. The compound was used directly in the next step.

υ_{max} (film): 1504, 1126, 1096 cm^{-1}.

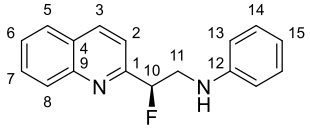
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.7 Hz, 1H, C(3)*H*), 8.11 (d, *J* = 8.4 Hz, 1H, C(8)*H*), 7.83 (d, *J* = 8.1 Hz, 1H, C(5)*H*), 7.74 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H, C(7)*H*), 7.65 – 7.60 (m, 1H, C(2)*H*), 7.56 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H, C(6)*H*), 6.68 (q, $^4J_{HF}$ = 1.8 Hz, 1H, C(11)*H*), 6.25 (q, $^4J_{HF}$ = 1.4 Hz, 1H, C(11)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 151.0 (*C*(1)), 148.0 (*C*(9)), 138.5 (q, ^2J = 27.7 Hz, *C*(10)), 137.0 (*C*(3)), 130.2 (*C*(7)), 130.0 (*C*(8)), 127.8 (*C*(4)), 127.6 (*C*(5)), 127.3 (*C*(6)), 124.5 (q, ^1J = 273.4 Hz, *C*(12)), 123.3 (q, ^3J = 6.3 Hz, *C*(11)), 119.2 (*C*(2)).

^{19}F NMR (470 MHz, $CDCl_3$): δ −63.61.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{12}H_9F_3N$) requires *m/z* 224.0682, found *m/z* 224.0677.

(*R*)-*N*-(2-Fluoro-2-(quinolin-2-yl)ethyl)aniline 2.43



Chemical Formula: $C_{17}H_{15}FN_2$
Exact Mass: 266.1219
Molecular Weight: 266.3194

Racemic:

Prepared according to General Procedure C using 2-(1-fluorovinyl)quinoline (17.3 mg, 0.10 mmol, 1.0 equiv), aniline (27 µL, 0.30 mmol, 3.0 equiv), TFA (1.5 µL, 0.02 mmol, 20 mol%), and THF (200 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure C (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (20.6 mg, 77%).

Enantioenriched:

Prepared according to General Procedure D using 2-(1-fluorovinyl)quinoline (17.3 mg, 0.10 mmol, 1.0 equiv), aniline (27 µL, 0.30 mmol, 3.0 equiv), (*S*)-TRIP catalyst (15.1 mg, 0.02 mmol, 20 mol%), and THF (200 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure D (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (21.8 mg, 82%).

υ_{max} (film): 1600, 1504, 1320, 1262 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (d, *J* = 8.5 Hz, 1H, C(3)*H*), 8.11 (d, *J* = 8.5 Hz, 1H, C(8)*H*), 7.85 (d, *J* = 8.2 Hz, 1H, C(5)*H*), 7.79 – 7.71 (m, 1H, C(7)*H*), 7.64 (dd, *J* = 8.5, 1.2 Hz, 1H, C(2)*H*), 7.60 – 7.54 (m, 1H, C(6)*H*), 7.23 – 7.15 (m, 2H, C(14)*H*), 6.79 – 6.70 (m, 3H, C(13)*H*, C(15)*H*), 5.91 (ddd, $^{2}J_{HF}$ = 48.7 Hz, *J* = 7.3, 3.7 Hz, 1H, C(10)*H*), 3.95 (ddd, $^{3}J_{HF}$ = 26.3 Hz, $^{2}J_{HH}$ = 14.0 Hz, *J* = 3.8 Hz, 1H, C(11)H_a), 3.73 (ddd, $^{3}J_{HF}$ = 19.7 Hz, $^{2}J_{HH}$ = 14.0 Hz, *J* = 7.3 Hz, 1H, C(11)H_b).

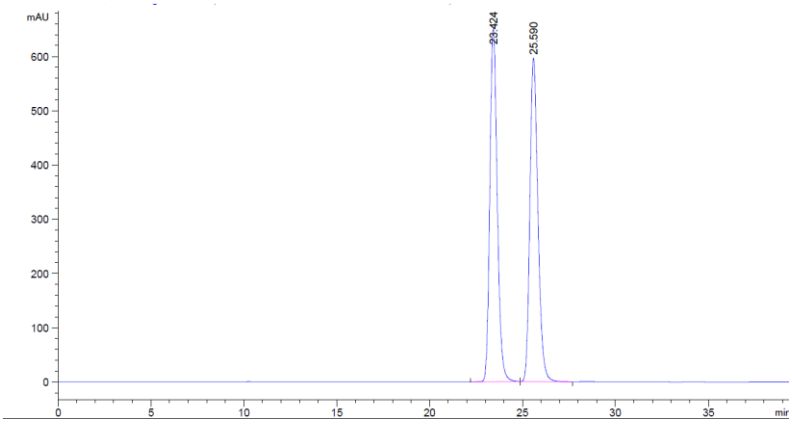
^{13}C NMR (126 MHz, $CDCl_3$): δ 158.1 (d, ^{2}J = 24.5 Hz, *C*(1)), 147.6 (*C*(12)), 147.5 (*C*(9)), 137.3 (*C*(3)), 130.1 (*C*(7)), 129.5 (*C*(14)), 129.3 (*C*(8)), 127.9 (*C*(5)), 127.9 (*C*(4)), 127.0 (*C*(6)), 118.2 (*C*(15)), 117.9 (d, ^{3}J = 6.7 Hz, (*C*(2)), 113.5 (*C*(13)), 93.4 (d, ^{1}J = 174.8 Hz, *C*(10)), 48.6 (d, ^{2}J = 22.5 Hz, *C*(11)).

^{19}F NMR (376 MHz, $CDCl_3$): δ −191.33.

HRMS (NSI): exact mass calculated for $[M+H]^+$ ($C_{17}H_{16}N_2F$) requires *m/z* 267.1292, found *m/z* 267.1293.

The enantiomeric purity of the product was determined by HPLC analysis: 96:4 e.r. (Chiralpak IA, hexane/*i*-PrOH = 90/10, flow rate 0.5 mL/min, λ = 250 nm), t_r (major) = 23.1 min, t_r (minor) = 25.2 min;

$[\alpha]_D^{23}$ = +21.7 (*c* 1.01, $CHCl_3$).

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==================================================================
                      Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
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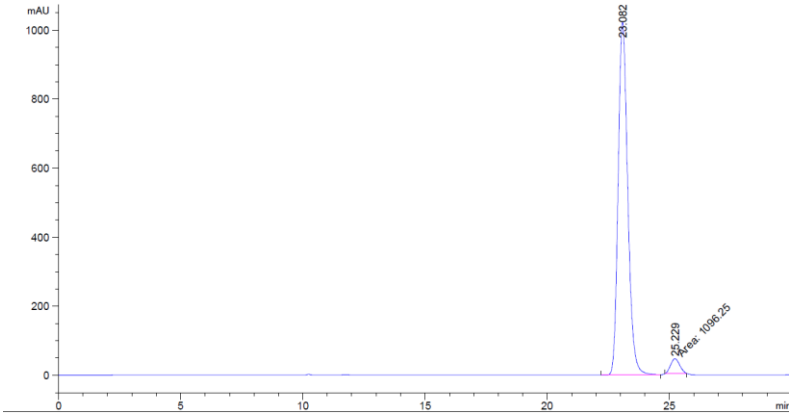


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==================================================================
                      Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  23.082 BV    0.4204 2.79043e4  1022.16467  96.2199
   2  25.229 MM    0.4293 1096.24890   42.55674   3.7801
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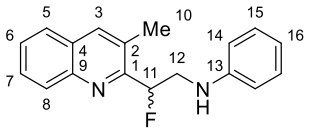
(±)-*N*-(2-Fluoro-2-(3-methylquinolin-2-yl)ethyl)aniline 2.44



Chemical Formula: $C_{18}H_{17}FN_2$
Exact Mass: 280.1376
Molecular Weight: 280.3464

Prepared according to General Procedure C using 3-methyl-2-(1-fluorovinyl)quinoline (18.8 mg. 0.10 mmol, 1.0 equiv), aniline (27 µL, 0.30 mmol, 3.0 equiv), TFA (1.5 µL, 0.02 mmol, 20 mol%), and THF (200 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure C (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (24.7 mg, 88%).

υ_{max} (film): 1603, 1506, 1325, 1261 cm^{-1}.

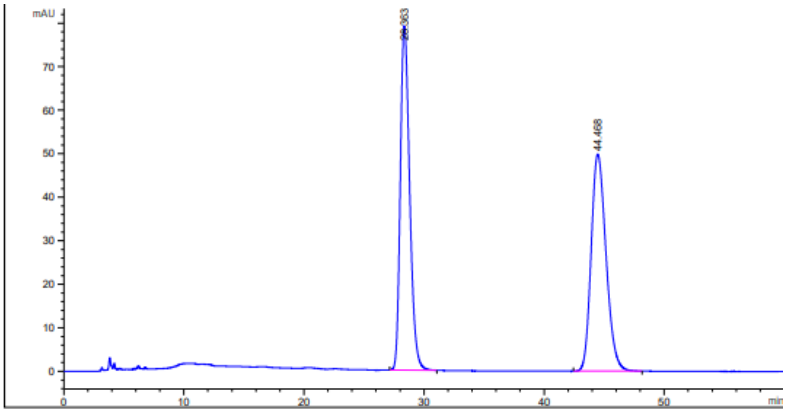
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.4 Hz, 1H, C(8)*H*), 7.96 (s, 1H, C(3)*H*), 7.76 (d, *J* = 8.1 Hz, 1H, C(5)*H*), 7.69 (t, *J* = 7.6 Hz, 1H, C(6)*H*), 7.55 (t, *J* = 7.5 Hz, 1H, C(7)*H*), 7.21 (t, *J* = 7.8 Hz, 2H, C(15)*H*), 6.74 (dd, *J* = 10.9, 7.9 Hz, 3H, C(14)*H*, C(16)*H*), 6.00 (ddd, $^2J_{HF}$ = 48.1 Hz, *J* = 7.2, 4.9 Hz, 1H, C(11)*H*), 4.41 (s, 1H, N*H*), 4.12 – 3.91 (m, 2H, C(12)*H*), 2.58 (s, 3H, C(10)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 155.2 (d, ^2J = 18.1 Hz, *C*(1)), 147.7 (*C*(13)), 146.0 (*C*(9)), 137.3 (*C*(3)), 129.9 (*C*(2)), 129.5 (*C*(7)), 129.4 (*C*(15)), 129.0 (*C*(8)), 128.2 (*C*(4)), 127.2 (*C*(5)), 126.8 (*C*(6)), 117.9 (*C*(16)), 113.2 (*C*(14)), 90.2 (d, ^1J = 172.8 Hz, *C*(11)), 46.2 (d, ^2J = 24.6 Hz, *C*(12)), 18.6 (d, ^4J = 3.3 Hz, *C*(10)).

^{19}F NMR (376 MHz, $CDCl_3$): δ −183.72.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{18}H_{18}FN_2$) requires *m/z* 281.1449, found *m/z* 281.1441.

(Chiralcel OJ-H, hexane/*i*-PrOH = 50/50, flow rate 1.0 mL/min, λ = 250 nm), t_r (1) = 28.4 min, t_r (2) = 44.5 min;

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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
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   1  28.363 BB    0.8188 4269.78467   79.12798  49.9060
   2  44.468 BB    1.2874 4285.86523   49.82888  50.0940
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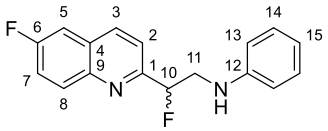
(±)-*N*-(2-Fluoro-2-(6-fluoroquinolin-2-yl)ethyl)aniline 2.45



Chemical Formula: $C_{17}H_{14}F_2N_2$
Exact Mass: 284.1125
Molecular Weight: 284.3098

Prepared according to General Procedure C using 6-fluoro-2-(1-fluorovinyl)quinoline (19.1 mg, 0.10 mmol, 1.0 equiv), aniline (27 µL, 0.30 mmol, 3.0 equiv), TFA (1.5 µL, 0.02 mmol, 20 mol%), and THF (200 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure C (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (25.9 mg, 91%).

υ_{max} (film): 1603, 1506, 1323, 1260, 1231 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.6 Hz, 1H, C(3)*H*), 8.10 (dd, *J* = 9.2, 5.3 Hz, 1H, C(8)*H*), 7.65 (d, *J* = 8.5 Hz, 1H, C(2)*H*), 7.52 (td, *J* = 8.7, 2.8 Hz, 1H, C(7)*H*), 7.46 (dd, *J* = 8.8, 2.8 Hz, 1H, C(5)*H*), 7.19 (t, *J* = 7.8 Hz, 2H, C(14)*H*), 6.78 – 6.70 (m, 3H, C(13)*H*, C(15)*H*), 5.88 (ddd, $^2J_{HF}$ = 48.6 Hz, *J* = 7.3, 3.6 Hz, 1H, C(10)*H*), 3.94 (ddd, $^3J_{HF}$ = 26.4 Hz, $^2J_{HH}$ = 14.1

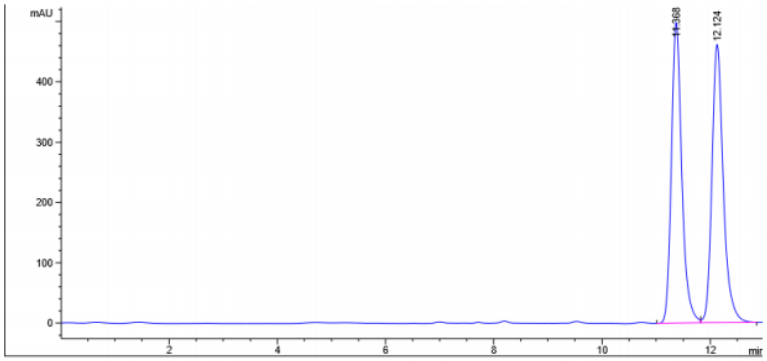
Hz, *J* = 3.7 Hz, 1H, C(11)H_a), 3.72 (ddd, $^3J_{HF}$ = 20.0 Hz, $^2J_{HH}$ = 14.1 Hz, *J* = 7.3 Hz, 1H, C(11)H_b).

^{13}C NMR (101 MHz, $CDCl_3$): δ 160.7 (d, ^1J = 248.7 Hz, *C*(6)), 157.48 (dd, ^2J = 24.7, 2.7 Hz, *C*(1)), 147.6 (*C*(12), 144.6 (*C*(9)), 136.6 (d, ^4J = 5.5 Hz, *C*(3)), 131.9 (d, ^3J = 9.2 Hz, *C*(8)), 129.5 (*C*(14)), 128.4 (d, ^3J = 10.1 Hz, *C*(4)), 120.4 (d, ^2J = 25.8 Hz, *C*(7)), 118.7 (d, ^3J = 6.4 Hz, *C*(2)), 118.2 (*C*(15)), 113.4 (*C*(13)), 110.8 (d, ^2J = 21.7 Hz, *C*(5)), 93.2 (d, ^1J = 174.5 Hz, *C*(10)), 48.5 (d, ^2J = 22.4 Hz, *C*(11)).

^{19}F NMR (376 MHz, $CDCl_3$): δ −112.80, −191.35.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{17}H_{15}F_2N_2$) requires *m/z* 285.1198, found *m/z* 285.1190.

(Chiralpak IA, hexane/*i*-PrOH = 50/50, flow rate 0.5 mL/min, λ = 250 nm), t_r (1) = 11.4 min, t_r (2) = 12.1 min;

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Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
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   1  11.368 VV    0.2018 6660.14502  498.86203  49.7094
   2  12.124 VB    0.2223 6738.01025  461.47482  50.2906
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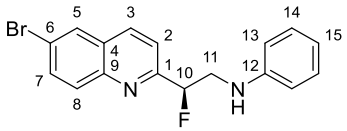
***(R)-N*-(2-(6-Bromoquinolin-2-yl)-2-fluoroethyl)aniline 2.46**



Chemical Formula: $C_{17}H_{14}BrFN_2$
Exact Mass: 344.0324
Molecular Weight: 345.2154

Racemic:

Prepared according to General Procedure C using 6-bromo-2-(1-fluorovinyl)quinoline (25.2 mg, 0.10 mmol, 1.0 equiv), aniline (27 µL, 0.30 mmol, 3.0 equiv), TFA (1.5 µL, 0.02 mmol, 20 mol%), and THF (200 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure C (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (30.7 mg, 89%).

Enantioenriched:

Prepared according to General Procedure E using 6-bromo-2-(1-fluorovinyl)quinoline (25.2 mg, 0.10 mmol, 1.0 equiv), aniline (27 µL, 0.30 mmol, 3.0 equiv), (*S*)-TRIP catalyst (15.1 mg, 0.02 mmol, 20 mol%), and CPME (200 µL, 0.5 M) at −10 °C for 3 d. The reaction mixture was subjected to the purification outlined in General Procedure E (silica gel, EtOAc:petroleum ether, 5:95 to 10:100) to afford the desired product as a pale brown oil (33.1 mg, 95%).

υ_{max} (film): 1603, 1508, 1491, 1319, 1261 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.5 Hz, 1H, C(3)*H*), 8.00 (d, *J* = 2.2 Hz, 1H, C(5)*H*), 7.96 (d, *J* = 9.0 Hz, 1H, C(8)*H*), 7.81 (dd, *J* = 9.0, 2.2 Hz, 1H, C(7)*H*), 7.65 (d, *J* = 8.5 Hz, 1H, C(2)*H*), 7.19 (app. t, *J* = 7.8 Hz, 2H, C(14)*H*), 6.78 – 6.69 (m, 3H, C(13)*H*, C(15)*H*), 5.87 (ddd, $^2J_{HF}$ = 48.7 Hz, *J* = 7.3, 3.6 Hz, 1H, C(10)*H*), 4.25 (s, 1H, N*H*), 3.95 (ddd, $^3J_{HF}$ = 26.4 Hz, $^2J_{HH}$ = 14.1 Hz, *J* = 3.6 Hz, 1H, C(11)H_a), 3.71 (ddd, $^3J_{HF}$ = 20.9 Hz, $^2J_{HH}$ = 14.1 Hz, *J* = 7.3 Hz, 1H, C(11)H_b).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.6 (d, ^2J = 24.8 Hz, *C*(1)), 147.5 (*C*(12)), 146.1 (d, ^4J = 2.4 Hz, (*C*(9)), 136.2 (*C*(3)), 133.5 (*C*(7)), 131.1 (*C*(5)), 129.9 (*C*(8)), 129.5 (*C*(14)), 128.9 (*C*(4)),

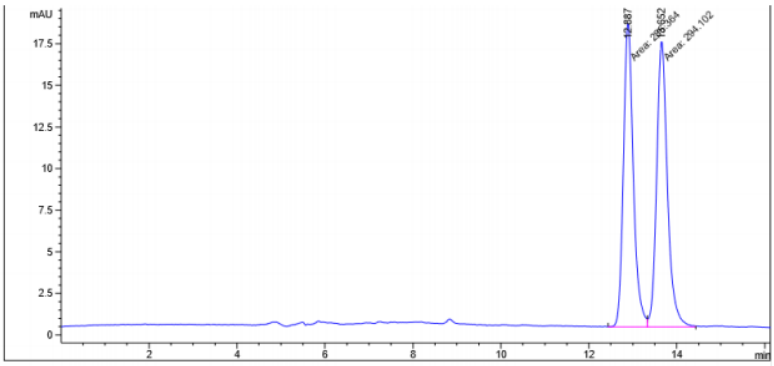
120.8 (*C*(6)), 118.8 (d, ^{3}J = 6.6 Hz, *C*(2)), 118.3 (*C*(15)), 113.4 (*C*(13)), 93.2 (d, ^{1}J = 174.8 Hz, *C*(10)), 48.5 (d, ^{2}J = 22.2 Hz, *C*(11)).

^{19}F NMR (376 MHz, $CDCl_3$): δ −191.78.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{17}H_{15}{}^{79}BrFN_2$) requires *m/z* 345.0397, found *m/z* 345.0393.

The enantiomeric purity of the product was determined by HPLC analysis: 93:7 e.r. (Chiralpak IA, hexane/*i*-PrOH = 50/50, flow rate 0.5 mL/min, λ = 250 nm), t_r (major) = 12.7 min, t_r (minor) = 13.4 min;

$[\alpha]_D^{20}$ = +11.8 (*c* 1.15, $CHCl_3$).

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Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
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   2  13.652 FM    0.2859  294.10202   17.14728  50.6665
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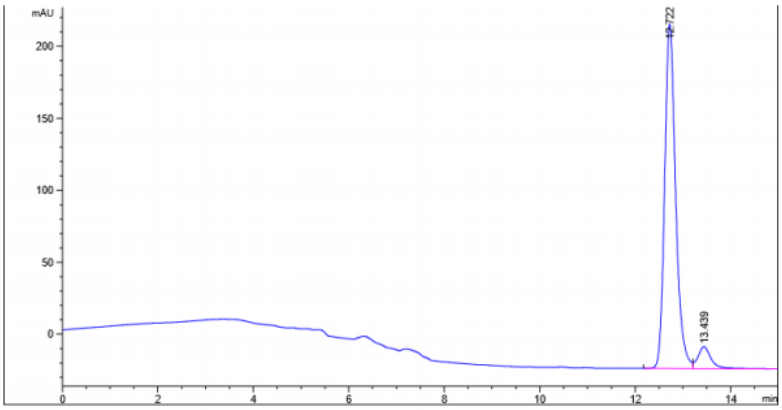


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                        Area Percent Report
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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
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   1  12.722 BV    0.2429 3816.47534  239.22580  92.9299
   2  13.439 VBA   0.2828  290.35831   15.18612   7.0701
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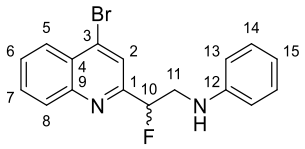
(±)-*N*-(2-(4-Bromoquinolin-2-yl)-2-fluoroethyl)aniline 2.47



Chemical Formula: $C_{17}H_{14}BrFN_2$
Exact Mass: 344.0324
Molecular Weight: 345.2154

Prepared according to General Procedure C using 4-bromo-2-(1-fluorovinyl)quinoline (25.2 mg, 0.10 mmol, 1.0 equiv), aniline (27 µL, 0.30 mmol, 3.0 equiv), TFA (1.5 µL, 0.02 mmol, 20 mol%), and THF (200 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure C (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (29.3 mg, 85%).

υ_{max} (film): 1603, 1508, 1491, 1319, 1261 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20 (dd, *J* = 8.4, 1.4 Hz, 1H, C(5)*H*), 8.09 (d, *J* = 8.4 Hz, 1H, C(8)*H*), 7.94 (d, *J* = 1.5 Hz, 1H, C(2)*H*), 7.80 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H, C(6)*H*), 7.66 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H, C(7)*H*), 7.19 (t, *J* = 7.7 Hz, 2H, C(14)*H*), 6.78 – 6.71 (m, 3H, C(13)*H*,

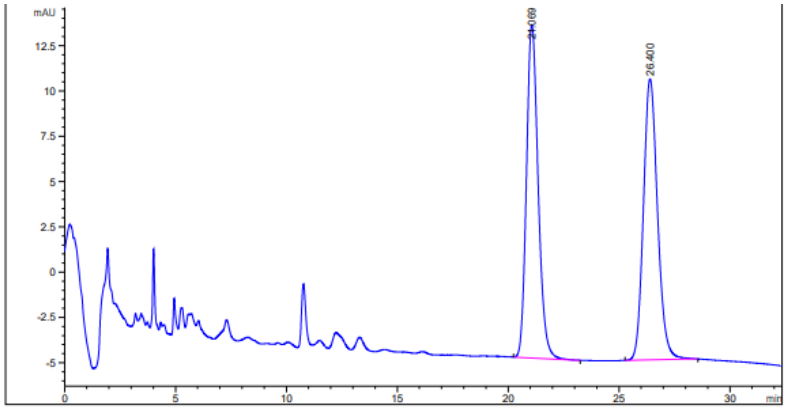
C(15)*H*), 5.86 (ddd, $^{2}J_{HF}$ = 48.6 Hz, *J* = 7.3, 3.6 Hz, 1H, C(10)*H*), 3.95 (ddd, $^{3}J_{HF}$ = 26.4 Hz, $^{2}J_{HH}$ = 14.2 Hz, *J* = 3.6 Hz, 1H, C(11)H_a), 3.78 – 3.66 (m, 1H, C(11)H_b).

^{13}C NMR (126 MHz, $CDCl_3$): δ 158.0 (d, ^{2}J = 25.0 Hz), 148.1 (*C*(9)), 147.5 (*C*(12)), 135.4 (*C*(3)), 131.0 (*C*(7)), 129.8 (*C*(8)), 129.5 (*C*(14)), 128.2 (*C*(5)), 127.4 (*C*(4)), 127.0 (*C*(6)), 122.0 (d, ^{3}J = 7.5 Hz, *C*(2)), 118.3 (*C*(15)), 113.5 (*C*(13)), 92.7 (d, ^{1}J = 175.8 Hz, *C*(10)), 48.5 (d, ^{2}J = 21.9 Hz, *C*(11)).

^{19}F NMR (470 MHz, $CDCl_3$): δ −192.02.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{17}H_{15}{}^{79}BrFN_2$) requires *m/z* 345.0397, found *m/z* 345.0394.

(Chiralcel OJ-H, hexane/*i*-PrOH = 50/50, flow rate 1.0 mL/min, λ = 250 nm), t_r (1) = 26.4 min, t_r (2) = 21.1 min;

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                    Area Percent Report
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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
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   1  21.069 BB    0.5653  673.27606   18.39787  49.5390
   2  26.400 BB    0.6788  685.80560   15.51562  50.4610
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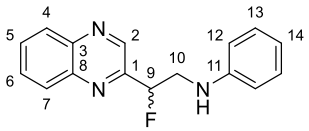
(±)-*N*-(2-Fluoro-2-(quinoxalin-2-yl)ethyl)aniline 2.48



Chemical Formula: $C_{16}H_{14}FN_3$
Exact Mass: 267.1172
Molecular Weight: 267.3074

Prepared according to General Procedure C using 2-(1-fluorovinyl)quinoxaline (17.4 mg, 0.10 mmol, 1.0 equiv), aniline (27 µL, 0.30 mmol, 3.0 equiv), TFA (1.5 µL, 0.02 mmol, 20 mol%), and THF (200 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure C (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (22.8 mg, 85%).

υ_{max} (film): 1603, 1495, 1323, 1259 cm^{-1}.

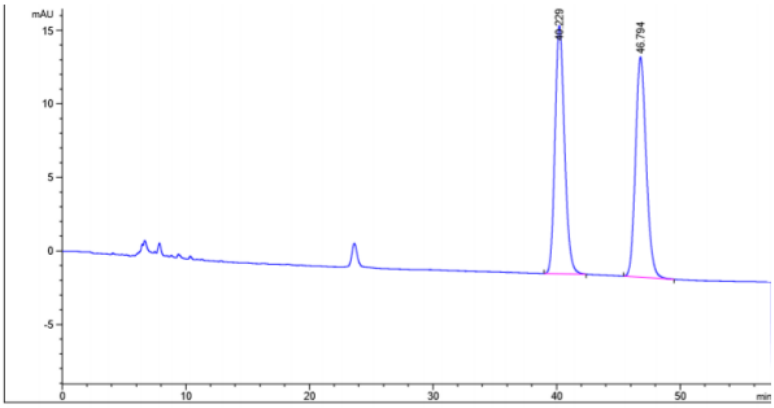
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.07 (s, 1H, C(2)*H*), 8.17 – 8.08 (m, 2H, C(4)*H*, C(7)*H*), 7.81 (qd, *J* = 7.0, 3.4 Hz, 2H, C(5)*H*, C(6)*H*), 7.19 (t, *J* = 7.9 Hz, 2H, C(13)*H*), 6.78 – 6.70 (m, 3H, C(12)*H*, C(14)*H*), 5.97 (ddd, $^2J_{HF}$ = 48.1 Hz, *J* = 7.1, 3.5 Hz, 1H, C(9)*H*), 4.00 (ddd, $^3J_{HF}$ = 26.1 Hz, $^2J_{HH}$ = 14.4 Hz, *J* = 3.6 Hz, 1H, C(10)H_a), 3.79 (ddd, $^3J_{HF}$ = 21.3 Hz, $^2J_{HH}$ = 14.4 Hz, *J* = 7.1 Hz, 1H, C(10)H_b).

^{13}C NMR (101 MHz, $CDCl_3$): δ 152.4 (d, ^2J = 24.2 Hz, *C*(1)), 147.3 (*C*(11)), 142.8 (d, ^4J = 7.3 Hz, *C*(3)), 142.5 (*C*(8)), 141.5 (*C*(2)), 130.7 (*C*(4)), 130.4 (*C*(6)), 129.6 (*C*(5)), 129.5 (*C*(13)), 129.4 (*C*(7)), 118.5 (*C*(14)), 113.5 (*C*(12)), 92.3 (d, ^1J = 174.1 Hz, *C*(9)), 48.2 (d, ^2J = 22.0 Hz, *C*(10)).

^{19}F NMR (376 MHz, $CDCl_3$): δ −193.73.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{16}H_{15}FN_3$) requires *m/z* 268.1245, found *m/z* 268.1243.

(Chiralcel OJ-H, hexane/*i*-PrOH = 50/50, flow rate 0.5 mL/min, λ = 250 nm), t_r (1) = 40.2 min, t_r (2) = 46.8 min;

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Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
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   1  40.229 BB    0.8238  902.49066   16.86399  49.9839
   2  46.794 BB    0.9099  903.07245   14.98448  50.0161
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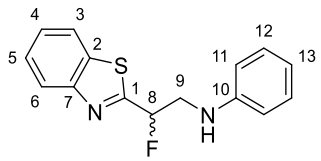
(±)-*N*-(2-(Benzo[*d*]thiazol-2-yl)-2-fluoroethyl)aniline 2.49



Chemical Formula: $C_{15}H_{13}FN_2S$
Exact Mass: 272.0783
Molecular Weight: 272.3414

Prepared according to General Procedure C using 2-(1-fluorovinyl)benzo[*d*]thiazole (17.9 mg, 0.10 mmol, 1.0 equiv), aniline (27 µL, 0.30 mmol, 3.0 equiv), TFA (1.5 µL, 0.02 mmol, 20 mol%), and THF (200 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure C (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (6.6 mg, 24%).

υ_{max} (film): 1603, 1508, 1317, 1260 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.2 Hz, 1H, C(6)*H*), 7.94 (d, *J* = 7.9 Hz, 1H, C(3)*H*), 7.53 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H, C(4)*H*), 7.44 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H, C(5)*H*), 7.22 (dd, *J* = 8.6, 7.3 Hz, 2H, C(12)*H*), 6.83 – 6.70 (m, 3H, C(11)*H*, C(13)*H*), 6.02 (ddd, $^2J_{HF}$ =

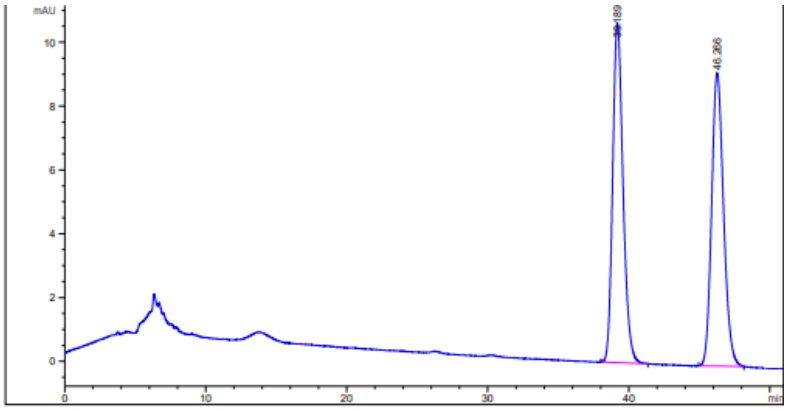
48.0 Hz, *J* = 7.2, 3.7 Hz, 1H, C(8)*H*), 4.02 (ddd, $^{3}J_{HF}$ = 26.1 Hz, $^{2}J_{HH}$ = 14.5 Hz, *J* = 3.7 Hz, 1H, C(9)H_a), 3.80 (ddd, $^{3}J_{HF}$ = 19.7 Hz, $^{2}J_{HH}$ = 14.5 Hz, *J* = 7.2 Hz, 1H, C(9)H_b).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.0 (d, ^{2}J = 28.0 Hz, *C*(1)), 153.1 (*C*(7)), 147.0 (*C*(10)), 134.9 (*C*(2)), 129.6 (*C*(12)), 126.6 (*C*(5)), 125.7 (*C*(3)), 123.6 (*C*(4)), 122.0 (*C*(6)), 118.7 (*C*(13)), 113.6 (*C*(11)), 90.7 (d, ^{1}J = 173.9 Hz, *C*(8)), 48.4 (d, ^{2}J = 22.0 Hz, *C*(9)).

^{19}F NMR (377 MHz, $CDCl_3$): δ −181.92.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{15}H_{14}FN_2S$) requires *m/z* 273.0856, found *m/z* 273.0853.

(Chiralcel OJ-H, hexane/*i*-PrOH = 50/50, flow rate 0.5 mL/min, λ = 250 nm), t_r (1) = 39.2 min, t_r (2) 46.3 = min;

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                        Area Percent Report
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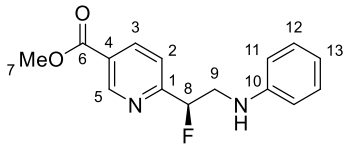
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  39.189 BB    0.7733  542.54297   10.65282  50.1830
   2  46.266 BB    0.8892  538.58551    9.18738  49.8170
```

Methyl (*R*)-6-(1-fluoro-2-(phenylamino)ethyl)nicotinate 2.50



Chemical Formula: $C_{15}H_{15}FN_2O_2$
Exact Mass: 274.1118
Molecular Weight: 274.2954

Racemic:

Prepared according to General Procedure C using 6-(1-fluorovinyl)nicotinate (18.1 mg, 0.10 mmol, 1.0 equiv), aniline (27 µL, 0.30 mmol, 3.0 equiv), TFA (1.5 µL, 0.02 mmol, 20 mol%), and THF (200 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure C (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale brown oil (13.2 mg, 48%).

Enantioenriched:

Prepared according to General Procedure E using methyl 6-(1-fluorovinyl)nicotinate (18.1 mg, 0.10 mmol, 1.0 equiv), aniline (27 µL, 0.30 mmol, 3.0 equiv), (*S*)-TRIP catalyst (15.1 mg, 0.02 mmol, 20 mol%), and CPME (200 µL, 0.5 M) at rt for 3 d. The reaction mixture was subjected to the purification outlined in General Procedure E (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale brown oil (6.8 mg, 25%).

υ_{max} (film): 1728, 1601, 1506, 1294, 1265, 1119 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.20 – 9.19 (m, 1H, C(5)*H*), 8.35 (dd, *J* = 8.2, 2.1 Hz, 1H, C(3)*H*), 7.60 (d, *J* = 8.2 Hz, 1H, C(2)*H*), 7.25 – 7.13 (m, 2H, C(12)*H*), 6.80 – 6.65 (m, 3H, C(11)*H*, C(13)*H*), 5.78 (ddd, $^2J_{HF}$ = 48.4 Hz, *J* = 7.2, 3.3 Hz, 1H, C(8)*H*), 4.03 – 3.82 (m, 4H, C(7)*H*, C(9)H_a), 3.61 (ddd, $^3J_{HF}$ = 21.3 Hz, $^2J_{HH}$ = 14.3 Hz, *J* = 7.2 Hz, 1H, C(9)H_b).

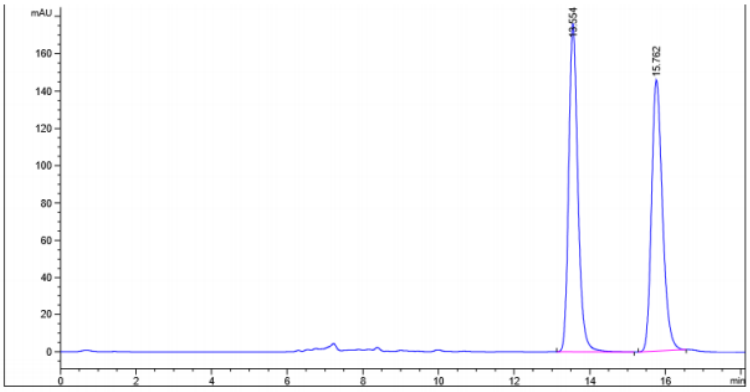
^{13}C NMR (101 MHz, $CDCl_3$): δ 165.6 (*C*(6)), 162.0 (d, ^2J = 24.7 Hz, *C*(1)), 150.4 (d, ^4J = 2.7 Hz, *C*(5)), 147.4 (*C*(10)), 138.2 (*C*(3)), 129.5 (*C*(12)), 125.6 (*C*(4)), 119.8 (d, ^3J = 7.4 Hz, *C*(2)), 118.3 (*C*(13)), 113.4 (*C*(11)), 92.7 (d, ^1J = 175.3 Hz, *C*(8)), 52.6 (*C*(7)), 48.4 (d, ^2J = 21.6 Hz, (*C*(9)).

^{19}F NMR (376 MHz, $CDCl_3$): δ −193.31.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{15}H_{16}FN_2O_2$) requires *m/z* 275.1190, found *m/z* 275.1190.

The enantiomeric purity of the product was determined by HPLC analysis: 88:12 e.r. (Chiralpak IA, hexane/*i*-PrOH = 50/50, flow rate 0.5 mL/min, λ = 250 nm), t_r (major) = 13.0 min, t_r (minor) = 14.8 min;

$[\alpha]_D^{20}$ = +2.95 (*c* 0.88, $CHCl_3$).

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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  13.554 BB    0.2588 2987.50024  176.31598  50.5592
   2  15.762 BB    0.3083 2921.41113  145.62823  49.4408
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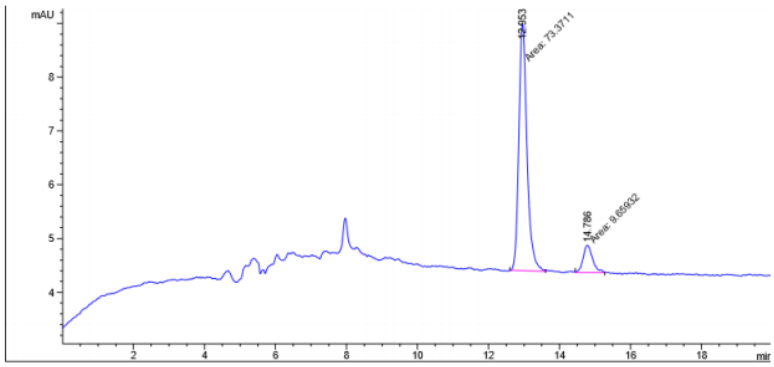


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                        Area Percent Report
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Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  12.953 MM    0.2664   73.37106    4.59014  88.3665
   2  14.786 MM    0.3154    9.65932 5.10492e-1  11.6335
```
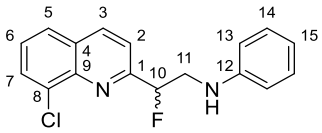

***(R)*-*N*-(2-(8-Chloroquinolin-2-yl)-2-fluoroethyl)aniline 2.51**



Chemical Formula: $C_{17}H_{14}ClFN_2$
Exact Mass: 300.0830
Molecular Weight: 300.7614

Racemic:

Prepared according to General Procedure C using 2-(1-fluorovinyl)-8-chloroquinoline (20.8 mg, 0.10 mmol, 1.0 equiv), aniline (27 µL, 0.30 mmol, 3.0 equiv), TFA (1.5 µL, 0.02 mmol, 20 mol%), and THF (200 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure C (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale brown oil (12.9 mg, 43%).

Enantioenriched:

Prepared according to General Procedure E using 2-(1-fluorovinyl)-8-chloroquinoline (10.4 mg, 0.05 mmol, 1.0 equiv), aniline (14 µL, 0.15 mmol, 3.0 equiv), (*S*)-TRIP catalyst (7.5 mg, 0.01 mmol, 20 mol%), and CPME (100 µL, 0.5 M) at 40 °C. The reaction mixture was subjected to the purification outlined in General Procedure E (silica gel,

EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale brown oil (9.5 mg, 63%).

υ_{max} (film): 1601, 1501, 1311, 1261 cm^{-1}.

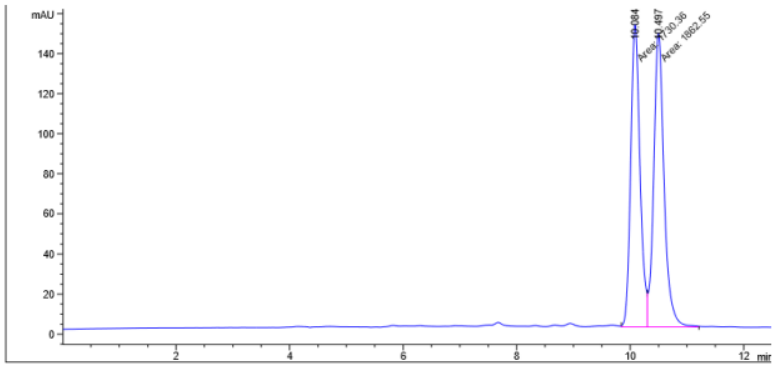
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, *J* = 8.5 Hz, 1H, C(3)*H*), 7.87 (dd, *J* = 7.5, 1.3 Hz, 1H, C(5)*H*), 7.75 (ddd, *J* = 16.5, 8.4, 1.6 Hz, 2H, C(2)*H*, C(7)*H*), 7.49 (dd, *J* = 8.2, 7.5 Hz, 1H, C(6)*H*), 7.24 – 7.15 (m, 2H, C(14)*H*), 6.81 – 6.69 (m, 3H, C(13)*H*, C(15)*H*), 5.95 (ddd, $^{2}J_{HF}$ = 48.1 Hz, *J* = 6.2, 5.0 Hz, 1H, C(10)*H*), 4.71 (s, 1H, N*H*), 4.03 – 3.77 (m, 2H, C(11)*H*).

^{13}C NMR (101 MHz, $CDCl_3$): δ 159.4 (d, ^{2}J = 25.7 Hz, *C*(1)), 147.8 (*C*(12)), 143.6 (*C*(9)), 137.7 (*C*(3)), 133.7 (*C*(8)), 130.1 (*C*(7)), 129.5 (*C*(14)), 129.0 (*C*(4)), 126.9 (*C*(5)), 126.9 (*C*(6)), 118.7 (d, ^{3}J = 6.9 Hz, (*C*(2)), 118.1 (*C*(15)), 113.5 (*C*(13)), 92.7 (d, ^{1}J = 175.2 Hz, *C*(10)), 48.4 (d, ^{2}J = 23.1 Hz, *C*(11)).

^{19}F NMR (376 MHz, $CDCl_3$): δ −191.99.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{17}H_{15}N_2{}^{35}ClF$) requires *m/z* 301.0902, found *m/z* 301.0898.

The enantiomeric purity of the product was determined by HPLC analysis: 51:49 e.r. (Chiralpak IA, hexane/*i*-PrOH = 50/50, flow rate 0.5 mL/min, λ = 250 nm), t_r (major) = 10.5 min, t_r (minor) = 10.1 min;

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Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
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   2  10.497 FM    0.2118 1862.54712  146.57484  51.8396
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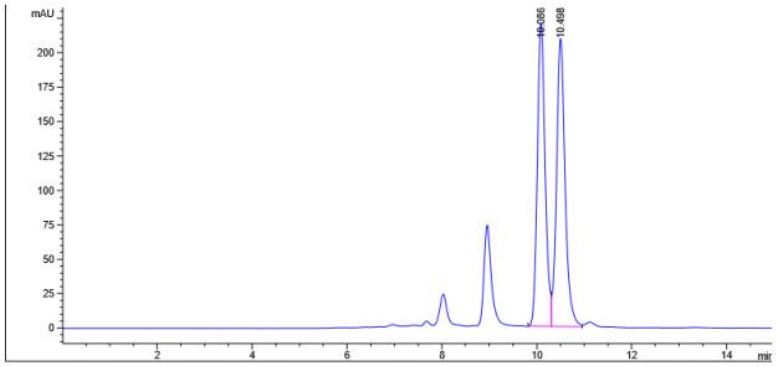


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Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.086 BV    0.1753 2519.43018  220.56381  49.0498
   2  10.498 VV    0.1898 2617.04395  209.41792  50.9502
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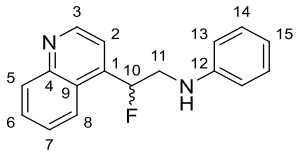
(±)-*N*-(2-Fluoro-2-(quinolin-4-yl)ethyl)aniline 2.52



Chemical Formula: $C_{17}H_{15}FN_2$
Exact Mass: 266.1219
Molecular Weight: 266.3194

Racemic:

Prepared according to General Procedure C using 4-(1-fluorovinyl)quinoline (17.3 mg, 0.10 mmol, 1.0 equiv), aniline (27 µL, 0.30 mmol, 3.0 equiv), TFA (1.5 µL, 0.02 mmol, 20 mol%), and THF (200 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure C (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (10.9 mg, 41%).

Enantioenriched:

Prepared according to General Procedure E using 4-(1-fluorovinyl)quinoline (17.3 mg, 0.10 mmol, 1.0 equiv), aniline (27 µL, 0.30 mmol, 3.0 equiv), (*S*)-TRIP catalyst (15.1 mg, 0.02 mmol, 20 mol%), and CPME (200 µL, 0.5 M) at rt for 3 d. The reaction mixture was subjected to the purification outlined in General Procedure E (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (17.9 mg, 68%).

υ_{max} (film): 1601, 1509, 1323, 1250 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.96 (d, *J* = 4.4 Hz, 1H, C(3)*H*), 8.20 (dt, *J* = 8.4, 1.1 Hz, 1H, C(5)*H*), 7.92 (dt, *J* = 8.5, 0.9 Hz, 1H, C(8)*H*), 7.77 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H, C(6)*H*), 7.62 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H, C(7)*H*), 7.55 (dd, *J* = 4.5, 0.8 Hz, 1H, C(2)*H*), 7.31 – 7.12 (m, 2H, C(14)*H*), 6.79 (app. tt, *J* = 7.3, 1.1 Hz, 1H, C(15)*H*), 6.76 – 6.65 (m, 2H, C(13)*H*), 6.50 – 6.25 (m, 1H, C(10)*H*), 4.17 (s, 1H, N*H*), 3.81 (ddd, $^3J_{HF}$ = 29.9 Hz, $^2J_{HH}$ = 14.4 Hz, *J* = 3.0 Hz, 1H, C(11)H_a), 3.61 (ddd, $^3J_{HF}$ = 18.3 Hz, $^2J_{HH}$ = 14.4 Hz, *J* = 8.1 Hz, 1H, C(11)H_b).

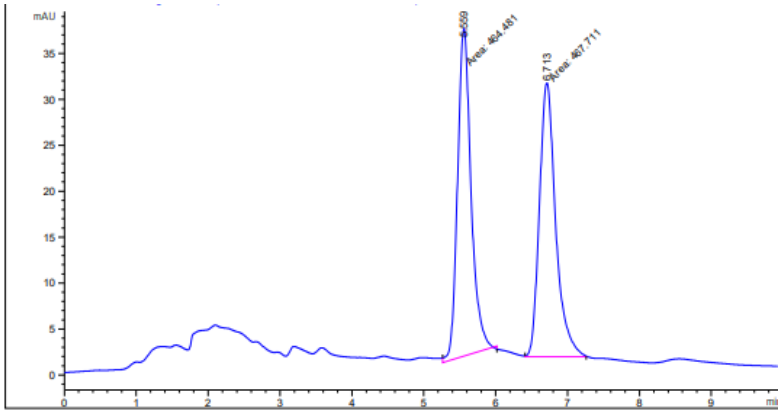
^{13}C NMR (101 MHz, $CDCl_3$): δ 150.2 (*C*(3)), 148.2 (*C*(4)), 147.1 (*C*(12)), 143.0 (d, ^2J = 19.2 Hz *C*(1)), 130.7 (*C*(5)), 129.6 (*C*(6)), 129.5 (*C*(14)), 127.3 (*C*(7)), 124.8 (d, ^3J = 4.8 Hz, *C*(9)),

122.4 (*C*(8)), 118.6 (*C*(15)), 117.7 (d, ^{3}J = 10.4 Hz, *C*(2)), 113.5 (*C*(13)), 89.9 (d, ^{1}J = 175.4 Hz, *C*(10)), 49.5 (d, ^{2}J = 23.6 Hz, *C*(11)).

^{19}F NMR (377 MHz, $CDCl_3$): δ −190.24.

HRMS(ESI): exact mass calculated for $[M+H]^+$ ($C_{17}H_{16}FN_2$) requires *m/z* 267.1292, found *m/z* 267.1285.

