Appendix 8

Phosphino(oxazoline)Ligand Parameterization for Ni-Catalyzed Reductive Cross-Coupling of Aryl Iodides and α-Chloronitriles[‡]

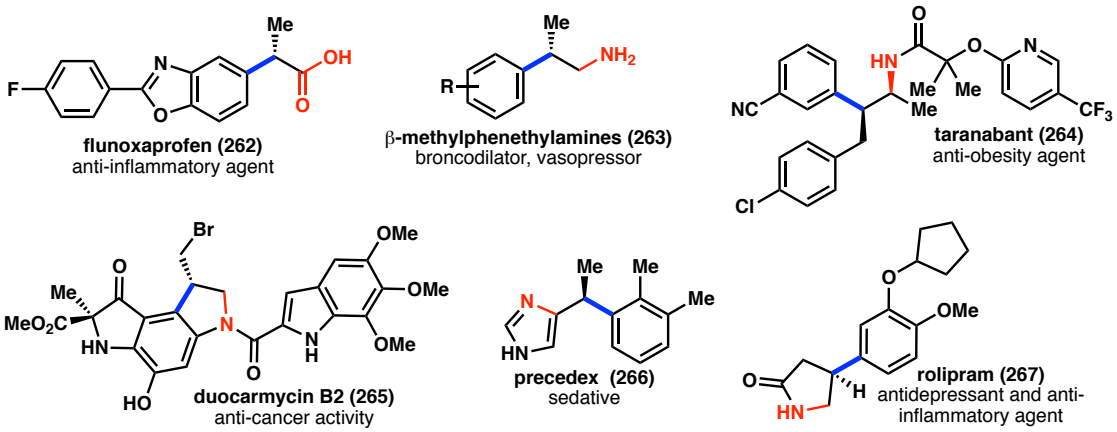
A8.1 INTRODUCTION

The ability to efficiently synthesize enantiopure small molecules is an important and ongoing synthetic challenge not only in academic research but also in the pharmaceutical industry as over 60% of FDA-approved medications contain C(sp^3)-hybridized stereocenters,[1] some of which are commercialized as a single enantiomer. Chiral benzylic stereocenters are a common structural motif found in a variety of drug molecules, some of which also contain β-disposed functional groups (Figure A8.1). When developing synthetic approaches to access enantioenriched pharmaceuticals, it is often

[‡]The research presented in this chapter was completed in collaboration with: 1) Nathaniel Kadunce (graudate student) and Raymond Turro (graduate student) in the Reisman group, as well as Iris Guo (graduate student) in the Sigman group.

imperative to dictate the absolute chirality of these stereocenters as opposite enantiomers of drug molecules often display drastically different efficacy.[2,3] Furthermore, increased C(sp^3) content has been correlated with improved aqueous solubility and clinical success.[1] In order to synthesize a broad range of target drug molecules, the need for a diverse set of reactions to form C–C bonds continues to drive the development of new synthetic methods.

Figure A8.1 *Pharmaceuticals containing chiral benzylic stereocenters.*

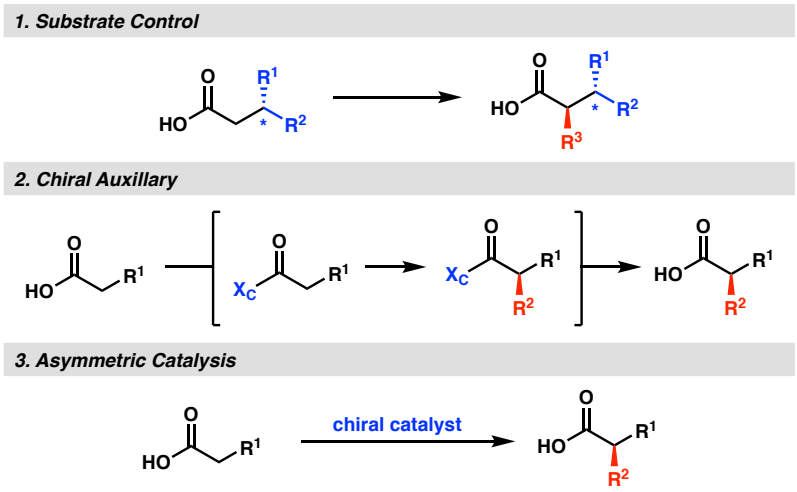


A8.1.1 Origins of Stereoinduction

In the context of organic synthesis, the introduction of enantioenriched C(sp^3)-hybridized stereocenters often relies on one of three different approaches: 1) substrate control, 2) appendage and removal of chiral auxillaries, or 3) the use of chiral catalysts (Scheme A8.1).[4–6] In each case, a diastereoselective approach is utilized to transfer chiral information to the newly formed stereogenic center, either from an existing chiral handle on the substrate or through coordination to a chiral catalyst. In cases where a reaction takes place on an existing C(sp^3)-hybridized carbon atom, the utility of stereospecific and stereoconvergent approaches, either through the use of organocatalysts or metal catalysts,[7] proves particularly useful. Asymmetric catalysis, unlike substrate control and chiral

auxillaries, does not require pre-installation of stereochemical information that may need to be removed downstream in a synthetic sequence. Furthermore, asymmetric catalysis allows one to finely tune the electronic and structural parameters of a catalyst, which at times can even override inherent substrate controlled diastereoselectivity.

Scheme A8.1 *Approaches to synthesize chiral C(sp³) stereocenters.*

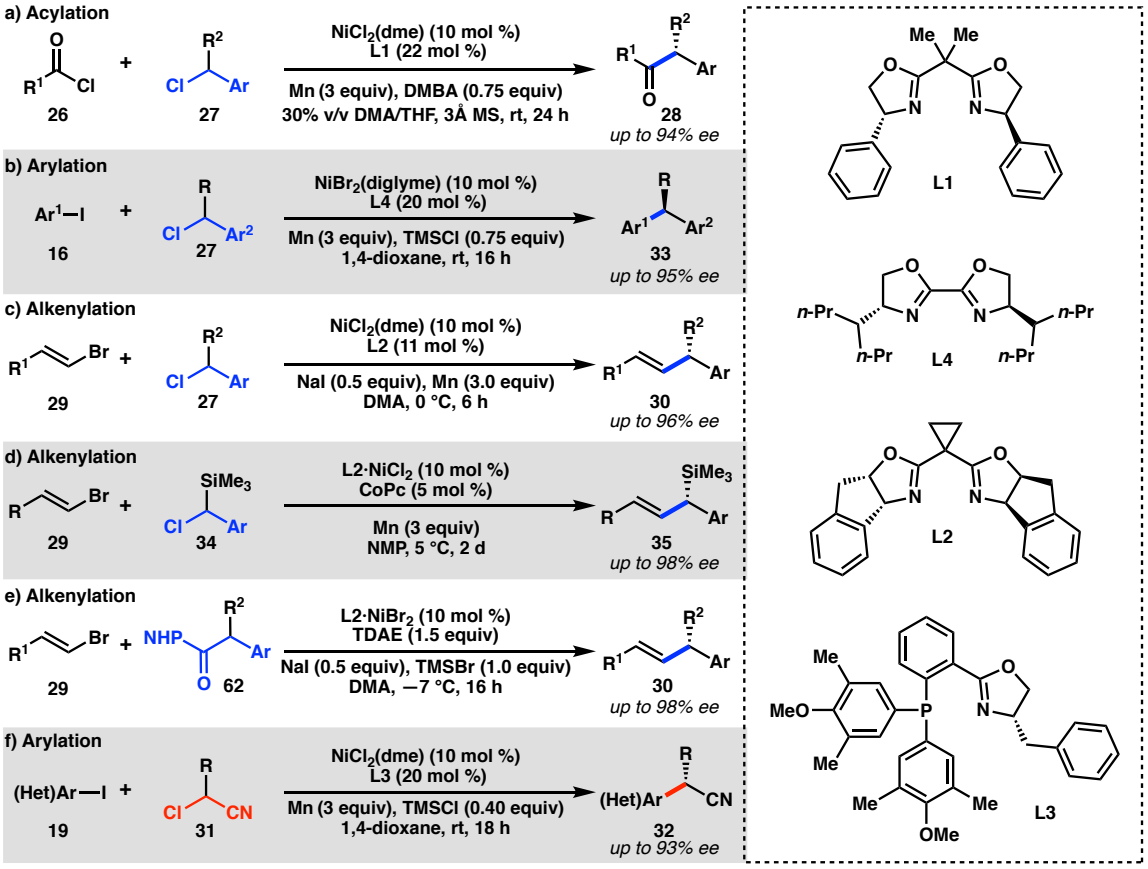


A8.1.2 Asymmetric Reductive Cross-Couplings

Our laboratory has recently published a number of asymmetric nickel-catalyzed cross-electrophile couplings using a broad scope of C(sp^2)-hybridized electrophiles (e.g. aryl iodides, alkenyl bromides, and acid chlorides) (Scheme A8.2).[8–13] Thus far we have discovered that diversifying the C(sp^3)-hybridized electrophile has proven challenging; in order to obtain high levels of reactivity and enantioselectivity, the C(sp^3)-hybridized electrophile requires the use of a radical stabilizing functional group adjacent to the electrophilic carbon, which has shown success when included as either an aromatic ring or nitrile moiety. For each new set of coupling partners, reactions were extensively reoptimized. To obtain high selectivity in the benzylic systems, the use of BOX ligands **L1**

or **L2**, or BiOX ligand **L4**, provided the products in up to 98% ee. In contrast, the α-chloronitrile reaction proceeded in poor yield when BOX and BiOX ligands were used, and it was found during initial optimization that PHOX ligands improved reactivity. A series of BnPHOX ligands were evaluated, and the use of an electron-rich PHOX ligand **L4** provided the products in up to 93% ee.

Scheme A8.2 *Asymmetric Reductive Cross-Coupling Reactions*



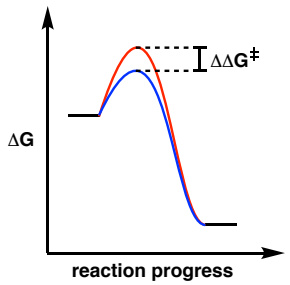
It is evident from these results that the PHOX ligand possess unique electronic and structural characteristics that promote good reactivity and selectivity for the α-chloronitrile system. In order to more efficiently develop novel asymmetric cross-coupling reactions, we became interested in studies that advance our understanding of reaction mechanisms.

In particular, we became interested in studying the PHOX ligand scaffold in the context of a ligand parameterization study in collaboration with the Sigman laboratory. A systematic study that probes how steric and electronic factors of the ligand perturb the yield and selectivity of this reductive cross-coupling reaction will allow for the future development of new cross-coupling reactions that proceed through α-nitrile radical intermediates. Furthermore, this study may also provide insight as we ask questions on how to utilize other radical stabilizing groups (e.g. esters, ketones, amides, alkenes, alkynes) as well as unactivated electrophiles in Ni-catalyzed asymmetric cross-couplings.

A8.1.3 Ligand Parameterization

The fine tuning of chiral catalysts, either by exploiting stabilizing or destabilizing interactions, can lead to highly enantiopure products as selectivity is governed by the reaction temperature and the Gibbs free energy difference ($\Delta\Delta G^{\ddagger}$) between the major and minor transition states (Figure A8.2). While the key principles of asymmetric catalysis are rooted in fundamental physical organic chemistry, they are often overlooked in reaction development and optimization. Although asymmetric catalysis has undeniably become a powerful approach to introduce chirality in target molecules, the straightforward

Figure A8.2 *Gibbs free energy difference for a given transition state.*

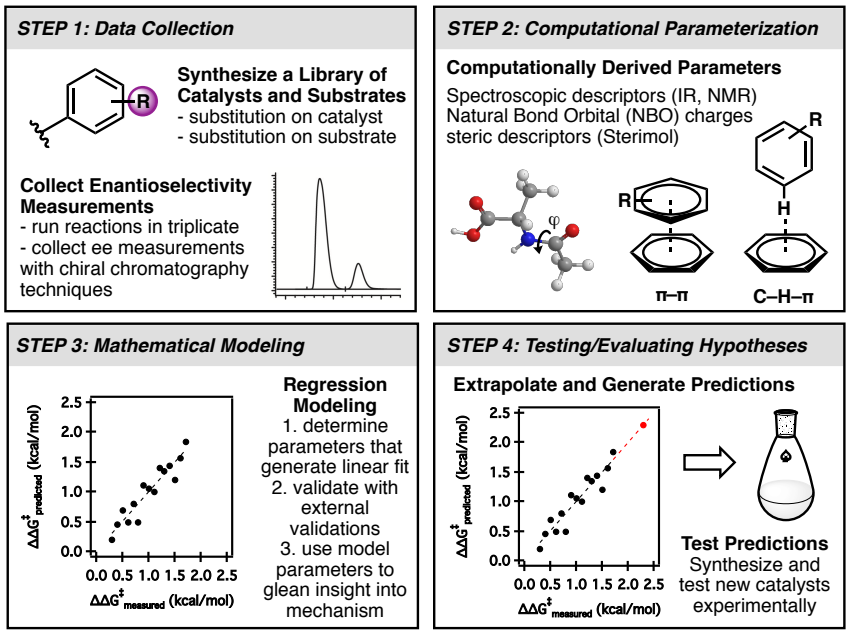


construction of stereogenic centers remains an ongoing challenge as success is often achieved through extensive screening processes. This empirical approach requires a significant amount of time and resources in order to fully optimize a given reaction.

