Chapter 3

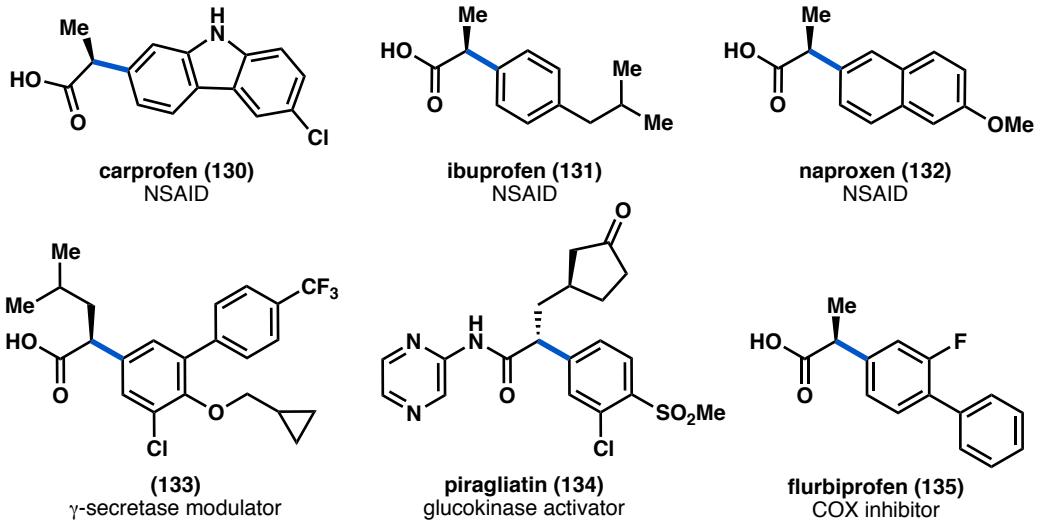
Nickel-Catalyzed Asymmetric Reductive Cross-Coupling of α-Chloroesters and Aryl Iodides

3.1 INTRODUCTION

Until recently, Ni-catalyzed asymmetric reductive cross-coupling was limited to benzyl chloride C(sp^3) electrophiles. In 2013, our group developed an asymmetric Ni-catalyzed reductive cross-coupling reaction between acid chlorides and benzyl chlorides to access α,α-disubstituted ketones.[1] Unfortunately, the conditions could not be applied to chloroformates or their derivatives to access α,α-disubstituted esters. This report was followed closely in 2014 with the cross-coupling of alkenyl bromides with benzyl chlorides.[2] In 2015, we expanded the scope of C(sp^3) electrophiles for this transformation to include α-chloronitriles.[3] We hypothesize that the successful coupling of a C(sp^3) electrophile is contingent upon radical stabilization by the α-substituent.[4] Based on this hypothesis, we could envision expanding this reactivity to include electrophiles with other radical-stabilizing α-substituents, such as α-halo carbonyl compounds. The

stereoconvergent cross-coupling of α-haloesters with C(sp^2) electrophiles, such as aryl iodides or alkenyl bromides, would allow us to access enantioenriched α,α-disubstituted esters, important motifs in both natural products and pharmaceuticals.[5]

Scheme 3.1. *Biologically active α-aryl carboxylic acid derivatives.*

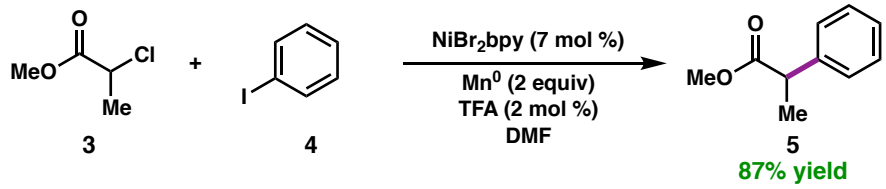


α-Functionalization of carbonyls has long been a challenge for synthetic chemists. Enantioenriched α,α-disubstituted carbonyl compounds are versatile synthetic intermediates and carboxylic acid derivatives containing α-aryl stereogenic centers are found in a number of biologically active compounds (Scheme 3.1).[5,6] Specifically, the nonsteroidal anti-inflammatory drugs (NSAIDs) are an FDA-approved class of molecules that contain an α-aryl carboxylic acid derivative. Often these compounds are synthesized in enantioenriched form by chiral resolution or through the use of chiral auxiliaries;[7–13] however, there has been much interest in developing catalytic, enantioselective alternatives to these processes.[14–19] A key challenge in this regard is identifying mild conditions under which the initially formed enantioenriched products are not racemized.[20]

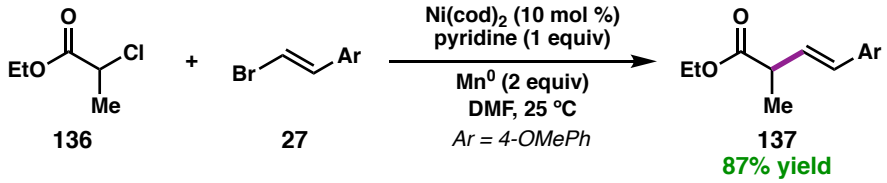
In recent years, several methods to access these compounds via Ni-catalysis have been disclosed.[21] Fu and coworkers have developed several asymmetric reactions to cross-couple α-halocarbonyl compounds with organometallic reagents.[22–26] In 2007, Durandetti reported the racemic reductive cross-coupling of α-chloroesters and aryl halides,[27,28] and in 2016, Gong disclosed the racemic reductive cross-coupling of α-chloroesters and -amides with alkenyl bromides (Scheme 3.2).[29] Drawing inspiration from these reports, we envisioned developing a Ni-catalyzed asymmetric reductive cross-electrophile coupling variant. While our lab's previous cross-coupling of α-chloronitriles generates enantioenriched products that can be derivatized to chiral α-aryl esters,[3] development of the cross-coupling with a different C(sp^3) electrophile may address the substrate limitations of the previous method. This alternative disconnection might broaden the scope of the C(sp^3) electrophile as well as enable the incorporation of more diverse aryl partners.

Scheme 3.2. *Ni-catalyzed reductive cross-coupling to access α-disubstituted carboxylic acid derivatives.*

a) Durandetti, 2007



b) Gong, 2016

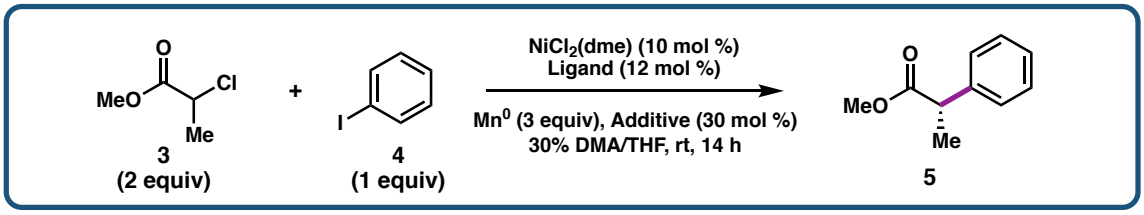


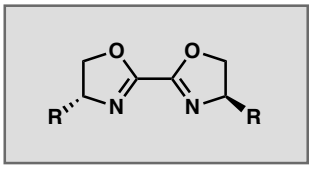
3.2 INITIAL EXPLORATION

3.2.1 Reaction Exploration

Our optimization efforts began with the arylation of methyl-2-chloropropionate (**3**), a commercially available substrate that was shown by Durandetti[27] to undergo Ni-catalyzed reductive coupling reactions. Exposure of a mixture of **3** and iodobenzene (**4**) to our standard conditions[1] using $NiCl_2$(dme) (10 mol %), Mn^0 as the reductant (3.0 equiv), in the presence of PhBOX (**L3**) failed to provide product. However, we discovered the use of bi(oxazoline) (BiOX) ligands provided more promising results,[30] with ^{i}PrBiOX **L19** delivering α-arylester **5** in 37% yield and 74% ee (Table 3.1, entry 3), perhaps due to the longer *N-N* distance tolerating the large steric profile of the aryl iodide coupling partner. Interestingly, use of the corresponding PhBiOX, **L21**, furnished the desired product in 26% yield, but with no enantiomeric excess (entry 1).