The enantiomeric purity of the product was determined by HPLC analysis: 50:50 e.r. (Chiralpak IA, hexane/*i*-PrOH = 50/50, flow rate 0.5 mL/min, λ = 250 nm), t_r (1) = 5.7 min, t_r (2) = 6.9 min;

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                        Area Percent Report
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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
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   2   6.713 MM    0.2617  467.71078   29.78292  50.1732
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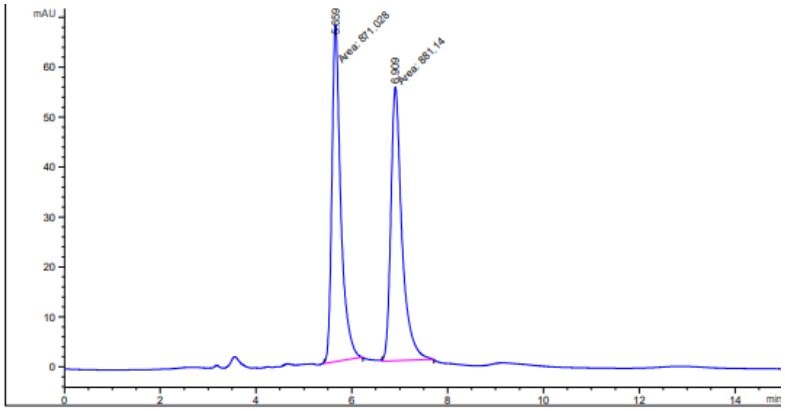


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================================================================
                    Area Percent Report
================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   5.659 MM    0.2156  871.02771   67.33373  49.7114
   2   6.909 MM    0.2678  881.13983   54.83912  50.2886
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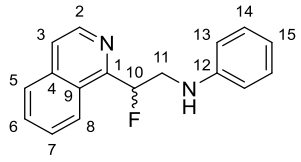
(±)-*N*-(2-Fluoro-2-(isoquinolin-1-yl)ethyl)aniline 2.53



Chemical Formula: $C_{17}H_{15}FN_2$
Exact Mass: 266.1219
Molecular Weight: 266.3194

Prepared according to General Procedure C using 1-(1-fluorovinyl)isoquinoline (17.3 mg, 0.10 mmol, 1.0 equiv), aniline (27 µL, 0.30 mmol, 3.0 equiv), TFA (1.5 µL, 0.02 mmol, 20 mol%), and THF (200 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure C (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (18.2 mg, 68%).

υ_{max} (film): 1603, 1504, 1321, 1261 cm^{-1}.

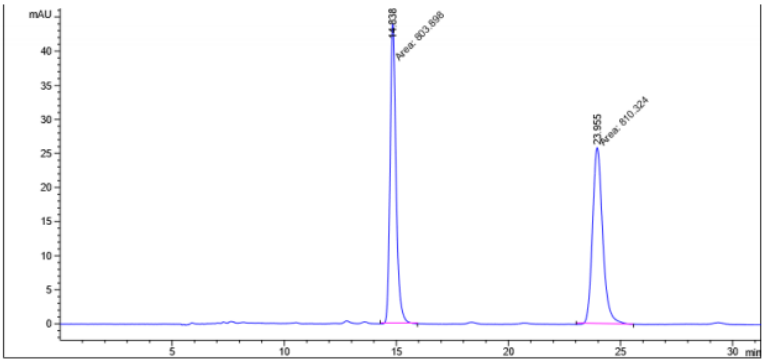
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (d, *J* = 5.7 Hz, 1H, C(2)*H*), 8.31 (d, *J* = 8.0 Hz, 1H, C(8)*H*), 7.88 (d, *J* = 8.2 Hz, 1H, C(5)*H*), 7.77 – 7.60 (m, 3H, C(3)*H*, C(6)*H*, C(7)*H*), 7.25 – 7.16 (m, 2H, C(14)*H*), 6.79 – 6.69 (m, 3H, C(13)*H*, C(15)*H*), 6.37 (ddd, $^2J_{HF}$ = 48.4, *J* = 6.9, 5.2 Hz, 1H, C(10)*H*), 4.33 (s, 1H, N*H*), 4.15 – 3.93 (m, 2H, C(11)*H*).

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.2 (d, ^2J = 18.6 Hz), 147.6 (*C*(12)), 141.7 (*C*(6)), 136.8 (*C*(5)), 130.4 (*C*(7)), 129.5 (*C*(14)), 128.0 (*C*(2)), 127.7 (*C*(8)), 126.9 (*C*(4)), 124.9 (d, ^3J = 4.8 Hz, *C*(9)), 122.0 (*C*(2)), 118.1 (*C*(15)), 113.4 (*C*(13)), 90.8 (d, ^1J = 173.5 Hz, *C*(10)), 46.9 (d, ^2J = 24.1 Hz, *C*(11)).

^{19}F NMR (376 MHz, $CDCl_3$): δ −180.92.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{17}H_{16}FN_2$) requires *m/z* 267.1292, found *m/z* 267.1290.

(Chiralpak IA, hexane/*i*-PrOH = 50/50, flow rate 0.5 mL/min, λ = 250 nm), t_r (1) = 14.8 min, t_r (2) = 23.9 min;

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Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  14.838 MM    0.3049  803.89758   43.94274  49.8009
   2  23.955 MM    0.5242  810.32446   25.76460  50.1991
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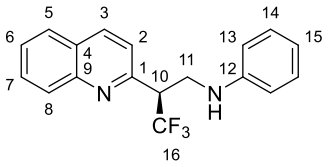
(*R*)-*N*-(3,3,3-Trifluoro-2-(quinolin-2-yl)propyl)aniline 2.54



Chemical Formula: $C_{18}H_{15}F_3N_2$
Exact Mass: 316.1187
Molecular Weight: 316.3272

Racemic:

Prepared according to General Procedure C using 2-(3,3,3-trifluoroprop-1-en-2-yl)quinoline (22.4 mg, 0.1 mmol, 1.0 equiv), aniline (27 µL, 0.30 mmol, 3.0 equiv), TFA (1.5 µL, 0.02 mmol, 20 mol%), and THF (200 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure C (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (22.8 mg, 72%).

Enantioenriched:

Prepared according to General Procedure E using 2-(3,3,3-trifluoroprop-1-en-2-yl)quinoline (11.2 mg, 0.05 mmol, 1.0 equiv), aniline (14 µL, 0.15 mmol, 3.0 equiv), (*S*)-TRIP catalyst (37.6 mg, 0.05 mmol, 1.0 equiv), and CPME (200 µL, 0.25 M) at −50 °C for 3 d. The reaction mixture was subjected to the purification outlined in General Procedure E (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (11.5 mg, 73%).

υ_{max} (film): 1601, 1504, 1315, 1165, 1111 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 – 8.14 (m, 2H, C(3)*H*, C(8)*H*), 7.85 (dd, *J* = 8.2, 1.4 Hz, 1H, C(5)*H*), 7.77 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H, C(7)*H*), 7.59 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H, C(6)*H*), 7.40 (d, *J* = 8.4 Hz, 1H, C(2)*H*), 7.20 – 7.14 (m, 2H, C(14)*H*), 6.73 (tt, *J* = 7.3, 1.1 Hz, 1H, C(15)*H*), 6.59 (dt, *J* = 7.7, 1.0 Hz, 2H, C(13)*H*), 4.20 – 3.82 (m, 4H, C(10)*H*, C(11)*H*, N*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 153.4 (*C*(1)), 148.0 (*C*(9)), 147.0 (*C*(12)), 137.1 (*C*(3)), 130.1 (*C*(7)), 129.7 (*C*(8)), 129.5 (*C*(14)), 127.7 (*C*(4)), 127.7 (*C*(5)), 127.2 (*C*(6)), 126.1 (q, ^1J =

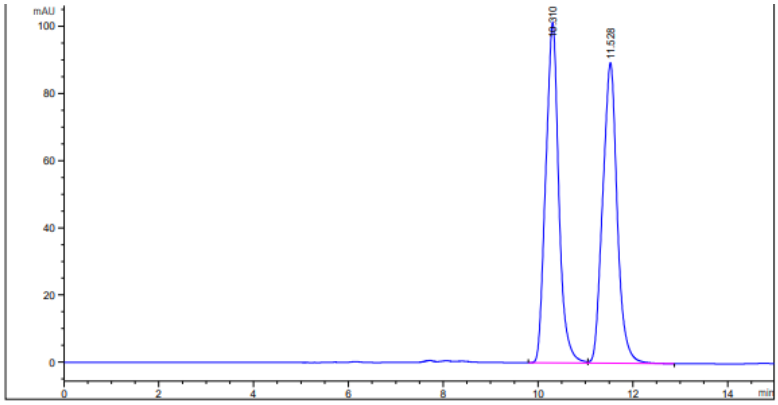
280.5 Hz, *C*(16)), 122.1 (*C*(2)), 118.2 (*C*(15)), 113.2 (*C*(13)), 51.1 (q, ^{2}J = 25.0 Hz, *C*(10)), 41.9 (*C*(11)).

^{19}F NMR (470 MHz, $CDCl_3$): δ −67.02.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{18}H_{16}F_3N_2$) requires *m/z* 317.1260, found *m/z* 317.1251.

The enantiomeric purity of the product was determined by HPLC analysis: 90:10 e.r. (Chiralpak IA, hexane/*i*-PrOH = 50/50, flow rate 1.0 mL/min, λ = 250 nm), t_r (major) = 9.1 min, t_r (minor) = 11.6 min;

$[\alpha]_D^{20}$ = −80.4 (*c* 1.00, $CHCl_3$).

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                    Area Percent Report
================================================================

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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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Peak RetTime Type  Width     Area      Height     Area
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   2  11.528 VB    0.3160 1898.84473   89.48219  49.4468
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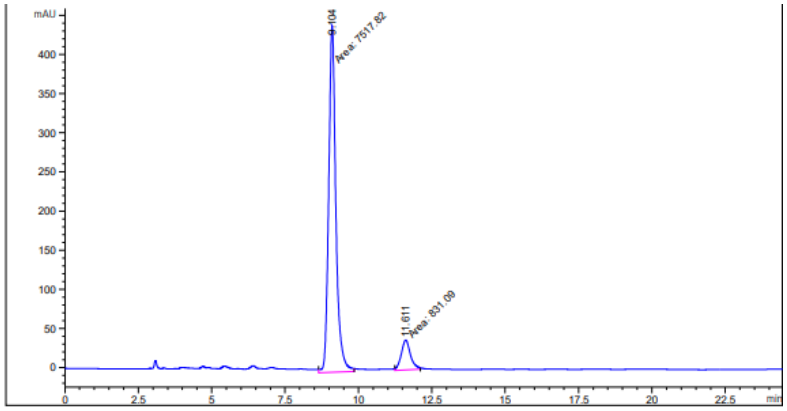


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=====================================================================
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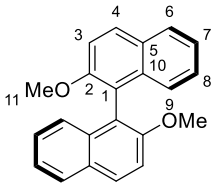
(*S*)-2,2'-Dimethoxy-1,1'-binaphthalene 2.61



Chemical Formula: $C_{22}H_{18}O_2$
Exact Mass: 314.1307
Molecular Weight: 314.3840

Prepared according to literature procedure.[63]

An oven dried 250 mL round-bottom flask equipped with a reflux condenser was charged with (*S*)-BINOL (5.73 g, 20.0 mmol, 1.0 equiv) and potassium carbonate (11.1 g, 80.0 mmol, 4.0 equiv). The flask was then capped and purged with N_2 before adding acetone (40 mL) and methyl iodide (4.98 mL, 80.0 mmol, 4.0 equiv). The resulting mixture was allowed to stir at reflux for 24 h. The mixture was then concentrated *in vacuo* and the resulting slurry was dissolved in H_2O (80 mL) and stirred for 2 h. The resulting precipitate was collected, washed with water, and dried *in vacuo* to give the desired product as a slight yellow solid (5.03 g, 80%).

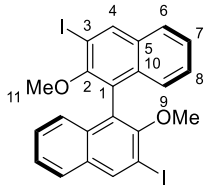
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, *J* = 9.0 Hz, 2H, C(4)*H*), 7.87 (d, *J* = 8.2 Hz, 2H, C(6)*H*), 7.47 (d, *J* = 9.0 Hz, 2H, C(3)*H*), 7.32 (ddd, *J* = 8.1, 6.7, 1.1 Hz, 2H, C(8)*H*), 7.21 (ddd, *J* = 8.1, 6.7, 1.2 Hz, 2H, C(7)*H*), 7.11 (d, *J* = 8.5 Hz, 2H, C(9)*H*), 3.77 (s, 6H, C(11)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 155.1, 134.1, 129.5, 129.3, 128.1, 126.4, 125.4, 123.6, 119.7, 114.3, 57.0.

$[\alpha]^{20}_D$: −50° (*c* 1.00, $CHCl_3$).

Spectroscopic data in agreement with literature values.[63]

(*S*)-3,3'-Diiodo-2,2'-dimethoxy-1,1'-binaphthalene 2.62



Chemical Formula: $C_{22}H_{16}I_2O_2$
Exact Mass: 565.9240
Molecular Weight: 566.1769

Prepared according to literature procedure.[64]

An oven dried 500 mL round-bottom flask was capped and purged with N_2. The flask was then charged with tetramethylethylenediamine (1.65 mL, 11.0 mmol, 2.2 equiv) and dry Et_2O (200 mL). To the resulting solution *n*-butyllithium (2.4 M in hexanes, 10.4 mL, 25.0 mmol, 3.5 equiv) was added dropwise at rt, the mixture was allowed to stir for 1 h. (*S*)-2,2'-Dimethoxy-1,1'-binaphthalene (1.57 g, 5.00 mmol, 1.0 equiv) was then added portion wise as a solid at rt and the resulting solution was allowed to stir for 3.5 h. The reaction was then cooled to −78 °C and a solution of I_2 (6.35 g, 25.0 mmol, 5.0 equiv) in dry Et_2O (50 mL) was added dropwise. The reaction was then warmed to rt and stirred for an additional 20 h. The reaction was then quenched with sat. Na_2SO_3 solution (200 mL) and allowed to stir for a further 1 h. The mixture was extracted with Et_2O (200 mL × 3). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the crude material through flash chromatography (silica gel, EtOAc:petroleum ether, 5:95) gave the desired product as a pale yellow powder (2.57 g, 91%).

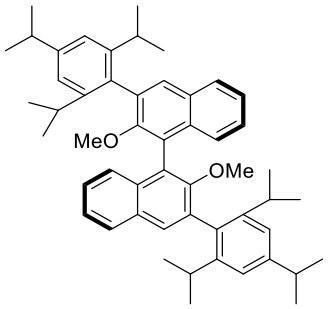
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.53 (s, 2H, C(4)*H*), 7.79 (d, *J* = 8.2 Hz, 2H, C(6)*H*), 7.41 (ddd, *J* = 8.1, 6.8, 1.1 Hz, 2H, C(8)*H*), 7.27 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 2H, C(7)*H*), 7.07 (d, *J* = 8.5 Hz, 2H, C(9)*H*), 3.41 (s, 6H, C(11)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 154.6, 140.0, 134.0, 132.3, 127.2, 127.1, 125.9, 125.8, 125.5, 92.5, 61.3.

$[\alpha]^{20}_D$: −26° (*c* 1.00, $CHCl_3$).

Spectroscopic data in agreement with literature values.[63]

(*S*)-2,2'-dimethoxy-3,3'-bis(2,4,6-tri*iso*propylphenyl)-1,1'-binaphthalene 2.64



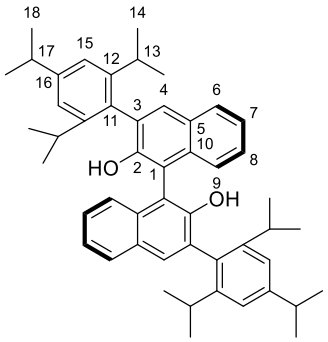
Chemical Formula: $C_{52}H_{62}O_2$
Exact Mass: 718.4750
Molecular Weight: 719.0660

Prepared according to literature procedure.[63]

An oven-dried 100 mL two-necked round-bottom flask equipped with a reflux condenser was charged with magnesium filings (6.38 g, 26.3 mmol, 1.75 equiv). The flask was capped and purged with N_2 and 20% of a solution of 1-bromo-2,4,6-tri*iso*propyl benzene (3.78 mL, 15.0 mmol, 1.0 equiv) in dry THF (30 mL) and 1,2-dibromoethane (0.05 mL) was then added using different syringes and added in a manner of maintaining the exothermic Grignard-reaction active. The reaction was heated to reflux and the remaining 1-bromo-2,4,6-triisopropyl benzene solution was added over 1 h. The reaction was then allowed to proceed at reflux for 16 h. The concentration of the formed Grignard solution was determined to be (0.4 M) by titration with salicylaldehyde phenylhydrazone. The resulting solution was used unmodified in the next step.

An oven-dried 100 mL two-necked round-bottom flask equipped with a reflux condenser was charged with (*S*)-3,3'-diiodo-2,2'-dimethoxy-1,1'-binaphthalene (1.36 g, 2.40 mmol, 1.0 equiv) and $Ni(PPh_3)_2Cl_2$ (157 mg, 0.24 mmol, 10 mol%). The flask was capped and purged with N_2 and dry THF (24 mL) was added to the mixture. To the resulting suspension the Grignard solution (30.0 mL, 0.4 M, 5.0 equiv) was then added dropwise at rt and the resulting mixture was refluxed for 16 h. The resulting solution was cooled to 0 °C and acidified with 1 M HCl (50 mL). The mixture was extracted with diethyl ether (40 mL × 3). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude product was subjected to the next step without further purification.

(*S*)-3,3'-Bis(2,4,6-tri*iso*propylphenyl)-1,1'-binaphthyl-2,2'-diol 2.65



Chemical Formula: $C_{50}H_{58}O_2$
Exact Mass: 690.4437
Molecular Weight: 691.0120

Prepared according to literature procedure.[63]

An oven-dried 100 mL round-bottom flask was charged with the crude (*S*)-2,2'-dimethoxy-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthalene (2.40 mmol, 1.0 equiv). The flask was capped and purged with N_2 and dry CH_2Cl_2 (24 mL) was added to the vessel. The solution was cooled to 0 °C and boron tribromide (12.0 mL, 1 M in hexanes, 12.0 mmol, 5.0 equiv) was added dropwise. The reaction was then stirred for 24 h at rt. The reaction was then quenched with water (24 mL) and then the mixture was extracted with Et_2O (20 mL × 3). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the crude material through flash

chromatography (silica gel, EtOAc:petroleum ether, 1:99) followed by trituration with hexanes gave the desired product as a white powder (1.16 g, 70%).

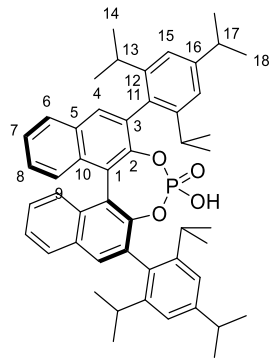
^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.92 – 7.88 (m, 2H, C(6)*H*), 7.77 (s, 2H, C(4)*H*), 7.39 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 2H, C(8)*H*), 7.33 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 2H, C(7)*H*), 7.24 (dd, *J* = 8.4, 1.3 Hz, 2H, C(9)*H*), 7.18 – 7.13 (m, 4H, C(15)*H*), 5.06 (s, 2H, O*H*), 2.97 (hept, *J* = 7.0 Hz, 2H, C(17)*H*), 2.83 (hept, *J* = 6.8 Hz, 2H, C(13)*H*a), 2.69 (hept, *J* = 6.9 Hz, 2H, C(13)*H*b), 1.31 (d, *J* = 6.9 Hz, 12H, C(18)*H*), 1.19 (d, J = 6.9 Hz, 6H, C(14)*H*a), 1.11 (t, *J* = 6.6 Hz, 12H, C(14)*H*b & C(14)*H*c), 1.04 (d, *J* = 6.9 Hz, 6H, C(14)*H*d).

^{13}C NMR (126 MHz, CD_2Cl_2): δ 151.4, 149.8, 148.4, 148.4, 133.9, 131.5, 131.3, 129.7, 129.7, 128.9, 127.3, 124.7, 124.4, 121.7, 113.3, 35.0, 31.5, 31.4, 24.6, 24.5, 24.4, 24.1, 24.0.

$[\alpha]^{20}_D$: −64° (*c* 1.00, in $CHCl_3$).

Spectroscopic data in agreement with literature values.[63]

(*S*)-3,3'-Bis(2,4,6-tri*iso*propylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate 2.60



Chemical Formula: $C_{50}H_{57}O_4P$
Exact Mass: 752.3994
Molecular Weight: 752.9758

Prepared according to literature procedure.[63]

An oven-dried 5 mL two-necked round-bottom flask equipped with a reflux condenser was charged with (*S*)-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diol (93.0 mg, 0.135 mmol, 1.0 equiv). The flask was capped and purged with N_2. Pyridine (0.75

mL) and $POCl_3$ (38.0 µL, 0.405 mmol, 3.0 equiv) were added to the vessel and the resulting mixture was refluxed for 14 h. The reaction was cooled to rt and H_2O (0.75 mL) was added to the reaction. The mixture was then refluxed for an additional 3 h. The reaction was then cooled to rt and CH_2Cl_2 (2 mL) was added. The resulting organic phase was washed with 1 M HCl (3 × 5 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the crude material by recrystallization in MeCN gave the desired product as a white powder (88.6 mg, 87%).

^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.91 (d, *J* = 8.2 Hz, 2H, C(6)*H*), 7.80 (s, 2H, C(4)*H*), 7.50 (ddd, *J* = 8.1, 6.6, 1.3 Hz, 2H, C(8)*H*), 7.35 – 7.23 (m, 4H, C(15)*H*), 6.98 (dd, *J* = 10.9, 1.8 Hz, 4H, C(7)*H*), 2.86 (p, *J* = 6.9 Hz, 2H, C(17)*H*), 2.56 (dsept, *J* = 22.9, 6.8 Hz, 4H, C(13)*H*), 1.23 (dd, *J* = 6.9, 1.1 Hz, 12H, C(18)*H*), 1.05 (d, *J* = 6.8 Hz, 6H, C(14)*H*a), 0.99 (d, *J* = 6.8 Hz, 6H, C(14)*H*b), 0.89 (d, *J* = 6.8 Hz, 6H, C(14)*H*c), 0.76 (d, *J* = 6.7 Hz, 6H, C(14)*H*d).

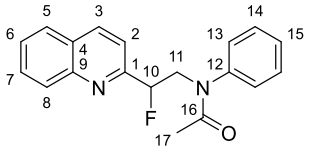
^{13}C NMR (126 MHz, CD_2Cl_2): δ 149.1, 148.5, 148.0, 146.3, 146.2, 133.2, 132.8, 132.5, 132.0, 131.5, 128.7, 127.6, 126.7, 126.2, 122.5, 121.6, 120.8, 34.8, 31.5, 31.3, 26.7, 25.2, 24.4, 24.2, 23.4, 23.1.

^{31}P NMR (202 MHz, CD_2Cl_2): δ 2.51 (s).

$[\alpha]^{20}_D$: +60° (*c* 1.00, $CHCl_3$).

Spectroscopic data in agreement with literature values.[63]

***N*-(2-Fluoro-2-(quinolin-2-yl)ethyl)-*N*-phenylacetamide 2.84**



Chemical Formula: $C_{19}H_{17}FN_2O$
Exact Mass: 308.1325
Molecular Weight: 308.3564

Prepared according to literature procedure.[66]

A 10 mL microwave vial was charged with *N*-(2-fluoro-2-(quinolin-2-yl)ethyl)aniline (151 mg, 0.57 mmol, 1.0 equiv). The vial was capped and purged with N_2. Dry CH_2Cl_2 (1 mL) and Ac_2O (54 µL, 0.57 mmol, 1.0 equiv) were added to the vessel and the reaction

mixture was allowed to stir at rt for 16 h. The reaction was then quenched with 2 M HCl (1 mL) and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the crude material *via* flash chromatography (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) gave the desired product as a pale yellow oil (51.0 mg, 29%).

υ_{max} (film): 1659, 1497, 1427, 1300, 1281 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.5 Hz, 1H, C(3)*H*), 8.03 (d, *J* = 8.5 Hz, 1H, C(8), 7.82 (d, *J* = 8.1 Hz, 1H, C(2)*H*), 7.71 (t, *J* = 7.7 Hz, 1H, C(6)*H*), 7.63 (d, *J* = 8.2 Hz, 1H, C(5)*H*), 7.55 (t, *J* = 7.5 Hz, 1H, C(7)*H*), 7.43 (t, *J* = 7.5 Hz, 2H, C(14)*H*), 7.38 – 7.31 (m, 3H, C(13)*H*, C(15)*H*), 5.99 – 5.84 (m, 1H, C(10)*H*), 4.42 – 4.26 (m, 2H, C(11)*H*), 1.90 (s, 3H, C(17)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 171.2, 157.4 (d, ^2J = 22.2 Hz), 147.5, 143.2, 137.2, 130.0, 129.9, 129.4, 128.6, 128.3, 127.9, 127.8, 127.0, 118.3 (d, ^3J = 5.6 Hz), 92.0 (d, ^1J = 176.9 Hz), 53.2 (d, ^2J = 22.7 Hz), 23.0.

^{19}F NMR (470 MHz, $CDCl_3$): δ −189.42.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{19}H_{18}FN_2O$) requires *m/z* 309.1398, found *m/z* 309.1388.

2.6.4 X-Ray Data

The datasets for the two compounds were collected using a Rigaku FR-X Ultrahigh Brilliance Microfocus RA generator/confocal optics with XtaLAB P200 diffractometer. The data for **(*R*)-2.43** was collected at 125K with Cu radiation (λ = 1.54187 Å), whereas the data for **(±)-2.84** were collected at 93 K with Mo radiation (λ = 0.71075 Å). Intensity data were collected using ω steps accumulating area detector images spanning at least a hemisphere of reciprocal space. All data were corrected for Lorentz polarization effects. A multiscan absorption correction was applied by using CrysAlisPro. The structure of **(*R*)-2.43** was solved using direct methods (SIR2011), whereas **(±)-2.84**were solved using dual space methods (SHELXT). The structures were refined by full-matrix least-squares against F^2 (SHELXL-2013). Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were refined using a riding model, with the

exception of H11 in **(*R*)-2.43**, which was located via the electron density map. All calculations for **(*R*)-2.43** were performed using the CrystalStructure interface and Olex2 for structure **(±)-2.84**. Selected crystallographic data are presented in Table 2.7. CCDC 1900849-1900851 contains the supplementary crystallographic data for this chapter. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

	(*R*)-2.43	**(±)-2.84**
Crystal Data		
Chemical formula	$C_{17}H_{15}FN_2$	$C_{19}H_{17}FN_2O$
M_r	266.32	308.35
Crystal system, space group	Orthorhombic, $P2_12_12_1$	Monoclinic, $C2/c$
Temperature (K)	125	93
a, b, c (Å)	5.44863 (10), 10.49560 (18), 23.5843 (4)	18.6107 (4), 7.75338 (14), 23.2547 (5)
α, β, γ (°)	90, 90, 90	90, 111.212 (2), 90
V (Å^3)	1348.71 (4)	3128.21 (12)
Z	4	8
Radiation type	Cu $K\alpha$	Mo $K\alpha$
μ (mm^{-1})	0.71	0.09
Crystal size (mm)	0.12 × 0.10 × 0.10	0.27 × 0.18 × 0.06
Data Collection		
T_{min}, T_{max}	0.889, 0.932	0.881, 0.995
No. of measured, independent and observed reflections	15722, 2741, 2729	22904, 3460, 3247
R_{int}	0.019	0.018
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.628	0.664
Refinement		

$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.027, 0.071, 1.09	0.040, 0.107, 1.02
No. of reflections	2741	3460
No. of parameters	186	209
No. of restraints	1	0
$\Delta\rangle_{max}$, $\Delta\rangle_{min}$ (e Å^{-3})	0.16, −0.18	0.50, −0.31
Absolute structure parameter	0.06 (4)	–

Table 2.7: Selected crystallographic data.

Computer programs: *CrysAlis PRO* 1.171.39.8d (Rigaku OD, 2015), *CrysAlis PRO* 1.171.40.29a (Rigaku OD, 2018), *SIR2011* (Burla, *et al.*, 2012), *SHELXT* Version 2014/4 (Sheldrick, 2014), *SHELXT* (Sheldrick, 2015), *SHELXL* Version 2014/7 (Sheldrick, 2008), *SHELXL* (Sheldrick, 2015), Olex2 (Dolomanov *et al.*, 2009), *CrystalStructure* 4.2 (Rigaku, 2015), *CrystalStructure* 4.3 (Rigaku, 2018).

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Chapter 3

Investigation of Chlorovinylheterocycles in the Aza-Michael Addition-Asymmetric Protonation-Ring Closure Reaction

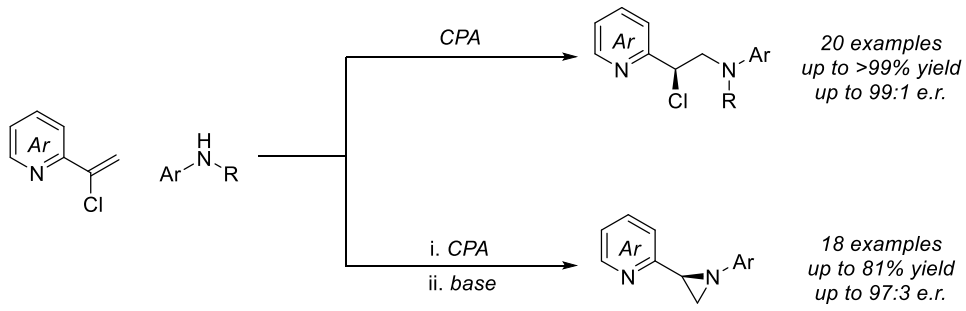
The chapter has the following contributions: Dr Liam McLean, Dr Jamie Fyfe, and I synthesized the required starting materials. I prepared the racemic HPLC references. I performed the optimization reactions. Dr Liam McLean, Dr Jamie Fyfe, and I performed substrate screening reactions. I prepared the XRD sample and Prof. Alexandra Slawin collected the XRD data.

Numbered compounds in chapter 3 will follow the order 3.1, 3.2, 3.3,…etc.

3 Investigation of Chlorovinylheterocycles in the Aza-Michael Addition-Asymmetric Protonation-Ring Closure Reaction

3.1 Synopsis

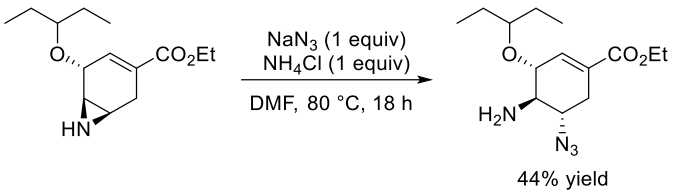
This chapter discusses the CPA-catalyzed Michael addition-asymmetric protonation reaction between chlorovinylheterocycles and arylamines. The reaction could afford heterocyclic phenethylamine products containing a benzylic stereocentre with a carbon-chlorine bond with good yields and excellent enantioselectivity. Further development of this methodology allowed for a one-pot procedure to afford chiral heterocyclic aziridine products with good yields and excellent enantioselectivity (Scheme 3.1). Finally, the synthetic utility of chiral heterocyclic aziridines to furnish chiral vicinal diamines was explored.



Scheme 3.1: Aza-Michael addition-asymmetric protonation reaction and one-pot aza-Michael addition-asymmetric protonation-ring closure reaction of chlorovinylheterocycles.

3.2 Background

The aziridine, a 3-membered nitrogen-containing heterocycle, is a powerful synthetic building block. A large amount of strain within the ring due to the 60° bond angles allows for nucleophilic ring-opening reactions to form β-substituted amines using various nucleophiles.[76] For instance, many groups have utilized a chiral aziridine to synthesize the anti-influenza drug oseltamivir.[77-81] One such example is within the commercial production of oseltamivir (Scheme 3.2).[82]



Scheme 3.2: Nucleophilic ring-opening reaction within the total synthesis of oseltamivir.

Many biologically active compounds contain the aziridine motif. For example, mitomycin C, isolated from *streptomyces verticillus*, is used as a chemotherapeutic agent due to its antitumor activity and is used to treat upper gastrointestinal, anal, breast, and bladder cancers.[83] Pyrrolo[*1,2-a*]benzimidazoles (PBI) and FR/FK compounds are pharmaceutical compounds that have also shown antitumor activity (Figure 3.1).[84,85]

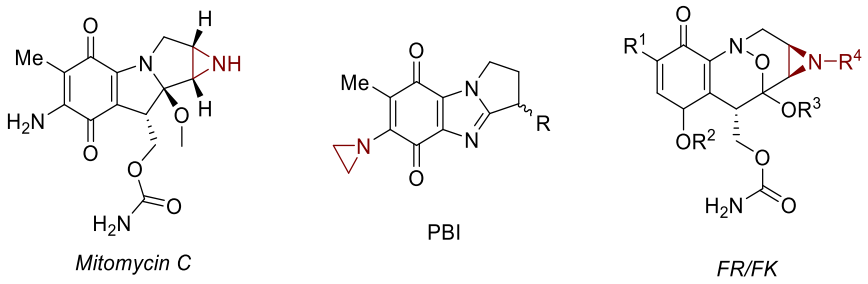
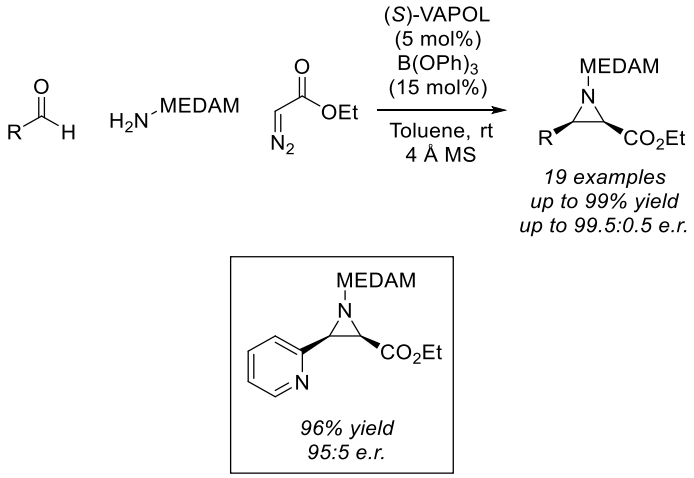


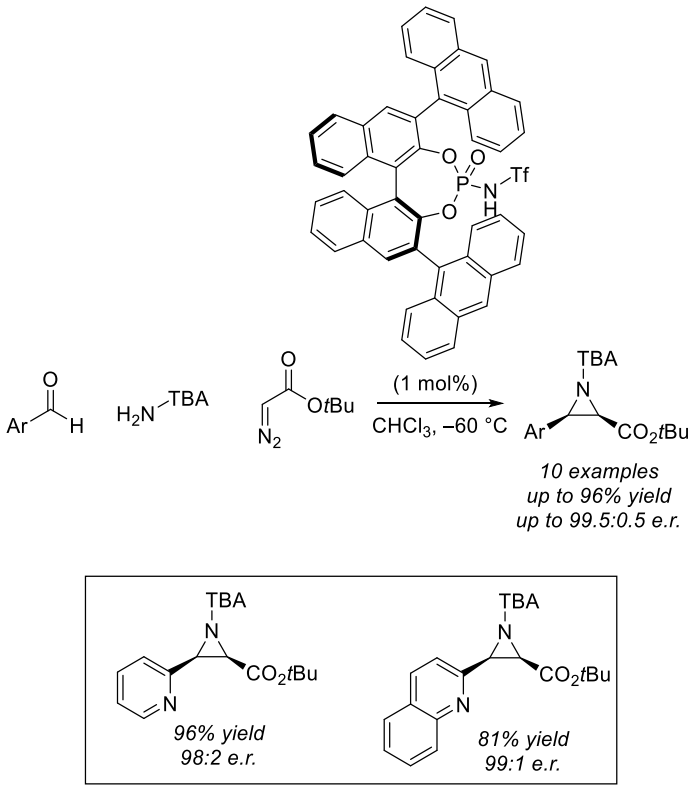
Figure 3.1: Biologically active compounds containing the aziridine functionality.

There have been many examples of synthesizing enantioenriched aziridines containing an *N*-heterocycle substituent. However, most of these procedures require a chiral auxiliary,[86-94] and only a few apply an asymmetric catalytic approach.[95-97] In 2011, the Wulff group showcased a multi-component aziridination catalyzed by a chiral boroxinate (Scheme 3.3).[95] The reaction was shown to furnish aziridines in excellent yields and enantioselectivity and tolerated *N*-heterocycles.



Scheme 3.3: Boroxine-catalyzed asymmetric aziridination with N-heterocyclic examples.

A similar approach utilizing CPA catalysis was developed in 2017 by the Bew group (Scheme 3.4).[96] This variation also furnished aziridines in excellent yields and enantioselectivities and was able to tolerate *N*-heterocycles.

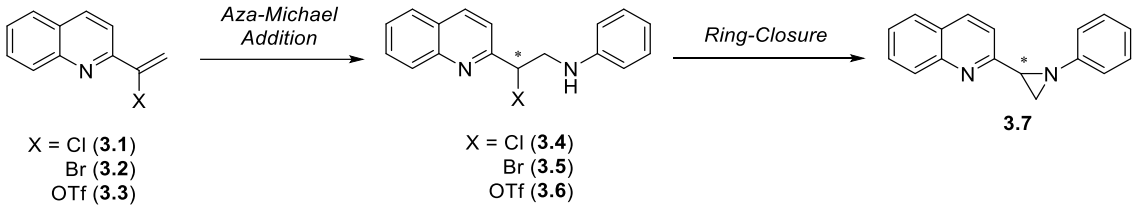


Scheme 3.4: CPA-catalyzed asymmetric aziridination with N-heterocyclic examples.

3.3 Preliminary Work

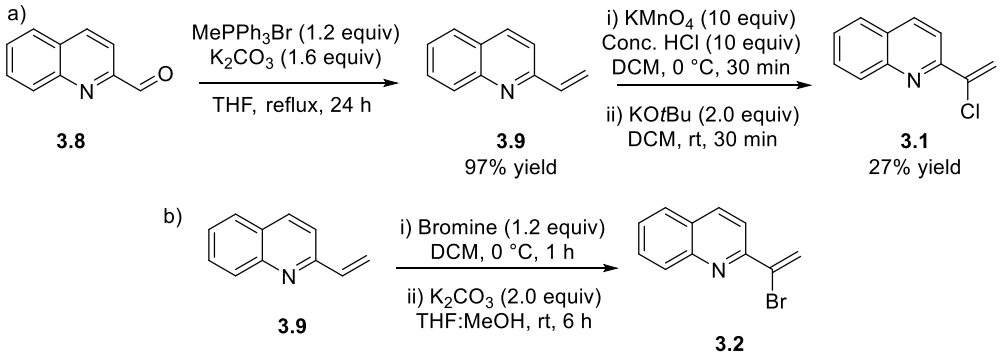
3.3.1 Starting Material Synthesis

The investigation began by identifying a suitable starting material for the aza-Michael-asymmetric protonation-ring closure reaction. Compounds **3.1**-**3.3** were chosen as potential candidates for aza-Michael addition-asymmetric protonation reaction as the products, **3.4**-**3.6**, were expected to undergo the following ring closure reaction to form the aziridine **3.7** (Scheme 3.5).



*Scheme 3.5: Proposed reaction for the synthesis of aziridine **3.7**.*

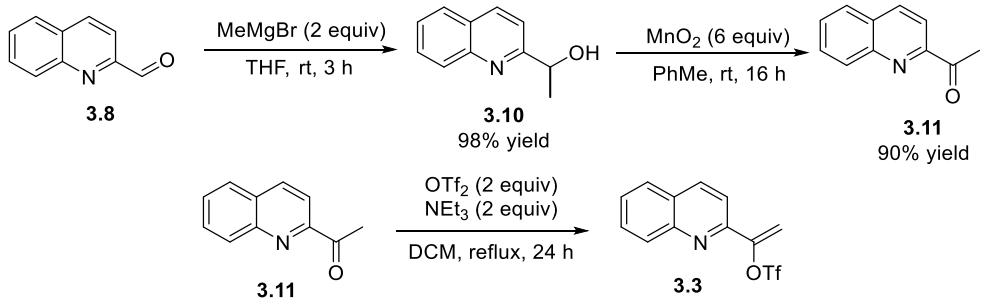
Compounds **3.1** and **3.2** were prepared from the common intermediate **3.9**, which was synthesized *via* Wittig olefination of aldehyde **3.8** using methyltriphenylphosphonium bromide.[98] Potassium permanganate and conc. hydrochloric acid was used to generate chlorine gas, which was bubbled through a solution of compound **3.9** in DCM. Treatment of the 1,2-dichlorinated intermediate with potassium *tert*-butoxide yielded the desired **3.1** (Scheme 3.6a). Bromination-elimination of **3.9** yielded compound **3.2** (Scheme 3.6b),[95] which was not bench stable and was used crude immediately after work-up.



*Scheme 3.6: Synthesis of compounds **3.1** and **3.2**.*

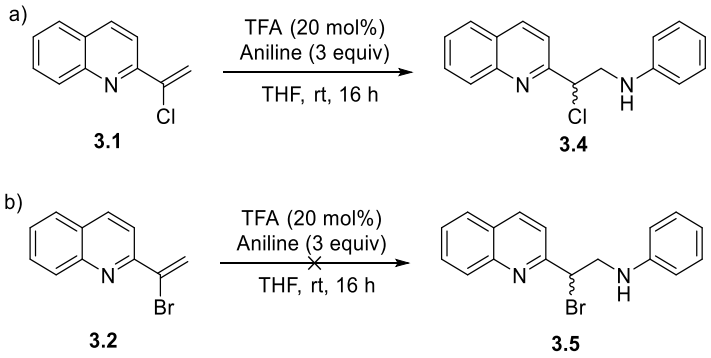
Synthesis of **3.3** began with the addition of methylmagnesium bromide into **3.8** and delivered the alcohol **3.10**. Compound **3.10** could be oxidized to the corresponding

ketone **3.11** with manganese oxide.[45] Treatment of compound **3.11** with triflic anhydride furnished **3.3** (Scheme 3.7).[99] However, compound **3.3** rapidly underwent hydrolysis to yield **3.11**, rendering it unusable.



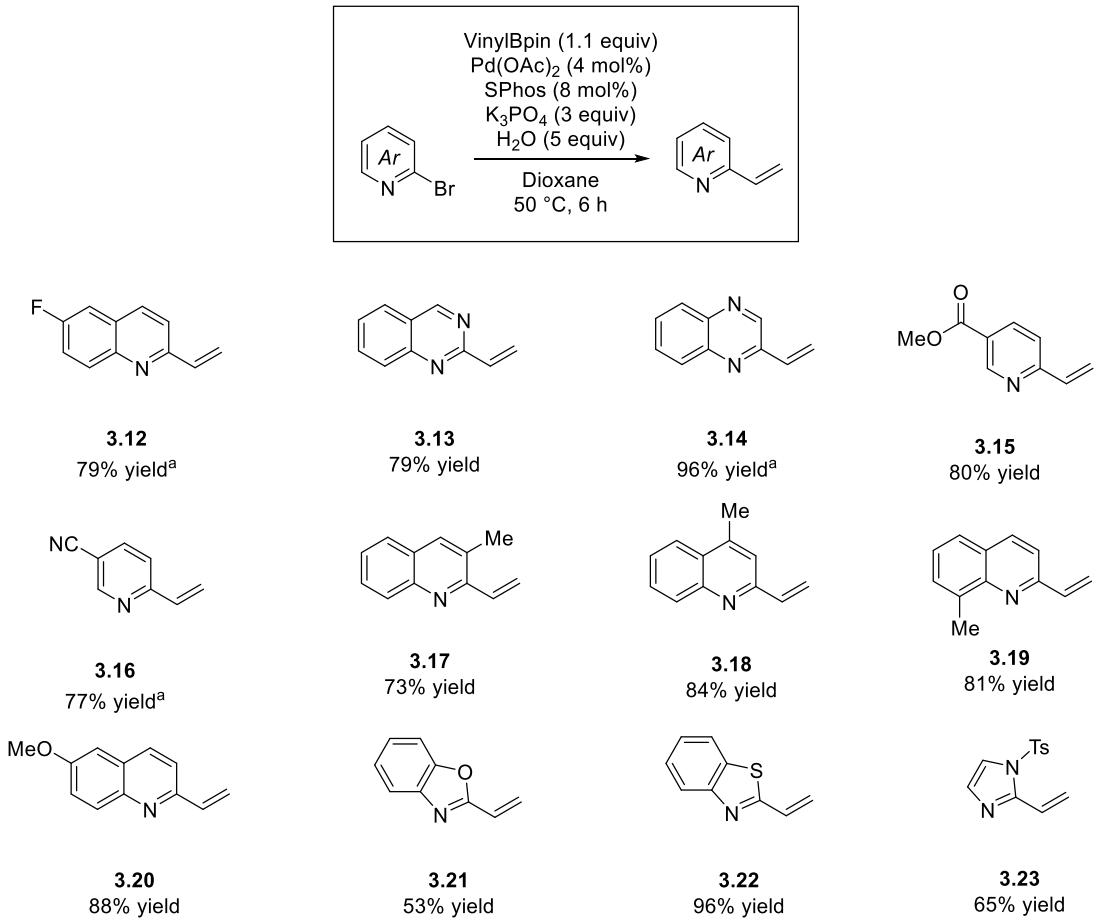
*Scheme 3.7: Attempted synthesis of compound **3.3**.*

The achiral acid-catalyzed aza-Michael addition of **3.1** yielded the desired product **3.4** (Scheme 3.8a). However, the achiral acid-catalyzed Michael addition of **3.2** using aniline failed to obtain the desired product **3.5**, and decomposition was observed (Scheme 3.8b). Therefore, compound **3.1** was deemed to be an ideal starting material for the investigation.



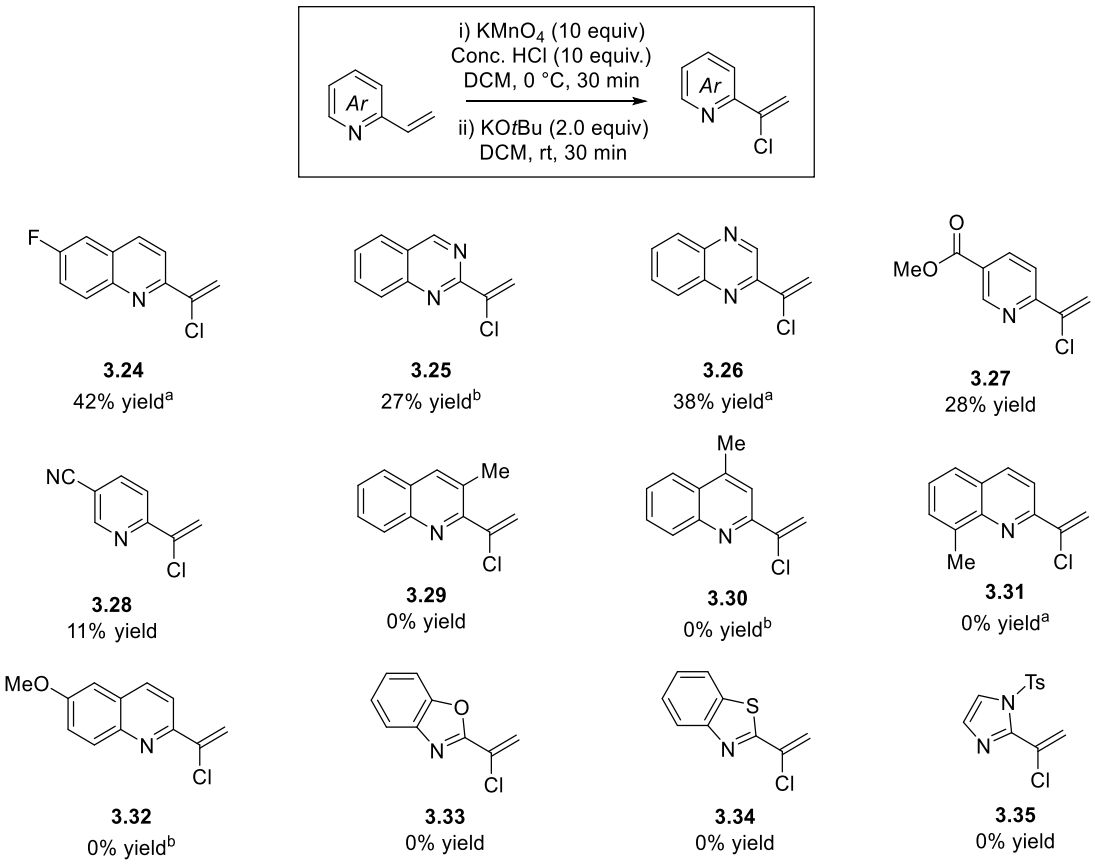
*Scheme 3.8: Synthesis of compounds **3.4** and **3.5***

To explore the substrate scope of the aza-Michael addition-asymmetric protonation reaction, a variety of chlorovinylheterocycles had to be synthesized. Firstly, vinylheterocycles **3.12**-**3.23** were prepared *via* a Suzuki-Miyaura reaction of vinylBpin and the corresponding haloheterocycle in excellent yields (Scheme 3.9).[62]



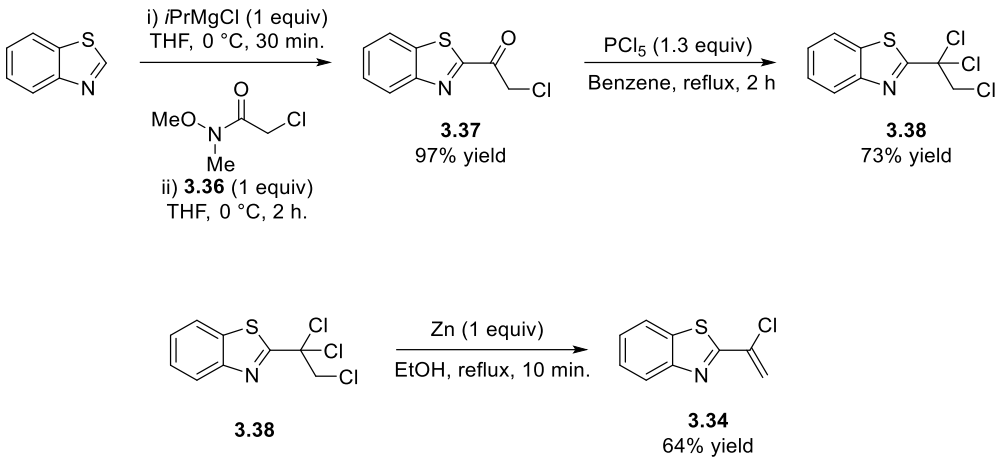
*Scheme 3.9: Synthesis of compounds **3.12**-**3.23**. [a]Reaction performed by Dr Jamie Fyfe.*

Access to the chlorovinylheterocycles **3.24**-**3.28** was achieved through a chlorination-elimination reaction (Scheme 3.10). However, there were some notable limitations to using this methodology. Compounds **3.29**-**3.31** were not achieved due to additional chlorination upon the methyl groups. Compound **3.32** was inaccessible as **3.20** underwent additional chlorination of the aromatic ring. Finally, the methodology was unable to access the azole-based heterocycles **3.33**-**3.35**, as decomposition of the starting material was observed.



