Chapter 4

Nickel-Catalyzed Asymmetric Reductive Cross-Coupling to Access 1,1-Di(hetero)arylalkanes◊

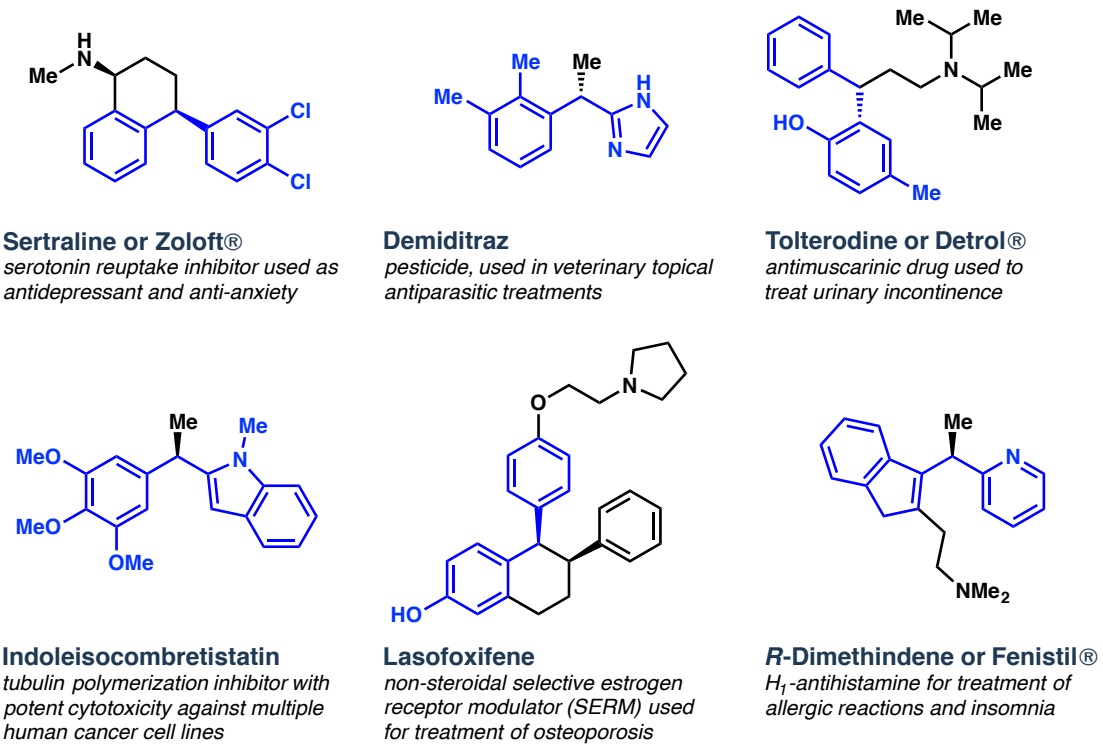
4.1 INTRODUCTION

4.1.1 Background and catalytic asymmetric approaches

1,1-Diarylalkanes are a common pharmacophore, present in biologically active natural products as well as marketed drugs for a diverse range of indications (**Figure 1**). In many cases, these bioactive molecules exhibit a substantial eudysmic ratio, in which one enantiomer is significantly more potent than the other.[1] As such, methods for the enantioselective preparation of diarylalkanes have become a proving ground in asymmetric catalysis, with methods to afford these products being reported by many synthetic laboratories.[2]

◊ Portions of this chapter have been reproduced from a manuscript in preparation and the supporting information found therein. This work was conducted with Kelsey Poremba, a graduate student in the Reisman lab. Preliminary investigations discussed herein were conducted by Dr. Alan H. Cherney, then a graduate student in the Reisman lab.

***Figure 4.1**. Selected bioactive chiral 1,1-diarylalkanes.*



Sertraline or Zoloft®
serotonin reuptake inhibitor used as antidepressant and anti-anxiety

Demiditraz
pesticide, used in veterinary topical antiparasitic treatments

Tolterodine or Detrol®
antimuscarinic drug used to treat urinary incontinence

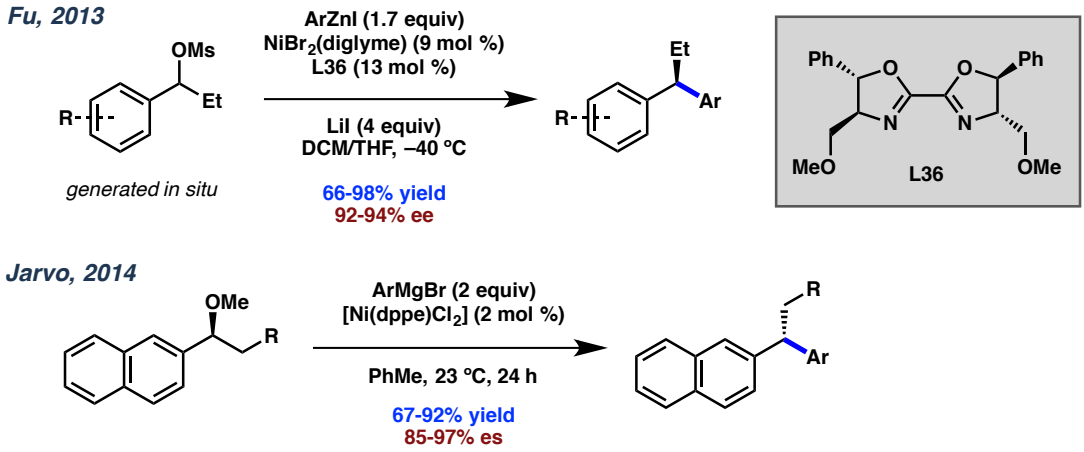
Indoleisocombretistatin
tubulin polymerization inhibitor with potent cytotoxicity against multiple human cancer cell lines

Lasofoxifene
non-steroidal selective estrogen receptor modulator (SERM) used for treatment of osteoporosis

***R*-Dimethindene or Fenistil®**
H_1-antihistamine for treatment of allergic reactions and insomnia

The pseudosymmetry of these molecules makes them particularly appealing targets for cross-coupling. Many methods employing asymmetric hydrogenation of 1,1-diarylethenes have been reported, affording the corresponding diarylalkanes in excellent ee.[3] However, these require a proximal desymmetrizing or directing group on one of the aryl rings to enable facial differentiation by the catalyst, greatly limiting the accessible product scope of these technologies. A cross-coupling disconnection circumvents this issue, accessing the product convergently from a C(sp^3) benzyl fragment and a C(sp^2) aryl partner. In redox-neutral couplings, one of these is a halide electrophile, while the other is some organometallic nucleophile, with both stereoconvergent[2d] and stereospecific[4] methods having been reported (**Scheme 4.1**).[2j] This disconnection also lends itself to reductive cross-coupling logic, with the two electrophilic fragments being differentiable by hybridization.

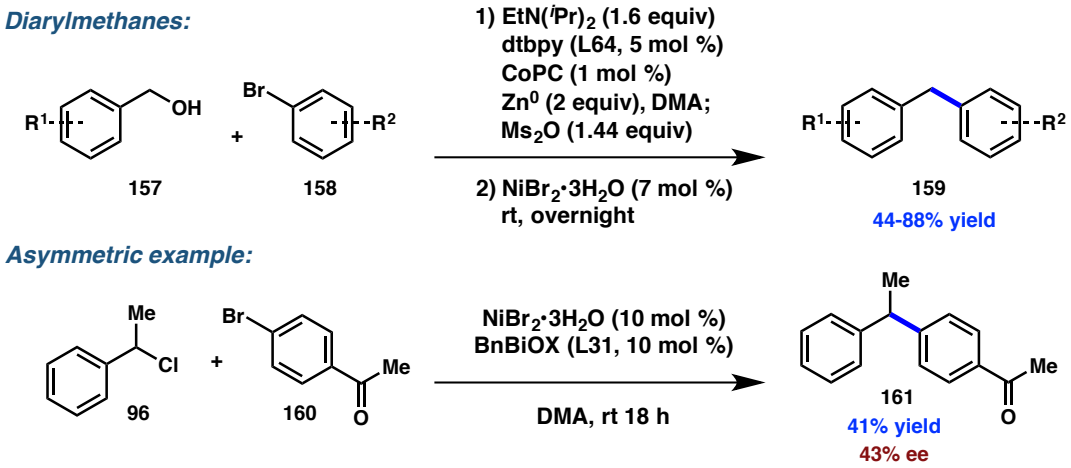
Scheme 4.1. *Selected recent asymmetric cross-couplings to access 1,1-diarylalkanes.*



4.1.2 Reductive cross-coupling approaches and preliminary investigations

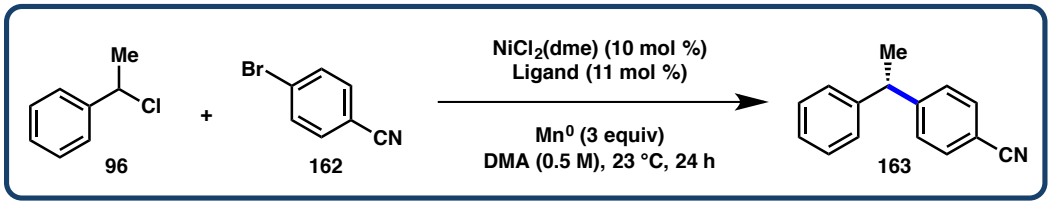
A racemic reductive cross-coupling strategy to access 1,1-diarylalkanes was first reported by Weix and coworkers in 2015, with the majority of the products disclosed being achiral diarylmethanes.[5] Employing benzylic alcohols, *in situ* mesylate formation generates the active C(sp^3) electrophile, which undergoes chemoselective Ni-catalyzed reductive coupling with aryl halide partners (**Scheme 4.2**). Interestingly, the authors report a single example of an asymmetric coupling, which requires the benzylic chloride substrate **96** to achieve modest enantioinduction, employing BnBiOX (**L31**) as the chiral ligand.[2k]

***Scheme 4.2**. Weix's reductive cross-couplings to access 1,1-diarylalkanes.*

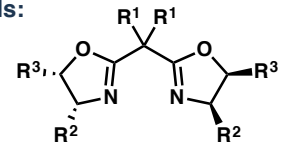


Concurrent with these efforts by the Weix group, our laboratory also investigated formation of these products as a platform for asymmetric catalysis development.[6] The earliest of these efforts employed conditions derived from the racemic couplings reported in the literature, similar to those described in **Chapter 2**. Employing amide solvents and an array of chiral ligands, the cross-coupling of 4-bromobenzonitrile (**162**) and 1-(chloroethyl)benzene (**96**) was targeted (**Table 4.1**). Unfortunately, these reactions were plagued with poor chemoselectivity, delivering homocoupled dimers of both substrates; however modest enantioselectivities were observed with both BOX and BiOX ligand scaffolds, suggesting promise for this enantioconvergent transformation. Further optimization identified NMP as an improved solvent at this stage, which afforded **163** in 62% yield and 37% ee when employing BnBiOX (**L31**), the best result achieved with this system.

***Table 4.1**. Initial ligand investigation with 4-bromobenzonitrile (**162**).*

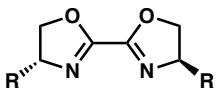


BOX Ligands:



Entry	R^1	R^2	R^3	% ee 163
L62	Me	^{i}Pr	H	19
L61	Me	^{t}Bu	H	0
L63	Me	Bn	H	1
L32	Me	Ph	H	49
L59	Me	Ph	Ph	14
L57	H	Ph	Ph	11
L56	H	Ph	H	1
L107	H	^{t}Bu	H	1
L108	H	indanyl		1
L46	Me	indanyl		3
L109	-CH_2CH_2-	indanyl		7

BiOX Ligands:

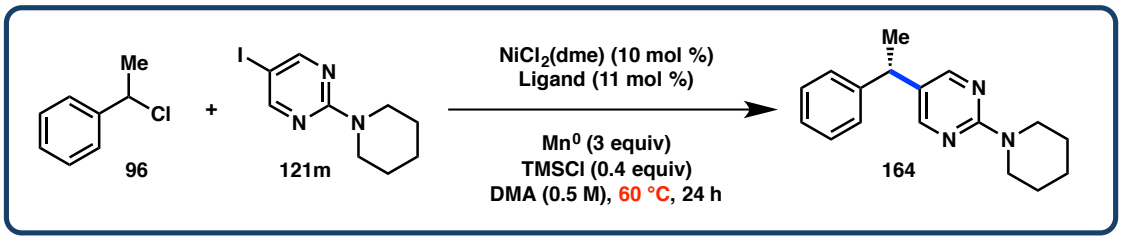


Entry	R	% ee 163
L67	^{i}Pr	24
L66	^{t}Bu	8
L31	Bn	33
L68	Ph	1
L110	Cy	25
L111	^{s}Bu	23
L112	$CHPh_2$	3
L113	CH_2(1-naph)	20
L114	CH_2(2-naph)	29

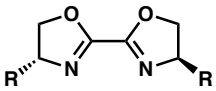
These initial efforts were suspended until the discovery of the conditions described in **Chapter 3**. Following the development of the cross-coupling described therein, we returned to this reaction and applied these new conditions in a follow-up ligand screen, now employing heteroaryl iodide **121m** (**Table 4.2**). We were pleased to observe tolerance for the heteroaryl partner, as well as improved enantioselectivity. Unfortunately, only modest yields were only obtained with heating to 60 ºC. Exploring a range of different ligands for this transformation, including a PHOX series, did not afford improved results or enable the lowering of the reaction temperature. Nonetheless, we felt

that this initial investigation held promise, providing proof-of-concept that the proposed reductive cross-coupling disconnection was amenable to asymmetric catalysis.

Table 4.2. *Initial ligand investigation with 5-iodo-2-(N-piperidinyl)pyrimidine.*



BiOX Ligands



Entry	R	Yield 164 (%)	ee 164 (%)
L67	^{i}Pr	2	26
L66	^{t}Bu	12	7
L31	Bn	43	53
L68	Ph	11	40
L110	Cy	30	55

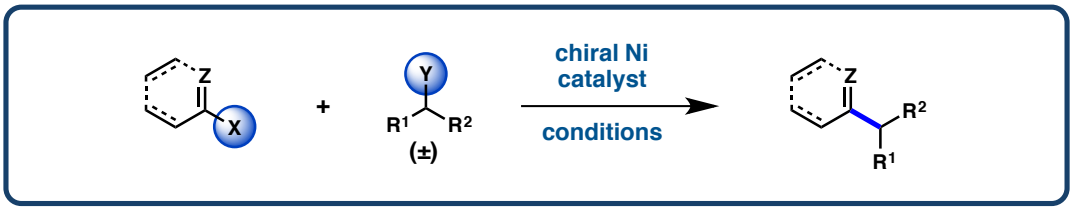
Entry	R	Yield 164 (%)	ee 164 (%)
L111	^{s}Bu	36	65
L112	$CHPh_2$	57	57
L115	^{i}Bu	44	58
L113	CH_2(1-naph)	58	47
L114	CH_2(2-naph)	46	55

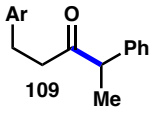
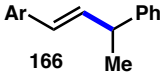
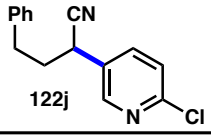
4.1.3 Reaction design: substrate and condition considerations

The cross-coupling of C(sp^3) benzylic halides with C(sp^2) (hetero)aryl halides represents an opportunity to consider the logic of asymmetric cross-coupling and substrate selection. We have demonstrated that each of the substrate classes in **Figure 4.2** is competent in asymmetric cross-electrophile coupling (see Chapters 2 and 3).[7] Therefore, it stands to reason that the stereoconvergent coupling between them should be achievable, as these partners should also be differentiable based on their hybridization.[8] Knowing that the substrates should be amenable and that the coupling was feasible, we imagined the development of this reaction as a venue to survey conditions for their generality: to build on the understanding gained in our previous efforts and to facilitate streamlined optimization in the future. The need for more general asymmetric reductive

coupling conditions is illustrated by **Figure 4.2**. None of our previously optimized conditions were high-performing in any of the other couplings, highlighting the difficulty of extending these conditions to new reaction development between novel electrophiles.