Table 3.1. *Preliminary bi(oxazoline) ligand screen.*[33]



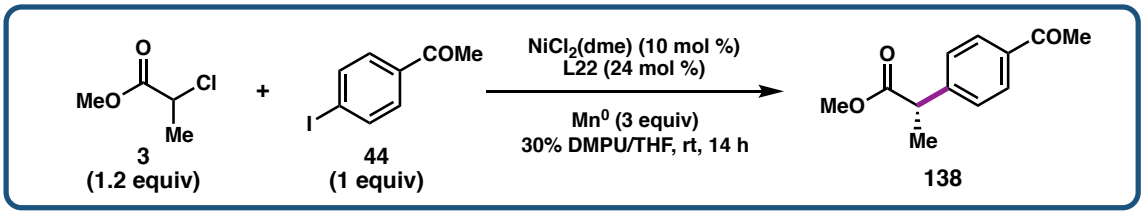


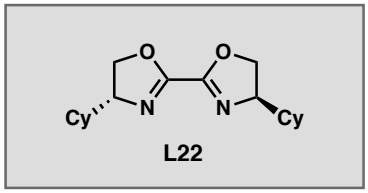
Ligand	R	Additive	Yield 5 (%)[a]	ee 5 (%)[b]
L21	Ph	—	26	0
L2	Bn	—	61	35
L19	^{i}Pr	—	37	74
L8	^{i}Bu	—	88	37
L19	^{i}Pr	TFA[c]	40	67
L19	^{i}Pr	TFA	73	76
L19	^{i}Pr	TMSCl	27	64

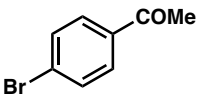
[a] Determined by GC using an internal standard. [b] Determined by GC using a chiral stationary phase. [c] 3 mol %.

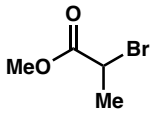
In these preliminary efforts to improve the yield, we determined that addition of co-catalytic trifluoroacetic acid (TFA) delivered arylation product **5** in 73% yield and 76% ee. The addition of TFA may serve to activate the Mn surface and improve reductive turnover of the catalyst, however additional studies are required to better understand the role it plays. Unfortunately, attempts to "pre-activate" the manganese surface by various acid washes delivered poor results, as well as other potential activators such as TMSCl.[31,32]

Table 3.2. *Investigation with a more functionalized aryl iodide.*[a]









Entry	Deviation	Yield 138 (%)[b]	ee 138 (%)[c]
1	L19	15	72
2	—	73	76
3	Zn^0	62	74
4	DMPU	40	65
5	THF	30	79
6	139 instead of 3	7	75
7	55 instead of 44	0	—
8	+ $NaBF_4$ (1 equiv)	78	76
9	+ NaI (0.5 equiv)	75	75

[a] Reactions conducted under inert atmosphere on 0.1 mmol scale. [b] Determined by ^1H NMR using an internal standard. [c] Determined by SFC using a chiral stationary phase.

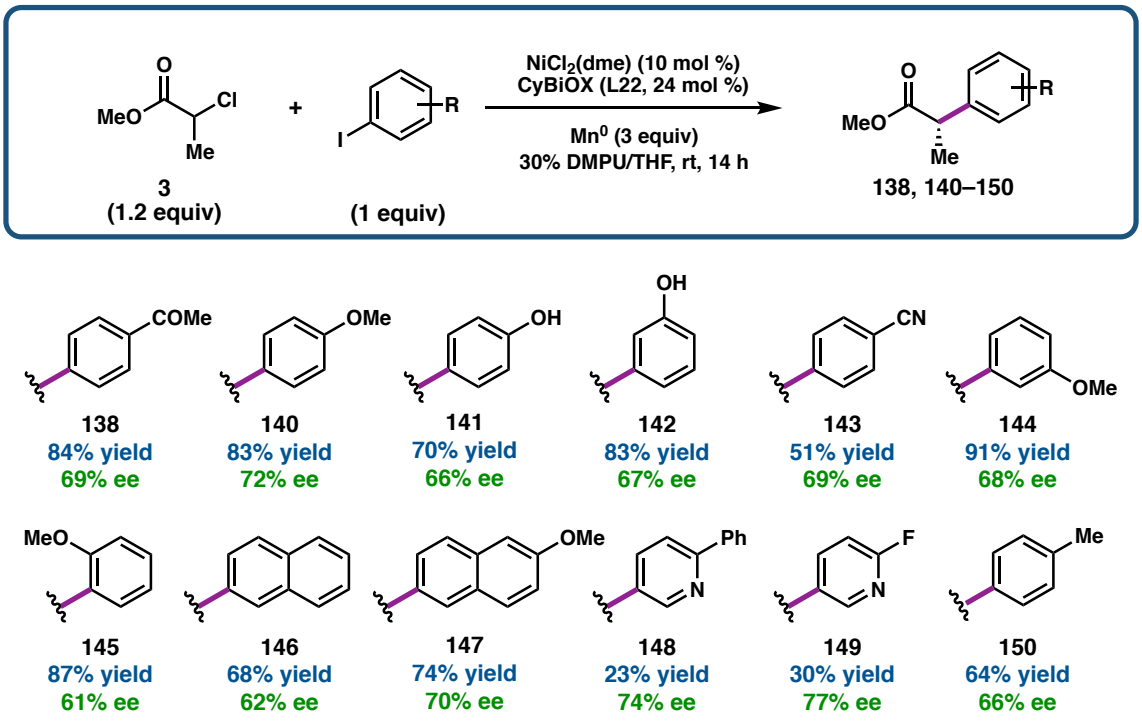
While these initial results were promising, we were disappointed to discover these conditions did not translate to functionalized aryl iodide coupling partners (Table 3.2, entry 1). Further exploration with aryl iodide **44** proved performing the reaction in a

solvent mixture of 30% DMPU/THF with bi(oxazoline) ligand **L22**, without the addition of catalytic TFA, effected formation of the product **138** in 73% yield and 76% ee (Table 3.2, entry 2). Zn^0 was similarly effective as a reductant in this reaction, giving **138** in slightly diminished yield, but 74% ee (entry 3). Interestingly, the yield of the reaction decreased significantly when performed in either DMPU or THF alone, though the ee decreases about 10% in DMPU (entries 4 and 5). The corresponding α-bromo ester **139** and aryl bromide **55** were both inferior coupling partners, giving trace or no product, respectively (entries 6 and 7), presumably because of mismatched rates of oxidative addition. Addition of additives such as $NaBF_4$ or NaI, which have aided previous reductive cross-coupling reactions,[3,34] provided no change to the yield or ee (entries 8 and 9).

3.2.2 Initial Substrate Scope

After initial exploration of reaction parameters, we sought to determine the substrate scope of the reaction. Aryl iodides bearing a variety of functional groups and substitution patterns were tolerated in good yield, but in only moderate levels of ee (Table 3.3). Coupling of **3** with aryl iodides bearing electron-withdrawing substituents were well tolerated, including nitrile-containing **143**. Electron-donating substituents were similarly viable in this reaction, including phenols (**141** and **142**) and methoxy groups (**140**, **144**–**145**). Importantly, substitution at both the *meta* and *ortho* positions was well tolerated for the anisole substrates (**140**, **144**–**145**). Finally, initial results for 4-iodo-2-halo-pyridyl substrates exhibit especially promising ee's, albeit in poor yields (**148** and **149**).

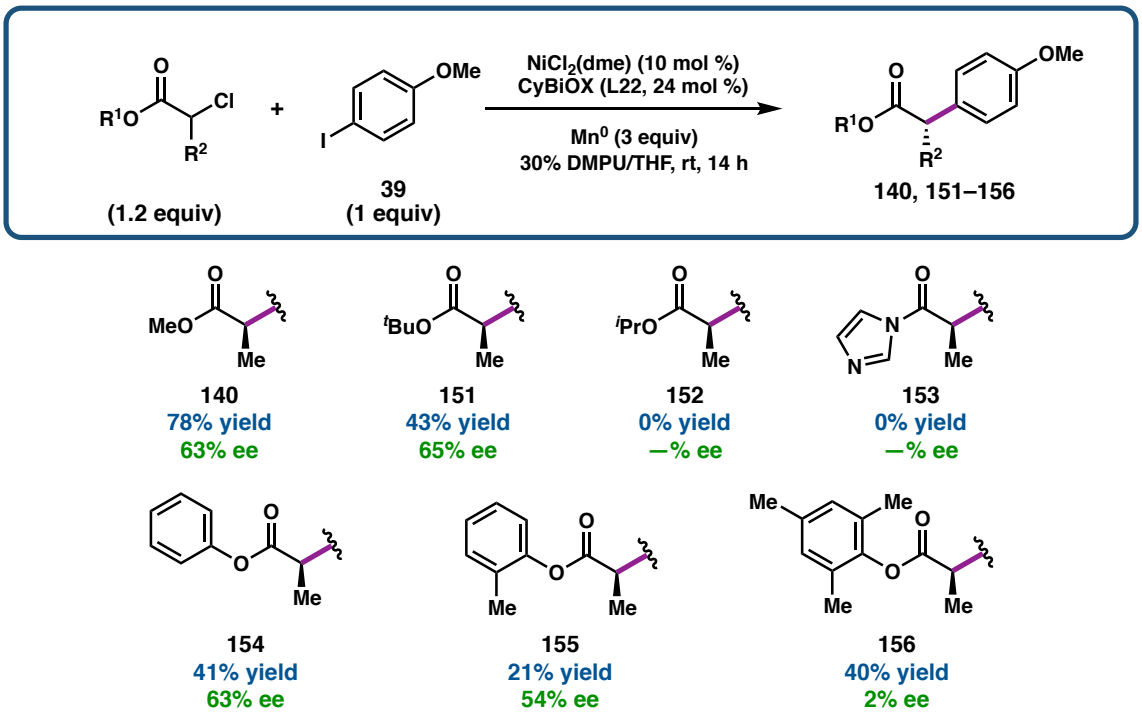
Table 3.3. *Preliminary aryl iodide substrate scope.*[a]



[a] NMR yields, reactions conducted on 0.2 mmol scale under a N_2 atmosphere. % ee determined by SFC using a chiral stationary phase.

