Chapter 5

Toward New Coupling Partners for Asymmetric Ni-Catalyzed Reductive Cross-Coupling

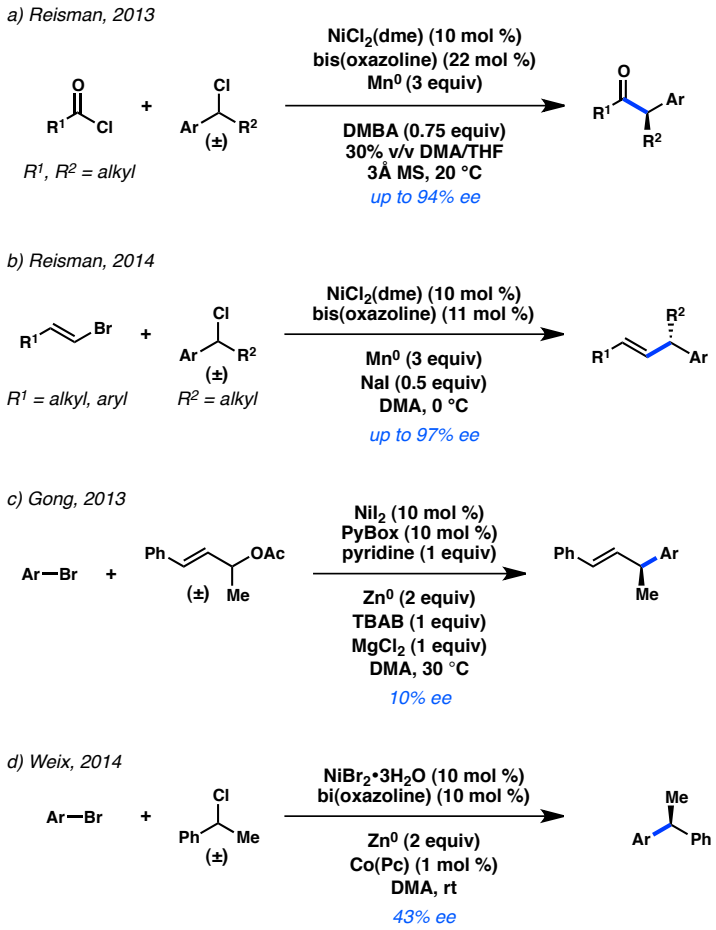
5.1 INTRODUCTION

The last several years have witnessed a renaissance in Ni-catalyzed reductive cross-coupling methodologies because of its wide functional group tolerance, operational simplicity, use of readily available air- and moisture-stable starting materials, and utilization of earth-abundant first-row transition metals (see Chapter 3).[1] Ni catalysts have also shown a proficiency in the coupling of $C(sp^3)$-hybridized reaction partners, allowing for a natural expansion of Ni-catalyzed reductive cross-couplings toward the regime of alkyl coupling.[2] The ability to generate $C(sp^3)$–$C(sp^x)$ bonds raises additional considerations with respect to control of the newly-formed stereogenic center.

Prior to our own studies, no enantioconvergent Ni-catalyzed reductive cross-couplings of organohalide electrophiles had been reported in the literature. In 2013, we

disclosed the highly enantioselective coupling of benzyl chlorides and acid chlorides to furnish α,α-disubstituted ketone products (Scheme 5.1, a).[3] The next year, we extended our protocol to the coupling of benzyl chlorides and vinyl bromides, achieving up to 97% ee (Scheme 5.1, b).[4] Concurrent investigations by other laboratories have also resulted in promising levels of enantioinduction. Gong and coworkers demonstrated that allylic acetates could be arylated in 10% ee by a Ni/PyBox system (Scheme 5.1, c).[5] Weix and coworkers have recently shown that a benzyl chloride and an aryl bromide can be coupled to yield a diarylalkane in 43% ee (Scheme 5.1, d).[6,7]

