Chapter 3

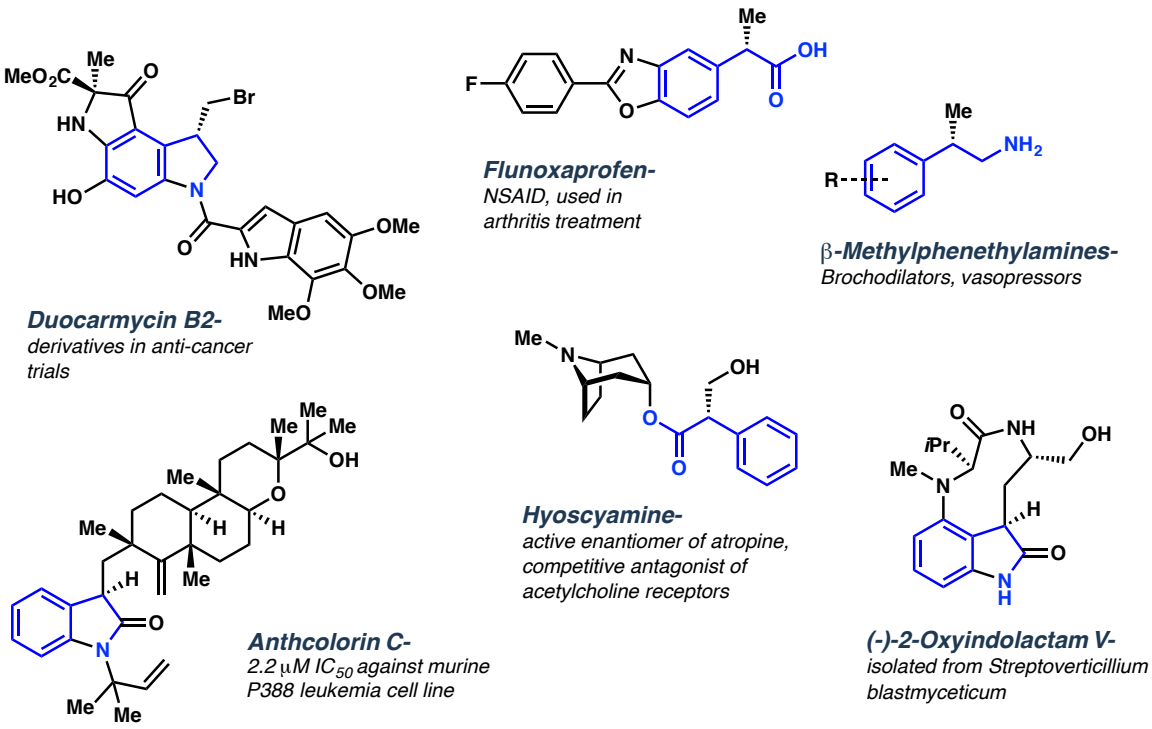
Nickel-Catalyzed Asymmetric Reductive Cross-Coupling Between Heteroaryl Iodides and α-Chloronitriles[◊]

3.1 INTRODUCTION

Benzylic nitriles are a chemically rich and important functionality in organic synthesis. These structural motifs and their derivatives are represented in natural products and bioactive compounds, including pharmaceuticals. They can also serve as valuable synthetic intermediates, being diversifiable to a wide range of more sensitive functionality, such as aldehydes and primary amines. As such, chiral benzylic nitriles present an entry point to enantioenriched products bearing many useful functional groups, as well as being present in desirable targets (**Figure 3.1**). Their hydrolysis to chiral carboxylic acids has been employed in the synthesis of nonsteroidal anti-inflammatories such as naproxen, and their reduction has enabled numerous total syntheses.

◊ Portions of this chapter have been reproduced from published studies (see reference **34**) and the supporting information found therein.

***Figure 3.1**. Bioactive compounds accessible from chiral benzylic nitriles.*

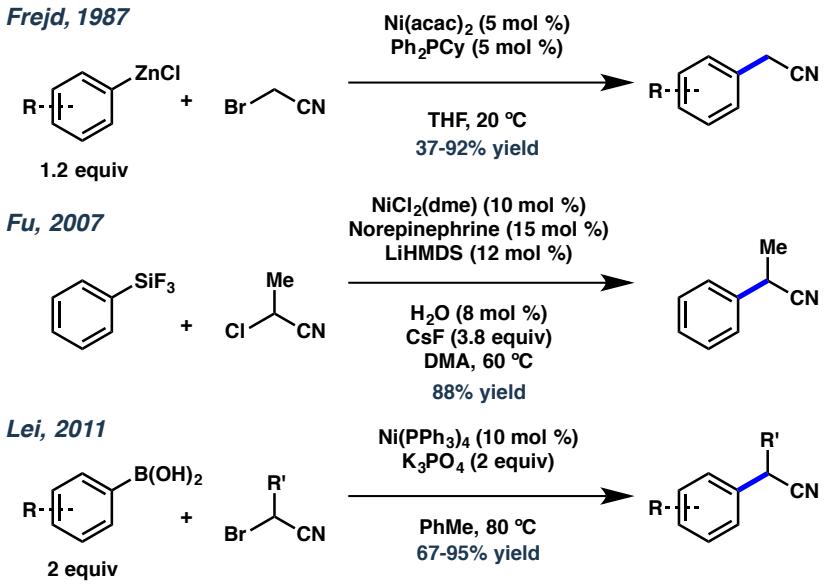


Routes to access these valuable chiral intermediates via asymmetric catalysis have been the focus of numerous research efforts.[1] These approaches have taken two major forms: a) hydrocyanation, including formal conjugate additions, and b) cross-coupling of cyanoelectrophiles. Asymmetric hydrocyanation has been the most widely explored catalytic approach to enantioenriched nitriles, employing HCN (or some surrogate, such as acetone cyanohydrin) and suitable olefin substrates. These reactions can proceed in excellent yield and selectivity, however the substrate scopes of these methods are limited when employing styrenyl olefins. Hydrocyanation of simple styrenes is not amenable to olefin substitution, giving only the α-methyl nitriles in high enantioselectivity. Conjugate cyanation, on the other hand, has been sparingly developed with β-aryl groups, giving sparse access to the benzylic nitrile class of products. In addition, these methods all

employ some stoichiometric HCN source, making these especially hazardous reactions to conduct.

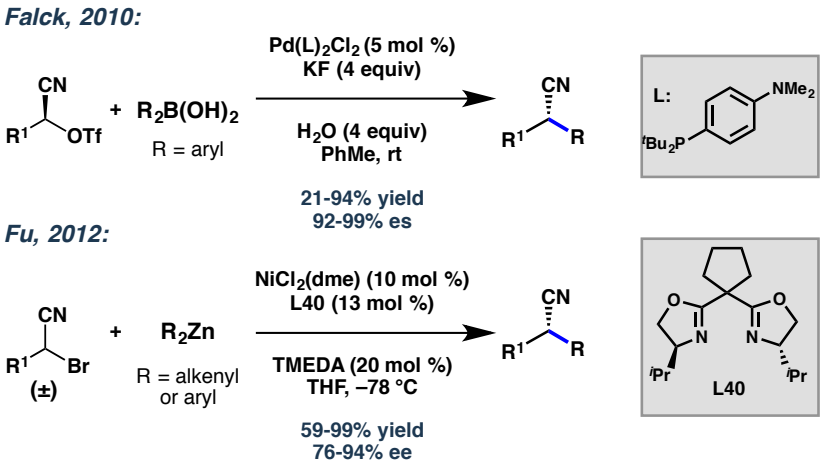
The cross-coupling of α-halonitriles represents a complementary approach to alkene hydrocyanation. Appealingly, this disconnection introduces the cyano moiety covalently bonded to a substrate, thereby precluding use of an exogenous, potentially hazardous source of cyanide. While asymmetric entries have been reported only recently, the utility of α-halonitrile electrophiles in cross-coupling was first established in 1987 by Frejd and coworkers (**Scheme 3.1**).[2] The Ni-catalyzed Negishi coupling of bromoacetonitrile with arylzinc reagents proceeds with good to excellent yields to afford the benzylic nitrile products, setting a precedent that went unexplored for another two decades. The next report of these electrophilic partners was by Fu and coworkers in 2007.[3] Importantly, this Hiyama coupling employed a secondary α-chloronitrile to afford a stereogenic product, albeit in a racemic sense. A similar Suzuki coupling has also been reported by Lei and coworkers with wider substrate scopes for both coupling partners.[4]

Scheme 3.1. *Racemic cross-coupling of α-halonitrile electrophiles.*



Examples of α-halonitriles participating in asymmetric cross-coupling reactions have emerged still more recently. Interestingly, both stereospecific and stereoselective examples have been disclosed (**Scheme 3.2**). Falck and coworkers reported the stereospecific Pd-catalyzed Suzuki coupling of enantioenriched cyanohydrin triflates (themselves accessible by asymmetric cyanosilylation of aldehyde precursors).[5] While only a handful of the substrates were prepared asymmetrically, the products of these couplings were furnished with excellent enantiospecificity. In 2012, Fu and coworkers developed a related stereoconvergent transformation: a Negishi coupling employing racemic α-bromonitriles.[6] Importantly, this report demonstrated the feasibility of a stereoconvergent coupling of halonitrile electrophiles, affording access to the benzylic nitrile products via a chiral Ni catalyst.

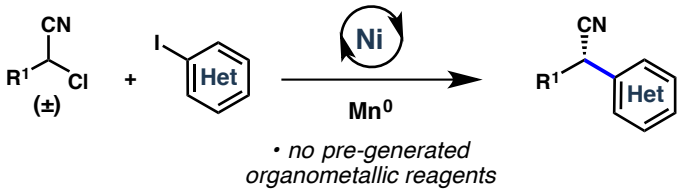
Scheme 3.2. *Asymmetric cross-coupling of α-halonitrile electrophiles*



With these precedents in mind, we identified α-halonitriles as desirable electrophiles for Ni-catalyzed asymmetric reductive cross-coupling. To date, the only C(sp^3) partners employed in enantioselective reductive couplings had been benzylic, providing products with limited prospects for further derivatization. In considering the

mechanistic hypotheses developed for these reactions, the aryl moiety is believed to serve as a radical stabilizing group: the benzylic halides are more susceptible to halide abstraction, generating a prochiral radical intermediate and enabling differentiation of the electrophilic partners (see **Chapter 1**). We hypothesized that a nitrile, while possessing a lower radical stabilization energy than an aryl group, could still facilitate cross-selective coupling with a C(sp^2) electrophile to afford enantioenriched cyano products (**Scheme 3.3**).[7]

Scheme 3.3. *Target asymmetric reductive cross-coupling α-halonitriles.*



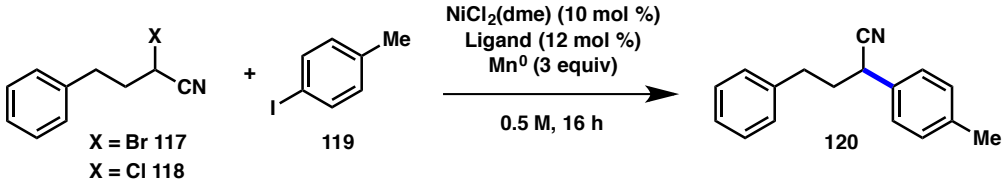
We were also cognizant of potential difficulties employing nitrile-bearing substrates, given that Lewis basic functionality had been poorly tolerated in our previous reaction development. Indeed, nitriles have been shown to form strongly bound σ- and π-adducts with Ni^0 complexes, providing a compelling mechanistic basis for catalyst poisoning.[8] However, we anticipated that if such challenges could be overcome, then other Lewis basic moieties such as heterocycles may be competent coupling partners as well, giving access to desirable products difficult to access via cross-coupling.[9] With this as our goal we set out to evaluate the feasibility of such an asymmetric reductive coupling.

3.2 REACTION DEVELOPMENT

Prior to our investigations, there had been no published reports of the catalytic reductive cross-coupling of halonitrile electrophiles. Therefore we chose to begin our

exploration employing achiral ligands to identify conditions capable of affording the desired products. We selected a hydrocinnamaldehyde-derived halonitrile (**117** or **118**) as the C(sp^3) partner and *p*-iodotoluene (**119**) as the aryl electrophilic component. Based on the conditions employed for the asymmetric reductive cross-coupling of benzylic chlorides with acyl chlorides (see **Chapter 2**), early optimization efforts were conducted employing $NiCl_2$(dme) as the precatalyst, Mn^0 as the reductant, polar amide/urea solvents, and various achiral ligands.

Table 3.1. *Initial exploration with achiral ligands.*

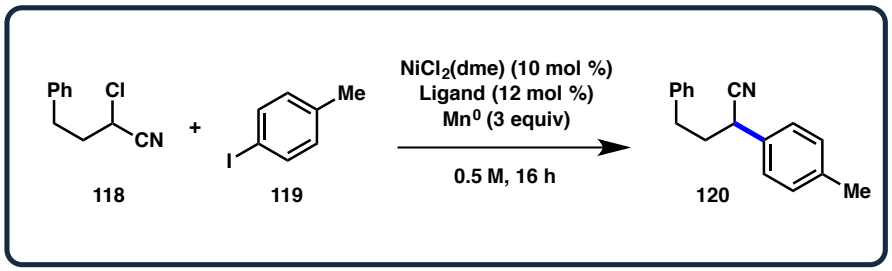


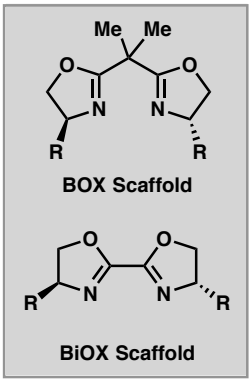
Entry	X	Additive	Ligand	Solvent	Temp.	Yield 120
1	Br	--	dtbpy (L64)	DMA	50 °C	--
2	Br	--	dtbpy	NMP	50 °C	--
3	Br	--	dtbpy	DME	50 °C	--
4	Br	--	dtbpy	DMPU	50 °C	5%
5	Br	--	bathophen (L65)	DMPU	50 °C	9%
6	Br	--	bathophen	DMPU	rt	--
7	Br	--	bathophen	DMPU	80 °C	5%
8	Br	TFA	bathophen	DMPU	rt	10%
9	Cl	TFA	dtbpy	DMPU	rt	--
10	Cl	TFA	dtbpy	DMPU	50 °C	10%
11	Cl	TMSCl	dtbpy	DMPU	50 °C	22%
12	Cl	TMSCl	dtbpy	DMPU	rt	8%

Illustrative results from this effort are collected in **Table 3.1**. Attempts to engage bromonitrile **117** (as in the stereoconvergent Fu example, see **Scheme 3.2**) in cross-coupling were met with poor yields not exceeding 10%. However some trends were still identifiable. DMPU was the only solvent in which product was observed, albeit only upon heating (entry 4). Employing acidic surface activating reagents, as reported by

Durandetti and coworkers, enabled some product formation at room temperature (entries 8-12).[10] Taking these results and switching to the analogous chloronitrile **118** proved to be more promising. In the presence of TFA or TMSCl, product could be observed at room temperature, and in excess of 20% yield at 50 ºC. In every case, complete consumption of the halonitrile was observed, with protodehalogenated starting material accounting for the remainder of the mass balance. This suggested a poor matching of the substrate reactivities, with the C(sp^3) partner being consumed and quenched much faster than the aryl component could engage the catalyst.

Table 3.2. *Preliminary evaluation of chiral ligands and solvents.*





Entry	Ligand	Additive	Temp	ee 120
1	^{t}BuBiOX (L66)	TFA	50 °C	--
2	^{i}PrBiOX (L67)	TFA	50 °C	30%
3	PhBiOX (L68)	TFA	50 °C	20%
4	BnBiOX (L31)	TFA	50 °C	11%
5	^{t}BuBOX (L61)	TFA	50 °C	3%
6	^{i}PrBOX (L62)	TFA	50 °C	6%
7	PhBOX (L32)	TFA	50 °C	16%
8	BnBOX (L63)	TFA	50 °C	5%
9	^{i}PrBiOX (L67)	TMSCl	rt	31%

employing ^{i}PrBiOX (L67):

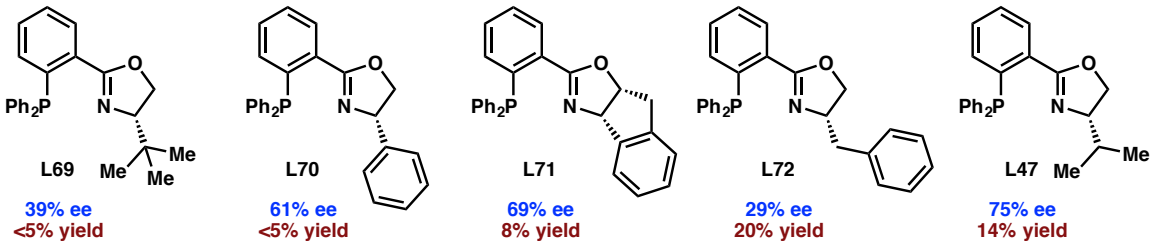
Entry	Solvent	Additive	Temp	ee 120
1	DMA	TMSCl	rt	8%
2	DMF	TMSCl	rt	4%
3	DME	TMSCl	rt	44%
4	DMSO	TMSCl	rt	--
5	Dioxane	TMSCl	rt	63%
6	NMP	TMSCl	rt	36%
7	EtOAc	TMSCl	rt	62%
8	THF/DMPU	TMSCl	rt	46%

At this stage, we turned our attention to an initial survey of solvents and chiral ligands. While yields did not improve with any of the surveyed BOX or BiOX ligand scaffolds, we were pleased to observe promising levels of enantioselectivity under the

conditions developed in **Table 3.1** when using ^{i}PrBiOX **L67** and TMSCl (0.4 equiv) as the activator (**Table3. 2a, Entry 9**). Running the reaction in 1,4-dioxane as solvent gave a dramatic boost in ee to 63% (**Table 3.2, Entry 5**).

While this result provided us with improved enantioselectivity, the yield (as determined by ^{1}H NMR spectroscopy of the crude reaction mixture) remained at approximately 10%, and a significant amount of protodehalogenated 118 was still observed. We hypothesized that slow oxidative addition of the aryl iodide relative to the rate of α-chloronitrile decomposition could be the source of the problem. Therefore we screened a panel of phosphino-oxazoline (PHOX) ligands, anticipating that the more strongly σ-donating phosphine would accelerate oxidative addition of the aryl iodide partner.[11] Gratifyingly, not only were the yields improved twofold (BnPHOX, **L72**), but several ee's were higher than our previous best results (**Figure 3.2**).

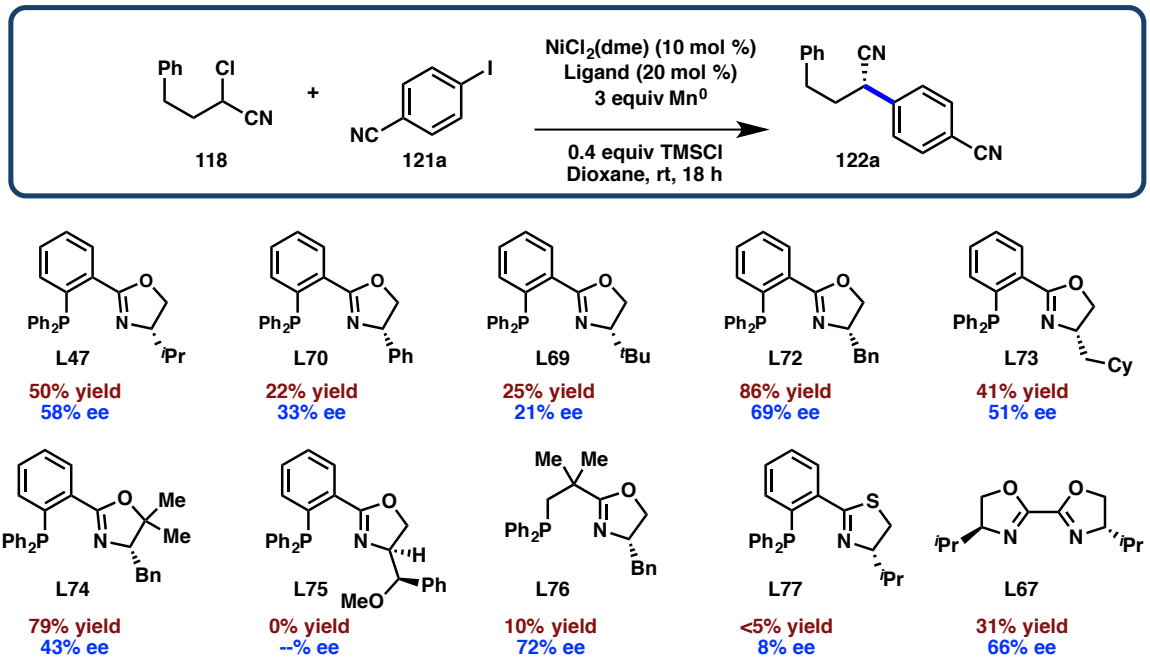
Figure 3.2. *Initial screen of PHOX ligands.*



Based on the improved reactivity using PHOX ligands, we hypothesized that yields might be further improved when coupling electron-deficient aryl halides, which should undergo faster oxidative addition to a Ni^{0} complex. This decision also enabled us to leverage our optimization effort toward another of our goals: the tolerance of Lewis basic functionality. We hypothesized that employing 4-iodobenzonitrile **121a** would not only accelerate oxidative addition by virtue of the electron-withdrawing cyano group, but

also incorporate another potentially coordinating functionality. It was our hope that reaction optimization with this substrate would select for conditions tolerant of coordinating groups. Therefore we were pleased to find that aryl iodide **121a** was an improved substrate for the cross-coupling, as shown in **Scheme 3.4**.

Scheme 3.4. *PHOX ligand evaluation employing 4-iodobenzonitrile (**121a**).*

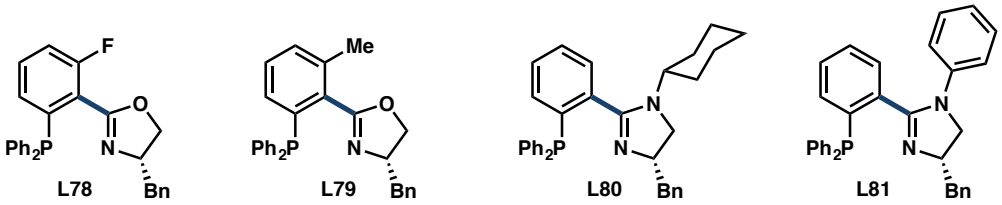


Several entries are included to illustrate the range of ligands explored at this stage. Incorporating branching at the chiral substituent was no longer optimal (^{i}PrPHOX, **L47**). Rather, BnPHOX (**L72**) was the best-performing ligand, affording **122a** in 86% yield and 69% ee. Scaffolds with steric bulk closer to the binding pocket gave lower yields (PhPHOX **L70** and ^{t}BuPHOX **L69**), although these did perform much better with this substrate than with the previously investigated 4-iodotoluene. A saturated analogue of **L72**, CH_2CyPHOX **L73** did not perform better. Introducing *gem*-dimethyl substitution on the oxazoline ring was expected to orient the Bn substituent toward the binding pocket, increasing its effective steric bulk.[12] This substitution afforded lower enantioselectivity

than the corresponding *des*-gem-dimethyl derivative **L72**. Introduction of a methoxy group in **L75** shut down reactivity entirely, suggesting that **L75** may bind Ni in a tridentate fashion, disrupting catalysis.[13] Changing the aryl core of BnPHOX to a neopentyl alkyl linker (**L76**) gave appreciably greater decomposition of the starting materials, indicating that such electron rich phosphine ligands are not well-tolerated.[14] Likewise, changing the oxazoline ring to a thiazoline (**L77**) gave poor reactivity and selectivity.[15] Finally, reinvestigating ^{i}PrBiOX (**L67**) with this substrate did show an improvement over its performance with 4-iodotoluene, but the ligand was not superior to the PHOX series.

At this stage, BnPHOX (**L72**) stood as the most optimal ligand we had explored, affording **122a** in synthetically useful yields but insufficient ee. To address this, we undertook a systematic exploration of the BnPHOX scaffold, with optimization efforts targeting: a) the bite angle, b) the oxazoline benzyl substituent, and c) the biarylphosphine arm.

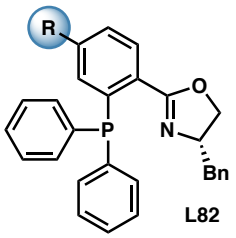
Figure 3.3. *Perturbation of PHOX ligand bite angles.*



Initial studies focused on perturbation of the ligand bite angle (**Figure 3.3**). Substitution of the aryl core *ortho* to the oxazoline was expected to introduce repulsive interactions between the two rings. First, *ortho*-fluoro derivative **L78** was explored, anticipating that an electronic repulsion between the fluoro substituent and the electron

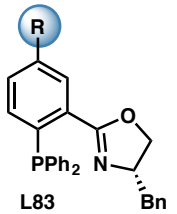
lone pairs of the oxazoline oxygen would lead to a narrowing of the bite angle.[16] While a significant effect was observed, unfortunately it was to the detriment of ee (although the yield was maintained). We then sought to perturb the torsion angle about the aryl-oxazoline bond (highlighted in blue). We anticipated that introduction of bulky substituents on either ring about this bond would lead to steric clashing, disrupting the coplanarity of the rings and therefore altering the ligand bite angle.[17] Therefore, we prepared *ortho*-methyl substituted **L79**, as well as two imidazoline derivatives bearing large groups on the nitrogen atom (**L80** and **L81**). Indeed, all of these ligands displayed a similar reaction profile, affording low yields of nearly racemic product.

Figure 3.4. *Electronic tuning of the BnPHOX core and Hammett parameters.*



L82

R	ee	σ_p	σ_m
OMe	11	-0.27	0.12
H	71	0	0
F	57	0.06	0.34
Cl	66	0.23	0.37
CF_3	45	0.54	0.43



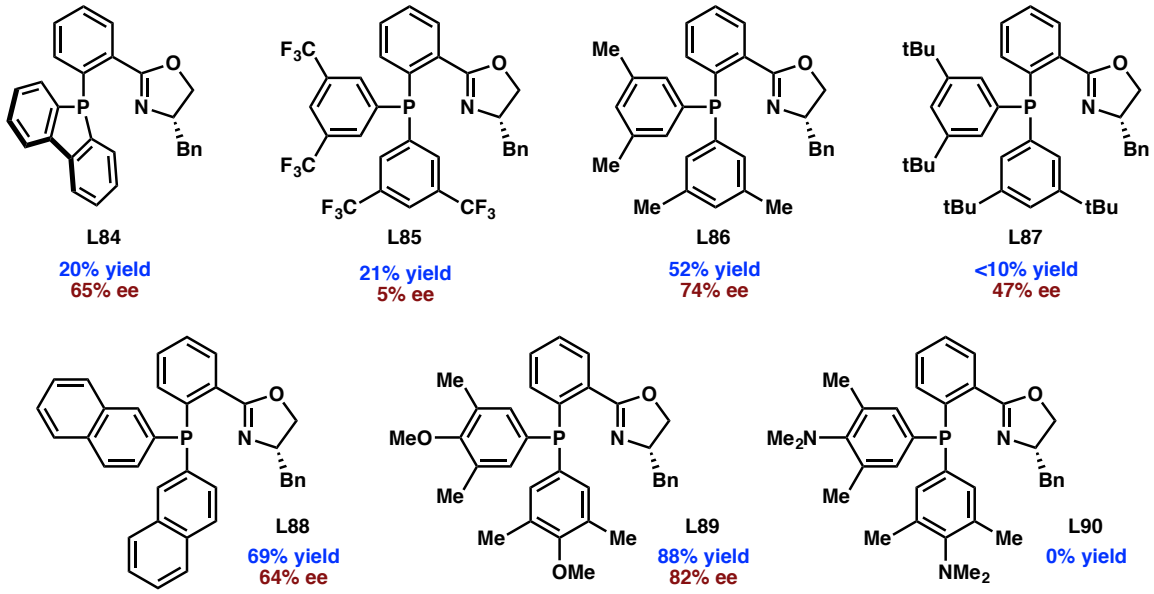
L83

R= MeO 63% ee
R= CF_3 53% ee

Next, we turned our attention to the electronic profile of the BnPHOX ligand scaffold. Bunt and coworkers have performed extensive studies on the performance of electronically differentiated PHOX ligands in Pd-catalyzed allylic substitution reactions.[18] In these investigations, a substituent at the 4-position (R in **L82**) has been shown to exert a significant effect on both the yield and selectivity of the reaction, an effect attributed to manipulation of the *trans* effect by the substituent. To conduct this study, we prepared the series of 4-substituted BnPHOX derivatives shown in **Figure 3.4**. Unfortunately, no correlation was observed between the product ee and the Hammett parameter σ_p or σ_m, and no substituent outperformed the unsubstituted BnPHOX **L72**. We hypothesize that

this is due to the second-order nature of the perturbation, in which both the oxazoline and phosphine arms are affected by the substituent. We also investigated substitution at the 5-position (**L83**), however neither electron-rich nor electron-withdrawing groups led to an improvement in enantioselectivity.

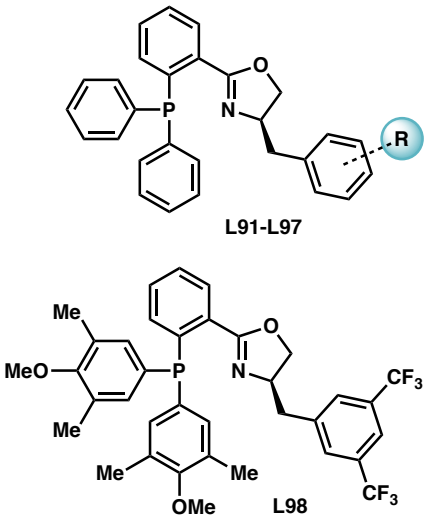
Figure 3.5. *Optimization of the BnPHOX diarylphosphine arm.*



Next, we shifted our focus to the biaryl phosphine arm of BnPHOX. While alkyl phosphines had earlier proven to be too reactive, we hoped that altering the steric and electronic profile of the triarylphosphine moiety might enable more subtle tuning of the reaction.[19] To this end, we first prepared dibenzophosphole-BnPHOX **L84**, in which the phenyl rings of the phosphine are tethered into a planar tricycle.[20] Unfortunately this led to a decrease in the yield of **122a**. Moving instead to substitution about the aryl rings, we focused on 3,5-disubstituted analogues. Preparing electron-deficient and electron-rich derivatives (**L85** and **L86**), we were delighted to see a clear divergence with the trifluoromethylated ligand **L85** giving nearly racemic product while the xylyl **L86** afforded a 5% boost in enantioselectivity over **L72**. While increasing the steric bulk of

the alkyl substituents to 3,5-di(^{t}Bu) **L87** nearly shut down reactivity, increasing the electron density of the aryl substituent had the opposite effect: 3,5-dimethyl-4-methoxyphenyl-BnPHOX (**L89**, DMMBnPHOX) afforded **122a** in 88% yield and 82% ee, the best results observed thus far.[11b] Attempts to further increase the electron density of the phenyl rings by introduction of dimethylamino substituents (**L90**) gave no product in the cross-coupling, perhaps due to catalyst destabilization by the aniline moieties.