Figure 4.2. *Cross-reactions of previously developed electrophile pairs and conditions.*

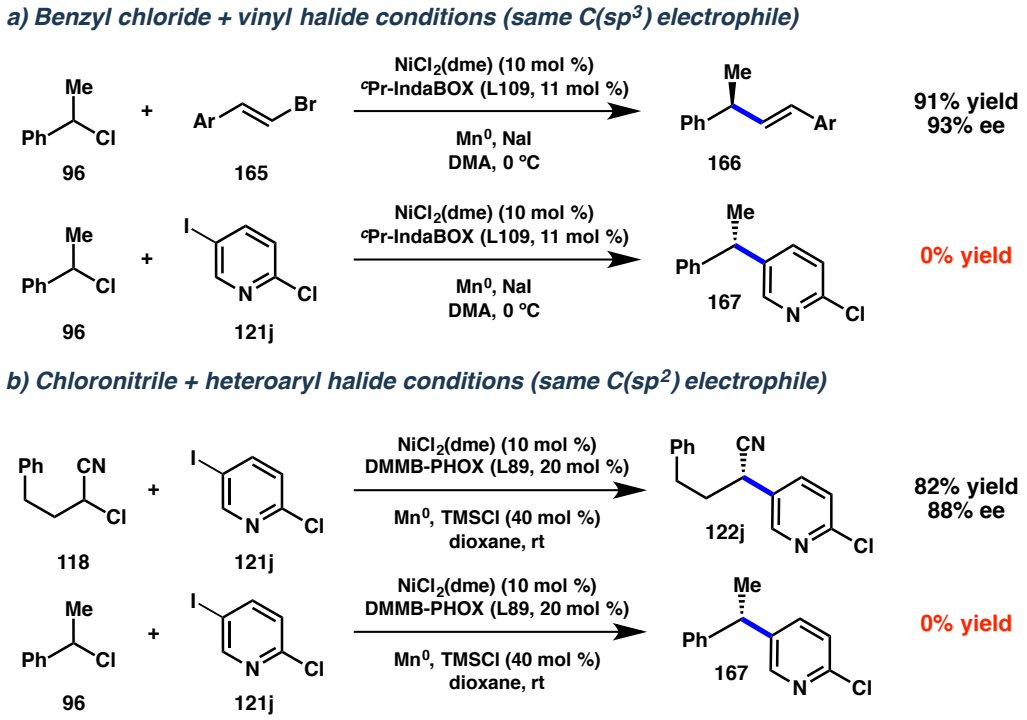


Products / Conditions	 109	 166	 122j
$NiCl_2$(dme), BOX L32 Mn^0, DMBA, 3Å MS DMA/THF, rt	Control 79% yield, 93% ee	41% yield, 2% ee	22% yield, 24% ee
$NiCl_2$(dme), BOX L109 Mn^0, NaI DMA, 0 °C	0% yield	Control 91% yield, 93% ee	0% yield
$NiCl_2$(dme), PHOX L89 Mn^0, TMSCl Dioxane, rt, 18 h	0% yield	0% yield	Control 78% yield, 85% ee

As an initial entrée to this campaign, we selected 2-chloro-5-iodopyridine **121j** as a model heteroaryl partner in the cross-coupling with benzyl chloride **96**. As anticipated based on the results in **Figure 4.2** and the difficulties encountered in our prior efforts, the conditions developed for couplings of these substrates in previous reactions did not afford product in the attempted cross-coupling between them (**Scheme 4.3**). These results serve to illustrate the two-part goal of this new reaction development: a) to develop an asymmetric cross-coupling to access valuable enantioenriched 1,1-diarylalkane products,

and b) to arrive at a more general set of conditions as an entry point for future asymmetric cross-couplings, in the hope of reducing optimization for each new substrate class. Herein we report the successful realization of these goals, with preliminary results toward future couplings being reported in Chapter 5.

Scheme 4.3. *Application of previously developed conditions.*



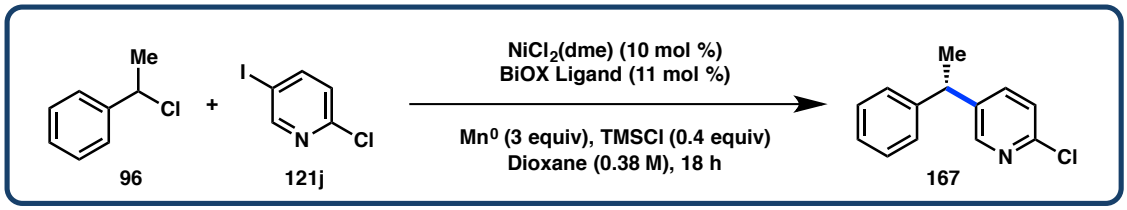
4.2 REACTION DEVELOPMENT

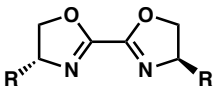
4.2.1 *Ligand exploration and condition optimization*

We began our optimization by considering the results in **Table 4.2**. The reaction conditions employing dioxane as solvent with TMSCl as a surface activator (as in **Chapter 3**) with BiOX ligands gave promising results, but only at elevated temperature. This was surprising, given that both electrophiles have been shown to be reactive under

similar conditions at room temperature. Therefore, we targeted a room temperature reaction, in order to improve enantioselectivity as well as chemoselectivity and yield. Employing the model system described above (**Scheme 4.3**), we conducted parallel ligand screens at 60 ºC, 40 ºC, and room temperature to assess the effect of temperature on this reaction (**Table 4.3**).

Table 4.3. *Screening temperature versus BiOX ligands.*





a) Temperature= 60 °C

Entry	R	Yield (%)	ee (%)
L31	Bn	70	39
L112	$CHPh_2$	53	54
L111	^{s}Bu	31	53
L115	^{i}Bu	68	45
L110	Cy	56	55

b) Temperature= 40 °C

Entry	R	Yield (%)	ee (%)
L31	Bn	61	43
L112	$CHPh_2$	69	66
L111	^{s}Bu	70	54
L115	^{i}Bu	69	62
L110	Cy	65	62

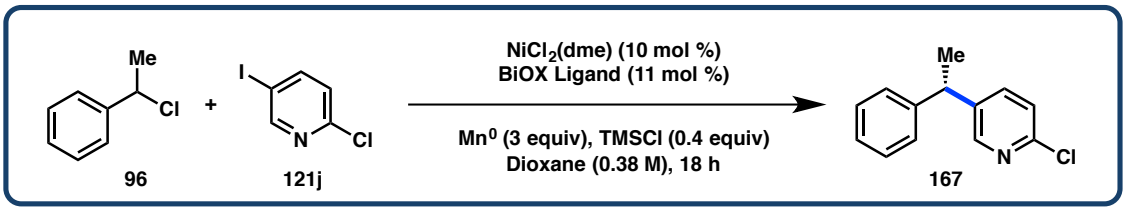
c) Temperature= 23 °C

Entry	R	Yield (%)	ee (%)
L31	Bn	39	44
L112	$CHPh_2$	37	67
L111	^{s}Bu	71	71
L115	^{i}Bu	68	56
L110	Cy	74	70

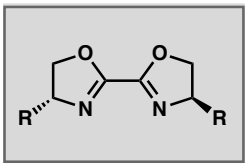
We were pleased to observe improvement with decreasing temperature among several of the ligands screened. Specifically, BiOX ligands bearing branched alkyl substituents (**L110**, **L111**, and **L115**) behaved favorably, giving significantly improved yields and enantioselectivities at room temperature. These ligands afforded a cleaner reaction profile at lower temperature (**Table 4.3c**), giving diminished amounts of homocoupled side products and favoring the desired reaction chemoselectively. Interestingly, BnBiOX **L31** (the ligand employed by Weix and coworkers, **Scheme 4.2**)

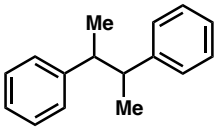
showed the opposite trend, affording **167** in the highest yield at elevated temperature, with only slight variation in ee across temperatures.

Table 4.4. *Evaluation of BiOX ligand scaffolds at room temperature.*



BiOX Ligands





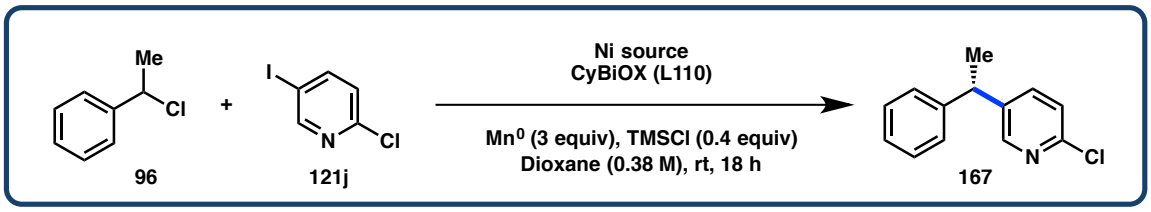
104
rac and meso

Entry	R	Yield BiBn 104 (%)	Yield 167 (%)	ee 167 (%)
L68	Ph	0	0	-
L113	CH_2-1-Nap	3	17	44
L114	CH_2-2-Nap	5	32	50
L116	*c*-Pentyl	15	81	75
L110	Cy	32	68	69
L117	*c*-Heptyl	28	72	75
L118	3-Pentyl	23	65	75
L119	4-Heptyl	16	81	80

We explored these trends further by conducting a wider BiOX ligand screen at room temperature, incorporating branched alkyl ligands, as well as arene-containing R-groups. All of the ligands bearing aryl substituents (**L68**, **L113**, and **L114**) afforded poor yields of product in moderate ee, reaffirming the result obtained with BnBiOX **L31**. Fortunately, the branched alkyl ligands tested all furnished **167** in good ee and high yield. We were particularly delighted to find that 4-HeptylBiOX **L119** gave 81% yield of **167** in 80% ee and with lower levels of homocoupling, the best result obtained by far. The role of these longer alkyl groups remains unclear at this stage. One can imagine the hydrophobic chains simply providing bulkier blocking of the quadrants, providing increased enantioinduction. However, the origin of the effect on chemoselectivity and

yield is less straightforward. Further studies are required to determine if these groups are significantly altering the solvent cage about the catalyst, changing ligand bite angles, or influencing some other mechanistic parameter to produce for the observed effects.

***Table 4.5**. Evaluation of Ni precatalysts, metal/ligand ratio, and catalyst loading.*



with 11 mol % CyBiOX (L110):

Ni Source (10 mol %)	Yield BiBn 104 (%)	Yield 167 (%)	ee 167 (%)
$NiCl_2$(dme)	30	69	69
$Ni(OAc)_2 \cdot 4H_2O$	0	22	72
$Ni(BF_4)_2 \cdot 6H_2O$	5	0	-
$Ni(acac)_2$	30	69	69
$NiBr_2$(dme)	25	74	72
$NiBr_2$(diglyme)	20	81	74

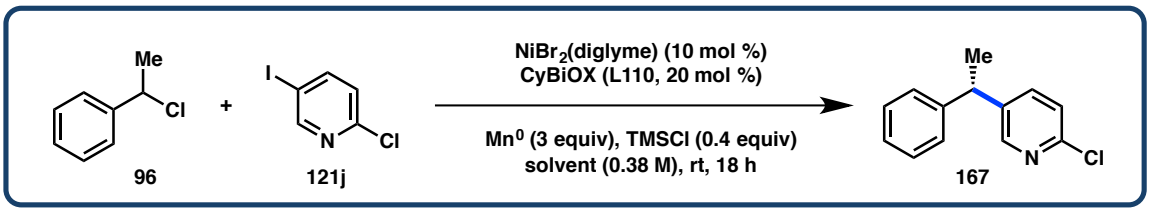
with $NiBr_2$(diglyme):

% Ni	M:L	Yield BiBn 104 (%)	Yield 167 (%)	ee 167 (%)
5%	1:1	15	71	75
5%	1:2	22	77	75
10%	1:1	16	68	74
10%	1:1.5	23	77	72
10%	1:2	25	75	74
10%	1:3	27	78	74
15%	1:1	29	71	71
15%	1:2	29	71	74

With these promising ligand results in hand, we turned our attention to the optimization of the remaining reaction parameters. Because of the synthetic challenge posed by the noncommercial amino acid-derived branched ligands (such as **L119**), we conducted these studies employing CyBiOX **L110**, anticipating that this more easily accessible branched-alkyl ligand would show analogous responses to varying reaction conditions. Beginning with a screen of Ni precatalysts, we were surprised and pleased to see a significant improvement in yield and selectivity upon switching to $NiBr_2$(diglyme), the first time that a Ni source other than $NiCl_2$(dme) has been optimal in our hands (**Table 4.5**). Employing this Ni salt, we conducted a screen of metal/ligand ratios and

catalyst loading. This survey revealed a remarkable tolerance for variability in these parameters. However a catalyst loading of 10 mol % with a 2:1 ligand: metal ratio gave the most reproducible results and was chosen as the standard condition for further studies.

***Table 4.6**. Evaluation of solvents and reaction concentration.*



Solvent	Yield BiBn 104 (%)	Yield 167 (%)	ee 167 (%)
1,4-Dioxane	26	74	74
1,3-Dioxane	0	0	-
THF	51	49	43
DME	41	54	55
DMPU	33	60	49
DMA	72	25	31
MeCN	47	44	6
DCM	50	10	44
MeOH	77	13	73

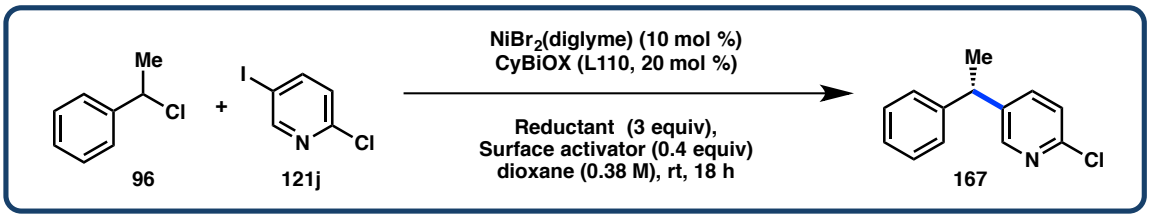
with 1,4-dioxane:

Concentration [M]	Conv 96 (%)	Yield 167 (%)	ee 167 (%)
0.05	54	37	69
0.1	61	42	66
0.2	91	76	74
0.36	77	69	75
1.0	35	30	70

Next, we screened a range of solvents to ensure that 1,4-dioxane remained optimal in this transformation (**Table 4.6**). As before, acyclic ethereal solvents such as TBME and Et_2O failed to suspend the Mn^0 dust, leading to no conversion (not shown). Other cyclic ethereal solvents proved to be inferior to 1,4-dioxane. A marked increase in homocoupling was observed with more polar solvents, such as DMA and MeOH. Therefore, we concluded that 1,4-dioxane was the best solvent for this reaction and proceeded to evaluate concentration as a parameter. Gratifyingly, some range of tolerance was identified, with the 0.2 M and 0.36 M conditions being identical within error. More

or less concentrated conditions led to lower conversions and yields. Attempts at lowering the reaction temperature through the use of mixed solvent systems containing 1,4-dioxane did not prove fruitful, affording only decreased yields with no significant improvement in selectivity. Therefore 0.36 M dioxane at room temperature was selected as the optimal solvent condition.