In order to address these challenges, the Sigman laboratory has studied catalyst optimization through a data-driven approach that focuses on understanding the fundamental physical principles of transition state stabilization by studying how structural parameters, electronic parameters, and non-covalent interactions between the catalyst and substrate impacts enantioselectivity. To study these interactions, the laboratory turns to the use of multi-variable linear free energy relationships and modern statistical analysis techniques in order to probe multiple components that affect the overall transition state energy.[14–19] This approach is particularly useful, as it also allows one to study catalyst effects without knowledge of the reaction mechanism; often ligand parameters can be used as catalyst surrogates.

The workflow of this analytical technique consists of four main parts: 1) data collection, 2) computational parameterization, 3) mathematical modeling, and 4) testing and evaluating hypotheses (Figure A8.3). The mathematical equation obtained through this process can be used to help predict better catalysts through virtual screening but perhaps of more importance it can allow one to glean insight into the reaction mechanism. This information can be further utilized in the development of novel reactivity. This research area fosters an innovative and collaborative environment where the overall goal is to develop a universal understanding of asymmetric catalysis from a physical organic perspective.

Figure A8.3 *Sigman parameterization workflow.*



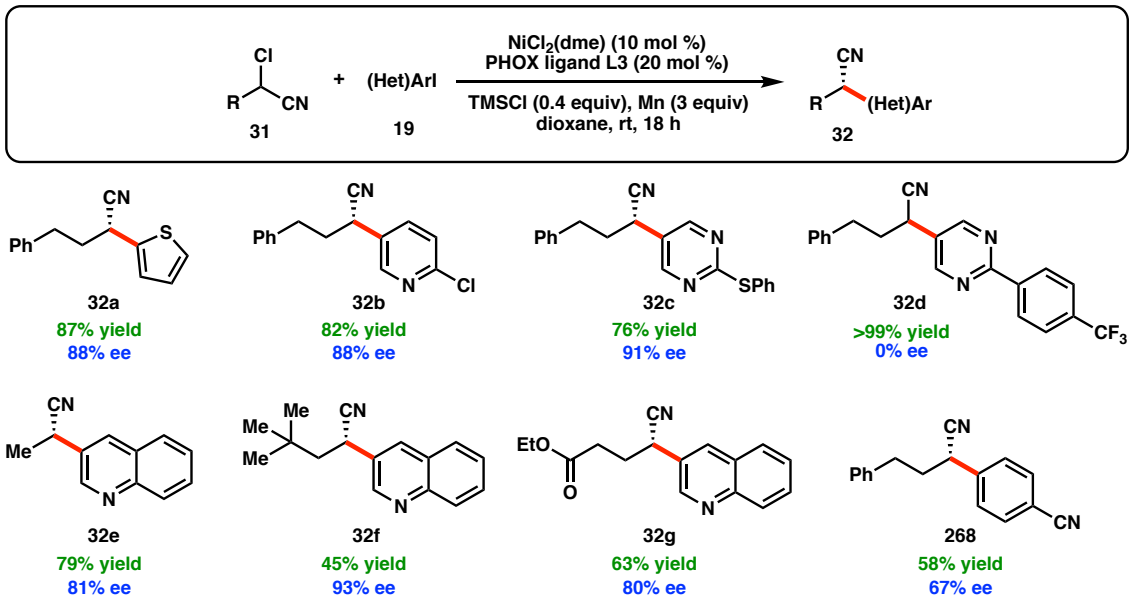
A8.2 PRELIMINARY RESULTS

A8.2.1 Cross-Coupling of α-Chloronitriles and Aryl Iodides

We set out to initiate a collaboration with the Sigman laboratory to better understand how different components of the PHOX ligand impacted the enantioselectivity of the α-arylated nitrile products (**32**). For the cross-coupling of α-chloronitriles (**31**) and aryl iodides (**16**) to generate chiral α-arylated nitriles (**32**), the developed reaction proceeded in good yield and enantioselectivity for a range of different substrates, which included heterocycles such as thiophenes (**32a**), pyridines (**32b**), pyrimidines (**32c**), and quinolines (**32e–g**) (Figure A8.4).[12] Although optimized, these conditions did possess some pitfalls. Typically, good yields and lower ee were observed for smaller α-substituents (i.e.

32e) while poorer yields and better ee are observed with bulkier substrates (i.e. **32f**). Furthermore, aryl iodides lacking a heterocyclic motif typically resulted in lower ee (**32h)**, and substrates containing 2-aryl pyrimidines provided racemic products (**32d**). Although the published method evaluated heteroaromatic iodides for the substrate scope, these reactions typically proceeded with higher levels of enantioselectivity. Therefore, we elected to pursue parameterization studies with a non-heteroaromatic aryl iodide (i.e. 4-bromobenzonitrile) in hopes to discover second-generation conditions to access a variety of new chiral products in synthetically tractable enantiopurities.

Figure A8.4 *Representative scope of α-chloronitrile and aryl iodide cross-coupling.*

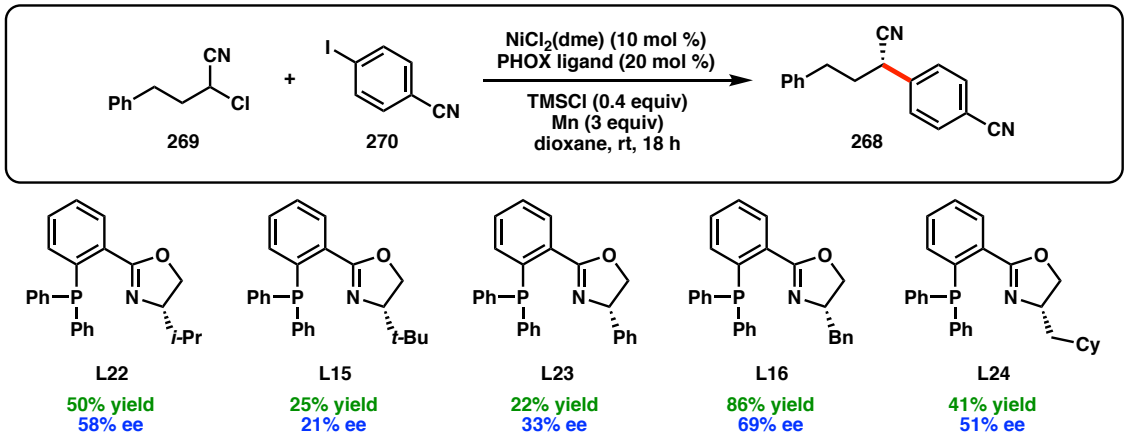


A8.2.2 Initial Data Set

During the initial optimization of the cross-coupling between α-chloronitrile **269** and aryl iodide **270**, an expansive ligand screen revealed that the benzyl PHOX ligand **L16** (readily synthesized from L-phenylalanine) was found to form the product (**268**) in high

yield (86%), albeit in a modest 69% ee. In contrast, the use of other commercially available PHOX ligands (i.e. *i*-Pr, *t*-Bu, Ph) provided the desired product with poor selectivity, and the use of BOX or BiOX ligands delivered **268** in trace yield (Figure A8.5). We hypothesized that the electron-rich nature of the PHOX ligand might be more strongly bound to the nickel center due to the softer nature of the P-donor and accelerate the rate of oxidative addition of aryl iodide **270** to an **L16**·Ni(0) complex.

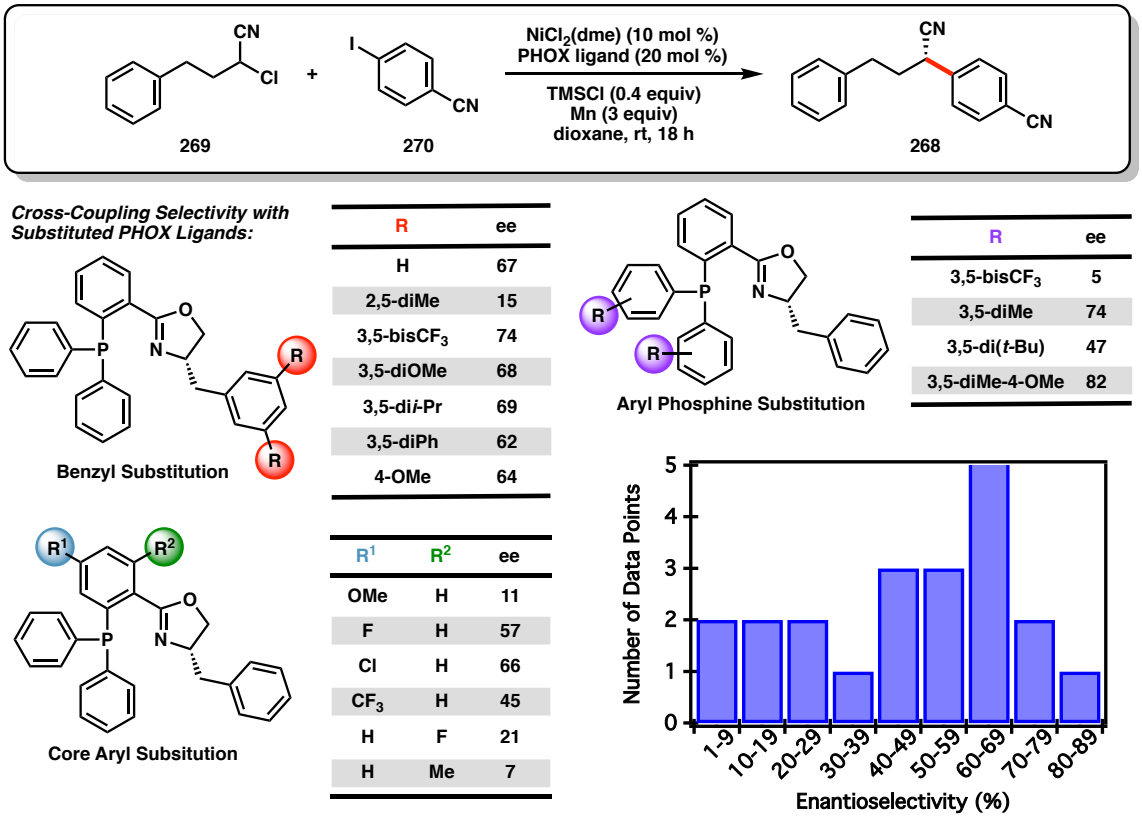
Figure A8.5 *Effect of chiral PHOX ligand on enantioselectivity.*



In order to optimize the ee of **268**, a series of 40 novel BnPHOX ligands were synthesized and evaluated in the cross-coupling between **269** and **270** (Figure A8.6). Ultimately, an electron rich phosphine was found to improve the enantioselectivity of **268**. Nevertheless, a significant amount of data was collected during this screening process which was used as the starting point for our parameterization study. With the exception of *ortho*-substitution, tuning arene substitution on the benzyl ring resulted in minimal effects in the observed enantioselectivity, however, altering the electronic nature of the core aryl ring or the phosphine aromatic groups proved more detrimental to enantioselectivity. Empirical observations show that the ee of **268** increases with more electron-rich

phosphines, although steric interactions (e.g. *t*-Bu) might also contribute to selectivity. A Hammett plot of the core substitution provides no correlation, indicating that selectivity is likely due to a complex function of parameters, and thus difficult to predict using empirical observations. Final evaluation of these ligands provided **268** across a significant range of enantioselectivities, a requirement for ligand parameterization studies.

Figure A8.6 *Representative scope of α-chloronitrile and aryl iodide cross-coupling.*



R	ee
H	67
2,5-diMe	15
3,5-bisCF$_3$	74
3,5-diOMe	68
3,5-di*i*-Pr	69
3,5-diPh	62
4-OMe	64

R^1	R^2	ee
OMe	H	11
F	H	57
Cl	H	66
CF$_3$	H	45
H	F	21
H	Me	7

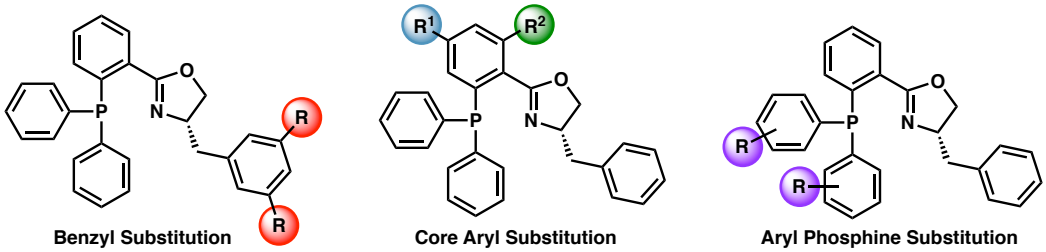
R	ee
3,5-bisCF$_3$	5
3,5-diMe	74
3,5-di(*t*-Bu)	47
3,5-diMe-4-OMe	82

A8.3 EXPERIMENTAL RESULTS

Based on the results in the initial data set, arene substitution studies can be broken down into three categories: 1) benzyl substitution, 2) core aryl substitution, and 3) aryl

phosphine substitution (Figure A8.7). Given the seemingly minimal effects on benzyl substitution, we first elected to study the other two parts of the ligand. Our plan for this project was for first synthesize the electrophiles and ligands necessary to repeat our enantioselectivity measurements in triplicate. Geometry optimizations of the PHOX ligands would then be obtained to conduct single point calculations. Various electronic and structural parameters can be extracted from these calculations and correlated to the enantioselectivity data. Finally, correlations between experimental data and calculated features of the catalyst will allow us to develop a model that can potentially identify features important to the enantioselectivity of this reaction, shed insight into the reaction mechanism, and allow us to predict a more selective PHOX ligand.