Figure 3.6. *Unnatural phenylalanine-derived PHOX ligands.*



Entry	R	Yield 122a	ee 122a
L72	H	86	69
L91	4-MeO	85	67
L92	2,5-diMe	61	69
L93	3,5-diMe	83	34
L94	3,5-bisCF_3	75	74
L95	3,5-diOMe	79	68
L96	3,5-diiPr	86	69
L97	3,5-diPh	79	33
L98	3,5-bisCF_3	82	45

Pleased to have identified an optimal diarylphosphine arm, we set out to study the benzyl substituent of BnPHOX. We hypothesized that increasing the steric bulk about the aryl ring of the chiral substituent may increase ee by better blocking the occupied quadrant of the coordination sphere, while electronic perturbations may alter subtle secondary interactions during catalysis. The targeted ligand series is shown in **Figure 3.6**. While the chiral oxazoline of all BnPHOX derivatives prepared previously had been derived from natural phenylalanine, the ligands for this study (**L91–L98**) required unnatural phenylalanine derivatives bearing aryl substitution. These were readily accessible via the procedure reported by Jackson and coworkers, a Negishi cross-

coupling between the desired aryl halide partner and the organozinc reagent formed from iodoserine.[21] Unfortunately, most substitutions about the benzyl ring led to catalysts performing no better than BnPHOX (**L72**), with some being markedly worse. However one ligand, 3,5-bis(trifluoromethyl)phenyl **L94** afforded **122a** in 74% ee, a 5% increase over the control.

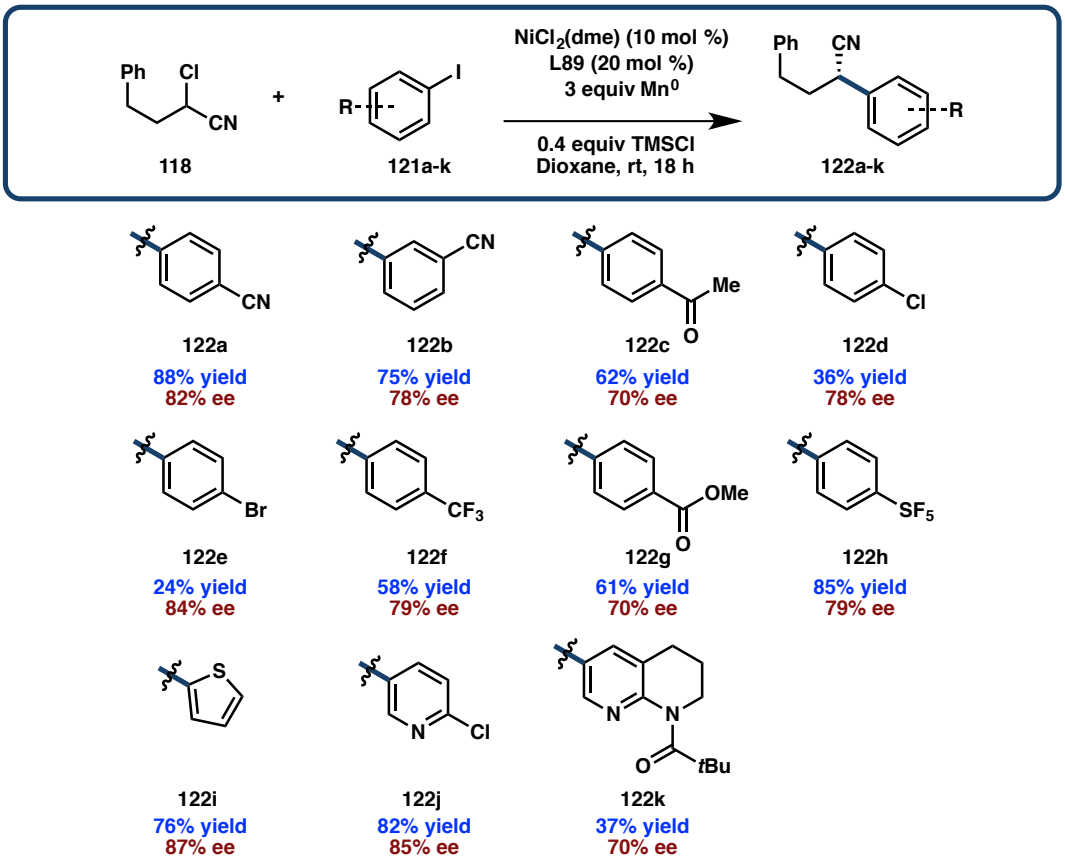
Having identified both a phosphine arm and a benzyl substituent that gave selectivities superior to BnPHOX (**L72**), we prepared the ligand bearing both components (**L98**). We were disappointed that while the yield remained high, the ee of **122a** furnished by this catalyst was only 45%. This result suggests that the two binding arms of the PHOX scaffold are not amenable to independent iterative optimization. Rather, it appears that the phosphine and oxazoline groups must be developed in concert, and that the interplay between the two halves of the ligand during catalysis is nontrivial.

3.3 SUBSTRATE SCOPE

With DMMBnPHOX (**L89**) identified as the optimal ligand for the model reductive coupling to afford **122a**, we set out to evaluate the substrate scope of this transformation. We began these studies with a survey of aryl iodide partners bearing various functional groups and a range of electronics (**Scheme 3.5**). It became immediately clear that electron-rich substrates such as 4-iodoanisole did not afford any cross-coupled product (not shown). We attribute this to sluggish oxidative addition of these substrates, even with the optimal PHOX ligand. Substrates bearing mildly electron-withdrawing substitution such as haloarenes **122d** and **122e** gave poor yields but notable chemoselectivity. More strongly electron-withdrawing functionality (**122f–h**) afforded much higher yields, but with ee's generally lower than the model substrate and too low to

be considered synthetically useful. However one class of entries underwent cross-coupling in good yields with enantioselectivities higher than the control: heteroaryl iodides **122i** and **122j**. Both the thiophene and chloropyridine entries reacted cleanly and with high ee.

Scheme 3.5. *Preliminary screen of aryl iodide substrates.*[a]

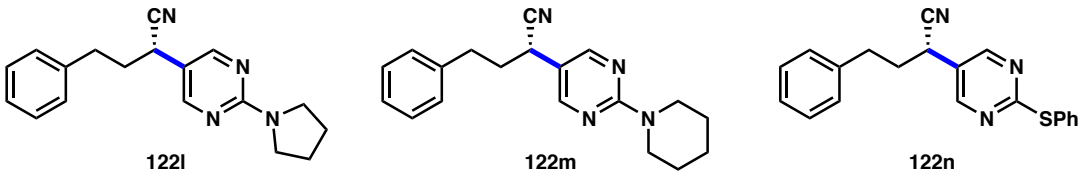


[a] Yields determined by ^{1}H NMR with an internal standard, reactions conducted on 0.2 or 0.05 mmol scale under an N_2 atmosphere in a glovebox. % ee determined by SFC using a chiral stationary phase.

One of our goals in developing the operative catalyst for this reaction was to select for tolerance of Lewis-basic functionality by utilizing two nitrile-bearing coupling partners. With the preliminary results from substrates **122i** and **122j**, we were hopeful that this had indeed been the outcome of the ligand optimization effort described in **Section 3.2**. Following up on this result, we set out to explore the range of heteroaryl

iodides that may be tolerated by these reaction conditions. We anticipated that these substrates would be of particular interest to the synthetic community, especially with respect to medicinal chemistry.[22] Successful incorporation of a wide range of heteroaryl moieties would also represent an advance in the field of reductive cross-coupling: Previously reported asymmetric examples only include simple arenes, while racemic couplings of heteroarenes require a wide range of varying reaction conditions to achieve only moderate yields in many cases.[23]

***Figure 3.7**. Heteroaryl cross-coupling behavior with two ligands.*



122l — 4,4'-dtbpy (L64): 0% yield; DMMBnPHOX (L89): 60% yield

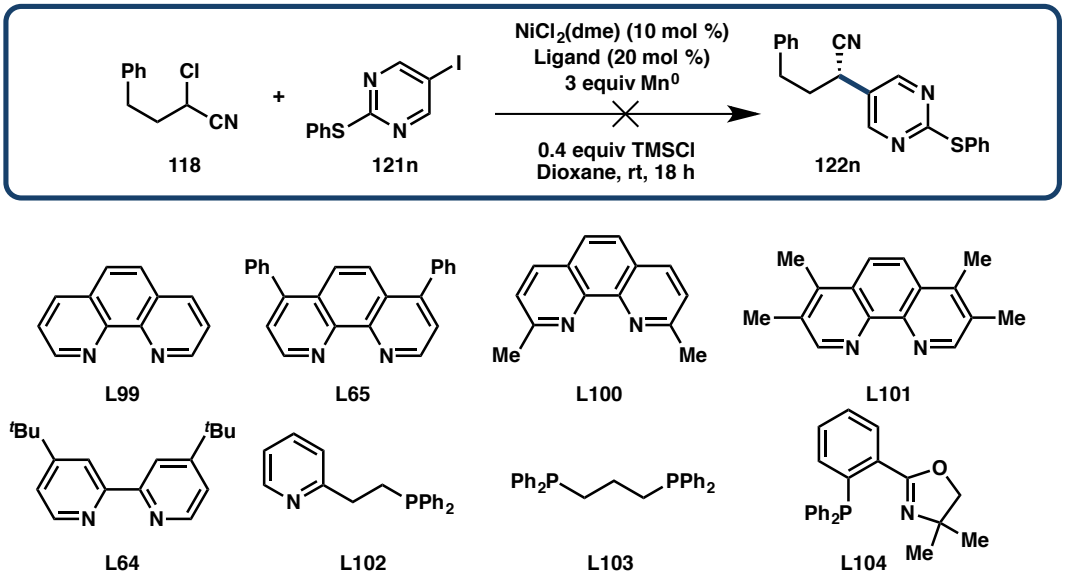
122m — 4,4'-dtbpy (L64): 65% yield; DMMBnPHOX (L89): 70% yield

122n — 4,4'-dtbpy (L64): No Product; DMMBnPHOX (L89): 95% yield

Highlighting the difficulty of utilizing heteroarenes in reductive cross-coupling is **Figure 3.7**, showing the results of employing various substituted iodopyrimidines with **L89** and achiral 4,4'-dtbpy (**L64**). For all coupling products discussed previously, **L64** was the achiral ligand used to obtain racemic material for the development of chiral separation conditions. While **L64** frequently afforded lower yields than the optimal chiral ligands, product was always obtained with both ligands for competent substrates. However, when employing heteroaryl iodides **122l** and **122n** bearing Lewis basic functionality, only DMMBnPHOX **L89** afforded the desired product. An interesting divergence was also observed between pyrrolidinylpyrimidine **122l** and piperidinylpyrimidine **122m** when using achiral **L64**: Product was only observed with the piperidyl substituent, perhaps because the wider C-N-C bond angle of the piperidine

enables blocking of the pyrimidine lone pairs by the methylene protons, preventing catalyst poisoning in this case.

***Scheme 3.6**. Unsuccessful achiral ligands for the coupling of **121n**.*

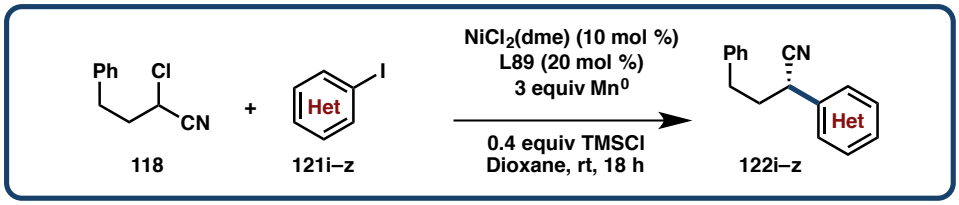


As a result of the difficulties encountered employing achiral ligand **L64** with some heteroaryl substrates, we required a more reliable achiral ligand for the preparation of racemic products (for assay development). Toward this end, we conducted a screen of various achiral ligands in the coupling of phenylthiopyrimidine **121n**. To our surprise, none of the ligands shown in **Scheme 3.6** afforded any cross-coupled product. While this served as a testament to the value of DMMBnPHOX (**L89**) for the cross-coupling of heteroarenes, it did not address the question of accessing racemic products. Ultimately, racemic BnPHOX **L72** prepared from racemic phenylalanine was employed for this purpose.

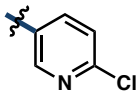
In the course of substrate evaluation and optimization, a wide range of reaction parameters and additives were evaluated. While most of these served only to establish the robustness of the transformation to various perturbations, two advancements were made.

First, the addition of $NaBF_4$ to some substrates favorably altered the reaction profile, affording higher yields of the desired products sometimes by increasing conversion and sometimes by decreasing protodehalogenation. Changes in enantioselectivity were also noted, however these tended to be subtler. This is similar to results reported by Molander and coworkers in their reductive cross-couplings of heteroaromatic substrates, which were the impetus for investigating $NaBF_4$. Studies of other salt additives were unfruitful, with only slight or detrimental impacts being observed. It is unclear if the role of $NaBF_4$ is as a halide-scavenging agent, a mild Lewis acid, or simply as an ionic electrolyte. Second, several heteroaryl substrates benefited from the use of two equivalents of aryl iodide. The excess substrate was easily recovered during column chromatography, making this a modest sacrifice in the service of improved yields.

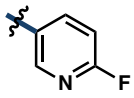
***Scheme 3.7**. Heteroaryl iodide scope.*



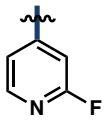
Pyridines and Quinolines:



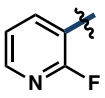
122j
82% yield
86% ee



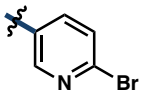
122o[a,b]
64% yield
87% ee



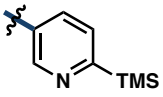
122p[b]
60% yield
79% ee



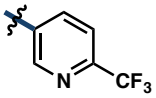
122q
35% yield
83% ee



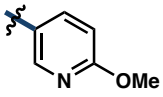
122r[b]
68% yield
88% ee



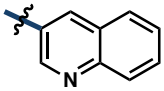
122s[a,b]
70% yield
78% ee



122t[b]
70% yield
85% ee

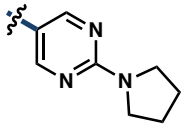


122u[a,b]
45% yield
83% ee

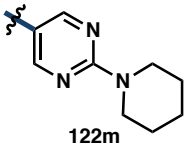


122v[b]
76% yield
92% ee

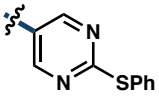
Pyrimidines:



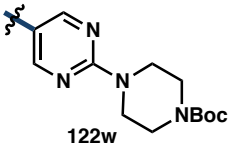
122l
60% yield
87% ee



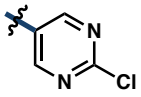
122m
70% yield
85% ee



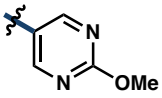
122n
76% yield
91% ee



122w
69% yield
85% ee



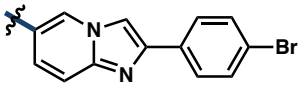
122x
41% yield
89% ee



122y[a,b]
71% yield
92% ee

Other heteroarenes:

122i
87% yield
88% ee



122z[a]
72% yield
83% ee

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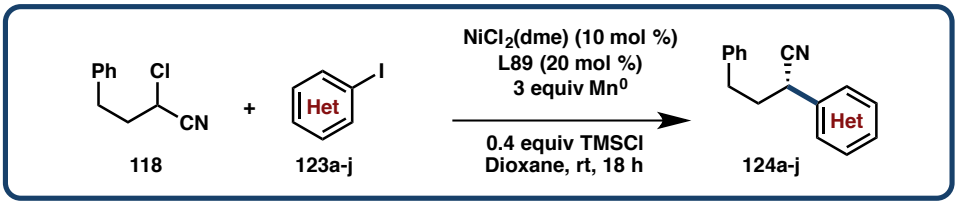
[a] 2 equiv aryl iodide employed. [b] 1 equiv $NaBF_4$ added. All yields are isolated on a 0.2 mmol scale. % ee determined by SFC using a chiral stationary phase.

The scope of successful heteroaryl iodide cross-coupling partners is shown in **Scheme 3.7**. We began our screening of these substrates with a series of pyridyl substrates, based on the preliminary success of chloropyridine **121j**. We were pleased to see that a wide range of 2-halopyridines coupled with perfect chemoselectivity for the iodo position, including 2-bromopyridine **121r**. An iodide walk about 2-fluoropyridine demonstrated that while *para* and *meta* substitution were tolerated, 2-fluoro-3-iodopyridine afforded only modest yield of **122q**, albeit with good enantioselectivity. Electron-donating as well as withdrawing groups behaved well, as in **122t** and **122u**. 3-iodoquinoline was an especially good substrate, providing **122v** in excellent ee and high yield. Importantly, 5-iodo-2-trimethylsilylpyridine underwent cross-coupling smoothly (**122s**), providing a nucleophilic handle for further derivatization or a route to access the unsubstituted pyridyl product via protodesilylation.[24]

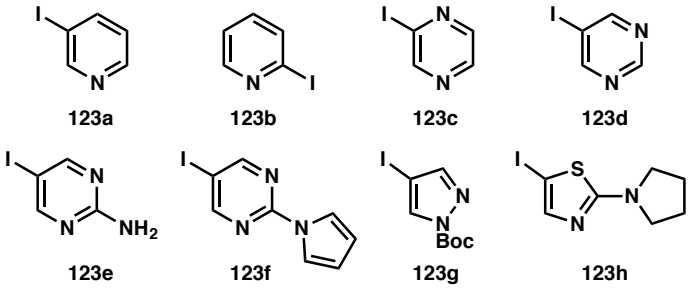
Inspired by the success of the pyridyl series, we went on to prepare and evaluate a range of iodopyrimidine substrates. A series of 2-aminopyrimidines bearing saturated nitrogen heterocycles was of particular interest (**122l**, **122m**, and **122w**), as these compounds find application in medicinal chemistry for a wide range of indications (oncological, cardiovascular, and anti-infective).[22] We were also pleased to find that 2-chloro-5-iodopyrimidine (**121x**) underwent reductive coupling chemoselectively and with excellent ee, providing a functional handle for later S_NAr or cross-coupling derivatization. Thioether-bearing **122n** was also accessible in high yield and ee, providing an entry to the unsubstituted pyrimidine product via hydrogenation.[25] Finally, we were gratified to find that other heterocyclic scaffolds behaved well in the reaction, including thiophene

122i and imidazopyridine **122z** bearing a pendant aryl bromide and containing a fused imidazole moiety.[26]

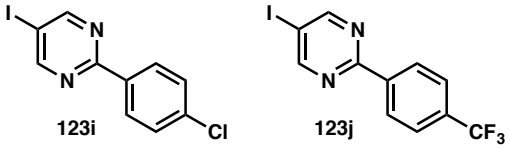
Scheme 3.8. *Unsuccessful heteroaryl iodides.*



No conversion observed:



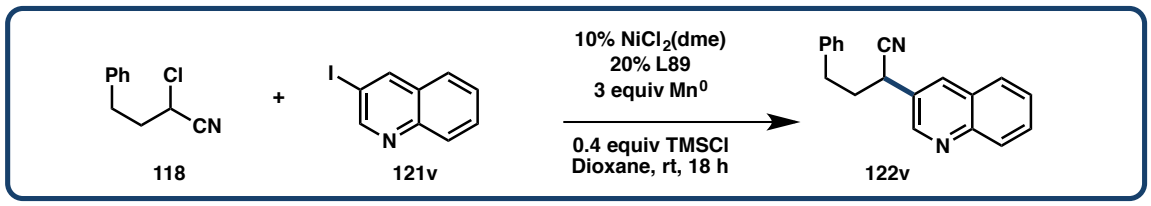
Racemic product obtained:



It is important to note current limitations of this methodology. Generally, heteroaromatics with no blocking group adjacent to the heteroatom (**123a** and **123d**) failed to afford product. In addition, placement of the electrophilic iodide at this position also failed to give any reactivity (**123b** and **123c**). Basic amines were generally not tolerated, even when incorporated into electron-withdrawing scaffolds such as **123e**. All of these observations may be attributable to catalyst poisoning by the Lewis basic heteroatoms in these substrates. While we succeeded in introducing a remarkable degree of tolerance for some Lewis basic sites (see **Figure 3.7**), clearly this issue remains a challenge for future development. Much less explicable was the result obtained by

employing 2-arylpyrimidines (**123i** and **123j**). While these substrates afforded the cross-coupled products in excellent yields, the material obtained was racemic. At this time it is unclear whether some mechanistic difference is at play with these substrates, or whether the products obtained are configurationally labile.

Table 3.3. *Control experiments.*

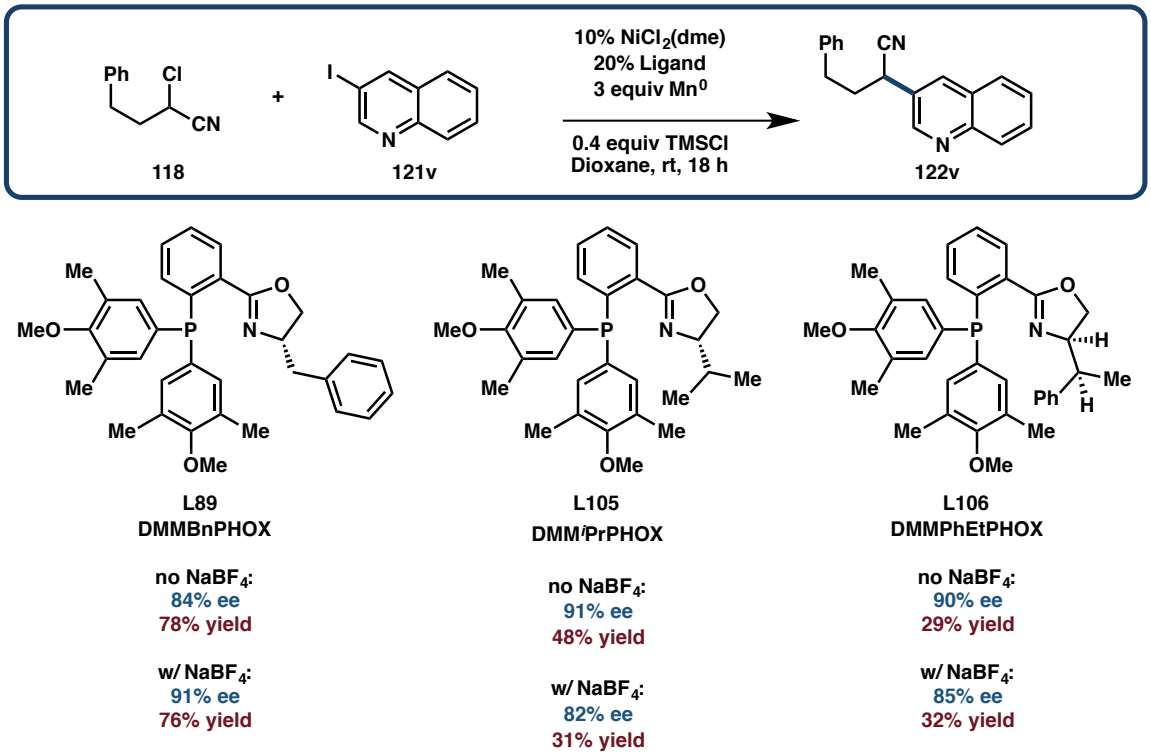


Entry	Deviation	Yield 122v	ee 122v	Yield -Cl
1	None	78	84	20
2	DMA, no dioxane	0	--	62
3	No Ni	0	--	0
4	No Mn^0	0	--	0
5	No L89	4	0	23
6	No TMSCl	<5	82	<5
7	Zn^0, no Mn^0	25	10	32
8	TFA, no TMSCl	48	78	37
9	+ 1 equiv $NaBF_4$	76	90	24
10	+ 0.25 equiv NaI	71	84	29
11	RCH(CN)Br, no 118	9	84	36

At this stage, we sought to verify that our reaction conditions were indeed optimal and to establish the necessity of all the reagents employed. **Table 3.3** shows the results of these control experiments conducted with 3-iodoquinoline **121v**. As expected, the reaction does not proceed in the absence of the Ni precatalyst or the Mn^0 reductant, with Mn^0 being superior to Zn^0 in this role. The coupling is also highly ligand-dependent, with only trace product being observed in the absence of ligand. TMSCl was critical for reactivity, with TFA being able to recapitulate only a portion of its effect. For 3-iodoquinoline (**121v**), $NaBF_4$ proved to be a beneficial additive, while NaI did not

improve reactivity. Finally, employing bromonitrile **117** in place of **118** led to higher levels of protodehalogenation, as well as elimination to form the acrylonitrile.

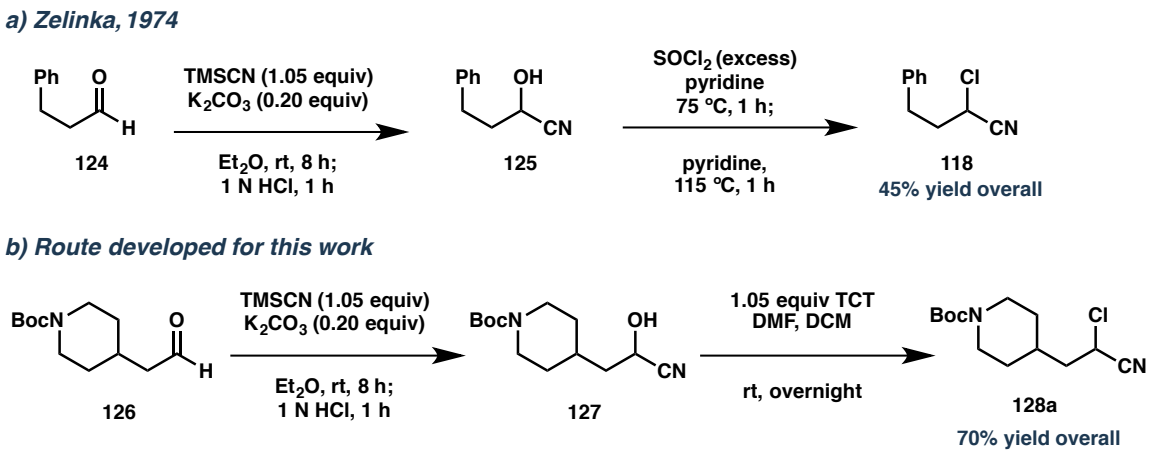
Scheme 3.9. *DMM-PHOX derivative series.*



In a final effort toward optimization, we returned to the PHOX ligand scaffold. Having seen the impact on yield, enantioselectivity, and functional group tolerance exerted by **L89** as a result of the DMM-phosphine arm, we prepared a small series of ligands bearing this phosphine component (**Scheme 3.9**). Because ^{i}PrPHOX (**L34**) had been an early high-performing ligand, we prepared its DMM-phosphine analogue **L105**. Interestingly, **L105** did not benefit from the presence of $NaBF_4$, but excellent ee's were still obtainable, albeit in lower yields. This prompted us to prepare one final DMMBnPHOX analogue, incorporating diastereotopic branching on the benzyl substituent. DMMPhEtPHOX (**L106**) was accessible from the known unnatural amino

acid β-methylphenylalanine, prepared via asymmetric hydrogenation.[27] Unfortunately, only one diastereomer is easily prepared, with the other requiring commercially unavailable ligands for the analogous hydrogenation step. However **L106** did not provide improved results, affording only the reduced yields of DMM*i*PrPHOX in similar ee. At this point we determined that **L89** was the optimal ligand for this transformation and elected to move forward with substrate scope evaluation.

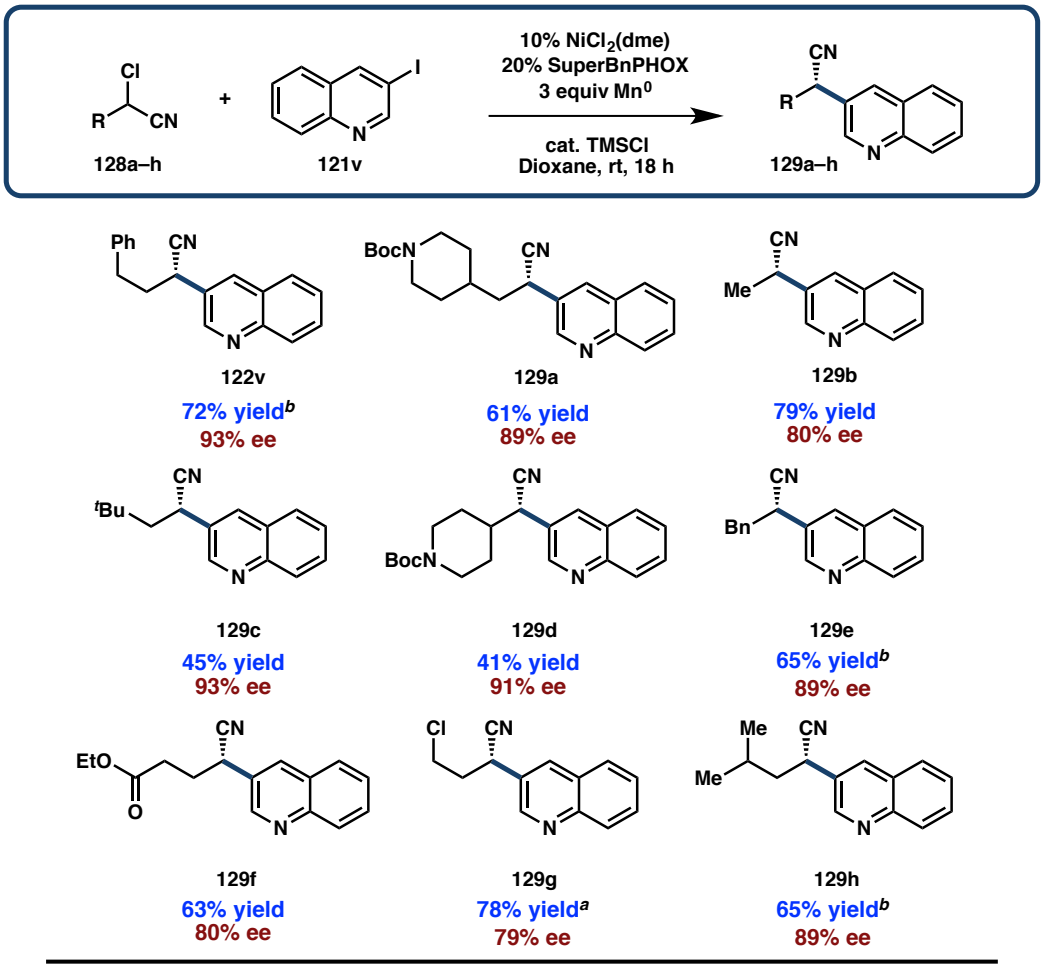
Scheme 3.10. *Preparation of α-chloronitriles.*



Having explored a significant range of heteroaryl iodides and established our optimal reaction conditions, we turned our attention to the scope of α-chloronitrile partners for this reaction. However, before addressing the cross-coupling of these substrates, a method for their general synthesis was required. Indeed, at the time of our investigations, routes for the preparation of α-chloronitriles were sparsely reported and relied on very harsh reaction conditions. The literature method for the preparation of model chloronitrile **118** is shown in **Scheme 3.10a**.[28] While this procedure did afford sufficient **118** for our initial investigations, it seemed unlikely that these conditions would enable the synthesis of chloronitriles bearing more sensitive functionality. Fortunately,

mild conditions for the chlorination of functionalized alcohols reported by Giacomelli and coworkers furnished chloronitriles from the corresponding cyanohydrins in excellent yields, employing trichlorotriazine (TCT) and DMF (**Scheme 3.10b**).[29] Importantly, these conditions tolerated functional groups such as esters and Boc-protected amines (e.g. **128a**) that would likely have been incompatible with the harsh conditions employed initially. We were pleased that these substrates proved to be not only accessible, but also remarkably stable, undergoing no decomposition over months when stored at –20 °C.