***Table 4.7**. Evaluation of reductants and activating reagents.*



with TMSCl:

Entry	Reductant	Yield (%)	ee (%)
1	Mn^0	83	72
2	Zn^0	20	30
3	$Zn^0 + MgCl_2$	6	0
4	In^0	0	-
5	TDAE	6	31
6	TDAE (-TMSCl)	6	43

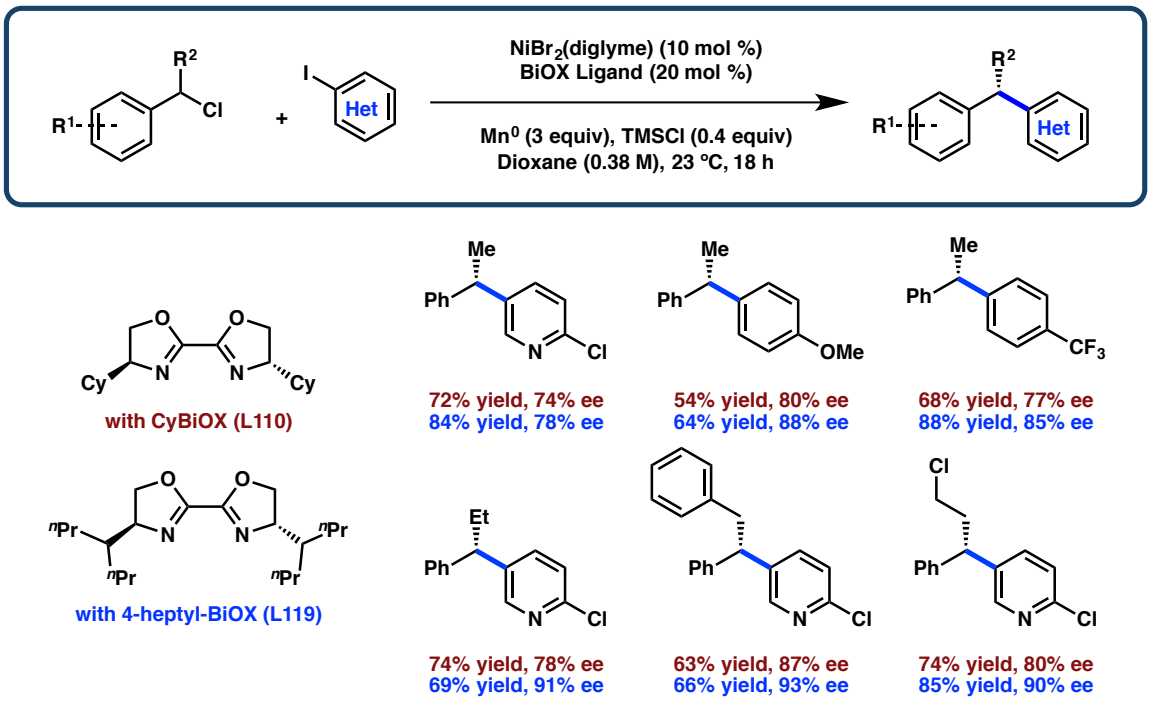
with Mn^0:

Entry	Surface activator	Yield (%)	ee (%)
1	TMSCl	74	74
2	TFA	3	0
3	TMSOTf	18	64
4	TfOH	1	3
5	4 M HCl/dioxane	4	60

Finally, with temperature and solvent conditions identified, we revisited the stoichiometric reductant and surface-activating reagent. In a survey of reductants, Mn^0 emerged as the most efficacious in this series, with Zn^0 giving lower yield and selectivity. The difference in reactivity may be attributable to the difference in reduction potential between the metals. However, the change in enantioselectivity is harder to rationalize. It is possible that the reductants favor different mechanisms, or one can imagine that the Lewis-acidic stoichiometric salt byproducts may exert significant influence over the course of the reaction. Poor yields were achieved employing the soluble organic

reductant TDAE, with lower selectivity. However these entries demonstrate the feasibility of the reaction in the absence of stoichiometric metal, suggesting that improvement of the organic reductant scaffold may be a useful line of inquiry.

Scheme 4.4. *Comparison of CyBiOX (**L110**) with 4-HeptylBiOX (**L119**).*

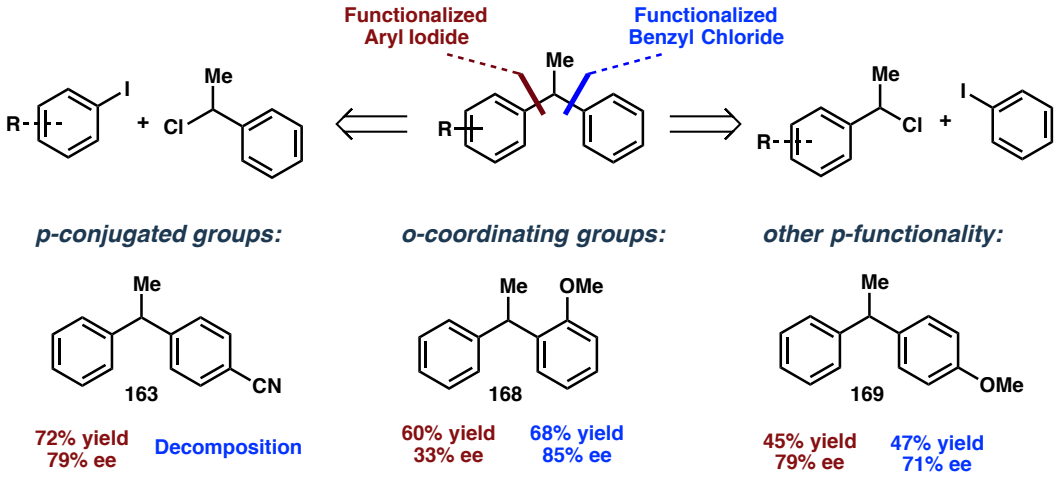


At this stage, we had succeeded in optimizing all of the reaction parameters and components, arriving at the conditions in **Scheme 4.4**. We returned our focus then to the BiOX ligand scaffold, to evaluate the performance and necessity of 4-HeptylBiOX **L119** with multiple test substrates. We were gratified to find that the optimization carried out with CyBiOX **L110** indeed led to improved results in all cases with **L119**, affording the best results to date for a series of products (**Scheme 4.4**). Confident now that these composed the final set of reaction conditions, we sought to prepare 4-HeptylBiOX (**L119**) on large scale and set out to evaluate the substrate scope of this transformation more thoroughly.

4.2.2 *Substrate scope and disconnection strategy*

Before investigating a wide range of substrates, we first wanted to assess the strategy of substrate selection to access these pseudosymmetric products. That is, to prepare any desired mono-substituted 1,1-diarylalkane, substitution may be placed on either the benzyl component or the aryl partner. If various classes of functional groups perform better on one partner than the other, this knowledge is critical in designing an ideal disconnection of the target. This versatility, in which any product can be disconnected in two ways, is a significant advantage of this cross-coupling methodology. Therefore, we initially explored a small series of simply substituted electrophiles to compare their performance in the reaction. Selected examples are shown in **Figure 4.3** to illustrate the trends we observed.

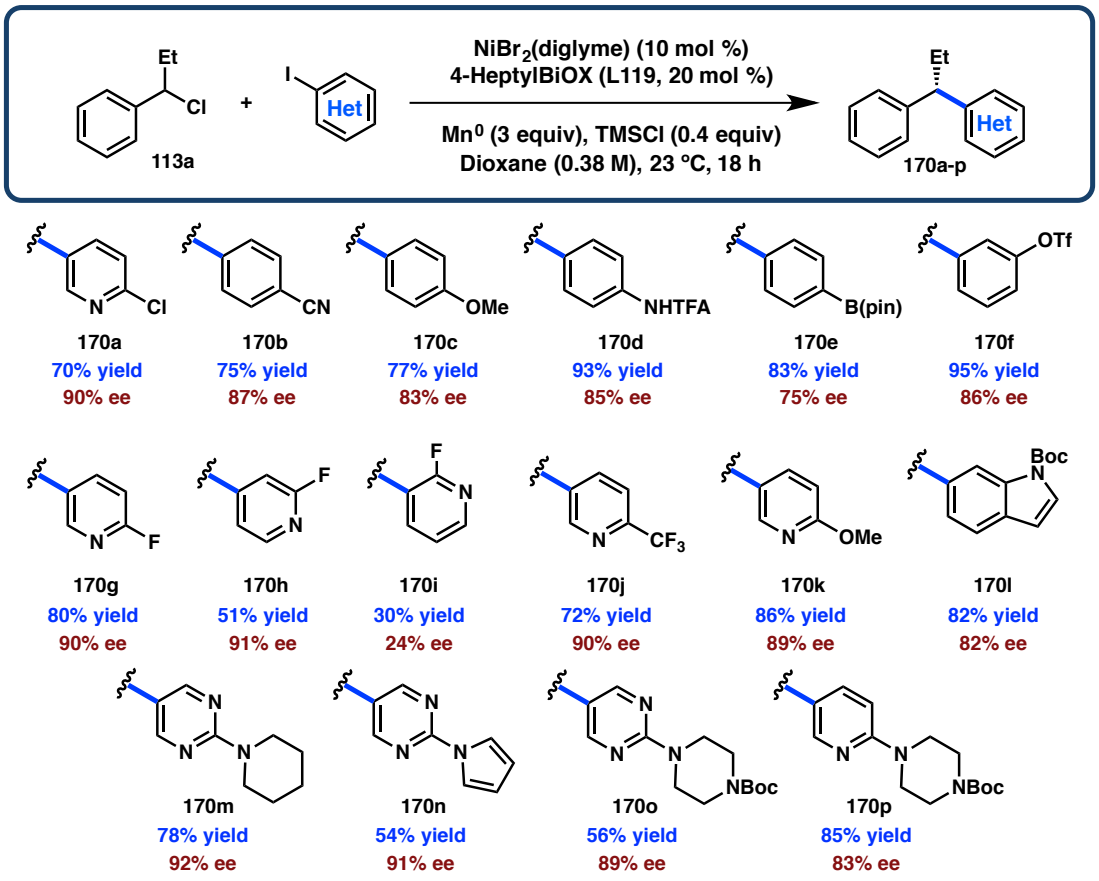
Figure 4.3. *Possible disconnections of psuedosymmetric 1,1-diarylalkanes.*



Benzyl chlorides bearing conjugated electron-withdrawing groups such as nitriles (**163**) underwent rampant decomposition, affording low yields and messy reaction profiles. We hypothesize that this may be attributable to the delocalization of benzylic radical intermediates, affording a complicated mixture of products. Fortunately, these

groups behaved well when incorporated via the aryl iodide partner. The opposite trend was observed with *ortho*-coordinating groups, such as *o*-methoxy **168**. These groups afforded good yields and very high ee's when brought in on the benzyl chloride partner, but gave low enantioselectivity when placed on the aryl iodide. Non-conjugated groups at the *para* and *meta* positions gave only slight and unpredictable variability between the two partners, as exemplified by *para*-methoxy **169**. Finally, non-coordinating *ortho*-substituents such as methyl performed very poorly on both substrates (not shown).

Scheme 4.5. *(Hetero)aryl iodide scope.*[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.

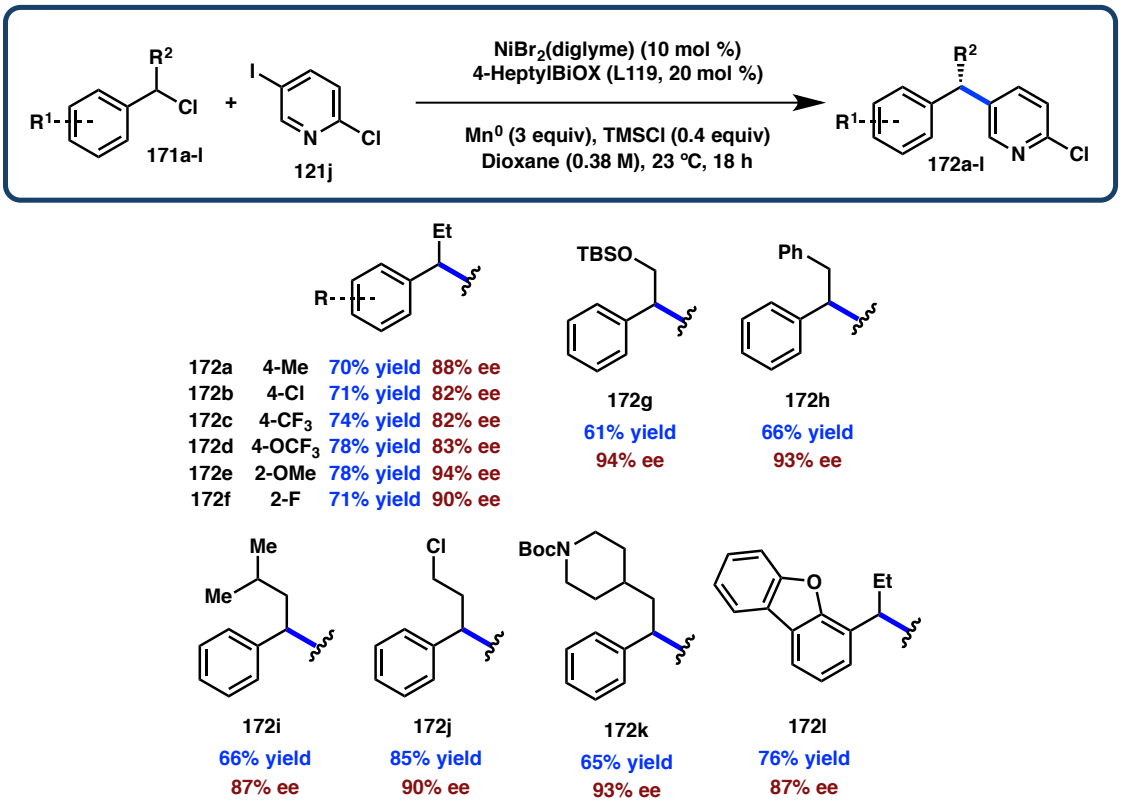
With an understanding of the basic reactivity trends and functional group tolerance for each reaction partner, we focused our attention on the (hetero)aryl iodide

scope. Based on the above results, we selected 1-(chloropropyl)benzene (**113a**) as a representative model benzyl chloride substrate for these studies. Beginning with phenyl-based arenes, we were very pleased to see that electron-withdrawing (**170b**) as well as electron-donating (**170c**) substituents afforded products in high yield and ee (**Scheme 4.5**). Acidic protons were tolerated, as shown by trifluoroacetanilide **170d**, with no protodehalogenated side-products observed. The reaction was also orthogonal to nucleophilic boronates (**170e**) as well electrophilic triflates (**170f**), providing useful handles for further functionalization or elaboration via cross-coupling.[9]

At this point, we moved on to explore heteroaryl iodides, beginning with substituted pyridines. 2-Chloro- and 2-fluoropyridines afforded the cross-coupled products (**170a**, **g–i**) in excellent ee and moderate to high yields, with the exception of 2-fluoro-3-iodopyridine, highlighting the difficulty of introducing *ortho*-substituents via the aryl iodide partner. Notably, these substrates coupled with complete chemoselectivity, reacting exclusively at the iodo position.[10] Electron withdrawing (**170j**) as well as donating (**170k**) groups performed well, including 2-(N-Boc-piperazinyl)pyridine **170p**. Gratifyingly, pyrimidine substrates also behaved well in the reaction, generating 2-aminopyrimidine derivatives **170m–o** with excellent enantioselectivity, including 2-(N-pyrrolo)pyrimidine **170n**, which had not been successful in the cross-coupling with chloronitriles (**Chapter 4.3**). We also noted that 4-iodo-2-(N-piperidinyl)pyrimidine **121m** cross-coupled in high yield and excellent ee at room temperature, in contrast to the initial studies shown in **Table 4.2**. This result suggests that **L119** is critical to the success of these mild conditions with heteroaromatics. Finally, we were pleased to find that N-Boc-6-iodoindole cross-coupled in very high yield and ee. Importantly, no condition

modification was necessary between substrates. This is in contrast to our previous work in asymmetric reductive cross-coupling, as well as the work of other groups studying the cross-coupling of heteroaromatic electrophiles.[11]