Figure A8.7 *Types of substitution on the BnPHOX ligand.*

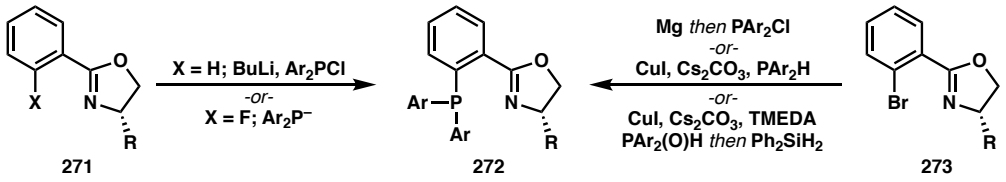


A8.3.1 Ligand Synthesis

We set out to synthesize and characterize a systematic scope of BnPHOX ligands. The PHOX ligand synthesis can be carried out via a number of different routes (Scheme A8.3). *Ortho*-lithiation of the arene (**271**, X=H) followed by substitution with chlorodiphenylphosphine[20] or the substitution of aryl fluorides (**271**, X=F) with a diarylphosphine anion[21] provides the desired ligands (**272**). The most common way PHOX ligands are synthesized is from the aryl bromide (**273**), either through a Grignard addition

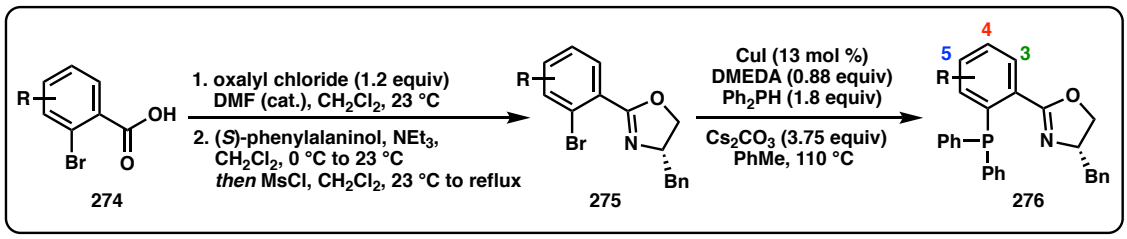
into chlorodiarylphosphine,[22] Cu-catalyzed coupling with diarylphosphine,[23] or Cu-catalyzed coupling of diarylphosphine oxide followed by reduction with diphenylsilane.[24]

Scheme A8.3 *Synthesis of PHOX ligands.*



Although the synthesis of aryl bromide core **271** has been previously developed, it required isolation of the intermediate amide or alkyl electrophile. In order to streamline the ligand synthesis, we discovered alternate one-pot conditions (Table 8.1). When amide bond formation was conducted in the presence of NEt_3, the addition of MsCl not only induced

Table A8.1 *Synthesis of PHOX ligands with core substituents.*



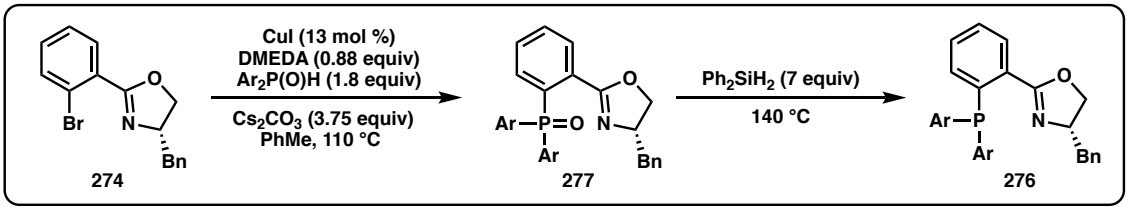
Entry	R	275 yield (g)	275 yield (%)	276 yield (mg)	276 yield (%)	276 = L
1	H	43.0	91	620	49	L16
2	3-Me	4.7	72	830	64	L25
3[a]	3-F	4.8	72	840	64	L26
4	4-OMe	5.1	74	580	43	L27
5	4-Me	5.9	89	410	32	L28
6[a]	4-F	5.3	79	860	66	L29
7[a,b]	4-Cl	3.9	56	620	45	L30
8	4-CF_3	5.2	75	460	31	L31
9	5-OMe	5.6	82	1050	78	L32
10	5-Me	4.7	72	1090	83	L33
11[a]	5-F	5.0	72	510	39	L34
12[a,b]	5-Cl	3.4	49	740	54	L35
13	5-CF_3	4.3	63	600	41	L36

[a]1 equiv Ph_2PH, [b]3.6 equiv $(COCl)_2$

mesylation but also produced the oxazoline product upon heating. Subsequent Cu-catalyzed coupling of diphenyl phosphine proceeded smoothly to afforded a variety of substituted PHOX ligands.

In order to prepare PHOX ligands with various aryl substitution on the phosphine, the corresponding diaryl phosphine oxides were instead coupled to aryl bromide core **274** with the same Cu-catalyzed conditions (Table A8.2). This alleviated the need to prepare the necessary air sensitive diaryl phosphine reagents. Reduction of the triaryl phosphine oxide was achieved by heating **277** in neat diphenyl silane at 140 °C.

Table A8.2 *Synthesis of PHOX ligands with phosphine aryl substituents.*



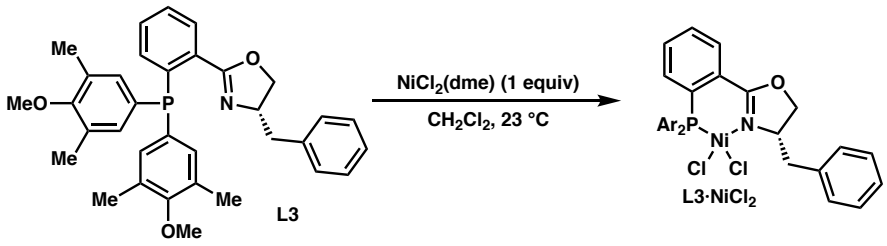
Entry	Ar	277 yield (mg)	277 yield (%)	276 yield (mg)	276 yield (%)	276 = L
1	*p*-Me	330	72	640	78	L37
2	*p*-*t*-Bu	1320	64	600	77	L38
3	*p*-Cl	1550	52	370	76	L39
4	*p*-F	1076	39	410	91	L40
5	*p*-CF_3	770	43	450	81	L41
6	*p*-OMe	950	70	—	—	L42

A8.3.2 Cyclic Voltammetry Studies

With a range of synthesized PHOX ligands, we set out to measure electrochemical properties of synthetic PHOX·$NiCl_2$ complexes to compare their redox properties to the observed enantioselectivity of **268**.[20] Complexation of **L3** with $NiCl_2$(dme) in CH_2Cl_2 at room temperature provides **L3**·$NiCl_2$ complex, which can be characterized by nuclear magnetic resonance (NMR) spectroscopy (Scheme A8.4). The broad ^{1}H NMR signals and

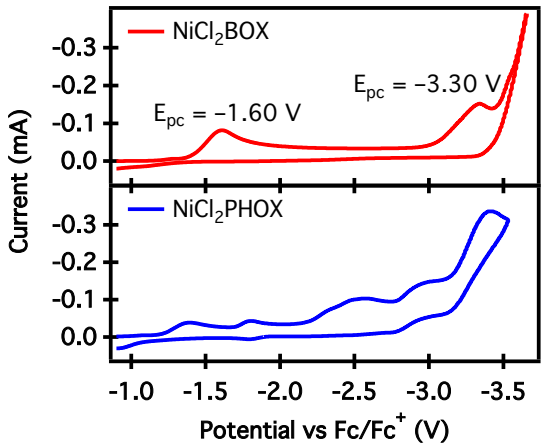
lack of ^{31}P resonance demonstrates the paramagnetic nature of the complex, thus confirming a distorted tetrahedral geometry when in solution. In contrast to **L2**·$NiCl_2$,

Scheme A8.4 *Synthesis of* ***L3***·$NiCl_2$ *complex.*



where a square planar geometry would position the chloride anion directly into the ligand arm, **L3**·$NiCl_2$ is not C_2 symmetric and has more rotational freedom to position halides. Although attempts to crystallize **L3**·$NiCl_2$ to obtain solid state geometries were unsuccessful, analogous Ni(II) achiral complexes have been synthesized and reported by X-ray crystallography, which also dictate a tetrahedral geometry.[22] With **L3**·$NiCl_2$ in hand, we sought to analyze its electrochemical properties (Figure A8.8). While the reduction of BOX complex **L2**·$NiCl_2$ demonstrates two one-electron reductions at E_{pc} = –1.60 V (Ni^{II}/Ni^{I}) and E_{pc} = –3.30 V (Ni^{I}/Ni^{0}) vs. Fc/Fc^{+}, the reduction of **L3**·$NiCl_2$ does

Figure A8.8 *Cyclic voltammetry traces for the reduction of Ni complexes.*

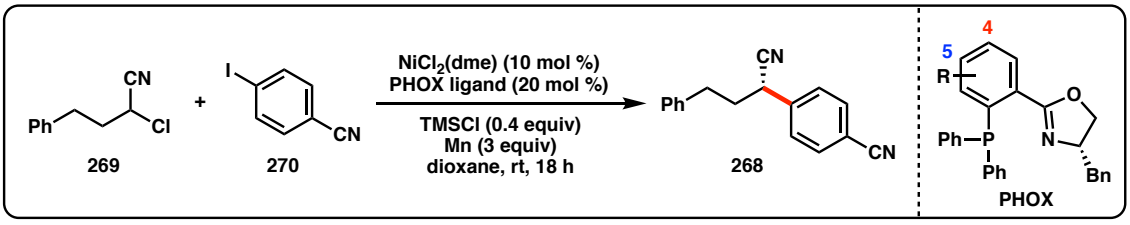


not proceed cleanly. These results support the notion to pursue ligand parametrization studies with computational data given the challenges of obtaining clean redox potentials.

A8.3.3 Iodobenzonitrile Aryl Electrophile

We then investigated the enantioselectivity of **268** with the PHOX ligand series containing core aryl substitution at both the 4-position and the 5-position (**L25**–**L36**). Ligands were evaluated in the cross-coupling reaction until n=5 data points were obtained (Table A8.3); any outliers were removed via the t-test at 95% confidence interval. Although the variation between subsequent runs in the data set was still quite large, we decided to move forward and analyze the results relative to reported Hammett coefficients to determine any trends. Since core aryl substitutions and the ligand are both in *meta* and *para* positions depending if they are in reference to the phosphine or oxazoline, Hammett plot

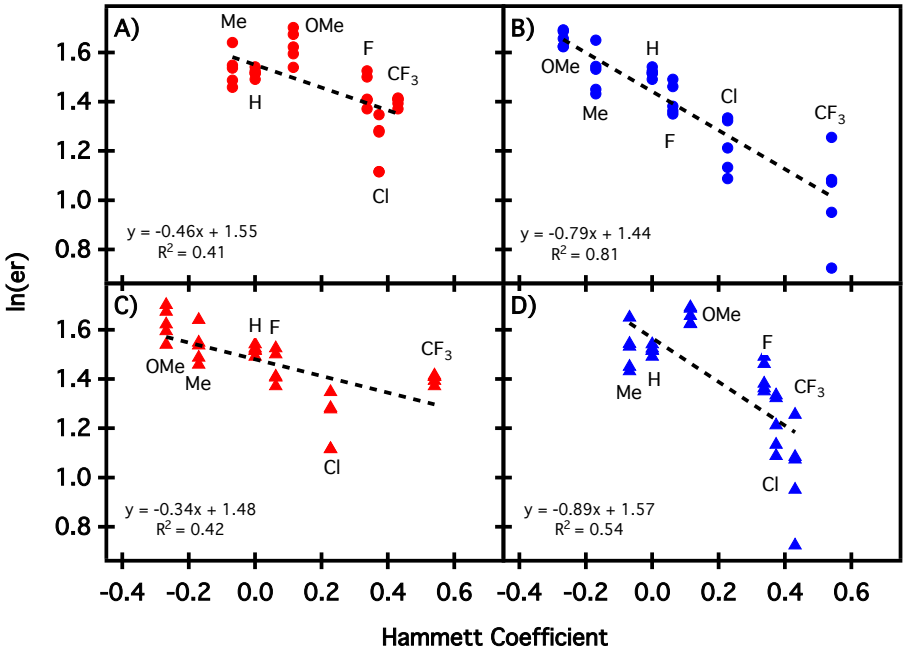
Table A8.3 *Evaluation of core substitution.*



Entry	R	PHOX	ee (%)	ee (%)	ee (%)	ee (%)	ee (%)
1	H	L16	64	64	65	64	63
2	4-OMe	L27	65	66	69	68	67
3	4-Me	L28	65	68	63	65	62
4	4-F	L29	61	60	61	64	64
5	4-Cl	L30	59	57	51	51	56
6	4-CF_3	L31	61	61	61	60	60
7	5-OMe	L32	67	68	69	67	69
8	5-Me	L33	65	68	64	61	62
9	5-F	L34	60	59	63	62	59
10	5-Cl	L35	51	50	54	58	58
11	5-CF_3	L36	35	49	56	44	49

correlations for each combination was plotted (Figure A8.9). Data points collected with 4-position substitution (red data) showed poor Hammett plot correlations when analyzed with respect to the oxazoline (circles, A), however a better trend is observed with respect to the phosphine (triangles, C). In contrast, data points collected with 5-position substitution (blue data) showed poor Hammett plot correlations when analyzed with respect to the phosphine (triangles, D), however a linear trend is observed with respect to the oxazoline (circles, B).