Scheme 5.1. *Enantioconvergent Ni-catalyzed reductive cross-coupling.*

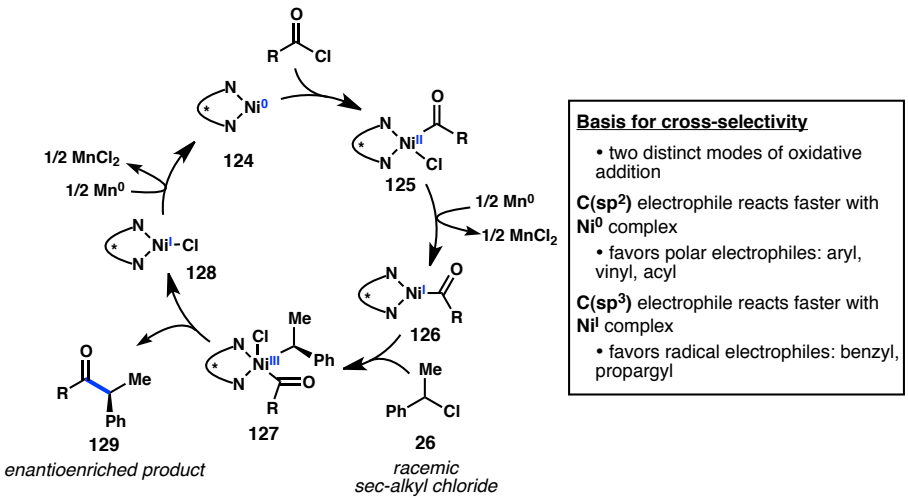


While these results illustrate the general potential of asymmetric Ni-catalyzed reductive cross-coupling, a number of challenges still remain for the development of novel transformations. For example, all highly enantioselective reductive couplings in the literature have required the use of a benzyl halide starting material. Furthermore, while certain racemic reductive couplings are tolerant of heteroaromatic groups, such a substrate scope has not yet been achieved under asymmetric conditions employing bis(oxazoline) ligands. Lastly, while achiral ligand tuning is often performed to minimize homocoupling in reductive methodologies, it is still difficult to engineer a ligand that simultaneously delivers high enantioinduction as well as high cross-selectivity.

Greater mechanistic understanding of these transformations will increase our ability to rationally optimize reaction conditions and will also provide a basis for initial identification of reaction partners. While further mechanistic investigations are necessary, we currently look to a sequential reduction mechanism as a model for thinking about our desired reactivity (Figure 5.1, also see Chapter 3). Importantly, this model can help explain the origin of cross-selectivity in our systems. We hypothesize that this selectivity arises from two distinct modes of oxidative addition within the sequential reduction mechanism: 1) oxidative addition by a Ni^0 complex, which often proceeds via a polar two-electron mechanism that allows polar-type electrophiles, including aryl, vinyl, and acyl halides to react readily and 2) oxidative addition by a Ni^I complex that is more likely to occur through single-electron elementary steps. These steps include halide abstraction to form a Ni^{II} complex and a carbon-centered radical, followed by rapid recombination to give Ni^{III} complex **127**. Electrophiles that can stabilize the formation of a transient radical, such as benzyl or propargyl halides, would react faster under these conditions

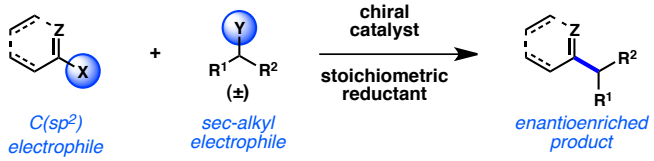
than polar-type electrophiles. Homocoupling can arise if Ni^0 reacts with benzyl chloride **26** in an S_N2-type oxidative addition, followed by a second radical-type oxidative addition of Ni^I to **26** and subsequent reductive elimination.

Figure 5.1. *Model for cross-selectivity.*



With these concepts in mind, we became interested in the idea that these couplings could serve as a general platform for the synthesis of enantioenriched small molecule building blocks. We envisioned that with a judicious choice of both a polar electrophile and a radical electrophile, a wide variety of enantioselective Ni-catalyzed reductive cross-couplings could be developed, provided that an appropriate chiral catalyst is identified (Figure 5.2). Critically, in order to facilitate enantioinduction, we reasoned that the alkyl coupling partner must either contain a directing group or bear sterically- or electronically-differentiated R^1 and R^2 groups.