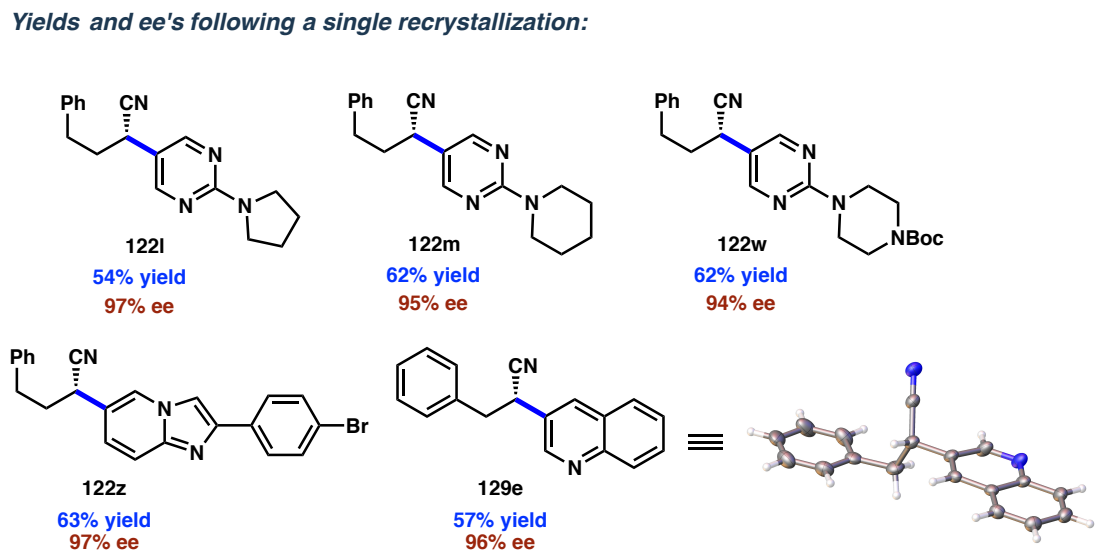
Scheme 3.11. *α-Chloronitrile substrate scope.*



[a] 2 equiv aryl iodide employed. [b] 1 equiv $NaBF_4$ added. All yields are isolated on a 0.2 mmol scale. % ee determined by SFC using a chiral stationary phase.

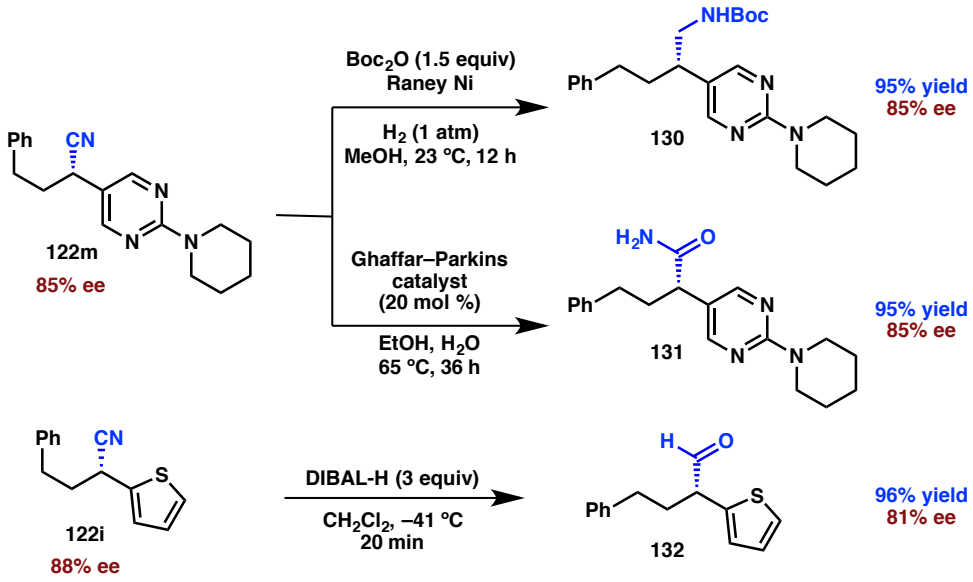
Employing this route, we were able access a series of diverse α-chloronitrile substrates from commercially available aldehydes. With the substrates in hand, we evaluated their performance in the reductive cross-coupling reaction utilizing 3-iodoquinoline **121v** as the model aryl iodide. This substrate was chosen because of its simple functionality and high performance in the aryl iodide screen discussed above. What emerged was the trend illustrated in **Scheme 3.11**: Sterically encumbered substrates such as neopentyl **128c** and branched piperidine **128d** afforded the cross-coupled products in excellent ee but with moderate yields, while less hindered substrates such as 2-chloropropionitrile proceeded in excellent yields but with slightly diminished enantioselectivity. Functional group tolerance in this series was excellent, with electrophilic functionality such as pendent ester **128f** and primary alkyl chloride **128g** reacting cleanly and in high yield. Boc protected piperidines **128a** and **128d** were also well-tolerated, demonstrating the feasibility of heteroatom incorporation in the arene, the nitrile moiety, and the alkyl chain of the products.

Figure 3.8. *Recrystallization of selected substrates.*



We noted that many of the products of our substrate scope investigations were isolable as crystalline solids, suggesting that they may be amenable to enantioenrichment via recrystallization. Taking the most promising of these, we subjected the purified products to vapor diffusion recrystallization, affording highly enantioenriched products as shown in **Figure 3.8**. This also enabled the conclusive determination of the absolute stereochemistry of these products as the (*S*)-series, via X-ray diffraction of **129e**.

Scheme 3.12. *Derivatization of enantioenriched benzylic nitriles.*



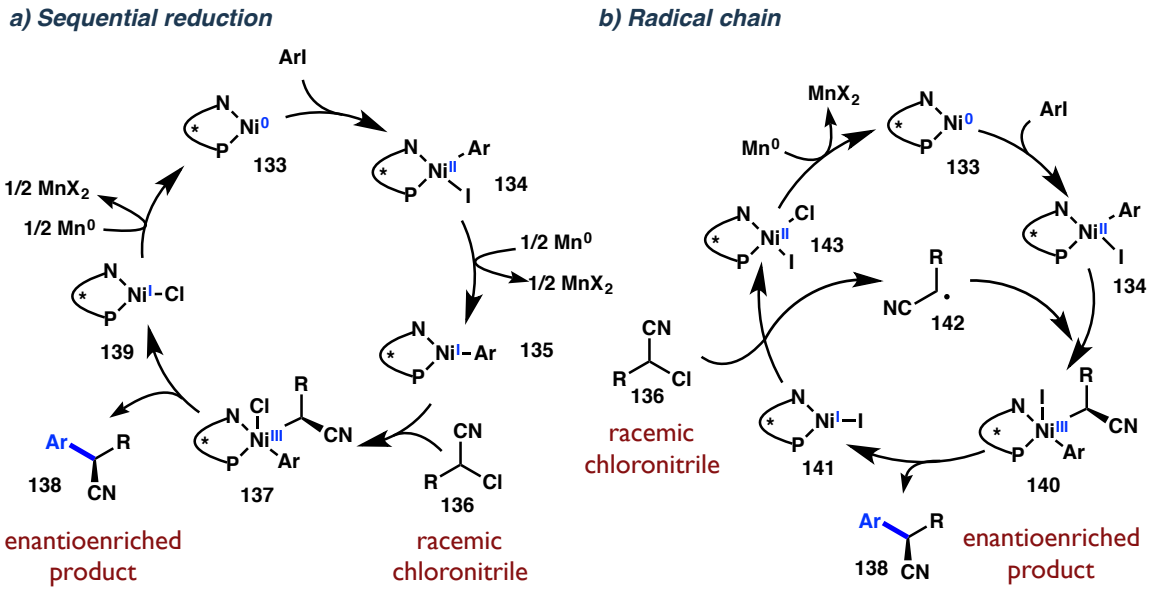
As our final investigation with respect to the substrate scope of this transformation, we set out to demonstrate that the enantioenriched benzylic nitriles obtained via the reductive cross-coupling could be further derivatized to diverse functionality (**Scheme 3.12**). To this end, we subjected piperidylpyrimidine **122m** first to standard Raney Ni hydrogenation in the presence of Boc anhydride, affording the Boc-protected arylethylamine **130** in nearly quantitative yield and with complete preservation of stereochemistry. We anticipate this sequence of reductive cross-coupling followed by hydrogenation to be a valuable route for the preparation of enantioenriched

arylethylamines, a potently bioactive class of molecules.[30] We also subjected **122m** to Pt-catalyzed hydrolysis, employing the mild conditions developed by Ghaffar and Parkins, to generate the carboxamide product **131** with no loss of ee.[31] Finally, beginning with enantioenriched thiophene **122i**, we conducted a DIBAL-mediated reduction of the stereogenic nitrile to the corresponding aldehyde **132** in excellent yield with only slight degradation of ee under these basic conditions.[32]

3.4 MECHANISTIC STUDIES

As described in **Chapter 1**, we hypothesize that asymmetric reductive cross-couplings of radical-stabilized $C(sp)^3$ electrophiles may proceed through the intermediacy of prochiral radicals derived from halide abstraction. While this hypothesis inspired our substrate selection and helped guide reaction development, we set out to verify the presence of radical intermediates and to elucidate their nature. Two possible mechanisms for this transformation are shown in **Figure 3.9**: a sequential reduction mechanism (**a**) and a radical chain mechanism (**b**).

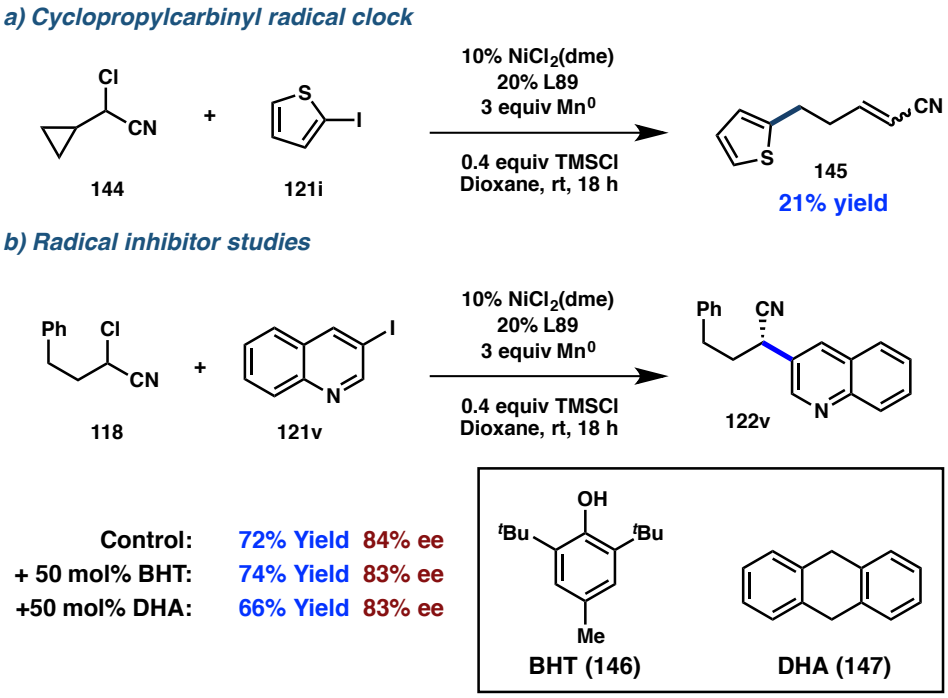
Figure 3.9. *Possible mechanisms for the asymmetric reductive cross-coupling.*



In both mechanisms, cross-selectivity is achieved by matching of substrate hybridization with catalyst oxidation state, affording sequenced oxidative addition steps. That is, the $C(sp^2)$ aryl iodide coupling partner undergoes facile concerted oxidative addition to Ni^0 species **133**, while the $C(sp^3)$ α-chloronitrile is expected to favor single-electron oxidative addition via reaction with an odd-electron Ni^I intermediate (**135** or

141). We postulate that stereoselective recombination of prochiral α-cyano radical **142** with a chiral Ni^{II} complex (**137** or **140**) may be the enantiodetermining step. However if this combination is reversible, then reductive elimination from Ni^{III} **137** or **140** may be enantiodetermining via a Curtin-Hammett-type mechanism. The difference between mechanisms **a** and **b** lies in the lifetime of radical **142**. If **142** recombines rapidly with the Ni^{II} center that abstracted the halide (a radical rebound process), then sequential reduction is favored. If **142** is sufficiently long-lived to escape the solvent cage and combine with a different Ni^{II} center (**134**), then the radical chain process is favored.

Scheme 3.13. *Mechanistic experiments.*



To ascertain the presence of radicals derived from the $C(sp^3)$ electrophile, we prepared cyclopropane-bearing chloronitrile **144 (Scheme 3.13a)**.[33] Subjecting **144** to the reductive cross-coupling conditions with 2-iodothiophene (**121i**), we observed rearranged product **145** as the only cross-coupled product (as a mixture of the *cis* and *trans* isomers).

The remainder of the aryl iodide was unreacted, while the remainder of the α-chloronitrile afforded volatile decomposition products. This is consistent with the generation of an α-cyanocyclopropylcarbinyl radical intermediate.

Given the results with radical clock **114**, it was somewhat surprising that the reaction was not impacted by up to 50 mol % of the radical inhibitors BHT or DHA (**Scheme 3.13b**). We would anticipate that cage-escaped radicals generated in the reaction would be quenched by these inhibitors, leading to lower yields or complete inhibition. However, it may be possible that short-lived radicals not escaping the solvent cage may be unaffected by inhibitors. The success of the cross-coupling in the presence of these inhibitors is not consistent with our expectations for a radical chain mechanism, although further studies are required to elucidate if the sequential reduction mechanism is operative or if more complex pathways are at work.

3.5 CONCLUSION

In conclusion, a Ni-catalyzed asymmetric reductive cross-coupling between α-chloronitriles and heteroaryl iodides has been developed.[34] A new chiral PHOX ligand was identified that provides α,α-disubstituted nitriles in good yields and with high enantioinduction. This is the first example of a Ni-catalyzed asymmetric reductive cross-coupling reaction that tolerates N- and S-heterocyclic coupling partners and demonstrates the feasibility of developing related transformations of electrophiles containing Lewis basic functional groups. The development of such novel asymmetric reductive cross-coupling reactions as well as mechanistic investigations are the subject of ongoing research in our laboratory.

3.6 EXPERIMENTAL SECTION

3.6.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Methylene chloride, diethyl ether, tetrahydrofuran, and toluene were dried by passing through activated alumina. All other commercially obtained reagents were used as received unless specifically indicated. Aryl iodides were purchased from Sigma Aldrich, Combi-Blocks, or Astatech. Manganese powder (>99.9%) was purchased from Sigma Aldrich. $NiCl_2$(dme) was purchased from Strem. Ghaffar-Parkins catalyst was purchased from Strem. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm). Silica gel column chromatography was performed as described by Still et al. (W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem*. **1978**, *43*, 2923.) using silica gel (particle size 0.032-0.063) purchased from Silicycle. ^{1}H and ^{13}C NMR were recorded on a Varian Inova 500 (at 500 MHz and 125 MHz respectively) or a Varian Inova 600 (at 600 MHz and 150 MHz respectively and are reported relative to internal chloroform (^{1}H, δ = 7.26, ^{13}C, δ = 77.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system with Chiralcel AD-H, OD-H, AS-H, OB-H, and IA columns (4.6 mm x 25 cm). HRMS were acquired using either an Agilent 6200 Series TOF with an Agilent G1978A Multimode

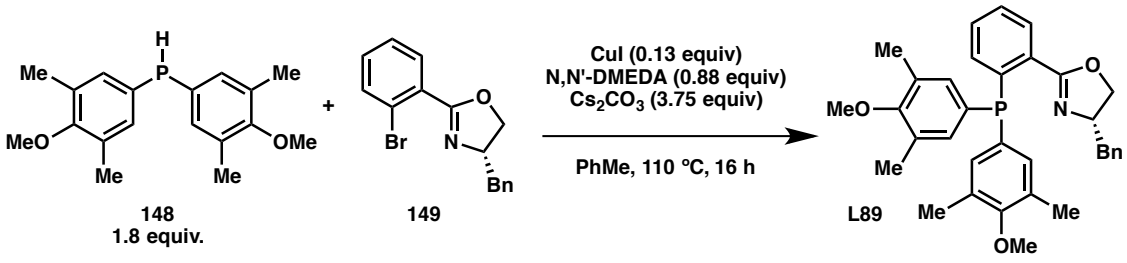
source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed (MM) ionization mode. Low-temperature X-ray diffraction data (ϕ-and ω-scans) were collected on a Bruker AXS D8 VENTURE KAPPA diffractometer coupled to a PHOTON 100 CMOS detector with Cu-$K\alpha$ radiation (λ = 1.54178 Å) from an IμS micro-source.

3.6.2 Ligand and Substrate Preparation

a. General Procedure 1 for the preparation of BnPHOX derivatives

To a flame-dried flask was added CuI (0.13 equiv), followed by anhydrous toluene (0.5 mL/1 mmol bromoarene). To this solution was added N,N'-DMEDA (0.88 equiv) and diarylphosphine (1.8 equiv). These were stirred for 15 minutes at room temperature. To the reaction was then added Cs_2CO_3 (3.75 equiv), followed by bromoarene (1 equiv) as a solution in toluene (0.5 mL/1 mmol bromoarene). The reaction was heated to 110 ºC for 16 h. After cooling to room temperature, the reaction was filtered through a plug of Celite and washed with degassed anhydrous DCM. The solution was concentrated and quickly purified via column chromatography using a positive pressure of argon and degassed solvent to afford the BnPHOX ligand.

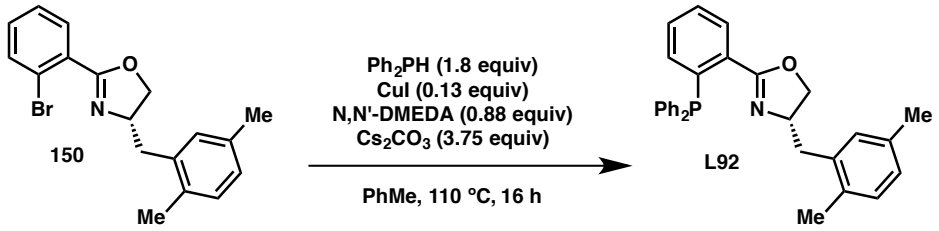
(*S*)-4-benzyl-2-(2-(bis(4-methoxy-3,5-dimethylphenyl)phosphanyl)phenyl)-4,5-dihydrooxazole (L89, DMMBnPHOX)



Prepared according to General Procedure 1: To a flame-dried flask was added CuI (0.13 equiv, 241 mg, 1.3 mmol), followed by anhydrous toluene (40 mL). To this solution was added N,N'-DMEDA (0.88 equiv, 0.93 mL, 8.6 mmol) and diarylphosphine **148** (1.8 equiv, 5.3 g, 17.5 mmol). These were stirred for 15 minutes at room temperature. To the reaction was then added Cs_2CO_3 (3.75 equiv, 12.4 g, 36.7 mmol), followed by bromoarene **149** (1 equiv, 3.1 g, 9.8 mmol) as a solution in toluene (40 mL). The reaction was heated to 110 ºC for 16 h. After cooling to room temperature, the reaction was filtered through a plug of Celite and washed with degassed anhydrous DCM. The solution was concentrated and quickly purified via column chromatography using a positive pressure of argon and degassed solvent (10-40% Et_2O/Hexanes) to afford **L89** as a white foamy solid (1.62 g, 3.01 mmol, 31% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.90 – 7.82 (m, 1H), 7.40 – 7.32 (m, 2H), 7.32 – 7.27 (m, 2H), 7.26 – 7.20 (m, 1H), 7.15 – 7.10 (m, 2H), 7.05 (dd, *J* = 12.7, 7.9 Hz, 4H), 6.93 (ddd, *J* = 7.7, 4.5, 1.5 Hz, 1H), 4.44 – 4.29 (m, 1H), 4.06 (dd, *J* = 9.3, 8.3 Hz, 1H), 3.78 (dd, *J* = 8.4, 7.4 Hz, 1H), 3.75 (d, *J* = 4.0 Hz, 6H), 2.99 (dd, *J* = 13.7, 5.0 Hz, 1H), 2.28 (d, *J* = 13.0 Hz, 12H), 2.17 – 2.06 (m, 1H); ^{13}C NMR (126 MHz, cdcl$_3$) ^{13}C NMR (126 MHz, cdcl$_3$) δ 164.32, 164.30, 157.71, 157.63, 139.88, 139.68, 138.19, 135.02, 134.84, 134.72, 134.54, 133.40, 133.38, 132.43, 132.41,

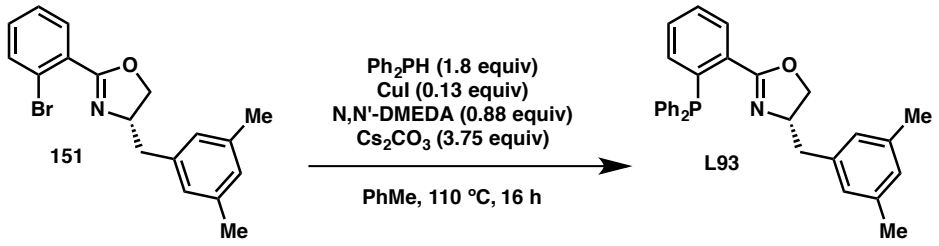
132.36, 132.33, 131.49, 131.35, 131.01, 130.95, 130.90, 130.83, 130.36, 129.91, 129.89, 129.08, 128.48, 127.65, 126.34, 71.55, 67.90, 59.68, 59.62, 41.25, 16.22, 16.17; ^{31}P NMR (121 MHz, cdcl$_3$) δ -6.15; IR (NaCl/thin film): 3564.92, 2935.84, 1651.78, 1474.78, 1274.72, 1217.33, 1113.02, 1014.45, 909.83, 732.11, 700.48, 607.77 cm^{-1}; $[\alpha]_D^{25}$ = +37.355 (*c* = 1.285, $CHCl_3$). HRMS (MM) calc'd for $[M+H_2O]^+$ 555.2533, found 555.2544.

(*S*)-4-(2,5-dimethylbenzyl)-2-(2-(diphenylphosphanyl)phenyl)-4,5-dihydrooxazole (L92)



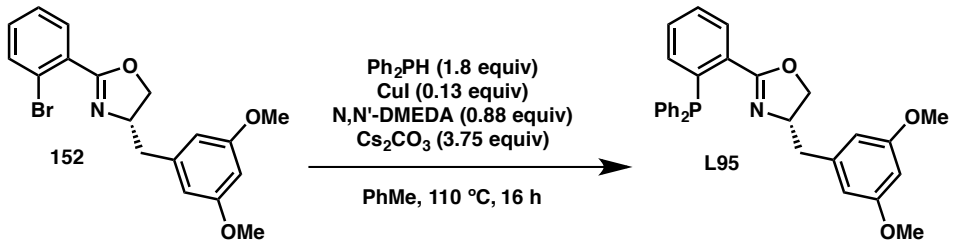
Prepared from bromoarene **150** (4.24 mmol, 1.46 g) according to General Procedure 1 and purified by flash column chromatography in 10-20% EtOAc/hexanes to afford 1.1 g (58% yield) of **L92** a clear tacky resin. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.97 (ddd, *J* = 7.6, 3.5, 1.5 Hz, 1H), 7.46 – 7.29 (m, 12H), 7.07 (d, *J* = 7.7 Hz, 1H), 7.00 – 6.85 (m, 3H), 4.41 (tdd, *J* = 9.6, 7.2, 4.8 Hz, 1H), 4.09 (t, *J* = 8.8 Hz, 1H), 3.87 (dd, *J* = 8.4, 7.2 Hz, 1H), 2.96 (dd, *J* = 14.3, 4.9 Hz, 1H), 2.34 (s, 3H), 2.27 (s, 3H), 2.12 (dd, *J* = 14.3, 9.9 Hz, 1H).

(*S*)-4-(3,5-dimethylbenzyl)-2-(2-(diphenylphosphanyl)phenyl)-4,5-dihydrooxazole (L93)



Prepared from bromoarene **151** (4.24 mmol, 1.46 g) according to General Procedure 1 and purified by flash column chromatography in 10-20% EtOAc/hexanes to afford 210 mg (11% yield) of **L93** a clear tacky resin. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.90 (s, 1H), 7.45 – 7.18 (m, 12H), 6.95 – 6.79 (m, 2H), 6.71 (s, 2H), 4.49 – 4.21 (m, 1H), 4.02 (t, *J* = 8.9 Hz, 1H), 3.81 (d, *J* = 8.1 Hz, 1H), 2.89 (d, *J* = 13.8 Hz, 1H), 2.28 (d, *J* = 0.7 Hz, 6H), 2.02 (q, *J* = 12.0, 10.4 Hz, 1H).

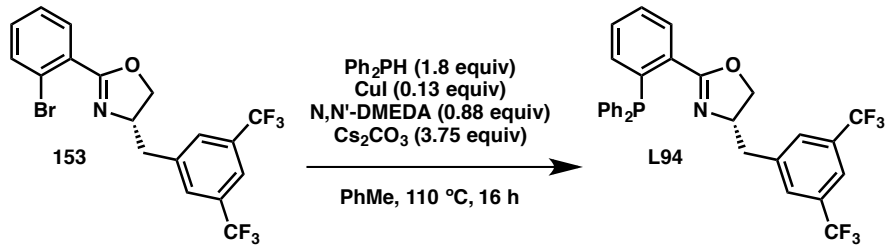
(*S*)-4-(3,5-dimethoxybenzyl)-2-(2-(diphenylphosphanyl)phenyl)-4,5-dihydrooxazole (L95)



Prepared from bromoarene **152** (5.60 mmol, 2.11 g) according to General Procedure 1 and purified by flash column chromatography in 10-50% EtOAc/hexanes to afford 414 mg (15% yield) of **L95** a white solid. ^{1}H NMR (300 MHz, Acetonitrile-d_3) δ 7.86 – 7.74 (m, 1H), 7.52 – 7.22 (m, 12H), 6.98 – 6.88 (m, 1H), 6.39 (d, *J* = 2.3 Hz, 2H), 6.35 (t, *J* = 2.3 Hz, 1H), 4.45 – 4.23 (m, 1H), 4.13 (dd, *J* = 9.4, 8.3 Hz, 1H), 3.76 (m, 7H),

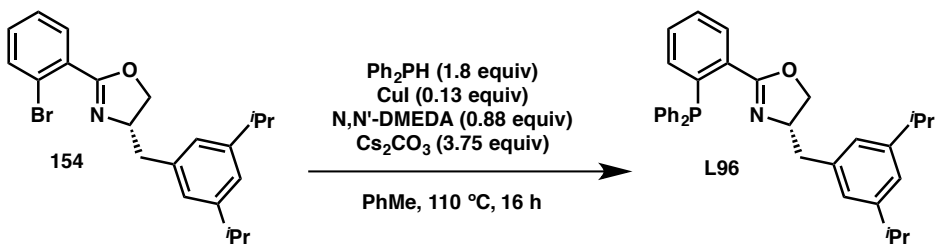
2.68 (dd, *J* = 13.7, 6.4 Hz, 1H), 2.32 (dd, *J* = 13.7, 7.4 Hz, 1H).; ^{31}P NMR (121 MHz, cd_3cn) δ -6.56.

(*S*)-4-(3,5-bis(trifluoromethyl)benzyl)-2-(2-(diphenylphosphanyl)phenyl)-4,5-dihydrooxazole (L94)



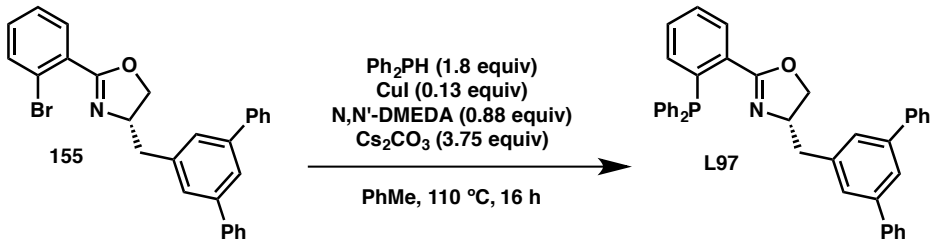
Prepared from bromoarene **153** (1.05 mmol, 475 mg) according to General Procedure 1 and purified by flash column chromatography in 10-20% EtOAc/hexanes to afford 240 mg (41% yield) of **L94** a colorless viscous oil. ^{1}H NMR (300 MHz, Acetonitrile-d_3) δ 7.88 (s, 3H), 7.82 – 7.72 (m, 1H), 7.52 – 7.10 (m, 12H), 6.98 – 6.85 (m, 1H), 4.49 – 4.29 (m, 1H), 4.25 (dd, *J* = 9.5, 8.3 Hz, 1H), 3.84 (dd, *J* = 8.3, 7.3 Hz, 1H), 2.84 (dd, *J* = 14.0, 5.0 Hz, 1H), 2.69 (dd, *J* = 14.0, 8.2 Hz, 1H).; ^{31}P NMR (121 MHz, cd_3cn) δ -6.50.