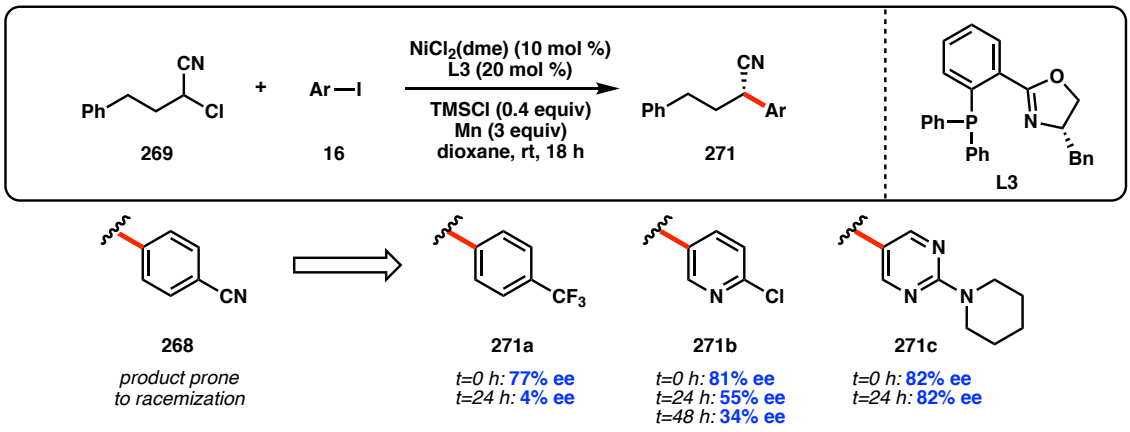
Figure A8.9 *Hammett plot correlations for core aryl substitution.*



Further attempts to improve the variability in the data, either by pre-stirring the reaction prior to the addition of the α-chloronitrile or by pre-complexing the PHOX ligand with $NiCl_2$(dme) proved unfruitful. After screening a wide variety of reaction conditions we serendipitously discovered the root cause to ee variability: the cross-coupled product **268** is not configurationally stable and racemizes over time in solution, sometimes providing racemic product after 24 hours. This begs the question on the origin of the

observed Hammett trend in Figure A8.9b. *Is the ee variation due to the cross-coupling or due to a racemization process?* A variety of workup conditions were evaluated, yet no solution was found to consistently prevent racemization of **268**. In order to circumvent this issue, other aryl halide electrophiles were used to evaluated their corresponding benzylic nitrile coupling products (**271a–c**) (Figure A8.10). Gratifyingly, pyrimidine **271c,** which is a crystalline product, was found to be configurationally stable in solution over the course of 24 hours.

Figure A8.10 *Racemization studies with various aryl iodide coupling partners.*

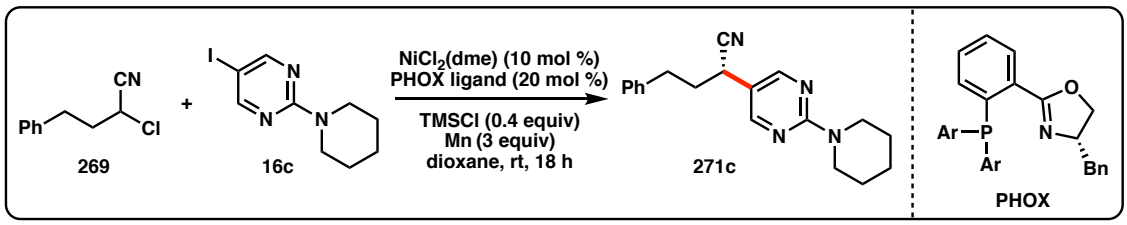


A8.3.4 Pyrimidine Heteroaryl Iodide Electrophile

With a configurationally stable product in hand, we turned to evaluate substitution effects on the diaryl phosphine motif (Table A8.4). In contrast to our initial data set, which showed drastic variability on the ee of **268** when 3,5-disubstituted aryl groups were evaluated on the phosphine portion of the PHOX ligand, *para*-substitution on the arene shows minimal effect on the enantioselectivity of **271c**. Of notable importance is the reproducible enantioselectivity measurements of cross-coupled product **271c**, which provides promising results to utilize this substrate in further screening efforts. However, if

electronic and conformational effects are to be parsed out when combining our experimental results to the computational studies conducted by the Sigman laboratory, larger differences in ee measurements between different ligands are necessary. Further studies are needed to evaluate additional 3,5-disubstituted arenes. Additionally, other parameters need to be evaluated with the new substrate: revisiting the core substitution and investigate other structural groups in the chiral pocket besides benzyl (i.e. Ph, *i*-Pr, *t*-Bu).

Table A8.4 *Evaluation of phosphine aryl substitution.*



Entry	Ar	ee (%)	ee (%)	ee (%)
1	*p-H*	82	82	82
2	*p*-Me	82	82	82
3	*p-t*-Bu	80	80	81
4	*p*-Cl	83	83	83
5	*p*-F	83	83	83
6	*p*-CF_3	81	81	81

A8.4 CONCLUSIONS AND FUTURE DIRECTIONS

In summary, we have shown that arene substitution on the BnPHOX ligand scaffold effects the enantioselectivity of the cross-coupling reaction between α-chloronitriles and aryl iodides, however the stability of the product plays a critical role in the ability to obtain statistically significant data to conduct a ligand parameterization study. For electron deficient aryl iodides, racemization of the cross-coupling product occurred following reaction workup. Whether or not substitution on the PHOX ligand contributes to the enantioselectivity of the product formation during the cross-coupling or effects

racemization processes has yet to be determined. These results highlight the importance of choosing the appropriate substrate in mechanistic investigations as the use of different substrates may render such studies intractable and probe different aspects of the catalytic cycle. Future studies are ongoing in order to further elucidate the role of the catalyst in altering product racemization as well as determine other ligand parameters that influence the enantiodetermining step for the cross-coupling with configurationally stable pyrimidine products formed with heteroaryl iodides.

A8.5 EXPERIMENTAL SECTION

A8.5.1 Materials and Methods

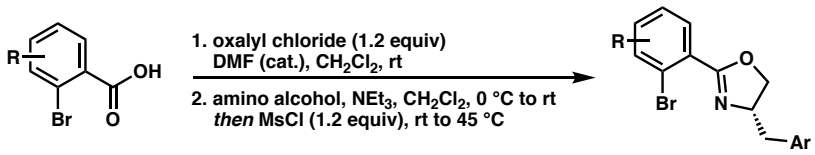
Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Toluene (PhMe) was dried by passing through activated alumina columns. Trimethylsilyl chloride (TMSCl) and anhydrous dioxane were purchased from Sigma Aldrich and stored in the glovebox. Manganese powder (–325 mesh, 99.3%) was purchased from Alfa Aesar. Nickel(II) chloride dimethoxyethane adduct ($NiCl_2$(dme)) was purchased from Strem. Unless otherwise stated, chemicals were used as received. All reactions were monitored by thin-layer chromatography (TLC) using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by ultraviolet (UV) light or with cerium ammonium molybdate (CAM) staining. Flash column chromatography was performed as described by Still et al.[25] using silica gel (230-400 mesh) purchased from Silicycle. Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ^{1}H and ^{13}C and NMR spectra were recorded on a Bruker Avance

III HD with Prodigy cyroprobe (at 400 MHz and 101 MHz, respectively). NMR data is reported relative to internal $CHCl_3$ (^1H, δ = 7.26), $CDCl_3$ (^{13}C, δ = 77.1), Data for ^1H 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. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). Analytical chiral SFC was performed with a Mettler SFC supercritical CO_2 chromatography system with Chiralcel AD-H, OD-H, AS-H, OB-H, and OJ-H columns (4.6 mm x 25 cm).

A8.5.2 PHOX Ligand Synthesis

Note: Not all synthesized PHOX ligands are characterized in the following section. The project remains ongoing at the time of thesis submission and current work is being carried out by graduate student Raymond Turro.

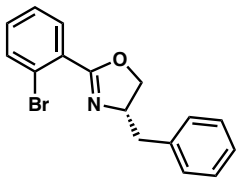
General Procedure 1: Oxazoline Formation



The following procedure was conducted using benchtop solvents and under an air atmosphere. The benzoic acid (1.0 equiv, 20 mmol) was added to a 100 mL round bottom flask equipped with a stir bar and suspended in 35 mL CH_2Cl_2 and 8 drops of DMF. The oxalyl chloride (2 mL, 1.2 equiv, 24 mmol) was added and the reaction was stirred at room temperature until the acid had completely dissolved *and* gas evolution ceased (ca. 1 hour). The reaction was concentrated under reduced pressure to afford the crude acid chloride,

which was used without further purification. The amino alcohol (1.0 equiv, 20 mmol) was added to a 200 mL round bottom flask equipped with a stir bar and dissolved in 35 mL CH_2Cl_2. The triethylamine (11.1 mL, 4.0 equiv, 80 mmol) was added and the solution was cooled to 0 °C. The acid chloride was dissolved in 35 mL CH_2Cl_2 and slowly added to the amino alcohol. The reaction was warmed to room temperature and stirred for 15 minutes before the addition of methanesulfonyl chloride (1.9 mL, 1.2 equiv, 24 mmol). The reaction stirred at room temperature for 15 minutes before being heated to reflux (45 °C) and continued to stir overnight. The reaction was cooled to room temperature before being quenched with aq. NH_4Cl (20 mL) and water (60 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica, EtOAc/hexane) to afford the desired product.

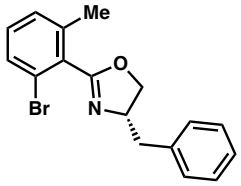
(*S*)-4-benzyl-2-(2-bromophenyl)-4,5-dihydrooxazole (275a)



Prepared from 2-bromobenzoic acid (30.15 g, 150 mmol) and (*S*)-phenylalaninol (22.68 g, 150 mmol) following General Procedure 1 except 1.1 equiv (14.15 mL, 165 mmol) of oxalyl chloride was used. The crude residue was purified filtering over a plug of silica and eluting with 40% EtOAc/hexane to yield 43.04 g (91% yield) of **275a** as a light yellow-green oil. $[\boldsymbol{a}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –11° (c = 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.69 – 7.61 (m, 2H), 7.36 – 7.22 (m, 7H), 4.65 (dddd, *J* = 9.4, 8.4, 7.3, 5.4 Hz, 1H), 4.38 (dd, *J* = 9.4, 8.5 Hz, 1H), 4.18 (dd, *J* = 8.5, 7.3 Hz, 1H), 3.25 (dd, *J* = 13.8, 5.3 Hz, 1H), 2.82 (dd, *J* = 13.7, 8.4 Hz, 1H). **^{13}C NMR**

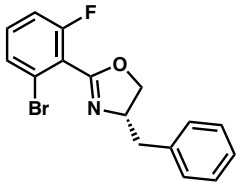
(101 MHz, $CDCl_3$): δ 163.4, 137.8, 133.8, 131.7, 131.3, 129.8, 129.4, 128.6, 127.1, 126.6, 121.9, 71.9, 68.2, 41.6.

(*S*)-4-benzyl-2-(2-bromo-6-methylphenyl)-4,5-dihydrooxazole (275b)



Prepared from 2-bromo-6-methylbenzoic acid (4.30 g, 20 mmol) and (*S*)-phenylalaninol (3.02 g, 20 mmol) following General Procedure 1. The crude residue was purified by column chromatography (silica, 5 to 20% EtOAc/hexane) to yield 4.05 g (72% yield) of **275b** as a light yellow oil. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –19° (c = 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.45 – 7.39 (m, 1H), 7.37 – 7.27 (m, 4H), 7.27 – 7.21 (m, 1H), 7.19 – 7.12 (m, 2H), 4.67 (dddd, *J* = 9.4, 8.4, 7.4, 5.8 Hz, 1H), 4.41 (dd, *J* = 9.4, 8.5 Hz, 1H), 4.20 (dd, *J* = 8.5, 7.4 Hz, 1H), 3.27 (dd, *J* = 13.8, 5.8 Hz, 1H), 2.85 (dd, *J* = 13.8, 8.4 Hz, 1H), 2.34 (d, *J* = 0.6 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 163.1, 139.4, 138.0, 130.9, 130.8, 130.0, 129.4, 129.0, 128.7, 126.6, 122.4, 72.1, 68.4, 41.8, 20.0.