*Scheme 3.10: Synthesis of **3.24**-**3.35**. [a]Reaction ran by Dr Jamie Fyfe. [b]Reaction ran by Dr Liam McLean.*

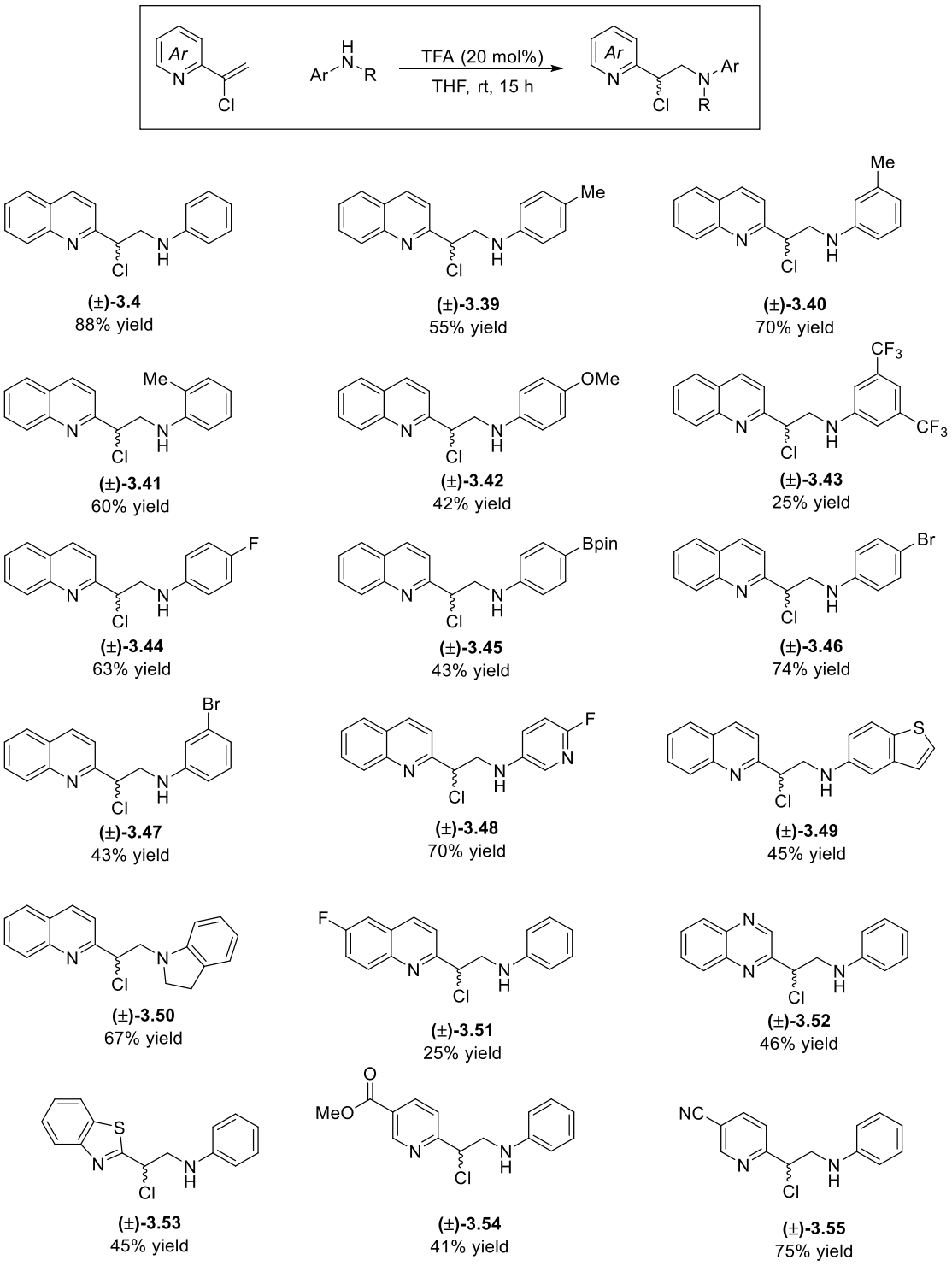
Due to the incompatibility of heterocycles **3.17**-**3.23** with the chlorination-elimination reaction, an alternative route for synthesizing chlorovinylheterocycles was pursued (Scheme 3.11). First, benzothiazole was treated with *i*-propylmagnesium chloride and then reacted with the Weinreb amide **3.36** to furnish the compound **3.37** in an excellent yield. Next, deoxychlorination of compound **3.37** using phosphorus pentachloride provided the compound **3.38** in a great yield. Finally, treatment of compound **3.38** with zinc furnished the chlorovinylheterocycle **3.34** with a moderate yield.



*Scheme 3.11: Alternative synthesis of **3.34**. Reactions performed by Dr Liam McLean.*

3.3.2 Preparation of Racemic Standards

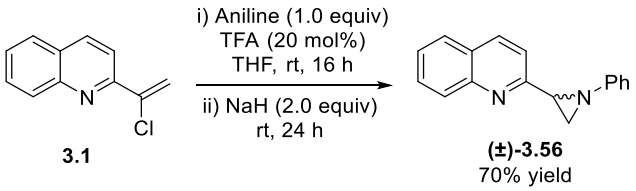
Although the primary goal of this project was to develop a one-pot methodology for the synthesis of aziridines, it appeared advantageous to further show the utility of this methodology by isolating the vicinal chloroamine intermediate. Vicinal haloamines are useful precursors to vicinal diamines and α,β-dehydroamino acids.[100-102] The achiral acid-catalyzed aza-Michael addition afforded a scope of racemic vicinal chloroamines **(±)-3.4** and **(±)-3.39**-**3.55** in moderate to good yields (Scheme 3.12).



*Scheme 3.12: Synthesis of racemic compounds **(±)-3.4, (±)-3.39-3.55**.*

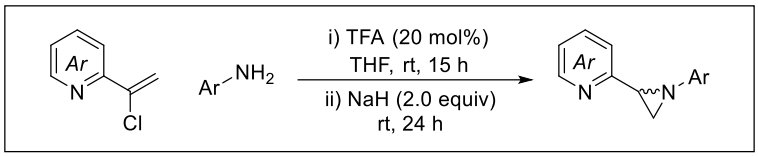
With the racemic compounds **(±)-3.4**, **(±)-3.39**-**3.55** in hand, the focus moved on to synthesizing racemic aziridine compounds. The racemic aziridine **(±)-3.56** was prepared

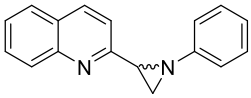
as an analytical standard *via* a one-pot Michael addition-ring closure reaction (Scheme 3.13).



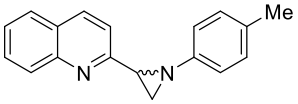
*Scheme 3.13: Synthesis of **(±)-3.56**.*

Utilizing the procedure used to synthesize **(±)-3.56**, the racemic aziridines **(±)-3.57**-**3.69** were prepared as analytical standards (Scheme 3.14). Unfortunately, aziridines **(±)-3.70** and **(±)-3.71** could not be prepared using these conditions. In basic conditions, **(±)-3.53** furnished the racemic aziridine **(±)-3.70**; however, decomposition was observed for **(±)-3.54** in basic conditions and no product was furnished (Scheme 3.15).

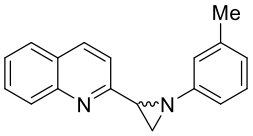




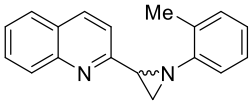
(±)-3.56
70% yield



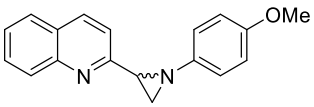
(±)-3.57
56% yield



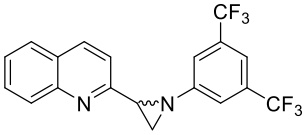
(±)-3.58
59% yield



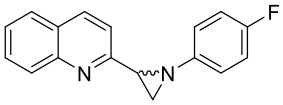
(±)-3.59
52% yield



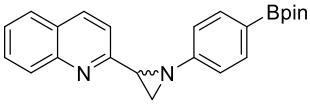
(±)-3.60
44% yield



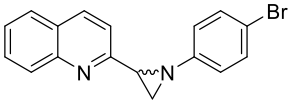
(±)-3.61
38% yield



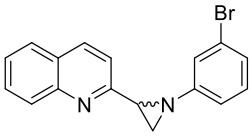
(±)-3.62
49% yield



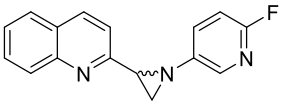
(±)-3.63
84% yield



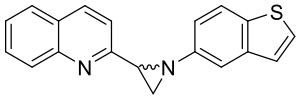
(±)-3.64
83% yield



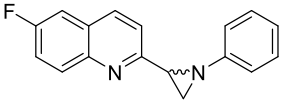
(±)-3.65
67% yield



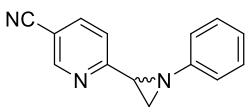
(±)-3.66
39% yield



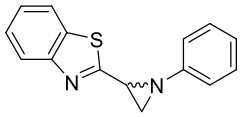
(±)-3.67
9% yield



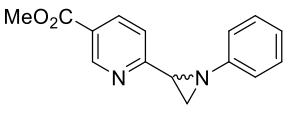
(±)-3.68
25% yield



(±)-3.69
24% yield

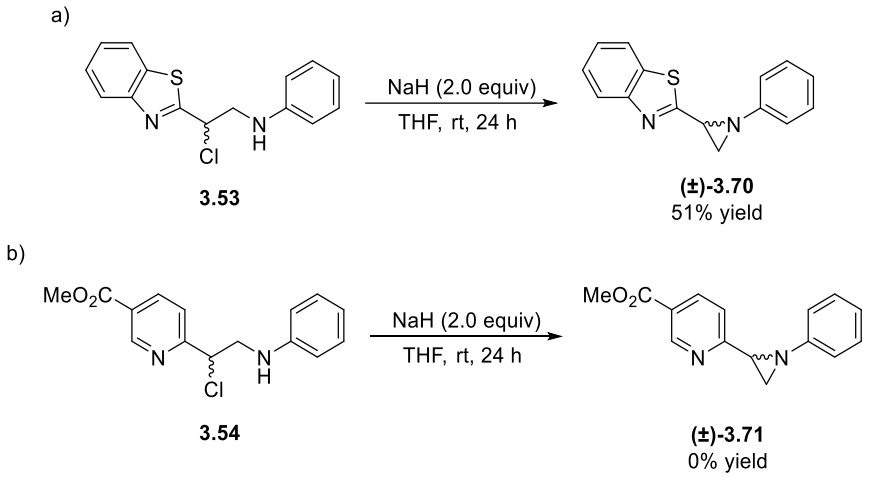


(±)-3.70
0% yield



(±)-3.71
0% yield

*Scheme 3.14: Synthesis of racemic compounds **(±)-3.56-3.71.***

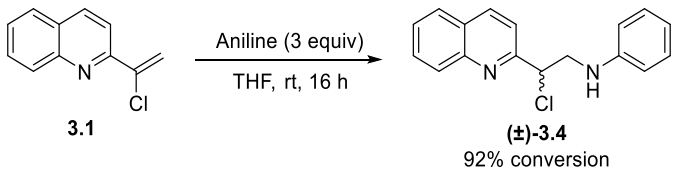


*Scheme 3.15: Synthesis of racemic compounds **(±)-3.70** and **(±)-3.71.***

3.4 Reaction Discussion

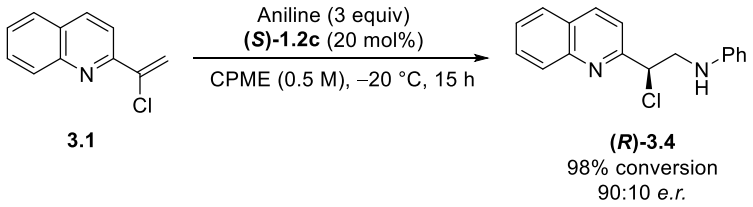
3.4.1 Optimization of the Aza-Michael addition-Asymmetric Protonation Reaction of Chlorovinylheterocycles

Firstly, control reactions were conducted for the investigation of the aza-Michael addition-asymmetric protonation of chlorovinylheterocycles. Excluding acid furnished **(±)-3.4** with 92% conversion (Scheme 3.16). No reaction was observed for the uncatalyzed aza-Michael addition at −20 °C; however, conversion to **(±)-3.4** was observed once the reaction mixture was subjected to work-up at room temperature.



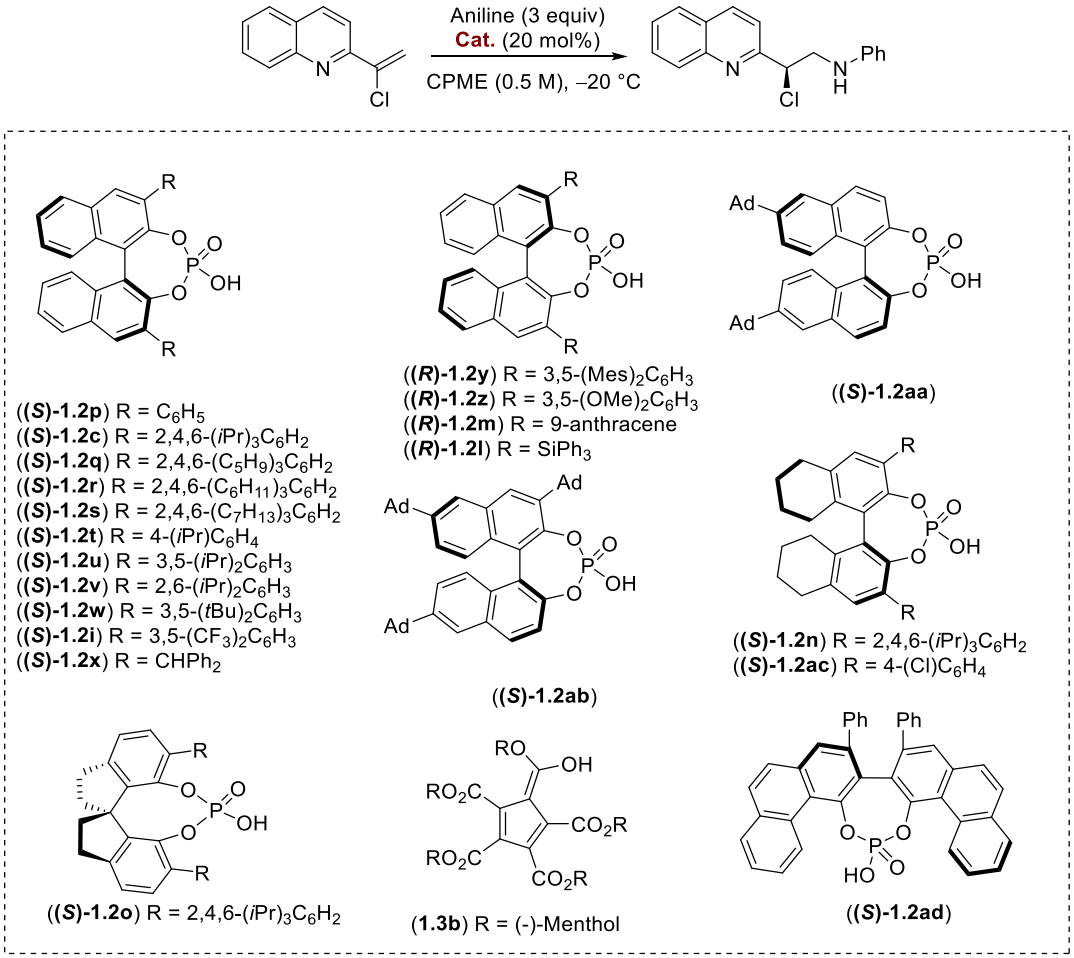
*Scheme 3.16: Uncatalyzed aza-Michael reaction of **3.1**.*

To prevent the background reaction occurring during handling of the work-up and analysis, the starting material must be consumed before working up. In this case, each reaction was set up twice, one for monitoring starting material consumption by NMR aliquots and the other for analysis of conversion and enantioselectivity. Applying the optimized conditions from section 2.2.1 at −20 °C, after 15 h, the reaction furnished **(*R*)-3.4** with a conversion of 98% and an *e.r.* of 90:10 (Scheme 3.17). Therefore, this was chosen as the starting point for the optimization.



*Scheme 3.17: CPA-catalyzed aza-Michael addition-asymmetric protonation of **3.1**. The conversion was determined by ^{1}H NMR with an internal standard, and e.r. was determined by HPLC analysis.*

Firstly, the choice of catalyst was investigated within the CPA-catalyzed aza-Michael addition-asymmetric protonation of chlorovinylheterocycles (Table 3.8).



Entry	*Catalyst*	*Time (h)*	*Conv. (%)*	e.r.
1	**(*S*)-1.2p**	39	71	64:36
2	**(*S*)-1.2c**	15	98	90:10
3	**(*S*)-1.2q**	15	95	90:10
4	**(*S*)-1.2r**	15	96	96:4

5	**(*S*)-1.2s**	15	95	97:3
6	**(*S*)-1.2t**	15	97	67:33
7	**(*S*)-1.2u**	15	73	74:26
8	**(*S*)-1.2v**	15	77	88:12
9	**(*S*)-1.2w**	144	70	71:29
10	**(*S*)-1.2i**	15	90	70:30
11	**(*S*)-1.2x**	39	97	57:43
12	**(*R*)-1.2y**	15	90	44:56
13	**(*R*)-1.2z**	15	92	43:47
14	**(*R*)-1.2m**	15	84	18:82
15	**(*R*)-1.2l**	48	98	42:58
16	**(*S*)-1.2aa**	39	91	53:47
17	**(*S*)-1.2ab**	96	87	68:32
18	**(*S*)-1.2n**	15	85	87:13
19	**(*S*)-1.2ac**	96	92	65:35
20	**(*S*)-1.2o**	15	91	26:74
22	**1.3b**	15	95	52:48
23	**(*S*)-1.2ad**	24	95	68:32

Table 3.8: Catalyst study of the CPA-catalyzed aza-Michael addition-asymmetric protonation reaction. The conversion was determined by ^{1}H NMR with an internal standard, and e.r. was determined by HPLC analysis.

There were a few notable trends observed. Firstly, **(*S*)-1.2t**, **(*S*)-1.2u**, and **(*S*)-1.2v** demonstrated that the positioning of the alkyl groups was critical in enantiocontrol. Alkyl groups in the ortho-positions provided the greatest enantioselectivity (Table 3.8, Entries 6, 7, and 8). Catalyst **(*S*)-1.2c** provided a comparable result to **(*S*)-1.2v** (Table 3.8, Entries 2 and 8). Additionally, catalysts **(*S*)-1.2p** and **(*S*)-1.2t** provided comparable enantioselectivity (Table 3.8, Entries 1 and 6), suggesting the alkyl group in the 4-position imposes a small amount of stereocontrol (Figure 3.2).

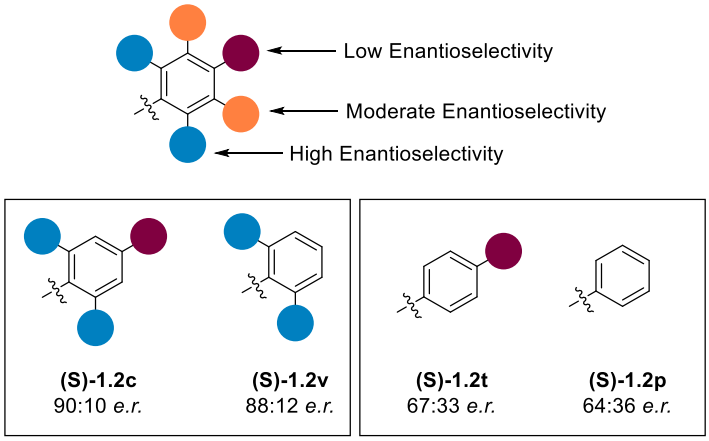


Figure 3.2: Illustration of regiochemistry of alkyl groups upon CPAs and the effects of enantioselectivity.

As seen previously (See Section 2.2.1), the use of the [H8]-BINOL CPA **(*S*)-1.2n** provided comparable results to **(*S*)-1.2c** (Table 3.8, Entries 2 and 18), and the SPINOL CPA **(*S*)-1.2o** provided a decrease in enantioselectivity. Recently, there has been much interest in the use of catalyst **(*S*)-1.2r** in CPA-catalyzed reactions.[103-105] Catalyst **(*S*)-1.2r** has shown to provide greater enantioselectivity compared to **(*S*)-1.2c**. The use of cycloalkyl groups **(*S*)-1.2q**, **(*S*)-1.2r**, and **(*S*)-1.2s** showed that **(*S*)-1.2q** gave comparable results to **(*S*)-1.2c** (Table 3.8, Entries 2 and 3). Increasing the ring size (**(*S*)-1.2r** and **(*S*)-1.2s**) increased enantioselectivity (Table 3.8, Entry 4 and 5), DFT calculations by Dr. Andrew Leach are currently underway to account for this observed trend (Figure 3.3). Therefore, CPA **(*S*)-1.2r** was deemed to be optimal, and the optimization proceeded with this catalyst.

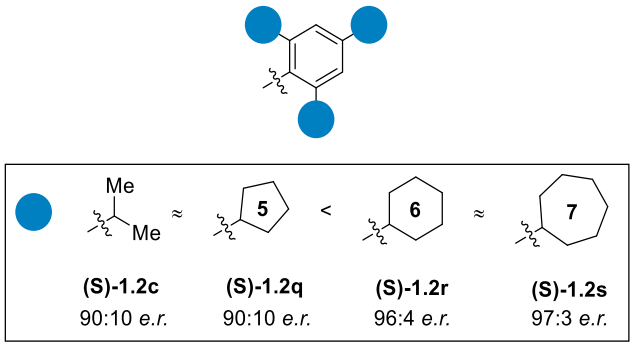
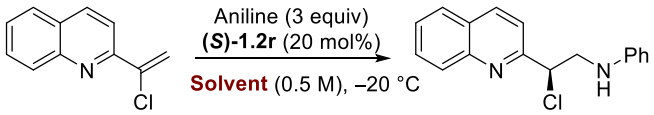


Figure 3.3: Illustration of alkyl group variation upon CPAs and the effects of enantioselectivity.

The solvent effects for the aza-Michael addition-asymmetric protonation of **3.1** were investigated. Ethereal solvents typically provided the best enantioselectivity (Table 3.9, Entries 1-7), similar to the observations in section 2.2.1 and previous work within the

group,[45] with CPME and 2-MeTHF providing the best results (Table 3.9, Entries 1 and 4). Non-polar solvents, hexane and toluene, provided decreased enantioselectivity (Table 3.9, Entries 8 and 9). DCM also provided a significant decrease in enantioselectivity (Table 3.9, Entries 10). DEC and EtOAc were able to provide high enantioselectivity (Table 3.9, Entries 11 and 12). Lastly, the protic solvent IPA provided no enantioselectivity (Table 3.9, Entry 13).

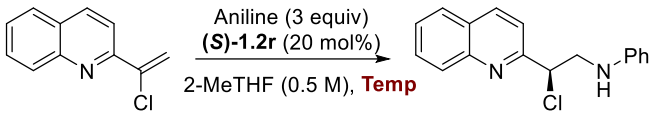


Entry	*Solvent*	*Time (h)*	*Conv. (%)*	e.r.
1	CPME	15	96	96:4
2	THF	15	74	94:6
3	Et_2O	15	99	91:9
4	2-MeTHF	15	91	96:4
5	DME	15	79	80:20
6	Anisole	15	97	89:11
7	TBME	15	95	95:5
8	Hexane	15	76	74:26
9	Toluene	15	98	71:29
10	DCM	15	98	68:32
11	DEC	15	92	91:9
12	EtOAc	15	93	88:12
13	IPA	15	87	51:49

Table 3.9: A solvent study of the CPA-catalyzed aza-Michael addition-asymmetric protonation reaction. The conversion was determined by ^{1}H NMR with an internal standard, and e.r. was determined by HPLC analysis.

The effects of the temperature were investigated (Table 3.10). Decreasing the temperature below −20 °C would provide no increase in enantioselectivity but increased the reaction duration (Table 3.10, Entries 5 and 6). Decreasing the temperature to −78 °C provided trace reactivity (Table 3.10, Entry 7). Increasing the temperature to −10 °C provided the same enantioselectivity (Table 3.10, Entry 3). Increasing the temperature

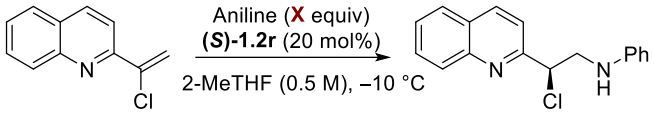
further decreased the observed enantioselectivity (Table 3.10, Entries 1 and 2). Therefore, −10 °C was deemed to be the optimal temperature for this reaction.



Entry	*Temp. (°C)*	*Time (h)*	*Conv. (%)*	e.r.
1	rt	15	93	90:10
2	0	15	97	95:5
3	−10	15	95	96:4
4	−20	15	96	96:4
5	−50	24	95	96:4
6	−70	39	96	96:4
7	−78	39	Trace Reaction Observed	

Table 3.10: Temperature study of the CPA-catalyzed aza-Michael addition-asymmetric protonation reaction. The conversion was determined by ^{1}H NMR with an internal standard, and e.r. was determined by HPLC analysis.

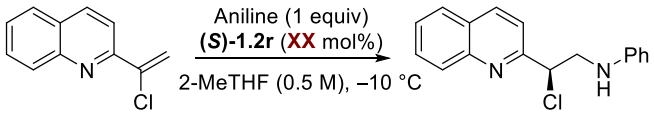
Studying the stoichiometry of aniline within the reaction showed comparable results between 3.0 equivalents and 1.0 equivalent (Table 3.11, Entries 2-5). Increasing to 5.0 equivalents would see a slight decrease in enantioselectivity (Table 3.11, Entry 1). Therefore, 1.0 equivalent of aniline was deemed optimal, as it reduced the overall waste generated from the reaction.



Entry	*Aniline Equiv.*	*Time (h)*	*Conv. (%)*	e.r.
1	5.0	15	94	95:5
2	3.0	15	95	96:4
3	2.0	15	97	96:4
4	1.5	15	97	96:4
5	1.0	15	94	96:4

Table 3.11: Aniline stoichiometry study of the CPA-catalyzed aza-Michael addition-asymmetric protonation reaction. The conversion was determined by ^{1}H NMR with an internal standard, and e.r. was determined by HPLC analysis with an internal standard.

The catalyst loading was then investigated. As the loading was decreased, a slight decrease in enantioselectivity was observed (Table 3.12, Entries 1-5). Decreasing the temperature to −20 °C at 5 mol% catalyst loading, the enantioselectivity was comparable to 20 mol% at −10 °C (Table 3.12, Entry 6). Due to the cost of the catalyst, it was more practical to reduce to 5% catalyst loading at −20 °C.

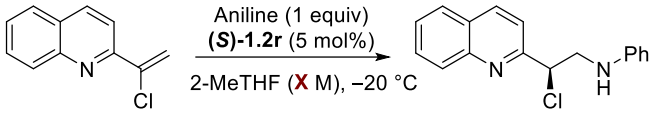


Entry	*Cat. Loading. (mol%)*	*Time (h)*	*Conv. (%)*	e.r.
1	1	15	92	92:8
2	2	15	94	94:6
3	5	15	97	95:5
4	10	15	94	95:5
5	20	15	94	96:4
6	5 (−20 °C)	15	94	96:4

Table 3.12: Catalyst stoichiometry study of the CPA-catalyzed aza-Michael addition-asymmetric protonation reaction. The conversion was determined by ^{1}H NMR with an internal standard, and e.r. was determined by HPLC analysis.

The reaction concentration was studied, and it was shown that 0.50 M and 0.25 M would provide comparable results (Table 3.13, Entries 1 and 2). Decreasing the concentration

further to 0.10 M decreased the reaction rate, with comparable conversion achieved after 24 h (Table 3.13, Entry 3). Increasing the concentration to 1.00 M provided a heterogeneous mixture and provided a reaction that would not complete. Therefore, 0.50 M was determined to be optimal.

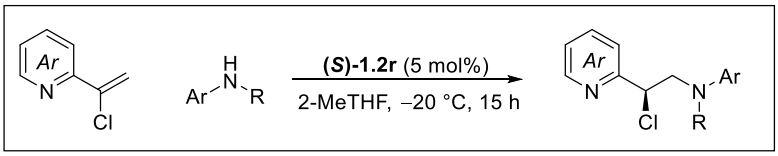


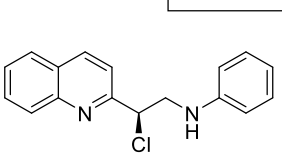
Entry	*Concentration (M)*	*Time (h)*	*Conv. (%)*	e.r.
1	0.50	15	94	96:4
2	0.25	15	93	96:4
3	0.10	24	90	95:5

Table 3.13: Catalyst study of the CPA-catalyzed aza-Michael addition-asymmetric protonation reaction. The conversion was determined by ^{1}H NMR with an internal standard, and e.r. was determined by HPLC analysis.

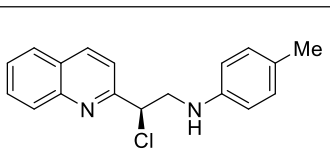
3.4.2 Substrate Scope of the Aza-Michael Addition-Asymmetric Protonation Reaction of Chlorovinylheterocycles

The scope of arylamines and chlorovinylheterocycles for the aza-Michael addition-asymmetric protonation reaction was explored (Scheme 3.12). In most cases, the reaction provided high yields and excellent enantioselectivity. Substrates with an ortho-substituent **(*R*)-3.41**, strong electron-donating group **(*R*)-3.42**, or boronate group **(*R*)-3.45** on the arylamine required longer reaction times. Arylamines with a strong electron-withdrawing group did not react at −20 °C and only showed reactivity at room temperature, which provided a racemic sample of **(*R*)-3.43**. Substrates **(*R*)-3.45**, **(*R*)-3.47**, **(*R*)-3.48**, and **(*R*)-3.50** were produced with greater enantioselectivity in CPME than 2-MeTHF. The reaction could tolerate various *N*-heterocycles, providing great enantioselectivity for quinazoline **(*R*)-3.52**, quinoxaline **(*R*)-3.72**, benzothiazole **(*R*)-3.53**, and pyridine **(*R*)-3.54** and **(*R*)-3.55** substrates.

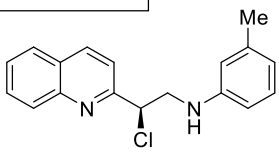




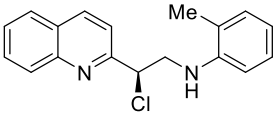
(*R*)-3.4
79% yield
97:3 *e.r.*



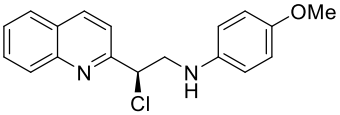
(*R*)-3.39
85% yield
97:3 *e.r.*



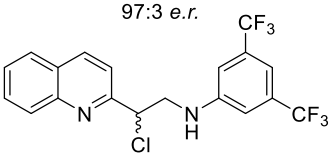
(*R*)-3.40
>99% yield
97:3 *e.r.*



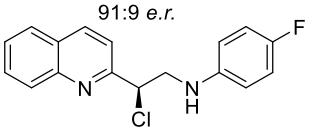
(*R*)-3.41[a]
68% yield
91:9 *e.r.*



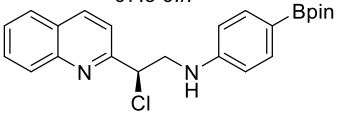
(*R*)-3.42[a]
62% yield
97:3 *e.r.*



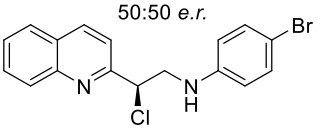
(±)-3.43[b]
72% yield
50:50 *e.r.*



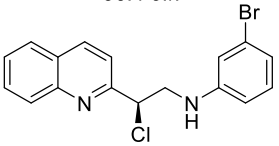
(*R*)-3.44
88% yield
96:4 *e.r.*



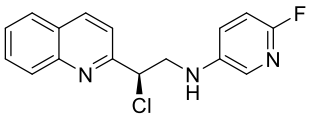
(*R*)-3.45[a,c]
64% yield
94:6 *e.r.*



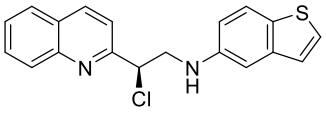
(*R*)-3.46
82% yield
95:5 *e.r.*



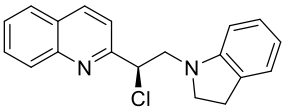
(*R*)-3.47[c]
76% yield
95:5 *e.r.*



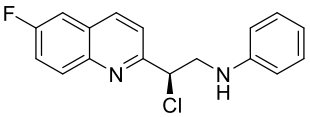
(*R*)-3.48[c]
76% yield
93:7 *e.r.*



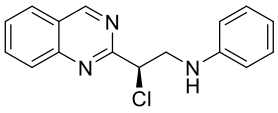
(*R*)-3.49
82% yield
94:6 *e.r.*



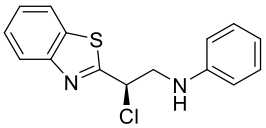
(*R*)-3.50[c]
84% yield
93:7 *e.r.*



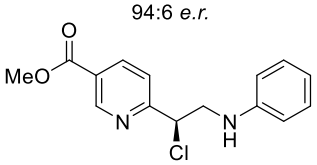
(*R*)-3.51[d]
79% yield
94:6 *e.r.*



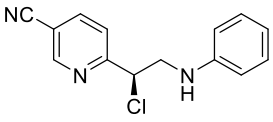
(*R*)-3.52[e,f]
69% yield
85:15 *e.r.*



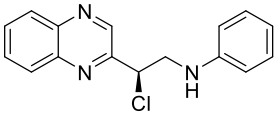
(*R*)-3.53
48% yield
99:1 *e.r.*



(*R*)-3.54[d,g]
51% yield
94:6 *e.r.*



(*R*)-3.55[g,h]
64% yield
91:9 *e.r.*



(*R*)-3.72[d,g]
54% yield
94:6 *e.r.*

Scheme 3.18: CPA-catalyzed aza-Michael addition-asymmetric protonation reaction substrate scope. [a]The reaction was run for 39 h. [b]The reaction was run at rt. [c]CPME was used as a solvent. [d]The reaction was run for 4 d. [e]The reaction was run for 5 d. [f]The reaction was run by Dr Liam McLean. [g]The reaction was run by Dr Jamie Fyfe. [h]The reaction was run for 60 h.

X-ray diffraction of **(*R*)-3.47** was performed to confirm the absolute configuration of the major enantiomer (Figure 3.4). The solid-state conformation of **(*R*)-3.47** showed a dihedral angle between the carbon-chlorine bond and the carbon-nitrogen bond of 180°, similar to the conformation shown by **(*R*)-2.43** (Section 2.4.4). This conformation may result from a stabilizing effect caused by the nitrogen lone pair donating electron density into the C-Cl σ* orbital.

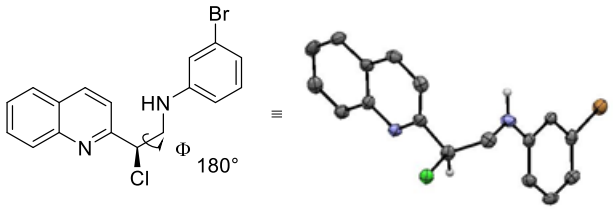
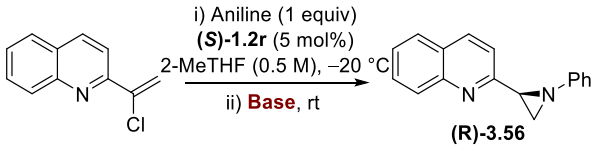


*Figure 3.4: Crystal structure of **(R)-3.47**.*

3.4.3 Optimization of the Aza-Michael addition-Asymmetric Protonation-Ring Closure Reaction of Chlorovinylheterocycles

A base screen for the second step was run. Most bases provided no conversion to the product **(*R*)-3.56** (Table 3.14, Entries 3-8). Sodium hydride and potassium *t*-butoxide furnished the aziridine **(*R*)-3.56**, albeit with diminished stereospecificity (Table 3.14, Entries 1 and 2). Decreasing the stoichiometry of sodium hydride and potassium *t*-butoxide did not improve the stereospecificity of the reaction (Table 3.14, Entries 9 and 10). *n*-Butyllithium was able to proceed with excellent stereospecificity; however, it provided a poor conversion to product (Table 3.14, Entry 11). Other lithium-based bases were equally stereospecific (Table 3.14, Entry 12 and 13), with LiHMDS providing the highest conversion of 83%. Additionally, LiO*t*Bu would only return starting material (Table 3.14, Entry 14). Monitoring the reaction using LiHMDS showed the reaction reaching a plateau after 30 min (Table 3.14, Entry 15). Using 1.2 equivalents of LiHMDS elevated conversion to 95% and *e.r.* to 95:5 after just 30 min. (Table 3.14, Entry 16), this was deemed optimal. It was hypothesized that the observed erosion of stereospecificity was due to an S_N1 characteristic of the ring closure reaction. Similarly, S_N1 reactivity has previously been observed with nucleophilic reactions at benzylic centers.[106]

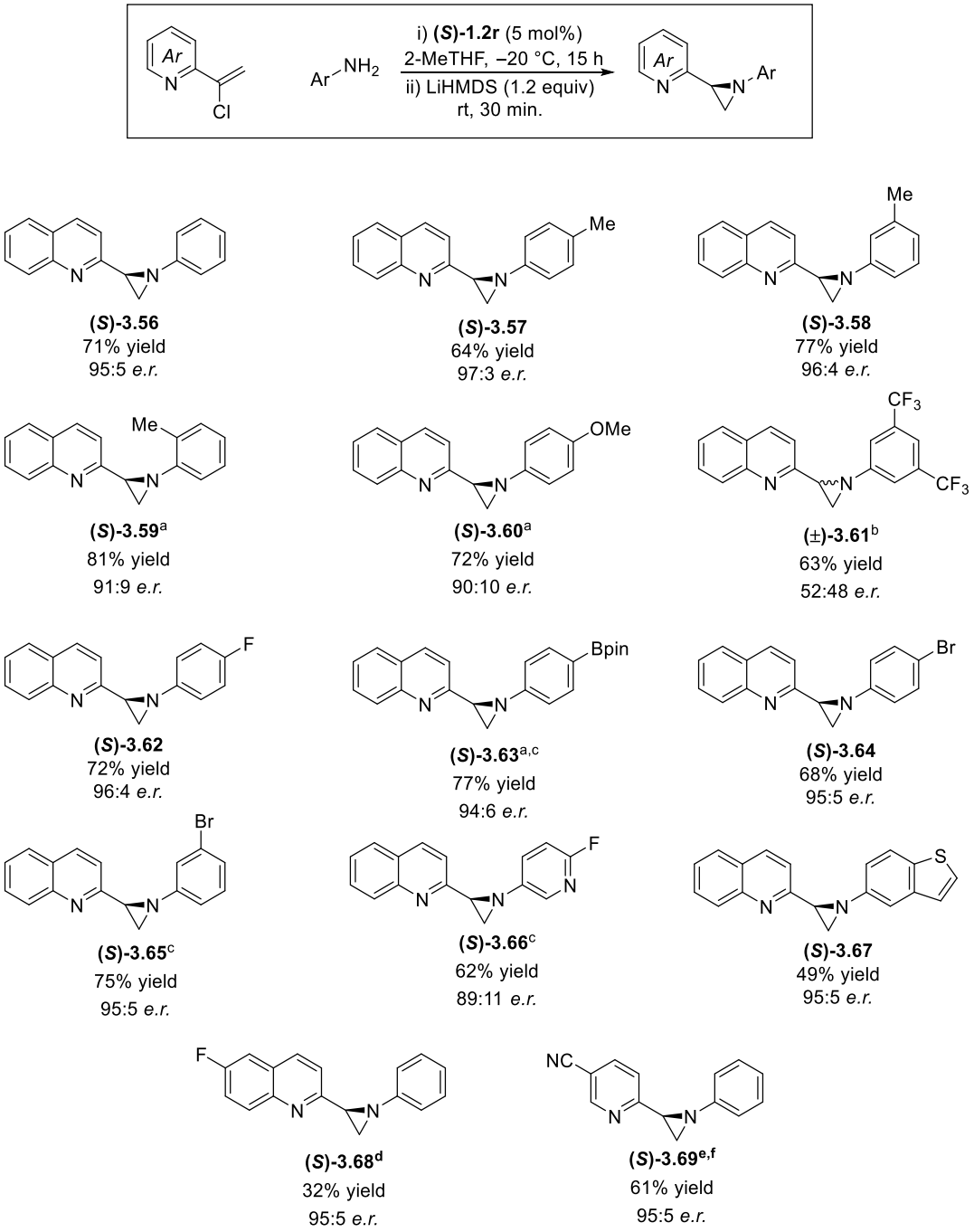


Entry	*Base*	*Equivalents*	*Time*	*Conversion (%)*	*e.r.*
1	NaH	2.0	5	28	91:9
2	KO*t*Bu	2.0	5	81	73:27
3	K_2CO_3	2.0	5	0	--
4	K_3PO_4	2.0	5	0	--
5	TEA	2.0	5	0	--
6	DBU	2.0	5	0	--
7	DIPEA	2.0	5	0	--
8	Pyridine	2.0	5	0	--
9	NaH	1.05	5	trace	--
10	KO*t*Bu	1.05	5	60	74:26
11	*n*BuLi	1.05	5	22	95:5
12	LDA	1.05	5	43	95:5
13	LiHMDS	1.05	5	83	95:5
14	LiO*t*Bu	1.05	5	0	--
15	LiHMDS	1.05	0.5	79	95:5
16	LiHMDS	1.2	0.5	95	95:5

Table 3.14: A base study of the CPA-catalyzed aza-Michael addition-asymmetric protonation-ring closure reaction. The conversion was determined by ^{1}H NMR with an internal standard, and e.r. was determined by HPLC analysis.

3.4.4 Substrate Scope of the Aza-Michael Addition-Asymmetric Protonation-Ring Closure Reaction of Chlorovinylheterocycles

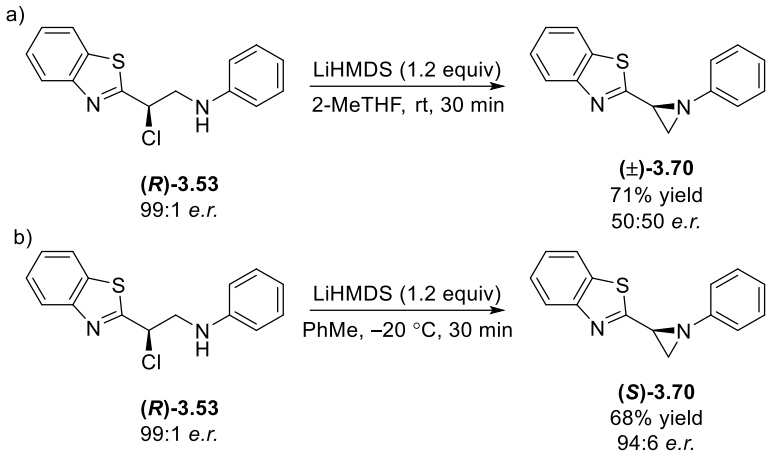
The scope of arylamines and *N*-heterocycles for the aza-Michael addition-asymmetric protonation-ring closure reaction was explored (Scheme 3.19). Typically, the reaction was well tolerated with excellent stereoselectivity for most arylamines, and the same observations occurred from the substrate scope of the aza-Michael addition-asymmetric protonation reaction of chlorovinylheterocycles (Section 3.2.2).



Scheme 3.19: CPA-catalyzed aza-Michael addition-asymmetric protonation reaction substrate scope. [a]The first step was run for 39 h. [b]The first step was run at rt. [c]CPME was used as a solvent. [d]The first step was run for 4 d. [e]The first step was run for 60 h. [f]The reaction was ran by Dr Jamie Fyfe.

As compound **(*S*)-3.70** could not be furnished from the one-pot aza-Michael addition-asymmetric protonation-ring closure reaction, the ring closure reaction of **(*R*)-3.53** was investigated. However, a racemic product was furnished under the optimized ring closure conditions (Scheme 3.20a). Therefore, it was hypothesized that the ring closure reaction was exhibiting S_N1 characteristics. As a result, utilizing toluene at low

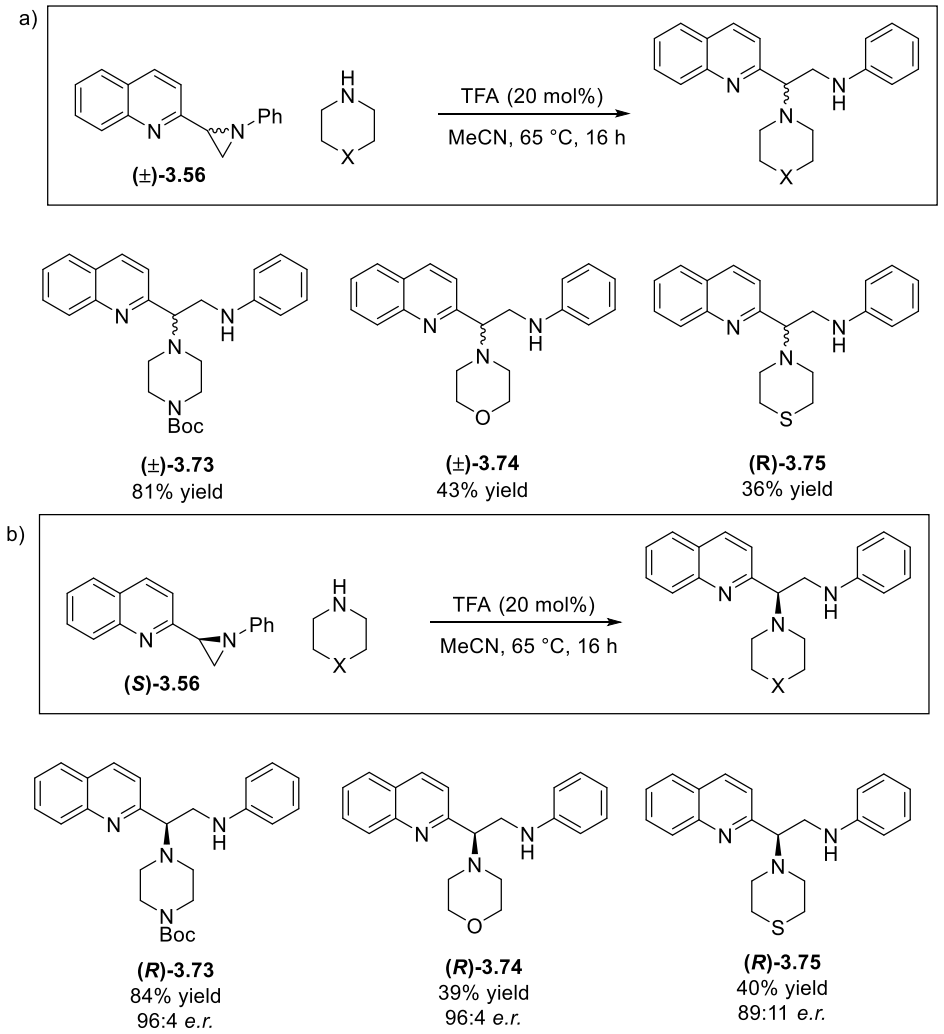
temperatures furnished the aziridine **(*S*)-3.70** with high stereospecificity (Scheme 3.20b).



*Scheme 3.20: Synthesis of aziridine **(R)-3.70**.*

3.4.5 Product Derivatisation

The synthesis of vicinal diamines *via* a nucleophilic ring-opening reaction was explored to demonstrate the synthetic utility of the aziridine products. The vicinal diamine functionality occurs in many biologically active compounds and organic catalysts.[107] Compound **(±)-3.56** was chosen to investigate the nucleophilic ring-opening reaction. In acidic conditions, compound **(±)-3.73** was obtained in 81% yield. The same conditions were used to provide compounds **(±)-3.74** and **(±)-3.75** (Scheme 3.21a). Using these conditions on aziridine **(*S*)-3.56** yielded compounds **(*R*)-3.73**-**3.75**. Compounds **(*R*)-3.73** and **(*R*)-3.74** were furnished with excellent stereospecificity, and compound **(*R*)-3.75** was obtained with diminished stereospecificity (Scheme 3.21b).