Unfortunately, the substrate scope of the α-chloroester coupling partner was limited almost exclusively to methyl-2-chloropropionate (**3**, Table 3.4). Other ester groups, including alkyl and aryl derivatives, delivered the corresponding cross-coupled product in decreased yield and often with worse ee (**151**– **152**, **154–156**). Amide **153** did not afford any of the desired product. The C(sp^3) electrophile was also limited at R^2, only tolerating methyl-substitution.

***Table 3.4**. Preliminary α-chloroester substrate scope.*[a]



[a] NMR yields, reactions conducted on 0.2 mmol scale under a N_2 atmosphere. % ee determined by SFC using a chiral stationary phase.

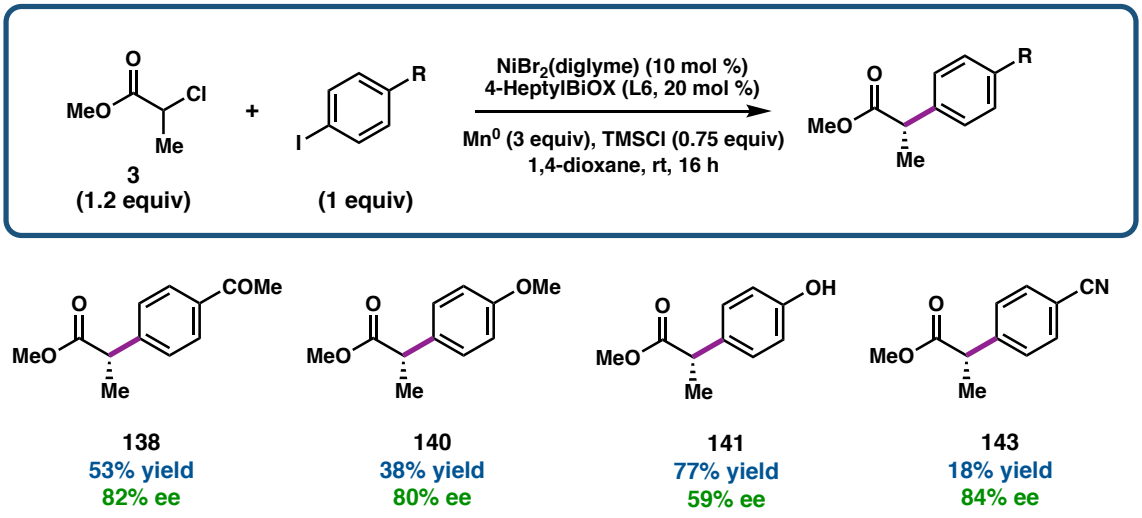
3.3 LIGAND EXPLORATION

3.3.1 Reaction Development

With significant limitations in both the substrate scope and enantioselectivity for this transformation, the development of this reaction was halted while the work described in **Chapter 2** was conducted. Upon the completion of that project, we sought to determine if the knowledge we gained in the development of the cross-coupling of benzyl chlorides and aryl iodides could be leveraged in the α-chloroester system, specifically how non-polar solvents with TMSCl and 4-HeptylBiOX (**L6**) would perform with this transformation. We were pleased to observe that upon subjection of **3** and **44** to $NiBr_2$(diglyme) (10 mol %), **L6** (20 mol %), Mn^0 as the reductant (3 equiv), TMSCl as an

additive (0.75 equiv), in 1,4-dioxane at room temperature (Table 3.5), **138** was formed in 82% ee, the highest ee we had observed in the cross-coupling of α-chloroesters to date by a significant margin. Similar results were observed with aryl iodide **39**, forming **140** in 80% ee, and 4-iodobenzonitrile, which gave **143** in 84% ee, again major increases from results with our previous conditions. While the yields of these three substrates decreased significantly, we felt confident that reinvestigation of this system would prove fruitful. Interestingly, the coupling of 4-iodophenol gave product **141** in reduced ee than previously observed, but in higher yield.

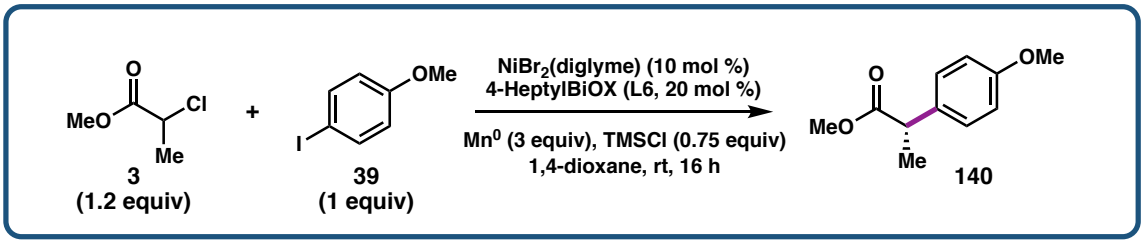
Table 3.5. *Application of 1,4-dioxane/TMSCl conditions.*

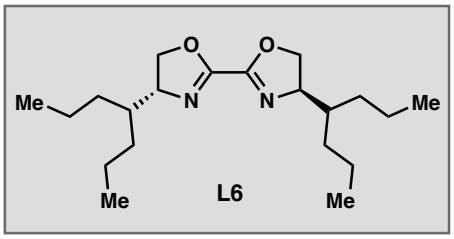


With these exciting results in hand, we renewed our investigation into the cross-coupling of **3** and **39**, starting from the conditions developed in **Chapter 2**. A screen of solvents revealed the yield of **140** increased to 60% in both THF and DMA, with little erosion of ee (Table 3.6, entries 2 and 3). However, while the yield increased to 75% when the reaction was performed in DMPU, the ee decreased significantly to 66% (entry 4). Addition of $NaBF_4$ to the reaction in 1,4-dioxane increased the yield of **140** from 28%

to 50% (entry 5), while increasing the equivalents of the aryl iodide coupling partner also improved the yield of **140** to 59% (entry 6). To our delight, increasing the equivalents of **39** in THF afforded **140** in 88% yield and 80% ee (entry 8). The combination of the addition of $NaBF_4$ with two equivalents of **39** in THF delivered **140** in 87% yield and 82% ee (entry 9).

***Table 3.6**. Investigation of reaction parameters with **L6**.*



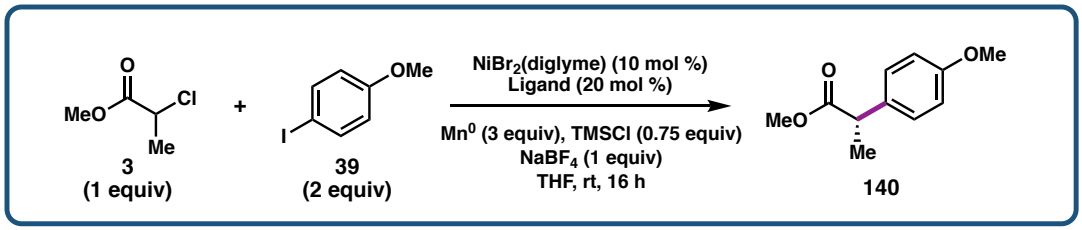


Entry	Solvent	Conditions	Yield 140 (%)	ee 140 (%)
1	1,4-dioxane	—	28	80
2	THF	—	59	75
3	DMA	—	60	77
4	DMPU	—	76	66
5	1,4-dioxane	+ $NaBF_4$ (1 equiv)	50	83
6	1,4-dioxane	2 equiv 39	59	82
7	THF	+ $NaBF_4$ (1 equiv)	59	81
8	THF	2 equiv 39	88	80
9	THF	+ $NaBF_4$, 2 equiv 39	87	82

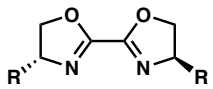
Performing the cross-coupling of methyl-2-chloropropionate (**3**) and 2 equiv of 4-iodoanisole (**39**), now in THF with both TMSCl and $NaBF_4$ as additives, we explored a series of bi(oxazoline) ligands (Table 3.7). Similar to results we observed in **Chapter 2**, aryl-substituted bi(oxazoline) ligands, such as **L21**, **L2**, and **L26** (entries 3-5), furnished the desired product in low yield and poor ee. Alkyl-substituted BiOX ligands, such as **L22** and **L19**, produced **140** in moderate yield and ee. Curiously, 4-HeptylBiOX was

significantly better than all other bi(oxazoline) ligand evaluated (entry 10), even compared to structurally similar **L33** (entry 9).