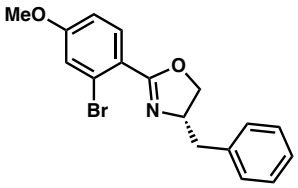
(*S*)-4-benzyl-2-(2-bromo-6-fluorophenyl)-4,5-dihydrooxazole (275c)



Prepared from 2-bromo-6-fluorobenzoic acid (4.36 g, 20 mmol) and (*S*)-phenylalaninol (3.02 g, 20 mmol) following General Procedure 1. The crude residue was purified by column chromatography (silica, 5 to 20% EtOAc/hexane) to yield 4.81 g (72% yield) of **275c** as a light yellow oil. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –21° (c = 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.41 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.37 – 7.21 (m, 6H), 7.09 (td, *J* = 8.6, 1.1 Hz, 1H), 4.67 (dddd, *J* = 9.5, 8.4, 7.3, 5.9 Hz, 1H), 4.43 (dd, *J* = 9.4, 8.4 Hz, 1H), 4.21 (dd, *J* = 8.5, 7.4 Hz, 1H), 3.26 (dd, *J* = 13.8, 5.9 Hz,

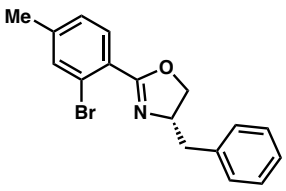
1H), 2.84 (dd, J = 13.8, 8.3 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 160.8 (d, J_{C-F} = 254.9 Hz), 159.1, 137.8, 132.2 (d, J_{C-F} = 9.1 Hz), 129.3, 128.7, 128.6 (d, J_{C-F} = 3.6 Hz), 126.6, 123.1 (d, J_{C-F} = 3.3 Hz), 120.2 (d, J_{C-F} = 18.6 Hz), 114.9 (d, J_{C-F} = 21.5 Hz), 72.4, 68.5, 41.7.

(*S*)-4-benzyl-2-(2-bromo-4-methoxyphenyl)-4,5-dihydrooxazole (275d)



Prepared from 2-bromo-4-methoxybenzoic acid (4.62 g, 20 mmol) and (*S*)-phenylalaninol (3.02 g, 20 mmol) following General Procedure 1. The crude residue was purified by column chromatography (silica, 5 to 20% EtOAc/hexane) to yield 5.65 g (82% yield) of **275d** as a light yellow oil which solidified in the freezer to give a white waxy solid. $[\boldsymbol{a}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +3° (c = 1.0, $CHCl_3$) (*Note: This aryl bromide core has + optical rotation*). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.65 (d, J = 8.7 Hz, 1H), 7.35 – 7.20 (m, 5H), 7.18 (d, J = 2.5 Hz, 1H), 6.86 (dd, J = 8.7, 2.6 Hz, 1H), 4.61 (dddd, J = 9.3, 8.5, 7.1, 5.2 Hz, 1H), 4.33 (dd, J = 9.3, 8.5 Hz, 1H), 4.14 (dd, J = 8.5, 7.2 Hz, 1H), 3.82 (s, 3H), 3.24 (dd, J = 13.7, 5.2 Hz, 1H), 2.78 (dd, J = 13.7, 8.6 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 163.2, 161.5, 138.0, 132.5, 129.4, 128.6, 126.6, 122.8, 121.8, 119.3, 113.2, 71.7, 68.2, 55.7, 41.8.

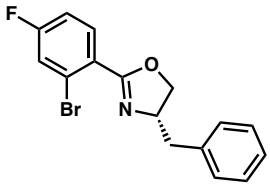
(*S*)-4-benzyl-2-(2-bromo-4-methylphenyl)-4,5-dihydrooxazole (275e)



Prepared from 2-bromo-4-methylbenzoic acid (4.30 g, 20 mmol) and (*S*)-phenylalaninol (3.02 g, 20 mmol) following General Procedure 1. The crude residue was purified by column chromatography (silica, 5 to 20% EtOAc/hexane) to yield 4.72 g (72% yield) of **275e** as a

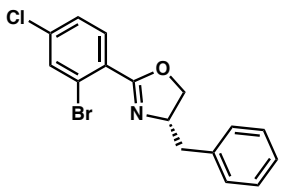
light yellow oil. $[a]_D^{25}$ = –3° (c = 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.57 (d, *J* = 7.9 Hz, 1H), 7.47 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.35 – 7.21 (m, 5H), 7.13 (ddd, *J* = 8.0, 1.7, 0.8 Hz, 1H), 4.63 (dddd, *J* = 9.4, 8.5, 7.2, 5.2 Hz, 1H), 4.35 (dd, *J* = 9.4, 8.5 Hz, 1H), 4.16 (dd, *J* = 8.5, 7.2 Hz, 1H), 3.25 (dd, *J* = 13.7, 5.2 Hz, 1H), 2.79 (dd, *J* = 13.7, 8.5 Hz, 1H), 2.35 (d, *J* = 0.7 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 163.4, 142.4, 137.9, 134.4, 131.2, 129.4, 128.6, 128.0, 126.8, 126.6, 121.7, 71.8, 68.2, 41.7, 21.1.

(*S*)-4-benzyl-2-(2-bromo-4-fluorophenyl)-4,5-dihydrooxazole (275f)



Prepared from 2-bromo-4-fluorobenzoic acid (4.36 g, 20 mmol) and (*S*)-phenylalaninol (3.02 g, 20 mmol) following General Procedure 1. The crude residue was purified by column chromatography (silica, 5 to 20% EtOAc/hexane) to yield 4.76 g (71% yield) of **275f** as a light yellow oil. $[a]_D^{25}$ = –13° (c = 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.69 (dd, *J* = 8.7, 6.0 Hz, 1H), 7.39 (dd, *J* = 8.3, 2.6 Hz, 1H), 7.35 – 7.21 (m, 5H), 7.06 (ddd, *J* = 8.7, 7.8, 2.6 Hz, 1H), 4.64 (dddd, *J* = 9.4, 8.4, 7.3, 5.4 Hz, 1H), 4.37 (dd, *J* = 9.4, 8.5 Hz, 1H), 4.17 (dd, *J* = 8.5, 7.3 Hz, 1H), 3.23 (dd, *J* = 13.7, 5.3 Hz, 1H), 2.80 (dd, *J* = 13.8, 8.4 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 163.3 (d, $J_{C\text{-}F}$ = 255.2 Hz), 162.6, 137.7, 132.9 (d, $J_{C\text{-}F}$ = 9.1 Hz), 129.4, 128.7, 126.69, 126.1 (d, $J_{C\text{-}F}$ = 3.6 Hz), 122.7 (d, $J_{C\text{-}F}$ = 9.8 Hz), 121.4 (d, $J_{C\text{-}F}$ = 24.6 Hz), 114.6 (d, $J_{C\text{-}F}$ = 21.3 Hz), 72.0, 68.3, 41.7.

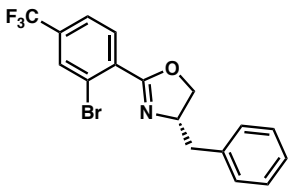
(*S*)-4-benzyl-2-(2-bromo-4-chlorophenyl)-4,5-dihydrooxazole (275g)



Prepared from 2-bromo-4-chlorobenzoic acid (4.71 g, 20 mmol) and (*S*)-phenylalaninol (3.02 g, 20 mmol) following General Procedure 1 except 3.6 equiv (6.2 mL, 72 mmol) of oxalyl

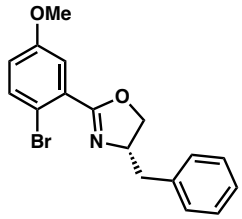
chloride was used. The crude residue was purified by column chromatography (silica, 5 to 20% EtOAc/hexane) to yield 3.45 g (49% yield) of **275g** as a light yellow oil. $[\boldsymbol{a}]_D^{25}$ = –3° (c = 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.67 (d, *J* = 2.1 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.35 – 7.22 (m, 6H), 4.64 (dddd, *J* = 9.4, 8.3, 7.2, 5.3 Hz, 1H), 4.37 (dd, *J* = 9.4, 8.5 Hz, 1H), 4.17 (dd, *J* = 8.5, 7.3 Hz, 1H), 3.23 (dd, *J* = 13.8, 5.3 Hz, 1H), 2.80 (dd, *J* = 13.8, 8.3 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 162.6, 137.7, 137.1, 133.7, 132.2, 129.5, 128.7, 128.2, 127.5, 126.7, 122.5, 72.0, 68.3, 41.6.

(*S*)-4-benzyl-2-(2-bromo-4-(trifluoromethyl)phenyl)-4,5-dihydrooxazole (275h)



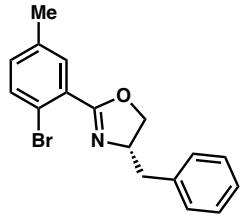
Prepared from 2-bromo-4-(trifluoromethyl)benzoic acid (4.84 g, 18 mmol) and (*S*)-phenylalaninol (2.72 g, 18 mmol) following General Procedure 1. The crude residue was purified by column chromatography (silica, 5 to 20% EtOAc/hexane) to yield 3.34 g (48% yield) of **275h** as a light yellow oil which solidified in the freezer to give a white crystalline solid. $[\boldsymbol{a}]_D^{25}$ = –14° (c = 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.91 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.78 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.60 (ddd, *J* = 8.1, 1.7, 0.8 Hz, 1H), 7.36 – 7.22 (m, 6H), 4.68 (dddd, *J* = 9.4, 8.2, 7.3, 5.4 Hz, 1H), 4.42 (dd, *J* = 9.5, 8.5 Hz, 1H), 4.21 (dd, *J* = 8.5, 7.3 Hz, 1H), 3.23 (dd, *J* = 13.8, 5.4 Hz, 1H), 2.84 (dd, *J* = 13.8, 8.2 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 162.4, 137.6, 133.6 (q, $J_{C\text{-}F}$ = 33.4 Hz), 133.3 (q, $J_{C\text{-}F}$ = 1.1 Hz), 131.9, 130.9 (q, $J_{C\text{-}F}$ = 3.9 Hz), 129.5, 128.7, 126.8, 124.1 (q, $J_{C\text{-}F}$ = 3.6 Hz), 122.9 (q, $J_{C\text{-}F}$ = 273.1 Hz), 122.4, 72.2, 68.4, 41.6.

(*S*)-4-benzyl-2-(2-bromo-5-methoxyphenyl)-4,5-dihydrooxazole (275i)



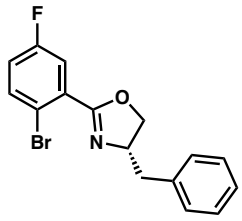
Prepared from 2-bromo-5-methoxybenzoic acid (4.62 g, 20 mmol) and (*S*)-phenylalaninol (3.02 g, 20 mmol) following General Procedure 1. The crude residue was purified by column chromatography (silica, 5 to 20% EtOAc/hexane) to yield 5.05 g (73% yield) of **275i** as a light yellow oil. $[\boldsymbol{a}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –4° (c = 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.50 (d, *J* = 8.8 Hz, 1H), 7.36 – 7.21 (m, 5H), 7.18 (d, *J* = 3.1 Hz, 1H), 6.85 (dd, *J* = 8.9, 3.1 Hz, 1H), 4.64 (dddd, *J* = 9.4, 8.4, 7.2, 5.2 Hz, 1H), 4.38 (dd, *J* = 9.4, 8.5 Hz, 1H), 4.18 (dd, *J* = 8.5, 7.3 Hz, 1H), 3.80 (s, 3H), 3.25 (dd, *J* = 13.8, 5.2 Hz, 1H), 2.81 (dd, *J* = 13.8, 8.4 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 163.4, 158.6, 137.8, 134.7, 130.5, 129.5, 128.7, 126.7, 118.5, 116.1, 112.3, 72.0, 68.3, 55.7, 41.7.

(*S*)-4-benzyl-2-(2-bromo-5-methylphenyl)-4,5-dihydrooxazole (275j)



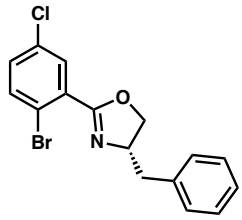
Prepared from 2-bromo-5-methylbenzoic acid (4.30 g, 20 mmol) and (*S*)-phenylalaninol (3.02 g, 20 mmol) following General Procedure 1. The crude residue was purified by column chromatography (silica, 5 to 20% EtOAc/hexane) to yield 5.43 g (82% yield) of **275j** as a light yellow oil. $[\boldsymbol{a}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –5° (c = 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.50 (d, *J* = 8.2 Hz, 1H), 7.49 – 7.47 (m, 1H), 7.35 – 7.21 (m, 5H), 7.11 – 7.07 (m, 1H), 4.63 (dddd, *J* = 9.4, 8.5, 7.3, 5.2 Hz, 1H), 4.37 (dd, *J* = 9.4, 8.5 Hz, 1H), 4.18 (dd, *J* = 8.5, 7.3 Hz, 1H), 3.25 (dd, *J* = 13.7, 5.2 Hz, 1H), 2.80 (dd, *J* = 13.8, 8.5 Hz, 1H), 2.31 (d, *J* = 0.8 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 163.7, 137.9, 137.2, 133.6, 132.6, 132.0, 129.5, 129.4, 128.7, 126.6, 118.4, 72.0, 68.2, 41.7, 20.8.