*Scheme 3.21: Nucleophilic ring-opening reaction of **3.56** under acidic conditions.*

3.5 Conclusion

In conclusion, the aza-Michael addition-asymmetric protonation reaction of chlorovinylheterocycles to furnish 1,2-chloroamine products was optimized. Additionally, a one-pot aza-Michael addition-asymmetric protonation-ring closure reaction was optimized. The scope of arylamines and chlorovinylheterocycles was explored for both reactions, and their enantiomeric ratios were directly compared to the prepared racemic samples. Both reactions provided high yields and enantioselectivity. Further molecular complexity could be afforded in the products by nucleophilic ring-opening of the chiral aziridines to afford chiral 1,2-diamines. Catalyst variation experiments provided insight into the enantioselectivity imposed by the catalyst, and DFT calculations are ongoing to elucidate this further.

3.6 Experimental

3.6.1 General Information

Purification of Solvents

Dry THF, DCM, hexane, toluene, and Et_2O for reactions were obtained from a PureSolv SPS-400-5 solvent purification system. All other solvents for reactions were obtained from commercial suppliers and purification was carried out according to standard laboratory methods.[72] Et_2O, EtOAc, toluene, and hexane for purification purposes were used as obtained from suppliers without further purification.

Experimental Details

Reactions were carried out using conventional glassware (preparation of intermediates), or in 2 mL HPLC vials. The glassware was oven-dried (150 °C) and purged with N_2 before use. Purging refers to a vacuum/nitrogen-refilling procedure. Room temperature (rt) was generally *ca.* 18 °C. Reactions were carried out at elevated temperatures using a temperature-regulated hotplate/stirrer with a sand bath. Reactions were carried out at 0, −10, −20, −50, and −78 °C using an acetone bath cooled by a Thermo Haake EK90 cryocooler. Reactions were carried out at 0 °C using an ice/water bath.

Purification of Products

Thin layer chromatography was carried out using Merck silica plates coated with fluorescent indicator UV254. These were analyzed under 254 nm UV light, developed using potassium permanganate or vanillin solutions. Normal phase flash chromatography was carried out using ZEOprep 60 HYD 40-63 µm silica gel.

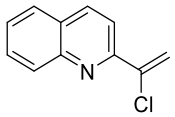
Analysis of Products

Fourier Transformed Infra-Red (FTIR) spectra were obtained on a Shimadzu IRAffinity-1 machine. ^{19}F NMR spectra were obtained on a Bruker AV 500 spectrometer at 470 MHz, respectively. ^{11}B NMR spectra were obtained on a Bruker AV 300 spectrometer at 96 MHz. ^{1}H and ^{13}C NMR spectra were obtained on either a Bruker AV 400 at 400 MHz and 101 MHz, respectively, or Bruker DRX 500 at 500 MHz and 126 MHz, respectively.

Chemical shifts are reported in ppm and coupling constants are reported in Hz with $CDCl_3$ referenced at 7.26 (^1H) and 77.0 ppm (^{13}C). ^{11}B NMR spectra are referenced to $BF_3{\cdot}Et_2O$. Unless otherwise stated, *J* refers to $^3J_{HH}$ and J_{CF} in ^1H and ^{13}C NMR, respectively. High-resolution mass spectra were obtained through analysis at the University of St Andrews. High performance liquid chromatography (HPLC) was performed on an Agilent 1200 series HPLC using a chiral stationary phase column (column, Daicel Co. CHIRALCEL OJ-H, or CHIRALPAK IA; eluent: *n*-hexane/*i*-PrOH). All solvents used were HPLC-grade solvents purchased from Fisher. The column employed and the respective solvent mixture are indicated for each experiment. The retention time for a compound can be influenced by factors such as column degradation and temperature of the column, as the Agilent 1200 series was not equipped with a column oven retention time drifting was observed. For compounds **3.57**, **3.67**, **3.70**, and **3.74** a peak drift of >5% was observed. Optical rotations were obtained on a Perkin Elmer Model 341 polarimeter.

3.6.2 General Experimental Procedures

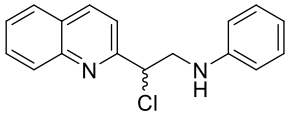
General Procedure A: Dichlorination and Dehydrochlorination of Vinylheterocycles (Example 3.1, 2-(1-chlorovinyl)quinoline)



A 100 mL oven-dried RBF containing a magnetic stirrer and wrapped in aluminium foil was charged with 2-vinylquinoline (3.88 g, 25.0 mmol, 1.0 equiv.) capped and purged with nitrogen. Dry DCM (50 mL) was then added and the solution was cooled to −78 °C (Flask A). Seperately, a 100 mL oven-dried RBF was charged with $KMnO_4$ (15.8 g, 250 mmol, 10.0 equiv). The flask was capped and purged with nitrogen (Flask B). Rubber tubing, with syringes fitted with needles at both ends filled with calcium chloride, pierced both round bottomed flasks, and with the needle submerged within the solution of Flask A. An unfilled balloon was then fitted to Flask A, and 37% aqueous HCl (20.9 mL, 250 mmol, 10.0 equiv) was then added dropwise to the Flask B (Caution Cl_2 gas is produced). After 10 minutes the rubber tubing was removed. The reaction in Flask A was left to stir at −78 °C for 30 min. The reaction was then quenched with a sat. sol. of sodium sulfite (50 mL). The phases were separated and the aqueous phase was washed with DCM (50 mL × 2). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo* (25 °C bath). The crude was used directly in the next step.

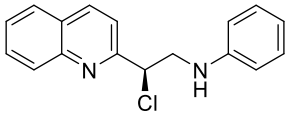
A 100 mL RBF containing a magnetic stirrer was then charged with the crude dichloro species (assumed 25 mmol) the flask was capped and purged with nitrogen. The flask was submerged in an ice bath and dry DCM (50 mL) was added followed by KOtBu (5.61 g, 50.0 mmol, 2 equiv), and the reaction was stirred for 30 min at 0 °C (Caution! Reaction is exothermic). The reaction was then diluted with water, the phases were separated and the aqueous phase was washed with DCM (50 mL × 2). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo* (25 °C bath). The crude material was purified by flash column chromatography (Et_2O:Hex 1:99) to yield the desired product as a yellow solid (1.28 g, 27%).

General Procedure B: Aza-Michael reaction catalyzed using an achiral acid (Example (±)-3.4, *N*-(2-chloro-2-(quinolin-2-yl)ethyl)aniline))



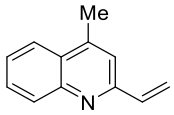
A 2 mL HPLC vial was charged with 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv). The vial was then capped and purged with N_2 before addition of THF (500 µL, 0.5 M), aniline (23 µL, 0.25 mmol, 1.0 equiv) and TFA (3.8 µL, 0.05 mmol, 20 mol%). The resulting mixture was then allowed to stir at rt for 15 h before being quenched by sat. aq. $NaHCO_3$ solution (2 mL) and diluted with EtOAc (2 mL). The phases were separated and the aqueous phase was washed with EtOAc (2 mL × 2). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the crude product *via* flash chromatography (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) gave the desired product as a pale yellow solid (62.3 mg, 88%).

General Procedure C: Aza-Michael reaction catalyzed using a chiral acid (Example (*R*)-3.4, *N*-(2-chloro-2-(quinolin-2-yl)ethyl)aniline)



A 2 mL HPLC vial was charged with 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), and (*S*)-TCYP (12.4 mg, 12.5 µmol, 5 mol%). The vial was then capped and purged with N_2 before addition of 2-MeTHF (500 µL, 0.5 M). The reaction mixture was cooled to −20 °C for 15 min before the addition of aniline (23 µL, 0.25 mmol, 1.0 equiv). The resulting mixture was then allowed to stir at −20 °C for 15 h before being quenched by sat. aq. $NaHCO_3$ solution (2 mL) and diluted with EtOAc (2 mL). The phases were separated and the aqueous phase was washed with EtOAc (2 mL × 2). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the crude product *via* flash chromatography (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) gave the desired product as a pale yellow solid (55.9 mg, 79%). The enantiomeric ratio (97:3) was determined by chiral HPLC in comparison with the racemate.

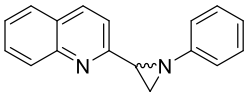
General Procedure D: Suzuki-Miyaura coupling (Example 3.18, 2-vinylquinoline)



Prepared according to literature procedure.[62]

An oven-dried 100 mL round bottomed flask equipped with a reflux condenser was charged with 2-chloro-4-methylquinoline (888 mg, 5.00 mmol, 1.0 equiv), vinylboronic acid pinacol ester (847 mg, 5.50 mmol, 1.1 equiv), palladium(II) acetate (44.9 mg, 0.20 mmol, 4 mol%), SPhos (164 mg, 0.40 mmol, 8 mol%), potassium phosphate (3.18 g, 15.0 mmol, 3.0 equiv). The system was capped and purged. Dioxane (20 mL) and water (450 µL, 25.0 mmol, 5 equiv) were added and the reaction was stirred at 80 °C for 6 h. The mixture was then allowed to cool to rt, filtered through celite, and concentrated *in vacuo*. The crude product was purified using flash column chromatography (Silica, pet ether:EtOAc 95:5) to afford the desired product as a yellow liquid (707 mg, 4.18 mmol, 84%).

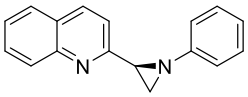
General Procedure E: **One-Pot Aza-Michael-Ring Closure Reaction catalyzed using an achiral acid (Example (±)-3.56, 2-(1-phenylaziridin-2-yl)quinoline)**



A 2 mL HPLC vial was charged with 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv). The vial was then capped and purged with N_2 before addition of 2-MeTHF (500 µL, 0.5 M), aniline (23 µL, 0.25 mmol, 1.0 equiv), and TFA (3.8 µL, 0.05 mmol, 20 mol%). The resulting mixture was then allowed to stir at rt for 15 h. NaH (60% dispersion in mineral oil, 20 mg, 0.50 mmol, 2.0 equiv) was added, and the reaction was allowed to stir for a further 24 h at rt before being quenched by sat. aq. NH_4Cl solution (2 mL) and diluted with EtOAc (2 mL). The phases were separated and the aqueous phase was washed with EtOAc (2 mL × 2). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the crude product *via* flash column

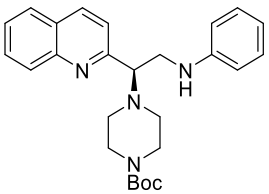
chromatography (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) gave the desired product as a pale yellow solid (42.9 mg, 70%).

General Procedure F: **One-Pot Aza-Michael-Ring Closure Reaction catalyzed using a chiral acid (Example (*R*)-3.56, 2-(1-phenylaziridin-2-yl)quinoline)**



A 2 mL HPLC vial was charged with 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), and (*S*)-TCYP (12.4 mg, 12.5 µmol, 5 mol%). The vial was then capped and purged with N_2 before addition of 2-MeTHF (500 µL, 0.5 M). The reaction mixture was cooled to −20 °C for 15 min before the addition of aniline (23 µL, 0.25 mmol, 1.0 equiv). The resulting mixture was then allowed to stir at −20 °C for 15 h. The reaction was then allowed to warm to rt and a 0.6 M solution of LiHMDS in THF (0.5 mL, 0.3 mmol, 1.2 equiv) was added, and the reaction was allowed to stir for a further 30 min at rt before being quenched by sat. aq. NH_4Cl solution (2 mL) and diluted with EtOAc (2 mL). The phases were separated and the aqueous phase was washed with EtOAc (2 mL × 2). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the crude product *via* flash column chromatography (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) gave the desired product as a pale yellow solid (41.1 mg, 67%). The enantiomeric ratio (95:5) was determined by chiral HPLC in comparison with the racemate.

General Procedure G: Nucleophilic Ring-Opening Reaction (Example 3. (*R*)-3.73, *t*-Butyl 4-(2-(phenylamino)-1-(quinolin-2-yl)ethyl)piperazine-1-carboxylate)

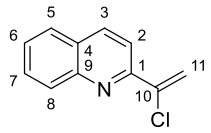


A 2 mL HPLC vial was charged with (*R*)-2-(1-phenylaziridin-2-yl)quinoline (24.6 mg, 0.10 mmol, 1.0 equiv) and *N*-boc-piperazine (18.6 mg, 0.10 mmol, 1.0 equiv). The vial was then capped and purged with N_2 before addition of MeCN (200 µL, 0.5 M) and TFA (1.5

µL, 0.02 mmol, 20 mol%). The reaction mixture was heated to 65 °C and left to stir for 16 h before being quenched by sat. aq. $NaHCO_3$ solution (2 mL) and diluted with EtOAc (2 mL). The phases were separated and the aqueous phase was washed with EtOAc (2 mL × 2). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the crude product *via* flash column chromatography (silica gel, EtOAc:petroleum ether, 20:80) gave the desired product as a pale yellow solid (36.4 mg, 84%). The enantiomeric ratio (96:4) was determined by chiral HPLC in comparison with the racemate.

3.6.3 Characterization Data for Compounds

2-(1-chlorovinyl)quinoline 3.1



Chemical Formula: $C_{11}H_8ClN$
Exact Mass: 189.0345
Molecular Weight: 189.6420

Prepared according to General Procedure A using 2-vinylquinoline (3.88 g, 25.0 mmol, 1.0 equiv), $KMnO_4$ (15.8 g, 250 mmol, 10 equiv), conc. HCl (20.9 mL, 250 mmol, 10 equiv), KOtBu (5.61 g, 50.0 mmol, 2 equiv) and DCM (100 mL). The reaction mixture was subjected to the purification outlined in General Procedure A (silica gel, Et_2O:Hex, 1:99) to afford the desired product as a yellow solid (1.28 g, 27%).

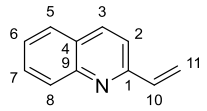
υ_{max} (film): 1589, 1489, 750 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (dd, *J* = 8.7, 0.9 Hz, 1H, C(3)*H*), 8.13 (d, *J* = 8.5 Hz, 1H, C(8)*H*), 7.88 (d, *J* = 8.6 Hz, 1H, C(2)*H*), 7.82 (dd, *J* = 8.3, 1.4 Hz, 1H, C(5)*H*), 7.74 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H, C(7)*H*), 7.56 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H, C(8)*H*), 6.64 (d, *J* = 1.4 Hz, 1H, C(11)*H*), 5.85 (d, *J* = 1.3 Hz, 1H, C(11)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 153.3 (*C*(1)), 147.5 (*C*(9)), 139.1 (*C*(10)), 137.1 (*C*(3)), 130.2 (*C*(7)), 129.9 (*C*(8)), 127.8 (*C*(4)), 127.5 (*C*(5)), 127.3 (*C*(6)), 118.7 (*C*(2)), 117.4 (*C*(11)).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{11}H_9{}^{35}ClN$) requires 190.0418 m/z, found 190.0412 m/z.

2-Vinylquinoline 3.9



Chemical Formula: $C_{11}H_9N$
Exact Mass: 155.0735
Molecular Weight: 155.2000

Prepared according to adapted literature procedure.[98]

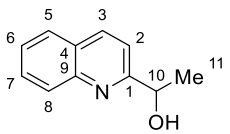
A 500 mL oven-dried round bottom flask equipped with a reflux condenser was charged with quinoline-2-carboxaldehyde (15.7 g, 100 mmol, 1.0 equiv), potassium carbonate (22.1 g, 160 mmol, 1.6 equiv), and methyltriphenylphosphonium bromide (42.9 g, 120 mmol, 1.2 equiv) in anhydrous tetrahydrofuran (150 mL), and heated at reflux for 16 hours. The reaction mixture was cooled, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (15% EtOAc/Hex) to give 2-vinylquinoline as a yellow liquid (14.5 g, 93%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.6 Hz, 1H, C(3)*H*), 8.08 (d, *J* = 8.5 Hz, 1H, C(8)*H*), 7.78 (d, *J* = 8.1 Hz, 1H, C(5)*H*), 7.70 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H, C(7)*H*), 7.61 (d, *J* = 8.6 Hz, 1H, C(2)*H*), 7.50 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H, C(6)*H*), 7.05 (dd, *J* = 17.7, 10.9 Hz, 1H, C(10)*H*), 6.29 (dd, *J* = 17.7, 0.8 Hz, 1H, C(11)H_{trans}), 5.68 (dd, *J* = 10.9, 0.8 Hz, 1H, C(11)H_{cis}).

^{13}C NMR (126 MHz, $CDCl_3$): δ 156.2, 148.1, 138.1, 136.5, 129.8, 129.5, 127.6, 126.4, 120.0, 118.5.

Spectroscopic data in agreement with literature values.[98]

1-(Quinolin-2-yl)ethan-1-ol 3.10



Chemical Formula: $C_{11}H_{11}NO$
Exact Mass: 173.0841
Molecular Weight: 173.2150

Prepared according to adapted literature procedure.[45]

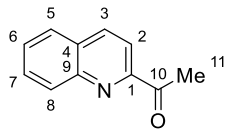
An oven dried 250 mL round bottomed flask was charged with quinoline-2-carbaldehyde (1.57 g, 10 mmol, 1 equiv), and THF (100 mL, 0.1 M) under nitrogen. The mixture was cooled to 0 °C with ice bath and methylmagnesium bromide (6.7 mL, 3 M solution in diethyl ether, 20.0 mmol, 2.0 equiv) was added dropwise. The reaction mixture was then allowed to stir at 0 °C for 1 h before stirring at rt for 3 h. The resulting mixture was cooled to 0 °C and quenched by addition of 2 M HCl (5 mL) and diluted with brine (100 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (100 mL x 2). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the crude product through flash chromatography (silica gel, EtOAc:petroleum ether, 20:80) gave the desired product as a pale yellow solid (1.69 g, 98%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.6 Hz, 1H, C(3)*H*), 8.07 (d, *J* = 8.3 Hz, 1H, C(8)*H*), 7.82 (d, *J* = 8.3 Hz, 1H, C(5)*H*), 7.72 (ddd, *J* = 8.4, 7.0, 1.5 Hz, 1H, C(7)*H*), 7.54 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H, C(6)*H*), 7.35 (d, *J* = 8.5 Hz, 1H, C(2)*H*), 5.01 – 5.06 (m, 2H, C(10)*H*, O*H*), 1.58 (d, *J* = 6.4 Hz, 3H, C(11)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 163.0, 146.2, 136.8, 129.5, 128.5, 127.4, 127.2, 126.1, 117.8, 68.9, 23.9.

Spectroscopic data in agreement with literature values.[87]

1-(quinolin-2-yl)ethan-1-one 3.11



Chemical Formula: $C_{11}H_9NO$
Exact Mass: 171.0684
Molecular Weight: 171.1990

Prepared according to adapted literature procedure.[45]

An oven dried 250 mL round bottomed flask was charged with 1-(quinolin-2-yl)ethan-1-ol (1.68 g, 9.70 mmol, 1.0 equiv), MnO_2 (5.10 g, 58.7 mmol, 6.0 equiv) and PhMe (100 mL). The mixture was allowed to stir at r.t. for 16 h before filtration through a short pad of celite. The filter cake was rinsed with ethyl acetate (50 mL x 2). The organic phases

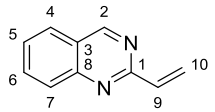
were combined and concentrated *in vacuo*. Purification of the crude product through flash chromatography (silica gel, EtOAc:petroleum ether, 10:90) gave the desired product as a pale yellow solid (1.49 g, 90%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (d, *J* = 8.0 Hz, 1H, C(3)*H*), 8.20 (d, *J* = 8.8 Hz, 1H, C(8)*H*), 8.13 (d, *J* = 8.8 Hz, 1H, C(5)*H*), 7.87 (d, *J* = 8.0 Hz, 1H, C(2)*H),* 7.79 (td, *J* = 6.8, 1.2 Hz, 1H, C(7)*H*), 7.65 (td, *J* = 8.0, 1.2 Hz, 1H, C(6)*H*), 2.88 (s, 3H, C(11)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 200.7, 153.3, 147.3, 136.8, 130.6, 130.0, 129.5, 128.5, 127.6, 117.9, 25.5.

Spectroscopic data in agreement with literature values.[88]

2-Vinylquinazoline 3.13



Chemical Formula: $C_{10}H_8N_2$
Exact Mass: 156.0687
Molecular Weight: 156.1880

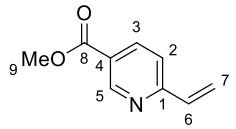
Prepared according to General Procedure D using 2-chloroquinazoline (823 mg, 5.00 mmol, 1.0 equiv), vinylboronic acid pinacol ester (847 mg, 5.50 mmol, 1.1 equiv), palladium(II) acetate (44.9 mg, 0.20 mmol, 4 mol%), SPhos (164 mg, 0.40 mmol, 8 mol%), potassium phosphate (3.18 g, 15.0 mmol, 3.0 equiv), water (450 µL, 25.0 mmol, 5.0 equiv), and 1,4-dioxane (20 mL) at 80 °C for 3 h. The reaction mixture was subjected to the purification outlined in General Procedure D (silica gel, EtOAc:Hexane, 10:90) to afford the desired product as a yellow liquid (614 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$): 9.37 (s, 1H, C(2)*H*), 8.01 (d, *J* = 8.2 Hz, 1H, C(4)*H*), 7.92 – 7.86 (m, 2H, C(5)*H*, C(7)*H*), 7.63 – 7.58 (m, 1H, C(6)*H*), 7.05 (dd, *J* = 17.3, 10.5 Hz, 1H, C(9)*H*), 6.79 (d, *J* = 17.3 Hz, 1H, C(10)H_{trans}), 5.85 (d, *J* = 10.5 Hz, 1H, C(10)H_{cis}).

^{13}C NMR (126 MHz, $CDCl_3$): 160.9, 160.4, 150.5, 137.1, 134.3, 128.4, 127.5, 127.3, 124.4, 123.7.

Spectroscopic data in agreement with literature values.[109]

Methyl 6-vinylnicotinate 3.15



Chemical Formula: $C_9H_9NO_2$
Exact Mass: 163.0633
Molecular Weight: 163.1760

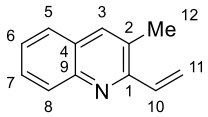
Prepared according to General Procedure D using methyl 6-bromonicotinate (2.16 g, 10.0 mmol, 1.0 equiv), vinylboronic acid pinacol ester (1.69 g, 11.0 mmol, 1.1 equiv), palladium(II) acetate (89.8 mg, 0.40 mmol, 4 mol%), SPhos (328 mg, 0.80 mmol, 8 mol%), potassium phosphate (6.37 g, 15.0 mmol, 3.0 equiv), water (900 µL, 25.0 mmol, 5.0 equiv), and 1,4-dioxane (40 mL) at 80 °C for 3 h. The reaction mixture was subjected to the purification outlined in General Procedure D (silica gel, EtOAc:Hexane, 10:90) to afford the desired product as a yellow liquid (1.30 g, 80%).

^{1}H NMR (MHz, $CDCl_3$): 8.87 (d, *J* = 2.0 Hz, 1H, C(5)*H*), 7.91 (dd, *J* = 8.2, 2.2 Hz, 1H, C(3)*H*), 7.09 (d, *J* = 8.2 Hz, 1H, C(2)*H*), 6.57 (dd, *J* = 17.4, 10.8 Hz, 1H, C(6)*H*), 6.09 (dd, *J* = 17.4, 1.1 Hz, 1H, C(7)H_{trans}), 5.33 (dd, *J* = 10.8, 1.1 Hz, 1H, C(7)H_{cis}), 3.65 (s, 3H, C(9)*H*).

^{13}C NMR (MHz, $CDCl_3$): 165.1, 158.7, 150.3, 137.1, 135.8, 124.0, 120.5, 120.3, 51.8.

Spectroscopic data in agreement with literature values.[110]

3-Methyl-2-vinylquinoline 3.17



Chemical Formula: $C_{12}H_{11}N$
Exact Mass: 169.0891
Molecular Weight: 169.2270

Following General Procedure D using 2-chloro-3-methylquinoline (888 mg, 5.00 mmol, 1.0 equiv), vinylboronic acid pinacol ester (847 mg, 5.50 mmol, 1.1 equiv), palladium(II) acetate (44.9 mg, 0.20 mmol, 4 mol%), SPhos (164 mg, 0.40 mmol, 8 mol%), potassium phosphate (3.18 g, 15.0 mmol, 3.0 equiv), water (450 µL, 25.0 mmol, 5.0 equiv), and 1,4-dioxane (20 mL) at 80 °C for 3 h. The reaction mixture was subjected to the purification

outlined in General Procedure D (silica gel, EtOAc:Hexane, 10:90) to afford the desired product as a yellow liquid (620 mg, 73% yield).

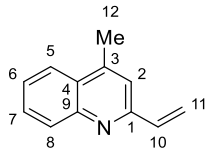
υ_{max} (film): 1489, 1423 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): 8.07 (dd, *J* = 8.5, 1.0 Hz, 1H, C(8)*H*), 7.87 (app. t, *J* = 1.0 Hz, 1H, C(3)*H*), 7.70 (dd, *J* = 8.2, 1.4 Hz, 1H, C(5)*H*), 7.62 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H, C(7)*H*), 7.46 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H, C(6)*H*), 7.17 (dd, *J* = 17.0, 10.7 Hz, 1H, C(10)*H*), 6.55 (dd, *J* = 17.0, 2.1 Hz, 1H, C(11)H_{trans}), 5.64 (dd, *J* = 10.7, 2.1 Hz, 1H, C(11)H_{cis}), 2.53 (d, *J* = 1.0 Hz, 3H, C(12)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): 155.2 (*C*(1)), 146.9 (*C*(4)), 136.4 (*C*(3)), 133.6 (*C*(10)), 129.3 (*C*(8)), 129.2 (*C*(2)), 128.8 (*C*(7)), 128.1 (*C*(4)), 126.8 (*C*(5)), 126.3 (*C*(6)), 121.5 (*C*(11)), 19.5 (*C*(12)).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{12}H_{12}N$) requires 170.0964 m/z , found 170.0962 m/z.

4-Methyl-2-vinylquinoline 3.18



Chemical Formula: $C_{12}H_{11}N$
Exact Mass: 169.0891
Molecular Weight: 169.2270

Prepared according to General Procedure D using 2-chloro-4-methylquinoline (888 mg, 5.00 mmol, 1.0 equiv), vinylboronic acid pinacol ester (847 mg, 5.50 mmol, 1.1 equiv), palladium(II) acetate (44.9 mg, 0.20 mmol, 4 mol%), SPhos (164 mg, 0.40 mmol, 8 mol%), potassium phosphate (3.18 g, 15.0 mmol, 3.0 equiv), water (450 µL, 25.0 mmol, 5.0 equiv), and 1,4-dioxane (20 mL) at 80 °C for 3 h. The reaction mixture was subjected to the purification outlined in General Procedure D (silica gel, EtOAc:Hexane, 10:90) to afford the desired product as a yellow liquid (707 mg, 84%).

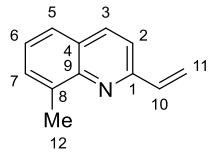
υ_{max} (film): 1506, 1416 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): 8.06 (ddd, *J* = 8.5, 1.2, 0.5 Hz, 1H, C(8)*H*), 7.93 (d, *J* = 8.3 Hz, 1H, C(5)*H*), 7.68 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H, C(7)*H*), 7.51 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H, C(6)*H*), 7.43 (s, 1H, C(2)*H*), 6.99 (dd, *J* = 17.7, 10.9 Hz, 1H, C(10)*H*), 6.26 (dd, *J* = 17.7, 0.8 Hz, 1H, C(11)H_{trans}), 5.64 (dd, *J* = 10.9, 0.8 Hz, 1H, C(11)H_{cis}), 2.69 (s, 3H, C(12)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): 155.8 (*C*(1)), 147.9 (*C*(9)), 144.5 (*C*(3)), 138.2 (*C*(10)), 130.0 (*C*(8)), 129.4 (*C*(7)), 127.7 (*C*(4)), 126.2 (*C*(6)), 123.7 (*C*(5)), 119.7 (*C*(11)), 119.1 (*C*(2)), 19.0 (*C*(12)).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{12}H_{12}N$) requires m/z 170.0964, found m/z 170.0959.

8-Methyl-2-vinylquinoline 3.19



Chemical Formula: $C_{12}H_{11}N$
Exact Mass: 169.0891
Molecular Weight: 169.2270

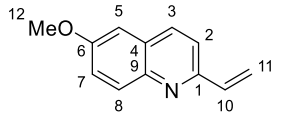
Prepared according to General Procedure D using 2-chloro-8-methylquinoline (888 mg, 5.00 mmol, 1.0 equiv), vinylboronic acid pinacol ester (847 mg, 5.50 mmol, 1.1 equiv), palladium(II) acetate (44.9 mg, 0.20 mmol, 4 mol%), SPhos (164 mg, 0.40 mmol, 8 mol%), potassium phosphate (3.18 g, 15.0 mmol, 3.0 equiv), water (450 µL, 25.0 mmol, 5.0 equiv), and 1,4-dioxane (20 mL) at 80 °C for 3 h. The reaction mixture was subjected to the purification outlined in General Procedure D (silica gel, EtOAc:Hexane, 10:90) to afford the desired product as a yellow liquid (683 mg, 81%).

^{1}H NMR (500 MHz, $CDCl_3$): 8.07 (d, *J* = 8.5 Hz, 1H, C(2)*H*), 7.62 (dd, *J* = 8.2, 1.4 Hz, 1H, C(5)*H*), 7.58 – 7.52 (m, 2H, C(2)*H*, C(7)*H*), 7.39 (dd, *J* = 8.1, 7.0 Hz, 1H, C(6)*H*), 7.08 (dd, *J* = 17.6, 10.8 Hz, 1H, C(10)*H*), 6.37 (dd, *J* = 17.6, 1.1 Hz, 1H, C(11)H_{trans}), 5.64 (dd, *J* = 10.9, 1.1 Hz, 1H, C(11)H_{cis}), 2.85 (s, 3H, C(12)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): 154.8, 147.1, 138.4, 137.5, 136.6, 129.8, 127.5, 126.1, 125.5, 119.3, 118.5, 18.0.

Spectroscopic data in agreement with literature values.[111]

6-Methoxy-2-vinylquinoline 3.20



Chemical Formula: $C_{12}H_{11}NO$
Exact Mass: 185.0841
Molecular Weight: 185.2260

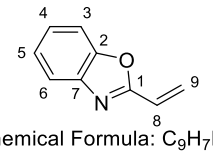
Prepared according to General Procedure D using 2-chloro-6-methoxyquinoline (968 mg, 5.00 mmol, 1.0 equiv), vinylboronic acid pinacol ester (847 mg, 5.50 mmol, 1.1 equiv), palladium(II) acetate (44.9 mg, 0.20 mmol, 4 mol%), SPhos (164 mg, 0.40 mmol, 8 mol%), potassium phosphate (3.18 g, 15.0 mmol, 3.0 equiv), water (450 µL, 25.0 mmol, 5.0 equiv), and 1,4-dioxane (20 mL) at 80 °C for 3 h. The reaction mixture was subjected to the purification outlined in General Procedure D (silica gel, EtOAc:Hexane, 10:90) to afford the desired product as a yellow liquid (745 mg, 88%).

^{1}H NMR (500 MHz, $CDCl_3$): 7.98 (d, *J* = 8.6 Hz, 1H, C(3)*H*), 7.95 (d, *J* = 9.2 Hz, 1H, C(8)*H*), 7.55 (d, *J* = 8.5 Hz, 1H, C(2)*H*), 7.34 (dt, *J* = 9.2, 2.1 Hz, 1H, C(7)*H*), 7.04 – 6.95 (m, 2H, C(5)*H*, C(10)*H*), 6.20 (dd, *J* = 17.7, 1.0 Hz, 1H, C(11)H_{trans}), 5.59 (dd, *J* = 11.0, 0.9 Hz, 1H, C(11)H_{cis}), 3.91 (s, 3H, C(12)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): 157.8, 154.0, 144.1, 138.0, 135.2, 130.9, 128.6, 122.4, 118.8, 118.7, 105.3, 55.6.

Spectroscopic data in agreement with literature values.[111]

2-Vinylbenzo[*d*]oxazole 3.21



Chemical Formula: C_9H_7NO
Exact Mass: 145.0528
Molecular Weight: 145.1610

Prepared according to General Procedure D using 2-chlorobenzoxazole (768 mg, 5.00 mmol, 1.0 equiv), vinylboronic acid pinacol ester (847 mg, 5.50 mmol, 1.1 equiv),

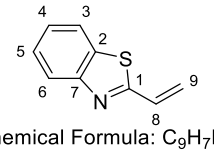
palladium(II) acetate (44.9 mg, 0.20 mmol, 4 mol%), SPhos (164 mg, 0.40 mmol, 8 mol%), potassium phosphate (3.18 g, 15.0 mmol, 3.0 equiv), water (450 µL, 25.0 mmol, 5.0 equiv), and 1,4-dioxane (20 mL) at 80 °C for 3 h. The reaction mixture was subjected to the purification outlined in General Procedure D (silica gel, EtOAc:Hexane, 10:90) to afford the desired product as a yellow liquid (382 mg, 53%).

^{1}H NMR (500 MHz, $CDCl_3$): 7.74 – 7.68 (m, 1H, C(6)*H*), 7.55 – 7.44 (m, 1H, C(3)*H*), 7.36 – 7.31 (m, 2H, C(4)*H*, C(5)*H*), 6.75 (dd, *J* = 17.7, 11.1 Hz, 1H, C(8)*H*), 6.46 (d, *J* = 17.6 Hz, 1H, C(9)H_{trans}), 5.84 (d, *J* = 11.1 Hz, 1H, C(9)H_{cis}).

^{13}C NMR (126 MHz, $CDCl_3$): 162.2, 150.4, 141.9, 125.6, 125.5, 124.6, 124.0, 120.3, 110.6.

Spectroscopic data in agreement with literature values.[112]

2-Vinylbenzo[*d*]thiazole 3.22



Chemical Formula: C_9H_7NS
Exact Mass: 161.0299
Molecular Weight: 161.2220

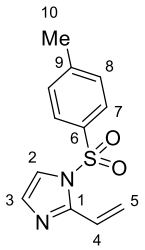
Prepared according to General Procedure D using 2-bromobenzothiazole (1.07 g, 5.00 mmol, 1.0 equiv), vinylboronic acid pinacol ester (847 mg, 5.50 mmol, 1.1 equiv), palladium(II) acetate (44.9 mg, 0.20 mmol, 4 mol%), SPhos (164 mg, 0.40 mmol, 8 mol%), potassium phosphate (3.18 g, 15.0 mmol, 3.0 equiv), water (450 µL, 25.0 mmol, 5.0 equiv), and 1,4-dioxane (20 mL) at 80 °C for 3 h. The reaction mixture was subjected to the purification outlined in General Procedure D (silica gel, EtOAc:Hexane, 10:90) to afford the desired product as a yellow liquid (770 mg, 96%).

^{1}H NMR (500 MHz, $CDCl_3$): 8.00 (d, *J* = 8.6 Hz, 1H, C(6)*H*), 7.84 (d, *J* = 8.0 Hz, 1H, C(3)*H*), 7.46 (t, *J* = 7.7 Hz, 1H, C(5)*H),* 7.37 (t, *J* = 7.6 Hz, 1H, C(4)*H*), 7.04 (dd, *J* = 17.5, 10.9 Hz, 1H, C(8)*H*), 6.18 (d, *J* = 17.5 Hz, 1H, C(9)H_{trans}), 5.76 (d, *J* = 10.9 Hz, 1H, C(9)H_{cis}).

^{13}C NMR (126 MHz, $CDCl_3$): 167.3, 153.7, 134.4, 131.5, 126.4, 125.7, 123.4, 123.3, 121.7.

Spectroscopic data in agreement with literature values.[111]

1-Tosyl-2-vinyl-1*H*-imidazole 3.23



Chemical Formula: $C_{12}H_{12}N_2O_2S$
Exact Mass: 248.0619
Molecular Weight: 248.3000

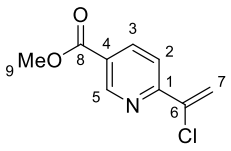
Prepared according to General Procedure D using 1-tosyl-2-bromo-1H-imidazole (602 mg, 2.00 mmol, 1.0 equiv), vinylboronic acid pinacol ester (339 mg, 2.20 mmol, 1.1 equiv), palladium(II) acetate (18.0 mg, 0.08 mmol, 4 mol%), SPhos (65.7 mg, 0.16 mmol, 8 mol%), potassium phosphate (1.27 g, 6.00 mmol, 3.0 equiv), water (180 µL, 10.0 mmol, 5.0 equiv), and 1,4-dioxane (8 mL) at 80 °C for 3 h. The reaction mixture was subjected to the purification outlined in General Procedure D (silica gel, EtOAc:Hexane, 10:90) to afford the desired product as a yellow solid (325 mg, 65%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.5 Hz, 2H, C(7)*H*), 7.44 (d, *J* = 1.6 Hz, 1H, C(2)*H*), 7.34 (d, *J* = 8.0 Hz, 2H, C(8)*H*), 7.13 (dd, *J* = 17.2, 11.1 Hz, 1H, C(4)*H*), 7.03 (d, *J* = 1.6 Hz, 1H, C(3)*H*), 6.28 (d, *J* = 17.1 Hz, 1H, C(5)H_{trans}), 5.55 (dd, *J* = 11.1, 1.1 Hz, 1H, C(5)H_{cis}), 2.43 (s, 3H, C(10)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 146.3, 145.9, 135.0, 130.4, 128.9, 127.3, 122.9, 122.1, 119.6, 21.7.

Spectroscopic data in agreement with literature values.[113]

Methyl 6-(1-chlorovinyl)nicotinate 3.28



Chemical Formula: $C_9H_8ClNO_2$
Exact Mass: 197.0244
Molecular Weight: 197.6180

Prepared according to General Procedure A using methyl 6-vinylnicotinate (4.08 g, 25.0 mmol, 1.0 equiv), $KMnO_4$ (15.8 g, 250 mmol, 10 equiv), conc. HCl (20.9 mL, 250 mmol, 10 equiv), KOtBu (5.61 g, 50.0 mmol, 2 equiv) and DCM (100 mL). The reaction mixture was subjected to the purification outlined in General Procedure A (silica gel, Et_2O:Hex, 1:99) to afford the desired product as a yellow solid (1.38 g, 28%).

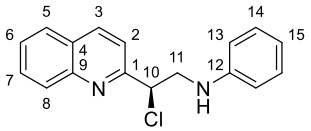
υ_{max} (film): 1730, 1296, 1285, 1125, 791 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): 9.17 (d, *J* = 1.6 Hz, 1H, C(5)*H*), 8.34 (dd, *J* = 8.3, 2.1 Hz, 1H, C(3)*H*), 7.84 (d, *J* = 8.3 Hz, 1H, C(2)*H*), 6.70 (d, *J* = 0.9 Hz, 1H, C(7)*H*), 5.82 (d, *J* = 0.9 Hz, 1H, C(7)*H*), 3.97 (s, 3H, C(9)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): 165.5 (*C*(8)), 156.6 (*C*(1)), 150.4 (*C*(5)), 138.4 (*C*(3)), 137.7 (*C*(6)), 125.6 (*C*(4)), 120.4 (*C*(2)), 118.6 (*C*(7)), 52.6 (*C*(9)).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_9H_9{}^{35}ClNO_2$) requires m/z 198.0316, found m/z 198.0311.

(*R*)-*N*-(2-chloro-2-(quinolin-2-yl)ethyl)aniline 3.4



Chemical Formula: $C_{17}H_{15}ClN_2$
Exact Mass: 282.0924
Molecular Weight: 282.7710

Racemic:

Prepared according to General Procedure B using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), aniline (23 µL, 0.25 mmol, 1.0 equiv), TFA (3.8 µL, 0.05 mmol, 20 mol%), and THF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure B (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (62.3 mg, 88%).

Enantioenriched:

Prepared according to General Procedure C using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), aniline (23 µL, 0.25 mmol, 1.0 equiv), (S)-TCYP (12.4 mg, 12.5

µmol, 5 mol%), and 2-MeTHF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure C (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (55.9 mg, 79%). The enantiomeric ratio (97:3) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 3302, 1599, 1497, 770 cm^{-1}.

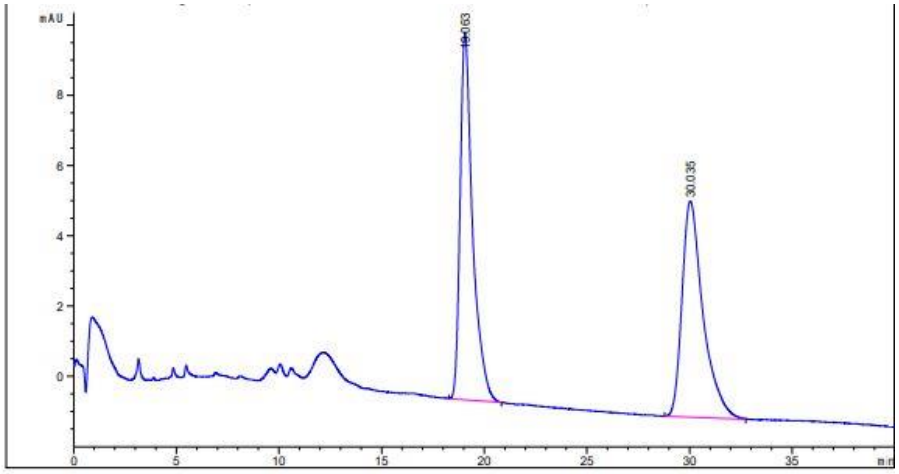
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.5 Hz, 1H, C(3)*H*), 8.14 (d, *J* = 8.5 Hz, 1H, C(8)*H*), 7.84 (d, *J* = 8.1 Hz, 1H, C(5)*H*), 7.81 – 7.74 (m, 1H, C(7)*H*), 7.64 – 7.55 (m, 2H, C(2)*H*, C(6)*H*), 7.21 – 7.14 (m, 2H, C(14)*H*), 6.73 (t, *J* = 7.3 Hz, 1H, C(15)*H*), 6.68 (d, *J* = 7.7 Hz, 2H, C(13)*H*), 5.38 (app. t, *J* = 6.7 Hz, 1H, C(10)*H*), 4.13 (dd, *J* = 14.0, 6.5 Hz, 1H, C(11)*H*), 3.88 (dd, *J* = 14.0, 7.0 Hz, 1H, C(11)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 158.1 (*C*(1)), 147.2 (*C*(9)), 147.1 (*C*(12)), 137.6 (*C*(3)), 130.2 (*C*(7)), 129.5 (*C*(14)), 129.5 (*C*(8)), 127.8 (*C*(4)), 127.7 (*C*(5)), 127.3 (*C*(6)), 120.5 (*C*(2)), 118.3 (*C*(15)), 113.5 (*C*(13)), 61.0 (*C*(10)), 49.6 (*C*(11)).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{17}H_{16}{}^{35}ClN_2$) requires 283.0997 m/z, found 283.0994 m/z.

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 50:50 hexane:isopropanol, 250 nm, t_{major} = 19.4 min, t_{minor} = 30.9 min.

$[\alpha]_D^{23}$ −72.8° (*c* = 1.0, $CHCl_3$).

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Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
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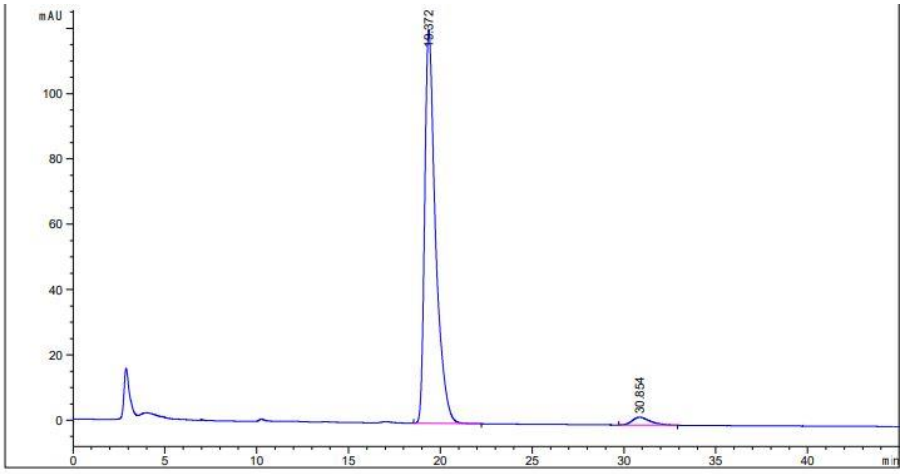


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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
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   2  30.854 BB    0.8721  163.87349    2.40941   3.1988
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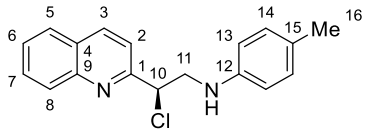
(*R*)-*N*-(2-chloro-2-(quinolin-2-yl)ethyl)-4-methylaniline 3.39



Chemical Formula: $C_{18}H_{17}ClN_2$
Exact Mass: 296.1080
Molecular Weight: 296.7980

Racemic:

Prepared according to General Procedure B using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), *p*-toluidine (26.8 mg, 0.25 mmol, 1.0 equiv), TFA (3.8 µL, 0.05 mmol, 20 mol%), and THF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure B (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (41.0 mg, 55%).

Enantioenriched:

Prepared according to General Procedure C using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), *p*-toluidine (26.8 mg, 0.25 mmol, 1.0 equiv), (S)-TCYP (12.4 mg, 12.5 µmol, 5 mol%), and 2-MeTHF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure C (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (62.8 mg, 85%). The enantiomeric ratio (97:3) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 1616, 1527, 770 cm^{-1}.

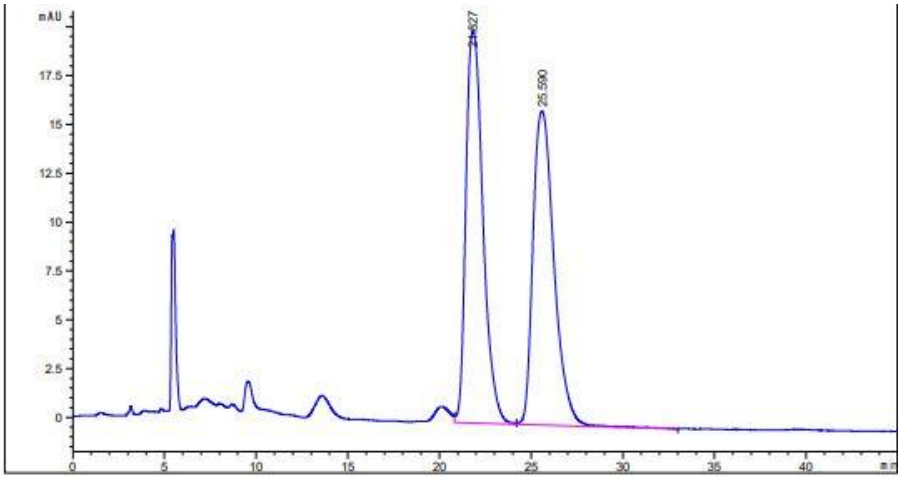
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.5 Hz, 1H, C(3)*H*), 8.13 (d, *J* = 8.6 Hz, 1H, C(8)*H*), 7.83 (d, *J* = 8.1 Hz, 1H, C(5)*H*), 7.76 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H, C(7)*H*), 7.62 – 7.55 (m, 2H, C(2)*H*, C(6)*H*), 7.01 (d, *J* = 8.1 Hz, 2H, C(14)*H*), 6.66 – 6.59 (m, 2H, C(13)*H*), 5.36 (app. t, *J* = 6.7 Hz, 1H, C(10)*H*), 4.11 (dd, *J* = 14.0, 6.4 Hz, 1H, C(11)*H*), 3.86 (dd, *J* = 14.0, 7.1 Hz, 1H, C(11)*H*), 2.26 (s, 3H, C(16)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 158.2 (*C*(1)), 147.4 (*C*(9)), 144.8 (*C*(12)), 137.4 (*C*(3)), 130.0 (*C*(7)), 130.0 (*C*(14)), 129.6 (*C*(8)), 127.7 (*C*(4), *C*(5)), 127.6 (*C*(15)), 127.2 (*C*(6)), 120.5 (*C*(2)), 113.7 (*C*(13)), 61.3 (*C*(10)), 50.0 (*C*(11)), 20.5 (*C*(16)).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{18}H_{18}{}^{35}ClN_2$) requires 297.1153 m/z, found 297.1151 m/z.

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 50:50 hexane:isopropanol, 250 nm, t_{major} = 22.0 min, t_{minor} = 25.9 min.

$[\alpha]_D^{23}$ −83.7° (*c* = 1.0, $CHCl_3$).