Table 3.7. *Bi(oxazoline) ligand screen in THF.*



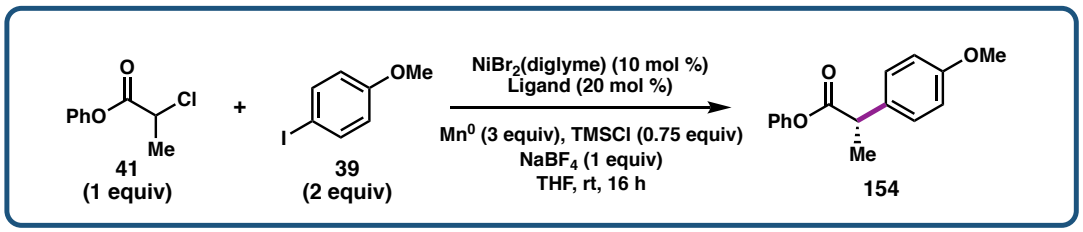
Bi(oxazoline) Ligand Scaffold



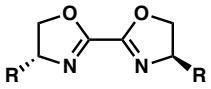
Entry	Ligand	R	Yield 140 (%)	ee 140 (%)
1	L22	Cy	40	64
2	L34	-CH_2Cy	41	32
3	L21	Ph	4	12
4	L2	Bn	41	29
5	L26	-CH_2-2-Nap	47	29
6	L19	^{i}Pr	33	66
7	L8	^{i}Bu	36	33
8	L20	^{t}Bu	3	21
9	L33	3-Pentyl	43	68
10	L6	4-Heptyl	87	82

At this time, a brief investigation into the substrate scope of the reaction in these updated reaction conditions revealed the surprising efficacy of phenyl-2-chloropropionate (**41**) as the C(sp^3) coupling partner (Table 3.8). An identical BiOX ligand screen was performed on the cross-coupling of **41** and **39** and we were pleased to observe a significant increase in yield across all ligands evaluated. Notably, *sec*-alkyl BiOX ligands **L33** and **L6** gave the product in nearly quantitative yield and 77% and 80% ee, respectively (entries 9-10).

Table 3.8. *Bi(oxazoline) ligand screen with phenyl-2-chloropropionate (**41**).*



Bi(oxazoline) Ligand Scaffold

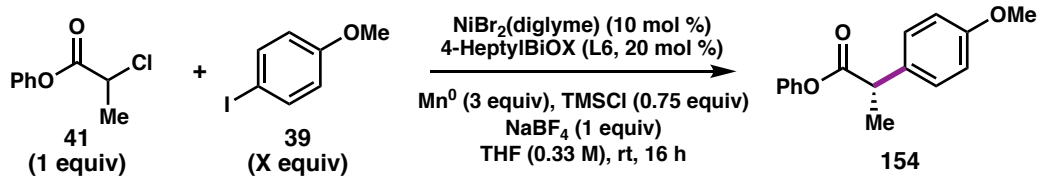


Entry	Ligand	R	Yield 154 (%)	ee 154 (%)
1	L22	Cy	80	70
2	L34	-CH_2Cy	81	35
3	L21	Ph	0	—
4	L2	Bn	58	30
5	L26	-CH_2-2-Nap	70	34

Entry	Ligand	R	Yield 154 (%)	ee 154 (%)
6	L19	^{i}Pr	72	74
7	L8	^{i}Bu	83	34
8	L20	^{t}Bu	7	21
9	L33	3-Pentyl	97	77
10	L6	4-Heptyl	99	80

Having successfully improved the yield of the coupling, we revisited the effect of equivalents of aryl iodide in the reaction. We were pleased to see that decreasing the equivalents of **39** from 2 to 1.5 afforded **154** in 93% yield and 82% ee (Scheme 3.3). However, lowering **39** to 1 equiv resulted in a decrease to 76% yield. Further reaction development was conducted with 1 equiv of the α-chloroester and 1.5 equiv of aryl iodide.

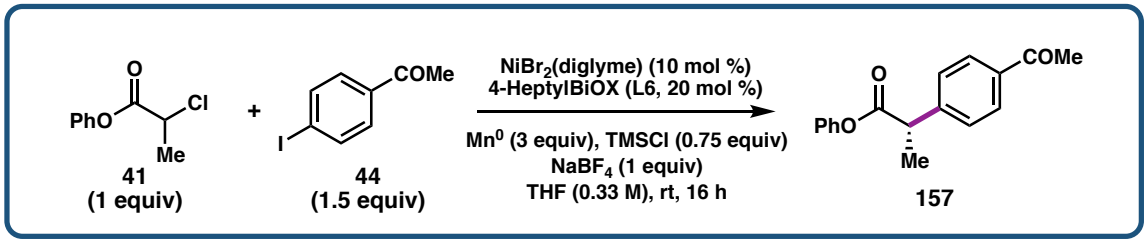
Scheme 3.3. *Equivalents of aryl iodide coupling partner.*



1.5 equiv 39: 93% yield, 82% ee
1.0 equiv 39: 76% yield, 82% ee

At this point in our optimization efforts, we chose to proceed with 4-iodoacetophenone (**44**), which, under the updated conditions, cross-coupled with **41** in only 67% yield and 85% ee. Intent on improving both the yield and enantioselectivity of this transformation, every reaction parameter was examined. Investigation of several Ni catalysts demonstrated $NiBr_2$(diglyme) was still the optimal catalyst in the reaction (Table 3.9, entry 1), but performed similarly to $NiBr_2$(glyme), $Ni(acac)_2$, and $Ni(cod)_2$ (entries 2, 4 and 5). Interestingly, anhydrous NiI_2, $NiCl_2$, and NiF_2 gave only a small amount of **157** in approximately 80% ee (entries 6-8), most likely due to solubility issues in THF.

Table 3.9. *Evaluation of reaction parameters.*



Catalyst Screen:

Entry	Catalyst	Yield 157 (%)	ee 157 (%)
1	$NiBr_2$(diglyme)	67	84
2	$NiBr_2$(glyme)	64	84
3	$NiCl_2$(glyme)	49	84
4	$Ni(acac)_2$	63	83
5	$Ni(cod)_2$	63	84
6	NiI_2	20	83
7	$NiCl_2$	13	79
8	NiF_2	19	81

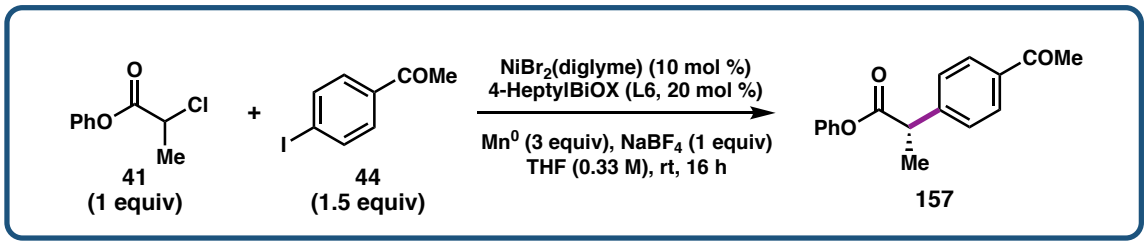
Additive Screen:

Entry	Conditions	Yield 157 (%)	ee 157 (%)
9	Control	67	85
10	–TMSCl	62	85
11	$–NaBF_4$	47	85
12	–TMSCl, $–NaBF_4$	59	84

We were interested to see if both TMSCl and $NaBF_4$ were necessary as additives for the reaction in THF. Control experiments removing one or both reagents

demonstrated that TMSCl was unnecessary (Table 3.9, entry 10), but the yield decreases in the absence of $NaBF_4$ (entries 11 and 12). The higher yields observed with $NaBF_4$ can be attributed to increased conversion, similar to results reported by Molander and coworkers in their reductive cross-couplings of heteroaromatic substrates.[35] Currently, it is unclear if the role of $NaBF_4$ is to act as a halide-scavenging agent, a mild Lewis acid, or simply an electrolyte.