(*S*)-4-benzyl-2-(2-bromo-5-fluorophenyl)-4,5-dihydrooxazole (275k)



Prepared from 2-bromo-5-fluorobenzoic acid (4.36 g, 20 mmol) and (*S*)-phenylalaninol (3.02 g, 20 mmol) following General Procedure 1. The crude residue was purified by column chromatography (silica, 5 to 20% EtOAc/hexane) to yield 5.10 g (76% yield) of **275k** as a light yellow oil. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –13° (c = 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.60 (dd, *J* = 8.9, 5.1 Hz, 1H), 7.41 (dd, *J* = 8.9, 3.1 Hz, 1H), 7.36 – 7.22 (m, 5H), 7.02 (ddd, *J* = 8.8, 7.7, 3.1 Hz, 1H), 4.66 (dddd, *J* = 9.4, 8.3, 7.3, 5.4 Hz, 1H), 4.39 (dd, *J* = 9.4, 8.5 Hz, 1H), 4.19 (dd, *J* = 8.5, 7.3 Hz, 1H), 3.23 (dd, *J* = 13.7, 5.4 Hz, 1H), 2.82 (dd, *J* = 13.8, 8.3 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 162.3 (d, $J_{C\text{-}F}$ = 2.3 Hz), 161.4 (d, $J_{C\text{-}F}$ = 248.1 Hz), 137.6, 135.4 (d, $J_{C\text{-}F}$ = 7.8 Hz), 131.3 (d, $J_{C\text{-}F}$ = 8.1 Hz), 129.4, 128.7, 126.7, 119.0 (d, $J_{C\text{-}F}$ = 22.3 Hz), 118.6 (d, $J_{C\text{-}F}$ *J* = 24.7 Hz), 116.3 (d, $J_{C\text{-}F}$ = 3.6 Hz), 72.1, 68.3, 41.6.

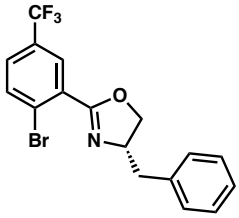
(*S*)-4-benzyl-2-(2-bromo-5-chlorophenyl)-4,5-dihydrooxazole (275l)



Prepared from 2-bromo-5-chlorobenzoic acid (4.71 g, 20 mmol) and (*S*)-phenylalaninol (3.02 g, 20 mmol) following General Procedure 1 except 3.6 equiv (6.2 mL, 72 mmol) of oxalyl chloride was used. The crude residue was purified by column chromatography (silica, 5 to 20% EtOAc/hexane) to yield 3.89 g (56% yield) of **275l** as a light yellow oil. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –8° (c = 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.66 (d, *J* = 2.6 Hz, 1H), 7.56 (d, *J* = 8.6 Hz, 1H), 7.36 – 7.30 (m, 2H), 7.29 – 7.22 (m, 4H), 4.65 (dddd, *J* = 9.4, 8.2, 7.3, 5.3 Hz, 1H), 4.39 (dd, *J* = 9.4, 8.5 Hz, 1H), 4.18 (dd, *J* = 8.5, 7.3 Hz, 1H), 3.23 (dd, *J* = 13.7, 5.3 Hz, 1H), 2.81 (dd, *J* =

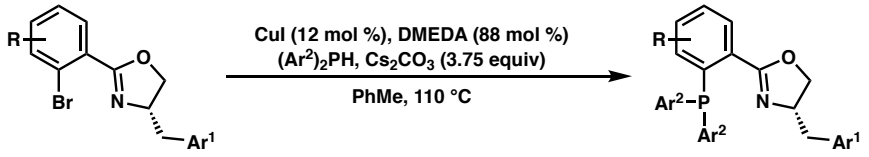
13.8, 8.3 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 162.3, 137.6, 135.1, 133.4, 131.8, 131.4, 131.2, 129.5, 128.7, 126.8, 119.9, 72.2, 68.4, 41.6.

(*S*)-4-benzyl-2-(2-bromo-5-(trifluoromethyl)phenyl)-4,5-dihydrooxazole (275m)



Prepared from 2-bromo-5-(trifluoromethyl)benzoic acid (4.84 g, 18 mmol) and (*S*)-phenylalaninol (2.72 g, 18 mmol) following General Procedure 1. The crude residue was purified by column chromatography (silica, 5 to 20% EtOAc/hexane) to yield 5.20 g (75% yield) of **275m** as a light yellow oil. $[\boldsymbol{a}]_D^{25}$ = –12° (c = 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.93 (d, *J* = 2.3 Hz, 1H), 7.78 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.52 (ddt, *J* = 8.4, 2.4, 0.7 Hz, 1H), 7.36 – 7.23 (m, 5H), 4.69 (dddd, *J* = 9.4, 8.2, 7.3, 5.3 Hz, 1H), 4.42 (dd, *J* = 9.5, 8.5 Hz, 1H), 4.22 (dd, *J* = 8.6, 7.3 Hz, 1H), 3.24 (dd, *J* = 13.8, 5.3 Hz, 1H), 2.85 (dd, *J* = 13.8, 8.2 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 162.2, 137.5, 134.7, 130.7, 129.9 (q, J_{C-F} = 33.5 Hz), 129.5, 128.7, 128.4 (q, J_{C-F} = 3.9 Hz), 128.1 (q, J_{C-F} = 3.6 Hz), 126.8, 126.0 (q, J_{C-F} = 1.6 Hz), 123.5 (q, J_{C-F} = 272.4 Hz), 72.2, 68.4, 41.5.

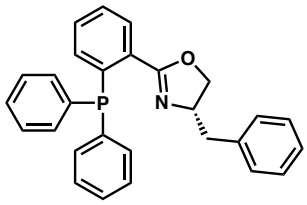
General Procedure 2: Ullman Coupling with Phosphine



The following procedure was conducted under an N_2 atmosphere in a glovebox. The CuI (74 mg, 0.39 mmol, 0.13 equiv) was added to a 150 mL heavy wall pressure flask equipped with a stir bar and dissolved in 20 mL of anhydrous toluene. The DMEDA (375 μL, 2.64

mmol, 0.88 equiv) and diarylphosphine (3.0-5.4 mmol, 1.0-1.8 equiv) was added and stirred for 10 minutes. The Cs_2CO_3 (3.66 g, 11.25 mmol, 3.75 equiv) was added, followed by the aryl bromide (3.0 mmol, 1.0 equiv) dissolved in 10 mL of toluene. The flask was sealed with a screw cap fitted with a viton o-ring, removed from the glovebox, and stirred overnight at 110 °C. The reaction was then cooled to room temperature and filtered over a pad of celite, eluting with CH_2Cl_2. The crude mixture was concentrated under reduced pressure and purified by column chromatography under a flow of N_2 to afford the desired product.

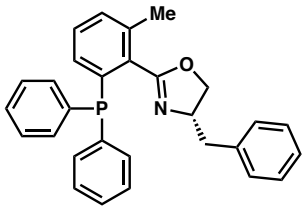
(*S*)-4-benzyl-2-(2-(diphenylphosphaneyl)phenyl)-4,5-dihydrooxazole (L16)



Prepared from (*S*)-4-benzyl-2-(2-bromophenyl)-4,5-dihydro-oxazole **275a** (949 mg, 3.0 mmol, 1.0 equiv) and diphenylphosphine (940 μL, 1.00 g, 5.4 mmol, 1.8 equiv) following General Procedure 2. The reaction stirred overnight for 24 hours. The crude residue was purified by column chromatography (silica, 0 to 3% Et_2O/DCM) under a flow of N_2 to yield 622 mg (49% yield) of **L16** as a sticky white solid. $[\boldsymbol{a}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +28° (c = 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.88 (ddd, *J* = 7.5, 3.5, 1.5 Hz, 1H), 7.42 – 7.23 (m, 14H), 7.22 – 7.16 (m, 1H), 7.12 – 7.05 (m, 2H), 6.87 (ddd, *J* = 7.6, 4.3, 1.3 Hz, 1H), 4.36 (tdd, *J* = 9.3, 7.4, 5.1 Hz, 1H), 4.04 (dd, *J* = 9.3, 8.4 Hz, 1H), 3.78 (dd, *J* = 8.4, 7.4 Hz, 1H), 2.93 (dd, *J* = 13.8, 5.1 Hz, 1H), 2.11 (dd, *J* = 13.8, 9.2 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 163.9 (d, $J_{C\text{-}P}$ = 2.9 Hz), [Ar region: 139.02, 138.77, 138.18, 137.94, 137.90, 137.82, 137.81, 134.54, 134.33, 133.98, 133.78, 133.55, 133.53, 131.61, 131.43,

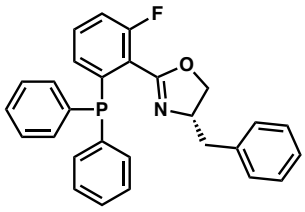
130.52, 129.96, 129.94, 129.09, 128.77, 128.61, 128.56, 128.48, 128.45, 128.40, 127.96, 126.31], 71.5, 68.0, 41.1.

(*S*)-4-benzyl-2-(2-(diphenylphosphaneyl)-6-methylphenyl)-4,5-dihydrooxazole (L25)



Prepared from (*S*)-4-benzyl-2-(2-bromo-6-methylphenyl)-4,5-dihydrooxazole **275b** (991 mg, 3.0 mmol, 1.0 equiv) and diphenylphosphine (940 μL, 1.00 g, 5.4 mmol, 1.8 equiv) following General Procedure 2. The reaction stirred overnight for 24 hours. The crude residue was purified by column chromatography (silica, 0 to 3% Et_2O/DCM) under a flow of N_2 to yield 834 mg (64% yield) of **L25** as a sticky white solid. $[\boldsymbol{a}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +8° (c = 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.42 – 7.30 (m, 10H), 7.30 – 7.24 (m, 2H), 7.24 – 7.12 (m, 5H), 6.88 – 6.79 (m, 1H), 4.47 (ddddd, *J* = 9.4, 8.5, 7.5, 5.7, 0.9 Hz, 1H), 4.10 (dd, *J* = 9.4, 8.4 Hz, 1H), 3.95 (dd, *J* = 8.4, 7.5 Hz, 1H), 3.16 (dd, *J* = 13.8, 5.7 Hz, 1H), 2.65 (dd, *J* = 13.8, 8.6 Hz, 1H), 2.37 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 163.8 (d, $J_{C\text{-}P}$ = 2.5 Hz), [Ar region: 138.45, 137.73, 137.57, 137.55, 137.50, 137.43, 137.40, 137.29, 134.60, 134.32, 134.11, 134.05, 133.91, 133.85, 131.30, 130.72, 129.63, 129.29, 128.71, 128.60, 128.56, 128.49, 126.44], 71.6, 68.5, 41.7, 20.0 (d, $J_{C\text{-}P}$ = 1.6 Hz).

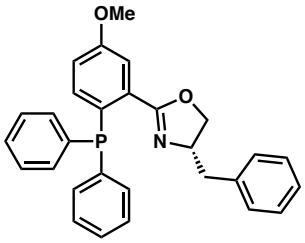
(*S*)-4-benzyl-2-(2-(diphenylphosphaneyl)-6-fluorophenyl)-4,5-dihydrooxazole (L26)



Prepared from (*S*)-4-benzyl-2-(2-bromo-6-fluorophenyl)-4,5-dihydrooxazole **275c** (1.00 g, 3.0 mmol, 1.0 equiv) and diphenylphosphine (522 μL, 559 mg, 3.0 mmol, 1.0 equiv) following General Procedure 2. The reaction stirred overnight for 12 hours. The crude

residue was purified by column chromatography (silica, 5 to 15% EtOAc/hexane) under a flow of N_2 to yield 840 mg (64% yield) of **L26** as a white solid. $[\boldsymbol{a}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +20° (c = 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.40 – 7.33 (m, 10H), 7.31 – 7.24 (m, 3H), 7.23 – 7.17 (m, 1H), 7.16 – 7.12 (m, 2H), 7.09 (ddt, *J* = 9.3, 8.4, 0.9 Hz, 1H), 6.71 (ddd, *J* = 7.7, 3.7, 1.1 Hz, 1H), 4.38 (tdd, *J* = 9.2, 7.7, 5.5 Hz, 1H), 4.02 (dd, *J* = 9.4, 8.4 Hz, 1H), 3.82 (dd, *J* = 8.4, 7.7 Hz, 1H), 3.09 (dd, *J* = 13.8, 5.5 Hz, 1H), 2.38 (dd, *J* = 13.8, 9.0 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 159.9, [Ar region: 162.37, 162.30, 159.84, 159.77, 141.48, 141.25, 138.25, 136.72, 136.65, 136.60, 136.54, 134.35, 134.32, 134.14, 134.12, 131.48, 131.40, 129.21, 129.18, 129.15, 129.13, 129.12, 129.10, 128.78, 128.76, 128.70, 128.69, 128.62, 126.48, 121.71, 121.57, 121.46, 121.32, 116.21, 115.99], 71.8, 68.3, 41.4.