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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

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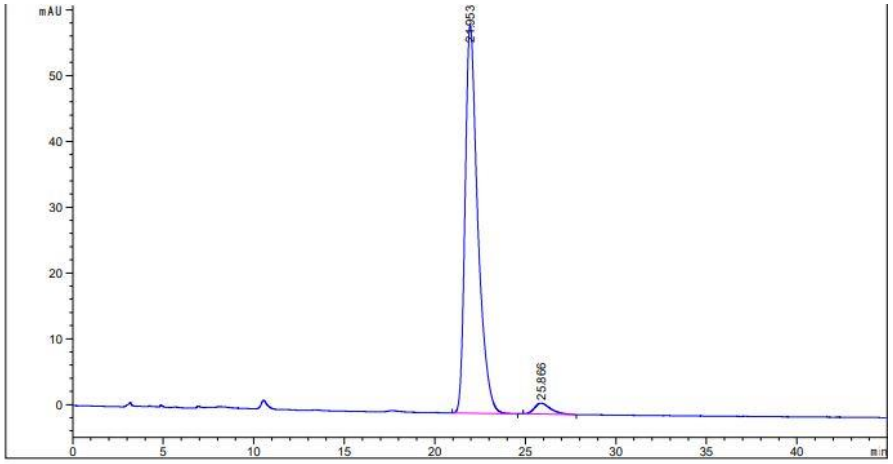


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
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   1  21.953 BB    0.7246 2868.87549   58.99772  96.5300
   2  25.866 BB    0.9038  103.12813    1.65677   3.4700
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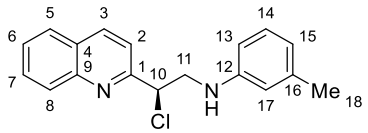
(*R*)-*N*-(2-chloro-2-(quinolin-2-yl)ethyl)-3-methylaniline 3.40



Chemical Formula: $C_{18}H_{17}ClN_2$
Exact Mass: 296.1080
Molecular Weight: 296.7980

Racemic:

Prepared according to General Procedure B using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), *m*-toluidine (26 µL, 0.25 mmol, 1.0 equiv), TFA (3.8 µL, 0.05 mmol, 20 mol%), and THF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure B (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (52.0 mg, 70%).

Enantioenriched:

Prepared according to General Procedure C using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), *m*-toluidine (26 µL, 0.25 mmol, 1.0 equiv), (S)-TCYP (12.4 mg, 12.5 µmol, 5 mol%), and 2-MeTHF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure C (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (74.2 mg, >99%). The enantiomeric ratio (97:3) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 3298, 1607, 1491, 768 cm^{-1}.

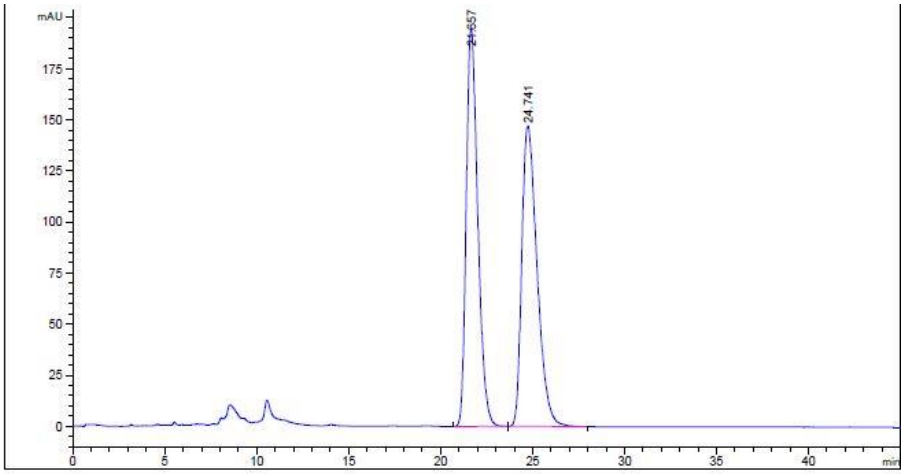
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.5 Hz, 1H, C(3)*H*), 8.15 (d, *J* = 8.5 Hz, 1H, C(8)*H*), 7.84 (d, *J* = 8.1 Hz, 1H, C(5)*H*), 7.77 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H, C(7)*H*), 7.63 – 7.56 (m, 2H, C(2)*H*, C(6)*H*), 7.11 – 7.03 (m, 1H, C(14)*H*), 6.56 (d, *J* = 7.5 Hz, 1H, C(15)*H*), 6.53 – 6.48 (m, 2H, C(13)*H*, C(17)*H*), 5.40 (app. t, *J* = 6.7 Hz, 1H, C(10)*H*), 4.12 (dd, *J* = 14.0, 6.6 Hz, 1H, C(11)*H*), 3.89 (dd, *J* = 14.0, 6.9 Hz, 1H, C(11)*H*), 2.26 (s, 3H, C(18)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 158.1 (*C*(1)), 147.0 (*C*(12)), 147.0 (*C*(9)), 139.3 (*C*(16)), 137.6 (*C*(3)), 130.2 (*C*(7)), 129.4 (*C*(8), *C*(14)), 127.7 (*C*(4)), 127.7 (*C*(5)), 127.3 (*C*(6)), 120.5 (*C*(2)), 119.3 (*C*(15)), 114.3 (*C*(17)), 110.6 (*C*(13)), 61.0 (*C*(10)), 49.7 (*C*(11)), 21.7 (*C*(18)).

HRMS (ESI): exact mass calculated for [M+H] ($C_{18}H_{18}{}^{35}ClN_2$) requires 297.1153 m/z, found m/z 297.1148.

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 50:50 hexane:isopropanol, 250 nm, t_{major} 21.4 = min, t_{minor} 24.2 = min.

$[\alpha]_D^{23}$ −62.2° (*c* = 1.0, $CHCl_3$).

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Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

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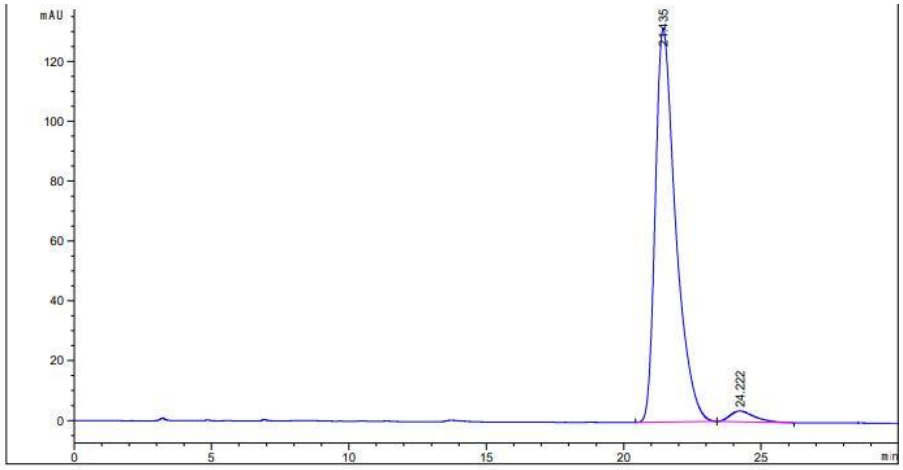


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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
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   1  21.435 BB    0.7719 6778.82275  131.46518  96.8647
   2  24.222 BB    0.8426  219.41626    3.60480   3.1353
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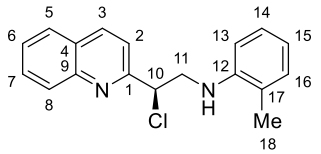
(*R*)-*N*-(2-chloro-2-(quinolin-2-yl)ethyl)-2-methylaniline 3.41



Chemical Formula: $C_{18}H_{17}ClN_2$
Exact Mass: 296.1080
Molecular Weight: 296.7980

Racemic:

Prepared according to General Procedure B using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), *o*-toluidine (27 µL, 0.25 mmol, 1.0 equiv), TFA (3.8 µL, 0.05 mmol, 20 mol%), and THF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure B (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow oil (44.5 mg, 60%).

Enantioenriched:

Prepared according to General Procedure C using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), *o*-toluidine (27 µL, 0.25 mmol, 1.0 equiv), (S)-TCYP (12.4 mg, 12.5 µmol, 5 mol%), and 2-MeTHF (500 µL, 0.5 M) for 39 h. The reaction mixture was subjected to the purification outlined in General Procedure C (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow oil (50.8 mg, 68%). The enantiomeric ratio (91:9) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 1605, 1505, 746 cm^{-1}.

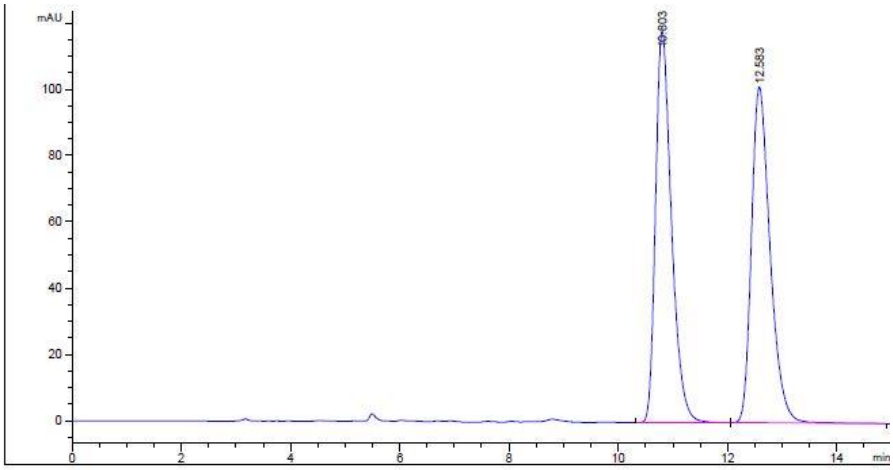
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.5 Hz, 1H), C(3)H, 8.13 (d, *J* = 8.5 Hz, 1H, C(8)*H*), 7.84 (d, *J* = 8.1 Hz, 1H, C(5)*H*), 7.80 – 7.73 (m, 1H, C(7)*H*), 7.63 (d, *J* = 8.5 Hz, 1H, C(2)*H*), 7.59 (t, *J* = 7.5 Hz, 1H, C(6)*H*), 7.15 (t, *J* = 7.7 Hz, 1H, C(14)*H*), 7.06 (d, *J* = 7.3 Hz, 1H, C(16)*H*), 6.76 (d, *J* = 8.0 Hz, 1H, C(13)*H*), 6.70 (t, *J* = 7.3 Hz, 1H, C(15)*H*), 5.41 (app. t, *J* = 6.7 Hz, 1H, C(10)*H*), 4.43 (s, 1H, N*H*), 4.14 (dd, *J* = 13.8, 6.5 Hz, 1H, C(11)*H*), 3.94 (dd, *J* = 13.8, 6.9 Hz, 1H, C(11)*H*), 2.10 (s, 3H, C(18)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 158.2 (*C*(1)), 147.3 (*C*(9)), 145.2 (*C*(12)), 137.5 (*C*(3)), 130.5 (*C*(16)), 130.2 (*C*(7)), 129.5 (*C*(8)), 127.7 (*C*(5)), 127.7 (*C*(4)), 127.3 (*C*(14)), 127.3 (*C*(6)), 122.8 (*C*(17)), 120.4 (*C*(2)), 117.8 (*C*(15)), 110.2 (*C*(16)), 61.0 (*C*(10)), 49.6 (*C*(11)), 17.5 (*C*(18)).

HRMS (ESI): exact mass calculated for [M+H] ($C_{18}H_{18}{}^{35}ClN_2$) requires 297.1153 m/z, found 297.1150 m/z.

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 50:50 hexane:isopropanol, 250 nm, t_{major} = 10.8 min, t_{minor} = 12.6 min.

$[\alpha]_D^{23}$ −58.9° (*c* = 1.0, $CHCl_3$).

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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

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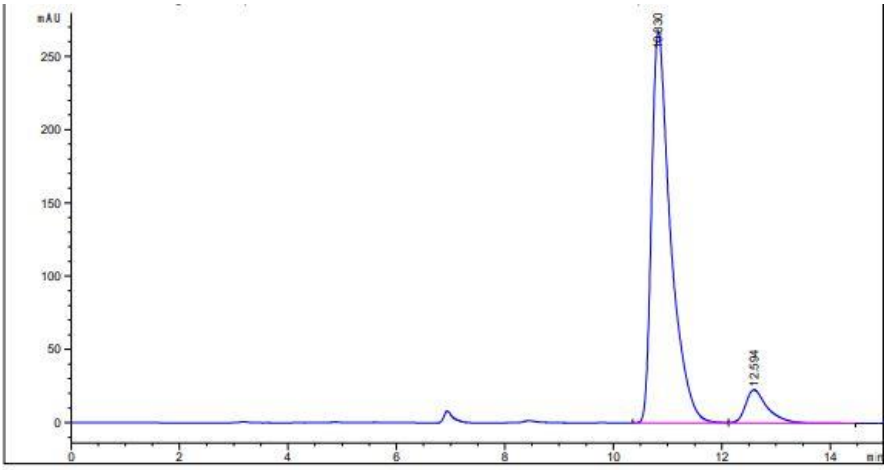


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
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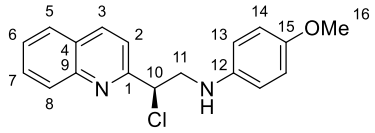
   1  10.830 BV    0.3588 6508.39795  266.82861  91.0994
   2  12.594 VB    0.4111  635.88080   22.70988   8.9006
```

(*R*)-*N*-(2-chloro-2-(quinolin-2-yl)ethyl)-4-methoxyaniline 3.42



Chemical Formula: $C_{18}H_{17}ClN_2O$
Exact Mass: 312.1029
Molecular Weight: 312.7970

Racemic:

Prepared according to General Procedure B using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), *p*-anisidine (30.8 mg, 0.25 mmol, 1.0 equiv), TFA (3.8 µL, 0.05 mmol, 20 mol%), and THF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure B (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow oil (32.8 mg, 42%).

Enantioenriched:

Prepared according to General Procedure C using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), *p*-anisidine (30.8 mg, 0.25 mmol, 1.0 equiv), (S)-TCYP (12.4 mg, 12.5 µmol, 5 mol%), and 2-MeTHF (500 µL, 0.5 M) for 39 h. The reaction mixture was subjected to the purification outlined in General Procedure C (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (48.6 mg, 62%). The enantiomeric ratio (97:3) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 3292, 1530, 1506, 772 cm^{-1}.

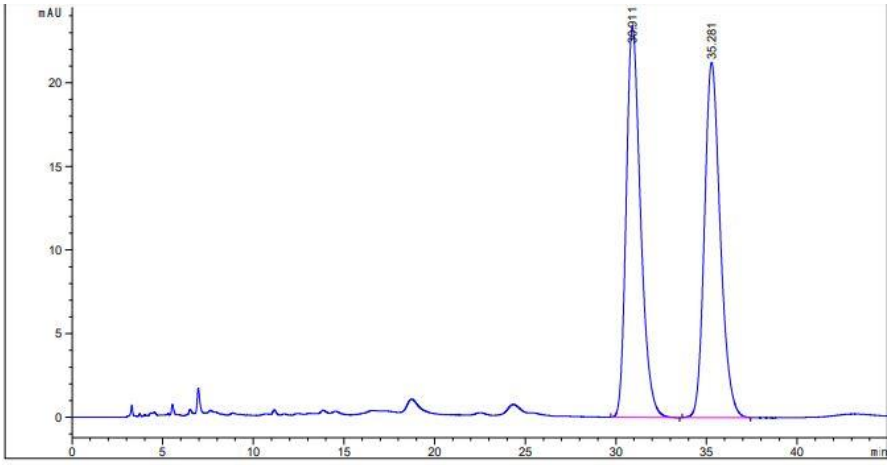
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.5 Hz, 1H, C(3)*H*), 8.11 (d, *J* = 8.5 Hz, 1H, C(8)*H*), 7.83 (d, *J* = 8.1 Hz, 1H, C(5)*H*), 7.75 (t, *J* = 7.7 Hz, 1H, C(7)*H*), 7.63 – 7.54 (m, 2H, C(2)*H*, C(6)*H*), 6.80 – 6.75 (m, 2H, C(13)*H*), 6.70 – 6.63 (m, 2H, C(14)*H*), 5.34 (app. t, *J* = 6.7 Hz, 1H, C(10)*H*), 4.09 (s, 1H, N*H*), 4.05 (dd, *J* = 14.0, 6.2 Hz, 1H, C(11)*H*), 3.81 (dd, *J* = 13.9, 7.2 Hz, 1H, C(11)*H*), 3.75 (s, 3H, C(16)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 158.2 (*C*(1)), 152.8 (*C*(15)), 147.5 (*C*(12)), 141.2 (*C*(9)), 137.4 (*C*(3)), 130.1 (*C*(7)), 129.6 (*C*(8)), 127.7 (*C*(4), *C*(5)), 127.2 (*C*(6)), 120.4 (*C*(2)), 115.2 (*C*(14)), 115.1 (*C*(13)), 61.5 (*C*(10)), 55.9 (*C*(16)), 50.9 (*C*(11)).

HRMS (ESI): exact mass calculated for [M+H] ($C_{18}H_{18}{}^{35}ClN_2O$) requires 313.1102 m/z, found 313.1101 m/z .

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 50:50 hexane:isopropanol, 250 nm, t_{major} = 39.5 min, t_{minor} = 34.5 min.

$[\alpha]_D^{23}$ −79.0° (*c* = 1.0, $CHCl_3$).

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Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
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   1  30.911 BB    0.8367 1287.89966   23.36685  50.0175
   2  35.281 BB    0.9252 1286.99915   21.24463  49.9825

Totals :                  2574.89880   44.61148
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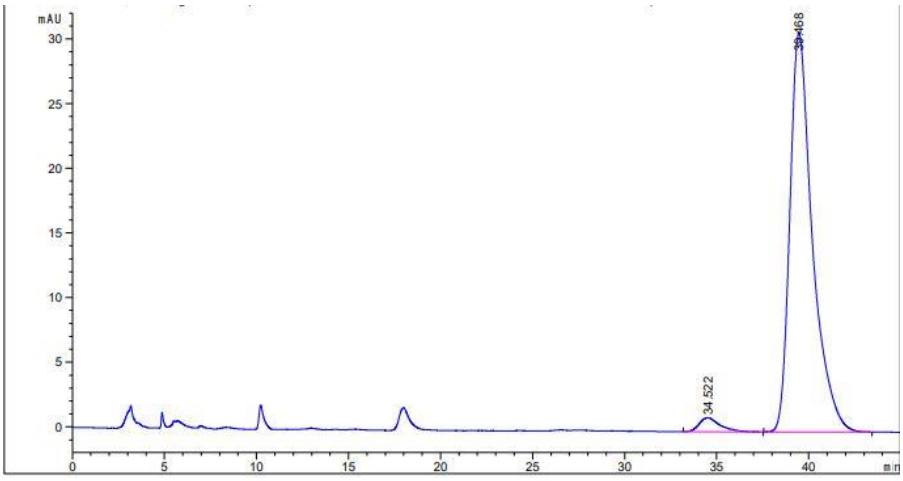


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  34.522 BB    1.0145   85.46322    1.08916   3.1477
   2  39.468 BB    1.2679 2629.61621   30.85828  96.8523
```
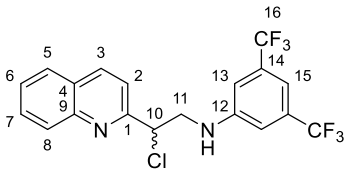

(*R*)-*N*-(2-chloro-2-(quinolin-2-yl)ethyl)-3,5-bis(trifluoromethyl)aniline 3.43



Chemical Formula: $C_{19}H_{13}ClF_6N_2$
Exact Mass: 418.0671
Molecular Weight: 418.7674

Racemic:

Prepared according to General Procedure B using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), 3,5-bis(trifluoromethyl)aniline (39 µL, 0.25 mmol, 1.0 equiv), TFA (3.8 µL, 0.05 mmol, 20 mol%), and THF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure B (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (26.2 mg, 25%).

Enantioenriched:

Prepared according to General Procedure C using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), 3,5-bis(trifluoromethyl)aniline (39 µL, 0.25 mmol, 1.0 equiv), (S)-TCYP (12.4 mg, 12.5 µmol, 5 mol%), and 2-MeTHF (500 µL, 0.5 M) at rt. The reaction mixture was subjected to the purification outlined in General Procedure C (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (75.5 mg, 72%). The enantiomeric ratio (50:50) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 1620, 1393, 1273, 1121, 681 cm^{-1}.

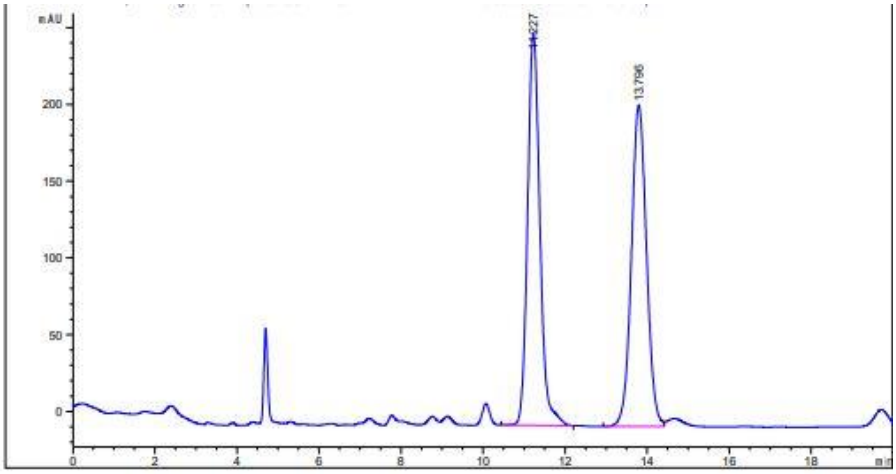
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (d, *J* = 8.5 Hz, 1H, C(3)*H*), 8.11 (d, *J* = 8.4 Hz, 1H, C(8)*H*), 7.84 (d, *J* = 8.1 Hz, 1H, C(5)*H*), 7.78 (t, *J* = 7.6 Hz, 1H, C(7)*H*), 7.67 – 7.56 (m, 2H, C(2)*H*, C(6)*H*), 7.15 (s, 1H, C(15)*H*), 7.00 (s, 2H, C(13)*H*), 5.34 (app. t, *J* = 6.3 Hz, 1H, C(10)*H*), 4.92 (s, 1H, N*H*), 4.17 (app. dt, *J* = 13.0, 6.1 Hz, 1H, C(11)*H*), 3.99 (app. dt, *J* = 13.1, 5.8 Hz, 1H, C(11)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 157.4 (*C*(1)), 148.1 (*C*(12)), 147.3 (*C*(9)), 137.8 (*C*(3)), 132.6 (q, ^{2}J = 32.7 Hz, *C*(14)), 130.4 (*C*(7)) , 129.5 (*C*(8)), 127.8 (*C*(4), C(5)), 127.5 (*C*(6)), 123.6 (q, ^{1}J = 272.7 Hz, *C*(16)), 120.4 (*C*(2)), 112.7 – 112.1 (m, *C*(13)), 111.1 – 110.9 (m, *C*(15)), 60.6 (*C*(10)), 49.0 (*C*(11)).

^{19}F NMR (470 MHz, $CDCl_3$): δ −63.17.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{19}H_{14}{}^{35}ClF_6N_2$) requires m/z 419.0744, found 419.0738 m/z .

HPLC analysis using a chiral column: Chiral Art Amylose-C 5 µm column, 1.0 mL/min, 99:1 hexane:isopropanol, 250 nm, t_1 = 14.9 min, t_2 = 12.1 min.

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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
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   2  13.796 BV    0.3962 5365.27246  209.58109  50.1414
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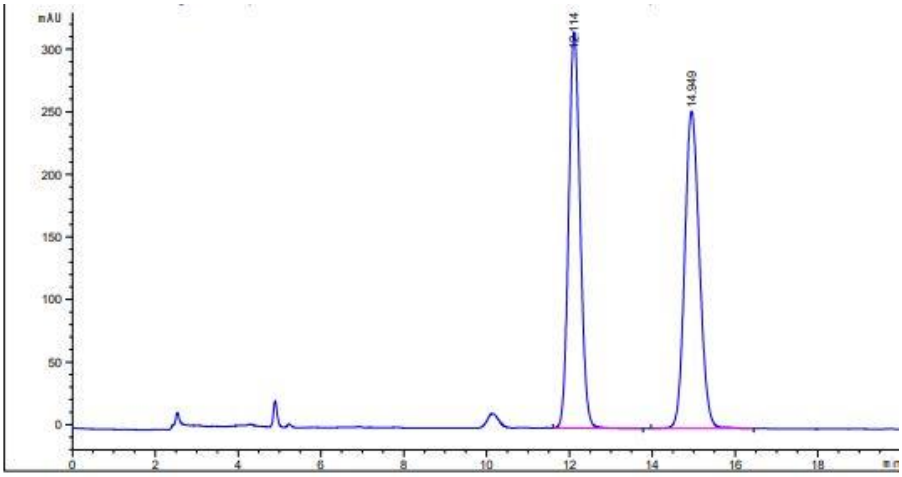


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
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   1  12.114 VB    0.2984 6080.30811  316.47055  49.3371
   2  14.949 BB    0.3819 6243.69092  253.55573  50.6629
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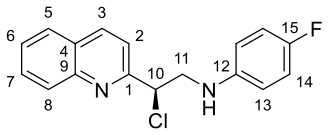
(*R*)-*N*-(2-chloro-2-(quinolin-2-yl)ethyl)-4-fluoroaniline 3.44



Chemical Formula: $C_{17}H_{14}ClFN_2$
Exact Mass: 300.0830
Molecular Weight: 300.7614

Racemic:

Prepared according to General Procedure B using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), 4-fluoroaniline (27 µL, 0.25 mmol, 1.0 equiv), TFA (3.8 µL, 0.05 mmol, 20 mol%), and THF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure B (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow oil (47.0 mg, 63%).

Enantioenriched:

Prepared according to General Procedure C using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), 4-fluoroaniline (27 µL, 0.25 mmol, 1.0 equiv), (S)-TCYP (12.4 mg, 12.5 µmol, 5 mol%), and 2-MeTHF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure C (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (66.0 mg, 88%). The enantiomeric ratio (96:4) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 1506, 1223, 770 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.5 Hz, 1H, C(3)*H*), 8.11 (d, *J* = 8.5 Hz, 1H, C(8)*H*), 7.83 (d, *J* = 8.1 Hz, 1H, C(5)*H*), 7.78 – 7.72 (m, 1H, C(7)*H*), 7.63 – 7.56 (m, 2H, C(2)*H*, C(6)*H*), 6.95 – 6.85 (m, 2H, C(13)*H*), 6.66 – 6.58 (m, 2H, C(14)*H*), 5.34 (app. t, *J* = 6.7 Hz, 1H, C(10)*H*), 4.26 (s, 1H, N*H*), 4.07 (dd, *J* = 14.0, 6.3 Hz, 1H, C(11)*H*), 3.83 (dd, *J* = 13.9, 7.1 Hz, 1H, C(11)*H*).

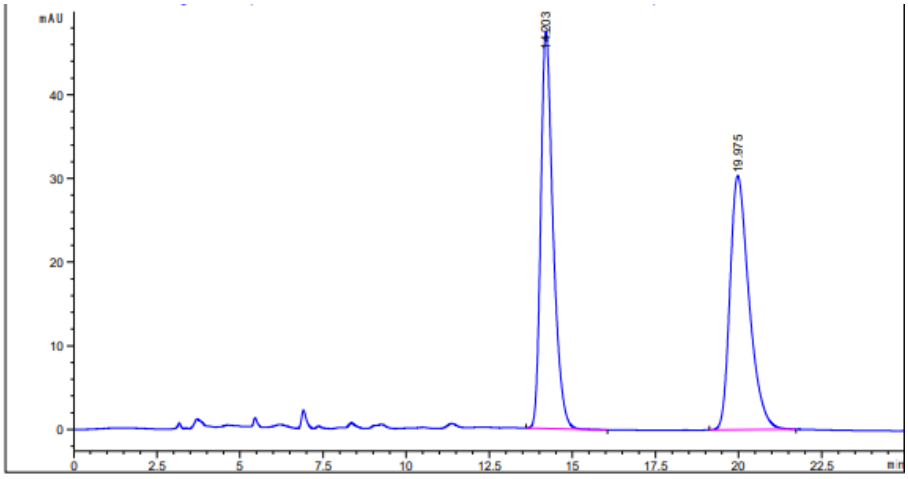
^{13}C NMR (126 MHz, $CDCl_3$): δ 158.0 (*C*(1)), 156.3 (d, ^{1}J = 235.8 Hz, (*C*(15)), 147.4 (*C*(9)), 143.4 (d, ^{4}J = 1.6 Hz, *C*(12)), 137.5 (*C*(3)), 130.1 (*C*(7)), 129.6 (*C*(8)), 127.7 (*C*(5), *C*(4)), 127.3 (*C*(6)), 120.4 (*C*(2)), 116.0 (d, ^{2}J = 22.4 Hz, *C*(14)), 114.5 (d, ^{3}J = 7.4 Hz, *C*(13)), 61.3 (*C*(10)), 50.4 (*C*(11)).

^{19}F NMR (470 MHz, $CDCl_3$): δ −126.98.

HRMS (ESI): exact mass calculated for [M+H] ($C_{17}H_{15}{}^{35}ClFN_2$) requires 301.0902 m/z, found 301.0898 m/z .

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 50:50 hexane:isopropanol, 250 nm, t_{major} = 14.2 min, t_{minor} = 19.9 min.

$[\alpha]_D^{23}$ −51.8° (*c* = 1.0, $CHCl_3$).

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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
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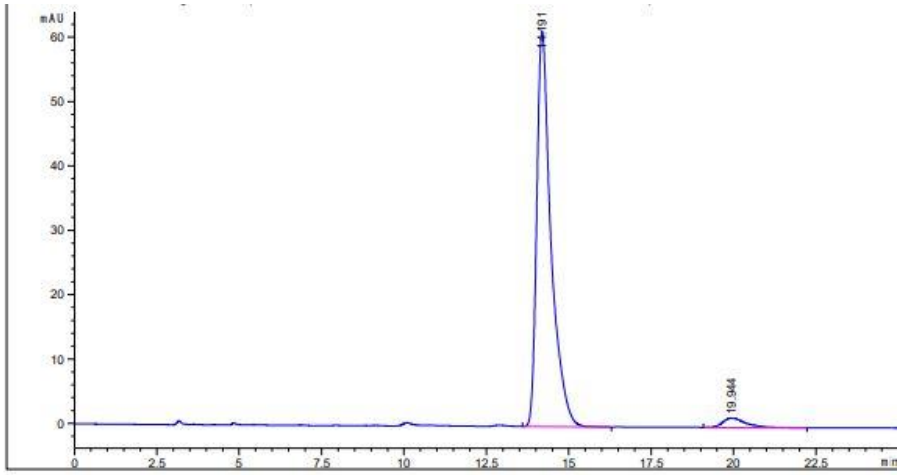


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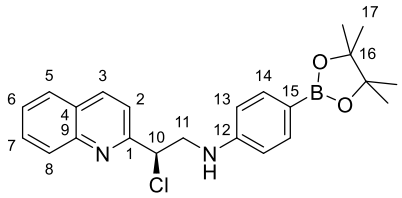
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  14.191 VB    0.4406 1842.79871   61.36278  96.2827
   2  19.944 BB    0.7161   71.14742    1.48522   3.7173

Totals :                  1913.94612   62.84800
```

(*R*)-*N*-(2-chloro-2-(quinolin-2-yl)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline 3.45



Chemical Formula: $C_{23}H_{26}BClN_2O_2$
Exact Mass: 408.1776
Molecular Weight: 408.7330

Racemic:

Prepared according to General Procedure B using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), 4-aminophenylboronic acid pinacol ester (54.8 mg, 0.25 mmol, 1.0 equiv), TFA (3.8 µL, 0.05 mmol, 20 mol%), and THF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure B (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (44.2 mg, 43%).

Enantioenriched:

Prepared according to General Procedure C using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), 4-aminophenylboronic acid pinacol ester (54.8 mg, 0.25 mmol, 1.0 equiv), (S)-TCYP (12.4 mg, 12.5 µmol, 5 mol%), and CPME (500 µL, 0.5 M) for 39 h. The reaction mixture was subjected to the purification outlined in General Procedure C (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (93.2 mg, 91%). The enantiomeric ratio (94:6) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 1605, 1358, 1142, 756, 656 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.5 Hz, 1H, C(3)*H*), 8.12 (d, *J* = 8.4 Hz, 1H, C(8)*H*), 7.83 (d, *J* = 8.1 Hz, 1H, C(5)*H*), 7.79 – 7.72 (m, 1H, C(7)*H*), 7.64 (d, *J* = 8.5 Hz, 2H, C(14)*H*), 7.61 – 7.51 (m, 2H, C(2)*H*, C(6)*H*), 6.65 (d, *J* = 8.6 Hz, 2H, C(13)*H*), 5.35 (app. t, *J* = 6.7 Hz,

1H, C(10)*H*), 4.55 (s, 1H, N*H*), 4.17 (dd, *J* = 14.0, 6.7 Hz, 1H, C(11)*H*), 3.93 (dd, *J* = 14.0, 6.8 Hz, 1H, C(11)*H*), 1.32 (s, 12H, C(17)*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ 157.9 (*C*(1)), 149.7 (*C*(12)), 147.3 (*C*(9)), 137.5 (*C*(3)), 136.6 (*C*(14)), 130.2 (*C*(7)), 129.5 (*C*(8)), 127.7 (*C*(4), *C*(5)), 127.3 (*C*(6)), 120.6 (*C*(2)), 112.4 (*C*(13)), 83.4 (*C*(16)), 60.8 (*C*(10)), 48.9 (*C*(11)), 25.0 (*C*(17)).

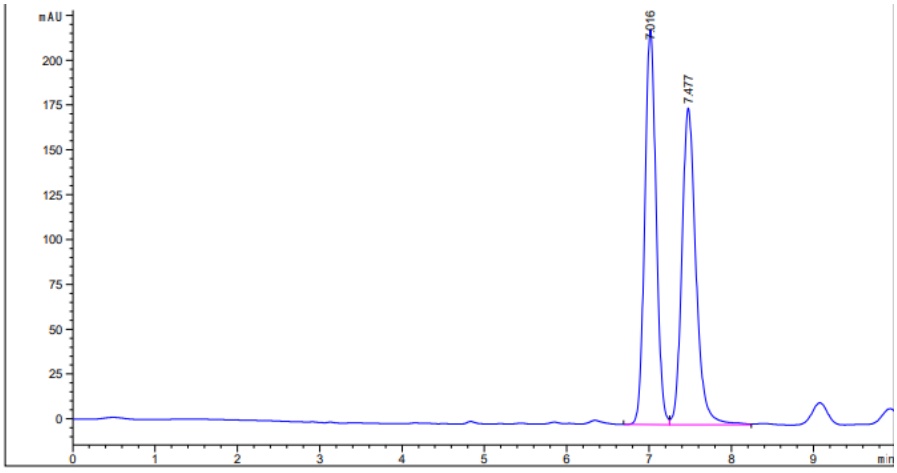
n.b. the carbon bearing boron is not observed due to quadrapolar relaxation.

^{11}B NMR (96 MHz, $CDCl_3$): δ 30.67.

HRMS (ESI): exact mass calculated for [M+H] ($C_{23}H_{27}{}^{11}B^{35}ClN_2O_2$) requires 409.1849 m/z, found 409.1844 m/z.

HPLC analysis using a chiral column: Chiral Art Amylose-C 5 µm column, 1.0 mL/min, 90:10 hexane:isopropanol, 250 nm, t_{major} = 13.2 min, t_{minor} = 12.2 min.

$[\alpha]_D^{23}$ −89.8° (*c* = 1.0, $CHCl_3$).

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Sorted By             :      Signal
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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
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   1   7.016 BV    0.1479 2105.34839  220.19962  50.1230
   2   7.477 VV    0.1807 2095.01221  176.55792  49.8770
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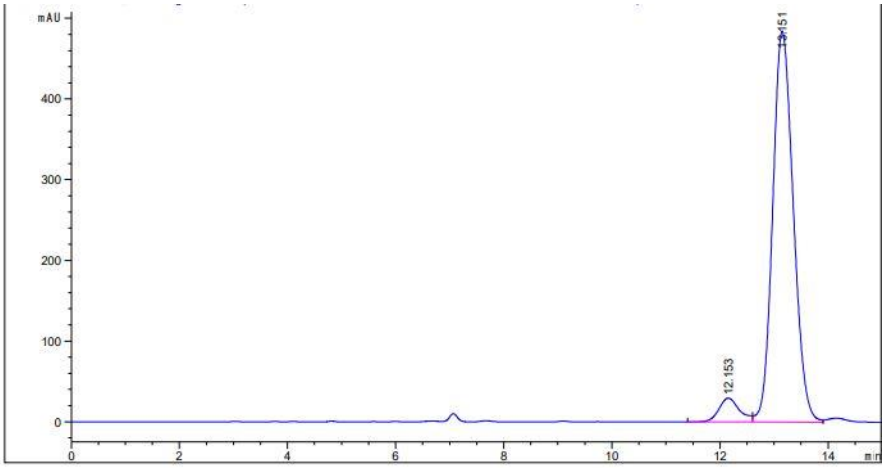


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  12.153 BV    0.4014  790.22559   29.63072   5.7910
   2  13.151 VV    0.4130 1.28556e4   484.37842  94.2090
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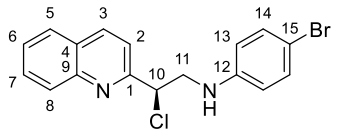
(*R*)-4-Bromo-*N*-(2-chloro-2-(quinolin-2-yl)ethyl)aniline 3.46



Chemical Formula: $C_{17}H_{14}BrClN_2$
Exact Mass: 360.0029
Molecular Weight: 361.6670

Racemic:

Prepared according to General Procedure B using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), 4-bromoaniline (43.0 mg, 0.25 mmol, 1.0 equiv), TFA (3.8 µL, 0.05 mmol, 20 mol%), and THF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure B (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (66.6 mg, 74%).

Enantioenriched:

Prepared according to General Procedure C using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), 4-bromoaniline (43.0 mg, 0.25 mmol, 1.0 equiv), (S)-TCYP (12.4 mg, 12.5 µmol, 5 mol%), and 2-MeTHF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure C (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (74.0 mg, 82%). The enantiomeric ratio (95:5) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 1591, 1489, 812, 776 cm^{-1}.

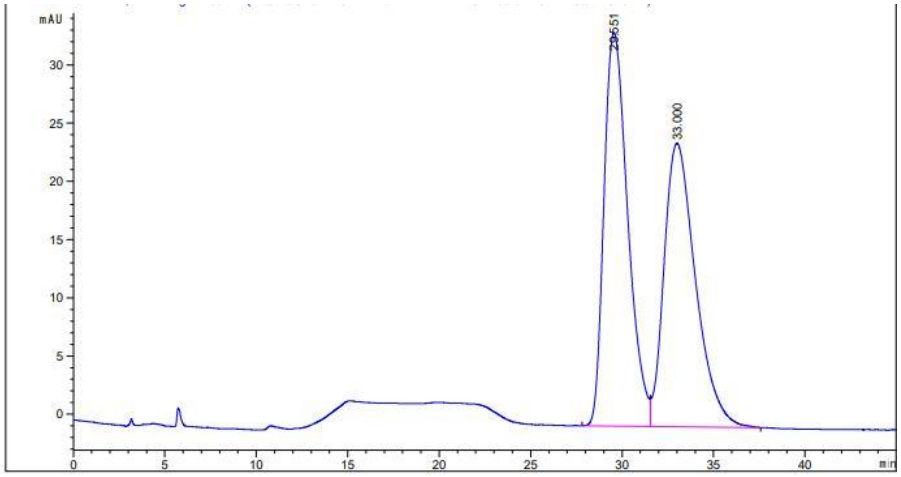
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.5 Hz, 1H, C(3)*H*), 8.11 (d, *J* = 8.5 Hz, 1H, C(8)*H*), 7.84 (d, *J* = 8.1 Hz, 1H, C(5)*H*), 7.80 – 7.73 (m, 1H, C(7)*H*), 7.62 – 7.56 (m, 2H, C(2)*H*, C(6)*H*), 7.24 (d, *J* = 8.8 Hz, 2H, C(14)*H*), 6.55 (d, *J* = 8.8 Hz, 2H, C(13)*H*), 5.33 (app. t, *J* = 6.7 Hz, 1H, C(10)*H*), 4.40 (s, 1H, N*H*), 4.08 (dd, *J* = 14.1, 6.5 Hz, 1H, C(11)*H*), 3.85 (dd, *J* = 14.0, 7.0 Hz, 1H, C(11)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 157.8 (*C*(1)), 147.2 (*C*(9)), 146.1 (*C*(12)), 137.7 (*C*(3)), 132.2 (*C*(14)), 130.3 (*C*(7)), 129.4 (*C*(8)), 127.8 (*C*(4)), 127.7 (*C*(5)), 127.4 (*C*(6)), 120.5 (*C*(2)), 115.0 (*C*(13)), 109.8 (*C*(15)), 60.8 (*C*(10)), 49.5 (*C*(11)).

HRMS (ESI): exact mass calculated for [M+H] ($C_{17}H_{15}{}^{79}Br^{35}ClN_2$) requires 361.0102 m/z, found 361.0090 m/z.

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 50:50 hexane:isopropanol, 250 nm, t_{major} = 30.3 min, t_{minor} = 34.6 min.

$[\alpha]_D^{23}$ −51.8° (*c* = 1.0, $CHCl_3$).

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Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]    [mAU]       %
----|-------|----|-------|----------|----------|--------|
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   2  33.000 VB    1.7665 2909.53345   24.32852  48.7704
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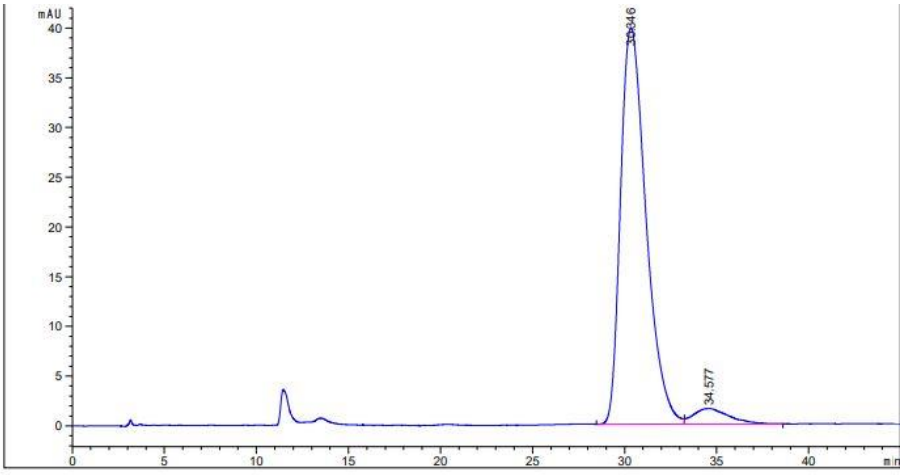


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]    [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  30.346 BV    1.4894 3834.53394   39.85372  94.8562
   2  34.577 VB    1.5780  207.93488    1.55450   5.1438
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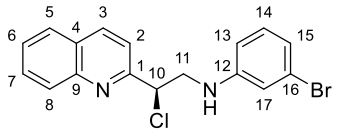
(*R*)-3-Bromo-*N*-(2-chloro-2-(quinolin-2-yl)ethyl)aniline 3.47



Chemical Formula: $C_{17}H_{14}BrClN_2$
Exact Mass: 360.0029
Molecular Weight: 361.6670

Racemic:

Prepared according to General Procedure B using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), 3-bromoaniline (27 µL, 0.25 mmol, 1.0 equiv), TFA (3.8 µL, 0.05 mmol, 20 mol%), and THF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure B (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (39.2 mg, 43%).

Enantioenriched:

Prepared according to General Procedure C using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), 3-bromoaniline (27 µL, 0.25 mmol, 1.0 equiv), (S)-TCYP (12.4 mg, 12.5 µmol, 5 mol%), and CPME (500 µL, 0.5 M) for 39 h. The reaction mixture was subjected to the purification outlined in General Procedure C (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (68.3 mg, 76%). The enantiomeric ratio (95:5) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 1595, 1503, 1481, 829, 762 cm^{-1}.

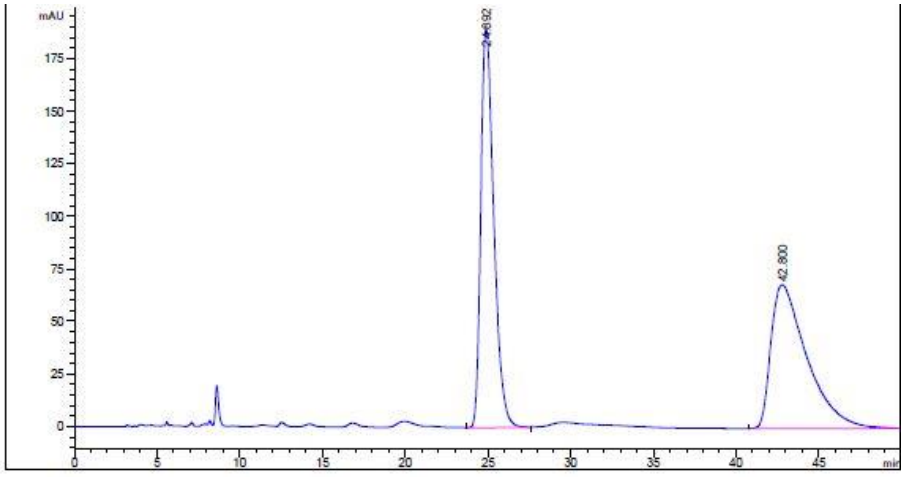
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.5 Hz, 1H, C(3)*H*), 8.12 (d, *J* = 8.5 Hz, 1H, C(8)*H*), 7.84 (d, *J* = 8.1 Hz, 1H, C(5)*H*), 7.77 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H, C(7)*H*), 7.69 – 7.51 (m, 2H, C(2)*H*, C(6)*H*), 7.00 (app. t, *J* = 7.9 Hz, 1H, C(14)*H*), 6.89 – 6.75 (m, 2H, C(13)*H*, C(17)*H*), 6.66 – 6.48 (m, 1H, C(15)*H*), 5.33 (app. t, *J* = 6.7 Hz, 1H, C(10)*H*), 4.45 (s, 1H, N*H*), 4.10 (dd, *J* = 14.0, 6.5 Hz, 1H, C(11)*H*), 3.86 (dd, *J* = 14.0, 6.8 Hz, 1H, C(11)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 157.8 (*C*(1)), 148.5 (*C*(12)), 147.3 (*C*(9)), 137.6 (*C*(3)), 130.7 (*C*(14)), 130.2 (*C*(7)), 129.5 (*C*(8)), 127.7 (*C*(4), *C*(5)), 127.3, (*C*(6)), 123.5 (*C*(16)), 121.0 (*C*(13)), 120.5 (*C*(2)), 116.0 (*C*(17)), 112.0 (*C*(15)), 60.8 (*C*(10)), 49.2 (*C*(11)).

HRMS (ESI): exact mass calculated for [M+H] ($C_{17}H_{15}{}^{79}Br^{35}ClN_2$) requires m/z 361.0102, found m/z 361.0102.

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 50:50 hexane:isopropanol, 250 nm, t_{major} = 26.3 min, t_{minor} = 50.3 min.

$[\alpha]_D^{23}$ −56.4° (*c* = 1.0, $CHCl_3$).

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Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  24.692 BB    0.8401 1.03628e4   189.93922  50.1372
   2  42.800 BBA   2.1648 1.03260e4    68.44814  49.8628

Totals :                  2.07088e4   258.38737
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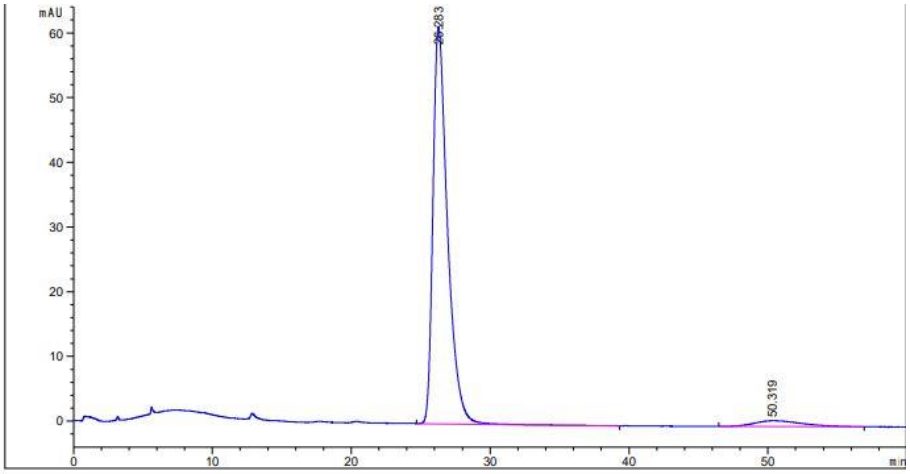


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                        Area Percent Report
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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]    [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  26.283 VB    1.0889 4471.84326   61.36694  95.3081
   2  50.319 BB    2.8918  220.14313 8.97178e-1   4.6919
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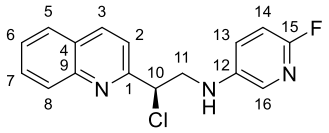
(*R*)-*N*-(2-Chloro-2-(quinolin-2-yl)ethyl)-6-fluoropyridin-3-amine 3.48



Chemical Formula: $C_{16}H_{13}ClFN_3$
Exact Mass: 301.0782
Molecular Weight: 301.7494

Racemic:

Prepared according to General Procedure B using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), 5-amino-2-fluoropyridine (28.0 mg, 0.25 mmol, 1.0 equiv), TFA (3.8 µL, 0.05 mmol, 20 mol%), and THF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure B (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (52.6 mg, 70%).

Enantioenriched:

Prepared according to General Procedure C using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), 5-amino-2-fluoropyridine (28.0 mg, 0.25 mmol, 1.0 equiv), (S)-TCYP (12.4 mg, 12.5 µmol, 5 mol%), and CPME (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure C (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (57.7 mg, 76%). The enantiomeric ratio (93:7) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 3308, 1602, 1497, 772 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (d, *J* = 8.5 Hz, 1H, C(3)*H*), 8.13 (d, *J* = 8.4 Hz, 1H, C(8)*H*), 7.84 (d, *J* = 8.1 Hz, 1H, C(5)*H*), 7.77 (t, *J* = 7.7 Hz, 1H, C(7)*H*), 7.65 (d, *J* = 8.5 Hz, 1H, C(2)*H*), 7.62 – 7.55 (m, 2H, C(6)*H*, C(16)*H*), 7.13 – 7.06 (m, 1H, C(13)*H*), 6.71 (dd, *J* = 8.7, 2.7 Hz, 1H, C(14)*H*), 5.39 (app. t, *J* = 6.4 Hz, 1H, C(10)*H*), 4.05 (dd, *J* = 13.9, 6.4 Hz, 1H, C(11)*H*), 3.87 (dd, *J* = 13.9, 6.8 Hz, 1H, C(11)*H*).

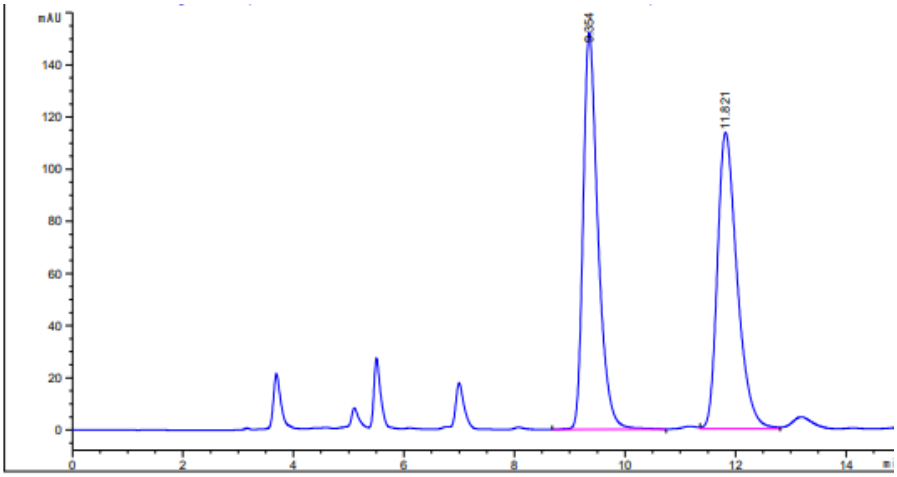
^{13}C NMR (126 MHz, $CDCl_3$): δ 157.5 (*C*(1)), 157.1 (d, ^{1}J = 230.0 Hz, *C*(15)), 146.6 (*C*(9)), 141.5 (d, ^{4}J = 3.7 Hz, *C*(12)), 138.2 (*C*(3)), 131.5 (d, ^{3}J = 14.8 Hz, *C*(16)), 130.6 (*C*(7)), 128.9 (*C*(8)), 127.8 (*C*(5)), 127.7 (*C*(4)), 127.6 (*C*(6)), 126.0 (d, ^{3}J = 6.9 Hz, *C*(13)), 120.3 (*C*(2)), 109.5 (d, ^{2}J = 39.5 Hz, *C*(14)), 60.5 (*C*(10)), 50.1 (*C*(11)).

^{19}F NMR (470 MHz, $CDCl_3$): δ −81.45.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{16}H_{13}{}^{35}ClFN_3$) requires 302.0855 m/z, found 302.0855 m/z.

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 2.0 mL/min, 50:50 hexane:isopropanol, 250 nm, t_{major} = 10.2 min, t_{minor} = 13.6 min.

$[\alpha]_D^{23}$ −70.4° (*c* = 1.0, $CHCl_3$).

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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
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   1   9.354 BB    0.2801 2838.99683  152.30174  50.1613
   2  11.821 VV    0.3768 2820.74316  113.70979  49.8387
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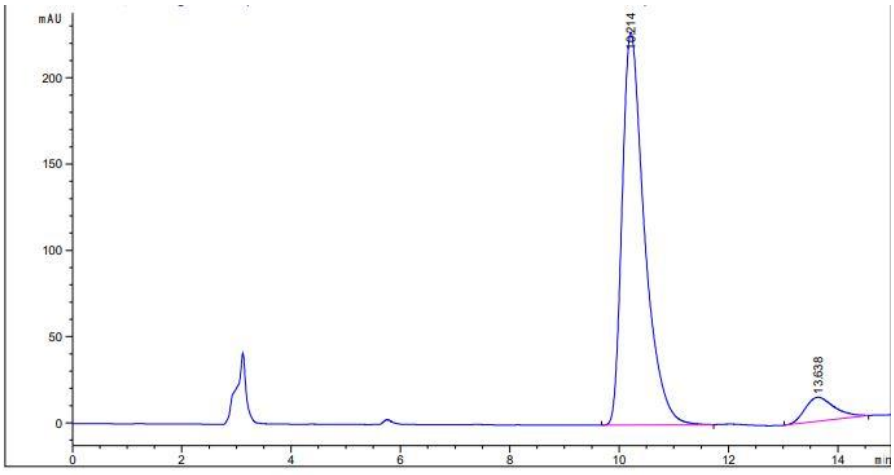


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.214 BB    0.4262 6467.63379  227.57758  92.5909
   2  13.638 BB    0.5680  517.53912   13.86512   7.4091
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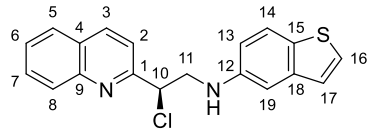
(*R*)-*N*-(2-chloro-2-(quinolin-2-yl)ethyl)benzo[*b*]thiophen-5-amine 3.49



Chemical Formula: $C_{19}H_{15}ClN_2S$
Exact Mass: 338.0644
Molecular Weight: 338.8530

Racemic:

Prepared according to General Procedure B using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), 5-aminobenzothiophene (37.3 mg, 0.25 mmol, 1.0 equiv), TFA (3.8 µL, 0.05 mmol, 20 mol%), and THF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure B (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (38.4 mg, 45%).

Enantioenriched:

Prepared according to General Procedure C using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), 5-aminobenzothiophene (37.3 mg, 0.25 mmol, 1.0 equiv), (S)-TCYP (12.4 mg, 12.5 µmol, 5 mol%), and 2-MeTHF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure C (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (69.3 mg, 82%). The enantiomeric ratio (94:6) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 1604, 1506, 772 cm^{-1}.

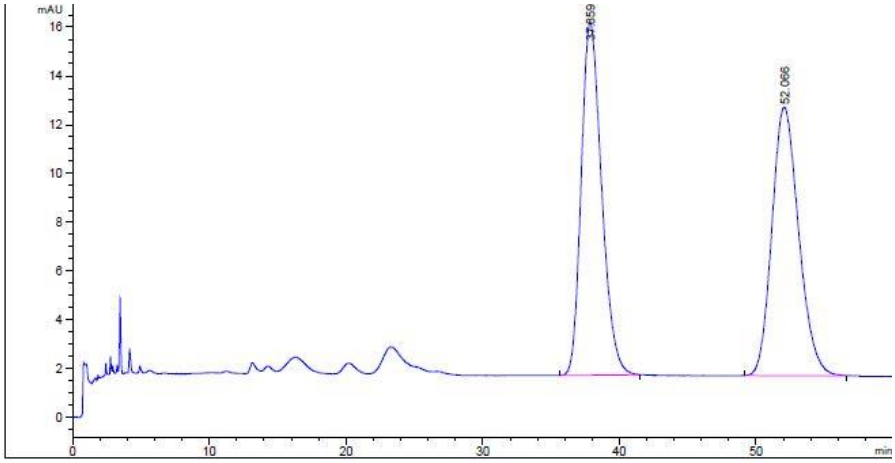
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.5 Hz, 1H, C(3)*H*), 8.14 (d, *J* = 8.3 Hz, 1H, C(8)*H*), 7.83 (dd, *J* = 8.1, 1.2 Hz, 1H, C(5)*H*), 7.77 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H, C(7)*H*), 7.67 – 7.54 (m, 3H, C(2)*H*, C(6)*H*, C(14)*H*), 7.38 (d, *J* = 5.4 Hz, 1H, C(16)*H*), 7.16 (dd, *J* = 5.4, 0.6 Hz, 1H, C(17)*H*), 7.09 (d, *J* = 2.3 Hz, 1H, C(19)*H*), 6.82 – 6.73 (m, 1H, C(13)*H*), 5.42 (app. t, *J* = 6.7 Hz, 1H, C(10)*H*), 4.18 (dd, *J* = 14.0, 6.5 Hz, 1H, C(11)*H*), 3.94 (dd, *J* = 14.0, 7.0 Hz, 1H, C(11)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 158.1 (*C*(1)), 147.4 (*C*(9)), 144.6 (*C*(12)), 141.1 (*C*(18)), 137.5 (*C*(3)), 130.1 (*C*(15)), 130.1 (*C*(7)), 129.6 (*C*(8)), 127.7 (*C*(4), *C*(5)), 127.2 (*C*(6)), 127.2 (*C*(16)), 123.4 (*C*(17)), 123.2 (*C*(14)), 120.5 (*C*(2)), 114.5 (*C*(13)), 105.9 (*C*(19)), 61.1 (*C*(10)), 50.2 (*C*(11)).

HRMS (ESI): exact mass calculated for [M+H] ($C_{19}H_{16}{}^{35}ClN_2S$) requires m/z 339.0717, found 339.0717 m/z.

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 2.0 mL/min, 50:50 hexane:isopropanol, 250 nm, t_{major} = 57.2 min, t_{minor} = 42.4 min.

$[\alpha]_D^{23}$ −119° (*c* = 1.0, $CHCl_3$).

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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
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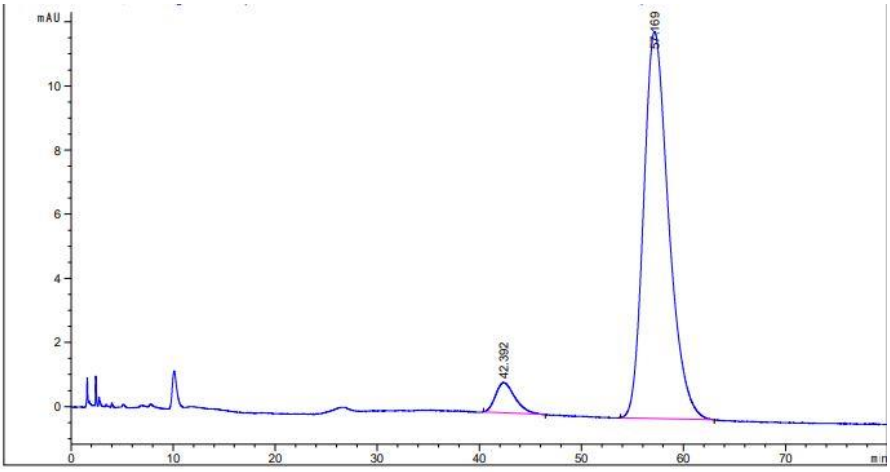


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  42.392 BB    1.5583  124.08217 9.41317e-1   5.6936
   2  57.169 BB    2.0809 2055.23291   12.07180  94.3064
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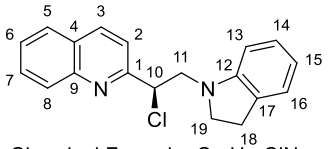
(*R*)-2-(1-chloro-2-(indolin-1-yl)ethyl)quinoline 3.50



Chemical Formula: $C_{19}H_{17}ClN_2$
Exact Mass: 308.1080
Molecular Weight: 308.8090

Racemic:

Prepared according to General Procedure B using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), indoline (28 µL, 0.25 mmol, 1.0 equiv), TFA (3.8 µL, 0.05 mmol, 20 mol%), and THF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure B (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (52.0 mg, 67%).

Enantioenriched:

Prepared according to General Procedure C using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), indoline (28 µL, 0.25 mmol, 1.0 equiv), (S)-TCYP (12.4 mg, 12.5 µmol, 5 mol%), and CPME (500 µL, 0.5 M) for 15 h. The reaction mixture was subjected to the purification outlined in General Procedure C (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (65.0 mg, 84%). The enantiomeric ratio (93:7) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 1607, 1489**,** 745 cm^{-1}.

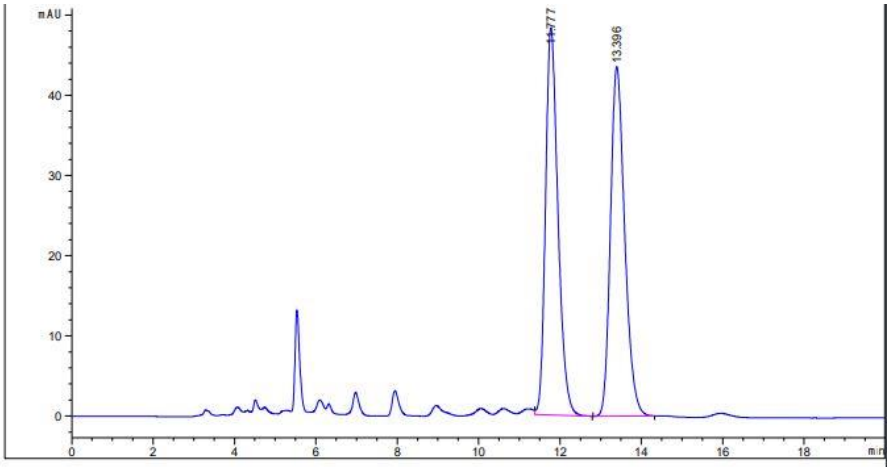
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.5 Hz, 1H, C(3)*H*), 8.15 (d, *J* = 8.5 Hz, 1H, C(8)*H*), 7.83 (d, *J* = 8.1 Hz, 1H, C(5)*H*), 7.76 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 1H, C(7)*H*), 7.66 (d, *J* = 8.5 Hz, 1H, C(2)*H*), 7.61 – 7.53 (m, 1H, C(6)*H*), 7.06 (t, *J* = 7.8 Hz, 2H, C(14)*H*, C(16)*H*), 6.66 (t, *J* = 7.3 Hz, 1H, C(15)*H*), 6.58 (d, *J* = 7.7 Hz, 1H, C(13)*H*), 5.38 (app. t, *J* = 6.9 Hz, 1H, C(10)*H*), 4.05 (dd, *J* = 14.4, 7.1 Hz, 1H, C(11)*H*), 3.84 (dd, *J* = 14.4, 6.7 Hz, 1H, C(11)*H*), 3.49 (app. q, *J* = 8.5 Hz, 1H, C(19)*H*), 3.39 (app. q, *J* = 8.5 Hz, 1H, C(19)*H*), 2.93 (app. t, *J* = 8.5 Hz, 2H, C(18)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 158.5 (*C*(1)), 151.9 (*C*(12)), 147.4 (*C*(9)), 137.3 (*C*(3)), 130.0 (*C*(7)), 129.5 (*C*(8)), 129.4 (*C*(17)), 127.8 (*C*(4)), 127.7 (*C*(5)), 127.4 (*C*(14)), 127.1 (*C*(6)), 124.6 (*C*(16)), 120.2 (*C*(2)), 117.8 (*C*(15)), 106.6 (*C*(13)), 61.4 (*C*(10)), 56.6 (*C*(11)), 54.2 (*C*(19)), 28.7 (*C*(18)).

HRMS (ESI): exact mass calculated for [M+H] ($C_{19}H_{18}{}^{35}ClN_2$) requires m/z 309.1153, found 309.1152 m/z.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{23}}$ +30.1° (*c* = 1.0, $CHCl_3$).

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 50:50 hexane:isopropanol, 250 nm, t_{major} = 13.2 min, t_{minor} = 15.4 min.

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Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
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   2  13.396 BB    0.3719 1056.78955   43.54992  50.7858
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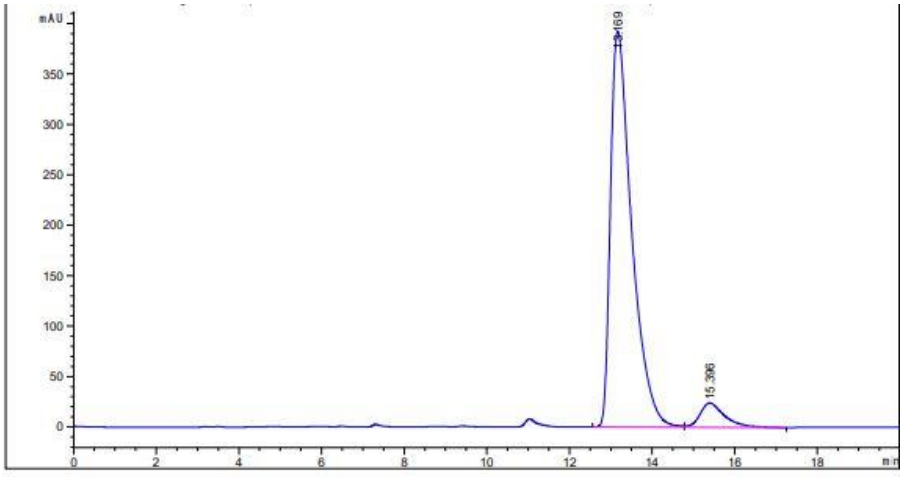


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  13.169 BV    0.5337 1.39850e4   392.39307  93.3601
   2  15.396 VB    0.6103  994.63593   24.06757   6.6399
```
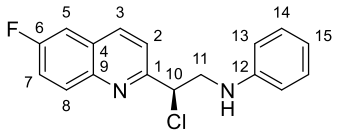