Table 3.10. *Investigation of solvent and salt additive.*



Solvent:

Entry	Solvent	Yield 157 (%)	ee 157 (%)
1	THF	64	85
2	1,4-dioxane	53	84
3	DMPU	74	58
4	DMA	51	65
5	DMF	30	57

$^-BF_4$ Additive:

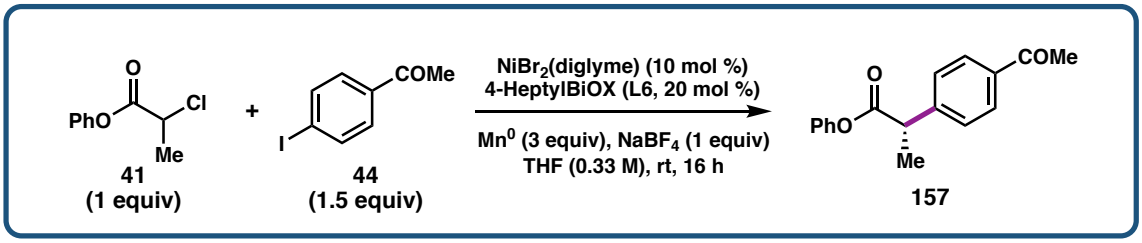
Entry	Additive	Yield 157 (%)	ee 157 (%)
6	$NaBF_4$	66	85
7	$LiBF_4$	77	73
8	KBF_4	50	84
9	$AgBF_4$	72	86

Conducting the reaction now without TMSCl, we reinvestigated solvent effect. While the same ee is achieved in THF as 1,4-dioxane (Table 3.10, entries 1 and 2), the yield of **157** decreases to 53% in 1,4-dioxane. Polar solvents such as DMPU, DMA and DMF give **157** with only moderate levels of enantioselectivity (entries 3–5). Looking closer at the role of $NaBF_4$ in the reaction, we evaluated a series of tetrafluoroborate salts (Table 3.10). While $LiBF_4$ gave **157** in higher yield (77%), the ee was reduced to 73%

(entry 7). $AgBF_4$ gave **157** in 72% yield and 86% ee (entry 9). Further investigation into the use of $AgBF_4$ is still needed on this system.

Next, we assessed catalyst and ligand loading and ratio (Table 3.11). Looking at 1:1, 1:2 and 1:3 ratios of Ni to **L6** at 5, 10 and 15 mol % Ni loading, we found that the optimal yield and ee was achieved at 10 mol % Ni and 20 mol % ligand (entry 4), which was the loading ratio we had been working with in previous screens. It is unclear why excess ligand is necessary for higher conversion, but one possibility is that the ligand is degraded during the course of the reaction. Unfortunately, we do not detect any remaining **L6** in the crude reaction mixtures.

Table 3.11. *Ni loading and concentration screens.*



Catalyst Loading:

Entry	Ni equiv	L equiv	Yield 157 (%)	ee 157 (%)
1	5%	5%	57	85
2	5%	10%	56	85
3	10%	10%	46	84
4	10%	20%	64	85
5	10%	30%	60	85
6	15%	15%	40	85
7	15%	30%	55	84

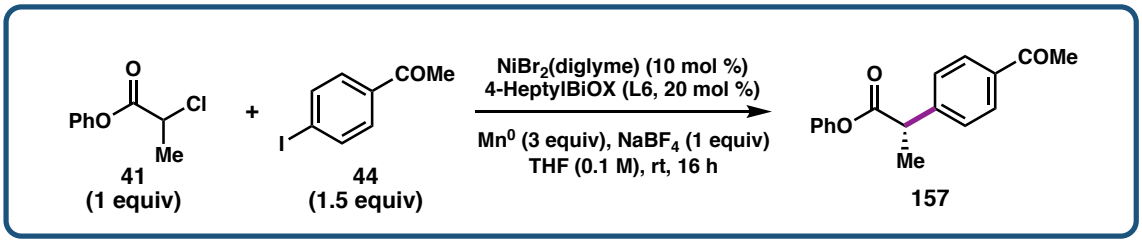
Concentration:

Entry	Concentration	Yield 157 (%)	ee 157 (%)
8	0.05 M	74	87
9	0.1 M	87	86
10	0.2 M	76	85
11	0.3 M	63	84
12	0.5 M	58	84
13	0.6 M	30	82
14	0.8 M	37	81
15	1.0 M	42	81

We then turned our attention toward determining the ideal concentration of the reaction (Table 3.11). Surveying the reaction at various molarities, we were delighted to

observe **157** was delivered in 87% yield at 0.1 M without any erosion of ee (entry 9). Presumably, the concentration of the reaction affects the rates of oxidative additive of each electrophile, changing the ratio of desired product to homocoupling products.

Table 3.12. *Temperature and dual solvent system exploration.*



Temperature:

Entry	Temperature (°C)	Yield 157 (%)	ee 157 (%)
1	10	72	87
2	23	72	86
3	40	80	86
4	60	61	85

Solvent:

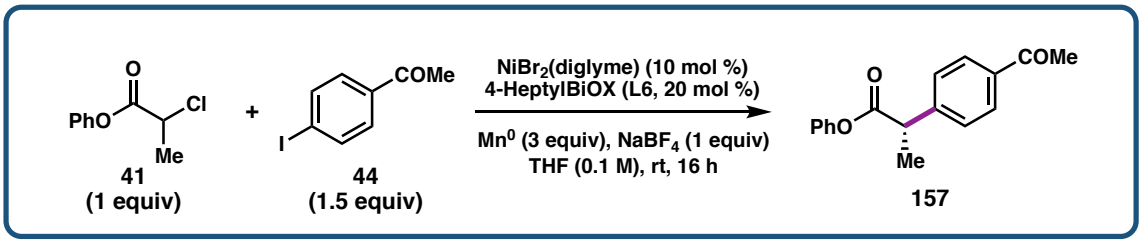
Entry	DMPU/THF	Yield 157 (%)	ee 157 (%)
6	0% DMPU	82	86
7	10% DMPU	84	82
8	20% DMPU	78	80
9	30% DMPU	62	76
10	40% DMPU	77	51

At this point in our optimization efforts, we hoped that lowering the reaction temperature would improve the ee, an effect our lab has observed previously.[2,36,37] Lowering the temperature to 10 ºC appeared to have no effect on the reaction (Table 3.12, entry 1). Further studies on lower temperatures are necessary to see if selectivity can increase without inhibiting product formation. Conversely, we also attempted increasing the reaction temperature to 40 and 60 ºC and observed a fluctuation in yield, but no change in ee (Table 3.12, entries 3 and 4). Now conducting the reaction at a more dilute concentration, we wondered if addition of a small amount of DMPU in THF could provide the synergistic effect we observed in our earliest optimization efforts (Table 3.2).

Unfortunately, the addition of any amount of DMPU in this system only resulted in a decrease in enantioselectivity (Table 3.12, entries 6-10).

Finally, we wanted to confirm that Mn^0 was still the optimal reductant in this transformation. When the reaction was performed with Mn^0, we observed product **157** forming in 82% yield and 86% ee with Mn^0 (Table 3.13, entry 1). Zn^0 provided identical ee, but lower 54% yield (entry 2). We did not observe product formation with TDAE acting as a terminal reductant (entry 3).