Scheme 4.6. *Benzyl chloride substrate scope.*[a]



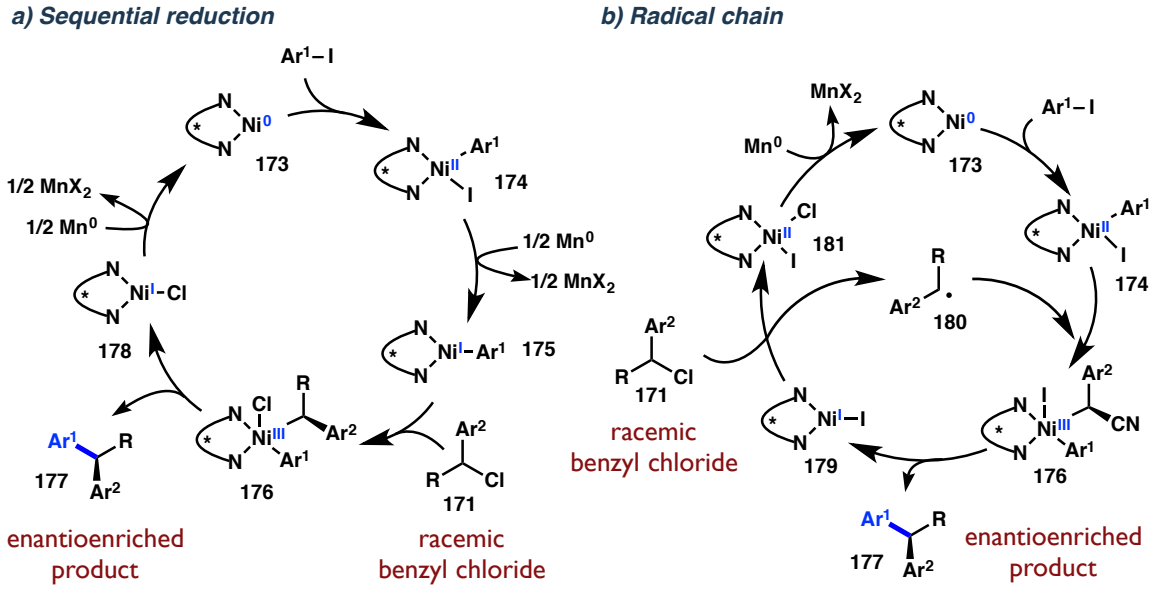
[a] Yields determined by ^{1}H NMR with an internal standard, reactions conducted on 0.2 or 0.05 mmol scale under an N_2 atmosphere in a glovebox. % ee determined by SFC using a chiral stationary phase.

We then shifted our focus to investigating the scope of the benzyl chloride partner. As shown in **Figure 4.3**, this electrophile scope unfortunately does not include conjugated electron-withdrawing substituents. However a synthetically useful range of other substituents on the aryl ring was well-tolerated, including electron-rich (**172a**) and electron-withdrawing groups (**172c** and **172d**), as well as an electrophilic chloride handle (**172b**) for further cross-coupling (**Scheme 4.6**). Most interestingly, *ortho*-substituted partners bearing functional groups capable of forming an attractive interaction with Ni

performed best in this reaction. *Ortho*-methoxy **172e** and *ortho*-fluoro **172f** were formed in high yields and excellent ee's. This is especially notable in contrast with the scope of the aryl iodide partner, where these groups performed very poorly (**Figure 4.3 168** and **Scheme 4.5 170i**). Inspired by these results, we also prepared 4-(1-chloropropyl)dibenzofuran, a bulkier substrate maintaining the *ortho* oxygen motif of **171l**. Gratifyingly, this substrate also performed very well, coupling to give **172l** in 76% yield and 87% ee. Finally, we explored a series of benzyl chlorides bearing substitution at the α-position, in order to access a more diverse range of diarylalkane products. We were very pleased to see that this series behaved well in the reaction, coupling in high yields and even better ee's than many of the simpler previous substrates. Importantly, the functional group tolerance at this position was excellent, allowing for the incorporation of silyl ether **172g**, primary alkyl chloride **172j**, and Boc-protected piperidine **172k**.

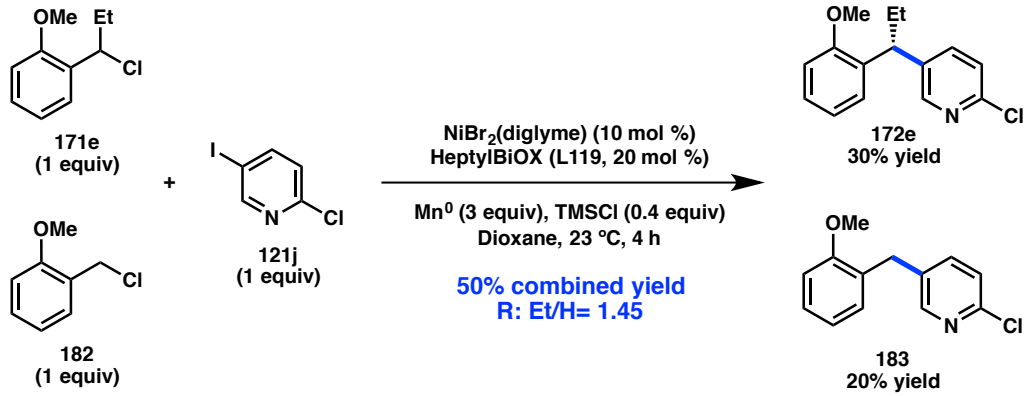
4.3 MECHANISTIC INVESTIGATIONS

Figure 4.4. *Potential mechanisms for the asymmetric reductive cross-coupling.*



Having evaluated a wide range of coupling partners for both substrate classes, we turned our attention to the mechanism of the asymmetric cross-coupling transformation. The two mechanistic hypotheses that guided our reaction development are shown in **Figure 4.4**. For a detailed consideration of the elementary steps, see **Chapter 1 and 3**, in which the mechanisms are discussed generally and for α-chloronitrile C(sp^3) electrophiles. As in our previous mechanistic explorations, we focused our efforts on elucidating the presence and nature of radical intermediates derived from the C(sp^3) electrophilic component, the benzyl chloride, in the proposed reaction with Ni^I **175** or **179**. This putative prochiral radical species (**180**) is expected to be critical to the success of the reaction, enabling differentiation of the electrophiles via sequential oxidative addition, and facilitating stereoconvergence of the racemic halide precursor.

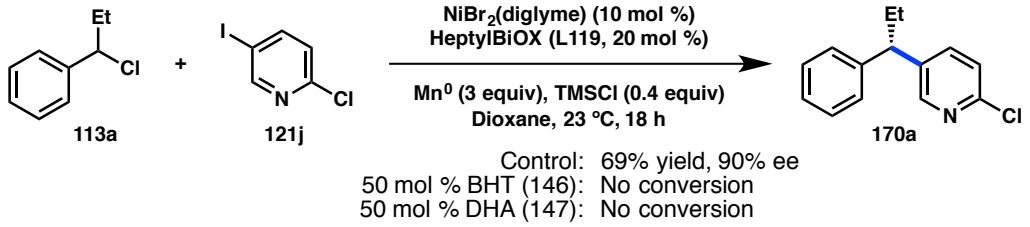
Scheme 4.7*. Competition experiment between 1° and 2° benzyl chlorides.*



As an initial probe to determine if the benzylic partner is reacting via a stabilized radical intermediate, we conducted a competition experiment between primary benzyl chloride **182** and secondary benzyl chloride **171e** (**Scheme 4.7**). While both partners could conceivably react via either an S_N2 oxidative addition or a halide abstraction radical oxidative addition, we anticipated that these substrates would undergo such

transformations at markedly different rates. That is, if the mechanism of benzylic oxidative addition were S_N2-like, then the less hindered primary chloride would be expected to react faster, favoring **183** in the reaction. On the other hand, if the oxidative addition step proceeds via halide abstraction to form a benzylic radical, then the more stabilized secondary chloride should react faster, forming more **172e**. Indeed, upon workup after 4 hours, the ratio of products favors the secondary cross-coupled **172e** by 1.45 to 1, suggesting that a radical mechanism may be at play.

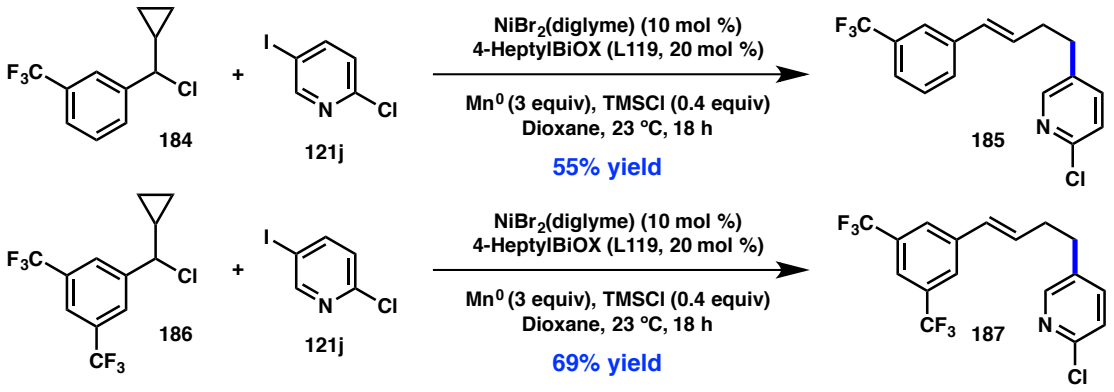
***Scheme 4.8**. Radical inhibitor studies.*



As a follow-up to this experiment, we explored the effect of radical inhibitors on the course of the reaction (**Scheme 4.8**). Employing 50 mol % of either BHT (**146**) or DHA (**147**), no conversion of either coupling partner was observed. This led us to conduct one final set of experiments, utilizing a radical clock substrate, to probe the presence of the radical intermediates (**Scheme 4.9**). Unfortunately, no reaction was observed employing benzylic electrophiles with tethered olefins, making cyclization clocks untenable. However, cyclopropylcarbinyl radical clocks proved more helpful.[12] While unsubstituted α-cyclopropyl benzyl chlorides are too unstable to be handled under the reaction conditions, trifluoromethylated versions **184** and **186** allowed for synthesis and isolation of the radical clock substrates.[13] Presumably, this is due to the destabilizing effect of the trifluoromethyl substituents on a benzylic carbocation intermediate, thus suppressing spontaneous heterolysis and decomposition. Subjecting these radical clocks

to the reaction conditions afforded only the rearranged cross-coupled products **185** and **187**, supporting the intermediacy of a cyclopropylcarbinyl radical derived from the benzyl chloride.

Scheme 4.9. *Radical clock experiments.*



The combined results of the inhibitor studies and the radical clock experiments are interesting when compared with previous studies of similar reactions. When employing α-chloronitriles as the C(sp^3) partner under very similar conditions, complete rearrangement of a cyclopropyl radical clock was observed. However no inhibition by BHT or DHA was noted (see **Chapter 3**). This is in contrast to our results here, where both rearrangement and complete inhibition were seen. This may suggest a divergence of mechanism between these two substrate classes. The cyanomethyl radical is less stable than the benzyl radical by 19 kJ/mol,[14] perhaps limiting its half-life and favoring a rapid recombination with Ni, leading to a sequential reduction mechanism. Under these conditions, the fleeting radical would not diffuse into the solvent, preventing inhibition by BHT or DHA. On the other hand, the more stable benzylic radicals may persist long enough to escape the solvent cage, favoring a radical chain mechanism and leading to poisoning by radical inhibitors. However, more research is needed to elucidate the

mechanisms of these transformations and the differences between them. These results suggest an interesting divergence that may serve as an entry point to these studies.

4.4 CONCLUSION

We have successfully developed a highly enantioselective reductive cross-coupling between secondary benzylic chlorides and (hetero)aryl iodides to afford a diverse range of 1,1-di(hetero)arylalkanes. This marks the conclusion of a longstanding effort in our laboratory and presents a novel approach to these valuable chiral molecules with unprecedented substrate scope. In so doing, we have demonstrated the second application of a dioxane/TMSCl solvent system in asymmetric reductive cross-coupling. The extension of these conditions to other substrate classes will be discussed in **Chapter 5**. It is our hope that these conditions will provide a useful starting point in the discovery of other transformations, facilitating methodology development and streamlining optimization for new substrate classes.

4.5 EXPERIMENTAL SECTION

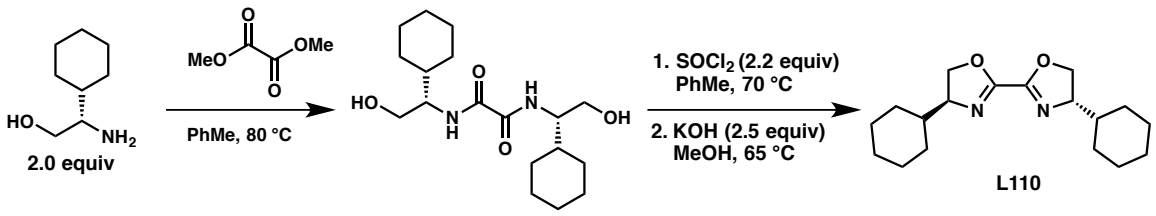
4.5.1 *Materials and methods*

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Methylene chloride (CH_2Cl_2), diethyl ether (Et_2O), tetrahydrofuran (THF), and toluene (PhMe) were dried by passing through activated alumina columns. 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.

$NiBr_2$(diglyme) 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.

4.5.2 *Ligand preparation*

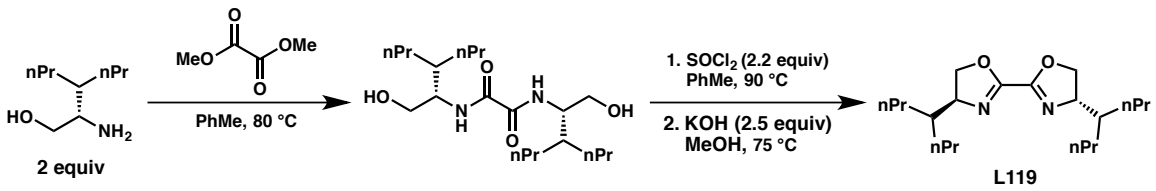
A. Preparation of (4*S*,4'*S*)-4,4'-dicyclohexyl-4,4',5,5'-tetrahydro-2,2'-bioxazole (L110, (*S*)-CyBiOX)



(*S*)-2-Amino-2-cyclohexylethan-1-ol (2 equiv, 1.00 g, 6.98 mmol) and dimethyloxalate (1 equiv, 0.438 g, 3.7 mmol) were dissolved in PhMe (75 mL) and heated to 80 °C. The reaction was allowed to stir overnight with the diamide precipitating out of solution as a white solid. Reaction was cooled to room temperature and concentrated *in vacuo* to afford the crude diol (1.260 g, 3.70 mmol). The crude diol was dissolved in PhMe (30 mL) and heated to 70 °C whereupon the thionyl chloride (2.2 equiv, 0.6 mL, 8.22 mmol) was added. Reaction was stirred at 70 °C for 30 minutes then heated to 90 °C for 90 minutes. Reaction was cooled to room temperature and poured into 20% KOH solution cooled to 0 °C. The aqueous layer was separated and extracted (x3) with DCM and the combined organic layers were washed with 20% KOH solution, $NaHCO_3$ and brine. The organic layer was dried with Na_2SO_4, filtered through a pad of Celite, and concentrated under reduced pressure. The crude dichloride (1.40 g, 3.71 mmol) was then dissolved in MeOH (35 mL) and KOH (0.52 g, 9.27 mmol) was added. Reaction was heated to reflux for 14 hours. Reaction was cooled to room temperature and concentrated to remove the MeOH. Crude mixture was loaded directly onto a silica gel column and eluted in 30% EtOAc/Hex to 40% EtOAc/Hex. The pure **L110** was obtained as a white solid (0.556 g, 49% over 3 steps). ^{1}H NMR (400 MHz, CD_3CN) δ 4.40 (dd, *J*

= 9.7, 8.2 Hz, 1H), 4.15–4.00 (m, 2H), 1.93– 1.85 (m, 1H), 1.77 (ddt, *J* = 9.4, 5.4, 1.4 Hz, 2H), 1.69 (dtd, *J* = 9.2, 3.1, 1.5 Hz, 1H), 1.58 (ddt, *J* = 12.4, 3.4, 1.8 Hz, 1H), 1.45 (tdt, *J* = 11.6, 6.7, 3.4 Hz, 1H), 1.35–1.15 (m, 3H), 1.15–0.94 (m, 2H). ^{13}C NMR (101 MHz, CD_3CN) δ 154.2, 71.9, 70.7, 42.3, 28.9, 28.8, 26.2, 25.7, 25.6; FTIR (NaCl, thin film): 2922, 2850, 1614, 1450, 1130, 1103 cm^{-1}; HRMS (MM) calc'd for $[M + H_3O]^+$ 323.2329, found 323.2319.