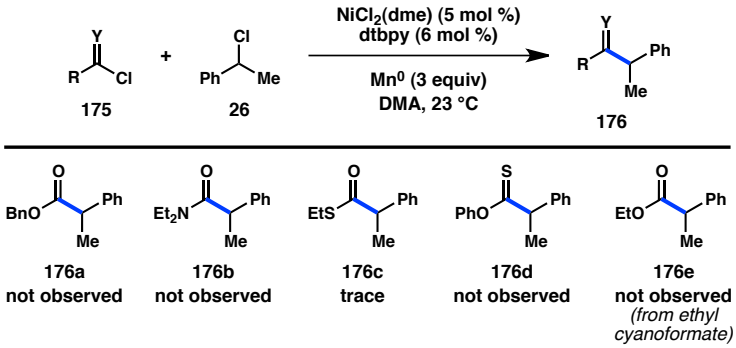
Figure 5.2. *Outline of a general platform for asymmetric reductive cross-coupling.*



5.2 DEVELOPMENT OF NEW NI-CATALYZED REDUCTIVE CROSS-COUPLINGS (RACEMIC OR ACHIRAL)

Acid chlorides are widely available starting materials that readily react with Ni catalysts under reductive conditions. In 2012, Weix and Gong independently disclosed the reductive cross-coupling of alkyl halides with alkyl or aryl acid chlorides, respectively.[8] Building on these results, we reported an asymmetric coupling of alkyl acid chlorides and benzyl chlorides.[3] In an attempt to increase the substrate scope toward other carbonyl derivatives, we investigated substrates of general formula **175** in the presence of $NiCl_2$(dme)/dtbpy (Figure 5.3). Under these conditions, we failed to observe product formation when using a chloroformate or a carbamoyl chloride. Thioester **176c** is generated in a trace amount, but competitive levels of homocoupling are also observed. Lastly, we found that cyanoformates do not provide **176e** as the desired product.

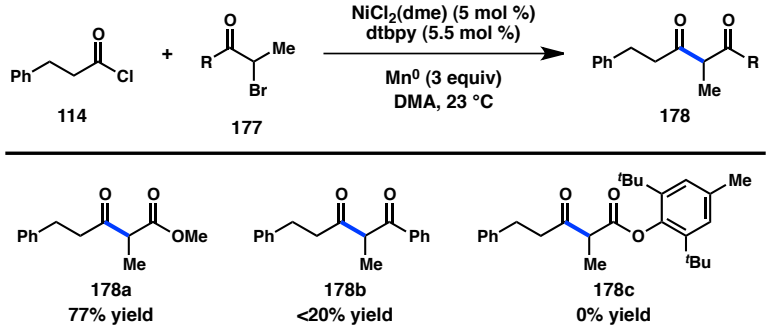
Figure 5.3. *Coupling of other carbonyl chlorides with benzyl chlorides.*



With respect to acid chlorides, we have tried to identify additional radical-type electrophiles that will facilitate cross-coupling over homocoupling. Durandetti and coworkers have demonstrated that α-chloroesters react with aryl halides under reductive Ni catalysis.[9] We investigated the racemic coupling of acid chloride **114** with several α-

bromocarbonyl compounds (Figure 5.4). α-Bromoester **177a** delivered β-ketoester **178a** in 77% yield; a screen of chiral ligands provided no enantioinduction, likely because the low pKa of **178a** would allow racemization under very mild conditions. Under identical coupling conditions, a lower yield was realized for α-bromoketone **177b** and no product was observed for aryl ester **177c**. The high selectivity for the coupling of α-bromoester **177a** should be studied further to better understand the reactivity that may permit the development of an enantioselective transformation.

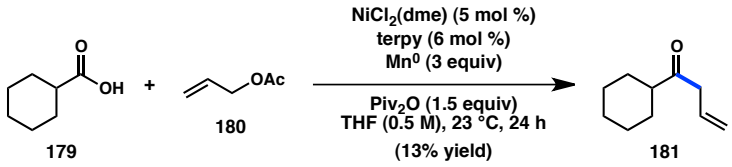
Figure 5.4. *Coupling of α-halocarbonyl compounds with acid chlorides.*



We next studied the reductive cross-coupling of acyl equivalents and allyl electrophiles. Over the last several years, allyl acetates[5,10] and carbonates[11] have each been shown to react with aryl and alkyl halides in the presence of a Ni catalyst. Allyl electrophiles are distinct from benzyl ones in that regioselectivity issues arise and that they can readily react with Ni^0 to form a π-allyl Ni complex. We questioned whether an in situ-generated mixed anhydride, prepared from a free carboxylic acid, would be amenable to reductive cross-coupling with allyl acetate (**180**).[8d,12] We commenced by screening several ligand (dtbpy, terpy, phen) and solvent (DMA, DMF, DMPU, THF) combinations with $NiCl_2$(dme), Mn^0, and Piv_2O (Scheme 5.2). Only when running the

reaction with terpy in THF were we able to form ketone **181**, resulting in a 13% yield; the isomerized α,β-unsaturated ketone was not detected in the crude reaction mixture.