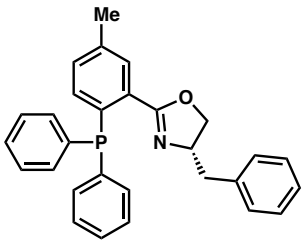
(*S*)-4-benzyl-2-(2-(diphenylphosphaneyl)-5-methoxyphenyl)-4,5-dihydrooxazole (L27)



Prepared from (*S*)-4-benzyl-2-(2-bromo-5-methoxyphenyl)-4,5-dihydrooxazole **275d** (1.04 g, 3.0 mmol, 1.0 equiv) and diphenylphosphine (940 μL, 1.00 g, 5.4 mmol, 1.8 equiv) following General Procedure 2. The reaction stirred overnight for 24 hours. The crude residue was purified by column chromatography (silica, 0 to 3% Et_2O/DCM) under a flow of N_2 to yield 579 mg (43% yield) of **L27** as a sticky white solid. $[\boldsymbol{a}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +28° (c = 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.43 (t, *J* = 2.9 Hz, 1H), 7.39 – 7.29 (m, 10H), 7.29 – 7.23 (m, 2H), 7.23 – 7.16 (m, 1H), 7.11 – 7.06 (m, 2H), 6.86 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.79 (dd, *J* = 8.6, 3.9 Hz, 1H), 4.40 (tdd, *J* = 9.2, 7.4, 5.1 Hz, 1H), 4.09 (dd, *J* = 9.3, 8.4 Hz, 1H), 3.88 – 3.79 (m, 4H), 2.95 (dd, *J* = 13.8, 5.1 Hz, 1H),

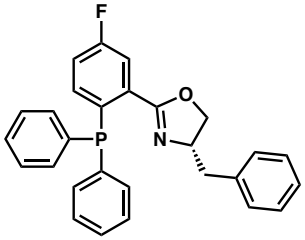
2.19 (dd, *J* = 13.8, 9.1 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 163.9 (d, J_{C-P} = 2.6 Hz), [Ar region: 159.52, 138.58, 138.54, 138.46, 138.44, 138.26, 135.36, 135.34, 134.44, 134.23, 133.92, 133.72, 133.30, 133.09, 129.61, 129.39, 129.24, 128.70, 128.60, 128.55, 128.53, 128.51, 128.44, 126.43, 116.99, 115.06, 115.03], 71.7, 68.1, 55.5, 41.3.

(*S*)-4-benzyl-2-(2-(diphenylphosphaneyl)-5-methylphenyl)-4,5-dihydrooxazole (L28)



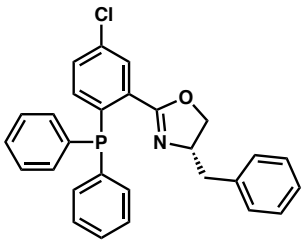
Prepared from (*S*)-4-benzyl-2-(2-bromo-5-methylphenyl)-4,5-dihydrooxazole **275e** (991 mg, 3.0 mmol, 1.0 equiv) and diphenylphosphine (940 μL, 1.00 g, 5.4 mmol, 1.8 equiv) following General Procedure 2. The reaction stirred overnight for 19 hours. The crude residue was purified by column chromatography (silica, 0 to 3% Et_2O/DCM) under a flow of N_2 to yield 416 mg (32% yield) of **L28** as a white solid. $[\boldsymbol{\alpha}]_D^{25}$ = +38° (c = 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.76 – 7.69 (m, 1H), 7.41 – 7.29 (m, 10H), 7.29 – 7.22 (m, 2H), 7.22 – 7.15 (m, 1H), 7.14 – 7.10 (m, 1H), 7.10 – 7.05 (m, 2H), 6.76 (dd, *J* = 7.9, 4.3 Hz, 1H), 4.36 (tdd, *J* = 9.3, 7.5, 5.1 Hz, 1H), 4.04 (dd, *J* = 9.3, 8.4 Hz, 1H), 3.77 (dd, *J* = 8.4, 7.5 Hz, 1H), 2.95 (dd, *J* = 13.8, 5.0 Hz, 1H), 2.36 (s, 3H), 2.11 (dd, *J* = 13.8, 9.3 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 164.3 (d, J_{C-P} = 2.8 Hz), [Ar region: 138.32, 138.30, 138.23, 138.18, 138.16, 138.13, 135.45, 135.22, 134.55, 134.34, 134.08, 133.88, 133.79, 133.77, 131.66, 131.51, 131.47, 130.81, 130.78, 129.20, 128.79, 128.65, 128.63, 128.57, 128.55, 128.47, 126.42], 71.6, 68.0, 41.3, 21.0.

(*S*)-4-benzyl-2-(2-(diphenylphosphaneyl)-5-fluorophenyl)-4,5-dihydrooxazole (L29)



Prepared from (*S*)-4-benzyl-2-(2-bromo-5-fluorophenyl)-4,5-dihydrooxazole **275f** (1.00 g, 3.0 mmol, 1 equiv) and diphenylphosphine (522 μL, 559 mg, 3.0 mmol, 1.0 equiv) following General Procedure 2. The reaction stirred overnight for 12 hours. The crude residue was purified by column chromatography (silica, 5 to 15% EtOAc/hexane) under a flow of N_2 to yield 860 mg (65% yield) of **L29** as a sticky colorless semi-solid. $[\boldsymbol{a}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +21° (c = 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.60 (dt, *J* = 9.5, 2.8 Hz, 1H), 7.40 – 7.29 (m, 10H), 7.29 – 7.23 (m, 2H), 7.23 – 7.17 (m, 1H), 7.10 – 7.05 (m, 2H), 7.01 (td, *J* = 8.3, 2.8 Hz, 1H), 6.85 (ddd, *J* = 8.7, 5.9, 3.7 Hz, 1H), 4.40 (tdd, *J* = 9.2, 7.4, 5.2 Hz, 1H), 4.08 (dd, *J* = 9.3, 8.4 Hz, 1H), 3.82 (dd, *J* = 8.4, 7.5 Hz, 1H), 2.91 (dd, *J* = 13.8, 5.2 Hz, 1H), 2.16 (dd, *J* = 13.9, 8.9 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 162.8 (dd, $J_{C\text{-}P}$ = 3.0 Hz, $J_{C\text{-}F}$ = 3.0 Hz), [Ar region: 163.71, 161.23, 138.10, 137.97, 137.94, 137.84, 135.90, 135.88, 135.82, 135.80, 134.75, 134.71, 134.54, 134.49, 134.45, 134.33, 133.93, 133.75, 133.73, 133.67, 133.55, 133.48, 129.22, 128.98, 128.80, 128.75, 128.68, 128.66, 128.59, 126.50, 117.75, 117.55, 117.39, 117.36, 117.16, 117.13], 71.7, 68.2, 41.2.

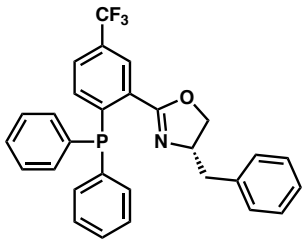
(*S*)-4-benzyl-2-(5-chloro-2-(diphenylphosphaneyl)phenyl)-4,5-dihydrooxazole (L30)



Prepared from (*S*)-4-benzyl-2-(2-bromo-5-chlorophenyl)-4,5-dihydrooxazole **275g** (1.05 g, 3.0 mmol, 1.0 equiv) and diphenylphosphine (522 μL, 559 mg, 3.0 mmol, 1.0 equiv) following General Procedure 2. The reaction stirred overnight

for 12 hours. The crude residue was purified by column chromatography (silica, 5 to 15% EtOAc/hexane) under a flow of N_2 to yield 621 mg (45% yield) of **L30** as a white solid. $[\alpha]_D^{25}$ = +27° (c = 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.88 (dd, *J* = 3.1, 2.3 Hz, 1H), 7.41 – 7.29 (m, 10H), 7.29 – 7.23 (m, 3H), 7.23 – 7.16 (m, 1H), 7.10 – 7.04 (m, 2H), 6.79 (dd, *J* = 8.4, 3.8 Hz, 1H), 4.37 (tdd, *J* = 9.2, 7.5, 5.1 Hz, 1H), 4.06 (dd, *J* = 9.3, 8.4 Hz, 1H), 3.79 (dd, *J* = 8.4, 7.5 Hz, 1H), 2.90 (dd, *J* = 13.9, 5.2 Hz, 1H), 2.12 (dd, *J* = 13.9, 9.1 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 162.8 (d, *J* = 3.3 Hz), [Ar region: 138.08, 137.88, 137.63, 137.61, 137.59, 137.51, 137.49, 135.12, 135.09, 134.59, 134.40, 134.37, 134.01, 133.80, 133.11, 132.93, 130.59, 130.04, 130.01, 129.20, 129.09, 128.91, 128.79, 128.72, 128.64, 128.60, 126.51], 71.8, 68.2, 41.2.

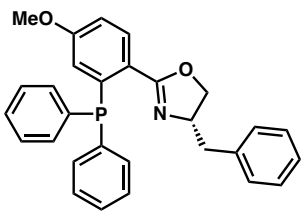
(*S*)-4-benzyl-2-(2-(diphenylphosphaneyl)-5-(trifluoromethyl)phenyl)-4,5-dihydro-oxazole (L31)



Prepared from (*S*)-4-benzyl-2-(2-bromo-5-(trifluoromethyl)-phenyl)-4,5-dihydrooxazole **275h** (1.15 g, 3.0 mmol, 1.0 equiv) and diphenylphosphine (940 μL, 1.00 g, 5.4 mmol, 1.8 equiv) following General Procedure 2. The reaction stirred overnight for 19 hours. The crude residue was purified by column chromatography (silica, 0 to 3% Et_2O/DCM) under a flow of N_2 to yield 457 mg (31% yield) of **L31** as a sticky white solid. $[\alpha]_D^{25}$ = +27° (c = 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.13 (t, *J* = 2.6 Hz, 1H), 7.52 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.43 – 7.30 (m, 10H), 7.30 – 7.23 (m, 2H), 7.23 – 7.17 (m, 1H), 7.10 – 7.04 (m, 2H), 6.99 (dd, *J* = 8.2, 3.8 Hz, 1H), 4.37 (tdd, *J* = 9.2, 7.5, 5.1 Hz,

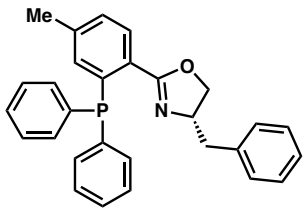
1H), 4.06 (dd, *J* = 9.3, 8.5 Hz, 1H), 3.80 (dd, *J* = 8.5, 7.5 Hz, 1H), 2.91 (dd, *J* = 13.8, 5.1 Hz, 1H), 2.09 (dd, *J* = 13.9, 9.1 Hz, 1H).

(*S*)-4-benzyl-2-(2-(diphenylphosphaneyl)-4-methoxyphenyl)-4,5-dihydrooxazole (L32)



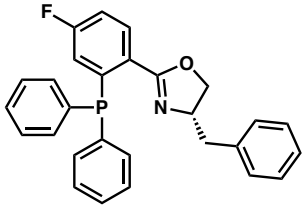
Prepared from (*S*)-4-benzyl-2-(2-bromo-4-methoxyphenyl)-4,5-dihydrooxazole **275i** (1.04 g, 3.0 mmol, 1.0 equiv) and diphenylphosphine (940 μL, 1.00 g, 5.4 mmol, 1.8 equiv) following General Procedure 2. The reaction stirred overnight for 19 hours. The crude residue was purified by column chromatography (silica, 0 to 5% Et_2O/DCM) under a flow of N_2 to yield 1055 mg (78% yield) of **L32** as a sticky white solid. $[\alpha]_D^{25}$ = +45° (c = 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.87 (dd, *J* = 8.6, 3.8 Hz, 1H), 7.40 – 7.30 (m, 10H), 7.28 – 7.22 (m, 2H), 7.22 – 7.15 (m, 1H), 7.09 – 7.03 (m, 2H), 6.85 (ddd, *J* = 8.6, 2.7, 0.6 Hz, 1H), 6.36 (dd, *J* = 4.4, 2.6 Hz, 1H), 4.33 (tdd, *J* = 9.3, 7.3, 5.0 Hz, 1H), 4.00 (dd, *J* = 9.2, 8.4 Hz, 1H), 3.73 (dd, *J* = 8.4, 7.3 Hz, 1H), 3.60 (s, 3H), 2.88 (dd, *J* = 13.8, 5.0 Hz, 1H), 2.03 (dd, *J* = 13.8, 9.4 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 163.6 (d, J_{C-P} = 3.6 Hz), [Ar region: 161.03, 141.48, 141.21, 138.44, 138.06, 138.01, 137.93, 137.91, 134.76, 134.54, 134.05, 133.84, 131.89, 131.86, 129.19, 128.96, 128.73, 128.67, 128.60, 128.57, 128.54, 128.50, 126.37, 123.84, 123.68, 119.74, 119.70, 112.78], 71.3, 68.0, 55.1, 41.3.