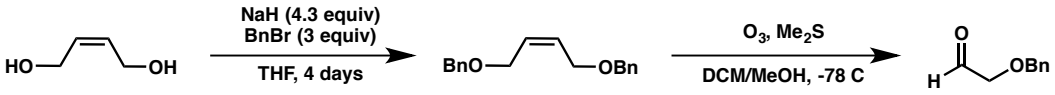
B. Preparation of (4*S*,4'*S*)-4,4'-diheptan-4-yl)-4,4',5,5'-tetrahydro-2,2'-bioxazole (L119, (S)-4-HeptylBiOX)



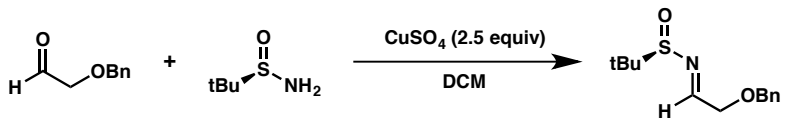
(*S*)-2-Amino-3-propylhexan-1-ol (2 equiv, 2.8 g, 17.6 mmol) and dimethyloxalate (1 equiv, 1.038 g, 8.8 mmol) were dissolved in PhMe (200 mL) and heated to 80 °C. The reaction was allowed to stir overnight with the diamide precipitating out of solution as a white solid. Reaction was cooled to room temperature and concentrated *in vacuo* to afford the crude diol (3.3 g, 8.86 mmol). The crude diol was dissolved in PhMe (60 mL) and heated to 70 °C whereupon the thionyl chloride (1.4 mL, 19.2 mmol) was added. Reaction was stirred at 70 °C for 30 minutes then heated to 90 °C for 90 minutes. Reaction was cooled to room temperature and poured into 20% KOH solution cooled to 0 °C. The aqueous layer was separated and extracted (x3) with DCM and the combined organic layers were washed with 20% KOH solution, $NaHCO_3$ and brine. The organic layer was dried with Na_2SO_4, filtered through a pad of Celite, and concentrated under

reduced pressure. The crude dichloride (3.6 g, 8.8 mmol) was then dissolved in MeOH (90 mL) and KOH (1.23 g, 21.9 mmol) was added. Reaction was heated to reflux for 14 hours. Reaction was cooled to room temperature and concentrated to remove the MeOH. Crude mixture was loaded directly onto a silica gel column and eluted in 10% EtOAc/Hex. The pure **L119** was obtained as a white solid (1.55 g, 53% over 3 steps). R_f =0.58 (50% EtOAc/Hex); ^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 4.43 (dd, *J* = 10.1, 8.3 Hz, 1H), 4.33 (ddd, *J* = 10.1, 8.5, 5.9 Hz, 1H), 4.11 (t, *J* = 8.4 Hz, 1H), 1.65 – 1.54 (m, 1H), 1.50 – 1.17 (m, 7H), 0.93 (td, *J* = 7.1, 2.6 Hz, 6H).

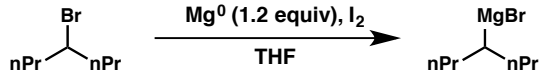
C. Preparation of (S)-2-amino-3-propylhexan-1-ol



(*Z*)-But-2-ene-1,4-diol was benzyl protected under known literature procedure. (*Z*)-1,4-bis(benzyloxy)but-2-ene (1 equiv, 15 g, 56 mmol) was dissolved in 3:1 solution of DCM/MeOH (150 mL) and cooled to -78 °C. Ozone was bubbled through the reaction until the solution turned blue, signaling O_3 saturation. Reaction sparged with O_2, then N_2 for 15 minutes. Dimethyl sulfide (12 equiv, 50 mL, 676 mmol) was added and the reaction was allowed to warm to room temperature and stir for 14 hours. Reaction was concentrated under reduced pressure and purified by column chromatography (30% EtOAc/Hex) to afford the aldehyde (16.6 g, 99% yield).

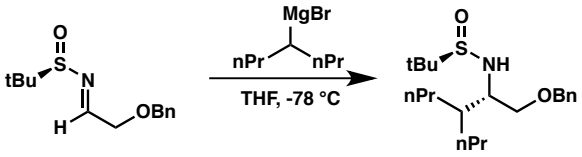


2-(benzyloxy)acetaldehyde (1 equiv, 16.6 g, 111 mmol) was dissolved in DCM (225 mL) at room temperature. (R)-(+)-*tert*-butylsulfinamide (1.1 equiv, 14.9 g, 123 mmol) and copper (II) sulfate (2.5 equiv, 44.1 g, 276 mmol) were added and the reaction was allowed to stir at room temperature for 36 hours. Reaction was filtered through a plug of Celite with DCM. Solution concentrated and purified by column chromatography (20% EtOAc/Hex) to afford imine product (17 g, 61% yield).



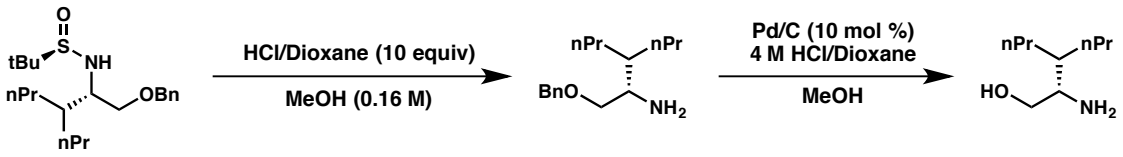
Grignard formation:

Magnesium (1.3 equiv, 4.00 g, 172 mmol) was activated with 1 M HCl, then washed with water, ethanol, and ether before transfer to a flame dried, 500 mL 3-neck flask equipped with a reflux condenser and stir bar. The Mg^0 was stirred under vacuum overnight. THF (170 mL) and a fleck of I_2 was added and the stirring mixture was heated to reflux with a heat gun periodically over 20 minutes until the brown solution turned dark, translucent gray. 4-bromoheptane (1 equiv, 21 mL, 134 mmol) was added slowly, portion-wise, with heating to reflux in the intervals between additions. After addition of alkyl bromide, reaction was heated to 80 °C for 1 hour, then cooled to room temperature and titrated (0.36 M, 49% yield).



Sulfinamide (1 equiv, 7.33 g, 28.9 mmol) was dissolved in THF (260 mL) and cooled to -78 °C. Freshly prepared, heptan-4-ylmagnesium bromide (1.6 equiv, 9.4 g,

46.2 mmol) was added via cannula. Reaction was stirred at -78 °C for 8 hours then allowed to stir overnight while the bath warmed slowly. The reaction mixture was quenched with water and Na_2SO_4 was added. Mixture was filtered through a plug of Celite and concentrated. Product was purified by silica gel chromatography (10% EtOAc/Hex to 30% EtOAc/Hex) to afford product (9.9 g, 97% yield, 97:3 d.r.). ^{1}H NMR (500 MHz, Benzene-d_6) δ 7.28 (dd, *J* = 8.1, 1.4 Hz, 2H), 7.20 – 7.14 (m, 2H), 7.09 – 7.02 (m, 1H), 4.39 (d, *J* = 11.9 Hz, 1H), 4.26 (d, *J* = 11.8 Hz, 1H), 3.64 – 3.56 (m, 2H), 3.52 (dd, *J* = 9.5, 4.7 Hz, 1H), 3.40 (dq, *J* = 8.4, 4.9 Hz, 1H), 1.72 (dtt, *J* = 10.0, 6.3, 3.6 Hz, 1H), 1.38 – 1.05 (m, 6H), 1.03 (s, 9H), 0.91 – 0.80 (m, 7H).



To a pale yellow solution of sulfinamine (1 equiv, 9.9 g, 28 mmol) in MeOH (175 mL) at room temperature, 4 M HCl/Dioxane (10 equiv, 70 mL) was added. Reaction was stirred for 1 hour and turned light amber. Reaction mixture was concentrated *in vacuo*. Crude oil was dissolved in minimal 50% EtOAc/Hex and loaded onto a silica gel column. 1 L of 50% EtOAc/Hex was eluted to remove sulfur impurities, then solvent system was switched to 10% MeOH/DCM to elute brown product band from the top of the silica (6.2g, 89% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.50 (s, 3H), 7.42 – 7.22 (m, 5H), 4.59 (d, *J* = 12.2 Hz, 1H), 4.52 (d, *J* = 12.1 Hz, 1H), 3.66 (d, *J* = 5.5 Hz, 2H), 3.34 (s, 1H), 1.91 – 1.80 (m, 1H), 1.61 – 1.50 (m, 1H), 1.45 – 1.12 (m, 6H), 0.88 (td, *J* = 7.2, 4.0 Hz, 6H).

Pd/C (5.9 g) was added to flask and dissolved in minimal EtOAc and put under N_2. Amine (1 equiv, 6.0 g, 24.1 mmol) was dissolved in MeOH (50 mL) and added to the

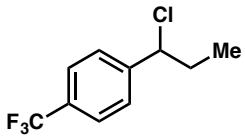
reaction flask via cannula. 4 M HCl/Dioxane (50 mL) was added and the N_2 atmosphere was exchanged with H_2 and the reaction was allowed to stir 14 h under H_2. Upon completion, the reaction was sparged with argon and filtered through a pad of Celite with EtOAc. The filtrate was concentrated then dissolved in 250mL EtOAc and added to 250 mL of 4 M NaOH. The organic layer was separated and extracted with 3x 200 mL EtOAc. The combined organic layers were dried, filtered, and concentrated under reduced pressure to afford pure amino alcohol (2.8 g, 74% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.58 (dd, *J* = 10.4, 4.0 Hz, 1H), 3.30 (dd, *J* = 10.4, 9.3 Hz, 1H), 2.81 (dt, *J* = 8.7, 4.0 Hz, 1H), 1.74 (s, 4H), 1.42 – 1.12 (m, 7H), 0.90 (td, *J* = 6.9, 2.0 Hz, 7H).

4.5.3 *Substrate preparation*

General procedure 1: Benzyl Chloride Synthesis from Benzylic Alcohols

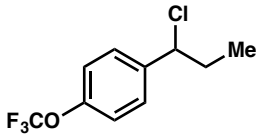
A flame-dried flask was charged with the benzylic alcohol substrate (1 equiv) and chloroform (0.30 M) and sealed with a rubber septum. This solution was cooled to 0 ºC in an ice bath and placed under a positive pressure of nitrogen. The flask was vented via a Teflon cannula into a saturated solution of $NaHCO_3$ to quench evolved SO_2 gas. To the cooled solution was slowly added thionyl chloride (1.05 equiv) via syringe. The reaction was allowed to stir overnight and the ice bath allowed to melt, unless otherwise noted. Reactions were then concentrated to typically afford the crude substrates as yellow oils containing a mixture of benzylic chloride and the styrenyl elimination product. Substrates were purified by column chromatography on silica gel in 100% hexanes to elute first the elimination product (strong staining by $KMnO_4$ and brightly fluorescent) followed by the desired chloride product (dimly fluorescent, no staining).

1-(1-chloropropyl)-4-(trifluoromethyl)benzene (171c)



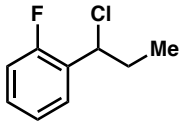
Prepared from 1-(4-(trifluoromethyl)phenyl)propan-1-ol (5.0 mmol, 1.02 g) following General Procedure 1 to yield 350 mg (31% yield, 1.57 mmol) of **171c** as a mobile clear liquid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.62 (dt, *J* = 8.1, 0.7 Hz, 2H), 7.53 – 7.47 (m, 2H), 4.81 (dd, *J* = 7.8, 6.4 Hz, 1H), 2.23 – 1.96 (m, 2H), 1.01 (t, *J* = 7.3 Hz, 3H).

1-(1-chloropropyl)-4-(trifluoromethoxy)benzene (171d)



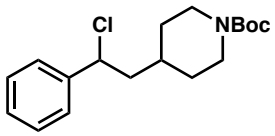
Prepared from 1-(4-(trifluoromethoxy)phenyl)propan-1-ol (13.1 mmol, 2.88 g) following General Procedure 1 to yield 2.51 g (80% yield, 10.48 mmol) of **171d** as a mobile clear liquid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.54 – 7.29 (m, 2H), 7.24 – 7.15 (m, 2H), 4.78 (dd, *J* = 7.9, 6.5 Hz, 1H), 2.24 – 1.95 (m, 2H), 1.00 (t, *J* = 7.3 Hz, 3H).

1-(1-chloropropyl)-2-fluorobenzene (171f)



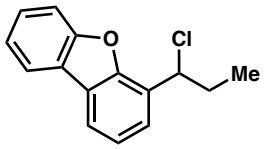
Prepared from 1-(2-fluorophenyl)propan-1-ol (19.7 mmol, 3.03 g) following General Procedure 1 to yield 2.63 g (77% yield, 15.2 mmol) of **171f** as a mobile clear liquid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.51 (td, *J* = 7.6, 1.9 Hz, 1H), 7.35 – 7.21 (m, 1H), 7.16 (ddd, *J* = 8.3, 7.4, 1.1 Hz, 1H), 7.11 – 6.97 (m, 1H), 5.24 – 5.11 (m, 1H), 2.27 – 1.98 (m, 2H), 1.02 (t, *J* = 7.3 Hz, 3H).

tert-butyl 4-(2-chloro-2-phenylethyl)piperidine-1-carboxylate (171k)



Prepared from *tert*-butyl 4-(2-hydroxy-2-phenylethyl)piperidine-1-carboxylate (6.2 mmol, 1.89 g) following General Procedure 1. The reaction was concentrated and loaded onto a silica plug. Elution with $CHCl_3$ delivered degradation products. Subsequent elution with 10% MeOH/DCM afforded the deprotected HCl salt of **171k** as a tan solid in 68% yield (4.22 mmol, 1.02 g). This product was not competent in the cross-coupling reaction. Reprotection with Boc_2O (1.05 equiv) in DCM with Et_3N (4 equiv) afforded the desired product cleanly. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.47 – 7.27 (m, 5H), 4.95 (dd, *J* = 9.2, 5.9 Hz, 1H), 4.09 (s, 2H), 2.67 (t, *J* = 12.9 Hz, 2H), 2.12 (ddd, *J* = 14.4, 9.2, 5.5 Hz, 1H), 1.88 (ddd, *J* = 14.0, 7.5, 5.9 Hz, 1H), 1.81 – 1.56 (m, 2H), 1.45 (s, 9H), 1.30 – 1.00 (m, 3H).