(*R*)-*N*-(2-chloro-2-(6-fluoroquinolin-2-yl)ethyl)aniline 3.51



Chemical Formula: $C_{17}H_{14}ClFN_2$
Exact Mass: 300.0830
Molecular Weight: 300.7614

Racemic:

Prepared according to General Procedure B using 2-(1-chlorovinyl)-6-fluoroquinoline (20.8 mg, 0.10 mmol, 1.0 equiv), aniline (9.1 µL, 0.10 mmol, 1.0 equiv), TFA (1.5 µL, 0.05 mmol, 20 mol%), and THF (200 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure B (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (12.6 mg, 42%).

Enantioenriched:

Prepared according to General Procedure C using 2-(1-chlorovinyl)-6-fluoroquinoline (51.9 mg, 0.25 mmol, 1.0 equiv), aniline (23 µL, 0.25 mmol, 1.0 equiv), (S)-TCYP (12.4 mg, 12.5 µmol, 5 mol%), and 2-MeTHF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure C (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (21.4 mg, 28%). The enantiomeric ratio (94:6) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 1600, 1504, 1234, 750 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 – 8.09 (m, 2H, C(3)*H*, C(8)*H*), 7.61 (d, *J* = 8.5 Hz, 1H, C(2)*H*), 7.56 – 7.49 (m, 1H, C(7)*H*), 7.45 (dd, *J* = 8.7, 2.8 Hz, 1H, C(5)*H*), 7.19 (t, *J* = 7.9 Hz, 2H, C(14)*H*), 6.75 (t, *J* = 7.3 Hz, 1H, C(15)*H*), 6.68 (d, *J* = 7.7 Hz, 2H, C(13)*H*), 5.34 (t, *J* = 6.7 Hz, 1H, C(10)*H*), 4.33 (s, 1H, N*H*), 4.12 (dd, *J* = 14.1, 6.4 Hz, 1H, C(11)*H*), 3.87 (dd, *J* = 14.1, 7.0 Hz, 1H, C(11)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 160.9 (d, ^1J = 249.2 Hz, *C*(6)), 157.5 (*C*(1)), 147.1 (*C*(12)), 144.5 (*C*(9), 136.8 (d, ^4J = 5.3 Hz, *C*(3)), 132.1 (d, ^3J = 9.1 Hz, *C*(8)), 129.6 (*C*(14)), 128.4 (d,

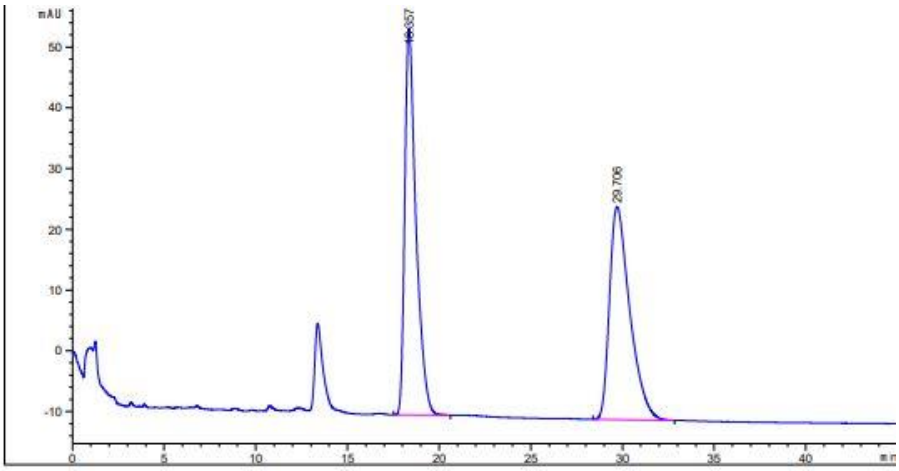
^{3}J = 10.2 Hz, *C*(4)), 121.3 (*C*(2)), 120.4 (d, ^{2}J = 25.8 Hz, *C*(7)), 118.4 (*C*(15)), 113.5 (*C*(13)), 110.8 (d, ^{2}J = 21.8 Hz, *C*(5)), 61.0 (*C*(10)), 49.5 (*C*(11)).

^{19}F NMR (376 MHz, $CDCl_3$): δ −112.37.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{17}H_{15}{}^{35}ClFN_2$) requires m/z 301.0902, found 301.0898 m/z.

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 50:50 hexane:isopropanol, 250 nm, t_{major} = 17.4 min, t_{minor} = 27.6 min.

$[\alpha]_D^{23}$ −8.4° (*c* = 1.0, $CHCl_3$).



Area Percent Report

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Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=250 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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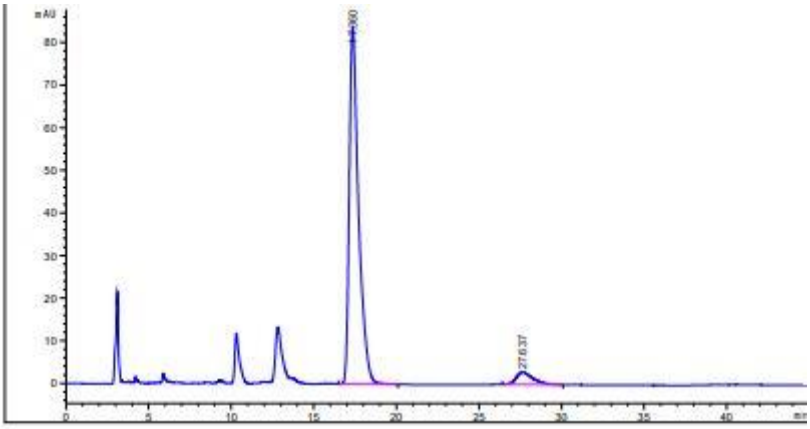
2	29.706	BB	1.1318	2700.18848	35.10372	49.8917



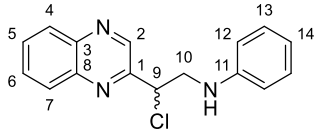
Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=250 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.360	BB	0.5741	3275.51611	83.77097	94.1416
2	27.637	BB	0.8746	203.83316	2.89224	5.8584

(±)-*N*-(2-chloro-2-(quinoxalin-2-yl)ethyl)aniline 3.52



Chemical Formula: $C_{16}H_{14}ClN_3$
Exact Mass: 283.0876
Molecular Weight: 283.7590

Prepared according to General Procedure B using 2-(1-chlorovinyl)quinoxaline (47.7 mg, 0.25 mmol, 1.0 equiv), aniline (23 µL, 0.25 mmol, 1.0 equiv), TFA (3.8 µL, 0.05 mmol, 20 mol%), and THF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure B (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (32.3 mg, 46%).

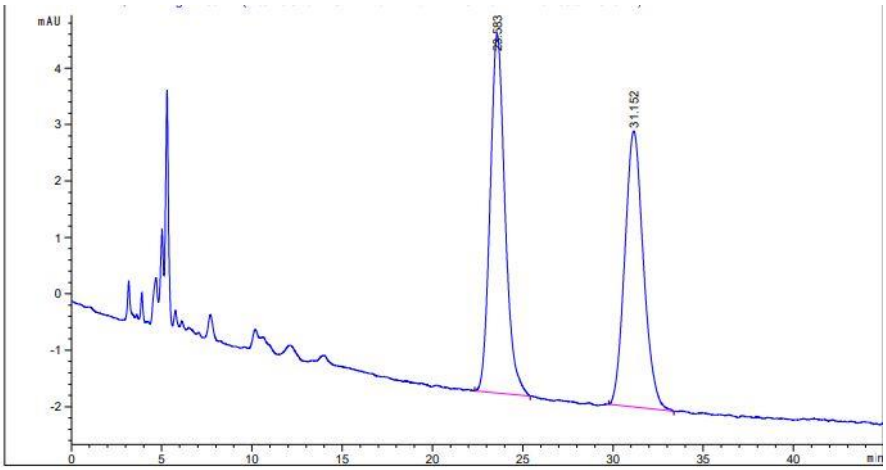
υ_{max} (film): 1491, 1198, 768 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.03 (s, 1H, C(2)*H*), 8.15 (ddt, *J* = 7.3, 4.0, 1.7 Hz, 2H, C(4)*H*, C(7)*H*), 7.90 – 7.77 (m, 2H, C(5)*H*, C(6)*H*), 7.22 (dd, *J* = 8.6, 7.4 Hz, 2H, C(13)*H*), 6.85 – 6.76 (m, 1H, C(14)*H*), 6.75 – 6.69 (m, 2H, C(12)*H*), 5.44 (app. t, *J* = 6.7 Hz, 1H, C(9)*H*), 4.22 (dd, *J* = 14.3, 6.6 Hz, 1H, C(10)*H*), 3.97 (dd, *J* = 14.3, 6.9 Hz, 1H, C(10)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 152.8 (*C*(1)), 146.3 (*C*(11)), 145.1 (*C*(2)), 142.1 (*C*(3)), 141.3 (*C*(8)), 130.7 (*C*(5 or 6)), 130.6 (*C*(5 or 6)), 129.5 (*C*(13)), 129.4 (*C*(4 or 7)), 129.4 (*C*(4 or 7)), 118.8 (*C*(14)), 113.6 (*C*(12)), 58.1 (*C*(9)), 49.1 (*C*(10)).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{16}H_{15}{}^{35}ClN_3$) requires m/z 284.0949, found 284.0940 m/z.

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 50:50 hexane:isopropanol, 250 nm, t_1 = 23.6 min, t_2 = 31.1 min.

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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
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   1  23.583 BB    0.8284  365.00168    6.35851  50.9716
   2  31.152 BB    0.9227  351.08710    4.89478  49.0284
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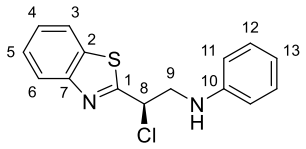
(*R*)-*N*-(2-(benzo[*d*]thiazol-2-yl)-2-chloroethyl)aniline 3.53



Chemical Formula: $C_{15}H_{13}ClN_2S$
Exact Mass: 288.0488
Molecular Weight: 288.7930

Racemic:

Prepared according to General Procedure B using 2-(1-chlorovinyl)benzo[*d*]thiazole (19.6 mg, 0.10 mmol, 1.0 equiv), aniline (9.3 µL, 0.10 mmol, 1.0 equiv), TFA (1.5 µL, 0.02 mmol, 20 mol%), and THF (200 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure B (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (13.1 mg, 45%).

Enantioenriched:

Prepared according to General Procedure C using 2-(1-chlorovinyl)benzo[*d*]thiazole (16.0 mg, 0.08 mmol, 1.0 equiv), aniline (7.5 µL, 0.08 mmol, 1.0 equiv), (*S*)-TCYP (4.1 mg, 4.1 µmol, 5 mol%), and 2-MeTHF (160 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure C (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a yellow oil (11.4 mg, 48%). The enantiomeric ratio (99:1) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 1600, 1499, 750 cm^{-1}.

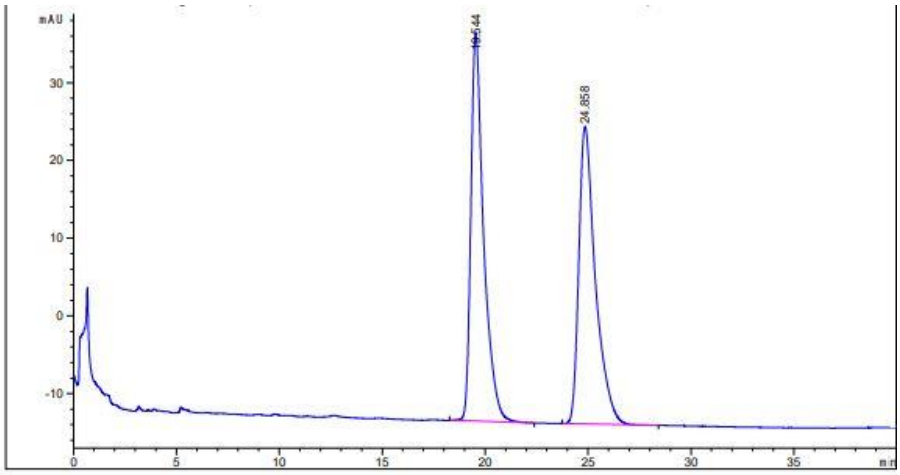
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.2 Hz, 1H, C(6)*H*), 7.90 (d, *J* = 8.0 Hz, 1H, C(3)*H*), 7.53 (ddd, *J* = 8.3, 7.3, 1.2 Hz, 1H, C(4)*H*), 7.44 (td, *J* = 7.8, 7.3, 1.1 Hz, 1H, C(5)*H*), 7.25 – 7.18 (m, 2H, C(12)*H*), 6.84 – 6.77 (m, 1H, C(13)*H*), 6.77 – 6.66 (m, 2H, C(11)*H*), 5.48 (dd, *J* = 6.9, 6.0 Hz, 1H, C(8)*H*), 4.15 (dd, *J* = 14.3, 5.9 Hz, 1H, C(9)*H*), 3.87 (dd, *J* = 14.3, 7.0 Hz, 1H, C(9)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 169.2 (*C*(1)), 152.9 (*C*(7)), 146.4 (*C*(10)), 135.5 (*C*(2)), 129.7 (*C*(12)), 126.6 (*C*(5)), 125.9 (*C*(3)), 123.7 (*C*(4)), 121.9 (*C*(6)), 118.9 (*C*(13)), 113.7 (*C*(11)), 57.3 (*C*(8)), 50.5 (*C*(9)).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{15}H_{14}{}^{35}ClN_2S$) requires m/z 289.0561, found 289.0557 m/z.

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 50:50 hexane:isopropanol, 250 nm, t_{major} = 18.8 min, t_{minor} = 23.8 min.

$[\alpha]_D^{23}$ −30.3° (*c* = 0.5, $CHCl_3$).



Area Percent Report

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Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=250 nm

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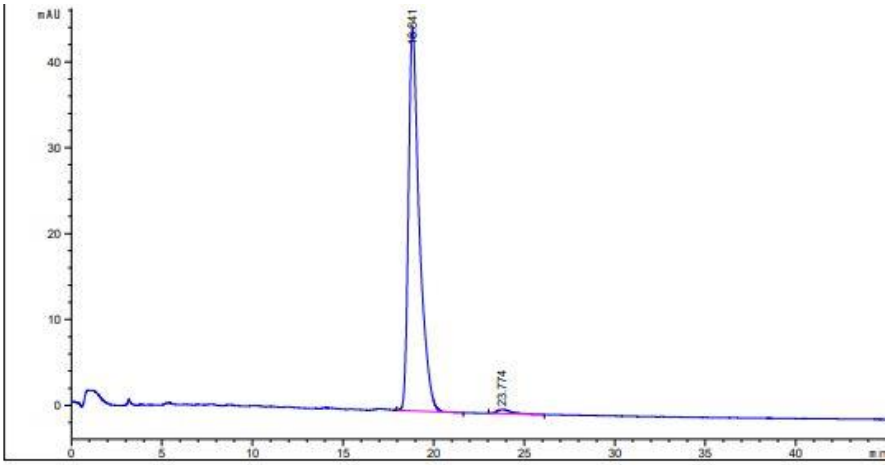


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Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  18.841 BB    0.6149 1860.93738   44.60484  98.6500
   2  23.774 BB    0.6725   25.46739 4.72502e-1   1.3500
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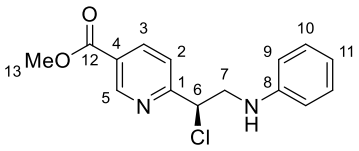
Methyl (*R*)-6-(1-chloro-2-(phenylamino)ethyl)nicotinate 3.54



Chemical Formula: $C_{15}H_{15}ClN_2O_2$
Exact Mass: 290.0822
Molecular Weight: 290.7470

Racemic:

Prepared according to General Procedure B using methyl 6-(1-chlorovinyl)nicotinate (49.4 mg, 0.25 mmol, 1.0 equiv), aniline (23 µL, 0.25 mmol, 1.0 equiv), TFA (3.8 µL, 0.05 mmol, 20 mol%), and THF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure B (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (29.8 mg, 41%).

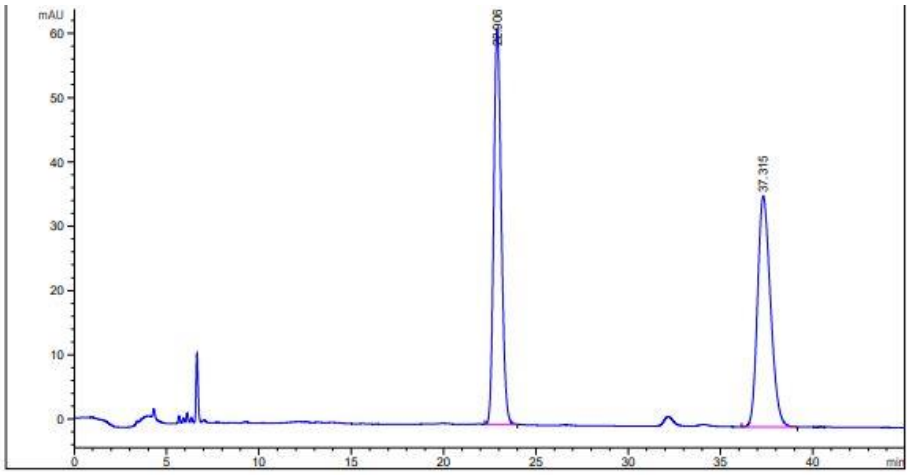
υ_{max} (film): 1726, 1599, 1506, 1288, 748 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.23 (dd, *J* = 2.2, 0.9 Hz, 1H, C(5)*H*), 8.33 (dd, *J* = 8.2, 2.2 Hz, 1H, C(3)*H*), 7.59 (dd, *J* = 8.1, 0.9 Hz, 1H, C(2)*H*), 7.24 – 7.18 (m, 2H, C(10)*H*), 6.77 (tt, *J* = 7.4, 1.1 Hz, 1H, C(11)*H*), 6.70 – 6.65 (m, 2H, C(9)*H*), 5.25 (dd, *J* = 7.2, 5.9 Hz, 1H, C(6)*H*), 4.03 (dd, *J* = 14.2, 6.0 Hz, 1H, C(7)*H*), 3.99 (s, 3H, C(13)*H*), 3.77 (dd, *J* = 14.3, 7.2 Hz, 1H, C(7)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 165.3 (*C*(12)), 162.0 (*C*(1)), 150.6 (*C*(5)), 146.7 (*C*(8)), 138.2 (*C*(3)), 129.5 (*C*(10)), 125.6 (*C*(4)), 122.5 (*C*(2)), 118.4 (*C*(11)), 113.3 (*C*(8)), 60.4 (*C*(6)), 52.6 (*C*(13)), 49.8 (*C*(7)).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{15}H_{16}{}^{35}ClN_2O_2$) requires m/z 291.0895, found 291.0887 m/z.

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 50:50 hexane:isopropanol, 250 nm, t_1 = 22.9 min, t_2 = 37.3 min.



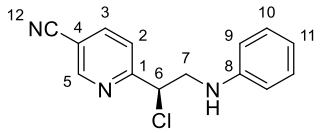
Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=250 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.906	BB	0.4407	1748.06372	61.52238	49.9957
2	37.315	BB	0.7562	1748.36353	35.88901	50.0043
Totals :				3496.42725	97.41140	

(*R*)-6-(1-chloro-2-(phenylamino)ethyl)nicotinonitrile 3.55



Chemical Formula: $C_{14}H_{12}ClN_3$
Exact Mass: 257.0720
Molecular Weight: 257.7210

Racemic:

Prepared according to General Procedure B using 6-(1-chlorovinyl)nicotinonitrile (19.6 mg, 0.25 mmol, 1.0 equiv), aniline (23 µL, 0.25 mmol, 1.0 equiv), TFA (3.8 µL, 0.05 mmol, 20 mol%), and THF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure B (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (13.1 mg, 45%).

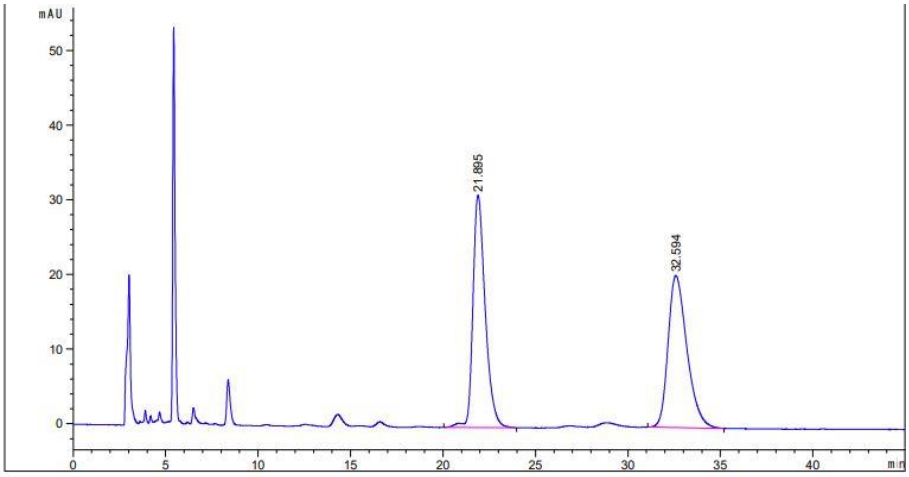
υ_{max} (film): 2232, 1601, 1479, 755 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.87 (dd, *J* = 2.1, 0.9 Hz, 1H, C(5)*H*), 7.95 (dd, *J* = 8.1, 2.1 Hz, 1H, C(3)*H*), 7.63 (dd, *J* = 8.2, 0.9 Hz, 1H, C(2)*H*), 7.25 – 7.20 (m, 2H, C(10)*H*), 6.86 (t, *J* = 7.3 Hz, 1H, C(11)*H*), 6.78 (d, *J* = 7.9 Hz, 2H, C(9)*H*), 5.28 (app. t, *J* = 6.5 Hz, 1H, C(6)*H*), 4.04 (dd, *J* = 14.2, 6.1 Hz, 1H, C(7)*H*), 3.76 (dd, *J* = 14.1, 7.0 Hz, 1H, C(7)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 162.1 (*C*(1)), 152.1 (*C*(5)), 146.4 (*C*(8)), 140.4 (*C*(3)), 129.6 (*C*(10)), 123.1 (*C*(2)), 118.8 (*C*(11)), 116.4 (*C*(12)), 113.5 (*C*(9)), 109.5 (*C*(4)), 60.1 (*C*(6)), 49.9 (*C*(7)).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{14}H_{12}{}^{35}ClN_3$) requires 258.0793 m/z, found 258.0786 m/z.

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 50:50 hexane:isopropanol, 250 nm, t_1 = 21.9 min, t_2 = 32.6 min.

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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  21.895 BB    0.7014 1440.15808   31.12913  49.9468
   2  32.594 BB    1.0300 1443.22522   20.38183  50.0532
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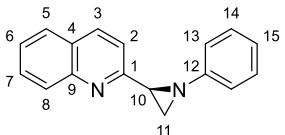
(*S*)-2-(1-Phenylaziridin-2-yl)quinoline 3.56



Chemical Formula: $C_{17}H_{14}N_2$
Exact Mass: 246.1157
Molecular Weight: 246.3130

Racemic:

Prepared according to General Procedure E using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), aniline (23 µL, 0.25 mmol, 1.0 equiv), TFA (3.8 µL, 0.05 mmol, 20 mol%), NaH (60% dispersion in mineral oil, 20 mg, 0.50 mmol, 2.0 equiv), and THF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure E (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (42.9 mg, 70%).

Enantioenriched:

Prepared according to General Procedure F using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), aniline (23 µL, 0.25 mmol, 1.0 equiv), (*S*)-TCYP (12.4 mg, 12.5 µmol, 5 mol%), 0.6 M LiHMDS in THF (0.5 mL, 0.3 mmol, 1.2 equiv), and 2-MeTHF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure F (silica gel, EtOAc:cyclohexane, 5:95 to 10:90) to afford the desired product as a pale yellow solid (41.1 mg, 67%). The enantiomeric ratio (95:5) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 1597, 1489 cm^{-1}.

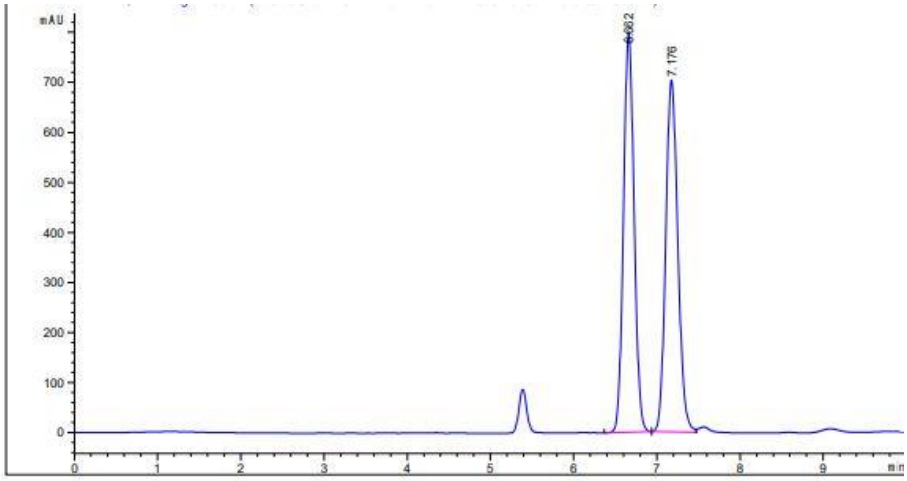
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.5 Hz, 1H, C(3)*H*), 8.11 (d, *J* = 8.5 Hz, 1H, C(8)*H*), 7.82 (d, *J* = 8.0 Hz, 1H, C(5)*H*), 7.75 – 7.69 (m, 1H, C(7)*H*), 7.56 – 7.50 (m, 1H, C(6)*H*), 7.48 (d, *J* = 8.5 Hz, 1H, C(2)*H*), 7.31 – 7.23 (m, 2H, C(14)*H*), 7.11 (d, *J* = 7.5 Hz, 2H, C(13)*H*), 7.02 (t, *J* = 7.4 Hz, 1H, C(15)*H*), 3.52 (dd, *J* = 6.5, 3.2 Hz, 1H, C(10)*H*), 2.64 – 2.59 (m, 2H, C(11)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.6 (*C*(1)), 154.0 (*C*(12)), 147.8 (*C*(9)), 137.1 (*C*(3)), 129.8 (*C*(7)), 129.2 (*C*(14)), 129.0 (*C*(8)), 127.8 (*C*(5)), 127.7 (*C*(4)), 126.4 (*C*(6)), 123.0 (*C*(15), 120.8 (*C*(13)), 117.9 (*C*(2)), 43.2 (*C*(10)), 37.3 (*C*(11)).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{17}H_{15}N_2$) requires 247.1230 m/z, found 247.1225 m/z.

HPLC analysis using a chiral column: Chiral Art Amylose-C 5 µm column, 1.0 mL/min, 90:10 hexane:isopropanol, 250 nm, t_{major} = 6.9 min, t_{minor} = 7.4 min.

$[\alpha]_D^{23}$ −174° (*c* = 1.0, $CHCl_3$).

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                          Area Percent Report
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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
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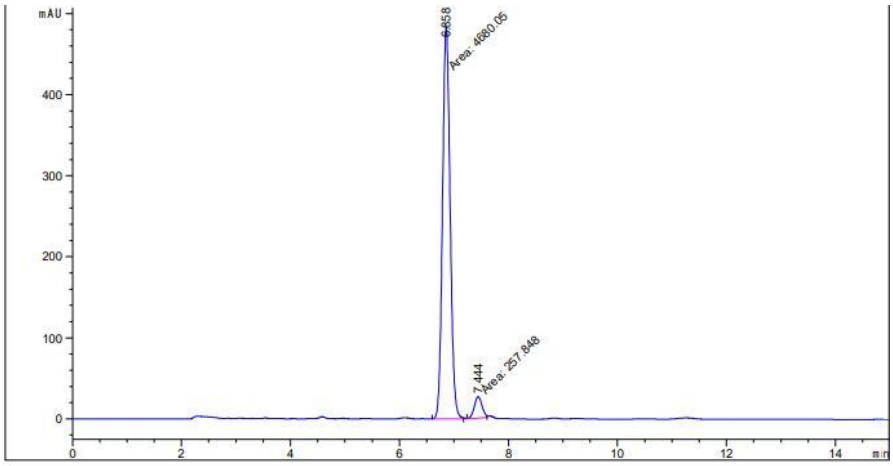


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                          Area Percent Report
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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.858 MM    0.1614 4680.05420  483.23697  94.7782
   2   7.444 MM    0.1638  257.84833   26.23678   5.2218
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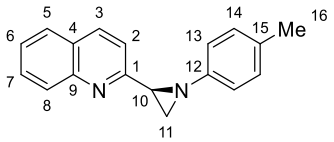
(*S*)-2-(1-(*p*-Tolyl)aziridin-2-yl)quinoline 3.57



Chemical Formula: $C_{18}H_{16}N_2$
Exact Mass: 260.1313
Molecular Weight: 260.3400

Racemic:

Prepared according to General Procedure E using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), *p*-toluidine (26.8 mg, 0.25 mmol, 1.0 equiv), TFA (3.8 µL, 0.05 mmol, 20 mol%), NaH (60% dispersion in mineral oil, 20 mg, 0.50 mmol, 2.0 equiv), and THF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure E (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (36.6 mg, 56%).

Enantioenriched:

Prepared according to General Procedure F using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), *p*-toluidine (26.8 mg, 0.25 mmol, 1.0 equiv), (*S*)-TCYP (12.4 mg, 12.5 µmol, 5 mol%), 0.6 M LiHMDS in THF (0.5 mL, 0.3 mmol, 1.2 equiv), and 2-MeTHF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure F (silica gel, EtOAc:cyclohexane, 5:95 to 10:90) to afford the desired product as a pale yellow solid (41.6 mg, 64%). The enantiomeric ratio (97:3) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 1601, 1504, 1485 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 – 8.11 (m, 2H, C(3)*H*, C(8)*H*), 7.80 (d, *J* = 7.8 Hz, 1H, C(5)*H*), 7.76 – 7.70 (m, 1H, C(7)*H*), 7.52 (t, *J* = 7.4 Hz, 1H, C(6)*H*), 7.47 (d, *J* = 8.5 Hz, 1H, C(2)*H*), 7.08 (d, *J* = 8.2 Hz, 2H, C(14)*H*), 7.02 (d, *J* = 8.3 Hz, 2H, C(13)*H*), 3.49 (dd, *J* = 6.5, 3.2 Hz, 1H, C(10)*H*), 2.60 (app. d, *J* = 2.5 Hz, 1H, C(11)*H*), 2.57 (app. d, *J* = 6.6 Hz, 1H, C(11)*H*), 2.30 (s, 3H, C(16)*H*).