(*S*)-4-(3,5-diisopropylbenzyl)-2-(2-(diphenylphosphanyl)phenyl)-4,5-dihydrooxazole (L96)



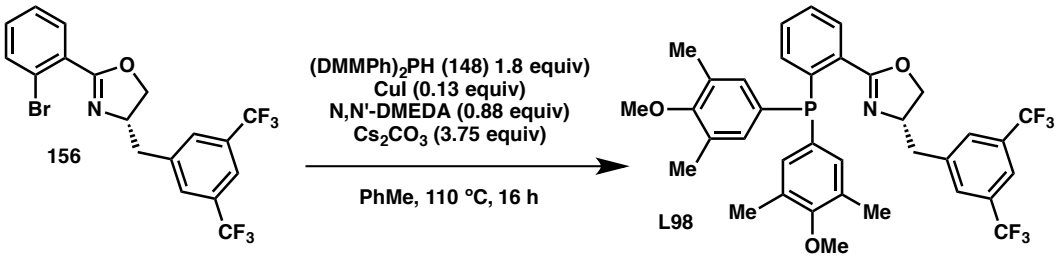
Prepared from bromoarene **154** (5.30 mmol, 2.12 g) according to General Procedure 1 and purified by flash column chromatography in 5-20% EtOAc/hexanes to afford 930 mg (35% yield) of **L96** a white solid. ^{1}H NMR (300 MHz, Acetonitrile-d_3) δ 7.85 – 7.74 (m, 1H), 7.50 – 7.21 (m, 10H), 6.99 (t, *J* = 1.7 Hz, 1H), 6.97 – 6.86 (m, 3H), 4.31 (dtd, *J* = 9.4, 7.4, 6.2 Hz, 1H), 4.10 (dd, *J* = 9.4, 8.3 Hz, 1H), 3.77 (dd, *J* = 8.3, 7.5 Hz, 1H), 2.86 (p, *J* = 6.9 Hz, 2H), 2.69 (dd, *J* = 13.7, 6.3 Hz, 1H), 2.37 (dd, *J* = 13.7, 7.3 Hz, 1H), 1.22 (d, *J* = 6.9 Hz, 12H).; ^{31}P NMR (121 MHz, cd_3cn) δ -6.43.

(*S*)-4-([1,1':3',1''-terphenyl]-5'-ylmethyl)-2-(2-(diphenylphosphanyl)phenyl)-4,5-dihydrooxazole (L97)



Prepared from bromoarene **155** (5.97 mmol, 2.80 g) according to General Procedure 1 and purified by flash column chromatography in 10-30% EtOAc/hexanes to afford 830 mg (24% yield) of **L97** a white solid. ^{1}H NMR (300 MHz, Acetonitrile-d_3) δ 7.93 – 7.77 (m, 1H), 7.77 – 7.69 (m, 5H), 7.53 (d, *J* = 1.7 Hz, 2H), 7.51 – 7.07 (m, 13H), 6.94 (ddd, *J* = 6.3, 3.8, 1.9 Hz, 1H), 4.54 – 4.34 (m, 1H), 4.33 – 4.16 (m, 1H), 4.00 – 3.82 (m, 1H), 2.89 – 2.60 (m, 2H).; ^{31}P NMR (121 MHz, cd_3cn) δ -7.08.

(*S*)-2-(2-(bis(4-methoxy-3,5-dimethylphenyl)phosphanyl)phenyl)-4-(3,5-bis(trifluoromethyl)benzyl)-4,5-dihydrooxazole (L98)

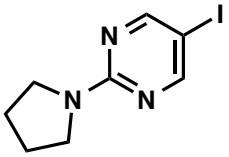


Prepared from bromoarene **156** (3.0 mmol, 1.36 g) according to General Procedure 1 and purified by flash column chromatography in 10-20% Et_2O/hexanes to afford 300 mg (15% yield) of **L98** a clear yellow oil. ^{1}H NMR (300 MHz, Acetonitrile-d_3) δ 8.07 – 7.63 (m, 3H), 7.57 – 7.15 (m, 3H), 6.95 (dd, J = 7.9, 4.0 Hz, 5H), 4.42 – 4.05 (m, 1H), 3.86 – 3.44 (m, 8H), 2.88 – 2.45 (m, 2H), 2.16 (s, 6H), 1.96 (s, 6H).; ^{19}F NMR (282 MHz, cd_3cn) δ -63.09.; ^{31}P NMR (121 MHz, cd_3cn) δ -6.78.

b. General Procedure 2 for preparation of heteroaryl iodides.

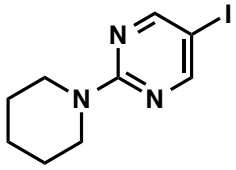
To a flame-dried flask was added copper(I) iodide (0.05 equiv), followed by 1,4-dioxane and N,N'-DMEDA (0.10 equiv), then aryl bromide (1.0 equiv) and sodium iodide (2.0 equiv). The reaction was heated to 110 ºC for 24 h. Upon cooling to room temperature, the reaction was filtered over Celite and washed with DCM. The solution was concentrated to afford the aryl iodide as a light solid. Purification by recrystallization was possible for all substrates but was generally unnecessary. Aryl iodides were employed in the coupling reactions as is.

5-iodo-2-(pyrrolidin-1-yl)pyrimidine (121l)



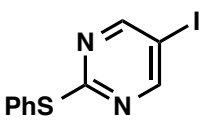
Prepared from 5-bromo-2-(pyrrolidin-1-yl)pyrimidine (10.3 mmol, 2.35 g) following General Procedure 2 to yield 2.75 g (97% yield) of **121l** as a very light pink solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.37 (s, 2H), 3.57 – 3.47 (m, 4H), 2.18 – 1.77 (m, 4H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 162.34, 158.19, 74.37, 46.74, 25.52; IR (NaCl/thin film): 2944.10, 2864.32, 1565.22, 1518.02, 1511.96, 1333.11, 1286.14, 1153.17, 940.39, 782.61, 639.66 cm^{-1}; HRMS (MM) calc'd for [M]$^{+}$ 274.9914, found 274.9874.

5-iodo-2-(piperidin-1-yl)pyrimidine (121m)



Prepared from 5-bromo-2-(piperidin-1-yl)pyrimidine (10.3 mmol, 2.49 g) following General Procedure 2 to yield 2.86 g (96% yield) of **121m** as a light yellow solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.34 (s, 2H), 3.78 – 3.69 (m, 4H), 1.71 – 1.63 (m, 2H), 1.59 (tt, *J* = 7.8, 4.5 Hz, 4H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 162.34, 159.63, 74.30, 44.87, 25.64, 24.71; IR (NaCl/thin film): 2929.42, 2849.82, 1558.04, 1505.31, 1360.11, 1266.59, 1253.66, 1023.84, 945.12, 851.36, 784.80, 642.34 cm^{-1}; HRMS (MM) calc'd for [M]$^{+}$ 289.0070, found 289.0033.

5-iodo-2-phenylthiopyrimidine (121n)



Prepared from 5-bromo-2-phenylthiopyrimidine (10.3 mmol, 2.75 g) following General Procedure 2 to yield 3.14 g (97% yield) of **121n** as a light tan solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.62 (s, 2H), 7.65 – 7.56 (m, 2H), 7.48 – 7.40 (m, 3H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 171.40, 162.64, 135.25, 129.61,

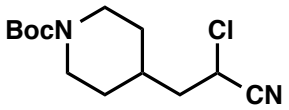
129.34, 128.88, 87.17; IR (NaCl/thin film): 3057.57, 1537.84, 1514.30, 1440.03, 1382.13, 1184.77, 994.96, 745.51, 687.91, 630.05 cm^{-1}; HRMS (MM) calc'd for $[M]^+$ 313.9369, found 313.9579.

c. General Procedure 3 for preparation of α-chloronitriles.

To a flame-dried flask was added aldehyde starting material (1 equiv) followed by anhydrous Et_2O and K_2CO_3 (0.2 equiv). To this suspension was added TMSCN (1.02 equiv) (Warning: acutely toxic, handle with care). Reaction was stirred at room temperature overnight. Reaction was then quenched with saturated aqueous $NaHCO_3$ (1 mL/mmol). Layers were separated and the aqueous phase was extracted twice with Et_2O. Organic layers were combined and concentrated. The resulting oil was suspended in 1 N HCl and stirred at rt for 2 hours. The reaction was then washed twice with Et_2O and the organics were dried over Na_2SO_4 and concentrated to afford the crude cyanohydrin. A new flame-dried flask was charged with a large stirbar and cyanuric chloride (1.05 equiv). To this was added DMF (1.1 mL/gram cyanuric chloride) and the suspension was stirred vigorously until a white solid was obtained. The solid was then suspended by addition of DCM (0.5 M). The crude cyanohydrin was added to the reaction as a solution in DCM and stirred at room temperature for 24 hours. The reaction was quenched by addition of water and stirred for 10 minutes. Layers were separated and the aqueous layer was washed with DCM. Organic phases were combined and washed with saturated Na_2CO_3, then 1 N HCl, then brine. Organics were then dried over Na_2SO_4 and concentrated to afford the crude chloronitrile. Crude oils were purified by column

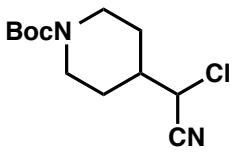
chromatography to afford clear oils or white solids. Substrate preparations were unoptimized and the reported reactions were performed once.

tert-Butyl-4-(2-chloro-2-cyanoethyl)piperidine-1-carboxylate (128a)



Prepared from 2-(1-Boc-4-piperidyl)acetaldehyde (1.0 g, 4.4 mmol) following General Procedure 3. The crude residue was purified by silica gel chromatography (5:95 to 20:80 EtOAc:hexanes) to yield 837 mg (70% yield) of **128a** as a white solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.49 (t, *J* = 7.6 Hz, 1H), 4.12 (bs, 2H), 2.71 (bs, 2H), 2.10 – 1.94 (m, 2H), 1.80 (ddd, *J* = 11.3, 7.6, 4.2 Hz, 1H), 1.72 – 1.67 (m, 2H), 1.45 (s, 9H), 1.28 – 1.06 (m, 2H); ^{13}C NMR (126 MHz, $cdcl_3$) δ 154.64, 117.08, 79.61, 43.72, 43.20, 42.63, 40.18, 33.02, 31.44, 31.08, 28.42; IR (NaCl/thin film): 2929.41, 1673.87, 1417.84, 1246.54, 1161.38, 1127.43, 966.65, 865.88, 769.18, 741.68, 677.80 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 273.1364, found 273.1352.

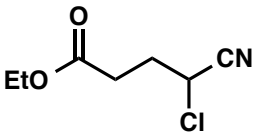
tert-Butyl-4-(chloro(cyano)methyl)piperidine-1-carboxylate (128d)



Prepared from 1-Boc-piperidine-4-carboxaldehyde (2.0 g, 9.39 mmol) following General Procedure 3. The crude residue was purified by silica gel chromatography (5:95 to 20:80 EtOAc:hexanes) to yield 570 mg (24% yield) of **128d** as a white solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.34 (d, *J* = 6.1 Hz, 1H), 4.24 (bs, 2H), 2.70 (bs, 2H), 2.10 – 1.98 (m, 1H), 1.98 – 1.84 (m, 2H), 1.46 (s, m, 11H); ^{13}C NMR (126 MHz, $cdcl_3$) δ 154.47, 115.76, 79.95, 47.27, 43.17, 42.70, 41.59, 28.39, 28.35, 27.96; IR (NaCl/thin film): 1976.08, 1945.79, 2859.74, 1682.85, 1422.81, 1366.50, 1280.82, 1239.82, 1166.99,

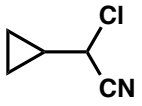
1128.02, 973.46, 866.39, 760.71 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 259.1208, found 259.1256.

Ethyl 4-chloro-4-cyanobutyrate (128f)



Prepared from ethyl hemisuccinaldehyde (1.82 g, 14 mmol) following General Procedure 3. The crude residue was purified by silica gel chromatography (5:95 to 20:80 EtOAc:hexanes) to yield 1.77 g (72% yield) of **128f** as a clear oil. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.70 (dd, *J* = 7.5, 6.2 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.73 – 2.53 (m, 2H), 2.49 – 2.28 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), ; ^{13}C NMR (126 MHz, $cdcl_3$) δ 171.34, 116.62, 61.14, 41.50, 31.39, 29.66, 14.15; IR (NaCl/thin film): 2983.27, 2249.74, 1734.19, 1608.59, 1564.56, 1419.07, 1378.34, 1193.90, 1096.48, 1024.20, 852.08, 795.42, 665.51 cm^{-1}; HRMS (MM) calc'd for $[M]^+$ 175.0395, found 175.0380.

2-chloro-2-cyclopropylacetonitrile (144)



Prepared from cyclopropane carboxaldehyde (1 mL, 13.4 mmol) following General Procedure 3. The crude residue was purified by kugelrohr distillation followed by silica gel chromatography (100% pentanes) to yield 205 mg (13% yield) of **144** as a clear mobile liquid. The product was isolated with some residual pentane due to its volatility. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.22 (d, *J* = 7.7 Hz, 1H), 1.53 (qt, *J* = 7.9, 4.8 Hz, 1H), 0.94 – 0.84 (m, 2H), 0.74 – 0.62 (m, 2H); ^{13}C NMR (126 MHz, $cdcl_3$) δ 115.79, 46.91, 16.59, 6.09, 5.40; IR (NaCl/thin film): 3091.35,

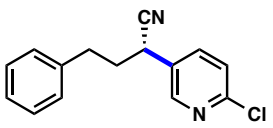
3013.92, 2958.47, 2247.22, 1732.61, 1430.84, 1220.80, 1029.90, 991.98, 926.86, 832.41, 728.05 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 116.0262, found 116.0258.

3.6.3 Enantioselective Reductive Cross-Coupling

General Procedure 4 for reductive cross-couplings.

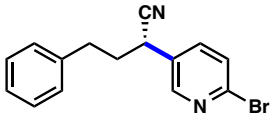
A 20 mL scintillation vial was charged with a cross stirbar, Mn^0 powder (3 equiv, 33 mg, 0.6 mmol), aryl iodide (*if solid*, 1 or 2 equiv, 0.2 or 0.4 mmol), $NiCl_2$(dme) (0.1 equiv, 4.4 mg, 0.02 mmol), **L89** (0.2 equiv, 21.6 mg, 0.04 mmol) and $NaBF_4$ if applicable (1 equiv, 22 mg, 0.2 mmol). To this was added 1,4-dioxane (0.68 mL, 0.3M), aryl iodide (*if liquid*, 1 or 2 equiv, 0.2 or 0.4 mmol) and TMSCl (0.4 equiv, 33 μL, 0.08 mmol), followed by chloronitrile (1 equiv, 0.2 mmol). Reaction was sealed with a Teflon-lined cap and stirred on the benchtop at 500 RPM for 16 hours. Over this interval reactions turn from dark purple to cloudy red or yellow with significant white precipitate. Reactions were diluted with 1 mL of hexane, leading to additional salt precipitation. This slurry was loaded directly onto a silica gel or florisil column and eluted in a hexane/EtOAc gradient. Excess aryl iodide could be recovered in the first several fractions, with cross-coupled product being the most polar component. Reaction success is critically dependent on stirring. A stirbar too small for the reaction vessel will fail to suspend the Mn powder and lead to low conversions. The reaction vessel should be sufficiently large (solvent height should be sufficiently low) to allow even distribution of Mn powder with vigorous stirring.

2-(6-chloropyridin-3-yl)-4-phenylbutanenitrile (122j)



Prepared from 2-chloro-5-iodopyridine (48.0 mg, 0.2 mmol) and 2-chloro-4-phenylbutanenitrile (36 mg, 0.2 mmol) following General Procedure 4. The crude residue was purified by silica gel chromatography (0:100 to 10:90 EtOAc:hexanes) to yield 39.8 mg (78% yield) of **122j** as a clear oil. The enantiomeric excess was determined to be 85% by chiral SFC analysis (AD, 2.5 mL/min, 8% IPA in CO_2, λ = 210 nm): t_R(minor) = 9.8 min, t_R(major) = 13.0 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.31 (d, *J* = 2.6 Hz, 1H), 7.66 (dd, *J* = 8.3, 2.7 Hz, 1H), 7.40 – 7.28 (m, 3H), 7.28 – 7.22 (m, 1H), 7.22 – 7.17 (m, 2H), 3.77 (dd, *J* = 9.2, 6.0 Hz, 1H), 2.87 – 2.81 (m, 2H), 2.34 – 2.27 (m, 1H), 2.16 (dddd, *J* = 13.7, 8.5, 7.6, 6.0 Hz, 1H).; ^{13}C NMR (126 MHz, cdcl$_3$) δ 151.54, 148.52, 138.91, 137.56, 130.54, 128.89, 128.40, 126.84, 124.78, 119.22, 37.00, 33.47, 32.86.; IR (NaCl/thin film): 3027.23, 2926.09, 2242.46, 1586.64, 1566.17, 1496.29, 1460.14, 1389.42, 1141.53, 1108.27, 1022.71, 832.61, 741. 61, 700.19 cm^{-1}; $[\alpha]_D^{25}$ = -12.081 (*c* = 1.410, $CHCl_3$). HRMS (MM) calc'd for $[M+Na]^+$ 279.0659, found 279.0702.

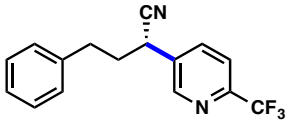
2-(6-bromopyridin-3-yl)-4-phenylbutanenitrile (122r)



Prepared from 2-bromo-5-iodopyridine (56.8 mg, 0.2 mmol) and 2-chloro-4-phenylbutanenitrile (36 mg, 0.2 mmol) with $NaBF_4$ (22 mg, 0.2 mmol) following General Procedure 4. The crude residue was purified by silica gel chromatography (0:100 to 10:90 EtOAc:hexanes) to yield 40.9 mg (68% yield) of **122r** as a clear oil. The enantiomeric excess was determined to be 88% by chiral SFC analysis (AD, 2.5 mL/min, 10% IPA in CO_2, λ = 280 nm): t_R(minor) = 9.5 min, t_R(major)

= 12.2 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.29 (dt, *J* = 2.5, 0.6 Hz, 1H), 7.54 (qd, *J* = 8.3, 1.7 Hz, 2H), 7.42 – 7.29 (m, 2H), 7.29 – 7.22 (m, 1H), 7.22 – 7.14 (m, 2H), 3.74 (dd, *J* = 9.2, 6.0 Hz, 1H), 2.90 – 2.78 (m, 2H), 2.29 (dddd, *J* = 13.9, 9.3, 8.0, 6.0 Hz, 1H), 2.16 (dddd, *J* = 13.7, 8.5, 7.6, 6.0 Hz, 1H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 148.97, 142.08, 138.88, 137.29, 130.97, 128.89, 128.57, 128.40, 126.85, 119.13, 36.95, 33.53, 32.85; IR (NaCl/thin film): 3026.73, 2925.74, 2859.37, 2242.11, 1734.00, 1581.13, 1561.56, 1496.15, 1455.35, 1385.97, 1090.22, 1019.79, 830.73, 735.64, 699.99 cm^{-1}; $[\alpha]_D^{25}$ = -4.695 (*c* = 1.180, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 301.0335, found 301.0341.

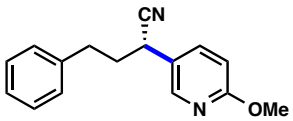
4-phenyl-2-(6-(trifluoromethyl)pyridin-3-yl)butanenitrile (122t)



Prepared from 5-iodo-2-trifluoromethylpyridine (54.6 mg, 0.2 mmol) and 2-chloro-4-phenylbutanenitrile (36 mg, 0.2 mmol) with $NaBF_4$ (22 mg, 0.2 mmol) following General Procedure 4. The crude residue was purified by silica gel chromatography (0:100 to 10:90 EtOAc:hexanes) to yield 39.7 mg (68% yield) of **122t** as a clear oil. The enantiomeric excess was determined to be 85% by chiral SFC analysis (AD, 2.5 mL/min, 7% IPA in CO_2, λ = 254 nm): t_R(minor) = 3.0 min, t_R(major) = 4.7 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.64 (d, *J* = 2.2 Hz, 1H), 7.89 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.73 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.40 – 7.29 (m, 2H), 7.29 – 7.22 (m, 1H), 7.22 – 7.14 (m, 2H), 3.87 (dd, *J* = 9.3, 5.9 Hz, 1H), 2.93 – 2.82 (m, 2H), 2.39 – 2.28 (m, 1H), 2.21 (dddd, *J* = 13.7, 8.5, 7.7, 5.9 Hz, 1H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 148.93, δ 148.18 (q, $J_{C\text{-}F}$ = 35.3 Hz), 138.77, 136.28, 134.83, 128.92, 128.40, 128.38, 126.91, 126.89, 120.81 (q, $J_{C\text{-}F}$ = 2.7 Hz),

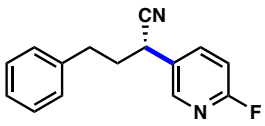
118.87, 37.02, 34.03, 32.90.; IR (NaCl/thin film): 3028.51, 2928.97, 2862.95, 2243.85, 1735.25, 1602.71, 1496.75, 1454.95, 1403.90, 1339.65, 1178.34, 1137.96, 1088.63, 1027.88, 850.30, 751.10, 700.69 cm^{-1}; $[\alpha]_D^{25}$ = -21.304 (*c* = 1.475, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 291.1104, found 291.1181.

2-(6-methoxypyridin-3-yl)-4-phenylbutanenitrile (122u)



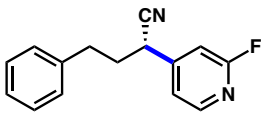
Prepared from 5-iodo-2-methoxypyridine (94.0 mg, 0.4 mmol) and 2-chloro-4-phenylbutanenitrile (36 mg, 0.2 mmol) with $NaBF_4$ (22 mg, 0.2 mmol) following General Procedure 4. The crude residue was purified by silica gel chromatography (0:100 to 20:80 EtOAc:hexanes) to yield 22.8 mg (45% yield) of **122u** as a clear oil. The enantiomeric excess was determined to be 83% by chiral SFC analysis (AD, 2.5 mL/min, 8% IPA in CO_2, λ = 245 nm): t_R(minor) = 6.5 min, t_R(major) = 7.5 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.07 (dt, *J* = 2.6, 0.6 Hz, 1H), 7.55 (ddd, *J* = 8.6, 2.6, 0.4 Hz, 1H), 7.37 – 7.28 (m, 2H), 7.26 – 7.21 (m, 1H), 7.21 – 7.17 (m, 2H), 6.78 (dd, *J* = 8.6, 0.7 Hz, 1H), 3.94 (s, 3H), 3.69 (dd, *J* = 8.8, 6.3 Hz, 1H), 2.81 (td, *J* = 8.1, 3.5 Hz, 2H), 2.35 – 2.21 (m, 1H), 2.14 (dddd, *J* = 13.8, 8.5, 7.5, 6.4 Hz, 1H).; ^{13}C NMR (126 MHz, $cdcl_3$) δ 164.04, 145.68, 139.41, 137.39, 128.77, 128.42, 126.64, 124.09, 120.16, 111.56, 53.67, 37.04, 33.28, 32.85.; IR (NaCl/thin film): 2925.19, 1849.43, 2240.05, 1608.56, 1572.83, 1494.73, 1395.28, 1290.62, 1024.55, 831.08, 750.29, 699.95 cm^{-1}; $[\alpha]_D^{25}$ = -9.806 (*c* = 0.790, $CHCl_3$). HRMS (MM) calc'd for $[M+Na]^+$ 275.1155, found 275.1175.

2-(6-fluoropyridin-3-yl)-4-phenylbutanenitrile (122o)



Prepared from 2-fluoro-5-iodopyridine (89.2 mg, 0.4 mmol) and 2-chloro-4-phenylbutanenitrile (36 mg, 0.2 mmol) following General Procedure 4. The crude residue was purified by silica gel chromatography (0:100 to 10:90 EtOAc:hexanes) to yield 30.7 mg (64% yield) of **122o** as a clear oil. The enantiomeric excess was determined to be 87% by chiral SFC analysis (AD, 2.5 mL/min, 8% IPA in CO_2, λ = 254 nm): t_R(minor) = 5.2 min, t_R(major) = 6.4 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.18 – 8.10 (m, 1H), 7.79 (ddd, *J* = 8.5, 7.2, 2.7 Hz, 1H), 7.38 – 7.28 (m, 2H), 7.28 – 7.22 (m, 1H), 7.22 – 7.16 (m, 2H), 6.99 (ddd, *J* = 8.5, 3.1, 0.6 Hz, 1H), 3.78 (dd, *J* = 9.2, 6.0 Hz, 1H), 2.93 – 2.77 (m, 2H), 2.31 (dddd, *J* = 14.0, 9.3, 8.1, 6.0 Hz, 1H), 2.17 (dddd, *J* = 13.7, 8.5, 7.6, 6.0 Hz, 1H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 163.33 (d, $J_{C\text{-}F}$ = 241.3 Hz), 146.57 (d, $J_{C\text{-}F}$ = 15.3 Hz), 140.02 (d, $J_{C\text{-}F}$ = 8.2 Hz), 138.98, 129.33 (d, $J_{C\text{-}F}$ = 4.7 Hz), 128.87, 128.40, 126.82, 119.45, 110.26 (d, $J_{C\text{-}F}$ = 37.6 Hz), 37.11, 33.29 (d, $J_{C\text{-}F}$ = 1.6 Hz), 32.88. ; IR (NaCl/thin film): 3027.76, 2926.65, 2859.25, 2242.02, 1599.81, 1484.95, 1399.59, 1256.76, 1127.35, 1025.00, 831.20, 748.87, 700.31 cm^{-1}; $[\alpha]_D^{25}$ = -27.336 (*c* = 1.155, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 241.1136, found 241.1210.

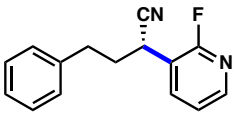
2-(2-fluoropyridin-4-yl)-4-phenylbutanenitrile (122p)



Prepared from 2-fluoro-4-iodopyridine (44.6 mg, 0.2 mmol) and 2-chloro-4-phenylbutanenitrile (36 mg, 0.2 mmol) with $NaBF_4$ (22 mg, 0.2 mmol) following General Procedure 4. The crude residue was purified by silica gel chromatography (0:100 to 10:90 EtOAc:hexanes) to yield 28.8 mg (60% yield) of

122p as a clear oil. The enantiomeric excess was determined to be 79% by chiral SFC analysis (AD, 2.5 mL/min, 8% IPA in CO_2, λ = 210 nm): t_R(minor) = 4.7 min, t_R(major) = 5.5 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.25 (d, *J* = 5.2 Hz, 1H), 7.36 – 7.31 (m, 2H), 7.29 – 7.23 (m, 1H), 7.22 – 7.18 (m, 2H), 7.17 – 7.14 (m, 1H), 6.92 (td, *J* = 1.5, 0.7 Hz, 1H), 3.79 (dd, *J* = 9.4, 5.6 Hz, 1H), 2.92 – 2.83 (m, 2H), 2.29 (dddd, *J* = 13.7, 9.5, 8.2, 5.5 Hz, 1H), 2.23 – 2.15 (m, 1H).; ^{13}C NMR (126 MHz, cdcl$_3$) δ 164.13 (d, $J_{C\text{-}F}$ = 240.5 Hz), 163.17, 150.09, 148.71 (d, $J_{C\text{-}F}$ = 15.3 Hz), 138.83, 128.91, 128.39, 126.90, 120.00 (d, $J_{C\text{-}F}$ = 4.4 Hz), 118.59, 108.40 (d, $J_{C\text{-}F}$ = 38.8 Hz), 36.61, 35.85 (d, $J_{C\text{-}F}$ = 3.3 Hz), 32.90. ; IR (NaCl/thin film): 2923.87, 2851.17, 2244.02, 1734.43, 1611.28, 1569.24, 1454.61, 1414.02, 1277.86, 839.28, 751.37, 700.44 cm^{-1}; $[\alpha]_D^{25}$ = -22.036 (*c* = 0.45, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 241.1136, found 241.1134.

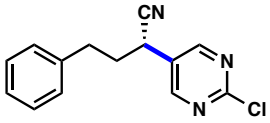
2-(2-fluoropyridin-3-yl)-4-phenylbutanenitrile (122q)



Prepared from 2-fluoro-3-iodopyridine (44.6 mg, 0.2 mmol) and 2-chloro-4-phenylbutanenitrile (36 mg, 0.2 mmol) following General Procedure 4. The crude residue was purified by silica gel chromatography (0:100 to 10:90 EtOAc:hexanes) to yield 16.7 mg (35% yield) of **122q** as a clear oil. The enantiomeric excess was determined to be 83% by chiral SFC analysis (AD, 2.5 mL/min, 6% IPA in CO_2, λ = 245 nm): t_R(minor) = 4.9 min, t_R(major) = 5.8 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.21 (ddd, *J* = 4.9, 1.9, 1.2 Hz, 1H), 7.98 – 7.87 (m, 1H), 7.35 – 7.29 (m, 2H), 7.29 – 7.22 (m, 2H), 7.22 – 7.18 (m, 2H), 4.03 (t, *J* = 7.4 Hz, 1H), 2.94 – 2.80 (m, 2H), 2.30 – 2.18 (m, 2H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 160.30 (d, $J_{C\text{-}F}$ = 239.3 Hz), 147.65 (d, $J_{C\text{-}F}$ = 14.8 Hz), 139.59 (d, $J_{C\text{-}F}$ = 4.3 Hz), 139.02, 128.78, 128.37, 126.74,

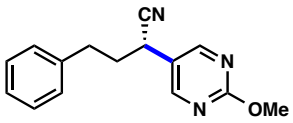
122.09 (d, $J_{C\text{-}F}$ = 4.3 Hz), 118.80, 118.23 (d, $J_{C\text{-}F}$ = 29.6 Hz), 35.26, 33.06, 30.83 (d, $J_{C\text{-}F}$ = 2.5 Hz); IR (NaCl/thin film): 2925.09, 2853.97, 2244.15, 1734.36, 1606.84, 1577.55, 1441.07, 1248.36, 1101.26, 805.44, 750.96, 699.91 cm^{-1}; $[\alpha]_D^{25}$ = -29.296 (*c* = 0.635, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 241.1136, found 241.1133.