4-(1-chloropropyl)dibenzo[*b*,*d*]furan (171l)



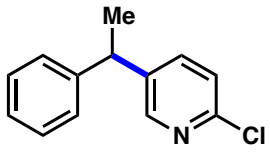
Prepared from 1-(dibenzo[*b*,*d*]furan-4-yl)propan-1-ol (9.2 mmol, 2.08 g) following General Procedure 1 to yield 1.74 g (84% yield, 7.7 mmol) of **171l** as a mobile clear liquid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.96 (ddd, *J* = 7.7, 1.4, 0.7 Hz, 1H), 7.90 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.61 (ddd, *J* = 8.3, 0.7 Hz, 1H), 7.57 (ddd, *J* = 7.7, 1.3, 0.5 Hz, 1H), 7.51 – 7.45 (m, 1H), 7.40 – 7.37 (m, 1H), 7.37 – 7.34 (m, 1H), 2.50 – 2.20 (m, 2H), 1.08 (t, *J* = 7.3 Hz, 3H).

4.5.4 *Enantioselective reductive cross-coupling*

General Procedure 2: Enantioselective reductive coupling of benzyl chlorides and (hetero)aryl iodides

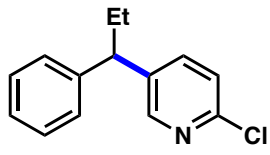
On the bench-top, a 20 mL scintillation vial was charged with a cross stirbar, Mn^0 powder (3 equiv, 33 mg, 0.6 mmol), aryl iodide (*if solid*, 1 equiv, 0.2 mmol), and **L119** (0.2 equiv, 13.5 mg, 0.04 mmol). The vial was transferred into a N_2-filled glovebox and charged with $NiBr_2$ (diglyme) (10 mol %, 7.1 mg, 0.02 mmol), aryl iodide (*if liquid*, 1 equiv, 0.2 mmol) and 1,4-dioxane (0.56 mL, 0.36 M). Reaction was allowed to stir at 100 rpm for several seconds before addition of TMSCl (20 uL, 0.8 equiv). After a short period of stirring, benzyl chloride (1 equiv, 0.2 mmol) was added. The vial was sealed with a Teflon cap and removed from the glovebox. The mixture was stirred at 480 rpm over a period of 14 hours, over which time the heterogeneous solution turned from dark gray to a light green, deep red or light gray color. The reaction was quenched by loading directly onto a short plug of silica, using 20% ethyl acetate/hexane eluent. The solution was concentrated to afford a clear oil which was then diluted in toluene and loaded onto a silica gel column and eluted in a hexane/EtOAc gradient. Remaining benzyl chloride could be recovered in the first couple fractions, with biaryl homocoupled 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-chloro-5-(1-phenylethyl)pyridine (167)



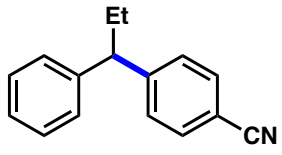
Prepared from 2-chloro-5-iodopyridine (1 equiv, 48.0 mg, 0.2 mmol) and 1-(chloroethyl)benzene (1 equiv, 28 mg, 0.2 mmol) following General Procedure 2. The crude residue was analyzed by NMR to give a 84% yield. The enantiomeric excess was determined to be 78% by chiral SFC analysis (AD-H, 2.5 mL/min, 7% IPA in CO_2, λ = 254 nm): t_R(minor) = 6.5 min, t_R(major) = 7.6 min. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.29 (dt, *J* = 2.6, 0.7 Hz, 1H), 7.44 (ddd, *J* = 8.2, 2.6, 0.6 Hz, 1H), 7.38 – 7.27 (m, 2H), 7.25 – 7.14 (m, 5H), 4.16 (q, *J* = 7.2 Hz, 1H), 1.65 (d, *J* = 7.2 Hz, 4H).

2-chloro-5-(1-phenylpropyl)pyridine (170a)



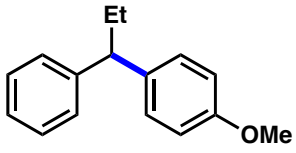
Prepared from 2-chloro-5-iodopyridine (1 equiv, 48.0 mg, 0.2 mmol) and 1-(chloropropyl)benzene (1 equiv, 31 mg, 0.2 mmol) following General Procedure 2. The crude residue was analyzed by NMR to give a 70% yield. The enantiomeric excess was determined to be 90% by chiral SFC analysis (AD-H, 2.5 mL/min, 8% IPA in CO_2, λ = 254 nm): t_R(major) = 6.4 min, t_R(minor) = 7.6 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.30 (d, *J* = 2.5 Hz, 1H), 7.47 (dd, *J* = 8.3, 2.5 Hz, 1H), 7.30 (dd, *J* = 8.2, 6.9 Hz, 2H), 7.25 – 7.16 (m, 3H), 3.80 (t, *J* = 7.8 Hz, 1H), 2.16 – 1.97 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $cdcl_3$) δ 149.37, 149.30, 143.37, 139.57, 138.24, 128.84, 127.86, 126.80, 124.17, 50.10, 28.37, 12.67.

4-(1-phenylpropyl)benzonitrile (170b)



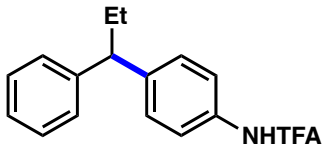
Prepared from 4-iodobenzonitrile (1 equiv, 46.0 mg, 0.2 mmol) and 1-(chloropropyl)benzene (1 equiv, 31 mg, 0.2 mmol) following General Procedure 2. The crude residue was analyzed by NMR to give a 75% yield. The enantiomeric excess was determined to be 87% by chiral SFC analysis (OB-H, 2.5 mL/min, 10% IPA in CO_2, λ = 254 nm): t_R(major) = 5.3 min, t_R(minor) = 7.2 min.^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.59 – 7.54 (m, 2H), 7.36 – 7.32 (m, 2H), 7.32 – 7.27 (m, 2H), 7.24 – 7.17 (m, 3H), 3.84 (t, *J* = 7.8 Hz, 1H), 2.15 – 2.01 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H).

1-methoxy-4-(1-phenylpropyl)benzene (170c)



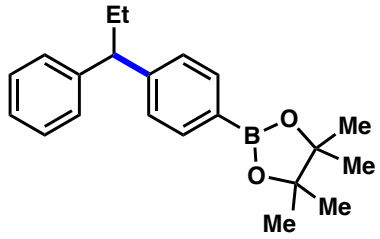
Prepared from 4-iodoanisole (1 equiv, 47.0 mg, 0.2 mmol) and 1-(chloropropyl)benzene (1 equiv, 31 mg, 0.2 mmol) following General Procedure 2. The crude residue was analyzed by NMR to give a 77% yield. The enantiomeric excess was determined to be 83% by chiral SFC analysis (OJ-H, 2.5 mL/min, 8% IPA in CO_2, λ = 210 nm): t_R(minor) = 8.8 min, t_R(major) = 10.9 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.30 – 7.23 (m, 3H), 7.23 – 7.19 (m, 2H), 7.17 – 7.12 (m, 2H), 6.84 – 6.80 (m, 2H), 3.77 (s, 4H), 3.74 (t, *J* = 7.8 Hz, 1H), 2.09 – 1.98 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H).

2,2,2-trifluoro-*N*-(4-(1-phenylpropyl)phenyl)acetamide (170d)



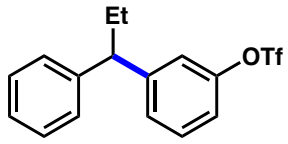
Prepared from 2,2,2-trifluoro-*N*-(4-iodophenyl)acetamide (1 equiv, 63.0 mg, 0.2 mmol) and 1-(chloropropyl)benzene (1 equiv, 31 mg, 0.2 mmol) following General Procedure 2. The crude residue was analyzed by NMR to give a 93% yield. The enantiomeric excess was determined to be 85% by chiral SFC analysis (OD-H, 2.5 mL/min, 10% IPA in CO_2, λ = 254 nm): t_R(minor) = 6.5 min, t_R(major) = 9.7 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.49 – 7.45 (m, 2H), 7.26 (s, 4H), 7.23 – 7.16 (m, 3H), 3.79 (t, *J* = 7.8 Hz, 1H), 2.06 (pd, *J* = 7.4, 2.4 Hz, 2H), 0.89 (t, *J* = 7.3 Hz, 3H).

4,4,5,5-tetramethyl-2-(4-(1-phenylpropyl)phenyl)-1,3,2-dioxaborolane (170e)



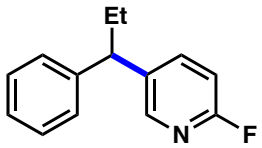
Prepared from 2-(4-iodophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1 equiv, 66.0 mg, 0.2 mmol) and 1-(chloropropyl)benzene (1 equiv, 31 mg, 0.2 mmol) following General Procedure 2. The crude residue was analyzed by NMR to give a 83% yield. The enantiomeric excess was determined to be 75% by chiral SFC analysis (AD-H, 2.5 mL/min, 7% IPA in CO_2, λ = 254 nm): t_R(minor) = 5.9 min, t_R(major) = 6.5 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.77 – 7.69 (m, 2H), 7.29 – 7.19 (m, 6H), 7.19 – 7.13 (m, 1H), 3.80 (t, *J* = 7.8 Hz, 1H), 2.12 – 2.04 (m, 2H), 1.32 (s, 12H), 0.89 (t, *J* = 7.3 Hz, 3H).

3-(1-phenylpropyl)phenyl trifluoromethanesulfonate (170f)



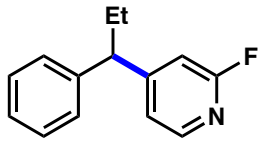
Prepared from 3-iodophenyl trifluoromethanesulfonate (1 equiv, 70.0 mg, 0.2 mmol) and 1-(chloropropyl)benzene (1 equiv, 31 mg, 0.2 mmol) following General Procedure 2. The crude residue was analyzed by NMR to give a 95% yield. The enantiomeric excess was determined to be 86% by chiral SFC analysis (OJ-H, 2.5 mL/min, 1% IPA in CO_2, λ = 210 nm): t_R(major) = 5.7 min, t_R(minor) = 6.4 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.37 – 7.27 (m, 2H), 7.26 – 7.17 (m, 4H), 7.14 (t, *J* = 2.1 Hz, 1H), 7.09 (ddd, *J* = 8.2, 2.5, 1.0 Hz, 1H), 3.83 (t, *J* = 7.8 Hz, 1H), 2.17 – 1.97 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 149.69, 148.34, 143.67, 130.06, 128.62, 128.05, 127.81, 126.55, 120.64, 118.81, 77.28, 77.02, 76.77, 52.78, 28.42, 12.57; ^{19}F NMR (282 MHz, cdcl$_3$) δ -72.76.

2-fluoro-5-(1-phenylpropyl)pyridine (170g)



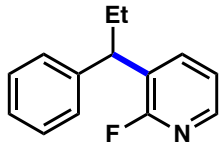
Prepared from 2-fluoro-5-iodopyridine (1 equiv, 45.0 mg, 0.2 mmol) and 1-(chloropropyl)benzene (1 equiv, 31 mg, 0.2 mmol) following General Procedure 2. The crude residue was analyzed by NMR to give a 80% yield. The enantiomeric excess was determined to be 90% by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ = 254 nm): t_R(major) = 5.5 min, t_R(minor) = 6.0 min.^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.11 (ddt, *J* = 2.5, 1.2, 0.6 Hz, 1H), 7.59 (dddd, *J* = 8.3, 7.7, 2.6, 0.5 Hz, 1H), 7.35 – 7.28 (m, 2H), 7.24 – 7.17 (m, 3H), 6.87 – 6.80 (m, 1H), 3.82 (t, *J* = 7.8 Hz, 1H), 2.15 – 2.00 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H).

2-fluoro-4-(1-phenylpropyl)pyridine (170h)



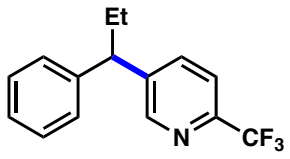
Prepared from 2-fluoro-4-iodopyridine (1 equiv, 45.0 mg, 0.2 mmol) and 1-(chloropropyl)benzene (1 equiv, 31 mg, 0.2 mmol) following General Procedure 2. The crude residue was analyzed by NMR to give a 51% yield. The enantiomeric excess was determined to be 91% by chiral SFC analysis (OJ-H, 2.5 mL/min, 5% IPA in CO_2, λ = 254 nm): t_R(minor) = 4.1 min, t_R(major) = 4.6 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.09 (dt, *J* = 5.2, 0.7 Hz, 1H), 7.34 – 7.29 (m, 2H), 7.27 – 7.17 (m, 3H), 7.03 (dddd, *J* = 5.3, 2.0, 1.4, 0.5 Hz, 1H), 6.79 (td, *J* = 1.4, 0.6 Hz, 1H), 3.81 (t, *J* = 7.8 Hz, 1H), 2.12 – 2.02 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H).

2-fluoro-3-(1-phenylpropyl)pyridine (170i)



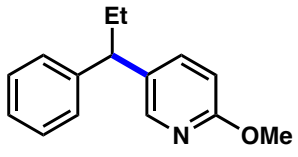
Prepared from 2-fluoro-3-iodopyridine (1 equiv, 45.0 mg, 0.2 mmol) and 1-(chloropropyl)benzene (1 equiv, 31 mg, 0.2 mmol) following General Procedure 2. The crude residue was analyzed by NMR to give a 30% yield. The enantiomeric excess was determined to be 24% by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ = 254 nm): t_R(major) = 4.2 min, t_R(minor) = 4.6 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.04 (ddd, *J* = 4.8, 1.9, 1.2 Hz, 1H), 7.66 (dddd, *J* = 9.6, 7.5, 2.0, 0.6 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.25 – 7.18 (m, 3H), 7.13 (ddd, *J* = 7.5, 4.8, 1.7 Hz, 1H), 4.08 (t, *J* = 7.9 Hz, 1H), 2.13 – 2.02 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H).

5-(1-phenylpropyl)-2-(trifluoromethyl)pyridine (170j)



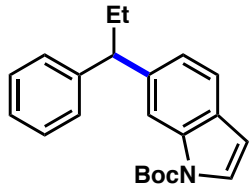
Prepared from 5-iodo-2-(trifluoromethyl)pyridine (1 equiv, 55.0 mg, 0.2 mmol) and 1-(chloropropyl)benzene (1 equiv, 31 mg, 0.2 mmol) following General Procedure 2. The crude residue was analyzed by NMR to give a 72% yield. The enantiomeric excess was determined to be 90% by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ = 254 nm): t_R(major) = 3.7 min, t_R(minor) = 4.1 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.63 (d, *J* = 2.1 Hz, 1H), 7.68 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.59 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.35 – 7.29 (m, 2H), 7.25 – 7.18 (m, 3H), 3.90 (t, *J* = 7.8 Hz, 1H), 2.20 – 2.06 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H).