Table 3.13. *Evaluation of reductants.*

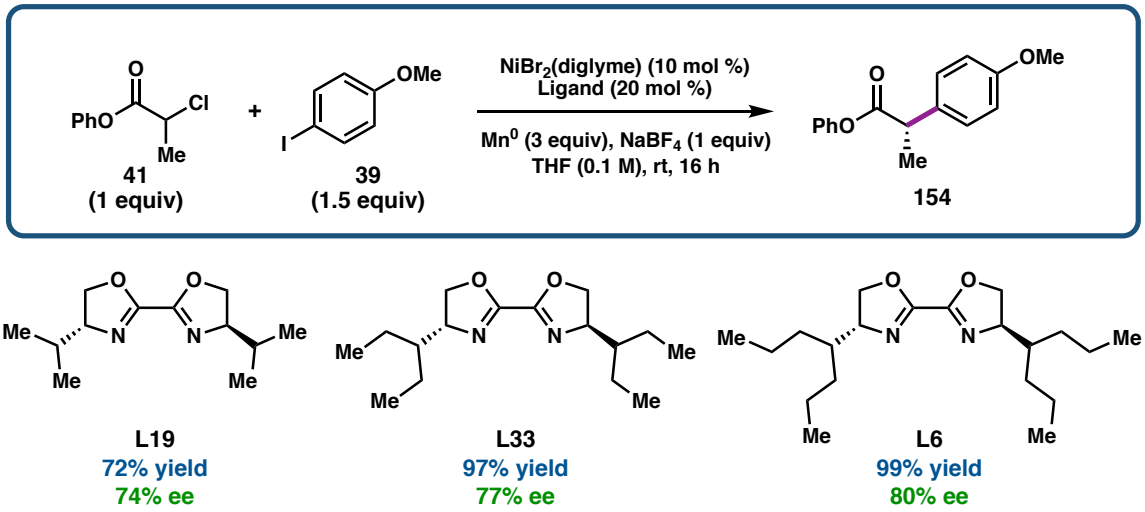


Entry	Reductant	Yield 157 (%)	ee 157 (%)
1	Mn	82	86
2	Zn	54	86
3	TDAE	0	—

3.3.2 Ligand Trends

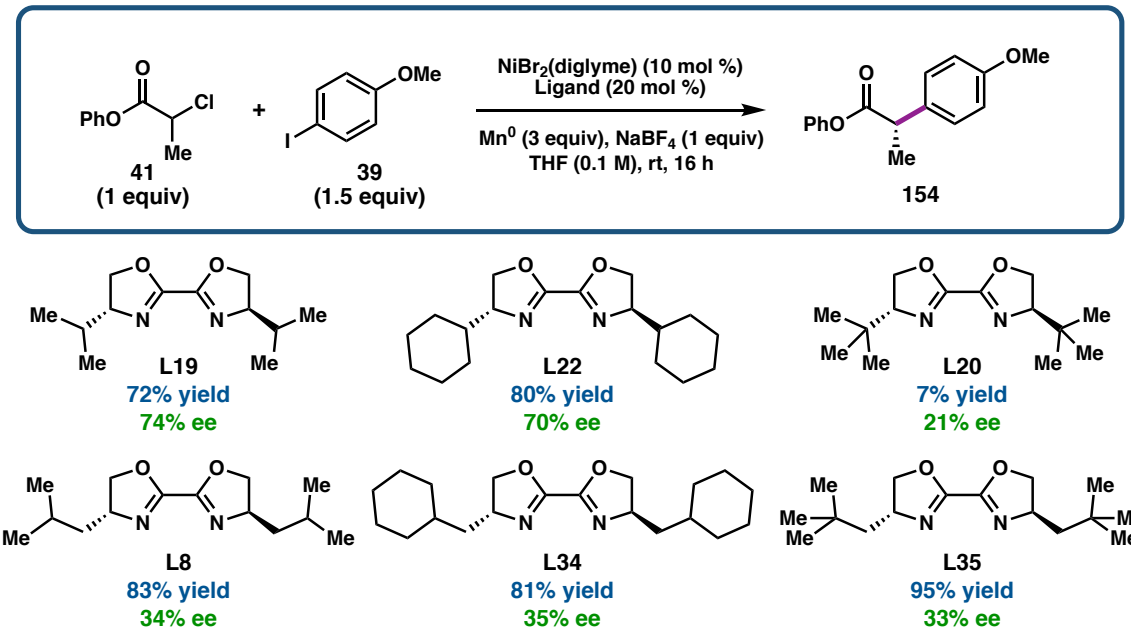
Having thoroughly explored several reaction parameters, we felt that in order to improve the selectivity, we needed to return to ligand design and more closely examine the effect of alkyl-substituted bi(oxazoline) ligands on this transformation. Interestingly, unlike the cross-coupling of benzyl chlorides and aryl iodides (**Chapter 2**), the ee of the desired product (**154**) does not change significantly as the length of the alkyl chains increase from ^{i}Pr (**L19**) to 4-Heptyl (**L6**, Table 3.14).

***Table 3.14**. Comparison of sec-alkyl substituted bi(oxazoline) ligands.*



However, upon closer inspection of the reactivity and selectivity trends across several alkyl-substituted ligands, it appears branching directly adjacent to the oxazoline core is crucial for selectivity (Table 3.15). While **154** is formed in 72% yield and 74% ee with **L19**, the corresponding ligand with a methylene unit separating the ^{i}Pr branching from the oxazoline (**L8**) gives **154** in still high 83% yield, but in only 34% ee. Similarly, **L22** produces **154** in 80% yield and 70% ee, but the addition of a methylene between the cyclohexyl group and the oxazoline (**L34**) decreases the ee of **154** to 35%, while still delivering the product in 81% yield. Finally, following this pattern, **L35** delivers **154** in 95% yield, but 33% ee. However, while the yield of **154** is consistently high amongst these alkyl-substituted ligands, **L20** with ^{t}Bu branching directly adjacent to the oxazoline proves to be too sterically hindered for productive reactivity. With these trends in mind, we must design and synthesize more alkyl-substituted BiOX ligands with sec-alkyl branching adjacent to the oxazoline, but with different branching scaffolds on the substituents, to try in this system.

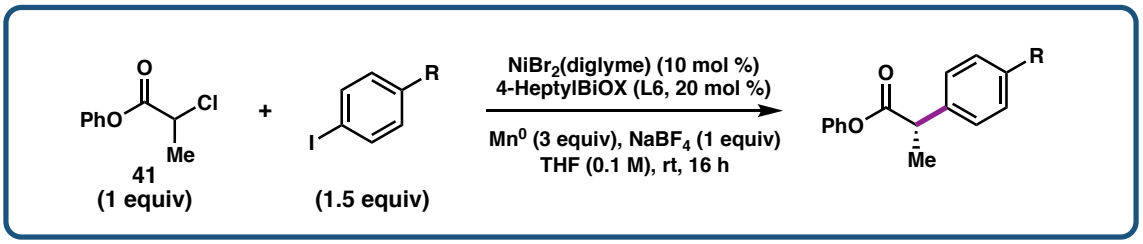
Table 3.15. *Alkyl bi(oxazoline) ligand substitution effects on cross-coupling.*

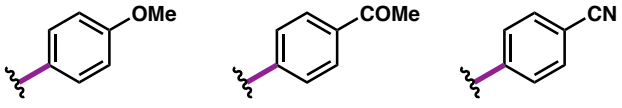


3.3.3 Improved Substrate Scope

Utilizing **L6** and running the cross-coupling of α-chloroesters and aryl iodides in THF with $NaBF_4$ as an additive has greatly expanded the substrate scope of the reaction. These seemingly subtle changes from the original DMPU/THF system have increased both the yields and ee of the cross-coupled products from several aryl iodides (Table 3.16). Substrates containing both electron-withdrawing and –donating groups are now coupling in up to 99% yield and 86% ee (Table 3.16). Notably, pyridine substrates **42** and **160** are now coupled in high yields, 94% and 67%, paving the way for further investigation into the use of (hetero)aryl iodides in this reaction. We look forward to full exploration of the functional groups tolerated in this reaction, as well as their substitution on the aryl iodide.

Table 3.16. *Current aryl iodide substrate scope.*[a]