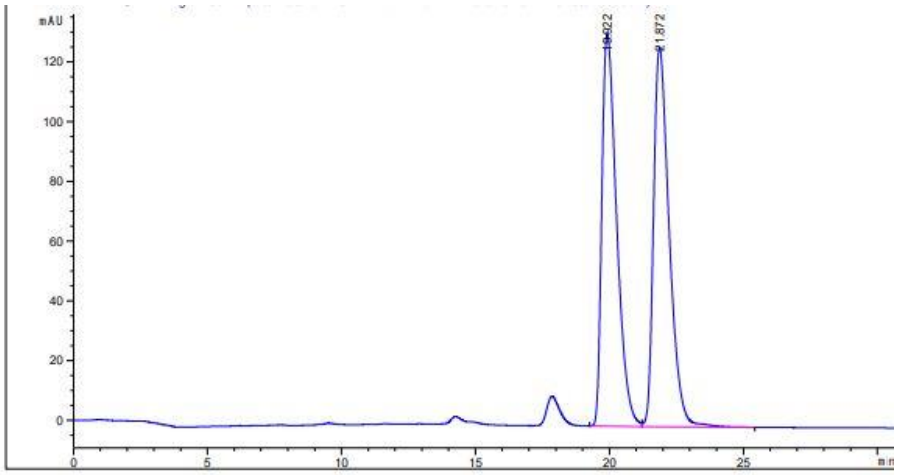
^{13}C NMR (126 MHz, $CDCl_3$): δ 159.6 (*C*(1)), 151.5 (*C*(12)), 147.7 (*C*(9)), 137.0 (*C*(3)), 132.3 (*C*(15)), 129.7 (*C*(7)), 129.7 (*C*(14)), 128.9 (*C*(8)), 127.7 (*C*(5)), 127.6 (*C*(4)), 126.2 (*C*(6)), 120.6 (*C*(13)), 117.8 (*C*(2)), 43.2 (*C*(10)), 37.4 (*C*(11)), 20.8 (*C*(16)).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{18}H_{17}N_2$) requires 261.1386 m/z, found 261.1378 m/z.

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 90:10 hexane:isopropanol, 250 nm, t_{major} = 25.5 min, t_{minor} = 23.6 min.

n.b. retention time drift is >5%, see section 3.6.1 for details.

$[\alpha]_D^{23}$ −20.8° (*c* = 1.0, $CHCl_3$).



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

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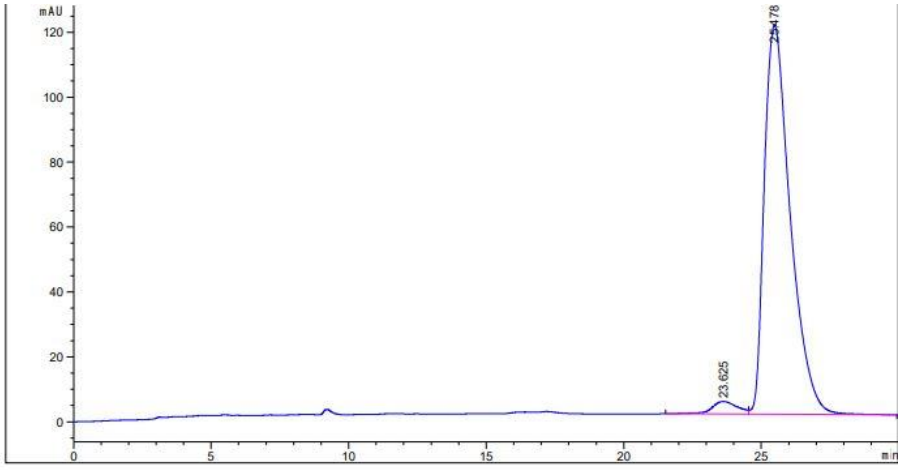
2	21.872	VB	0.6196	5159.43945	127.00171	50.5815

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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  23.625 BV    0.8964  254.11633    3.88838   3.1271
   2  25.478 VBA   1.0030 7872.26904  119.94492  96.8729
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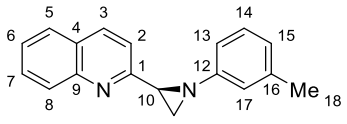
(*S*)-2-(1-(*m*-Tolyl)aziridin-2-yl)quinoline 3.58



Chemical Formula: $C_{18}H_{16}N_2$
Exact Mass: 260.1313
Molecular Weight: 260.3400

Racemic:

Prepared according to General Procedure E using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), *m*-toluidine (26.8 mg, 0.25 mmol, 1.0 equiv), TFA (3.8 µL, 0.05 mmol, 20 mol%), NaH (60% dispersion in mineral oil, 20 mg, 0.50 mmol, 2.0 equiv), and THF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure E (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (38.7 mg, 59%).

Enantioenriched:

Prepared according to General Procedure F using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), *m*-toluidine (26.8 mg, 0.25 mmol, 1.0 equiv), (*S*)-TCYP (12.4 mg, 12.5 µmol, 5 mol%), 0.6 M LiHMDS in THF (0.5 mL, 0.3 mmol, 1.2 equiv), and 2-MeTHF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure F (silica gel, EtOAc:cyclohexane, 5:95 to 10:90) to afford the desired product as a pale yellow solid (50.1 mg, 77%). The enantiomeric ratio (96:4) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 1601, 1504, 1485 cm^{-1}.

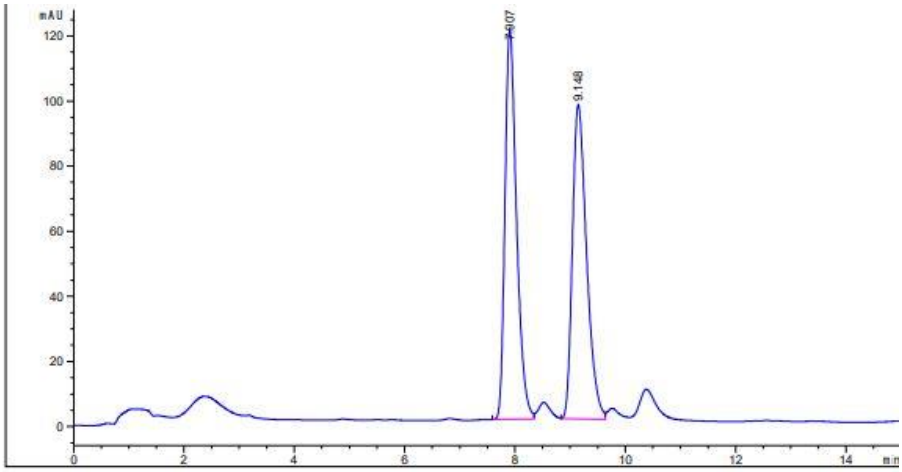
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.5 Hz, 1H, C(3)*H*), 8.11 (d, *J* = 8.4 Hz, 1H, C(8)*H*), 7.82 (d, *J* = 8.1 Hz, 1H, C(5)*H*), 7.73 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H, C(7)*H*), 7.53 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H, C(6)*H*), 7.47 (d, *J* = 8.5 Hz, 1H, C(2)*H*), 7.16 (t, *J* = 7.7 Hz, 1H, C(14)*H*), 6.95 – 6.89 (m, 2H, C(13)*H*, C(17)*H*), 6.84 (d, *J* = 7.5 Hz, 1H, C(15)*H*), 3.52 – 3.49 (m, 1H, C(10)*H*), 2.61 – 2.59 (m, 2H, C(11)*H*), 2.32 (s, 3H, C(18)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.7 (*C*(1)), 153.9 (*C*(12)), 147.8 (*C*(9)), 139.1 (*C*(16)), 137.1 (*C*(3)), 129.8 (*C*(7)), 129.1 (*C*(14)), 129.0 (*C*(8)), 127.8 (*C*(5)), 127.7 (*C*(4)), 126.3 (*C*(6)), 123.8 (*C*(15)), 121.5 (*C*(17)), 117.8 (*C*(13)), 117.8 (*C*(2)), 43.1 (*C*(10)), 37.4 (*C*(11)), 21.5 (*C*(18)).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{18}H_{17}N_2$) requires 261.1386 m/z, found 261.1376 m/z.

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 50:50 hexane:isopropanol, 250 nm, t_{major} = 8.2 min, t_{minor} = 9.9 min.

$[\alpha]_D^{23}$ −156° (*c* = 1.0, $CHCl_3$).



Area Percent Report

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Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=250 nm

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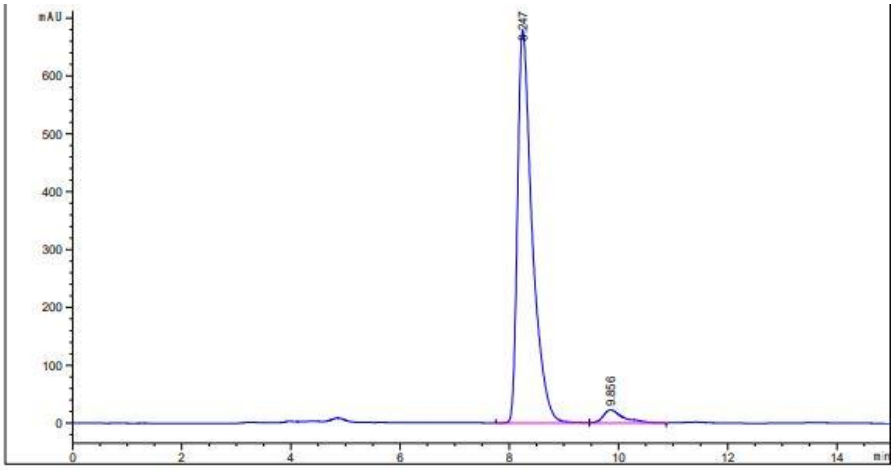
2	9.148	BV	0.2737	1721.87036	96.48779	49.7268

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                      Area Percent Report
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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.247 BV    0.2781 1.27008e4   678.57654  95.7379
   2   9.856 VB    0.3662  565.42218   22.48123   4.2621
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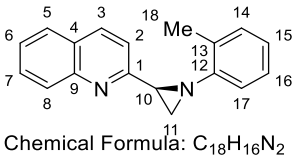
(*S*)-2-(1-(*o*-Tolyl)aziridin-2-yl)quinoline 3.59



Chemical Formula: $C_{18}H_{16}N_2$
Exact Mass: 260.1313
Molecular Weight: 260.3400

Racemic:

Prepared according to General Procedure E using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), *o*-toluidine (26.8 mg, 0.25 mmol, 1.0 equiv), TFA (3.8 µL, 0.05 mmol, 20 mol%), NaH (60% dispersion in mineral oil, 20 mg, 0.50 mmol, 2.0 equiv), and THF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure E (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (33.8 mg, 52%).

Enantioenriched:

Prepared according to General Procedure F using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), *o*-toluidine (26.8 mg, 0.25 mmol, 1.0 equiv), (*S*)-TCYP (12.4 mg, 12.5 µmol, 5 mol%), 0.6 M LiHMDS in THF (0.5 mL, 0.3 mmol, 1.2 equiv), and 2-MeTHF (500 µL, 0.5 M) for 39 h. The reaction mixture was subjected to the purification outlined in General Procedure F (silica gel, EtOAc:cyclohexane, 5:95 to 10:90) to afford the desired product as a pale yellow solid (50.1 mg, 77%). The enantiomeric ratio (90:10) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 1599, 1504, 1489 cm^{-1}.

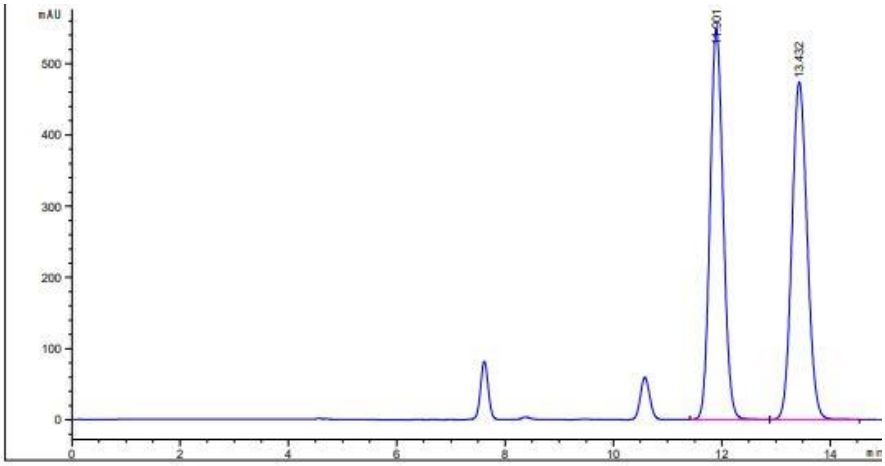
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.6 Hz, 1H, C(3)*H*), 8.11 (d, *J* = 8.5 Hz, 1H, C(8)*H*), 7.83 (dd, *J* = 8.1, 1.1 Hz, 1H, C(5)*H*), 7.73 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H, C(7)*H*), 7.57 – 7.50 (m, 2H, C(6)*H*, C(2)*H*), 7.20 – 7.11 (m, 2H, C(14)*H*, C(16)*H*), 7.02 – 6.94 (m, 2H, C(15)*H*, C(17)*H*), 3.41 (dd, *J* = 6.5, 3.2 Hz, 1H, C(10)*H*), 2.66 (dd, *J* = 6.5, 1.0 Hz, 1H, C(11)*H*), 2.62 (dd, *J* = 3.2, 1.1 Hz, 1H, C(11)*H*), 2.25 (s, 3H, C(18)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.7 (*C*(1)), 151.4 (*C*(12)), 147.8 (*C*(9)), 137.1 (*C*(3)), 131.0 (*C*(13)), 130.7 (*C*(14)), 129.8 (*C*(7)), 129.0 (*C*(8)), 127.8 (*C*(5)), 127.7 (*C*(4)), 126.6 (*C*(16)), 126.3 (*C*(6)), 122.9 (*C*(15)), 119.1 (*C*(17)), 117.6 (*C*(2)), 43.5 (*C*(10)), 37.4 (*C*(11)), 18.5 (*C*(18)).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{18}H_{17}N_2$) requires 261.1386 m/z, found 261.1377 m/z.

HPLC analysis using a chiral column: Chiral Art Amylose-C 5 µm column, 1.0 mL/min, 99:1 hexane:isopropanol, 250 nm, t_{major} = 12.2 min, t_{minor} = 13.9 min.

$[\alpha]_D^{23}$ −144° (*c* = 1.0, $CHCl_3$).

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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  11.901 VB    0.2618 9233.72168  548.90411  49.9473
   2  13.432 BB    0.3033 9253.20020  474.24991  50.0527
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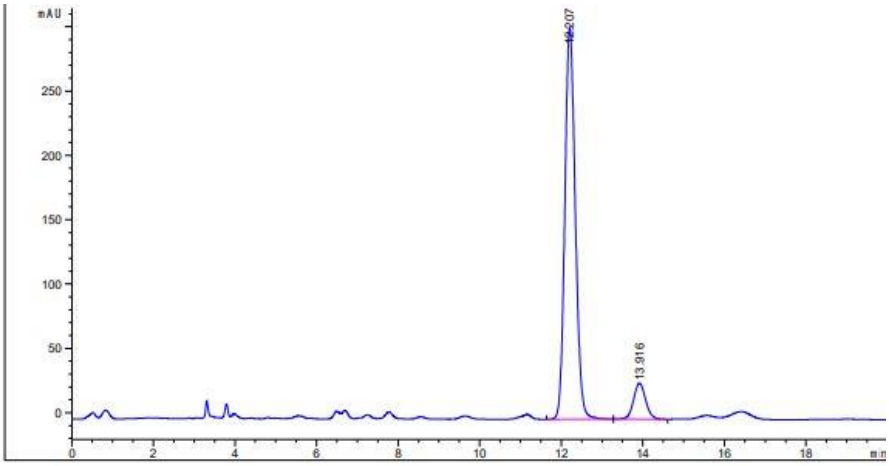


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  12.207 BB    0.2736 5393.33887  304.45407  90.4184
   2  13.916 BB    0.3173  571.52673   27.93714   9.5816
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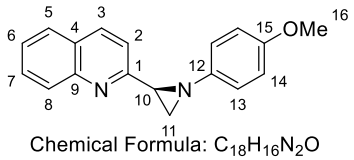
(*S*)-2-(1-(4-Methoxyphenyl)aziridin-2-yl)quinoline 3.60



Chemical Formula: $C_{18}H_{16}N_2O$
Exact Mass: 276.1263
Molecular Weight: 276.3390

Racemic:

Prepared according to General Procedure E using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), *p*-anisidine (30.8 mg, 0.25 mmol, 1.0 equiv), TFA (3.8 µL, 0.05 mmol, 20 mol%), NaH (60% dispersion in mineral oil, 20 mg, 0.50 mmol, 2.0 equiv), and THF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure E (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (30.2 mg, 44%).

Enantioenriched:

Prepared according to General Procedure F using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), *p*-anisidine (30.8 mg, 0.25 mmol, 1.0 equiv), (*S*)-TCYP (12.4 mg, 12.5 µmol, 5 mol%), 0.6 M LiHMDS in THF (0.5 mL, 0.3 mmol, 1.2 equiv), and 2-MeTHF (500 µL, 0.5 M) for 39 h. The reaction mixture was subjected to the purification outlined in General Procedure F (silica gel, EtOAc:cyclohexane, 5:95 to 10:90) to afford the desired product as a pale yellow solid (49.5 mg, 72%). The enantiomeric ratio (95:5) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 1504, 1240 cm^{-1}.

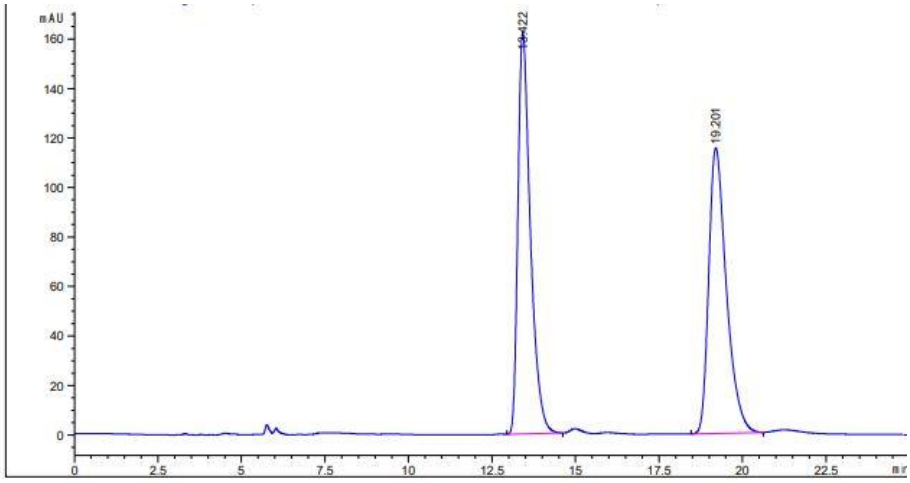
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.5 Hz, 1H, C(3)*H*), 8.10 (d, *J* = 8.5 Hz, 1H, C(8)*H*), 7.81 (d, *J* = 8.1 Hz, 1H, C(5)*H*), 7.72 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H, C(7)*H*), 7.52 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H, C(6)*H*), 7.46 (d, *J* = 8.5 Hz, 1H, C(2)*H*), 7.06 – 7.01 (m, 2H, C(13)*H*), 6.85 – 6.79 (m, 2H, C(14)*H*), 3.77 (s, 3H, C(16)*H*), 3.45 (dd, *J* = 6.5, 3.2 Hz, 1H, C(10)*H*), 2.59 (dd, *J* = 3.2, 1.1 Hz, 1H, C(11)*H*), 2.55 (dd, *J* = 6.6, 1.1 Hz, 1H, C(11)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.7 (*C*(1)), 155.5 (*C*(12)), 147.8 (*C*(9)), 147.3 (*C*(15)), 137.0 (*C*(3)), 129.8 (*C*(7)), 129.0 (*C*(8)), 127.8 (*C*(5)), 127.7 (*C*(4)), 126.3 (*C*(6)), 121.6 (*C*(13)), 117.9 (*C*(2)), 114.4 (*C*(14)), 55.6 (*C*(16)), 43.5 (*C*(10)), 37.6 (*C*(11)).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{18}H_{17}N_2O$) requires 277.1335 m/z, found 277.1326 m/z.

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 50:50 hexane:isopropanol, 250 nm, t_{major} = 20.0 min, t_{minor} = 13.9 min.

$[\alpha]_D^{23}$ −168° (*c* = 0.5, $CHCl_3$).

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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
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   2  19.201 BB    0.5551 4222.56250  115.38980  50.0970
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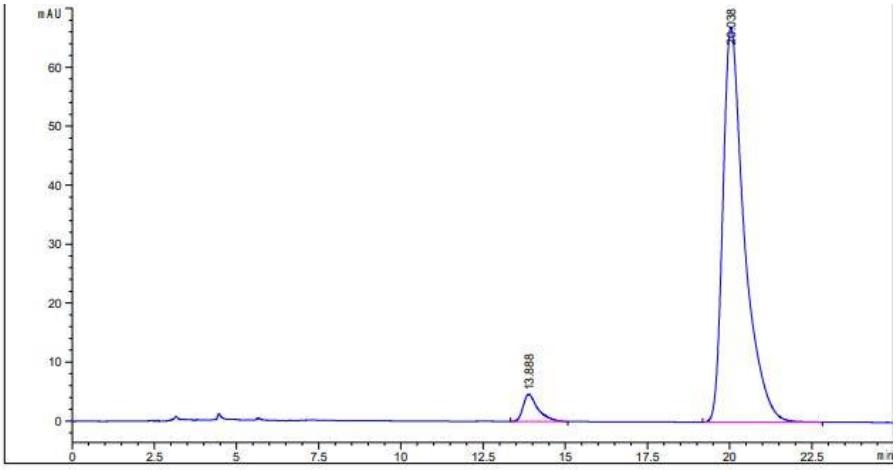


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
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   2  20.038 BB    0.6697 3040.76855   66.94771  95.4674
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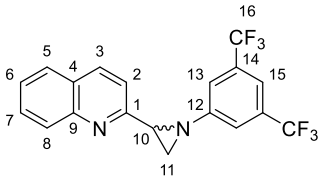
2-(1-(3,5-Bis(trifluoromethyl)phenyl)aziridin-2-yl)quinoline 3.61



Chemical Formula: $C_{19}H_{12}F_6N_2$
Exact Mass: 382.0905
Molecular Weight: 382.3094

Racemic:

Prepared according to General Procedure E using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), 3,5-bis(trifluoromethyl)aniline (39 µL, 0.25 mmol, 1.0 equiv), TFA (3.8 µL, 0.05 mmol, 20 mol%), NaH (60% dispersion in mineral oil, 20 mg, 0.50 mmol, 2.0 equiv), and THF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure E (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (36.6 mg, 38%).

Enantioenriched:

Prepared according to General Procedure F using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), 3,5-bis(trifluoromethyl)aniline (39 µL, 0.25 mmol, 1.0 equiv), (*S*)-TCYP (12.4 mg, 12.5 µmol, 5 mol%), 0.6 M LiHMDS in THF (0.5 mL, 0.3 mmol, 1.2 equiv), and 2-MeTHF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure F (silica gel, EtOAc:cyclohexane, 5:95 to 10:90) to afford the desired product as a pale yellow solid (60.6 mg, 63%). The enantiomeric ratio (52:48) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 1373, 1275, 1124 cm^{-1}.

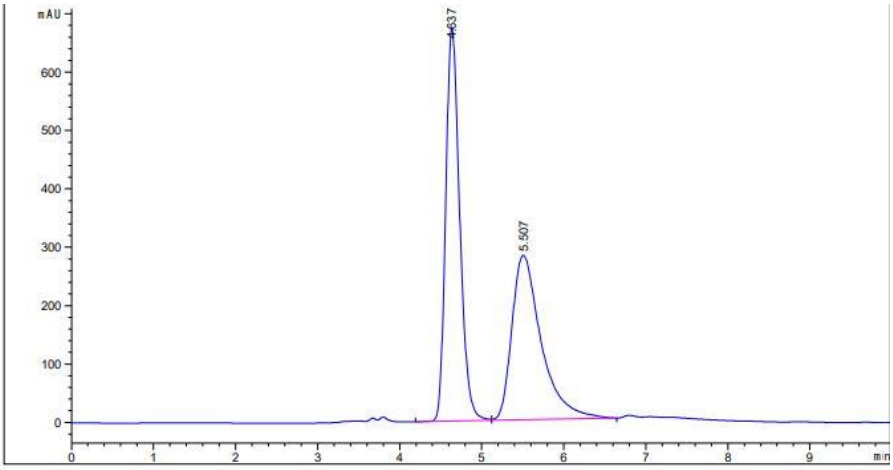
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 (d, *J* = 8.5 Hz, 1H, C(3)*H*), 8.11 (d, *J* = 8.5 Hz, 1H, C(8)*H*), 7.82 (d, *J* = 8.1 Hz, 1H, C(5)*H*), 7.74 (t, *J* = 7.7 Hz, 1H, C(7)*H*), 7.57 – 7.49 (m, 4H, C(6)*H*, C(13)*H*, C(15)*H*), 7.44 (d, *J* = 8.5 Hz, 1H, C(2)*H*), 3.63 (dd, *J* = 6.5, 3.2 Hz, 1H, C(10)*H*), 2.79 (app. d, *J* = 3.2 Hz, 1H, C(11)*H*), 2.69 (app. d, *J* = 6.6 Hz, 1H, C(11)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 157.8 (*C*(1)), 155.2 (*C*(12)), 147.8 (*C*(9)), 137.4 (*C*(3)), 132.6 (q, ^{2}J = 33.3 Hz, *C*(14)), 130.1 (*C*(7)), 129.0 (*C*(8)), 127.8 (*C*(4), *C*(5)), 126.7 (*C*(6)), 123.3 (q, ^{1}J = 272.8 Hz, *C*(16)), 121.2 – 120.8 (m, *C*(13)), 117.6 (*C*(2)), 116.6 – 116.4 (m, *C*(15)), 43.5 (*C*(10)), 37.5 (*C*(11)).

^{19}F NMR (470 MHz, $CDCl_3$): δ −62.96.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{19}H_{13}F_6N_2$) requires 383.0977 m/z, found 383.0974 m/z.

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 50:50 hexane:isopropanol, 250 nm, t_{major} = 4.6 min, t_{minor} = 5.5 min.

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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
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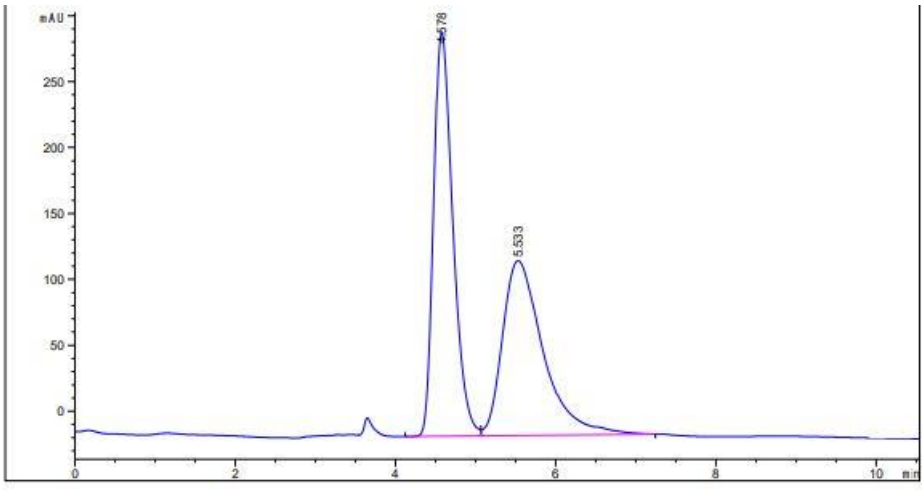


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   4.578 BV    0.2560 5113.68115  306.25858  52.2155
   2   5.533 VB    0.5477 4679.73389  132.40862  47.7845
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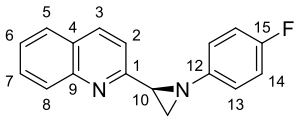
(*S*)-2-(1-(4-Fluorophenyl)aziridin-2-yl)quinoline 3.62



Chemical Formula: $C_{17}H_{13}FN_2$
Exact Mass: 264.1063
Molecular Weight: 264.3034

Racemic:

Prepared according to General Procedure E using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), 4-fluoroaniline (27 µL, 0.25 mmol, 1.0 equiv), TFA (3.8 µL, 0.05 mmol, 20 mol%), NaH (60% dispersion in mineral oil, 20 mg, 0.50 mmol, 2.0 equiv), and THF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure E (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (32.7 mg, 49%).

Enantioenriched:

Prepared according to General Procedure F using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), 4-fluoroaniline (27 µL, 0.25 mmol, 1.0 equiv), (*S*)-TCYP (12.4 mg, 12.5 µmol, 5 mol%), 0.6 M LiHMDS in THF (0.5 mL, 0.3 mmol, 1.2 equiv), and 2-MeTHF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure F (silica gel, EtOAc:cyclohexane, 5:95 to 10:90) to afford the desired product as a pale yellow solid (47.4 mg, 72%). The enantiomeric ratio (96:4) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 1501, 1215 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.5 Hz, 1H, C(3)*H*), 8.10 (d, *J* = 8.5 Hz, 1H, C(8)*H*), 7.81 (d, *J* = 8.1 Hz, 1H, C(5)*H*), 7.73 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H, C(7)*H*), 7.56 – 7.50 (m, 1H, C(6)*H*), 7.44 (d, *J* = 8.5 Hz, 1H, C(2)*H*), 7.07 – 7.01 (m, 2H, C(13)*H*), 6.98 – 6.91 (m, 2H, C(14)*H*), 3.47 (dd, *J* = 6.6, 3.2 Hz, 1H, C(10)*H*), 2.63 (dd, *J* = 3.2, 1.0 Hz, 1H, C(11)*H*), 2.57 (dd, *J* = 6.6, 1.0 Hz, 1H, C(11)*H*).

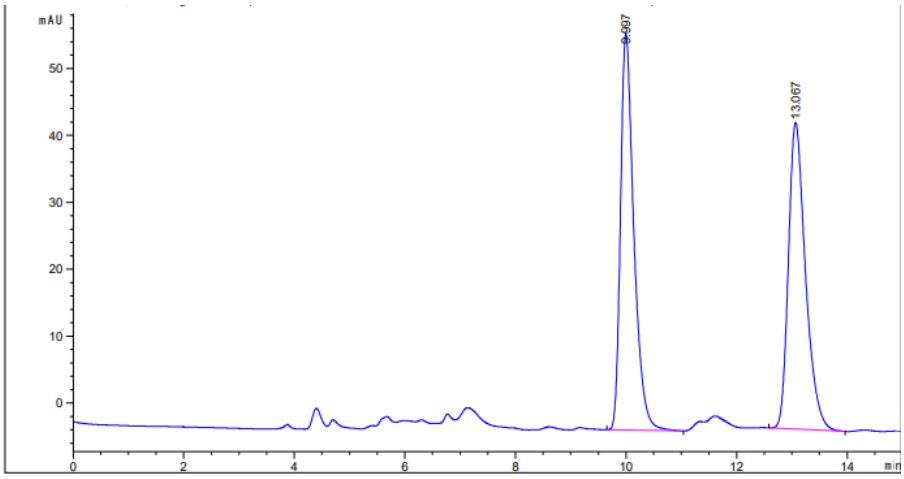
^{13}C NMR (126 MHz, $CDCl_3$): δ 159.2 (*C*(1)), 158.9 (d, ^{1}J = 240.8 Hz, *C*(15)), 150.0 (d, ^{4}J = 2.2 Hz, *C*(12)), 147.8 (*C*(9)), 137.1 (*C*(3)), 129.9 (*C*(7)), 129.0 (*C*(8)), 127.8 (*C*(5)), 127.7 (*C*(4)), 126.4 (*C*(6)), 121.8 (d, ^{3}J = 8.0 Hz, *C*(13)), 117.8 (*C*(2)), 115.8 (d, ^{2}J = 22.6 Hz, *C*(14)), 43.5 (*C*(10)), 37.5 (*C*(11)).

^{19}F NMR (470 MHz, $CDCl_3$): δ −120.87.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{17}H_{14}FN_2$) requires 265.1136 m/z, found 265.1129 m/z.

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 50:50 hexane:isopropanol, 250 nm, t_{major} = 11.1 min, t_{minor} = 8.5 min.

$[\alpha]_D^{23}$ −182° (*c* = 1.0, $CHCl_3$).

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Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
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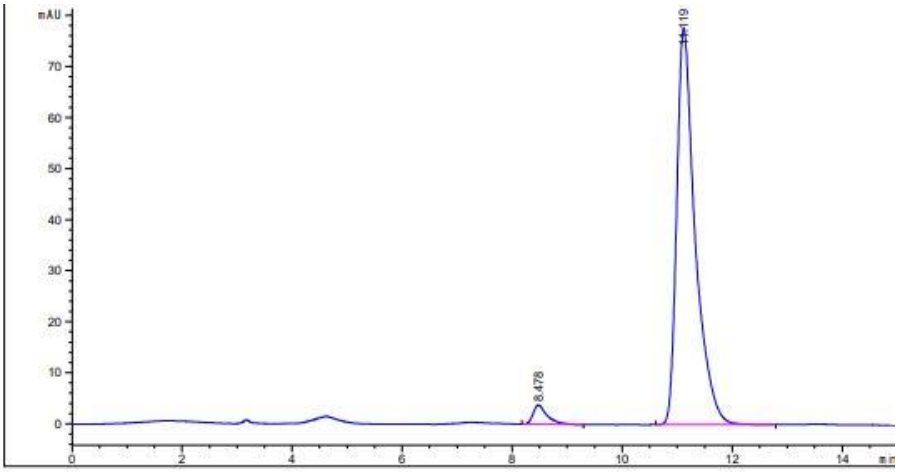


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.478 BB    0.2592   67.20209    3.76458   3.5852
   2  11.119 BB    0.3428 1807.23425   77.66723  96.4148
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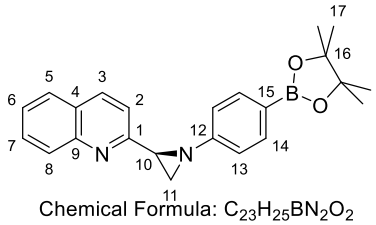
(*S*)-2-(1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)aziridin-2-yl)quinoline 3.63



Chemical Formula: $C_{23}H_{25}BN_2O_2$
Exact Mass: 372.2009
Molecular Weight: 372.2750

Racemic:

Prepared according to General Procedure E using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), 4-aminophenylboronic acid pinacol ester (54.8 mg, 0.25 mmol, 1.0 equiv), TFA (3.8 µL, 0.05 mmol, 20 mol%), NaH (60% dispersion in mineral oil, 20 mg, 0.50 mmol, 2.0 equiv), and THF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure E (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (78.4 mg, 84%).

Enantioenriched:

Prepared according to General Procedure F using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), 4-aminophenylboronic acid pinacol ester (54.8 mg, 0.25 mmol, 1.0 equiv), (*S*)-TCYP (12.4 mg, 12.5 µmol, 5 mol%), 0.6 M LiHMDS in THF (0.5 mL, 0.3 mmol, 1.2 equiv), and CPME (500 µL, 0.5 M) for 39 h. The reaction mixture was subjected to the purification outlined in General Procedure F (silica gel, EtOAc:cyclohexane, 5:95 to 10:90) to afford the desired product as a pale yellow solid (72 mg, 77%). The enantiomeric ratio (94:6) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 2978, 1601, 1356, 1142, 1086 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.5 Hz, 1H, C(3)*H*), 8.11 (d, *J* = 8.5 Hz, 1H, C(8)*H*), 7.81 (d, *J* = 8.1 Hz, 1H, C(5)*H*), 7.76 – 7.69 (m, 3H, C(7)*H*, C(14)*H*), 7.53 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H, C(6)*H*), 7.47 (d, *J* = 8.5 Hz, 1H, C(2)*H*), 7.11 (d, *J* = 8.4 Hz, 2H, C(13)*H*), 3.54 (dd, *J* = 6.5, 3.2 Hz, 1H, C(10)*H*), 2.65 (dd, *J* = 3.1, 1.1 Hz, 1H, C(11)*H*), 2.61 (dd, *J* = 6.5, 1.1 Hz, 1H, C(11)*H*), 1.33 (s, 12H, C(17)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.3 (*C*(1)), 156.8 (*C*(12)), 147.8 (*C*(9)), 137.1 (*C*(3)), 136.1 (*C*(14)), 129.8 (*C*(7)), 129.0 (*C*(8)), 127.8 (*C*(5)), 127.7 (*C*(4)), 126.4 (*C*(6)), 120.2 (*C*(13)), 117.9 (*C*(2)), 83.7 (*C*(16)), 43.1 (*C*(10)), 37.3 (*C*(11)), 25.0 (*C*(17)).

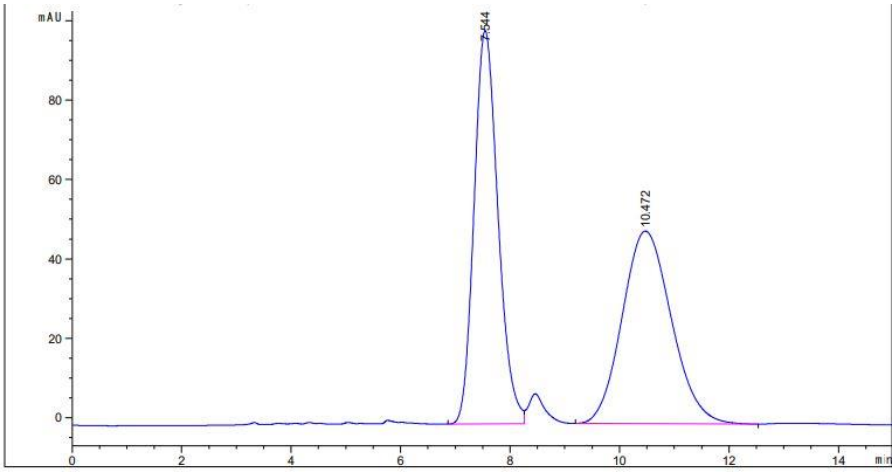
n.b. the carbon bearing boron is not observed due to quadrapolar relaxation.

^{11}B NMR (126 MHz, $CDCl_3$): δ 30.96.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{23}H_{26}{}^{11}BN_2O_2$) requires 373.2082 m/z, found 373.2073 m/z.

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 50:50 hexane:isopropanol, 250 nm, t_{major} = 10.5 min, t_{minor} = 7.4 min.

$[\alpha]_D^{23}$ −150° (*c* = 1.0, $CHCl_3$).

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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
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   2  10.472 BB    0.9668 3028.56104   48.53671  50.1308
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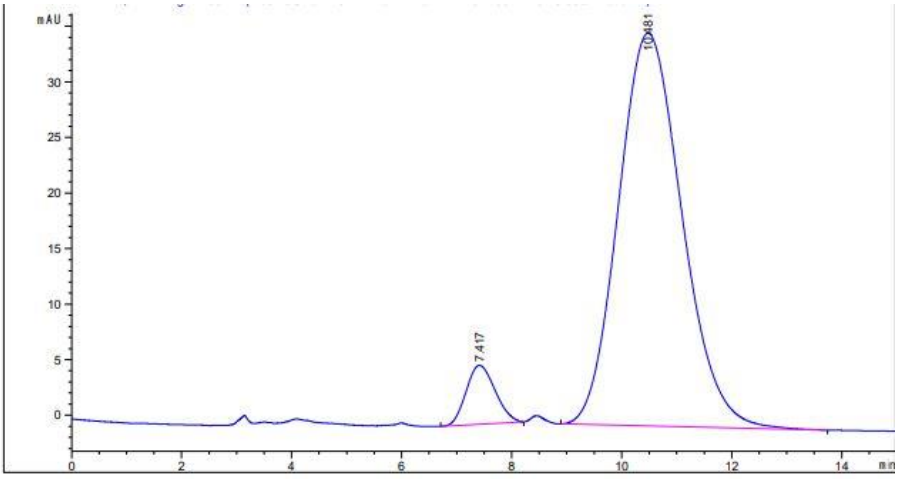


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.417 BB    0.5705  194.19775    5.31403   6.4034
   2  10.481 BB    1.2251 2838.55054   35.35181  93.5966
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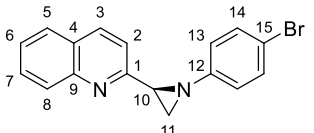
(*S*)-2-(1-(4-Bromophenyl)aziridin-2-yl)quinoline 3.64



Chemical Formula: $C_{17}H_{13}BrN_2$
Exact Mass: 324.0262
Molecular Weight: 325.2090

Racemic:

Prepared according to General Procedure E using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), 4-bromoaniline (43.0 mg, 0.25 mmol, 1.0 equiv), TFA (3.8 µL, 0.05 mmol, 20 mol%), NaH (60% dispersion in mineral oil, 20 mg, 0.50 mmol, 2.0 equiv), and THF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure E (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (67.1 mg, 83%).

Enantioenriched:

Prepared according to General Procedure F using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), 4-bromoaniline (43.0 mg, 0.25 mmol, 1.0 equiv), (*S*)-TCYP (12.4 mg, 12.5 µmol, 5 mol%), 0.6 M LiHMDS in THF (0.5 mL, 0.3 mmol, 1.2 equiv), and 2-MeTHF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure F (silica gel, EtOAc:cyclohexane, 5:95 to 10:90) to afford the desired product as a pale yellow solid (55.5 mg, 68%). The enantiomeric ratio (95:5) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 1483, 827 cm^{-1}.

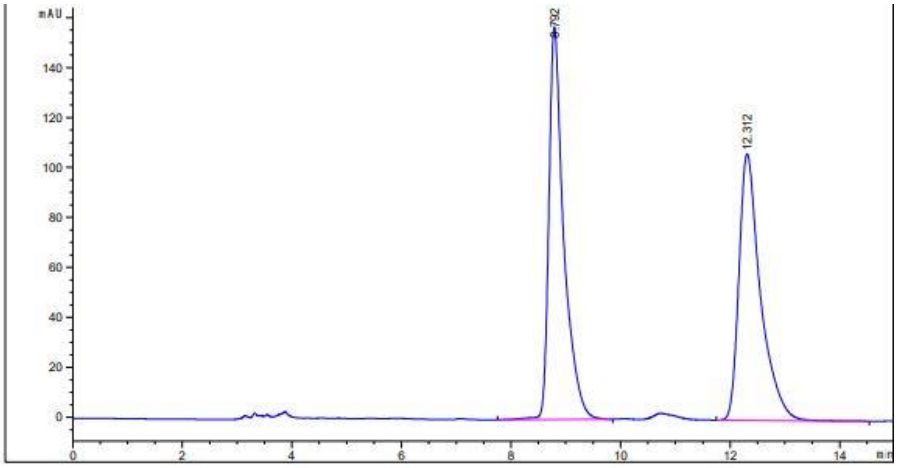
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.5 Hz, 1H, C(3)*H*), 8.10 (d, *J* = 8.5 Hz, 1H, C(8)*H*), 7.81 (d, *J* = 8.1 Hz, 1H, C(5)*H*), 7.73 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H, C(7)*H*), 7.56 – 7.50 (m, 1H, C(6)*H*), 7.43 (d, *J* = 8.5 Hz, 1H, C(2)*H*), 7.39 – 7.34 (m, 2H, C(14)*H*), 7.00 – 6.94 (m, 2H, C(13)*H*), 3.48 (dd, *J* = 6.6, 3.2 Hz, 1H, C(10)*H*), 2.65 (dd, *J* = 3.2, 1.0 Hz, 1H, C(11)*H*), 2.56 (dd, *J* = 6.6, 1.0 Hz, 1H, C(11)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 158.9 (*C*(1)), 153.1 (*C*(12)), 147.8 (*C*(9)), 137.2 (*C*(3)), 132.1 (*C*(14)), 129.9 (*C*(7)), 129.0 (*C*(8)), 127.8 (*C*(5)), 127.7 (*C*(4)), 126.5 (*C*(6)), 122.6 (*C*(13)), 117.8 (*C*(2)), 115.5 (*C*(15)), 43.4 (*C*(10)), 37.4 (*C*(11)).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{17}H_{14}{}^{7}BrN_2$) requires 325.0335 m/z, found 325.0326 m/z.

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 50:50 hexane:isopropanol, 250 nm, t_{major} = 12.6 min, t_{minor} = 9.0 min.

$[\alpha]_D^{23}$ −180° (*c* = 1.0, $CHCl_3$).



Area Percent Report

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Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=250 nm

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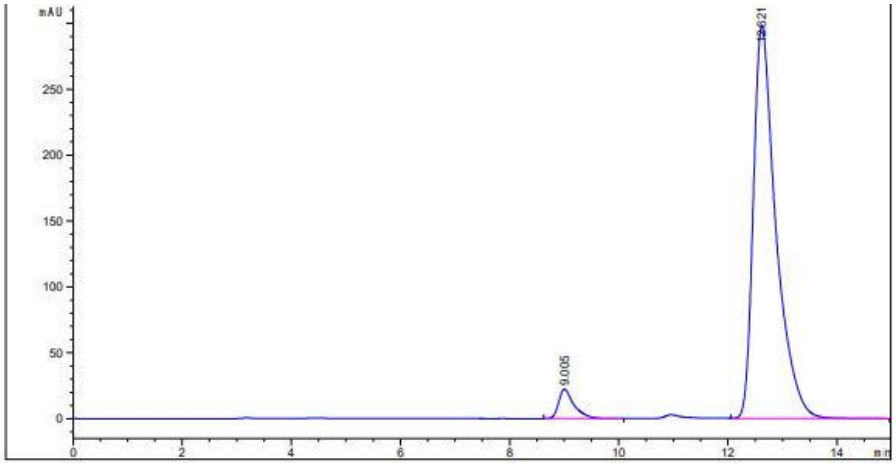
2	12.312	BB	0.4008	2905.71851	106.65909	49.4497

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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
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   2  12.621 VBA   0.4266 8590.33594  298.01236  95.1684
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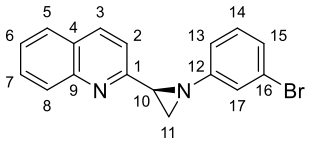
(*S*)-2-(1-(3-Bromophenyl)aziridin-2-yl)quinoline 3.65



Chemical Formula: $C_{17}H_{13}BrN_2$
Exact Mass: 324.0262
Molecular Weight: 325.2090

Racemic:

Prepared according to General Procedure E using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), 3-bromoaniline (27 µL, 0.25 mmol, 1.0 equiv), TFA (3.8 µL, 0.05 mmol, 20 mol%), NaH (60% dispersion in mineral oil, 20 mg, 0.50 mmol, 2.0 equiv), and THF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure E (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (54.7 mg, 67%).

Enantioenriched:

Prepared according to General Procedure F using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), 3-bromoaniline (27 µL, 0.25 mmol, 1.0 equiv), (*S*)-TCYP (12.4 mg, 12.5 µmol, 5 mol%), 0.6 M LiHMDS in THF (0.5 mL, 0.3 mmol, 1.2 equiv), and CPME (500 µL, 0.5 M) for 39 h. The reaction mixture was subjected to the purification outlined in General Procedure F (silica gel, EtOAc:cyclohexane, 5:95 to 10:90) to afford the desired product as a pale yellow solid (67.4 mg, 75%). The enantiomeric ratio (95:5) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 1587, 1473, 831 cm^{-1}.

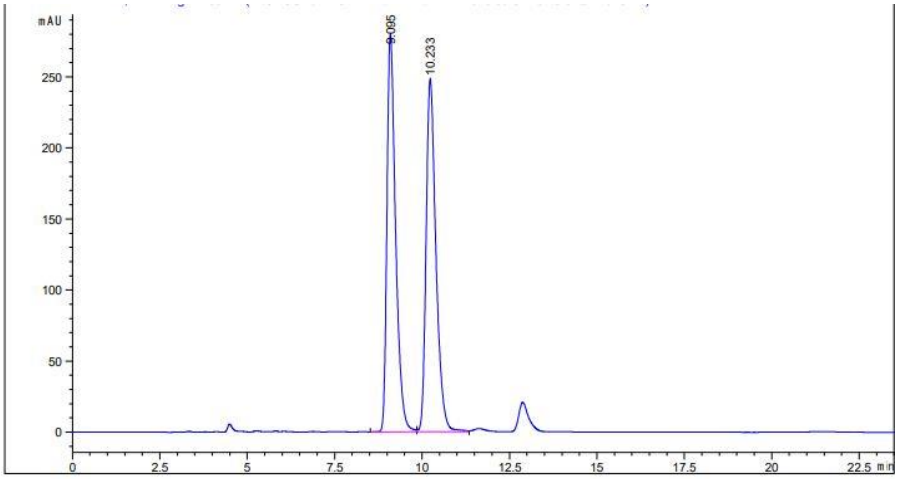
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.5 Hz, 1H, C(3)*H*), 8.10 (d, *J* = 8.5 Hz, 1H, C(8)*H*), 7.81 (d, *J* = 8.1 Hz, 1H, C(5)*H*), 7.73 (t, *J* = 7.7 Hz, 1H, C(7)*H*), 7.53 (t, *J* = 7.5 Hz, 1H, C(6)*H*), 7.43 (d, *J* = 8.5 Hz, 1H, C(2)*H*), 7.29 (s, 1H, C(17)*H*), 7.16 – 7.09 (m, 2H, C(14)*H*, C(15)*H*), 7.02 (d, *J* = 7.3 Hz, 1H, C(13)*H*), 3.54 – 3.50 (m, 1H, C(10)*H*), 2.65 (app. s, 1H, C(11)*H*), 2.60 (app. d, *J* = 6.5 Hz, 1H, C(11)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 158.8 (*C*(1)), 155.4 (*C*(12)), 147.8 (*C*(9)), 137.2 (*C*(3)), 130.5 (*C*(14)), 129.9 (*C*(7)), 129.0 (*C*(8)), 127.8 (*C*(5)), 127.7 (*C*(4)), 126.5 (*C*(6)), 126.1 (*C*(15)), 124.0 (*C*(17)), 122.7 (*C*(16)), 119.6 (*C*(13)), 117.8 (*C*(2)), 43.3 (*C*(10)), 37.3 (*C*(11)).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{17}H_{13}{}^{79}BrN_2$) requires 325.0335 m/z, found 325.0325 m/z.