2-(2-chloropyrimidin-5-yl)-4-phenylbutanenitrile (122x)



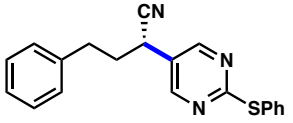
Prepared from 2-chloro-5-iodopyrimidine (48.1 mg, 0.2 mmol) and 2-chloro-4-phenylbutanenitrile (36 mg, 0.2 mmol) following General Procedure 4. The crude residue was purified by flash column chromatography using Florisil® stationary phase (0:100 to 15:85 EtOAc:hexanes) to yield 21.2 mg (41% yield) of **122x** as a clear oil. The enantiomeric excess was determined to be 89% by chiral SFC analysis (AD, 2.5 mL/min, 10% IPA in CO_2, λ = 210 nm): t_R(minor) = 6.2 min, t_R(major) = 7.0 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.59 (d, *J* = 0.5 Hz, 2H), 7.37 – 7.31 (m, 2H), 7.30 – 7.24 (m, 1H), 7.22 – 7.17 (m, 2H), 3.78 (dd, *J* = 9.4, 5.9 Hz, 1H), 2.95 – 2.84 (m, 2H), 2.34 (dddd, *J* = 13.6, 9.4, 7.7, 5.8 Hz, 1H), 2.19 (dtd, *J* = 13.8, 8.0, 5.9 Hz, 1H); ^{13}C NMR (126 MHz, $cdcl_3$) δ 161.50, 158.30, 138.35, 129.03, 128.39, 128.36, 127.07, 118.06, 36.65, 32.80, 31.36; IR (NaCl/thin film): 2923.61, 2850.58, 2243.80, 1735.29, 1580.36, 1550.38, 1401.12, 1160.95, 772.57, 748.86, 700.55, 640.20 cm^{-1}; $[\alpha]_D^{25}$ = -14.892 (*c* = 0.305, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 258.0793, found 258.0257.

2-(2-methoxypyrimidin-5-yl)-4-phenylbutanenitrile (122y)



Prepared from 5-iodo-2-methoxypyrimidine (89.2 mg, 0.4 mmol) and 2-chloro-4-phenylbutanenitrile (36 mg, 0.2 mmol) with $NaBF_4$ (22 mg, 0.2 mmol) following General Procedure 4. The crude residue was purified by florisil gel chromatography (0:100 to 40:60 EtOAc:hexanes) to yield 35.8 mg (71% yield) of **122y** as a clear oil. The enantiomeric excess was determined to be 92% by chiral SFC analysis (AS, 2.5 mL/min, 10% IPA in CO_2, λ = 254 nm): t_R(minor) = 4.5 min, t_R(major) = 5.0 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.47 (d, *J* = 0.4 Hz, 2H), 7.38 – 7.29 (m, 2H), 7.28 – 7.23 (m, 1H), 7.22 – 7.17 (m, 2H), 4.04 (s, 3H), 3.71 (dd, *J* = 9.1, 6.1 Hz, 1H), 2.89 – 2.82 (m, 2H), 2.31 (dddd, *J* = 13.9, 9.2, 7.9, 6.1 Hz, 1H), 2.16 (dddd, *J* = 13.7, 8.4, 7.6, 6.1 Hz, 1H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 165.54, 158.16, 138.84, 128.91, 128.40, 126.86, 122.72, 119.06, 55.30, 36.79, 32.79, 31.17; IR (NaCl/thin film): 3026.71, 2928.66, 2241.18, 1600.01, 1560.30, 1474.60, 1410.27, 1331.54, 1031.65, 803.93, 700.50 cm^{-1}; $[\alpha]_D^{25}$ = -17.013 (*c* = 0.395, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 254.1288, found 254.1310.

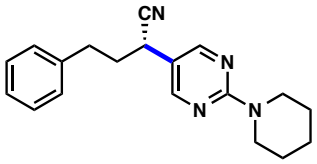
4-phenyl-2-(2-phenylthio)pyrimidin-5-yl)butanenitrile (122n)



Prepared from 5-iodo-2-phenylthiopyrimidine (62.8 mg, 0.2 mmol) and 2-chloro-4-phenylbutanenitrile (36 mg, 0.2 mmol) following General Procedure 4. The crude residue was purified by silica gel chromatography (0:100 to 30:70 EtOAc:hexanes) to yield 50.3 mg (76% yield) of **122n** as a clear oil. The enantiomeric excess was determined to be 91% by chiral SFC analysis (AD, 2.5 mL/min, 15% IPA in CO_2, λ = 280 nm): t_R(minor) = 11.3 min, t_R(major) = 12.7

min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.44 (s, 2H), 7.70 – 7.56 (m, 2H), 7.50 – 7.40 (m, 3H), 7.37 – 7.29 (m, 2H), 7.28 – 7.22 (m, 1H), 7.20 – 7.14 (m, 2H), 3.67 (dd, *J* = 9.0, 6.0 Hz, 1H), 2.89 – 2.79 (m, 2H), 2.28 (dddd, *J* = 13.9, 9.2, 7.9, 6.1 Hz, 1H), 2.13 (dddd, *J* = 13.7, 8.4, 7.7, 6.1 Hz, 1H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 173.10, 156.34, 138.73, 135.37, 129.65, 129.37, 128.92, 128.80, 128.38, 126.89, 124.93, 118.64, 36.64, 32.74, 31.50; IR (NaCl/thin film): 3025.13, 2926.01, 2242,07, 1734.06, 1580.58, 1539.37, 1399.77, 1170.57, 748.46, 701.21, 689.27 cm^{-1}; $[\alpha]_D^{25}$ = +10.214 (*c* = 1.965, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 332.1216, found 332.1746.

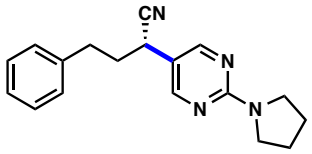
4-phenyl-2-(2-(piperidin-1-yl)pyrimidin-5-yl)butanenitrile (122m)



Prepared from 5-iodo-2-(piperidin-1-yl)pyrimidine (57.8 mg, 0.2 mmol) and 2-chloro-4-phenylbutanenitrile (36.0 mg, 0.2 mmol) following General Procedure 4. The crude residue was purified by silica gel chromatography (0:100 to 40:60 EtOAc:hexanes) to yield 43.1 mg (70% yield) of **122m** as a white solid. The enantiomeric excess was determined to be 85% by chiral SFC analysis (AD, 2.5 mL/min, 15% IPA in CO_2, λ = 254 nm): t_R(minor) = 7.5 min, t_R(major) = 8.6 min. The product could be further enriched via recrystallization by vapor diffusion of pentane to a saturated solution of **122m** in DCM, affording 38.4 mg (89% recovery) of white needles. The enantiomeric excess of recrystallized **7k** was determined to be 95%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.22 (s, 2H), 7.35 – 7.29 (m, 2H), 7.26 – 7.21 (m, 1H), 7.21 – 7.16 (m, 2H), 3.93 – 3.70 (m, 4H), 3.55 (dd, *J* = 8.6, 6.5 Hz, 1H), 2.81 (td, *J* = 8.0, 7.3, 2.1 Hz, 2H), 2.25 (dddd, *J* = 13.6, 8.6, 7.9, 6.5 Hz, 1H), 2.11 (dddd, *J* = 13.7, 8.3, 7.4, 6.5 Hz, 1H), 1.76 – 1.65 (m,

2H), 1.65 – 1.54 (m, 4H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 161.27, 156.64, 139.33, 128.78, 128.42, 126.64, 119.91, 115.78, 44.89, 36.74, 32.73, 31.18, 25.71, 24.78.; IR (NaCl/thin film): 2932.29, 2853.60, 2239.17, 1605.13, 1514.57, 1448.02, 1364.20, 1271.93, 1024.80, 947.51, 797.14, 700.19 cm^{-1}; $[\alpha]_D^{25}$ = +13.073 (*c* = 1.595, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 307.1917, found 307.1848.

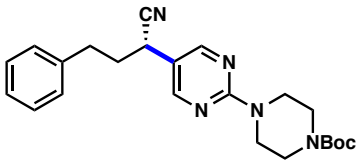
4-phenyl-2-(2-(pyrrolidin-1-yl)pyrimidin-5-yl)butanenitrile (122l)



Prepared from 5-iodo-2-(pyrrolidin-1-yl)pyrimidine (55 mg, 0.2 mmol) and 2-chloro-4-phenylbutanenitrile (36.0 mg, 0.2 mmol) following General Procedure 4. The crude residue was purified by silica gel chromatography (0:100 to 40:60 EtOAc:hexanes) to yield 35.0 mg (60% yield) of **122l** as a white solid. The enantiomeric excess was determined to be 85% by chiral SFC analysis (AD, 2.5 mL/min, 12% IPA in CO_2, λ = 235 nm): t_R(minor) = 10.8 min, t_R(major) = 12.5 min. The product could be further enriched via recrystallization by vapor diffusion of pentane to a saturated solution of **122l** in DCM, affording 31.8 mg (91% recovery) of white needles. The enantiomeric excess of recrystallized **122l** was determined to be 97%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.25 (s, 2H), 7.34 – 7.29 (m, 2H), 7.26 – 7.21 (m, 1H), 7.21 – 7.16 (m, 2H), 3.66 – 3.49 (m, 5H), 2.81 (t, *J* = 7.6 Hz, 2H), 2.26 (ddt, *J* = 13.7, 8.5, 7.2 Hz, 1H), 2.11 (dtd, *J* = 13.6, 7.8, 6.6 Hz, 1H), 2.05 – 1.96 (m, 4H).; ^{13}C NMR (126 MHz, cdcl$_3$) δ 156.64, 139.30, 128.79, 128.42, 126.65, 121.43, 119.93, 115.75, 46.78, 36.76, 32.72, 31.22, 25.52; IR (NaCl/thin film): 2927.97, 2866.57, 2238.90, 1603.00, 1524.42, 1483.96, 1460.18, 1335.03, 798. 26, 699.99 cm^{-1};

$[\alpha]_D^{25}$ = +12.942 (*c* = 1.130, $CHCl_3$). HRMS (MM) calc'd for $[M+H_3O]^+$ 311.1826, found 311.1825.

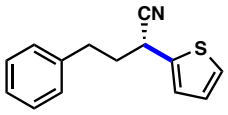
tert-butyl-4-(5-(1-cyano-3-phenylpropyl)pyrimidin-2-yl)piperazine-1-carboxylate (122w)



Prepared from 5-iodo-2-(4-Boc-piperazin-1-yl)pyrimidine (78.0 mg, 0.2 mmol) and 2-chloro-4-phenylbutanenitrile (36.0 mg, 0.2 mmol) following General Procedure 4. The crude residue was purified by silica gel chromatography (0:100 to 40:60 EtOAc:hexanes) to yield 56.5 mg (69% yield) of **122w** as a white solid. The enantiomeric excess was determined to be 85% by chiral SFC analysis (AD, 2.5 mL/min, 15% IPA in CO_2, λ = 235 nm): t_R(minor) = 7.5 min, t_R(major) = 9.0 min. The product could be further enriched via recrystallization by vapor diffusion of pentane to a saturated solution of **122w** in benzene, affording 51.0 mg (90% recovery) of white needles. The enantiomeric excess of recrystallized **122w** was determined to be 94%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.25 (s, 2H), 7.37 – 7.27 (m, 2H), 7.25 – 7.20 (m, 1H), 7.20 – 7.15 (m, 2H), 3.83 – 3.79 (m, 4H), 3.58 (dd, *J* = 8.7, 6.4 Hz, 1H), 3.50 (t, *J* = 5.3 Hz, 4H), 2.90 – 2.73 (m, 2H), 2.26 (dddd, *J* = 13.6, 8.7, 7.2, 4.1 Hz, 1H), 2.11 (dddd, *J* = 13.7, 8.4, 7.5, 6.4 Hz, 1H), 1.49 (s, 9H); ^{13}C NMR (126 MHz, $cdcl_3$) δ 161.27, 156.70, 154.78, 139.21, 128.81, 128.40, 126.69, 119.71, 117.11, 80.07, 43.65, 42.86 (br), 36.74, 32.74, 31.18, 28.43; IR (NaCl/thin film): 2977.91, 2927.86, 2861.14, 2243.21, 1687.28, 1607.00, 1517.48, 1496.25, 1424.34, 1364.59, 1247.24, 1176.22, 1129.18, 999.26, 793.95, 696.53 cm^{-1};

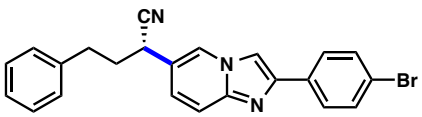
$[\alpha]_D^{25}$ = +13.500 (*c* = 1.980, $CHCl_3$). HRMS (MM) calc'd for $[M+Na]^+$ 430.2213, found 430.2294.

4-phenyl-2-(thiophen-2-yl)butanenitrile (122i)



Prepared from 2-iodothiophene (111 μL, 1.0 mmol) and 2-chloro-4-phenylbutanenitrile (180 mg, 1.0 mmol) following General Procedure 4. The crude residue was purified by silica gel chromatography (0:100 to 10:90 EtOAc:hexanes) to yield 170 mg (75% yield) of **122i** as a clear oil. The enantiomeric excess was determined to be 88% by chiral SFC analysis (AD, 2.5 mL/min, 8% IPA in CO_2, λ = 245 nm): t_R(minor) = 5.8 min, t_R(major) = 7.1 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.36 – 7.31 (m, 2H), 7.29 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.27 – 7.23 (m, 1H), 7.22 (dq, *J* = 7.6, 0.7 Hz, 2H), 7.08 (dt, *J* = 3.5, 1.0 Hz, 1H), 7.00 (dd, *J* = 5.1, 3.5 Hz, 1H), 4.03 (ddd, *J* = 8.6, 6.3, 0.8 Hz, 1H), 2.94 – 2.82 (m, 2H), 2.41 – 2.24 (m, 2H); ^{13}C NMR (126 MHz, $cdcl_3$) δ 139.49, 137.62, 128.76, 128.50, 127.13, 126.62, 126.31, 125.61, 119.74, 37.32, 32.85, 31.66; IR (NaCl/thin film): 3085.49, 3062.55, 3026.78, 2927.12, 2860.88, 2241.68, 1602.83, 1496.13, 1454.38, 1238.04, 1080.89, 1029.74, 833.92, 750.39, 699.80 cm^{-1}; $[\alpha]_D^{25}$ = -27.559 (*c* = 1.455, $CHCl_3$). HRMS (MM) calc'd for $[M+H_3O]^+$ 246.0947, found 246.1107.

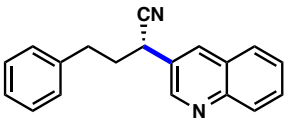
2-(2-(4-bromophenyl)imidazo[1,2-*a*]pyridin-6-yl)-4-phenylbutanenitrile (122z)



Prepared from 2-(4-bromophenyl)-6-iodoimidazo[1,2-*a*]pyridine (159.6 mg, 0.4 mmol) and 2-chloro-4-phenylbutanenitrile (36.0 mg, 0.2 mmol) following General Procedure 4. The crude

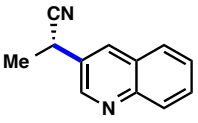
residue was purified by silica gel chromatography (5:95 to 20:80 acetone:hexanes) to yield 60.0 mg (72% yield) of **122z** as a white solid. The enantiomeric excess was determined to be 87% by chiral SFC analysis (IA, 2.5 mL/min, 40% IPA in CO_2, λ = 245 nm): t_R(minor) = 10.7 min, t_R(major) = 14.3 min. The product could be further enriched via recrystallization by vapor diffusion of pentane to a saturated solution of **7o** in DCM, affording 52.2 mg (87% recovery) of white needles. The enantiomeric excess of recrystallized **122z** was determined to be 97%. Following column chromatography, a UV active peak remained in the SFC trace (t_R = 8.6 min) that was not observed in any other analysis. This peak was significantly diminished following recrystallization. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.19 – 8.11 (m, 1H), 7.86 (d, *J* = 0.7 Hz, 1H), 7.85 – 7.78 (m, 2H), 7.64 (d, *J* = 9.4 Hz, 1H), 7.60 – 7.53 (m, 2H), 7.38 – 7.30 (m, 2H), 7.28 – 7.23 (m, 1H), 7.21 (dq, *J* = 7.7, 0.7 Hz, 2H), 7.07 (dd, *J* = 9.3, 1.9 Hz, 1H), 3.77 (dd, *J* = 9.0, 5.7 Hz, 1H), 2.93 – 2.83 (m, 2H), 2.33 (dddd, *J* = 13.8, 9.1, 8.2, 5.7 Hz, 1H), 2.25 (dddd, *J* = 13.7, 8.5, 7.7, 5.8 Hz, 1H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 145.73, 144.82, 139.13, 132.34, 131.93, 128.86, 128.41, 127.59, 126.80, 124.07, 123.75, 122.23, 121.06, 119.44, 118.31, 108.76, 36.51, 33.80, 32.88; IR (NaCl/thin film): 2924.20, 2854.07, 2240.70, 1472.83, 1435.81, 1354.99, 1208.78, 1067.55, 1009.04, 833.96, 806.47, 738.54, 700.04 cm^{-1}; $[\alpha]_D^{25}$ = +28.004 (*c* = 0.275, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 416.0757, found 416.0698.

4-phenyl-2-(quinolin-3-yl)butanenitrile (122v)



Prepared from 3-iodoquinoline (51.2 mg, 0.2 mmol) and 2-chloro-4-phenylbutanenitrile (36.0 mg, 0.2 mmol) with $NaBF_4$ (22.0 mg, 0.2 mmol) following General Procedure 4. The crude residue was purified by silica gel chromatography (0:100 to 40:60 EtOAc:hexanes) to yield 39.4 mg (72% yield) of **3a** as a light yellow oil that solidified on standing. The enantiomeric excess was determined to be 92% by chiral SFC analysis (AD, 2.5 mL/min, 20% IPA in CO_2, λ = 280 nm): t_R(major) = 6.1 min, t_R(minor) = 6.8 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.81 (s, 1H), 8.18 (d, *J* = 2.3 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.85 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.76 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.61 (ddd, *J* = 8.1, 6.8, 1.1 Hz, 1H), 7.38 – 7.28 (m, 2H), 7.28 – 7.15 (m, 3H), 3.99 (dd, *J* = 9.0, 5.9 Hz, 1H), 2.95 – 2.82 (m, 2H), 2.39 (dddd, *J* = 14.0, 9.2, 7.9, 6.2 Hz, 1H), 2.30 (dddd, *J* = 13.7, 8.5, 7.7, 5.9 Hz, 1H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 149.22, 147.75, 139.21, 134.28, 130.18, 129.42, 128.85, 128.57, 128.45, 127.78, 127.62, 127.56, 126.76, 119.74, 37.18, 34.39, 32.99; IR (NaCl/thin film): 3026.11, 2926.11, 2241.03, 1603.40, 1571.03, 1495.05, 1454.48, 1125.63, 906.13, 787.96, 751.66, 700.17 cm^{-1}; $[\alpha]_D^{25}$ = -1.617 (*c* = 0.952, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 273.1386, found 273.1589.

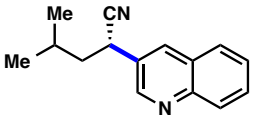
2-(quinolin-3-yl)propanenitrile (129b)



Prepared from 3-iodoquinoline (51.2 mg, 0.2 mmol) and 2-chloropropanenitrile (17 μL, 0.2 mmol) following General Procedure 4. The crude residue was purified by silica gel chromatography (0:100 to 20:80 EtOAc:hexanes) to yield 28.7 mg (79% yield) of **129b** as a clear oil. The enantiomeric

excess was determined to be 81% by chiral SFC analysis (AD, 2.5 mL/min, 10% IPA in CO_2, λ = 254 nm): t_R(major) = 7.8 min, t_R(minor) = 8.8 min. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.87 (d, *J* = 2.4 Hz, 1H), 8.23 (d, *J* = 2.4 Hz, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 7.92 – 7.84 (m, 1H), 7.77 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.62 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 4.16 (q, *J* = 7.3 Hz, 1H), 1.78 (dd, *J* = 7.3, 0.5 Hz, 3H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 149.01, 147.67, 133.57, 130.13, 129.83, 129.34, 127.78, 127.58, 127.54, 120.60, 29.26, 21.39; IR (NaCl/thin film): 2924.03, 2850.94, 2241.83, 1570.25, 1496.55, 1457.22, 1378.86, 1126.13, 1082.83, 966.72, 907.45, 787.48, 752.77, 617.35 cm^{-1}; $[\alpha]_D^{25}$ = -20.200 (*c* = .355, $CHCl_3$). HRMS (MM) calc'd for $[M+H_3O]^+$ 201.1022, found 201.1022.

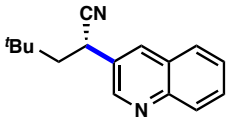
4-methyl-2-(quinolin-3-yl)pentanenitrile (129h)



Prepared from 3-iodoquinoline (51.2 mg, 0.2 mmol) and 2-chloro-4-methylpentanenitrile (26.2 mg, 0.2 mmol) following General Procedure 4. The crude residue was purified by silica gel chromatography (0:100 to 30:70 EtOAc:hexanes) to yield 29.1 mg (65% yield) of **129h** as a clear oil. The enantiomeric excess was determined to be 89% by chiral SFC analysis (OB-H, 2.5 mL/min, 5% IPA in CO_2, λ = 254 nm): t_R(minor) = 4.2 min, t_R(major) = 4.6 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.83 (d, *J* = 2.4 Hz, 1H), 8.19 (d, *J* = 2.4 Hz, 1H), 8.13 (dq, *J* = 8.5, 0.9 Hz, 1H), 7.85 (ddd, *J* = 8.1, 1.3, 0.7 Hz, 1H), 7.76 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1H), 7.61 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 4.05 (dd, *J* = 9.8, 6.2 Hz, 1H), 2.06 – 1.97 (m, 1H), 1.96 – 1.86 (m, 1H), 1.75 (ddd, *J* = 13.5, 8.6, 6.2 Hz, 1H), 1.04 (dd, *J* = 11.3, 6.6 Hz, 6H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 149.31, 147.66, 134.09, 130.08, 129.34, 129.21, 127.73,

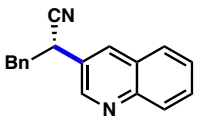
127.63, 127.50, 120.06, 44.85, 33.43, 26.23, 22.59, 21.58; IR (NaCl/thin film): 2957.60, 2928.61, 2238.86, 1653.55, 1570.26, 1494.77, 1467.80, 1369.63, 1280.03, 1116.26, 787.30, 752.79 cm^{-1}; $[\alpha]_D^{25}$ = -22.811 (*c* = 0.350, $CHCl_3$). HRMS (MM) calc'd for $[M+H_3O]^+$ 243.1492, found 243.1194.

4,4-dimethyl-2-(quinolin-3-yl)pentanenitrile (129c)



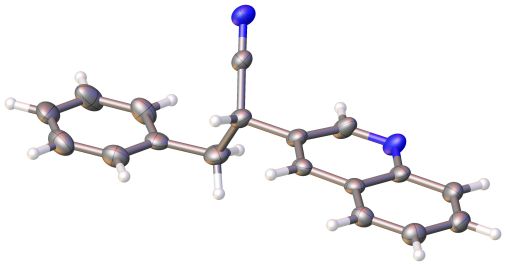
Prepared from 3-iodoquinoline (51.2 mg, 0.2 mmol) and 2-chloro-4,4-dimethylpentanenitrile (29.1 mg, 0.2 mmol) following General Procedure 4. The crude residue was purified by silica gel chromatography (0:100 to 30:70 EtOAc:hexanes) to yield 21.4 mg (45% yield) of **129c** as a clear oil. The enantiomeric excess was determined to be 93% by chiral SFC analysis (AD, 2.5 mL/min, 12% IPA in CO_2, λ = 280 nm): t_R(major) = 5.5 min, t_R(minor) = 6.8 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.81 (d, *J* = 2.4 Hz, 1H), 8.20 (d, *J* = 2.4 Hz, 1H), 8.12 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.84 (ddt, *J* = 8.1, 1.3, 0.6 Hz, 1H), 7.75 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.60 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 4.00 (dd, *J* = 10.3, 3.4 Hz, 1H), 2.15 (dd, *J* = 14.2, 10.4 Hz, 1H), 1.76 (dd, *J* = 14.2, 3.4 Hz, 1H), 1.12 (s, 9H); ^{13}C NMR (126 MHz, $cdcl_3$) δ 149.40, 147.52, 133.87, 130.57, 130.04, 129.32, 127.73, 127.61, 127.50, 121.19, 50.25, 31.37, 31.16, 29.40. IR (NaCl/thin film): 2956.95, 2239.66, 1734.18, 1495.05, 1477.11, 1280.54, 1116.30, 1012.66, 897.41, 788.79, 752.85, 619.63 cm^{-1}; $[\alpha]_D^{25}$ = -55.546 (*c* = 0.515, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 239.1543, found 239.1530.

3-phenyl-2-(quinolin-3-yl)propanenitrile (129e)

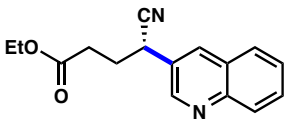


Prepared from 3-iodoquinoline (51.2 mg, 0.2 mmol) and 2-chloro-3-phenylpropanenitrile (33.1 mg, 0.2 mmol) with $NaBF_4$ (22 mg, 0.2 mmol) following General Procedure 4. The crude residue was purified by silica gel chromatography (0:100 to 30:70 EtOAc:hexanes) to yield 33.8 mg (65% yield) of **3e** as a light yellow solid. The enantiomeric excess was determined to be 90% by chiral SFC analysis (AD, 2.5 mL/min, 20% IPA in CO_2, λ = 280 nm): t_R(major) = 5.9 min, t_R(minor) = 6.8 min. The product could be further enriched via recrystallization by vapor diffusion of pentane to a saturated solution of **129e** in DCM, affording 29.7 mg (88% recovery) of clear pyramidal crystals suitable for X-Ray diffraction. The enantiomeric excess of recrystallized **3e** was determined to be 96%. The structure was solved by direct methods using SHELXS and refined against F^2 on all data by full-matrix least squares with SHELXL-2014 using established refinement techniques and with an extinction coefficient of 0.0069(7). All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included into the model at geometrically calculated positions and refined using a riding model. Compound **129e** crystallizes in the orthorhombic space group $P2_12_12_1$ and absolute configuration was determined by anomalous dispersion (Flack = -0.15(8)).^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.71 (d, *J* = 2.4 Hz, 1H), 8.16 – 8.10 (m, 1H), 8.07 (d, *J* = 2.3 Hz, 1H), 7.81 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.77 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.61 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.33 – 7.27 (m, 3H), 7.17 – 7.11 (m, 2H), 4.32 – 4.25 (m, 1H), 3.36 – 3.23 (m, 2H); ^{13}C NMR (126 MHz, $cdcl_3$) δ 149.35, 147.68, 135.32, 134.61, 130.18, 129.35, 129.29, 128.84, 127.96, 127.80, 127.76, 127.49, 127.45, 119.51, 41.90, 37.50; IR (NaCl/thin film): 3029.15, 2925.55, 2855.78, 2242.14,

1604.24, 1571.67, 1495.10, 1455.39, 1382.41, 1125.96, 908.49, 787.51, 752.04, 734.70, 699.30 cm^{-1}; $[\alpha]_D^{25}$ = -1.218 (*c* = 0.870, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 259.1230, found 259.1427.

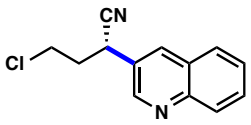


Ethyl 4-cyano-4-(quinolin-3-yl)butanoate (129f)



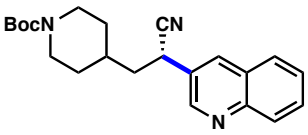
Prepared from 3-iodoquinoline (51.2 mg, 0.2 mmol) and ethyl 4-chloro-4-cyanobutyrate (35.1 mg, 0.2 mmol) following General Procedure 4. The crude residue was purified by silica gel chromatography (0:100 to 30:70 EtOAc:hexanes) to yield 34.0 mg (63% yield) of **129f** as a clear oil. The enantiomeric excess was determined to be 80% by chiral SFC analysis (AD, 2.5 mL/min, 12% IPA in CO_2, λ = 254 nm): t_R(major) = 7.2 min, t_R(minor) = 8.3 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.91 (s, 1H), 8.20 (s, 2H), 7.86 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.77 (d, *J* = 6.7 Hz, 1H), 7.61 (dd, *J* = 8.1, 6.8 Hz, 1H), 4.28 (dd, *J* = 8.7, 6.0 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 2.62 (dt, *J* = 16.9, 7.5 Hz, 1H), 2.53 (dt, *J* = 17.0, 6.5 Hz, 1H), 2.41 – 2.21 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 171.81, 149.29, 148.04, 134.40, 130.30, 129.54, 128.12, 127.83, 127.61, 127.59, 119.40, 61.01, 34.27, 30.92, 30.72, 14.17; IR (NaCl/thin film): 2979.77, 2926.59, 2242.45, 1731.81, 1495.27, 1377.67, 1312.77, 1189.37, 1024.39, 909.00, 788.82, 754.73 cm^{-1}; $[\alpha]_D^{25}$ = -9.319 (*c* = 0.860, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 269.1285, found 269.1313.

3-chloro-2-(quinolin-3-yl)propanenitrile (129g)



Prepared from 3-iodoquinoline (102.4 mg, 0.4 mmol) and 2,4-dichlorobutanenitrile (27.6 mg, 0.2 mmol) following General Procedure 4. The crude residue was purified by silica gel chromatography (0:100 to 30:70 EtOAc:hexanes) to yield 35.8 mg (78% yield) of **129g** as a clear oil that slowly solidified on standing. The enantiomeric excess was determined to be 79% by chiral SFC analysis (AD, 2.5 mL/min, 12% IPA in CO_2, λ = 254 nm): t_R(major) = 7.1 min, t_R(minor) = 9.7 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.88 (d, *J* = 2.4 Hz, 1H), 8.22 (d, *J* = 2.4 Hz, 1H), 8.14 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.90 – 7.83 (m, 1H), 7.78 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.63 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 4.41 (dd, *J* = 8.6, 6.7 Hz, 1H), 3.79 (ddd, *J* = 11.5, 8.2, 4.6 Hz, 1H), 3.60 (ddd, *J* = 11.4, 6.4, 4.8 Hz, 1H), 2.54 (dddd, *J* = 14.4, 8.7, 6.5, 4.5 Hz, 1H), 2.40 (dddd, *J* = 14.4, 8.2, 6.7, 4.8 Hz, 1H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 149.09, 147.92, 134.63, 130.42, 129.44, 127.77, 127.71, 127.51, 127.27, 119.08, 41.02, 38.07, 32.28; IR (NaCl/thin film): 2960.74, 2922.28, 2242.62, 1571.06, 1495.00, 1443.08, 1382.69, 1125.91, 957.61, 906.20, 787.55, 753.85, 619.73 cm^{-1}; $[\alpha]_D^{25}$ = +9.150 (*c* = 0.665, $CHCl_3$). HRMS (MM) calc'd for $[M+H_3O]^+$ 249.0789, found 249.0270.