2-methoxy-5-(1-phenylpropyl)pyridine (170k)



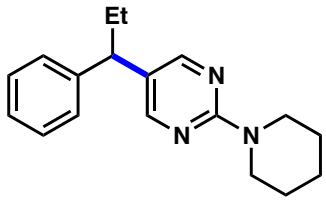
Prepared from 5-iodo-2-methoxypyridine (1 equiv, 47.0 mg, 0.2 mmol) and 1-(chloropropyl)benzene (1 equiv, 31 mg, 0.2 mmol) following General Procedure 2. The crude residue was analyzed by NMR to give a 86% yield. The enantiomeric excess was determined to be 89% by chiral SFC analysis (OJ-H, 2.5 mL/min, 4% IPA in CO_2, λ = 210 nm): t_R(minor) = 5.9 min, t_R(major) = 6.4 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.06 (d, *J* = 2.6 Hz, 1H), 7.40 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.28 (dd, *J* = 8.1, 7.1 Hz, 2H), 7.23 – 7.15 (m, 3H), 6.66 (d, *J* = 8.5 Hz, 1H), 3.90 (s, 3H), 3.74 (t, *J* = 7.8 Hz, 1H), 2.12 – 1.97 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H).

tert-butyl-6-(1-phenylpropyl)-1*H*-indole-1-carboxylate (170l)



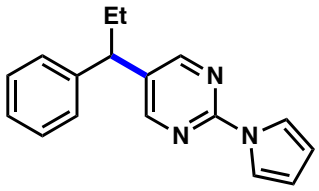
Prepared from *tert*-butyl 6-iodo-1*H*-indole-1-carboxylate (1 equiv, 69.0 mg, 0.2 mmol) and 1-(chloropropyl)benzene (1 equiv, 31 mg, 0.2 mmol) following General Procedure 2. The crude residue was analyzed by NMR to give a 82% yield. The enantiomeric excess was determined to be 82% by chiral SFC analysis (AD-H, 2.5 mL/min, 8% IPA in CO_2, λ = 254 nm): t_R(minor) = 7.5 min, t_R(major) = 8.7 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.33 – 7.26 (m, 6H), 6.90 – 6.82 (m, 1H), 6.51 (ddd, *J* = 13.3, 3.7, 0.8 Hz, 3H), 3.92 (t, *J* = 7.8 Hz, 1H), 2.15 (pd, *J* = 7.3, 1.3 Hz, 2H), 1.66 (s, 9H), 0.93 (t, *J* = 7.3 Hz, 3H).

5-(1-phenylpropyl)-2-(piperidin-1-yl)pyrimidine (170m)



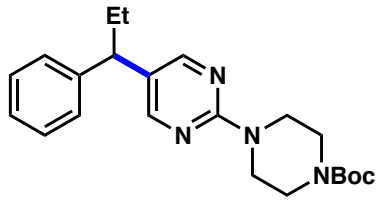
Prepared from 5-iodo-2-(piperidin-1-yl)pyrimidine (1 equiv, 58.0 mg, 0.2 mmol) and 1-(chloropropyl)benzene (1 equiv, 31 mg, 0.2 mmol) following General Procedure 2. The crude residue was analyzed by NMR to give a 78% yield. The enantiomeric excess was determined to be 98% by chiral SFC analysis (OB-H, 2.5 mL/min, 15% IPA in CO_2, λ = 254 nm): t_R(minor) = 5.8 min, t_R(major) = 7.5 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.17 (d, *J* = 0.5 Hz, 2H), 7.31 – 7.26 (m, 2H), 7.22 – 7.14 (m, 3H), 3.78 – 3.68 (m, 4H), 3.59 (t, *J* = 7.8 Hz, 1H), 2.11 – 1.92 (m, 2H), 1.71 – 1.62 (m, 2H), 1.62 – 1.52 (m, 4H), 0.90 (t, *J* = 7.3 Hz, 3H).

5-(1-phenylpropyl)-2-(1*H*-pyrrol-1-yl)pyrimidine (170n)



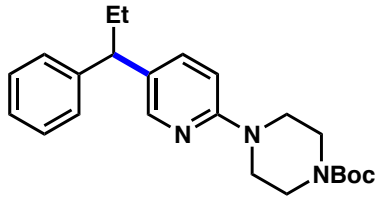
Prepared from 5-iodo-2-(1*H*-pyrrol-1-yl)pyrimidine (1 equiv, 54.0 mg, 0.2 mmol) and 1-(chloropropyl)benzene (1 equiv, 31 mg, 0.2 mmol) following General Procedure 2. The crude residue was analyzed by NMR to give a 54% yield. The enantiomeric excess was determined to be 91% by chiral SFC analysis (OB-H, 2.5 mL/min, 15% IPA in CO_2, λ = 254 nm): t_R(minor) = 9.3 min, t_R(major) = 11.2 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.47 (d, *J* = 0.5 Hz, 2H), 7.75 – 7.70 (m, 2H), 7.32 (tq, *J* = 7.7, 1.0 Hz, 2H), 7.25 – 7.18 (m, 3H), 6.33 – 6.29 (m, 2H), 3.79 (t, *J* = 7.8 Hz, 1H), 2.20 – 2.06 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H).

***tert*-butyl-4-(5-(1-phenylpropyl)pyrimidin-2-yl)piperazine-1-carboxylate (170o)**



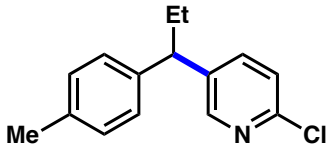
Prepared from *tert*-butyl 4-(5-iodopyrimidin-2-yl)piperazine-1-carboxylate (1 equiv, 78.0 mg, 0.2 mmol) and 1-(chloropropyl)benzene (1 equiv, 31 mg, 0.2 mmol) following General Procedure 2. The crude residue was analyzed by NMR to give a 56% yield. The enantiomeric excess was determined to be 89% by chiral SFC analysis (AD-H, 2.5 mL/min, 10% IPA in CO_2, λ = 254 nm): t_R(major) = 10.3 min, t_R(minor) = 11.7 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.20 (s, 2H), 7.29 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.19 (d, *J* = 7.5 Hz, 3H), 3.75 (t, *J* = 5.2 Hz, 4H), 3.62 (t, *J* = 7.8 Hz, 1H), 3.47 (t, *J* = 5.3 Hz, 4H), 2.10 – 1.95 (m, 3H), 1.48 (s, 9H), 0.91 (t, *J* = 7.3 Hz, 3H).

tert-butyl-4-(5-(1-phenylpropyl)pyridin-2-yl)piperazine-1-carboxylate (170p)



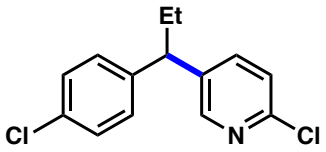
Prepared from *tert*-butyl 4-(5-iodopyridin-2-yl)piperazine-1-carboxylate (1 equiv, 78.0 mg, 0.2 mmol) and 1-(chloropropyl)benzene (1 equiv, 31 mg, 0.2 mmol) following General Procedure 2. The crude residue was analyzed by NMR to give an 85% yield. The enantiomeric excess was determined to be 83% by chiral SFC analysis (OJ-H, 2.5 mL/min, 15% IPA in CO_2, λ = 254 nm): t_R(major) = 6.9 min, t_R(minor) = 7.7 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.11 (d, *J* = 2.4 Hz, 1H), 7.33 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.31 – 7.23 (m, 2H), 7.23 – 7.13 (m, 3H), 6.58 (dd, *J* = 8.7, 0.8 Hz, 1H), 3.69 (t, *J* = 7.8 Hz, 1H), 3.52 (q, *J* = 3.9, 3.1 Hz, 4H), 3.49 – 3.44 (m, 4H), 2.10 – 1.95 (m, 2H), 1.48 (s, 9H), 0.89 (t, *J* = 7.2 Hz, 3H).

2-chloro-5-(1-(*p*-tolyl)propyl)pyridine (172a)



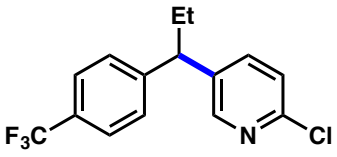
Prepared from 2-chloro-5-iodopyridine (1 equiv, 48.0 mg, 0.2 mmol) and 1-(1-chloropropyl)-4-methylbenzene (1 equiv, 34 mg, 0.2 mmol) following General Procedure 2. The crude residue was analyzed by NMR to give a 70% yield. The enantiomeric excess was determined to be 88% by chiral SFC analysis (AD-H, 2.5 mL/min, 8% IPA in CO_2, λ = 254 nm): t_R(major) = 6.8 min, t_R(minor) = 8.5 min. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.29 (d, *J* = 2.6 Hz, 1H), 7.46 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 1H), 7.15 – 7.04 (m, 4H), 3.76 (t, *J* = 7.8 Hz, 1H), 2.31 (s, 3H), 2.05 (qt, *J* = 13.6, 7.5 Hz, 2H), 0.90 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.22, 149.11, 140.27, 139.72, 138.09, 136.27, 129.40, 127.60, 124.02, 49.61, 28.30, 20.98, 12.57.

2-chloro-5-(1-(4-chlorophenyl)propyl)pyridine (172b)



Prepared from 2-chloro-5-iodopyridine (1 equiv, 48.0 mg, 0.2 mmol) and 1-chloro-4-(1-chloropropyl)benzene (1 equiv, 38 mg, 0.2 mmol) following General Procedure 2. The crude residue was analyzed by NMR to give a 71% yield. The enantiomeric excess was determined to be 82% by chiral SFC analysis (AD-H, 2.5 mL/min, 12% IPA in CO_2, λ = 210 nm): t_R(minor) = 6.1 min, t_R(major) = 6.5 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.27 (dt, *J* = 2.6, 0.7 Hz, 1H), 7.43 (ddd, *J* = 8.3, 2.6, 0.5 Hz, 1H), 7.31 – 7.26 (m, 2H), 7.25 – 7.21 (m, 1H), 7.16 – 7.09 (m, 2H), 3.78 (t, *J* = 7.8 Hz, 1H), 2.10 – 1.97 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 149.61, 149.31, 141.87, 139.05, 138.13, 132.64, 129.24, 129.01, 125.60, 124.29, 49.48, 28.35, 12.60.

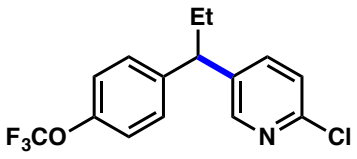
2-chloro-5-(1-(4-(trifluoromethyl)phenyl)propyl)pyridine (172c)



Prepared from 2-chloro-5-iodopyridine (1 equiv, 48.0 mg, 0.2 mmol) and 1-(1-chloropropyl)-4-(trifluoromethyl)benzene (1 equiv, 45 mg, 0.2 mmol) following General Procedure 2. The crude residue was analyzed by NMR to give a 74% yield. The enantiomeric excess was determined to be 82% by chiral SFC analysis (AD-H, 2.5 mL/min, 2% IPA in CO_2, λ = 210 nm): t_R(minor) = 14.7 min, t_R(major) = 15.3 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.29 (dt, *J* = 2.6, 0.6 Hz, 1H), 7.56 (dt, *J* = 7.9, 0.7 Hz, 2H), 7.45 (ddd, *J* = 8.3, 2.6, 0.5 Hz, 1H), 7.34 – 7.28 (m, 2H), 3.87 (t, *J* = 7.8 Hz, 1H), 2.17 – 2.01 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H).; ^{13}C NMR (126 MHz, cdcl$_3$)

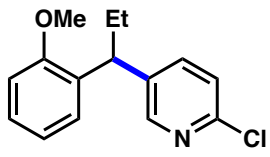
149.82, 149.35, 147.43, 138.53, 138.14, 136.99, 128.27, 125.86 (q, J = 3.7 Hz), 124.39, 119.02, 110.14, 49.95, 28.25, 12.59.

2-chloro-5-(1-(4-(trifluoromethoxy)phenyl)propyl)pyridine (172d)



Prepared from 2-chloro-5-iodopyridine (1 equiv, 48.0 mg, 0.2 mmol) and 1-(1-chloropropyl)-4-(trifluoromethoxy)benzene (1 equiv, 48 mg, 0.2 mmol) following General Procedure 2. The crude residue was analyzed by NMR to give a 78% yield. The enantiomeric excess was determined to be 83% by chiral SFC analysis (AD-H, 2.5 mL/min, 15% IPA in CO_2, λ = 210 nm): t_R(minor) = 9.8 min, t_R(major) = 10.2 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.28 (d, J = 2.4 Hz, 1H), 7.45 (ddd, J = 8.3, 2.5, 0.5 Hz, 1H), 7.25 – 7.18 (m, 3H), 7.18 – 7.12 (m, 2H), 3.82 (t, J = 7.8 Hz, 1H), 2.14 – 1.99 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 149.66, 149.34, 148.00 (q, J = 2.1 Hz), 142.11, 138.93, 138.15, 129.17, 124.34, 121.59, 121.37, 119.55, 49.46, 28.43, 12.62.

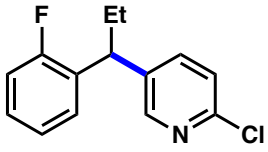
2-chloro-5-(1-(2-methoxyphenyl)propyl)pyridine (172e)



Prepared from 2-chloro-5-iodopyridine (1 equiv, 48.0 mg, 0.2 mmol) and 1-(1-chloropropyl)-2-methoxybenzene (1 equiv, 37 mg, 0.2 mmol) following General Procedure 2. The crude residue was analyzed by NMR to give a 78% yield. The enantiomeric excess was determined to be 94% by chiral SFC analysis (OJ-H, 2.5 mL/min, 7% IPA in CO_2, λ = 210 nm): t_R(minor) = 4.0 min, t_R(major) = 4.4 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.30 (d, J

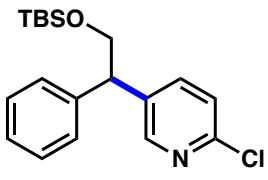
= 2.5 Hz, 1H), 7.46 (dd, *J* = 8.3, 2.5 Hz, 1H), 7.25 – 7.15 (m, 3H), 6.95 (td, *J* = 7.5, 1.2 Hz, 1H), 6.82 (dd, *J* = 8.2, 1.1 Hz, 1H), 4.20 (t, *J* = 7.9 Hz, 1H), 3.74 (s, 3H), 2.14 – 1.92 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 156.92, 149.83, 148.63, 139.47, 138.18, 131.65, 127.71, 127.04, 123.70, 120.60, 110.63, 55.27, 42.49, 27.17, 12.53.

2-chloro-5-(1-(2-fluorophenyl)propyl)pyridine (172f)



Prepared from 2-chloro-5-iodopyridine (1 equiv, 48.0 mg, 0.2 mmol) and 1-(1-chloropropyl)-2-fluorobenzene (1 equiv, 35 mg, 0.2 mmol) following General Procedure 3. The crude residue was analyzed by NMR to give a 71% yield. The enantiomeric excess was determined to be 90% by chiral SFC analysis (AD-H, 2.5 mL/min, 7% IPA in CO_2, λ = 254 nm): t_R(minor) = 5.7 min, t_R(major) = 6.6 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.35 – 8.27 (m, 1H), 7.53 – 7.45 (m, 1H), 7.25 – 7.17 (m, 2H), 7.11 (td, *J* = 7.5, 1.3 Hz, 1H), 7.00 (ddt, *J* = 11.4, 8.2, 1.7 Hz, 1H), 4.15 – 4.10 (m, 1H), 2.19 – 1.97 (m, 2H), 0.97 – 0.88 (m, 3H).

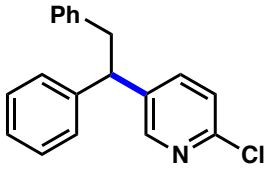
5-(2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethyl)-2-chloropyridine (172g)



Prepared from 2-chloro-5-iodopyridine (1 equiv, 48.0 mg, 0.2 mmol) and *tert*-butyl(2-chloro-2-phenylethoxy)dimethylsilane (1 equiv, 54.0 mg, 0.2 mmol) following General Procedure 2. The crude residue was analyzed by NMR to give a 61% yield. The enantiomeric excess was determined to be 94% by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ = 210 nm): t_R(minor) = 4.5 min, t_R(major) = 5.3 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ

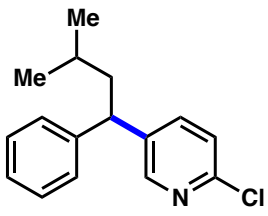
8.33 (dt, *J* = 2.5, 0.6 Hz, 1H), 7.52 (ddd, *J* = 8.3, 2.5, 0.5 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.26 – 7.21 (m, 2H), 7.20 – 7.15 (m, 2H), 4.22 – 4.03 (m, 3H), 0.82 (s, 9H), -0.04 (d, *J* = 5.0 Hz, 6H).