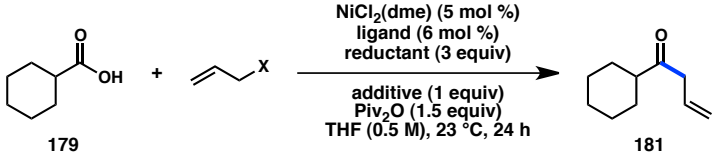
Scheme 5.2. *Initial result for an acyl-allyl reductive cross-coupling.*



Using these conditions as a starting point, we screened a variety of parameters to increase the yield of the coupling reaction. When either Mn^0 or Zn^0 is used as the reductant, allyl carbonate and allyl bromide fail to form ketone **181** (Table 5.1). In the presence of Mn^0, electron-rich ligand ^{t}Bu-terpy performs better than unsubstituted terpy (entries 1 and 4). While $MgCl_2$ inhibits product formation for Mn^0-mediated reactions, it was found to be critical to promote Zn^0-mediated reactivity (entries 6–9). Under these conditions, terpy delivered ketone **181** in 23% yield, but more electron-rich ^{t}Bu-terpy produced **181** in only 7% yield (entries 9 and 12). Additional studies examining Ni source, solvent, catalyst loading, and ligand loading were unsuccessful at increasing the product yield; Boc_2O was also inefficient as a replacement for Piv_2O. Interestingly, running the reaction at 60 °C provided the corresponding α,β-unsaturated ketone instead of desired β,γ-unsaturated ketone **181**.

For the reductive coupling of the free carboxylic acid to be successful, mixed anhydride formation must be fast relative to oxidative addition of the electrophiles. The coupling of pregenerated acyl electrophiles were studied in order to understand whether the low yields were due to inefficient anhydride formation or problematic steps in the catalytic cycle itself. 2-Pyridyl thioesters reacted poorly under the previously optimized

Table 5.1. *Exploration of an acyl-allyl reductive cross-coupling.*

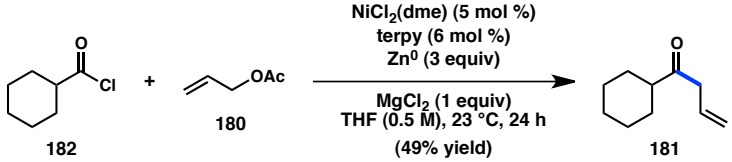


179 181

Entry	Reductant	Ligand	X	Additive	Yield (%)
1	Mn^0	terpy	OAc	--	13
2	Mn^0	terpy	OCO_2Me	--	0
3	Mn^0	terpy	Br	--	0
4	Mn^0	^{t}Bu-terpy	OAc	--	22
5	Mn^0	^{t}Bu-terpy	OCO_2Me	--	0
6	Mn^0	^{t}Bu-terpy	Br	--	0
7	Mn^0	terpy	OAc	$MgCl_2$	0
8	Zn^0	terpy	OAc	--	0
9	Zn^0	terpy	OAc	$MgCl_2$	23
10	Zn^0	terpy	OCO_2Me	$MgCl_2$	3
11	Zn^0	terpy	Br	$MgCl_2$	0
12	Zn^0	^{t}Bu-terpy	OAc	$MgCl_2$	7
13	Zn^0	^{t}Bu-terpy	OCO_2Me	$MgCl_2$	0
14	Zn^0	^{t}Bu-terpy	Br	$MgCl_2$	0

reaction conditions. When switching to acid chloride **182**, improvement in the yield of ketone **181** was not achieved with Mn^0 as the reductant. In contrast, Zn^0 allowed **181** to be formed in 49% yield from acid chloride **182** (Scheme 5.3). Further enhancement in the yield might be possible with an acid chloride lacking branching at the α position, as seen in our asymmetric reductive acyl coupling (see Chapter 3). Future efforts should also focus on more functionalized allylic acetates to assess regio- and enantioselectivity.