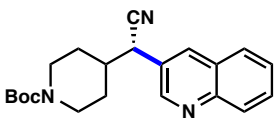
***tert*-butyl-4-(2-cyano-2-(quinolin-3-yl)ethyl)piperidine-1-carboxylate (129a)**



Prepared from 3-iodoquinoline (51.2 mg, 0.2 mmol) and *tert*-Butyl-4-(2-chloro-2-cyanoethyl)piperidine-1-carboxylate (54.6 mg, 0.2 mmol) following General Procedure 4. The crude residue was purified by silica gel chromatography (0:100 to 40:60 EtOAc:hexanes) to yield 44.7 mg (61% yield) of **129a** as a clear oil. The enantiomeric excess was

determined to be 89% by chiral SFC analysis (AD, 2.5 mL/min, 25% IPA in CO_2, λ = 280 nm): t_R(major) = 4.8 min, t_R(minor) = 6.0 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.81 (d, *J* = 2.3 Hz, 1H), 8.18 (d, *J* = 2.3 Hz, 1H), 8.12 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.84 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.76 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.60 (ddd, *J* = 8.1, 6.8, 1.1 Hz, 1H), 4.10 (br, dd, *J* = 10.1, 5.6 Hz, 3H), 2.72 (br, 2H), 2.13 – 1.99 (m, 1H), 1.94 – 1.63 (m, 4H), 1.46 (s, 9H), 1.33 – 1.12 (m, 2H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 154.68, 149.12, 147.72, 134.10, 130.21, 129.37, 128.78, 127.73, 127.60, 127.58, 119.77, 79.55, 43.88 (br), 43.20 (br), 42.58, 33.99, 32.58, 32.10, 31.22, 28.44; IR (NaCl/thin film): 2974.27, 2926.66, 2852.75, 2239.98, 1685.09, 1495.27, 1424.19, 1365.34, 1278.99, 1244.13, 1163.05, 1125.17, 970.82, 865.20, 787.79, 755.04, 736.24, 620.45 cm^{-1}; $[\alpha]_D^{25}$ = -4.158 (*c* = 1.900, $CHCl_3$). HRMS (MM) calc'd for $[M+Mg]^+$ 389.1948, found 389.2091.

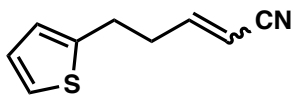
tert-butyl-4-(cyano(quinolin-3-yl)methyl)piperidine-1-carboxylate (129d)



Prepared from 3-iodoquinoline (51.2 mg, 0.2 mmol) and *tert*-Butyl-4-(chloro(cyano)methyl)piperidine-1-carboxylate (51.8 mg, 0.2 mmol) following General Procedure 4. The crude residue was purified by silica gel chromatography (0:100 to 40:60 EtOAc:hexanes) to yield 28.6 mg (41% yield) of **129d** as a clear oil. The enantiomeric excess was determined to be 91% by chiral SFC analysis (AD, 2.5 mL/min, 12% IPA in CO_2, λ = 280 nm): t_R(minor) = 18.5 min, t_R(major) = 19.5 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.79 (d, *J* = 2.4 Hz, 1H), 8.16 (d, *J* = 2.3 Hz, 1H), 8.13 (dq, *J* = 8.5, 0.8 Hz, 1H), 7.86 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.77 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.62 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 4.19 (s, 2H), 3.94 (d, *J* = 6.8 Hz, 1H), 2.64 (s, 2H), 2.03 (tdd, *J* = 12.0, 6.9, 3.5 Hz, 1H), 1.88 – 1.71 (m, 1H), 1.67 (dt, *J* = 12.9,

3.0 Hz, 1H), 1.45 (s, 11H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 154.49, 149.48, 147.80, 135.05, 130.33, 129.37, 127.79, 127.66, 127.41, 126.70, 118.57, 79.85, 43.53, 42.89, 41.41, 41.34, 30.11, 28.80, 28.40; IR (NaCl/thin film): 2975.09, 2929.55, 2853.85, 2240.07, 1688.65, 1424.27, 1365.82, 1248.34, 1165.15, 1121.49, 1059.13, 756.02 cm^{-1}; $[\alpha]_D^{25}$ = -21.275 (*c* = 0.640, $CHCl_3$). HRMS (MM) calc'd for $[M+Mg]^+$ 377.1948, found 377.2042.

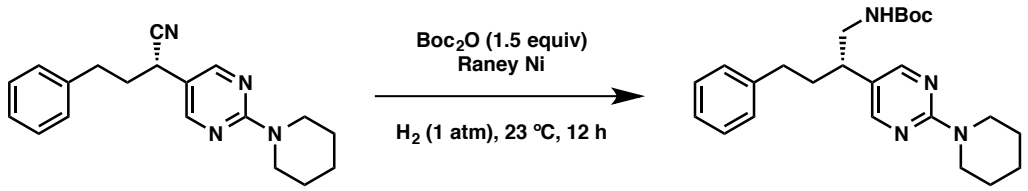
5-(thiophen-2-yl)pent-2-enenitrile (1:1 cis/trans) (145)



Prepared from 2-iodothiophene (11 μL, 0.1 mmol) and 2-chloro-2-cyclopropylacetonitrile (11.6 mg, 0.1 mmol) following General Procedure 4. The crude residue was purified by preperative thin layer chromatography (15:85 EtOAc:hexanes) to yield 3.5 mg (21% yield) of **145** as a clear oil as a 1:1 mixture of *cis*[*] and *trans*[§] isomers. Analysis of the crude NMR indicated no other conversion of the aryl iodide, with no cyclopropane-containing product detected. No unreacted chloronitrile was observed, presumably consumed by non-productive reaction pathways. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.16 (ddd, *J* = 5.1, 1.2, 0.7 Hz, 2H)[*§], 6.94 (ddd, *J* = 5.2, 3.4, 1.9 Hz, 2H)[*§], 6.86 – 6.77 (m, 2H)[*§], 6.73 (dt, *J* = 16.3, 6.9 Hz, 1H)[§], 6.50 (dt, *J* = 10.9, 7.5 Hz, 1H)[*], 5.45 – 5.27 (m, 2H)[*§], 3.02 (dtd, *J* = 15.6, 7.4, 0.8 Hz, 4H)[*§], 2.87 – 2.78 (m, 2H)[*], 2.62 (ddd, *J* = 7.7, 6.9, 1.7 Hz, 2H)[§]. ^{13}C NMR (126 MHz, cdcl$_3$) δ 153.94, 153.14, 142.38, 142.30, 126.95, 124.91, 123.78, 123.76, 100.98, 100.70, 35.11, 33.46, 28.43, 28.09; IR (NaCl/thin film): 2916.78, 2848.47, 2220.22, 1558.05, 1683.13, 848.26, 689.00, 668.02 cm^{-1}. HRMS (MM) calc'd for $[M]^+$ 163.0450, found 163.0765.

3.6.4 Derivatization of Enantioenriched Nitrile Products

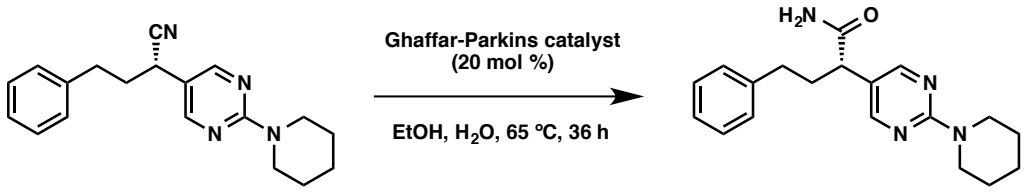
a. Hydrogenation of 122m over Raney Ni to Boc-amine 130.



Raney Ni (75 mg) was rinsed with dry MeOH 3 times to remove excess water and added to a flame-dried flask. To this was added dry MeOH (5 mL), 4-phenyl-2-(2-(piperidin-1-yl)pyrimidin-5-yl)butanenitrile (**122m**, 30 mg, 0.10 mmol, 85% ee), and Boc anhydride (33 mg, 0.15 mmol). The flask was purged with N_2 for 15 min, then flushed with two balloons of H_2. The flask was equipped with a balloon of H_2 and stirred for 3.5 hours. The reaction was then filtered over Celite with EtOAc to afford a viscous resinous clear oil. The crude residue was purified by silica gel chromatography (0:100 to 50:50 EtOAc:hexanes) to yield 39 mg (95% yield) of **130** as a clear oil that solidified slowly upon standing. The enantiomeric excess was determined to be 85% by chiral SFC analysis (AD, 2.5 mL/min, 15% IPA in CO_2, λ = 235 nm): t_R(major) = 10.5 min, t_R(minor) = 12.3 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.14 (s, 2H), 7.29 – 7.21 (m, 2H), 7.21 – 7.13 (m, 1H), 7.13 – 7.06 (m, 2H), 4.45 (s, 1H), 3.86 – 3.70 (m, 4H), 3.45 (dt, *J* = 13.1, 6.4 Hz, 1H), 3.12 (ddd, *J* = 13.9, 8.8, 5.4 Hz, 1H), 2.69 – 2.41 (m, 3H), 1.99 (dddd, *J* = 13.6, 9.8, 6.9, 4.8 Hz, 1H), 1.84 (dtd, *J* = 13.5, 9.8, 5.3 Hz, 1H), 1.74 – 1.55 (m, 6H), 1.40 (s, 9H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 161.26, 157.43, 155.82, 141.54, 128.42, 128.33, 125.93, 121.66, 79.40, 46.02, 44.85, 40.52, 34.57, 33.28, 28.34, 25.75, 24.84; IR (NaCl/thin film): 3337.97, 2930.35, 2853.42, 1712.79, 1602.18, 1504.75, 1449.34, 1364.47, 1271.22, 1255.54, 1169.92, 1028.05, 947.36, 798.75, 699.89 cm^{-1};

$[\alpha]_D^{25}$ = -15.883 (*c* = 2.365, $CHCl_3$). HRMS (MM) calc'd for $[M]^+$ 410.2676, found 410.2101.

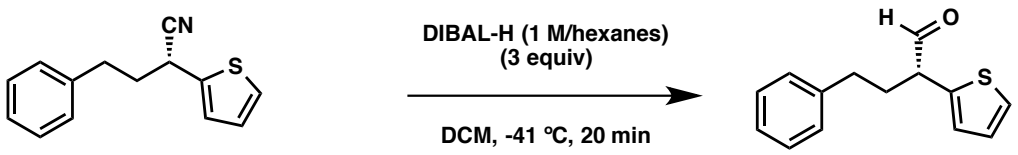
b. Hydrolysis of 122m with Ghaffar-Parkins catalyst to carboxamide 131.



In a 1-dram vial, 4-phenyl-2-(2-(piperidin-1-yl)pyrimidin-5-yl)butanenitrile (**122m**, 30 mg, 0.10 mmol, 85% ee) was suspended in EtOH (0.4 mL) and H_2O (0.1 mL). To this was added hydrido(dimethylphosphinous acid-kP)[hydrogen bis(dimethylphosphinito-kP)]platinum(II) (9 mg, 20 μmol). The reaction was sealed with a Teflon-lined cap and heated to 65 ºC for 36 h. After cooling to room temperature, the reaction was diluted with DCM and filtered through a short plug of silica gel and Na_2SO_4. The plug was washed with additional DCM and the organics were concentrated to afford the carboxamide as a clear oil. The crude residue was purified by silica gel chromatography (30:70 to 60:40 EtOAc:hexanes) to yield 30.8 mg (95% yield) of **131** as a viscous clear oil. The enantiomeric excess was determined to be 85% by ^{1}H NMR using Europium(III) tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorate] (30 mol %) as a chiral shift reagent. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.23 (s, 2H), 7.27 (d, *J* = 7.2 Hz, 2H), 7.22 – 7.16 (m, 1H), 7.16 – 7.11 (m, 2H), 5.66 (s, 1H), 5.45 (s, 1H), 3.92 – 3.61 (m, 4H), 3.12 (dd, *J* = 8.4, 6.8 Hz, 1H), 2.67 – 2.54 (m, 2H), 2.43 (ddt, *J* = 13.8, 8.7, 6.9 Hz, 1H), 2.12 – 1.97 (m, 1H), 1.68 (td, *J* = 6.7, 6.3, 4.7 Hz, 2H), 1.65 – 1.55 (m, 4H); ^{13}C NMR (126 MHz, $cdcl_3$) δ 175.22, 161.24, 157.30, 140.84, 128.51, 126.13, 119.40,

46.14, 44.86, 34.06, 33.17, 25.72, 24.82; IR (NaCl/thin film): 3333.85, 3190.50, 2932.50, 2853.02, 1667.77, 1602.06, 1504.96, 1446.89, 1364.61, 1271.06, 1256.15, 1178.28, 1024.54, 947.10, 797.03, 733.36, 699.53 cm^{-1} $[\alpha]_D^{25}$ = +35.005 (*c* = 2.455, $CHCl_3$). HRMS (MM) calc'd for $[M]^+$ 324.1945, found 324.1904.

c. DIBAL-H reduction of 122i to carboxaldehyde 132.

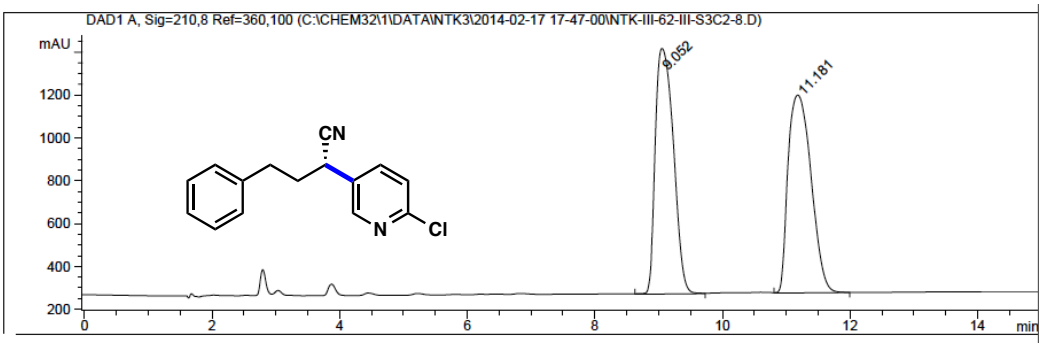


To a flame-dried flask was added 4-phenyl-2-(thiophen-2-yl)butanenitrile (**122i**, 46 mg, 0.2 mmol, 88% ee) and DCM (30 mL). The reaction was cooled to -41 ºC and a 1 M solution of DIBAL-H in hexanes (3 equiv, 0.6 mL, 0.6 mmol) was added slowly via syringe. The reaction was complete by TLC after 20 min. A 5% AcOH/H_2O solution (12 mL) was added and the reaction was allowed to warm to room temperature. The reaction was stirred vigorously for 30 min and then the layers were separated. The organics were washed with dilute sodium bicarbonate, dried over sodium sulfate, and concentrated to afford light yellow oil. The crude residue was purified by silica gel chromatography (0:100 to 10:90 EtOAc:hexanes) to yield 44 mg (96% yield) of **132** as a yellow oil that was stored frozen in benzene. The enantiomeric excess was determined to be 81% by chiral SFC analysis (AD, 2.5 mL/min, 8% IPA in CO_2, λ = 235 nm): t_R(minor) = 4.5 min, t_R(major) = 5.1 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.61 (d, *J* = 2.1 Hz, 1H), 7.34 – 7.28 (m, 3H), 7.25 – 7.20 (m, 1H), 7.18 (dq, *J* = 7.6, 0.7 Hz, 2H), 7.07 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.95 (ddd, *J* = 3.5, 1.2, 0.7 Hz, 1H), 3.79 (ddd, *J* = 8.4, 6.3, 2.1 Hz, 1H), 2.73

(ddd, *J* = 14.4, 9.0, 5.7 Hz, 1H), 2.64 (ddd, *J* = 13.8, 8.8, 7.0 Hz, 1H), 2.43 (dddd, *J* = 13.6, 9.0, 7.1, 6.3 Hz, 1H), 2.17 – 2.07 (m, 1H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 198.65, 140.80, 138.31, 128.54, 128.52, 127.54, 126.43, 126.22, 125.56, 52.86, 32.84, 32.05; IR (NaCl/thin film): 3025.79, 2924.74, 1725.05, 1496.21, 1454.03, 750.13, 699.05 cm^{-1}; $[\alpha]_D^{25}$ = +4.156 (*c* = 0.70, $CHCl_3$). HRMS (MM) calc'd for $[M]^+$ 410.2676, found 410.2101.

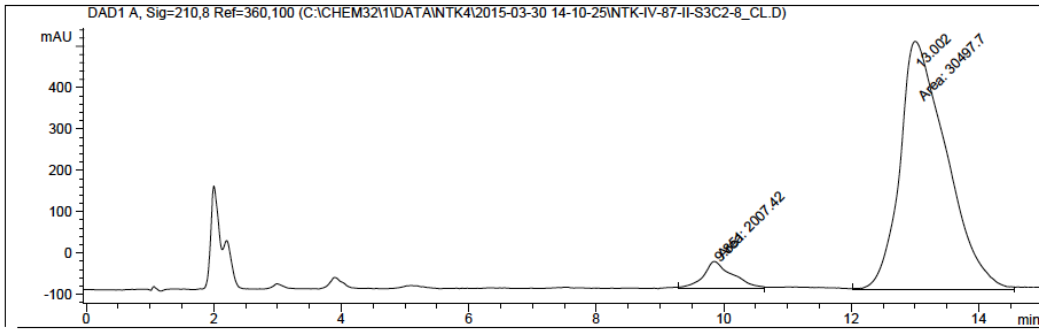
3.6.5 SFC Traces of Racemic and Enantioenriched Nitrile Products

122j racemic



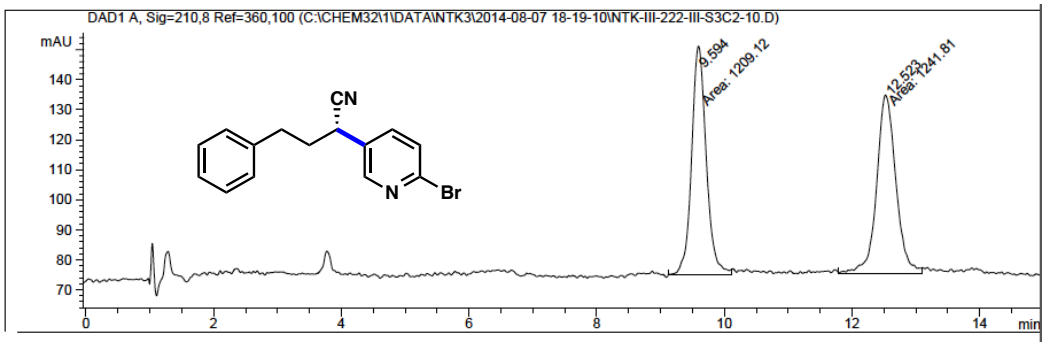
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.052	VV	0.3272	2.27197e4	1146.29651	49.3947
2	11.181	VB	0.4161	2.32765e4	923.30292	50.6053

122j enantioenriched, 88% ee



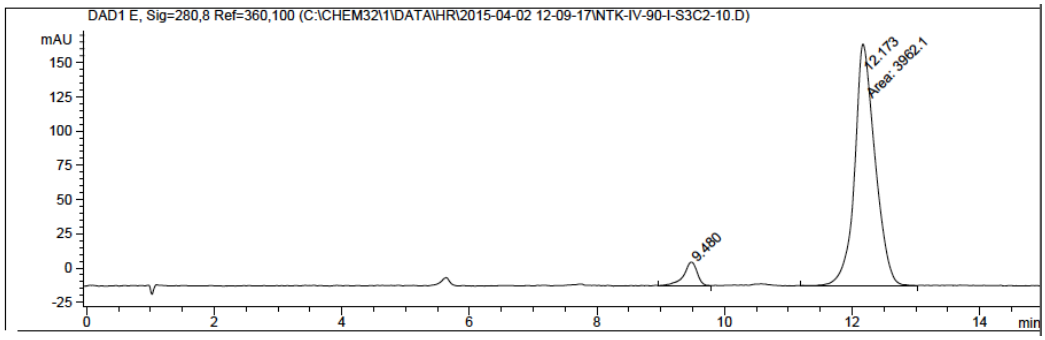
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.851	MM	0.5217	2007.42126	64.13335	6.1757
2	13.002	MM	0.8480	3.04977e4	599.40063	93.8243

122r racemic



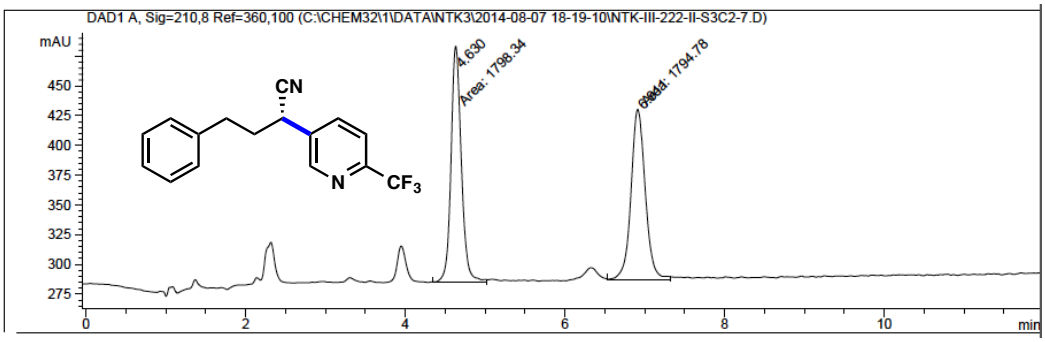
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.594	MM	0.2648	1209.12439	76.09144	49.3331
2	12.523	MM	0.3485	1241.81299	59.39444	50.6669

122r enantioenriched, 88% ee



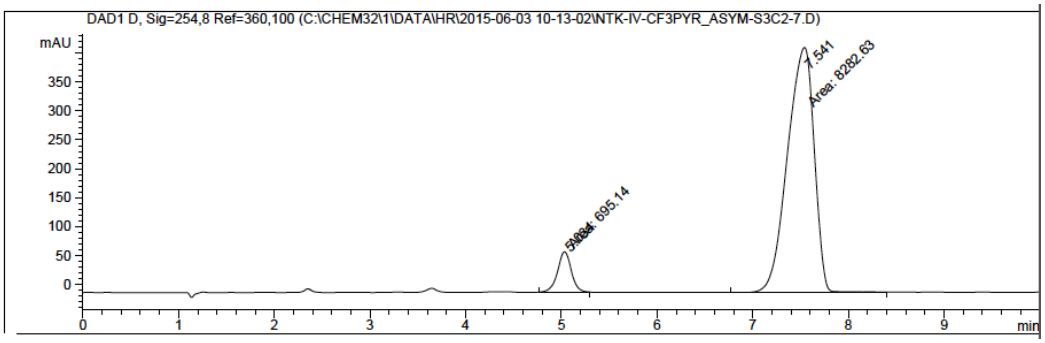
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.480	VV	0.2212	263.66074	17.35826	6.2394
2	12.173	MM	0.3738	3962.10059	176.66771	93.7606

122t racemic



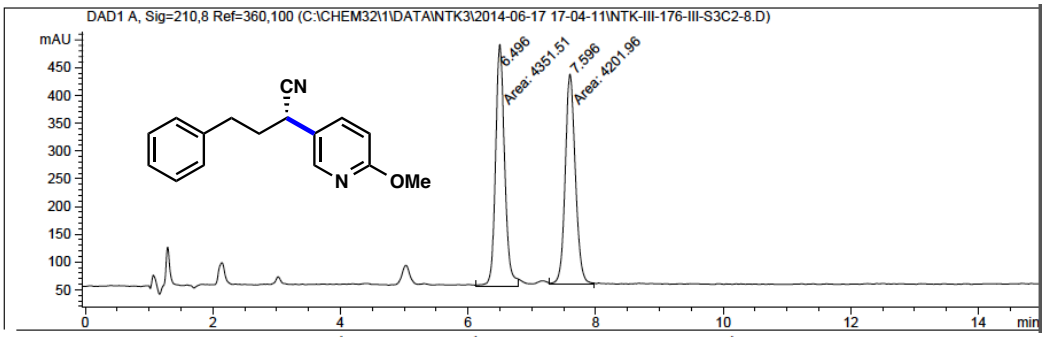
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.630	MM	0.1506	1798.33630	198.96516	50.0494
2	6.911	MM	0.2083	1794.78406	143.62846	49.9506

122t enantioenriched, 85% ee



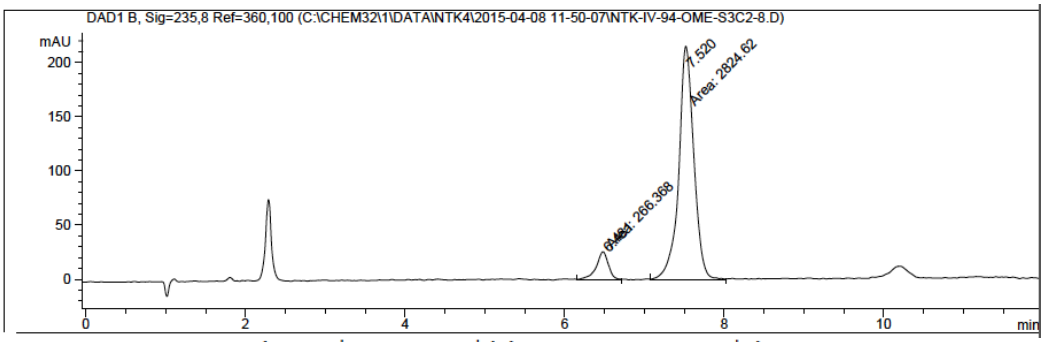
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.034	MM	0.1653	695.13959	70.09489	7.7429
2	7.541	MM	0.3253	8282.63379	424.41962	92.2571

122u racemic



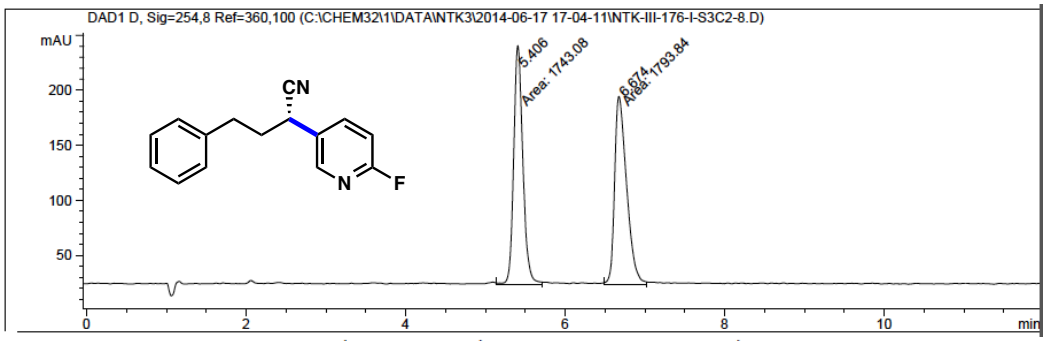
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.496	MM	0.1660	4351.50586	436.96753	50.8742
2	7.596	MM	0.1850	4201.95898	378.58496	49.1258

122u enantioenriched, 83% ee



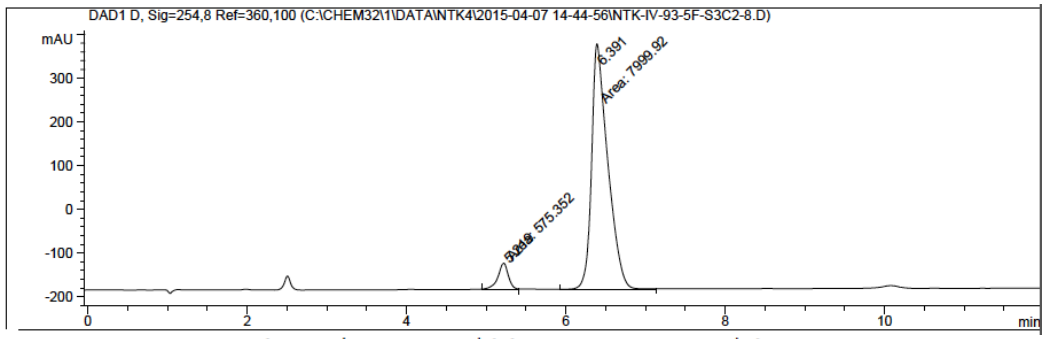
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.481	MM	0.1741	266.36813	25.50070	8.6176
2	7.520	MM	0.2185	2824.61865	215.49197	91.3824

122o racemic



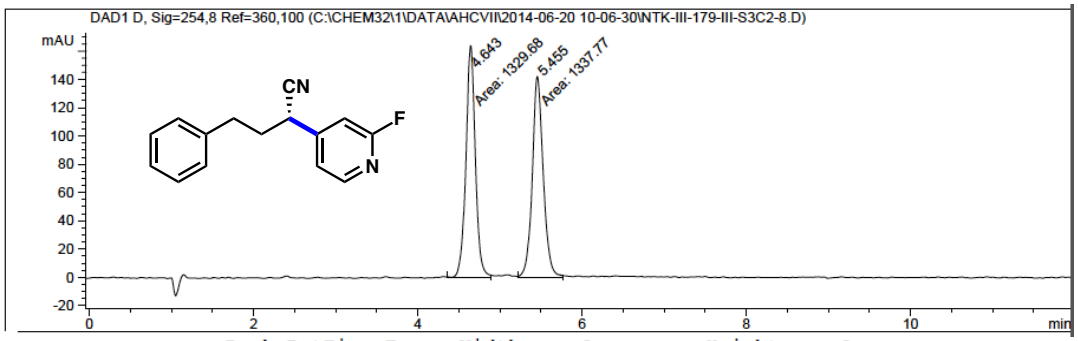
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.406	MM	0.1336	1743.07617	217.40483	49.2824
2	6.674	MM	0.1749	1793.83582	170.96077	50.7176

122o enantioenriched, 87% ee



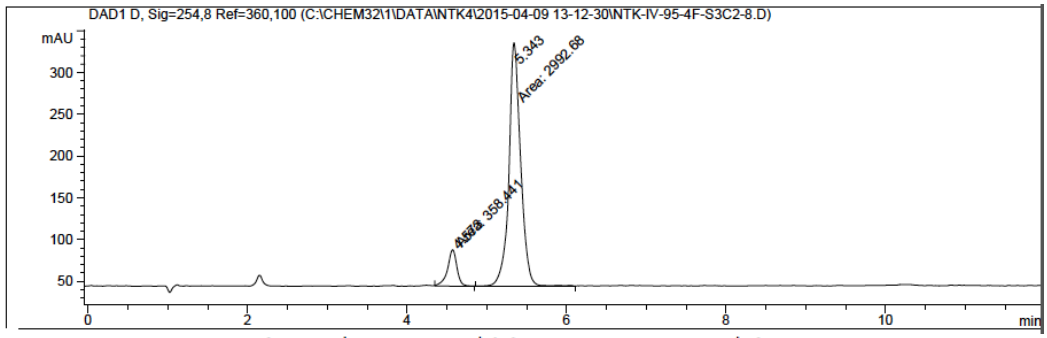
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.219	MM	0.1568	575.35193	61.17109	6.7094
2	6.391	MM	0.2369	7999.91992	562.87573	93.2906