2-chloro-5-(1,2-diphenylethyl)pyridine (172h)



Prepared from 2-chloro-5-iodopyridine (1 equiv, 48.0 mg, 0.2 mmol) and (1-chloroethane-1,2-diyl)dibenzene (1 equiv, 43.0 mg, 0.2 mmol) following General Procedure 2. The crude residue was analyzed by NMR to give a 66% yield. The enantiomeric excess was determined to be 93% by chiral SFC analysis (AD-H, 2.5 mL/min, 12% IPA in CO_2, λ = 210 nm): t_R(minor) = 6.3 min, t_R(major) = 9.7 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.16 (dt, *J* = 2.6, 0.6 Hz, 1H), 7.42 (ddd, *J* = 8.3, 2.6, 0.5 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.24 – 7.11 (m, 7H), 7.03 – 6.95 (m, 2H), 4.24 (dd, *J* = 8.9, 7.0 Hz, 1H), 3.41 (dd, *J* = 13.7, 7.0 Hz, 1H), 3.28 (dd, *J* = 13.6, 8.9 Hz, 1H).

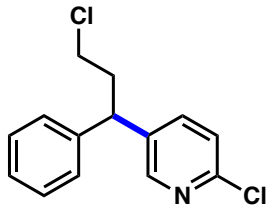
2-chloro-5-(3-methyl-1-phenylbutyl)pyridine (172i)



Prepared from 2-chloro-5-iodopyridine (1 equiv, 48.0 mg, 0.2 mmol) and (1-chloro-3-methylbutyl)benzene (1 equiv, 37.0 mg, 0.2 mmol) following General Procedure 2. The crude residue was analyzed by NMR to give a 66% yield. The enantiomeric excess was determined to be 87% by chiral SFC analysis (AD-H, 2.5 mL/min, 6% IPA in CO_2, λ = 210 nm): t_R(minor) = 7.3 min, t_R(major) = 8.3 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.30 (dt, *J* = 2.6, 0.6 Hz, 1H), 7.48 (ddd, *J* = 8.3, 2.6, 0.5 Hz, 1H), 7.30 (ddd, *J* = 8.6,

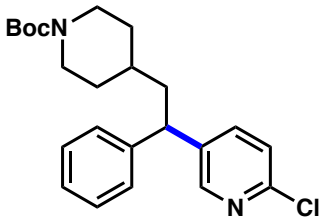
6.7, 0.6 Hz, 2H), 7.24 – 7.17 (m, 4H), 4.02 (t, *J* = 8.0 Hz, 1H), 1.90 (dddd, *J* = 41.4, 13.7, 8.0, 7.0 Hz, 2H), 1.42 (hept, *J* = 6.7 Hz, 1H), 0.92 (dd, *J* = 6.6, 1.6 Hz, 6H).

2-chloro-5-(3-chloro-1-phenylpropyl)pyridine (172j)



Prepared from 2-chloro-5-iodopyridine (1 equiv, 48.0 mg, 0.2 mmol) and (1,3-dichloropropyl)benzene (1 equiv, 38.0 mg, 0.2 mmol) following General Procedure 2. The crude residue was analyzed by NMR to give a 85% yield. The enantiomeric excess was determined to be 90% by chiral SFC analysis (AD-H, 2.5 mL/min, 8% IPA in CO_2, λ = 210 nm): t_R(minor) = 9.7 min, t_R(major) = 11.1 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.36 – 8.29 (m, 1H), 7.50 (ddd, *J* = 8.2, 2.6, 0.6 Hz, 1H), 7.37 – 7.30 (m, 2H), 7.29 – 7.18 (m, 4H), 4.27 (t, *J* = 7.8 Hz, 1H), 3.50 – 3.41 (m, 2H), 2.58 – 2.40 (m, 2H).

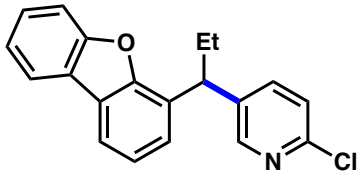
***tert*-butyl-4-(2-(6-chloropyridin-3-yl)-2-phenylethyl)piperidine-1-carboxylate (172k)**



Prepared from 2-chloro-5-iodopyridine (1 equiv, 48.0 mg, 0.2 mmol) and *tert*-butyl 4-(2-chloro-2-phenylethyl)piperidine-1-carboxylate (1 equiv, 65.0 mg, 0.2 mmol) following General Procedure 2. The crude residue was analyzed by NMR to give a 65% yield. The enantiomeric excess was determined to be 93% by chiral SFC analysis (OJ-H, 2.5 mL/min, 15% IPA in CO_2, λ = 210 nm): t_R(minor) = 5.3 min, t_R(major) = 10.9 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.29 (dt, *J* = 2.6, 0.6 Hz, 1H), 7.47 (ddd, *J* = 8.3, 2.6, 0.5 Hz, 1H), 7.34 – 7.28 (m, 2H), 7.25 – 7.17 (m, 4H), 4.05 (t, *J* = 8.0 Hz, 3H), 2.56 (s,

2H), 2.04 – 1.84 (m, 2H), 1.67 (t, *J* = 12.4 Hz, 2H), 1.44 (s, 9H), 1.32 – 1.22 (m, 1H), 1.16 (dd, *J* = 13.1, 9.2 Hz, 2H).

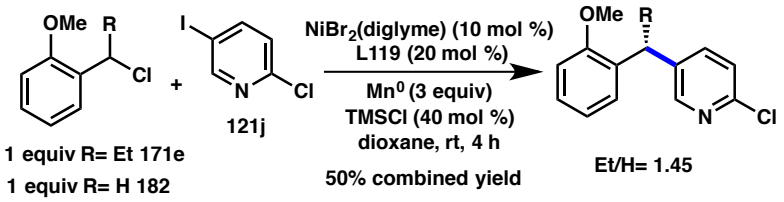
2-chloro-5-(1-(dibenzo[*b*,*d*]furan-4-yl)propyl)pyridine (172l)



Prepared from 2-chloro-5-iodopyridine (1 equiv, 48.0 mg, 0.2 mmol) and 4-(1-chloropropyl)dibenzo[*b*,*d*]furan (1 equiv, 49.0 mg, 0.2 mmol) following General Procedure 2. The crude residue was analyzed by NMR to give a 76% yield. The enantiomeric excess was determined to be 87% by chiral SFC analysis (OB-H, 2.5 mL/min, 10% IPA in CO_2, λ = 254 nm): t_R(minor) = 9.9 min, t_R(major) = 11.7 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.49 (dt, *J* = 2.5, 0.6 Hz, 1H), 7.93 (ddd, *J* = 7.7, 1.3, 0.7 Hz, 1H), 7.86 – 7.80 (m, 1H), 7.64 (ddd, *J* = 8.3, 2.6, 0.5 Hz, 1H), 7.56 (dt, *J* = 8.2, 0.8 Hz, 1H), 7.45 (ddd, *J* = 8.4, 7.3, 1.4 Hz, 1H), 7.37 – 7.29 (m, 3H), 7.23 – 7.18 (m, 1H), 4.46 (t, *J* = 7.9 Hz, 1H), 2.43 – 2.28 (m, 1H), 2.28 – 2.12 (m, 1H), 0.98 (t, *J* = 7.3 Hz, 3H).

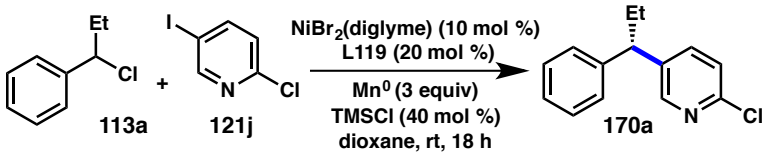
4.5.5 *Mechanistic experiments*

a. Competition Experiment



The experiment was conducted according to general procedure 2 for cross-coupling, except that 1-(1-chloropropyl)-2-methoxybenzene (**171e**, 0.05 mmol, 9.2 mg, 1 equiv) was added, followed by 2-methoxybenzyl chloride (**182**, 0.05 mmol, 7.8 mg, 1 equiv, Aldrich). After 4 h, the reaction was a cardinal red with some cloudy precipitate. The vial was opened and the reaction diluted with 20% EtOAc/hexanes and filtered through a short silica plug. Analysis of the crude reaction mixture by ^{1}H NMR showed a product ratio of Et/H = 1.45 by integration of the 2-pyridyl protons (δ^{Et} 8.31, δ^{H} 8.28) in a combined yield of 50%.

b. Inhibitor Studies

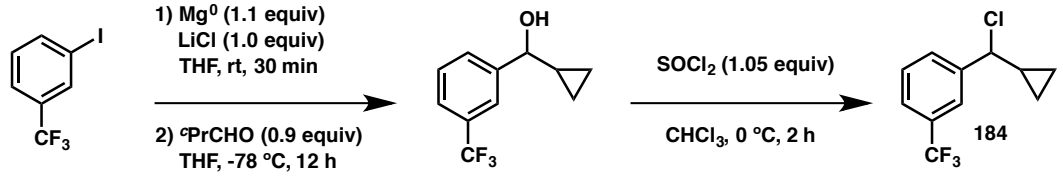


Control: 69% yield, 90% ee
50 mol % BHT (146): No conversion
50 mol % DHA (147): No conversion

The experiment was conducted according to general procedure 2 for cross-coupling, except that either BHT (0.025 mmol, 4.5 mg, 0.5 equiv) or DHA (0.025 mmol, 5.5 mg, 0.5 equiv) were added prior to pumping into the glovebox. After 18 h, the reactions were light grey with minimal precipitate. The vials were opened and the

reactions diluted with 20% EtOAc/hexanes and filtered through short silica plugs. Analysis of the crude reaction mixture by ^{1}H NMR showed no consumption of either coupling partner.

c. Radical Clock Experiment



In a glovebox, a flame-dried scintillation vial was charged with a cross-shaped stirbar, Mg^0 turnings (15.3 mmol, 371 mg, 1.1 equiv), LiCl (13.9 mmol, 589 mg, 1 equiv), and THF (10 mL) and sealed with a septum cap pierced with a vent needle. 3-Iodobenzotrifluoride (13.9 mmol, 2 mL, 1 equiv) was added in four portions with stirring. After each addition of 0.5 mL, the reaction was allowed to stir until a small exotherm was noted. After the final addition, the reaction was allowed to stir for 30 min until a muddy brown suspension was achieved with visible consumption of the Mg turnings. The vent needle was then removed and the vial was taken out of the glovebox. A separate flame-dried flask was charged with cyclopropylcarboxaldehyde (12 mmol, 0.9 mL, 0.9 equiv) and THF (33 mL), placed under N_2, and cooled to -78 ºC. The Grignard solution was then added dropwise via syringe. The vial was rinsed with additional THF (2 mL) and this was also added to the flask. The reaction was stirred overnight while the dry ice bath was allowed to warm to room temperature. The reaction was then quenched with 50% sat. aqueous NH_4Cl (30 mL). The layers were separated and the aqueous phase was extracted with Et_2O (2x 20 mL). Organics were combined, dried over Na_2SO_4, and concentrated to

afford the known benzylic alcohol as a yellow oil pure by ^{1}H NMR (97% yield, 11.7 mmol, 2.52 g).[1] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.71 (tq, *J* = 1.9, 0.7 Hz, 1H), 7.62 (dddt, *J* = 7.7, 1.9, 1.3, 0.6 Hz, 1H), 7.55 (ddt, *J* = 7.8, 1.8, 0.9 Hz, 1H), 7.47 (tt, *J* = 7.7, 0.8 Hz, 1H), 4.06 (dd, *J* = 8.5, 3.0 Hz, 1H), 1.33 – 1.12 (m, 1H), 0.68 (dddd, *J* = 9.4, 7.9, 5.5, 4.1 Hz, 1H), 0.65 – 0.58 (m, 1H), 0.54 – 0.47 (m, 1H), 0.43 (dtd, *J* = 9.6, 5.3, 4.4 Hz, 1H).

This material was subjected immediately to the chlorination procedure ($SOCl_2$ (1.05 equiv, 1.0 mL, 12.6 mmol) in $CHCl_3$ (40 mL)) and maintained at 0 ºC for 2 h until workup (according to known procedure except for shorter reaction time with monitoring by TLC). Care was taken to minimize exposure to light or heat during reaction, concentration, and handling. The material was stored at -20 ºC wrapped in foil. The product was isolated as a 4:1 inseparable mixture of the desired benzylic chloride **184** and the protodehalogenated, rearranged styrene product. This mixture was used as is according to literature procedure.[2] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.70 (dtt, *J* = 1.8, 1.2, 0.7 Hz, 1H), 7.64 (dddt, *J* = 7.7, 1.8, 1.1, 0.6 Hz, 1H), 7.58 (ddd, *J* = 7.9, 2.3, 1.0 Hz, 1H), 7.49 (tt, *J* = 7.9, 0.8 Hz, 1H), 4.32 (d, *J* = 9.3 Hz, 1H), 1.55 (dtt, *J* = 9.6, 8.0, 4.9 Hz, 1H), 0.86 (dddd, *J* = 9.0, 7.9, 6.0, 4.9 Hz, 1H), 0.73 (dddd, *J* = 8.9, 8.0, 6.1, 4.9 Hz, 1H), 0.62 (ddt, *J* = 9.7, 6.1, 4.9 Hz, 1H), 0.45 (ddt, *J* = 9.6, 6.0, 4.9 Hz, 1H).

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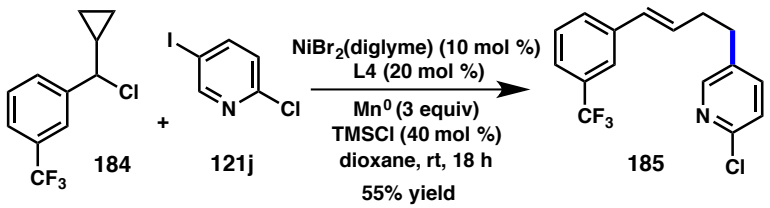

The cross coupling of radical clock substrate **184** was performed according to general procedure 2 employing 2-chloro-5-iodopyridine (1 equiv, 12.0 mg, 0.05 mmol) and 1-(chloro(cyclopropyl)methyl)-3-(trifluoromethyl)benzene (1 equiv, 16.0 mg, 0.05 mmol). The crude reaction mixture contained the rearranged product **185** as the only cross-coupled product. No cyclopropyl peaks were remaining in the crude ^{1}H NMR. **185** was isolated (55% yield, 8.6 mg, 0.028 mmol) by preparative TLC (5% Et_2O, 10% PhMe, 85% hexanes, RF= 0.15). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.21 (dd, *J* = 2.6, 0.7 Hz, 1H), 7.51 (q, *J* = 1.4 Hz, 1H), 7.48 – 7.39 (m, 4H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.22 (dd, *J* = 8.2, 0.7 Hz, 1H), 6.40 – 6.35 (m, 1H), 6.22 (dt, *J* = 15.8, 6.9 Hz, 1H), 2.76 (dd, *J* = 8.4, 6.9 Hz, 2H), 2.51 (dtd, *J* = 8.6, 6.9, 1.4 Hz, 2H). ^{13}C NMR (126 MHz, $cdcl_3$) δ 149.62, 149.26, 138.83, 137.93, 135.50, 130.41, 130.17, 129.17, 128.99, 123.96, 123.79 (q, *J* = 3.8 Hz), 122.68, 122.65, 34.23, 31.92. ^{19}F NMR (282 MHz, $cdcl_3$) δ -62.79.

4.6 NOTES AND REFERENCES

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