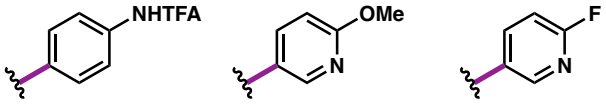




154
99% yield
80% ee

157
84% yield
86% ee

158
95% yield
75% ee



159
94% yield
85% ee

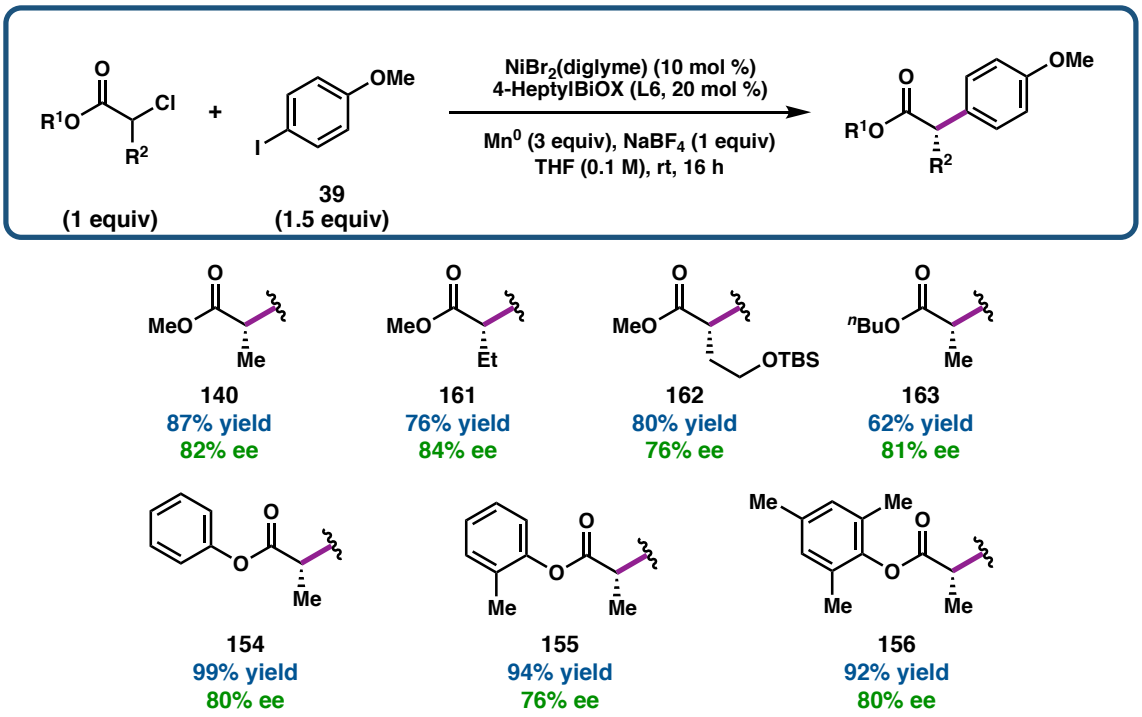
42
94% yield
84% ee

160
67% yield
82% ee

[a] NMR yields, reactions conducted on 0.05 mmol scale under a N_2 atmosphere. % ee determined by SFC using a chiral stationary phase.

More impressive, however, is the largely expanded tolerance of α-chloroester substrates in this transformation (Table 3.17). Before, methyl-2-chloropropionate (**3**) was the only effective C(sp^3) coupling partner. Now, several alkyl esters (**161**–**163**), as well as aryl esters (**154**–**156**) are tolerated in good to excellent yield and good ee. Moreover, groups larger than methyl are tolerated in the α-position, including ethyl (**161**) and silyloxyethyl (**162**). The promising expansion of the scope with more optimized conditions makes us hopeful for further substrate exploration and potential applications to the synthesis of bioactive targets.

***Table 3.17**. Current α-chloroester substrate scope.*[a]

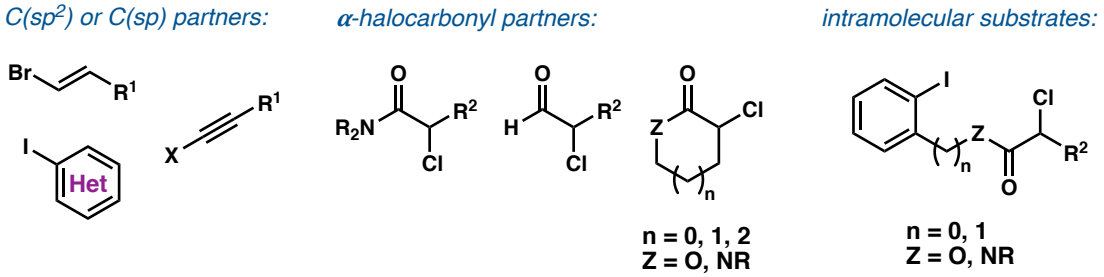


[a] NMR yields, reactions conducted on 0.05 mmol scale under a N_2 atmosphere. % ee determined by SFC using a chiral stationary phase.

3.3.4 Future Directions

In addition to novel ligand design and synthesis, we will seek to develop related reactions, including the cross-coupling of α-haloamides and α-haloaldehydes (Scheme 3.4). The latter substrates, which are prone to epimerization under mild conditions, will probe the mildness of the reaction conditions; given our success in preparing enantioenriched α-arylketones by Ni-catalyzed reductive coupling,[1] we are optimistic about this endeavor. The use of heteroaryl, vinyl, and alkynyl halides as coupling partners will also be investigated. As part of these studies, intramolecular reactions to make enantioenriched lactones and lactams will also be explored.

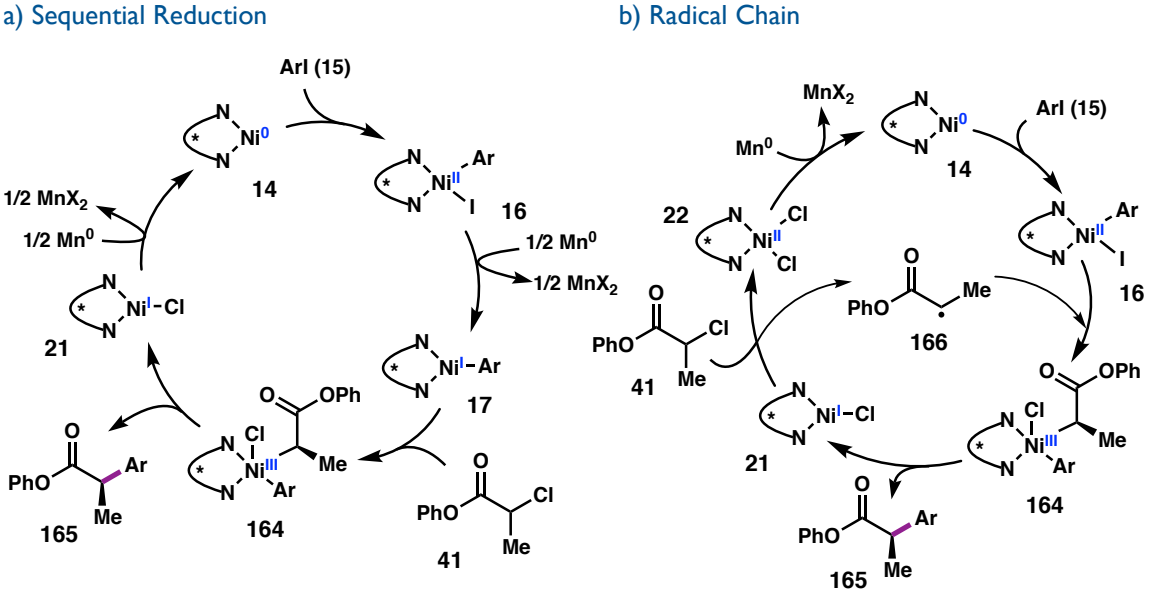
Scheme 3.4. *Further substrates for investigation.*



3.4 MECHANISTIC STUDIES

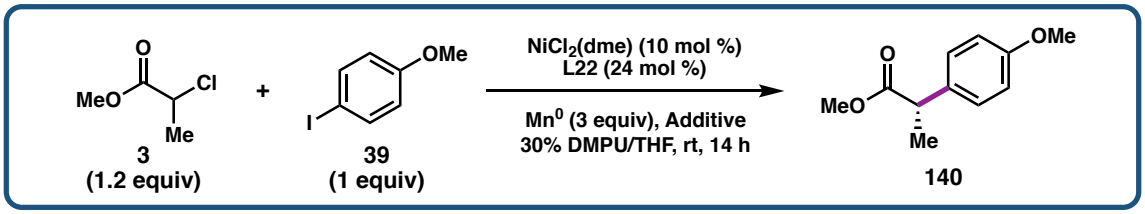
As described in **Chapter 1**, we hypothesize that asymmetric reductive cross-couplings of radical-stabilized C(sp^3) electrophiles may proceed through the intermediacy of prochiral radicals generated from a halide abstraction event. This can occur in either a sequential reduction mechanism, in which halide abstraction and radical addition occur rapidly in a radical rebound process (Figure 3.1a), or a radical chain reaction mechanism with a long-lived, cage escaped radical intermediate (Figure 3.1b).

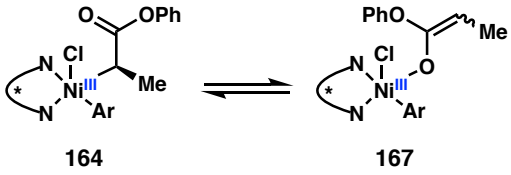
Figure 3.1. *Mechanistic hypotheses.*



A unique feature of the α-chloroester C(sp^3) electrophile is the ability of Ni to bind the substrate in an η^3 fashion. Competing carbon-bound and oxygen-bound Ni species (**167**, Table 3.18) could racemize a single diastereomer of Ni(III) complex **164** formed in an enantiodetermining oxidative addition step. We hypothesized that the addition of a Lewis acid could bind the carbonyl and favor a carbon-bound Ni species (**164**, Table 3.18). The reaction was treated with various Lewis acids to probe this phenomenon with an improvement in ee (Table 3.18). Unfortunately, these additives mostly inhibited reactivity and did not have a positive effect on the enantioselectivity.