122p racemic



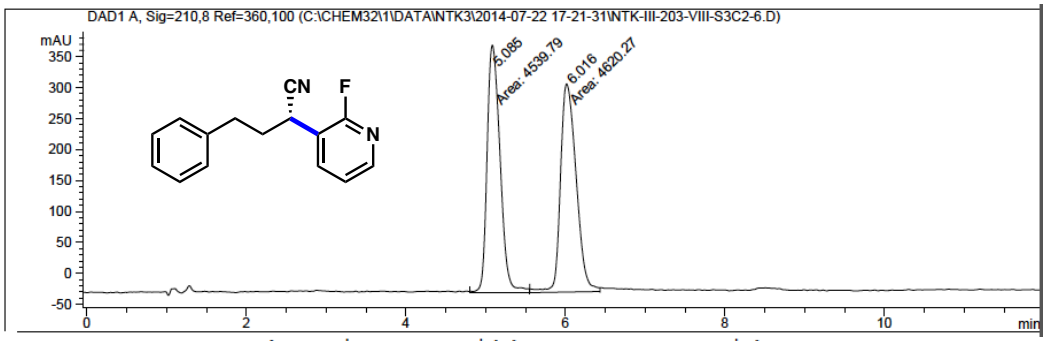
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.643	MM	0.1346	1329.67908	164.60115	49.8483
2	5.455	MM	0.1563	1337.77344	142.69563	50.1517

122p enantioenriched, 79% ee



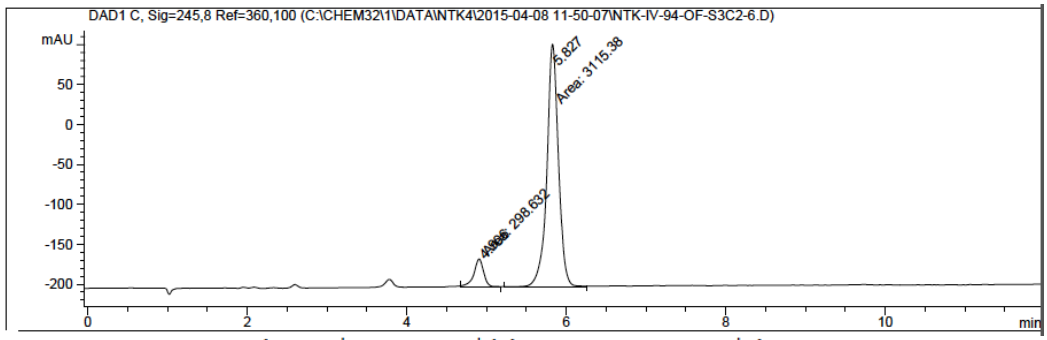
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.573	MM	0.1370	358.44107	43.60704	10.6961
2	5.343	MM	0.1709	2992.68384	291.82959	89.3039

122q racemic



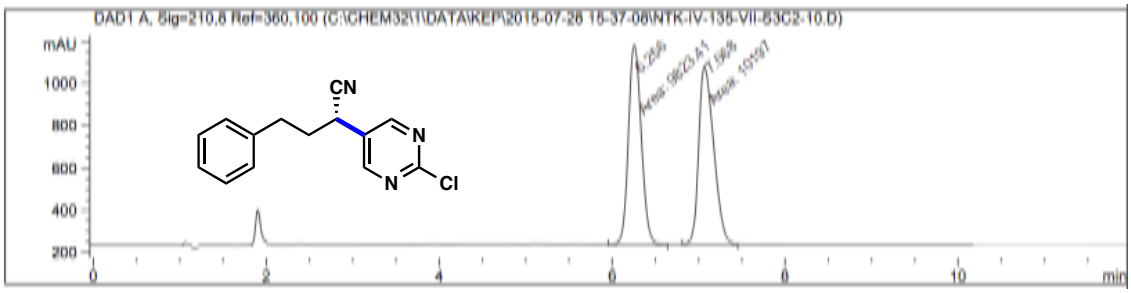
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.085	MM	0.1892	4539.78711	399.84052	49.5607
2	6.016	MM	0.2290	4620.26758	336.27573	50.4393

122q enantioenriched, 83% ee



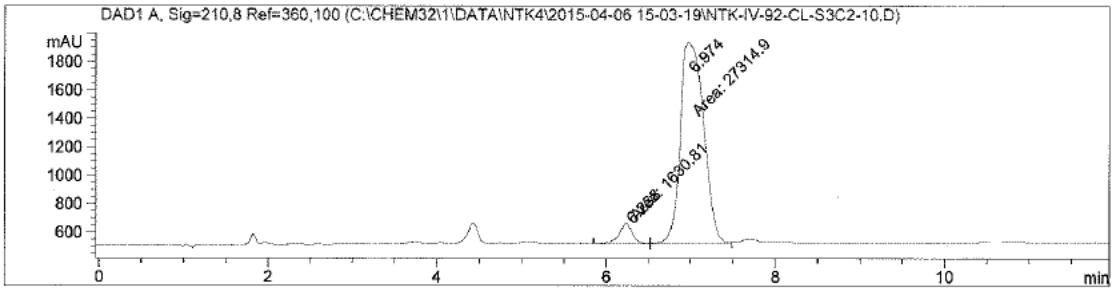
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.906	MM	0.1426	298.63181	34.89790	8.7472
2	5.827	MM	0.1706	3115.37988	304.37155	91.2528

122x racemic



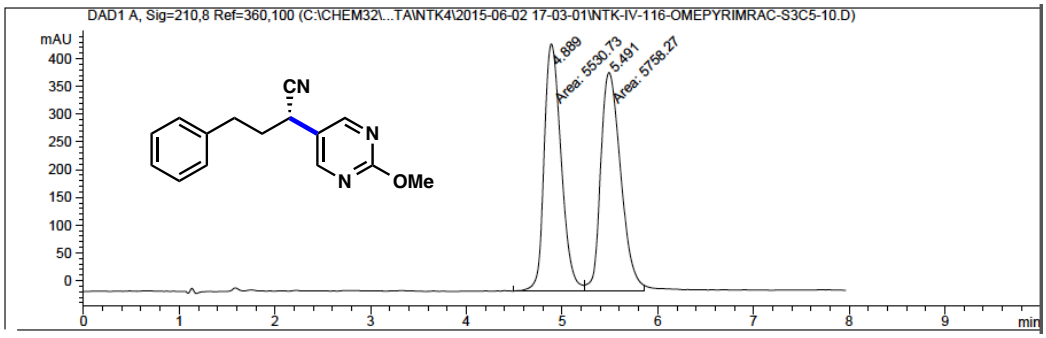
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.256	MM	0.1735	9823.40918	943.89240	49.0671
2	7.068	MM	0.2022	1.01970e4	840.62567	50.9329

122x enantioenriched, 89% ee



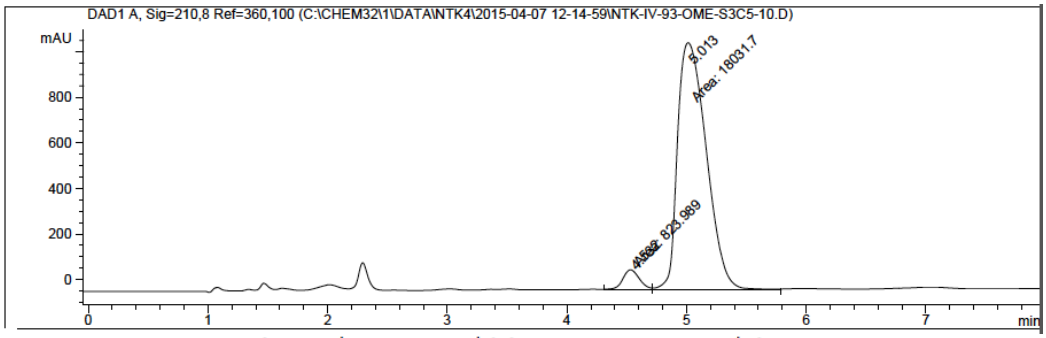
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.238	MM	0.1881	1630.80823	144.48898	5.6340
2	6.974	MM	0.3226	2.73149e4	1411.04395	94.3660

122y racemic



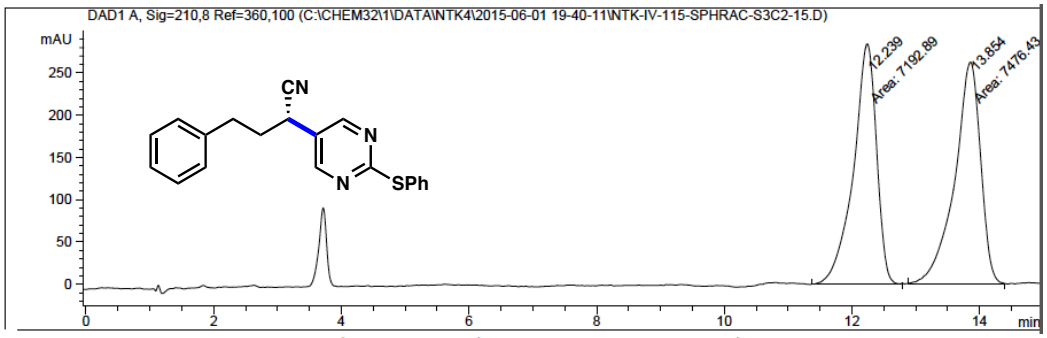
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.889	MM	0.2066	5530.73438	446.19595	48.9922
2	5.491	MM	0.2432	5758.27148	394.62100	51.0078

122y enantioenriched, 92% ee



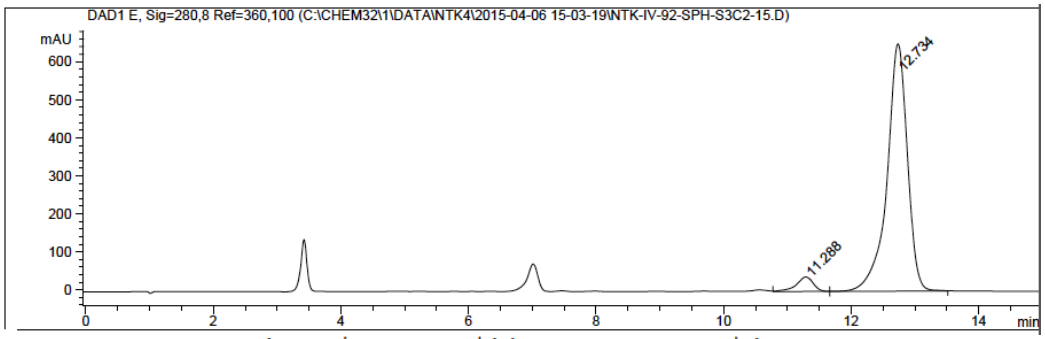
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.532	MM	0.1591	823.98859	86.30779	4.3700
2	5.013	MM	0.2775	1.80317e4	1083.14832	95.6300

122n racemic



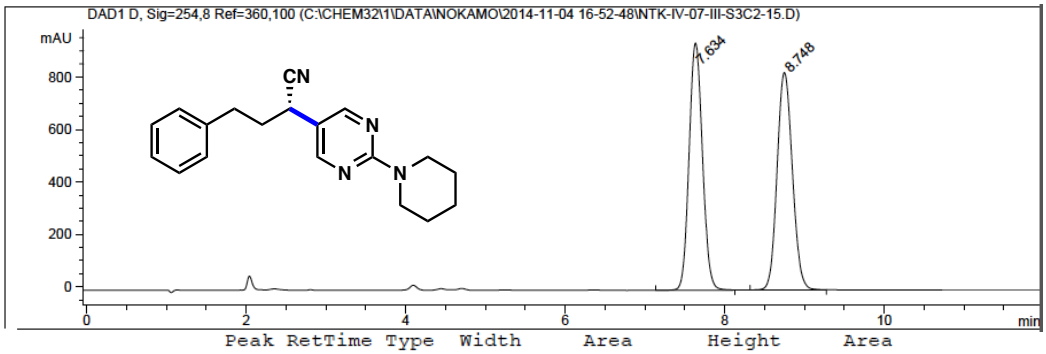
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.239	MM	0.4208	7192.89307	284.88919	49.0336
2	13.854	MM	0.4732	7476.43115	263.30313	50.9664

122n enantioenriched, 91% ee



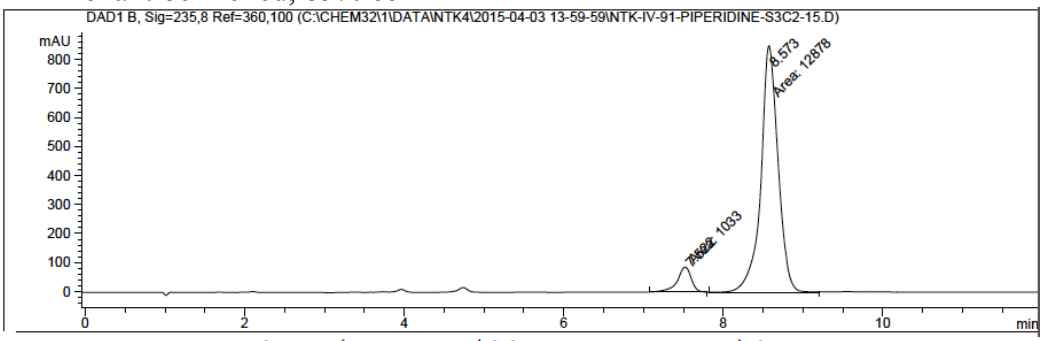
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.288	VV	0.2780	705.39868	38.10340	4.6587
2	12.734	VB	0.3328	1.44360e4	650.73560	95.3413

122m racemic



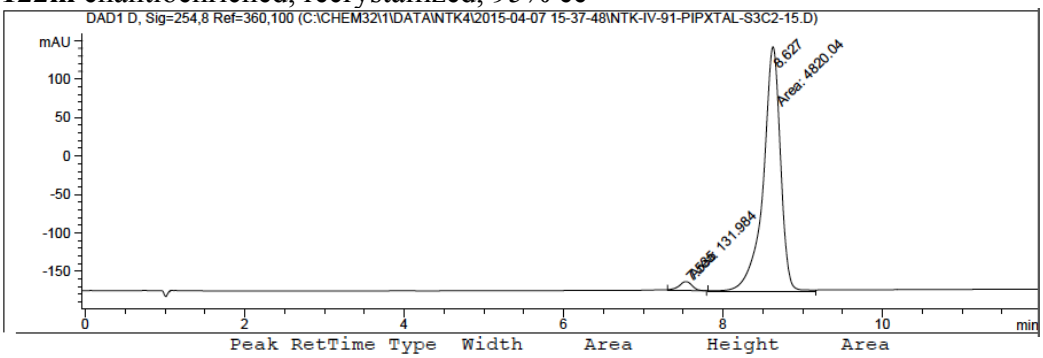
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.634	BB	0.1820	1.10005e4	943.78931	49.8831
2	8.748	VB	0.2095	1.10520e4	829.41107	50.1169

122m enantioenriched, 85% ee



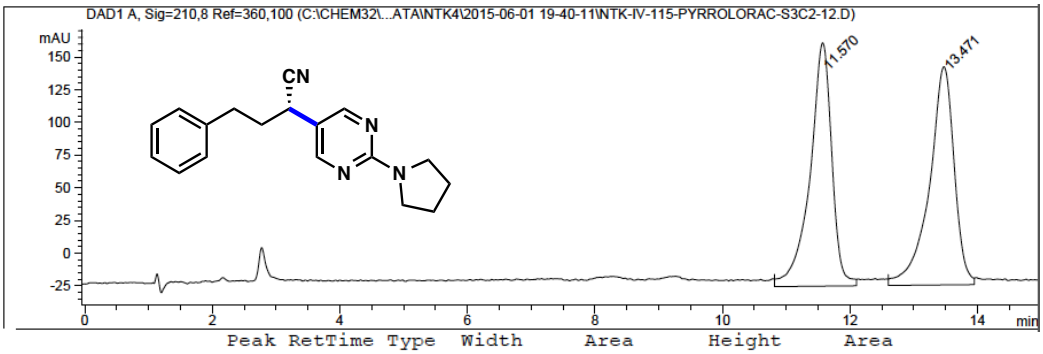
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.522	MM	0.2003	1033.00146	85.96810	7.4258
2	8.573	MM	0.2520	1.28780e4	851.85858	92.5742

122m enantioenriched, recrystallized, 95% ee



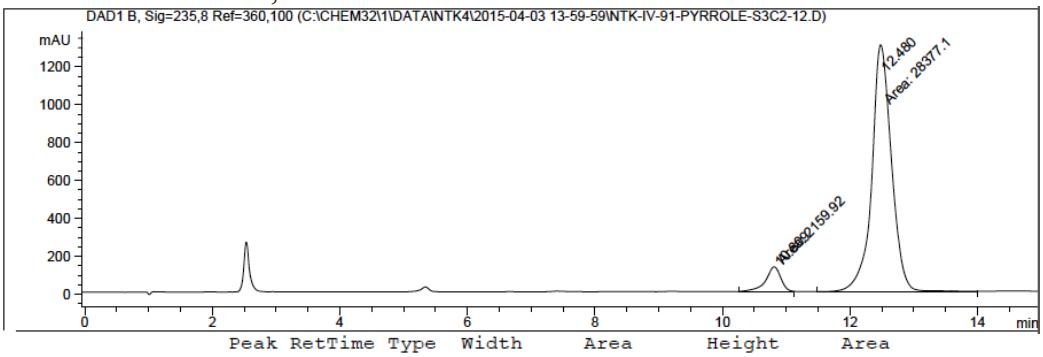
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.535	MM	0.1884	131.98436	11.67368	2.6653
2	8.627	MM	0.2526	4820.03613	318.05377	97.3347

122l racemic



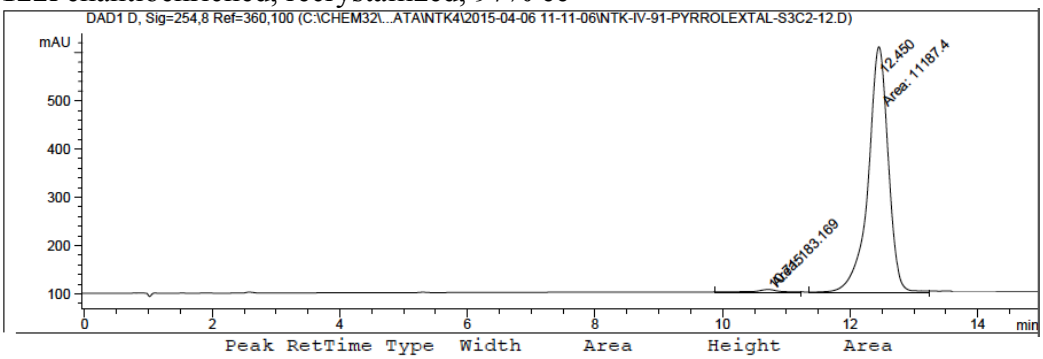
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.570	VV	0.3457	4429.45020	186.09850	49.4778
2	13.471	VV	0.3942	4522.94775	166.88538	50.5222

122l enantioenriched, 86% ee



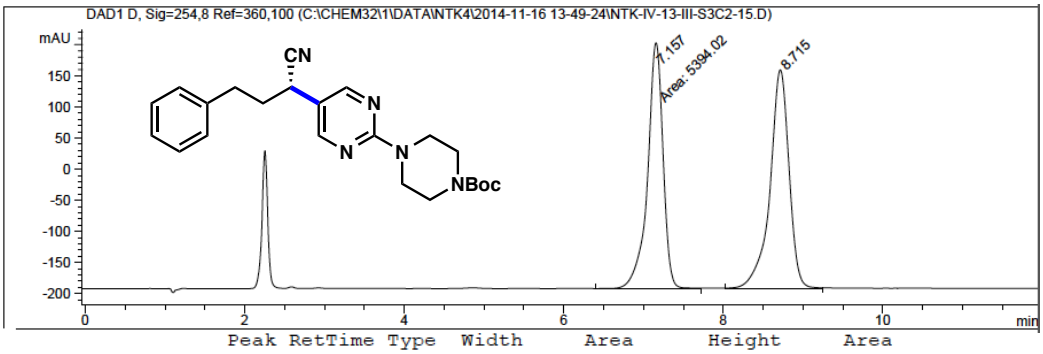
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.809	MM	0.2757	2159.91553	130.55109	7.0731
2	12.480	MM	0.3627	2.83771e4	1304.11511	92.9269

122l enantioenriched, recrystallized, 97% ee



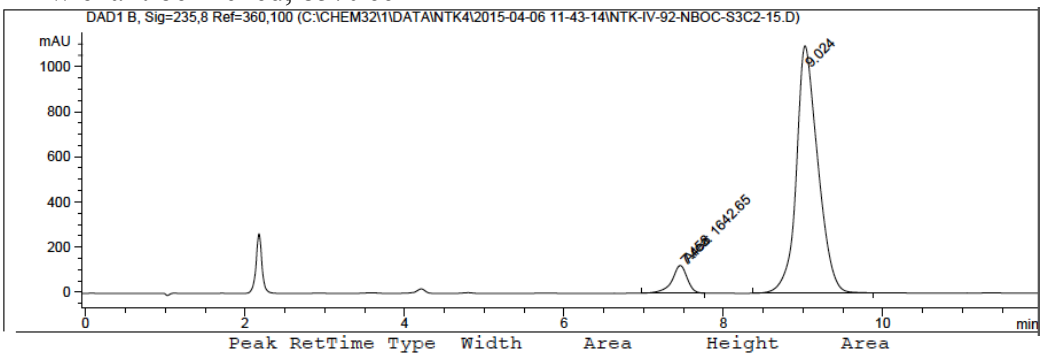
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.715	MM	0.4992	183.16939	6.11533	1.6109
2	12.450	MM	0.3661	1.11874e4	509.26865	98.3891

122w racemic



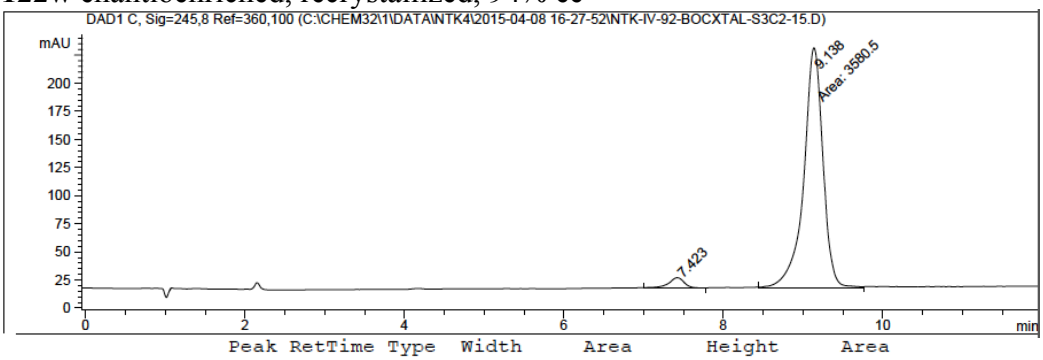
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.157	MM	0.2271	5394.01611	395.87903	48.0826
2	8.715	BB	0.2497	5824.20361	350.83545	51.9174

122w enantioenriched, 85% ee



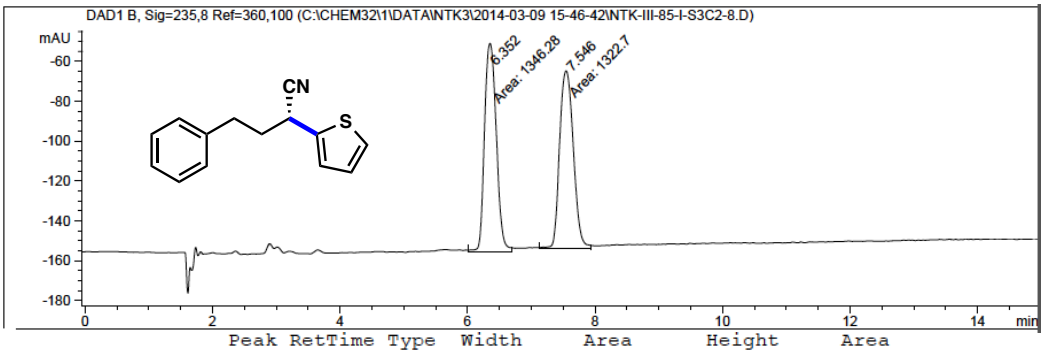
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.458	MM	0.2224	1642.64941	123.07285	7.3549
2	9.024	BV	0.2820	2.06913e4	1097.45300	92.6451

122w enantioenriched, recrystallized, 94% ee



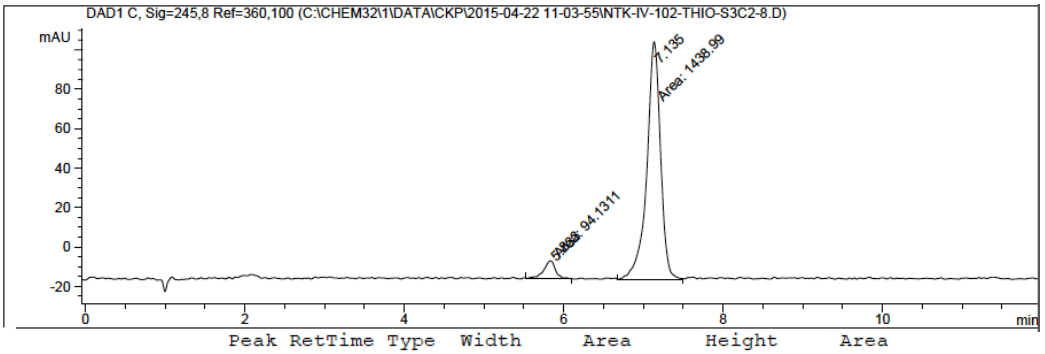
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.423	BB	0.1980	118.74174	8.99407	3.2099
2	9.138	MM	0.2796	3580.49634	213.42770	96.7901

122i racemic



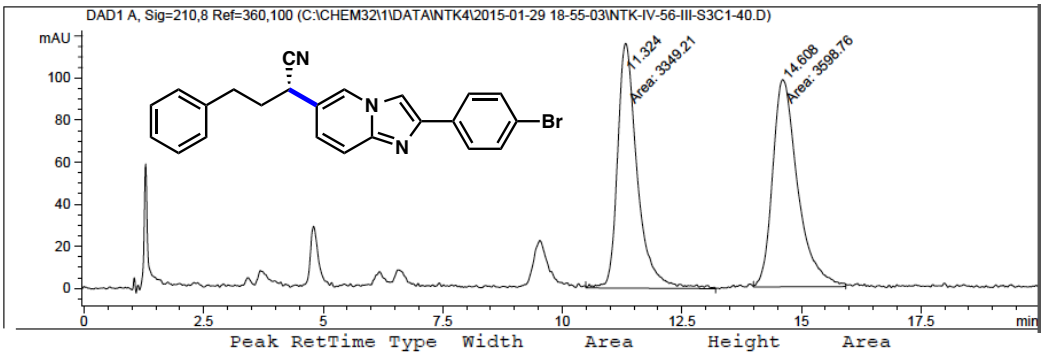
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.352	MM	0.2148	1346.28333	104.44119	50.4418
2	7.546	MM	0.2483	1322.70227	88.79099	49.5582

122i enantioenriched, 88% ee



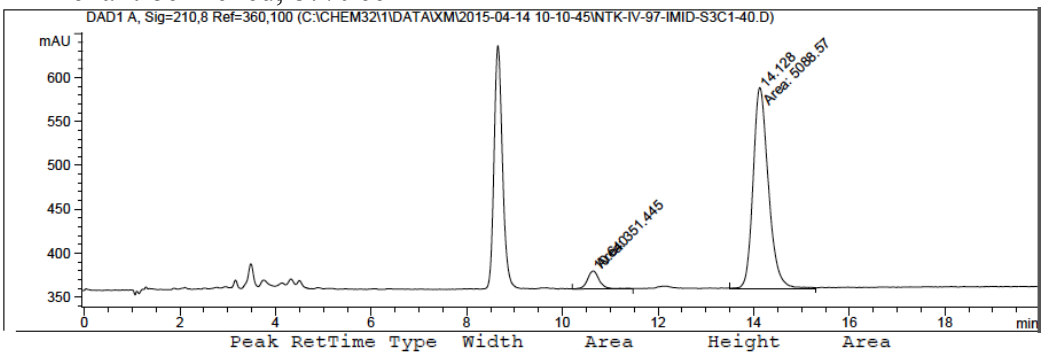
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.833	MM	0.1721	94.13110	9.11540	6.1398
2	7.135	MM	0.1990	1438.99097	120.52435	93.8602

122z racemic



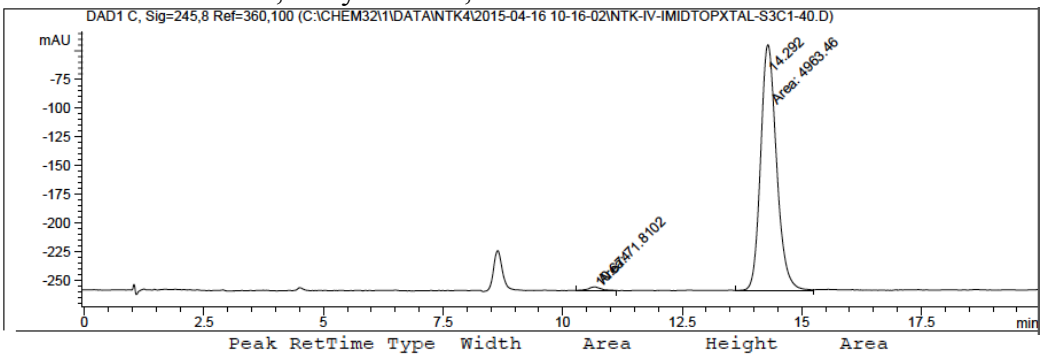
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.324	MM	0.4796	3349.21387	116.39689	48.2042
2	14.608	MM	0.6086	3598.75928	98.55891	51.7958

122z enantioenriched, 87% ee



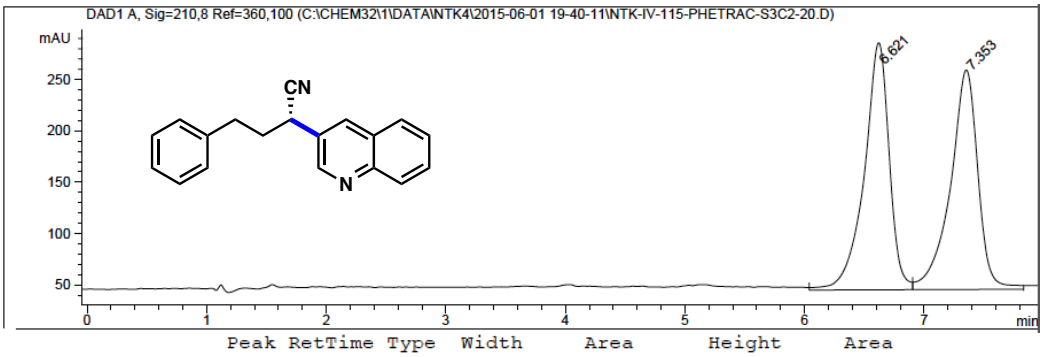
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.640	MM	0.2855	351.44522	20.51827	6.4604
2	14.128	MM	0.3712	5088.56689	228.46791	93.5396