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 50:50 hexane:isopropanol, 250 nm, t_{major} = 10.2 min, t_{minor} = 9.1 min.

$[\alpha]_D^{23}$ −141° (*c* = 1.0, $CHCl_3$).

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Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   9.095 BV    0.2588 4815.40674  280.04730  49.7402
   2  10.233 VV    0.2969 4865.71826  248.49672  50.2598

Totals :                  9681.12500  528.54402
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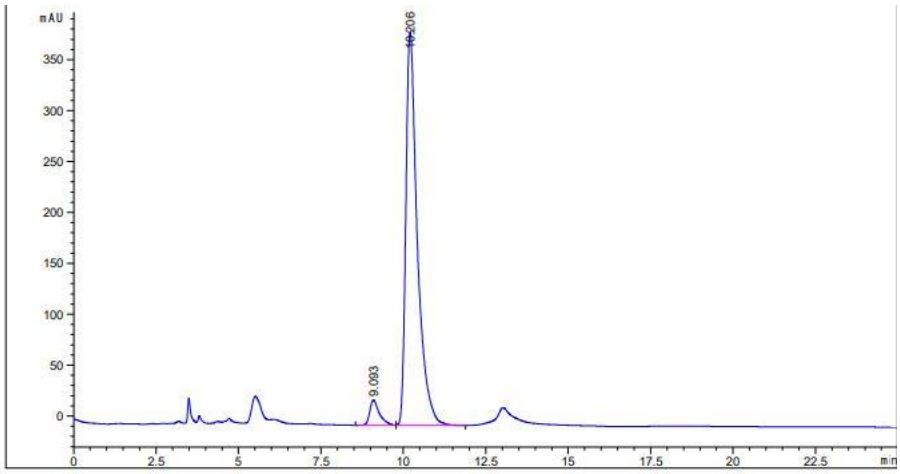


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   9.093 BV    0.2964  500.63089   24.82938   5.0918
   2  10.206 VB    0.3559 9331.48145  386.60541  94.9082
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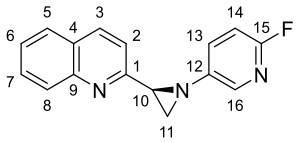
(*S*)-2-(1-(6-fluoropyridin-3-yl)aziridin-2-yl)quinoline 3.66



Chemical Formula: $C_{16}H_{12}FN_3$
Exact Mass: 265.1015
Molecular Weight: 265.2914

Racemic:

Prepared according to General Procedure E using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), 5-amino-2-fluoropyridine (28.0 mg, 0.25 mmol, 1.0 equiv), TFA (3.8 µL, 0.05 mmol, 20 mol%), NaH (60% dispersion in mineral oil, 20 mg, 0.50 mmol, 2.0 equiv), and THF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure E (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (25.9 mg, 39%).

Enantioenriched:

Prepared according to General Procedure F using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), 5-amino-2-fluoropyridine (28.0 mg, 0.25 mmol, 1.0 equiv), (*S*)-TCYP (12.4 mg, 12.5 µmol, 5 mol%), 0.6 M LiHMDS in THF (0.5 mL, 0.3 mmol, 1.2 equiv), and CPME (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure F (silica gel, EtOAc:cyclohexane, 5:95 to 10:90) to afford the desired product as a pale yellow solid (41.2 mg, 62%). The enantiomeric ratio (89:11) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 1477, 1244, 826 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.5 Hz, 1H, C(3)*H*), 8.08 (d, *J* = 8.5 Hz, 1H, C(8)*H*), 7.99 – 7.97 (m, 1H, C(16)*H*), 7.82 (d, *J* = 8.1 Hz, 1H, C(5)*H*), 7.75 – 7.70 (m, 1H, C(7)*H*), 7.57 – 7.47 (m, 2H, C(6)*H*, C(13)*H*), 7.42 (d, *J* = 8.5 Hz, 1H, C(2)*H*), 6.82 (dd, *J* = 8.7, 3.2 Hz, 1H, C(14)*H*), 3.49 (dd, *J* = 6.6, 3.3 Hz, 1H, C(10)*H*), 2.73 (app. d, *J* = 3.3 Hz, 1H, C(11)*H*), 2.59 (app. d, *J* = 6.6 Hz, 1H, C(11)*H*).

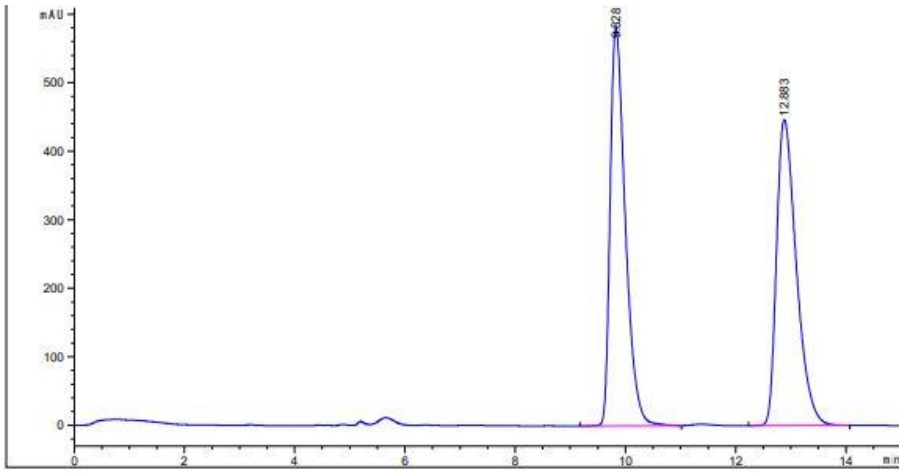
^{13}C NMR (126 MHz, $CDCl_3$): δ 159.6 (d, ^1J = 234.8 Hz, *C*(15)), 158.1 (*C*(1)), 148.0 (d, ^4J = 4.2 Hz, *C*(12)), 147.8 (*C*(9)), 139.4 (d, ^3J = 15.2 Hz, *C*(16)), 137.3 (*C*(3)), 133.7 (d, ^3J = 7.9 Hz, *C*(13)), 130.0 (*C*(7)), 129.0 (*C*(8)), 127.8 (*C*(5)), 127.8 (*C*(4)), 126.6 (*C*(6)), 117.8 (C(2)), 109.5 (d, ^2J = 39.5 Hz, *C*(14)), 43.3 (*C*(10)), 37.2 (*C*(11)).

^{19}F NMR (126 MHz, $CDCl_3$): δ −75.08.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{16}H_{12}FN_3$) requires 266.1080 m/z, found 266.1080 m/z.

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 50:50 hexane:isopropanol, 250 nm, t_{major} = 13.3 min, t_{minor} = 10.0 min.

$[\alpha]_D^{23}$ −144° (*c* = 1.0, $CHCl_3$)

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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
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   1   9.828 BV    0.2916 1.11195e4   581.30688  49.9746
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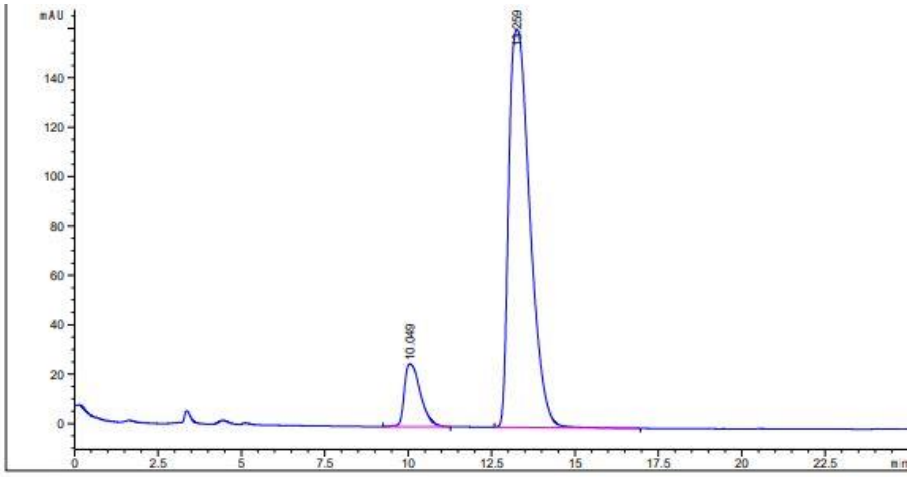


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.049 BB    0.5187  849.50165   25.37230  10.7217
   2  13.259 BB    0.6839 7073.71240  161.15097  89.2783
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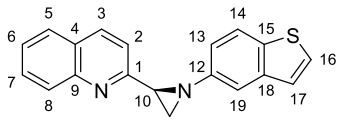
(*S*)-2-(1-(benzo[*b*]thiophen-5-yl)aziridin-2-yl)quinoline 3.67



Chemical Formula: $C_{19}H_{14}N_2S$
Exact Mass: 302.0878
Molecular Weight: 302.3950

Racemic:

Prepared according to General Procedure E using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), benzo[*b*]thiophen-5-amine (37.3 mg, 0.25 mmol, 1.0 equiv), TFA (3.8 µL, 0.05 mmol, 20 mol%), NaH (60% dispersion in mineral oil, 20 mg, 0.50 mmol, 2.0 equiv), and THF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure E (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (6.7 mg, 9%).

Enantioenriched:

Prepared according to General Procedure F using 2-(1-chlorovinyl)quinoline (47.4 mg, 0.25 mmol, 1.0 equiv), benzo[*b*]thiophen-5-amine (37.3 mg, 0.25 mmol, 1.0 equiv), (*S*)-TCYP (12.4 mg, 12.5 µmol, 5 mol%), 0.6 M LiHMDS in THF (0.5 mL, 0.3 mmol, 1.2 equiv), and 2-MeTHF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure F (silica gel, EtOAc:cyclohexane, 5:95 to 10:90) to afford the desired product as a pale yellow solid (37.3 mg, 49%). The enantiomeric ratio (95:5) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 1597, 1502, 1421 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.6 Hz, 1H, C(3)*H*), 8.13 (d, *J* = 8.4 Hz, 1H, C(8)*H*), 7.82 (dd, *J* = 8.2, 1.1 Hz, 1H, C(5)*H*), 7.74 (t, *J* = 7.7 Hz, 2H, C(7)*H*, C(14)*H*), 7.57 – 7.48 (m, 3H, C(2)*H*, C(6)*H*, C(19)*H*), 7.44 (d, *J* = 5.4 Hz, 1H, C(16)*H*), 7.26 – 7.21 (m, 1H, C(17)*H*), 7.19 (dd, *J* = 8.6, 2.0 Hz, 1H, C(13)*H*), 3.58 (dd, *J* = 6.5, 3.2 Hz, 1H, C(10)*H*), 2.69 (dd, *J* = 3.2, 1.2 Hz, 1H, C(11)*H*), 2.67 (dd, *J* = 6.6, 1.2 Hz, 1H, C(11)*H*).

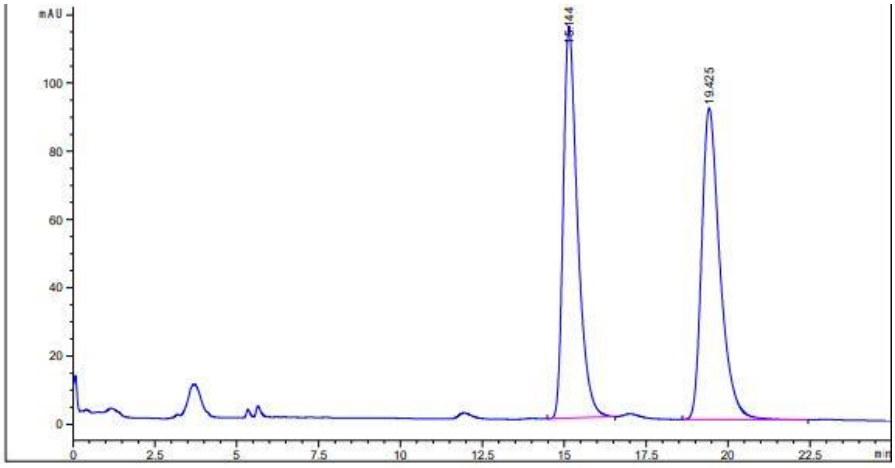
^{13}C NMR (101 MHz, $CDCl_3$): δ 159.5 (*C*(1)), 151.2 (*C*(12)), 147.8 (*C*(9)), 140.4 (*C*(18)), 137.1 (*C*(3)), 134.4 (*C*(15)), 129.8 (*C*(7)), 129.0 (*C*(8)), 127.8 (*C*(5)), 127.7 (*C*(4)), 127.6 (*C*(16)), 126.4 (*C*(6)), 123.5 (*C*(17)), 123.0 (*C*(14)), 119.2 (*C*(13)), 117.9 (*C*(2)), 114.3 (*C*(19)), 43.6 (*C*(10)), 37.7 (*C*(11)).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{19}H_{15}N_2S$) requires 303.0950 m/z, found 303.0943 m/z.

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 50:50 hexane:isopropanol, 250 nm, t_{major} = 21.7 min, t_{minor} = 16.7 min.

n.b. retention time drift is >5%, see section 3.6.1 for details.

$[\alpha]_D^{23}$ −181° (*c* = 1.0, $CHCl_3$).

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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
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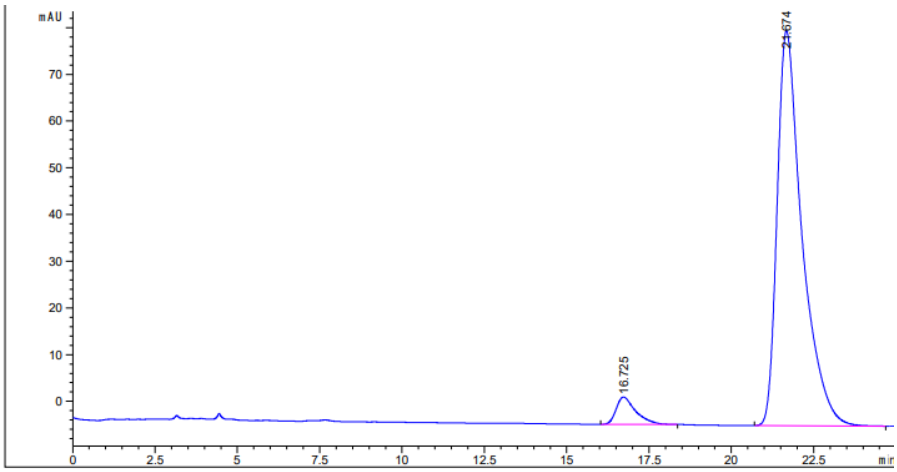


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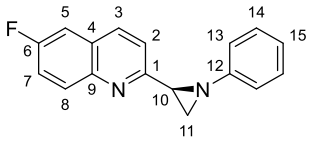
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|-------|
   1  16.725 BB    0.6031  240.30994    5.84907   5.1225
   2  21.674 BB    0.7744 4450.96240   84.54128  94.8775
```

(*R*)-*N*-(2-chloro-2-(6-fluoroquinolin-2-yl)ethyl)aniline 3.68



Chemical Formula: $C_{17}H_{13}FN_2$
Exact Mass: 264.1063
Molecular Weight: 264.3034

Racemic:

Prepared according to General Procedure E using 2-(1-chlorovinyl)-6-fluoroquinoline (20.9 mg, 0.10 mmol, 1.0 equiv), aniline (9.1 µL, 0.1 mmol, 1.0 equiv), TFA (1.5 µL, 0.05 mmol, 20 mol%), NaH (60% dispersion in mineral oil, 8.0 mg, 0.20 mmol, 2.0 equiv), and THF (200 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure E (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) to afford the desired product as a pale yellow solid (6.7 mg, 25%).

Enantioenriched:

Prepared according to General Procedure F using 2-(1-chlorovinyl)-6-fluoroquinoline (51.9 mg, 0.25 mmol, 1.0 equiv), aniline (23 µL, 0.25 mmol, 1.0 equiv), (*S*)-TCYP (12.4 mg, 12.5 µmol, 5 mol%), 0.6 M LiHMDS in THF (0.5 mL, 0.3 mmol, 1.2 equiv), and 2-MeTHF (500 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure F (silica gel, EtOAc:cyclohexane, 5:95 to 10:90) to afford the desired product as a pale yellow solid (21.4 mg, 32%). The enantiomeric ratio (95:5) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 1597, 1489, 1234 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 – 8.10 (m, 2H, C(3)*H*, C(8)*H*), 7.55 – 7.48 (m, 2H, C(2)*H*, C(7)*H*), 7.45 (dd, *J* = 8.8, 2.9 Hz, 1H, C(5)*H*), 7.33 – 7.27 (m, 2H, C(14)*H*), 7.16 – 7.10 (m, 2H, C(13)*H*), 7.05 (tt, *J* = 7.7, 1.2 Hz, 1H, C(15)*H*), 3.52 (dd, *J* = 6.5, 3.2 Hz, 1H, C(10)*H*), 2.66 – 2.62 (m, 2H, C(11)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 160.3 (d, ^1J = 247.7 Hz, *C*(6)), 158.8 (*C*(1)), 153.8 (*C*(12)), 144.8 (*C*(9)), 136.3 (d, ^4J = 5.3 Hz, *C*(3)), 131.4 (d, ^3J = 9.1 Hz, *C*(8)), 129.1 (*C*(14)), 128.2

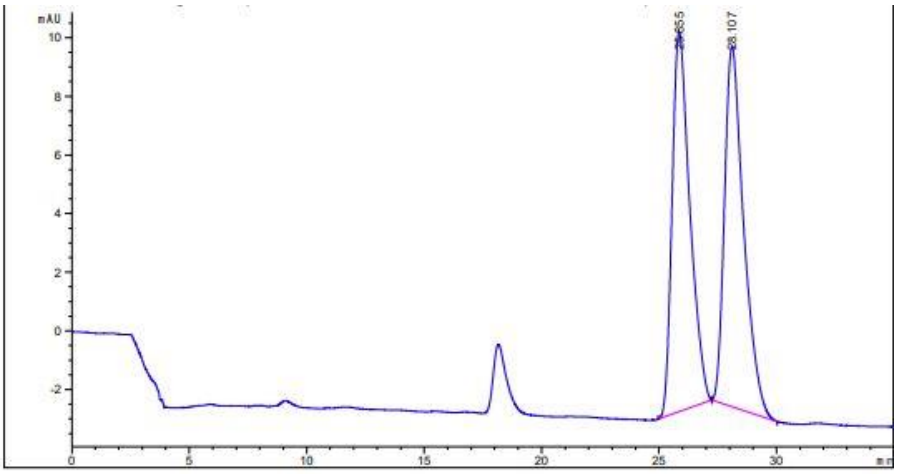
(d, ^3J = 10.0 Hz, *C*(4)), 122.9 (*C*(2)), 120.6 (*C*(13)), 119.9 (d, ^2J = 25.6 Hz, *C*(7)), 118.6 (*C*(15)), 110.7 (d, ^2J = 21.6 Hz, *C*(5)), 42.9 (*C*(10)), 37.2 (*C*(11)).

^{19}F NMR (376 MHz, $CDCl_3$): δ −113.86.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{17}H_{14}FN_2$) requires m/z 265.1136, found 265.1131 m/z.

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 90:10 hexane:isopropanol, 250 nm, t_{major} = 25.4 min, t_{minor} = 28.4 min.

$[\alpha]_D^{23}$ −154° (*c* = 0.5, $CHCl_3$).



Area Percent Report

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Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=250 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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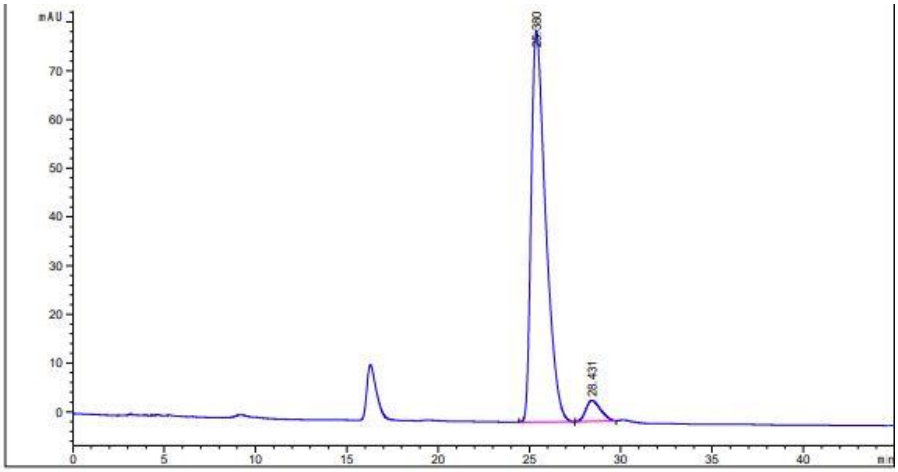
2	28.107	BB	0.8267	696.85138	12.27798	50.6253



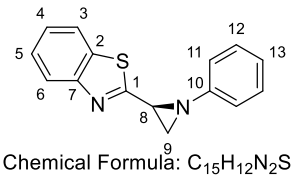
Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=250 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.380	BB	0.8235	4426.71533	80.32028	94.8030
2	28.431	BB	0.8129	242.66660	4.33755	5.1970

(*S*)-2-(1-phenylaziridin-2-yl)benzo[*d*]thiazole 3.70



Chemical Formula: $C_{15}H_{12}N_2S$
Exact Mass: 252.0721
Molecular Weight: 252.3350

Racemic:

A 2 mL HPLC vial was charged with *rac*-*N*-(2-(benzo[*d*]thiazol-2-yl)-2-chloroethyl)aniline (9.4 mg, 0.033 mmol, 1.0 equiv). The vial was then capped and purged with N_2 before addition of THF (500 µL, 0.5 M) and NaH (60% dispersion in mineral oil, 1.6 mg, 0.066 mmol, 2.0 equiv). The resulting mixture was then allowed to stir at rt for 24 h. The reaction was then quenched by sat. aq. NH_4Cl solution (2 mL) and diluted with EtOAc (2 mL). The phases were separated and the aqueous phase was washed with EtOAc (2 mL × 2). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the crude material *via* flash column chromatography (silica gel,

EtOAc:petroleum ether, 5:95 to 10:90) gave the desired product as a pale yellow solid (4.2 mg, 51%).

Enantioenriched:

A 2 mL HPLC vial was charged with (*R*)-*N*-(2-(benzo[*d*]thiazol-2-yl)-2-chloroethyl)aniline (11.2 mg, 0.039 mmol, 1.0 equiv). The vial was then capped and purged with N_2 before addition of toluene (78 µL, 0.5 M). The reaction mixture was cooled to −20 °C for 15 min before the addition of a 0.6 M solution of LiHMDS in toluene (0.078 mL, 0.047 mmol, 1.2 equiv), and the reaction was allowed to stir for a further 30 min before being quenched by sat. aq. NH_4Cl solution (2 mL) and diluted with EtOAc (2 mL). The phases were separated and the aqueous phase was washed with EtOAc (2 mL × 2). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the crude *via* flash column chromatography (silica gel, EtOAc:petroleum ether, 5:95 to 10:90) gave the desired product as a pale yellow solid (6.7 mg, 68%). The enantiomeric ratio (94:6) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 1597, 1489 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.1 Hz, 1H, C(6)*H*), 7.93 – 7.89 (m, 1H, C(3)*H*), 7.51 (ddd, *J* = 8.3, 7.3, 1.2 Hz, 1H, C(4)*H*), 7.41 (td, *J* = 7.7, 7.3, 1.1 Hz, 1H, C(5)*H*), 7.32 (td, *J* = 7.4, 1.9 Hz, 2H, C(12)*H*), 7.13 (dd, *J* = 8.5, 1.1 Hz, 2H, C(11)*H*), 7.10 – 7.05 (m, 1H, C(13)*H*), 3.68 (dd, *J* = 6.3, 3.0 Hz, 1H, C(8)*H*), 2.71 (dd, *J* = 3.0, 1.2 Hz, 1H, C(9)*H*), 2.69 (dd, *J* = 6.4, 1.2 Hz, 1H, C(9)*H*).

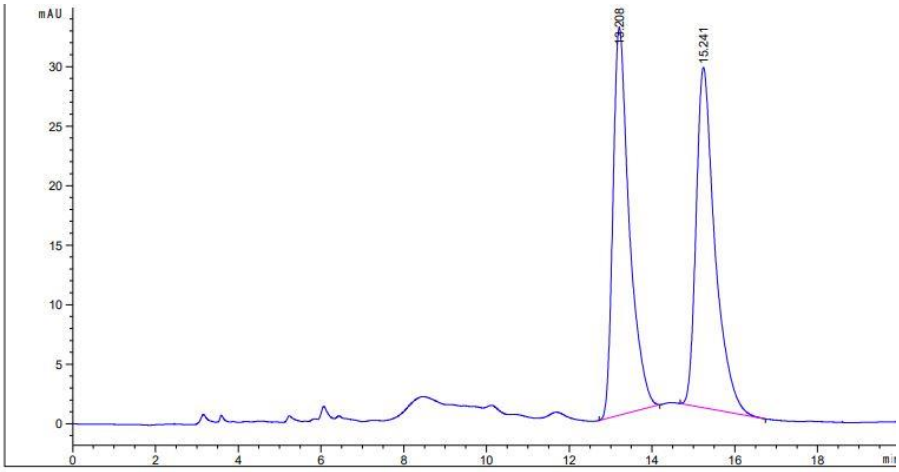
^{13}C NMR (126 MHz, $CDCl_3$): δ 172.2 (*C*(1)), 153.7 (*C*(7)), 152.5 (*C*(10)), 134.7 (*C*(2)), 129.3 (*C*(12)), 126.2 (*C*(4)), 125.1 (*C*(5)), 123.5 (*C*(13)), 122.7 (*C*(6)), 121.9 (*C*(3)), 120.5 (*C*(11)), 40.0 (*C*(8)), 38.7 (*C*(9)).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{15}H_{13}N_2S$) requires m/z 253.0794, found 253.0796 m/z.

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 50:50 hexane:isopropanol, 250 nm, t_{major} = 13.9 min, t_{minor} = 12.2 min.

n.b. retention time drift is >5%, see section 3.6.1 for details.

$[\alpha]_D^{23}$ −233° (*c* = 0.2, $CHCl_3$).

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Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
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   2  15.241 BB    0.4683  904.74438   28.58516  50.2485
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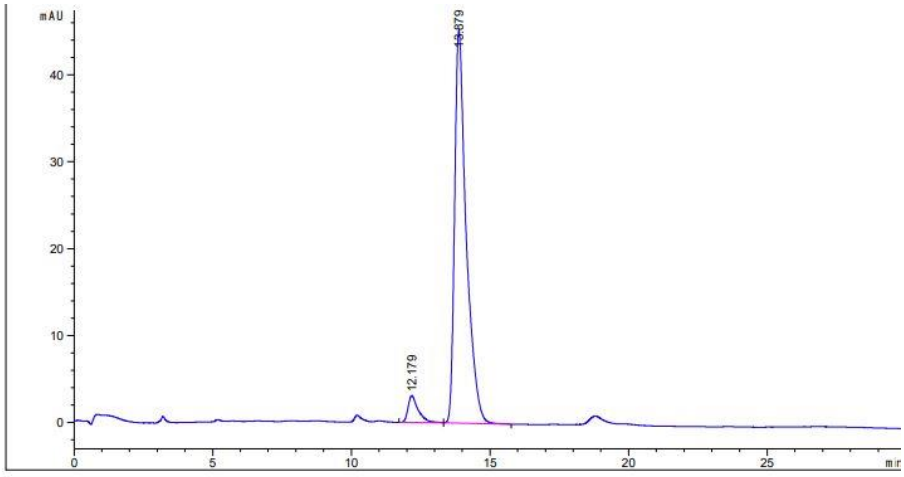


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  12.179 BB    0.3665   78.58322    3.09135   5.6488
   2  13.879 BB    0.4246 1312.56775   45.20705  94.3512
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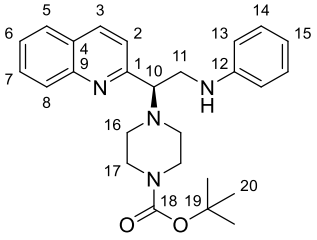
***t*-Butyl (*R*)-4-(2-(phenylamino)-1-(quinolin-2-yl)ethyl)piperazine-1-carboxylate 3.73**



Chemical Formula: $C_{26}H_{32}N_4O_2$
Exact Mass: 432.2525
Molecular Weight: 432.5680

Racemic:

Prepared according to General Procedure G (±)-2-(1-phenylaziridin-2-yl)quinoline (12.3 mg, 0.05 mmol, 1.0 equiv), *N*-Boc-piperazine (9.3 mg, 0.05 mmol, 1.0 equiv), TFA (0.8 µL, 0.02 mmol, 20 mol%), and MeCN (100 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure G (silica gel, EtOAc:petroleum ether, 20:80) to afford the desired product as a pale yellow solid (17.6 mg, 81%).

Enantioenriched:

Prepared according to General Procedure G (*R*)-2-(1-phenylaziridin-2-yl)quinoline (24.6 mg, 0.10 mmol, 1.0 equiv), *N*-Boc-piperazine (18.6 mg, 0.10 mmol, 1.0 equiv), TFA (1.5 µL, 0.02 mmol, 20 mol%), and MeCN (200 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure G (silica gel, EtOAc:petroleum ether, 20:80) to afford the desired product as a pale yellow solid (36.4 mg, 84%). The enantiomeric ratio (96:4) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 1688, 1601, 1503, 1423, 1246, 1169 cm^{-1}.

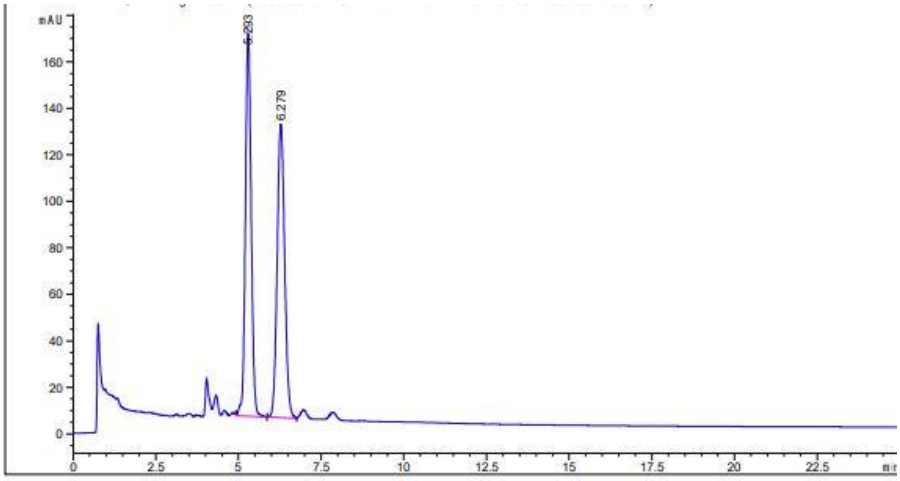
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.4 Hz, 1H, C(3)*H*), 8.12 (d, *J* = 8.5 Hz, 1H, C(8)*H*), 7.84 (d, *J* = 8.1 Hz, 1H, C(5)*H*), 7.75 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1H, C(7)*H*), 7.61 – 7.54 (m, 1H, C(6)*H*), 7.51 (d, *J* = 8.4 Hz, 1H, C(2)*H*), 7.22 – 7.15 (m, 2H, C(14)*H*), 6.74 – 6.69 (m, 1H, C(15)*H*), 6.67 (d, *J* = 7.7 Hz, 2H, C(13)*H*), 4.13 (app. s, 1H, C(10)*H*), 3.87 – 3.76 (m, 1H, C(11)*H*), 3.68 (dd, *J* = 12.3, 6.4 Hz, 1H, C(11)*H*), 3.49 (s, 4H, C(17)*H*), 2.64 (s, 4H, C(16)*H*), 1.44 (s, 9H, C(20)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.1 (*C*(1)), 154.6 (*C*(18)), 148.2 (*C*(9)), 147.6 (*C*(12)), 136.3 (*C*(3)), 129.6 (*C*(7)), 129.5 (*C*(14)), 129.3 (*C*(8)), 127.6 (*C*(4)), 127.5 (*C*(5)), 126.6 (*C*(6)), 121.4 (*C*(2)), 117.5 (*C*(15)), 113.1 (*C*(13)), 79.7 (*C*(19)), 69.0 (*C*(10)), 49.8 (*C*(16)), 43.5 (*C*(11), *C*(17)), 28.4 (*C*(20)).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{26}H_{33}N_4O_2$) requires m/z 433.2598, found 433.2594 m/z.

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 90:10 hexane:isopropanol, 250 nm, t_{major} = 5.3 min, t_{minor} = 6.3 min.

$[\alpha]_D^{23}$ +12.8° (*c* = 0.5, $CHCl_3$).

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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
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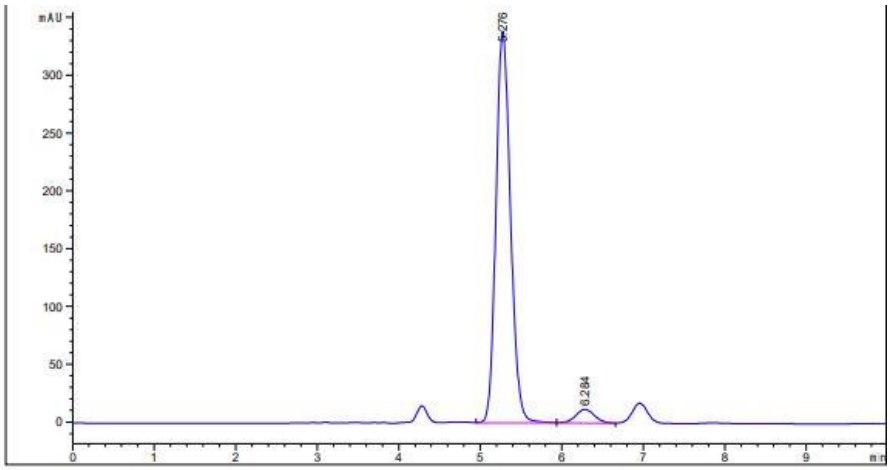


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   5.276 VV    0.1927 4198.18311  338.54330  95.5284
   2   6.284 VV    0.2546  196.51535   11.94362   4.4716
```
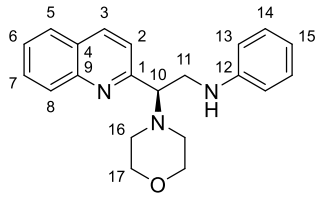

(*R*)-*N*-(2-morpholino-2-(quinolin-2-yl)ethyl)aniline 3.74



Chemical Formula: $C_{21}H_{23}N_3O$
Exact Mass: 333.1841
Molecular Weight: 333.4350

Racemic:

Prepared according to General Procedure G (±)-2-(1-phenylaziridin-2-yl)quinoline (24.6 mg, 0.10 mmol, 1.0 equiv), morpholine (8.8 µL, 0.10 mmol, 1.0 equiv), TFA (1.5 µL, 0.02 mmol, 20 mol%), and MeCN (200 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure G (silica gel, EtOAc:petroleum ether, 20:80) to afford the desired product as a pale yellow solid (14.5 mg, 43%).

Enantioenriched:

Prepared according to General Procedure G (*R*)-2-(1-phenylaziridin-2-yl)quinoline (24.6 mg, 0.10 mmol, 1.0 equiv), morpholine (8.8 µL, 0.10 mmol, 1.0 equiv), TFA (1.5 µL, 0.02 mmol, 20 mol%), and MeCN (200 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure G (silica gel, EtOAc:petroleum ether, 20:80) to afford the desired product as a pale yellow solid (13.0 mg, 39%). The enantiomeric ratio (96:4) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 1601, 1504, 1115 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 – 8.03 (m, 2H, C(3)*H*, C(8)*H*), 7.85 (d, *J* = 8.1 Hz, 1H, C(5)*H*), 7.76 (t, *J* = 7.6 Hz, 1H, C(7)*H*), 7.61 – 7.51 (m, 2H, C(6)*H*, C(2)*H*), 7.18 (t, *J* = 7.7 Hz, 2H, C(14)*H*), 6.82 – 6.60 (m, 3H, C(13)*H*, C(15)*H*), 4.09 (app. s, 1H, C(10)*H*), 3.79 (app. s, 5H, C(11)H_a, C(16)*H*), 3.67 (dd, *J* = 12.3, 6.3 Hz, 1H, C(11)H_b), 2.70 (app. s, 4H, C(17)*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ 148.1 (*C*(9)), 147.7 (*C*(12)), 136.5 (*C*(3)), 129.7 (*C*(7)), 129.4 (*C*(8)), 129.3 (*C*(14)), 127.6 (*C*(4)), 127.5 (*C*(5)), 126.7 (*C*(6)), 121.3 (*C*(2)), 117.5 (*C*(15)), 113.0 (*C*(13)), 69.5 (*C*(10)), 67.1 (*C*(16)), 50.6 (*C*(17)), 43.7 (*C*(11)).

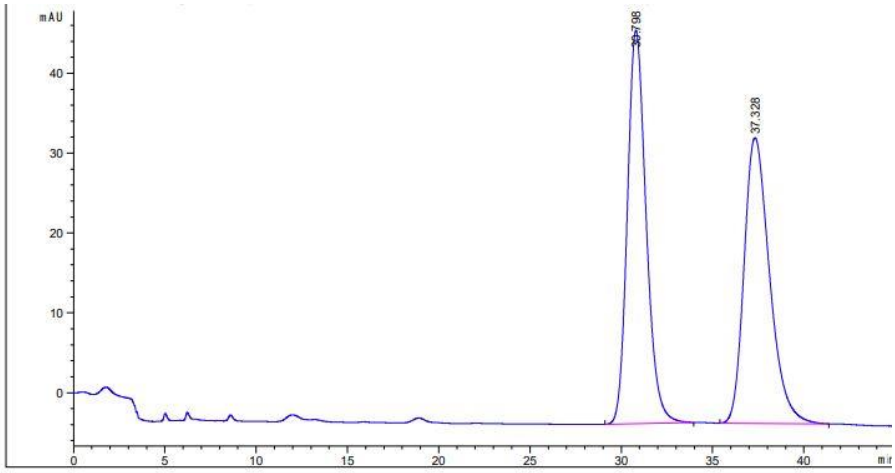
n.b. C(1) not observed in the ^{13}C NMR.

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{21}H_{24}N_3O$) requires m/z 334.1914, found 334.1907 m/z.

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 99:1 hexane:isopropanol, 250 nm, t_{major} = 36.9 min, t_{minor} = 44.8 min.

n.b. retention time drift is >5%, see section 3.6.1 for details.

$[\alpha]_D^{23}$ +15.8° (*c* = 0.5, $CHCl_3$).

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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
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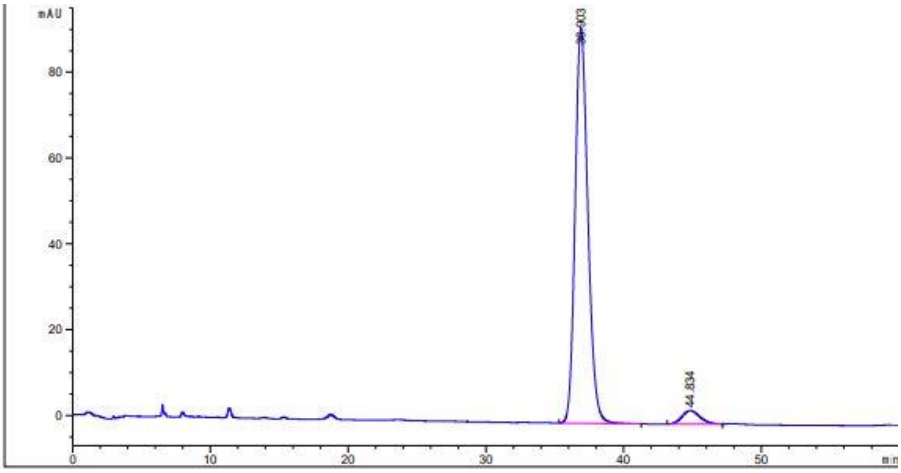


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  36.903 BB    0.9912 5935.18115   92.20330  95.4792
   2  44.834 BB    1.0755  281.02170    3.14207   4.5208
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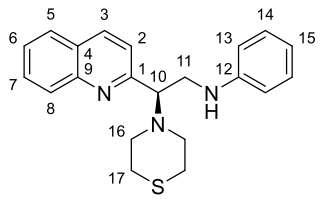
(*R*)-*N*-(2-(quinolin-2-yl)-2-thiomorpholinoethyl)aniline 3.75



Chemical Formula: $C_{21}H_{23}N_3S$
Exact Mass: 349.1613
Molecular Weight: 349.4960

Racemic:

Prepared according to General Procedure G (±)-2-(1-phenylaziridin-2-yl)quinoline (24.6 mg, 0.10 mmol, 1.0 equiv), thiomorpholine (12.0 µL, 0.10 mmol, 1.0 equiv), TFA (1.5 µL, 0.02 mmol, 20 mol%), and MeCN (200 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure G (silica gel, EtOAc:petroleum ether, 20:80) to afford the desired product as a pale yellow solid (12.6 mg, 36%).

Enantioenriched:

Prepared according to General Procedure G (*R*)-2-(1-phenylaziridin-2-yl)quinoline (24.6 mg, 0.10 mmol, 1.0 equiv), thiomorpholine (12 µL, 0.10 mmol, 1.0 equiv), TFA (1.5 µL, 0.02 mmol, 20 mol%), and MeCN (200 µL, 0.5 M). The reaction mixture was subjected to the purification outlined in General Procedure G (silica gel, EtOAc:petroleum ether, 20:80) to afford the desired product as a pale yellow solid (13.9 mg, 40%). The enantiomeric ratio (89:11) was determined by chiral HPLC in comparison with the racemate.

υ_{max} (film): 1597, 1489 cm^{-1}.

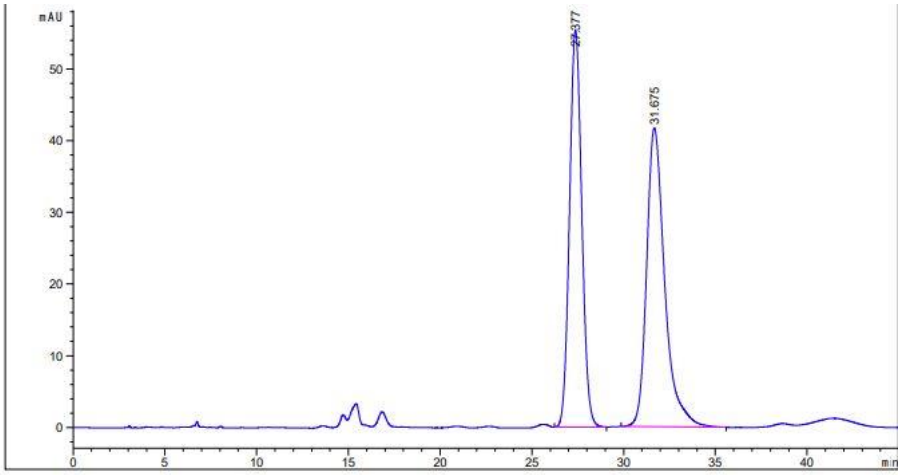
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.5 Hz, 1H, C(3)*H*), 8.12 (d, *J* = 8.1 Hz, 1H, C(8)*H*), 7.87 – 7.79 (m, 1H, C(5)*H*), 7.75 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H, C(7)*H*), 7.57 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H, C(6)*H*), 7.49 (d, *J* = 8.4 Hz, 1H, C(2)*H*), 7.20 (tt, *J* = 7.3, 2.1 Hz, 2H, C(14)*H*), 6.81 – 6.62 (m, 3H, C(13)*H*, C(15)*H*), 4.19 – 4.07 (m, 1H, C(10)*H*), 3.83 (dd, *J* = 12.4, 7.0 Hz, 1H, C(11)*H*), 3.71 (dd, *J* = 12.4, 6.7 Hz, 1H, C(11)*H*), 3.10 – 2.96 (m, 2H, C(16)*H*), 2.92 (app. s, 2H, C(16)*H*), 2.76 – 2.61 (m, 4H, C(17)*H*).

^{13}C NMR (101 MHz, $CDCl_3$): δ 159.2 (*C*(1)), 148.4 (*C*(9)), 147.6 (*C*(12)), 136.1 (*C*(3)), 129.5 (*C*(7), C(14)), 129.3 (*C*(8)), 127.6 (*C*(4)), 127.4 (*C*(5)), 126.5 (*C*(6)), 121.5 (*C*(2)), 117.4 (*C*(15)), 113.2 (*C*(13)), 69.6 (*C*(10)), 52.1 (*C*(16)), 42.6 (*C*(11)), 28.6 (*C*(17)).

HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{21}H_{24}N_3S$) requires m/z 350.1685, found 350.1681 m/z.

HPLC analysis using a chiral column: Chiralcel® OJ-H 5 µm column, 1.0 mL/min, 99:1 hexane:isopropanol, 250 nm, t_{major} = 26.9 min, t_{minor} = 31.2 min.

$[\alpha]_D^{23}$ +6.6° (*c* = 0.5, $CHCl_3$).

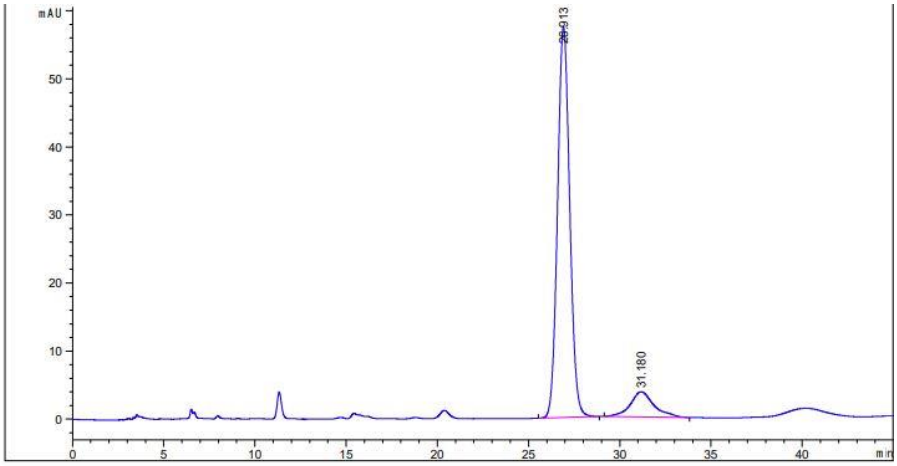



```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  27.377 BB    0.7183 2567.58594   55.40076  47.3292
   2  31.675 BB    1.0384 2857.36475   41.69018  52.6708
```




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=250 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  26.913 BB    0.7200 2664.57495   57.47184  88.9031
   2  31.180 BB    1.0601  332.59241    3.69580  11.0969
```

3.6.4 X-Ray Data

The dataset for the compound was collected using a Rigaku FR-X Ultrahigh Brilliance Microfocus RA generator/confocal optics with XtaLAB P200 diffractometer. The data was collected at 93 K with Mo radiation (λ = 0.71075 Å). Intensity data were collected using ω steps accumulating area detector images spanning at least a hemisphere of reciprocal space. All data was corrected for Lorentz and polarization effects. A multiscan absorption correction was applied by using REQAB. The structure was solved using direct methods (SHELXT). The structure were refined by full-matrix least-squares against F^2 (SHELXL). Non-hydrogen atoms were refined anisotropically, and some hydrogen atoms were refined isotropically and the rest were refined using a riding model. All calculations were performed using the CrystalStructure interface except for refinement, which was performed using SHELXL. Selected crystallographic data are presented in Table 3.14.

Crystal Data	Compound **(*R*)-3.47**
Chemical formula	$C_{17}H_{14}BrClN_2$
M_r	361.67
Crystal system, space group	Monoclinic, $P2_1$ (#4)
Temperature (K)	93
a, *b*, *c* (Å)	9.851 (5), 5.478 (3), 14.595 (9)
α, β, γ (°)	90, 105.850 (13), 90
V (Å^3)	757.7 (7)
Z	2
Radiation type	Mo *K*α
μ (mm^{-1})	2.8906
Crystal size (mm)	0.180 × 0.020 × 0.010
Data Collection	
T_{min}, T_{max}	0.488, 0.972
No. of measured, independent and observed reflections	7368, 2753, 2415
R_{int}	0.0659

$(\sin \theta/\lambda)_{max}$ ($Å^{-1}$)	0.6017
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.0350, 0.0627, 0.755
No. of reflections	2753
No. of parameters	194
No. of restraints	2
$\Delta\rangle_{max}$, $\Delta\rangle_{min}$ (e $Å^{-3}$)	0.41, −0.36
Absolute structure parameter	−0.013 (9)

Table 3.14: Selected crystallographic data.

Computer programs: *CrystalStructure* 4.3 (Rigaku, 2019), REQAB (Rigaku, 1998), *SHELXL* Version 2018/3 (Sheldrick, 2008), *SHELXT* Version 2018/2 (Sheldrick, 2014).

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