Table 3.18. *Investigation of Lewis acids.*



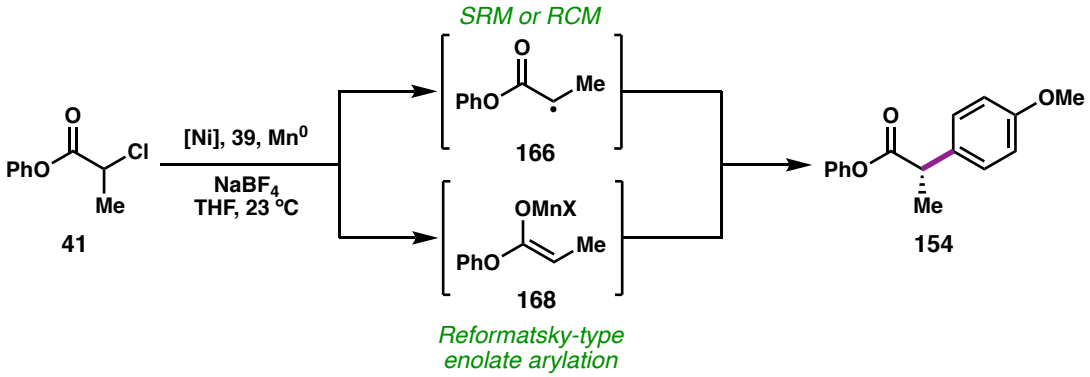


Entry	Additive	Yield 140 (%)	ee 140 (%)
1	none	41	69
2	$MnCl_2$	5	61
3	$ZnCl_2$	5	52
4	LiCl	2	47
5	$Sc(OTf)_3$	53	61
6	$Yb(OTf)_3$	13	45
7	$Zn(OTf)_2$	0	—

It is also possible that, rather than the sequential reduction mechanism or radical chain reaction mechanism hypothesized to be operative, the Ni-catalyzed reaction between **41** and an aryl iodide proceeds by a more conventional enolate arylation mechanism in which *in situ* formation of a manganese enolate is operative (Scheme

3.5).[38] If so, the steric and electronic profile of the metal enolate could potentially influence the reactivity and selectivity of the system.[39,40]

Scheme 3.5. *Possible Reformatsky-type enolate arylation mechanism.*



If this reaction proceeds by the formation of a manganese enolate, reduction of **41** by Mn^0 would provide enolate **168** (Scheme 3.5), which could undergo transmetalation with Ni(II) complex **16** to intercept a conventional enolate arylation mechanism. Thus, Mn^0 would not be required to turn over the catalyst, only to generate the enolate. In addition to determining the order in each component using kinetic analysis, it should be possible to distinguish between the Reformatsky-type mechanism and a radical chain reaction mechanism by stoichiometrically preparing the relevant manganese enolate.[41,42] If exposure of **168** to the standard reaction conditions in the absence of Mn^0 provides **154** in the same ee as the catalytic conditions, it would provide support for the Reformatsky-type mechanism. Alternatively, LNi(II)(Ph)I (**16**) could be prepared and treated with α-chloroester **41** in the presence and absence of Mn^0; if a radical chain reaction mechanism is operative, then addition of **16** to **41** would be expected to provide **154** in the absence of Mn^0.

3.5 CONCLUSION

In conclusion, the development of a Ni-catalyzed stereoconvergent reductive cross-coupling of α-chloroesters and aryl iodides to access enantioenriched α-arylpropionates is currently underway in our laboratory. Identification of a phenyl ester $C(sp^3)$ coupling partner suggests a promising substrate scope. Importantly, the enantioenriched α-arylated esters are stable and do not suffer from racemization under the mild reaction conditions. Further ligand synthesis is required to improve the enantioselectivity of the reaction.

3.6 EXPERIMENTAL SECTION

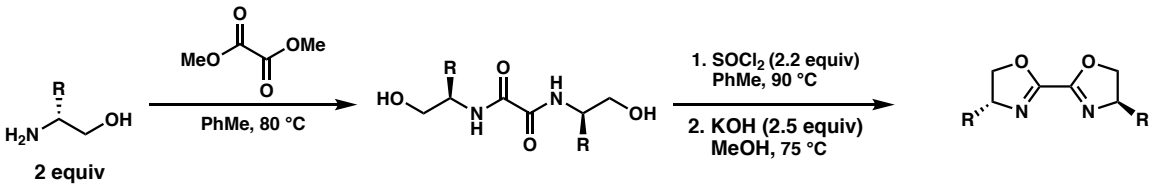
3.6.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Methylene chloride (DCM), diethyl ether (Et_2O), tetrahydrofuran (THF), 1,4-dioxane 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 and basic alumina 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 and aluminum oxide (activated, basic, Brockmann I, 58 Å pore size, powder) purchased from Sigma-Aldrich. ^1H and ^{13}C NMR were recorded on a Varian Inova 500 (at 500 MHz and 125 MHz respectively) or a Bruker Avance III HD with Prodigy cyroprobe (at 400 MHz and 101 MHz respectively). ^1H and ^{19}F NMR spectra were recorded on a Varian Inova 300 (at 300 MHz and 282 MHz, respectively). NMR data is reported relative to internal chloroform (^1H, δ = 7.26, ^{13}C, δ = 77.0) and C_6F_6 (^{19}F, δ = –164.9). 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, 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). SFC analysis performed at 100.0 bar and 40 ºC. 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.

3.6.2 Ligand Preparation

3.6.2.1 *General Procedure 1 for bi(oxazoline) ligand synthesis.*



Amino alcohol (2 equiv) and dimethyloxalate (1 equiv) were dissolved in PhMe (0.05 M) and heated to 80 °C. The reaction was allowed to stir overnight. Reaction was cooled to room temperature and concentrated *in vacuo* and placed under vacuum at room temperature for 3 h to remove all excess MeOH and afford the crude diol. The crude diol was dissolved in PhMe (0.15 M) and heated to 70 °C whereupon thionyl chloride (2.2 equiv) was added. Reaction was stirred at 70 °C for 30 minutes then heated to 90 °C for 90 minutes. The reaction was cooled to room temperature and poured into 20% KOH solution cooled to 0 °C. The aqueous layer was separated and extracted (3x) 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 to afford the dichloride. The crude dichloride was

immediately dissolved in MeOH (0.1 M) and KOH (2.5 equiv) was added. The reaction was heated to reflux for 14 hours. The reaction was cooled to room temperature and concentrated to remove MeOH. The crude mixture was purified by silica gel chromatography to afford pure ligand.

3.6.3 Substrate Preparation

3.6.3.1 *General Procedure 2 for preparation of aryl iodides.*[44]

To a flame-dried flask was added copper(I) iodide (0.05 equiv), followed by 1,4-dioxane and *N*,*N*'-DMEDA (0.10 equiv), then aryl bromide (1.0 equiv) and sodium iodide (2.0 equiv). The reaction was heated to 110 ºC for 24 h. Upon cooling to room temperature, the reaction was filtered over Celite and washed with DCM. The solution was concentrated to afford the aryl iodide as a light solid. Aryl iodides were employed in the coupling reactions without further purification. Purification by recrystallization was possible for all substrates, but was generally unnecessary.

3.6.3.2 *General Procedure 3 for preparation of α-chloroesters.*

To a solution of 2-chloropropionic acid chloride (1 equiv) was added alcohol (1 equiv) at 0 ºC in CH_2Cl_2 (0.65 M). Amine base (1.1 equiv) was added dropwise and HCl evolved. The reaction is gradually warmed to room temperature and stirred for 4 h. Water was added to quench the reaction and EtOAc was added for dilution. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x), dried over Na_2SO_4,

and concentrated to yield pure product after filtration through silica with 10% EtOAc/hexanes.

3.6.4 Ni-Catalyzed Enantioselective Reductive Cross-Coupling

3.6.4.1 General Procedure 4: Reaction on 0.05 mmol scale.

On a bench-top, to a 1-dram vial were added a stir bar, **L6** (3.4 mg, 20 mol %, 0.01 mmol), Mn^0 (8.2 mg, 3 equiv, 0.15 mmol), and aryl iodide, if solid (1.5 equiv, 0.1 mmol). The vial was transferred into a N_2-filled glovebox and charged with $NiBr_2$(diglyme) (1.8 mg, 10 mol %, 0.005 mmol), $NaBF_4$ (5.4 mg, 0.5 equiv, 0.025 mmol) and anhydrous THF (0.5 mL, 0.1 M). Finally, the aryl iodide (if liquid) was added, followed by α-chloroester (1.0 equiv, 0.05 mmol) and 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. The reaction was quenched by diluting with 1 mL of 20% EtOAc/hexanes and pushing through a short plug of silica with 20% EtOAc/hexanes into a scintillation vial (approximately 10 mL collected). The solution was concentrated and the crude reaction mixture was analyzed by ^{1}H NMR and chiral SFC.

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