122z enantioenriched, recrystallized, 97% ee



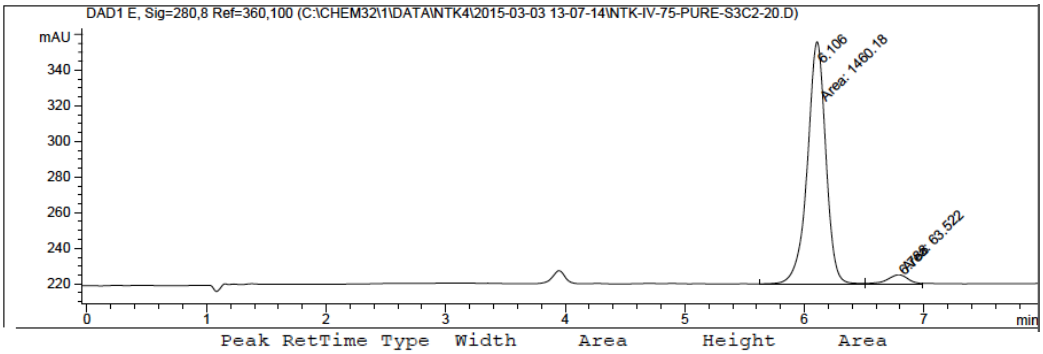
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.674	MM	0.3581	71.81017	3.34204	1.4261
2	14.292	MM	0.3870	4963.45557	213.77559	98.5739

122v racemic



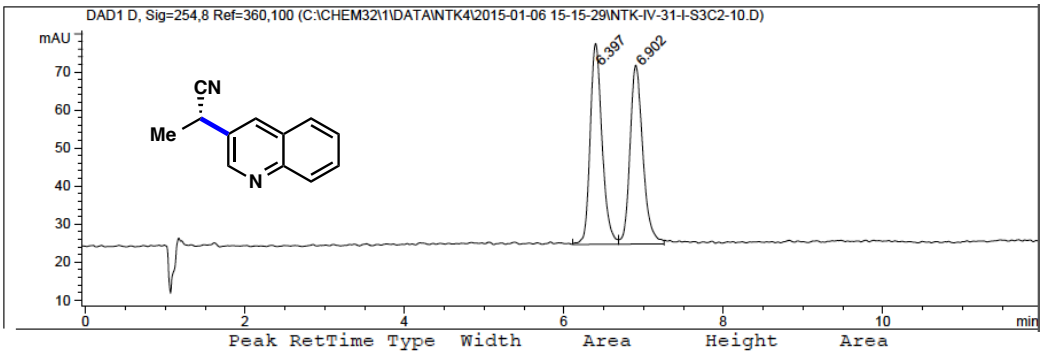
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.621	VV	0.2121	3510.11963	240.77718	50.5322
2	7.353	VB	0.2374	3436.18848	213.96890	49.4678

122v enantioenriched, 92% ee



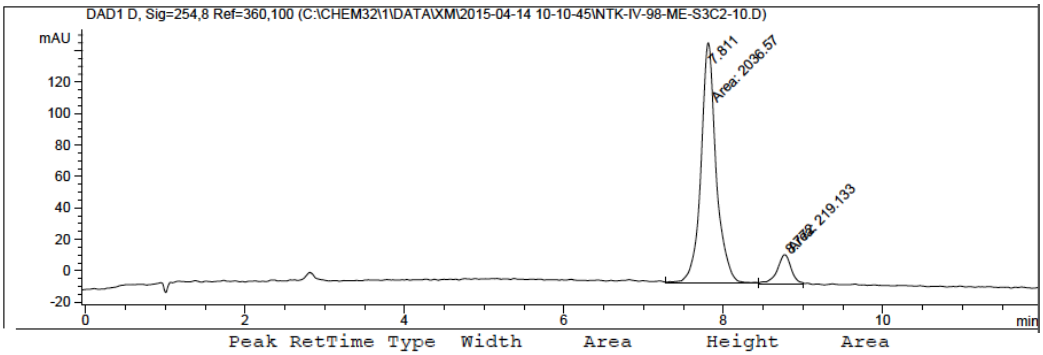
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.106	MM	0.1789	1460.18115	136.04520	95.8311
2	6.788	MM	0.2033	63.52196	5.20731	4.1689

129b racemic



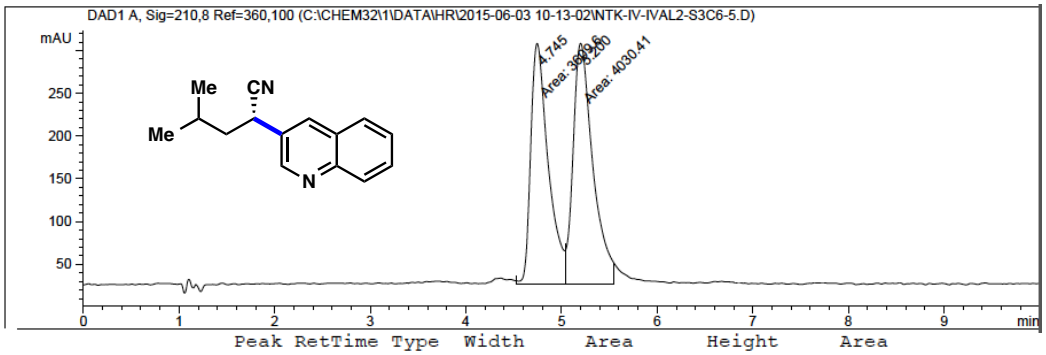
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.397	BV	0.1592	548.77161	52.81827	50.9276
2	6.902	VB	0.1731	528.77997	47.05341	49.0724

129b enantioenriched, 81% ee



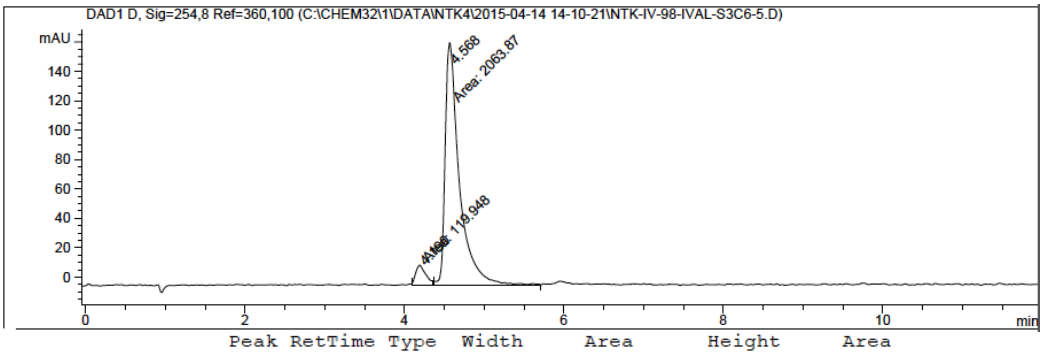
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.811	MM	0.2219	2036.56677	152.96375	90.2854
2	8.772	MM	0.1984	219.13271	18.40750	9.7146

129h racemic



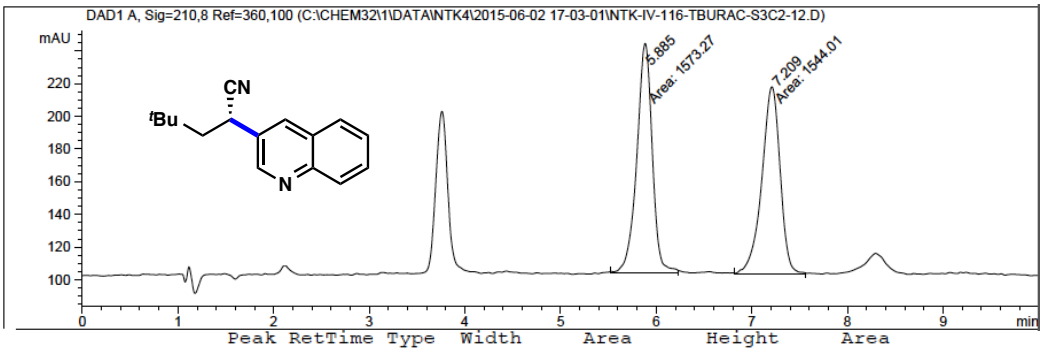
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.745	MM	0.2135	3609.59644	281.73523	47.2460
2	5.200	MM	0.2383	4030.41479	281.82928	52.7540

129h enantioenriched, 89% ee



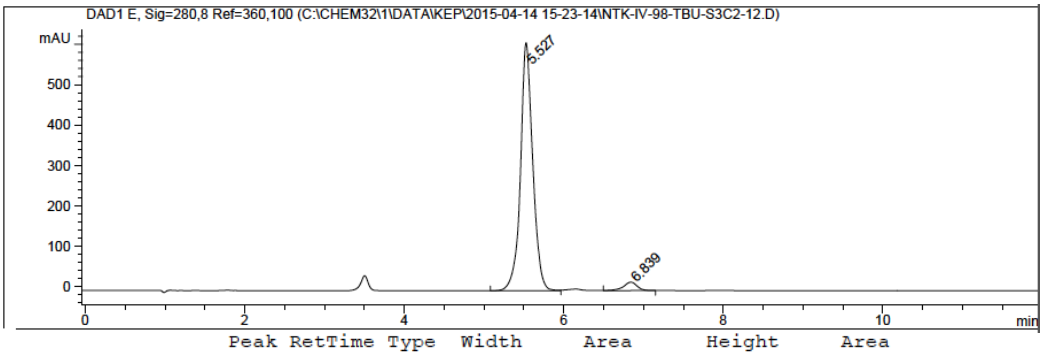
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.190	MM	0.1475	119.94836	13.55409	5.4926
2	4.568	MM	0.2080	2063.87280	165.40321	94.5074

129c racemic



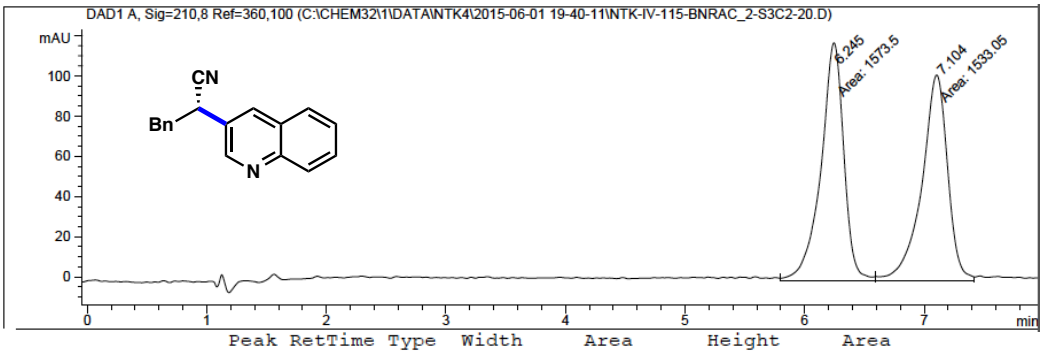
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.885	MM	0.1865	1573.26758	140.60291	50.4693
2	7.209	MM	0.2237	1544.00830	115.02839	49.5307

129c enantioenriched, 93% ee



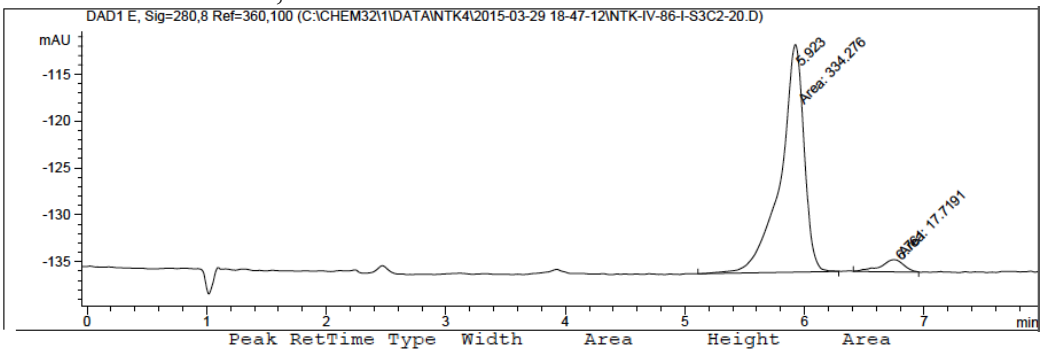
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.527	VB	0.1566	6555.89990	613.77045	96.3174
2	6.839	BB	0.1762	250.66086	20.86025	3.6826

129e racemic



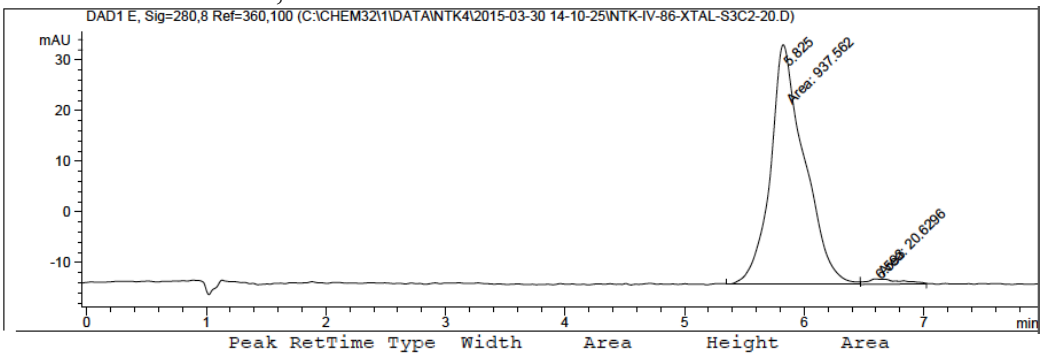
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.245	MM	0.2219	1573.49854	118.16628	50.6510
2	7.104	MM	0.2501	1533.05249	102.16112	49.3490

129e enantioenriched, 89% ee



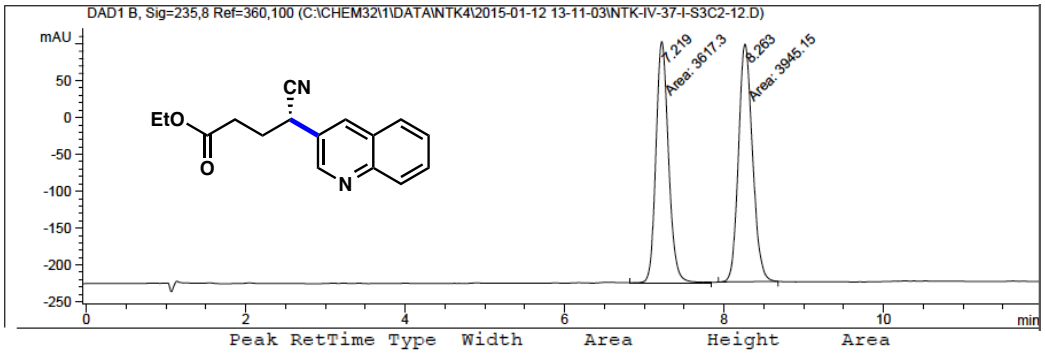
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.923	MM	0.2293	334.27615	24.29972	94.9661
2	6.761	MM	0.2285	17.71910	1.29258	5.0339

129e enantioenriched, 96% ee



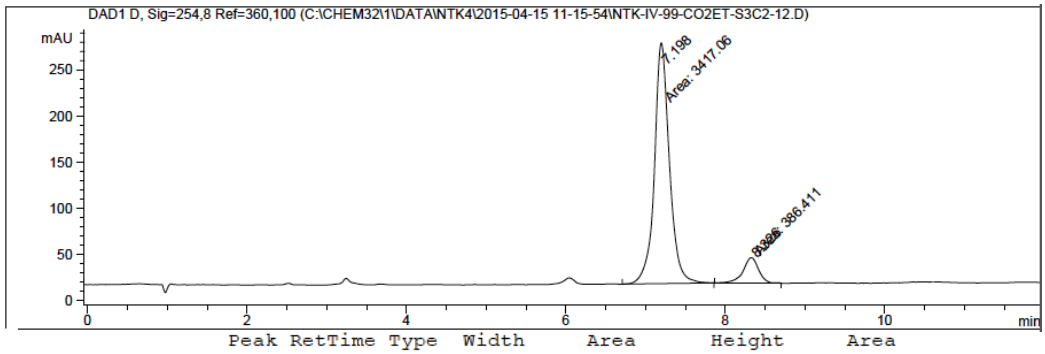
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.825	MM	0.3300	937.56195	47.34668	97.8470
2	6.593	MM	0.3294	20.62959	1.04379	2.1530

129f racemic



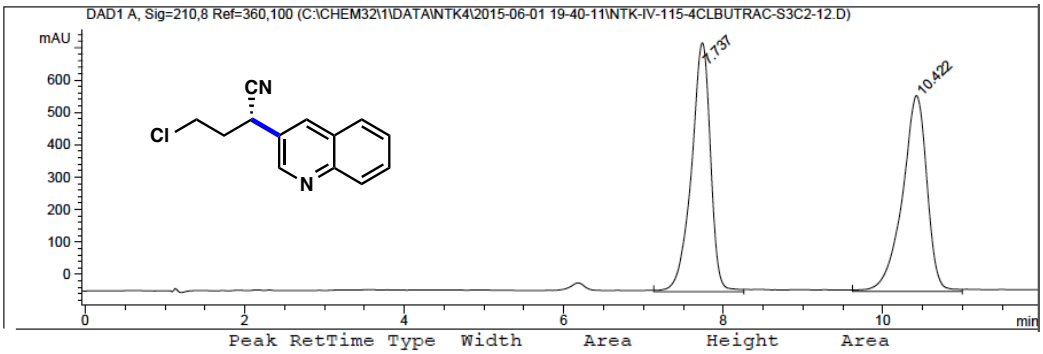
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.219	MM	0.1840	3617.29688	327.72406	47.8323
2	8.263	MM	0.2038	3945.15210	322.60925	52.1677

129f enantioenriched, 80% ee



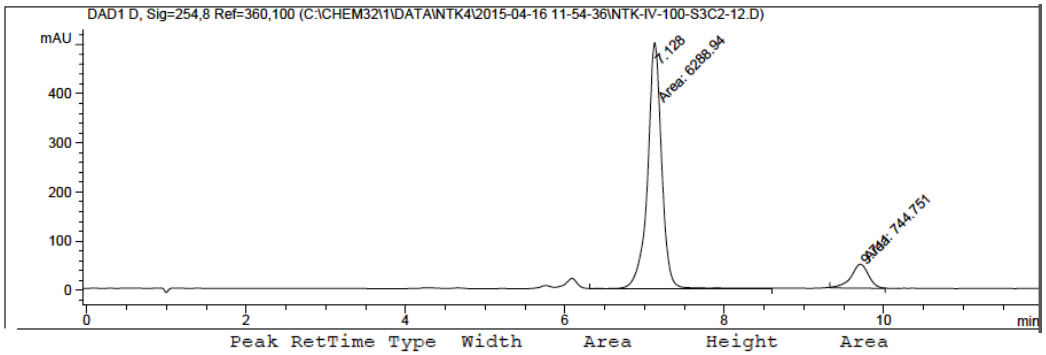
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.198	MM	0.2179	3417.05908	261.39404	89.8406
2	8.326	MM	0.2312	386.41061	27.85635	10.1594

129g racemic



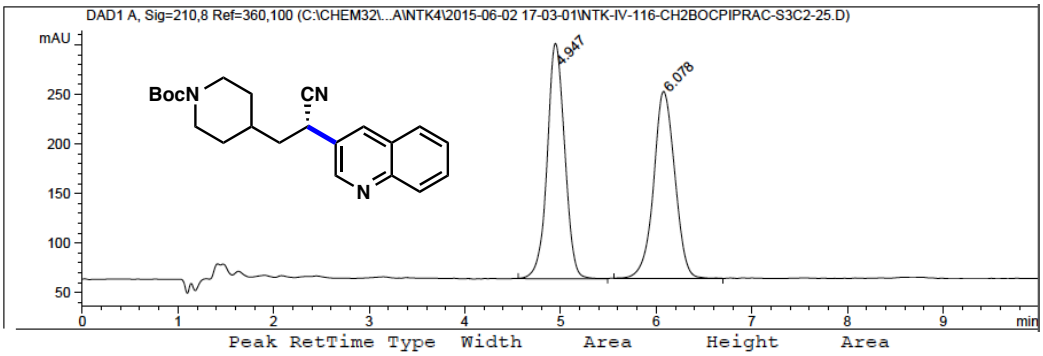
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.737	VV	0.2507	1.28238e4	768.61090	49.6251
2	10.422	VB	0.3214	1.30175e4	604.21277	50.3749

129g enantioenriched, 79% ee



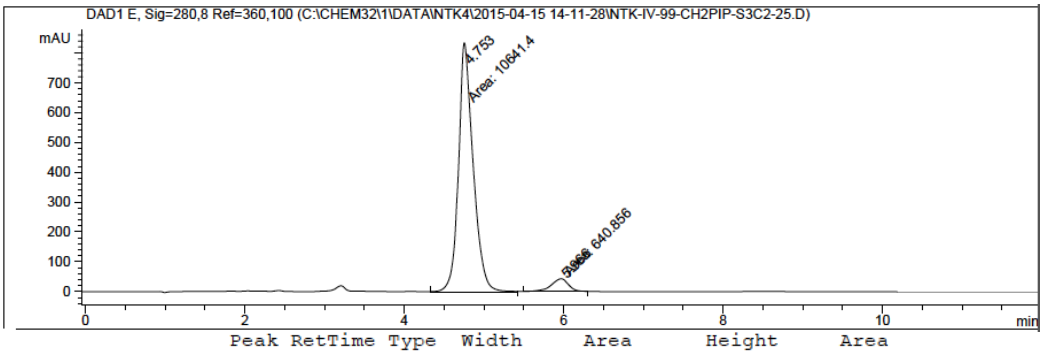
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.128	MM	0.2089	6288.94287	501.63721	89.4117
2	9.711	MM	0.2536	744.75104	48.93940	10.5883

129a racemic



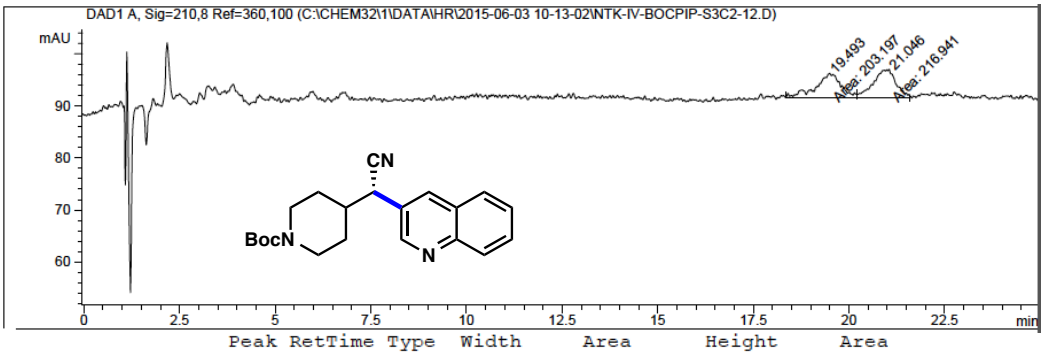
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.947	BB	0.2005	3022.36011	237.43880	50.7006
2	6.078	BB	0.2414	2938.82886	189.05597	49.2994

129a enantioenriched, 89% ee



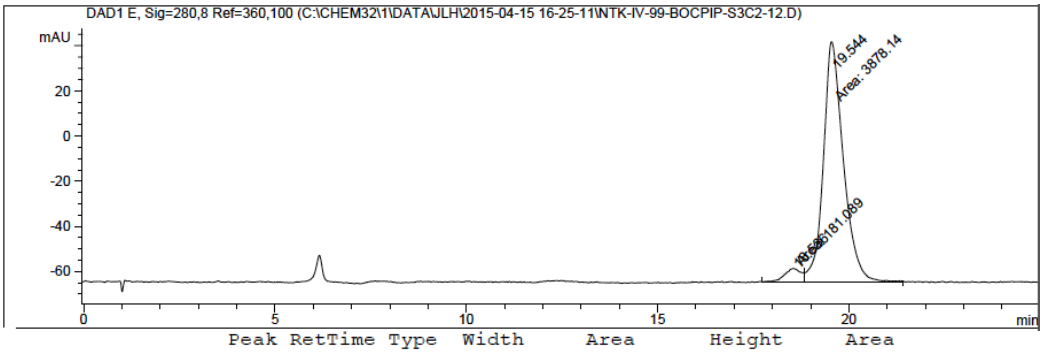
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.753	MM	0.2124	1.06414e4	835.02002	94.3198
2	5.966	MM	0.2495	640.85596	42.80384	5.6802

129d racemic



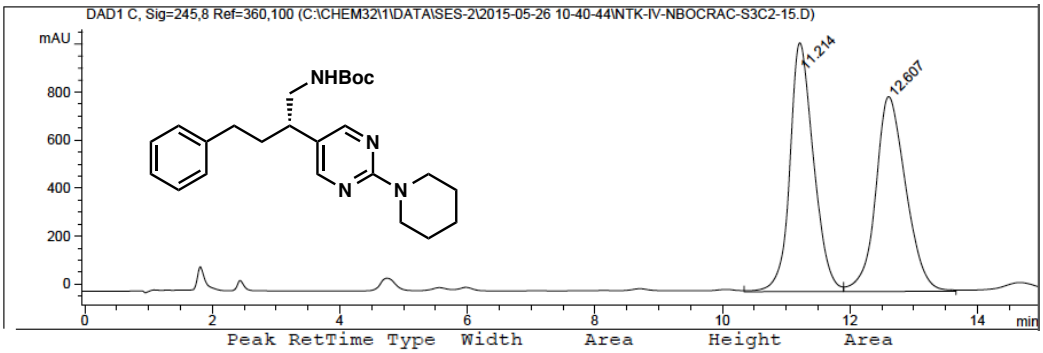
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.493	MM	0.7345	203.19673	4.61081	48.3643
2	21.046	MM	0.6714	216.94075	5.38557	51.6357

129d enantioenriched, 91% ee



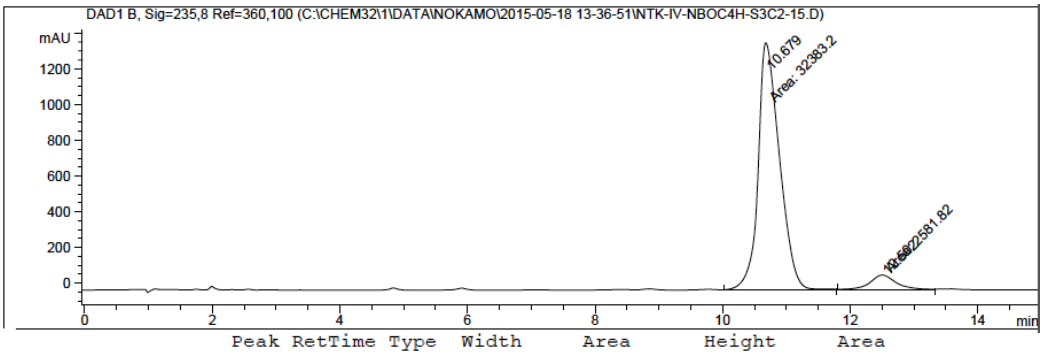
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.536	MM	0.5086	181.08897	5.93411	4.4612
2	19.544	MM	0.6079	3878.14355	106.32883	95.5388

130 racemic



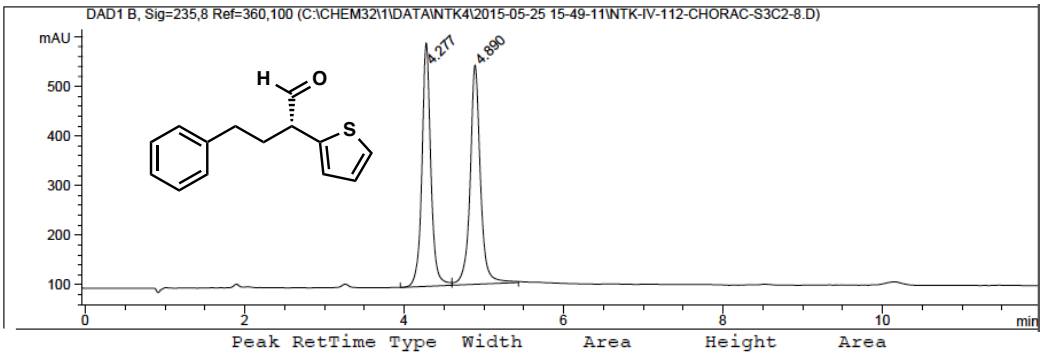
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.214	VV	0.3883	2.68637e4	1036.80664	50.1053
2	12.607	VB	0.4963	2.67508e4	812.12598	49.8947

130 enantioenriched, 85% ee



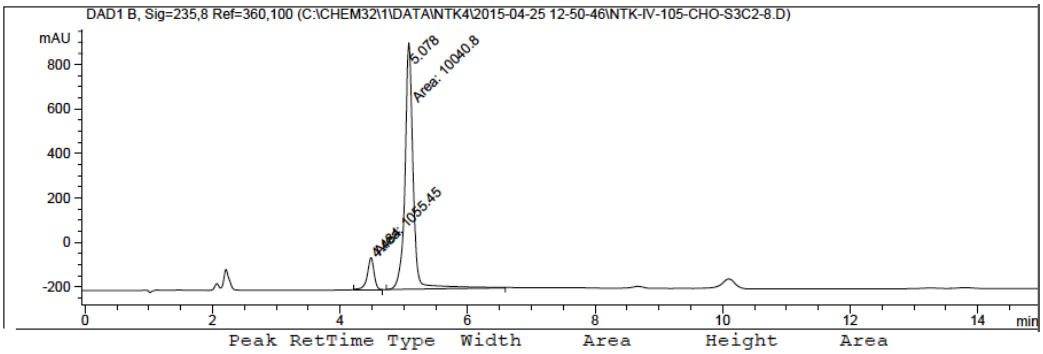
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.679	MM	0.3896	3.23832e4	1385.25745	92.6160
2	12.502	MM	0.5124	2581.82373	83.98371	7.3840

132 racemic



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.277	VV	0.1173	3844.47681	491.51151	49.0126
2	4.890	VB	0.1334	3999.37305	442.65036	50.9874

132 enantioenriched, 81% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.484	MM	0.1218	1055.44739	144.44736	9.5118
2	5.078	MM	0.1509	1.00408e4	1109.03845	90.4882

3.7 NOTES AND REFERENCES

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