(*S*)-4-benzyl-2-(2-(diphenylphosphaneyl)-4-methylphenyl)-4,5-dihydrooxazole (L33)



Prepared from (*S*)-4-benzyl-2-(2-bromo-4-methylphenyl)-4,5-dihydrooxazol **275j** (1.09 g, 3.0 mmol, 1.0 equiv) and diphenylphosphine (940 μL, 1.00 g, 5.4 mmol, 1.8 equiv) following General Procedure 2. The reaction stirred overnight for 24 hours. The crude residue was purified by column chromatography (silica, 0 to 3% Et_2O/DCM) under a flow of N_2 to yield 1088 mg (83% yield) of **L33** as a white solid. $[\alpha]_D^{25}$ = +35° (c = 1.0, $CHCl_3$) **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.78 (dd, *J* = 7.8, 3.7 Hz, 1H), 7.41 – 7.29 (m, 10H), 7.29 – 7.22 (m, 2H), 7.22 – 7.14 (m, 2H), 7.10 – 7.04 (m, 2H), 6.65 (dd, *J* = 4.7, 1.7 Hz, 1H), 4.34 (tdd, *J* = 9.3, 7.4, 5.0 Hz, 1H), 4.01 (dd, *J* = 9.3, 8.4 Hz, 1H), 3.75 (dd, *J* = 8.4, 7.4 Hz, 1H), 2.91 (dd, *J* = 13.8, 5.0 Hz, 1H), 2.20 (s, 3H), 2.07 (dd, *J* = 13.8, 9.3 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 164.03 (d, $J_{C\text{-}P}$ = 3.0 Hz), [Ar region: 140.75, 138.91, 138.66, 138.39, 138.19, 138.18, 138.08, 138.07, 134.69, 134.48, 134.28, 134.26, 134.08, 133.88, 130.12, 130.10, 129.21, 128.88, 128.84, 128.82, 128.70, 128.65, 128.62, 128.55, 128.47, 126.39], 71.5, 68.0, 41.3, 21.8.

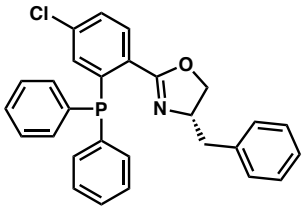
(*S*)-4-benzyl-2-(2-(diphenylphosphaneyl)-4-fluorophenyl)-4,5-dihydrooxazole (L34)



Prepared from (S)-4-benzyl-2-(2-bromo-4-fluorophenyl)-4,5-dihydrooxazole **275k** (1.00 g, 3.0 mmol, 1.0 equiv) and diphenylphosphine (522 μL, 559 mg, 3.0 mmol, 1.0 equiv) following General Procedure 2. The reaction stirred overnight for 13 hours. The crude residue was purified by column chromatography (silica, 5 to 15% EtOAc/hexane) under a

flow of N_2 to yield 515 mg (39% yield) of **L34** as a sticky colorless semi-solid. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +29° (c = 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.89 (ddd, *J* = 8.6, 5.7, 3.6 Hz, 1H), 7.42 – 7.30 (m, 10H), 7.30 – 7.23 (m, 2H), 7.23 – 7.17 (m, 1H), 7.10 – 7.05 (m, 2H), 7.05 – 6.99 (m, 1H), 6.55 (ddd, *J* = 9.8, 3.5, 2.6 Hz, 1H), 4.35 (tdd, *J* = 9.2, 7.4, 5.1 Hz, 1H), 4.03 (dd, *J* = 9.3, 8.4 Hz, 1H), 3.76 (dd, *J* = 8.4, 7.4 Hz, 1H), 2.89 (dd, *J* = 13.8, 5.1 Hz, 1H), 2.08 (dd, *J* = 13.8, 9.2 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 163.0 ($J_{C\text{-}P}$, *J* = 3.5 Hz), [Ar region: 165.14, 162.62, 143.29, 143.23, 143.00, 142.94, 138.21, 137.37, 137.36, 137.26, 137.25, 134.66, 134.45, 134.04, 133.83, 132.37, 132.35, 132.29, 132.26, 129.22, 129.19, 129.00, 128.85, 128.77, 128.75, 128.68, 128.57, 127.59, 127.56, 127.42, 127.39, 126.46, 120.72, 120.69, 120.49, 120.46, 115.11, 114.89], 71.6, 68.1, 41.2.

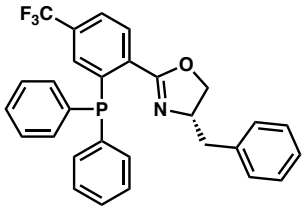
(*S*)-4-benzyl-2-(4-chloro-2-(diphenylphosphaneyl)phenyl)-4,5-dihydrooxazole (L35)



Prepared from (*S*)-4-benzyl-2-(2-bromo-4-chlorophenyl)-4,5-dihydrooxazole **275l** (1.05 g, 3.0 mmol, 1.0 equiv) and diphenylphosphine (522 μL, 559 mg, 3.0 mmol, 1.0 equiv) following General Procedure 2. The reaction stirred overnight for 18 hours. The crude residue was purified by column chromatography (silica, 5 to 15% EtOAc/hexane) under a flow of N_2 to yield 742 mg (54% yield) of **L35** as a white solid. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +40° (c = 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.81 (dd, *J* = 8.3, 3.5 Hz, 1H), 7.41 – 7.30 (m, 11H), 7.26 (tt, *J* = 6.6, 1.1 Hz, 2H), 7.22 – 7.16 (m, 1H), 7.09 – 7.03 (m, 2H), 6.80 (dd, *J* = 3.5, 2.1 Hz, 1H), 4.35 (tdd, *J* = 9.2, 7.4, 5.1 Hz, 1H), 4.03 (dd, *J* = 9.3, 8.4 Hz, 1H), 3.77 (dd, *J* = 8.4, 7.5 Hz, 1H), 2.89 (dd, *J* = 13.8, 5.1 Hz, 1H), 2.09 (dd, *J* = 13.9, 9.1 Hz, 1H).

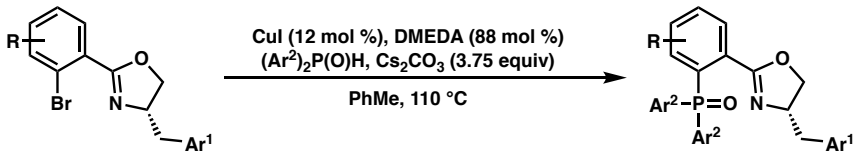
^{13}C NMR (101 MHz, $CDCl_3$): δ 163.08 (d, J_{C-P} = 3.4 Hz), [Ar region: 142.14, 141.84, 138.14, 137.26, 137.16, 137.13, 134.65, 134.44, 134.05, 133.84, 133.37, 133.34, 131.43, 131.40, 129.88, 129.71, 129.25, 129.20, 129.04, 128.86, 128.79, 128.77, 128.69, 128.59, 128.19, 128.18, 126.49], 71.6, 68.1, 41.2.

(*S*)-4-benzyl-2-(2-(diphenylphosphaneyl)-4-(trifluoromethyl)phenyl)-4,5-dihydro-oxazole (L36)



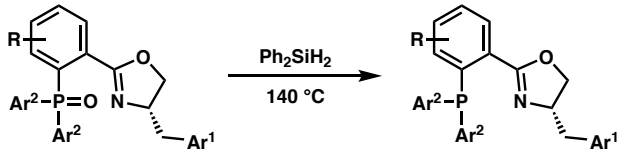
Prepared from (*S*)-4-benzyl-2-(2-bromo-4-(trifluoromethyl)-phenyl)-4,5-dihydrooxazole **275m** (1.15 g, 3.0 mmol, 1.0 equiv) and diphenylphosphine (940 μL, 1.00 g, 5.4 mmol, 1.8 equiv) following General Procedure 2. The reaction stirred overnight for 19 hours. The crude residue was purified by column chromatography (silica, 0 to 2% Et_2O/DCM) under a flow of N_2 to yield 602 mg (41% yield) of **L36** as a faint yellow oil. $[\alpha]_D^{25}$ = +24° (c = 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.97 (dd, *J* = 8.1, 3.3 Hz, 1H), 7.60 (ddt, *J* = 8.1, 1.7, 0.8 Hz, 1H), 7.44 – 7.30 (m, 10H), 7.30 – 7.23 (m, 2H), 7.23 – 7.17 (m, 1H), 7.13 – 7.09 (m, 1H), 7.09 – 7.05 (m, 2H), 4.38 (tdd, *J* = 9.2, 7.5, 5.2 Hz, 1H), 4.06 (dd, *J* = 9.4, 8.5 Hz, 1H), 3.80 (dd, *J* = 8.5, 7.5 Hz, 1H), 2.91 (dd, *J* = 13.8, 5.2 Hz, 1H), 2.12 (dd, *J* = 13.9, 9.1 Hz, 1H).

General Procedure 3: Ullman Coupling with Phosphine Oxide



The following procedure was conducted under an N_2 atmosphere in a glovebox. The CuI (74 mg, 0.39 mmol, 0.13 equiv) was added to a 150 mL heavy wall pressure flask equipped with a stir bar and dissolved in 20 mL of anhydrous toluene. The DMEDA (375 μL, 2.64 mmol, 0.88 equiv) and diarylphosphine oxide (1.8 mmol, 1.8 equiv) was added and stirred for 10 minutes. The Cs_2CO_3 (3.66 g, 11.25 mmol, 3.75 equiv) was added, followed by the aryl bromide (1 mmol, 1.0 equiv) dissolved in 10 mL of toluene. The flask was sealed with a screw cap fitted with a viton o-ring, removed from the glovebox, and stirred overnight at 110 °C. The reaction was then cooled to room temperature and filtered over a pad of celite, eluting with CH_2Cl_2. The crude mixture was concentrated under reduced pressure and purified by column chromatography to afford the desired product.

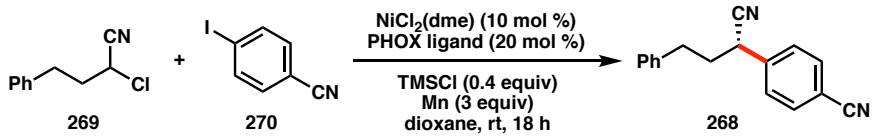
General Procedure 4: Phosphine Oxide Reduction



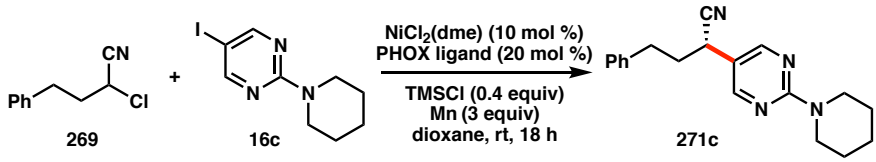
On a bench-top, the tertiary phosphine oxide (1.0–1.8 mmol, 1.0 equiv) was added to a 2-dram vial and equipped with a stir bar. The vial was then brought into the glovebox and diphenylsilane (7.0–12.60 mmol, 7.0 equiv) was added. The vial was sealed with a Teflon cap and electrical tape and brought out of the box. The reaction mixture was then added to an oil bath preheated to 140 ºC and stirred for 48 hours. After completion of the reaction, the vial cap was removed and replaced with a rubber septum. The oil bath was cooled to 65 ºC and the vial was placed under high vacuum and stirred overnight. The crude mixture was then further purified by column chromatography under a flow of Argon to afford the

desired product in the third fraction. Eluents for chromatography were sparged with argon for 3 hours prior to purification.

A8.5.3 Cross-Coupling Reactions



On a bench-top, the phosphine ligand (0.04 mmol, 0.2 equiv), manganese (0.6 mmol, 3 equiv), and aryl iodide **270** (0.2 mmol, 1 equiv) were added to a 1 dram vial equipped with a stir bar. The vial was then brought into the glovebox and sequentially charged with $NiCl_2$(dme) (0.01 mmol, 0.1 equiv), dioxane (0.35 mL), α-chloronitrile **269** (0.2 mmol, 1 equiv), benzyl ether internal standard, and TMSCl (0.08 mmol, 0.4 equiv). The vial was sealed with a Teflon cap and stirred at 700 rpm for 18 hours. The reaction was then dissolved in 20% EtOAc/hexane, loaded onto a silica plug, and flushed through with additional 20% EtOAc/hexane. The samples were concentrated to obtain yield by ^{1}H NMR spectroscopy. The crude samples were then purified by preparatory TLC and analyzed by chiral SFC in order to obtain the enantioselectivity of the product.



On a bench-top manganese (0.6 mmol, 3 equiv), and aryl iodide **16c** (0.2 mmol, 1 equiv) were added to a 1 dram vial equipped with a stir bar. The phosphine ligand (0.04 mmol,

0.2 equiv) was added to a separate 1 dram vial with a stir bar. The vials were then brought into the glovebox where $NiCl_2$(dme) (0.01 mmol, 0.1 equiv) was added to the vial containing the phosphine ligand. Then dioxane (0.35 mL) was added to the vial containing the catalyst and was stirred for 10 minutes to allow for complexation. The solution was then transferred to the vial containing manganese and the aryl iodide followed by α-chloronitrile **271c** (0.2 mmol, 1 equiv), benzyl ether internal standard, and TMSCl (0.08 mmol, 0.4 equiv). The vial was sealed with a Teflon cap and stirred at 1000 rpm for 18 hours. The reaction was then dissolved in 30% EtOAc/hexane, loaded onto a silica plug, and flushed through with additional 30% EtOAc/hexane. The samples were concentrated to obtain yield by ^{1}H NMR spectroscopy. The crude samples were then purified by preparatory TLC and analyzed by chiral SFC in order to obtain the enantioselectivity of the product.

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