Scheme 5.3. *Acyl-allyl reductive cross-coupling with an acid chloride.*



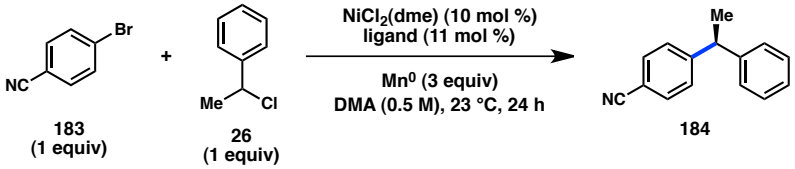
182 180 181

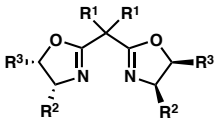
5.3 DEVELOPMENT OF NEW NI-CATALYZED REDUCTIVE CROSS-COUPLINGS (ASYMMETRIC)

In our studies on asymmetric reductive cross-couplings, we have identified (1-chloroethyl)benzene (**26**) as capable of inducing high enantioselectivity in couplings with C(sp^2)-hybridized electrophiles, such as acid chlorides and vinyl bromides. We hypothesized that the coupling of chloride **26** and aryl halides should also be amenable to enantioinduction. The union of these two fragments would generate enantioenriched diarylalkanes, prevalent motifs in medicinal chemistry.[13] Elegant studies by Fu and coworkers have shown that bi(oxazoline) ligands promote asymmetric Ni-catalyzed Negishi cross-couplings for the preparation of diarylalkanes.[14] Investigations by Weix and Molander under reductive conditions have also identified bi(oxazoline) ligands, but their asymmetric induction for diarylalkanes remains modest.[6,7]

In our preliminary studies on diarylalkanes, we realized that both coupling partners readily undergo homocoupling in addition to heterocoupling. Nonetheless, we performed a ligand screen for the coupling of 4-bromobenzonitrile (**183**) and benzyl chloride **26** (Figure 5.5). In general, bis(oxazoline) ligands delivered very low levels of enantioinduction (entries 1–11); encouragingly, phenyl-substituted **L36** provided diarylalkane **184** in 49% ee (entry 4). We next tested several bi(oxazoline) ligands and observed the highest ee of 33% with benzyl-substituted **L34** (entries 12–17). We tried to enhance our enantioinduction by incorporating diphenyl or naphthyl moieties into our ligand, but greater ee was not observed (entries 18–20). Other ligand families gave poor enantioselective results.

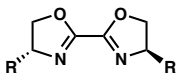
Figure 5.5. *Ligand screen for aryl-benzyl reductive cross-coupling.*





Bis(oxazoline) Ligand Scaffold

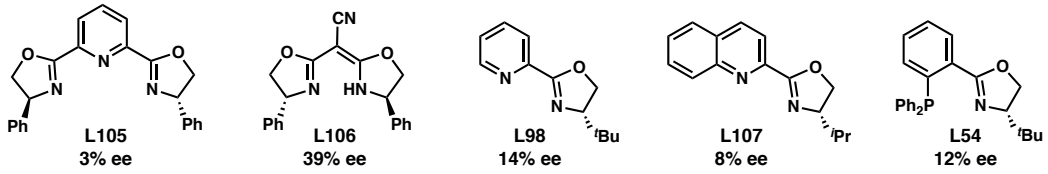
Entry	R^1	R^2	R^3	Ligand	ee (%)
1	Me	^{i}Pr	H	L99	19
2	Me	^{t}Bu	H	L66	0
3	Me	Bn	H	L100	1
4	Me	Ph	H	L36	49
5	Me	Ph	Ph	L109	14
6	H	Ph	Ph	L43	11
7	H	Ph	H	L101	1
8	H	^{t}Bu	H	L111	1
9	H	indanyl		L103	1
10	Me	indanyl		L51	3
11	$-CH_2CH_2-$	indanyl		L104	7



Bi(oxazoline) Ligand Scaffold

Entry	R	Ligand	ee (%)
12	^{i}Pr	L113	24
13	^{t}Bu	L114	8
14	Bn	L34	33
15	Ph	L115	1
16	Cy	L118	25
17	^{s}Bu	L119	23
18	$CHPh_2$	L120	3
19	CH_2(1-naph)	L121	20
20	CH_2(2-naph)	L122	29

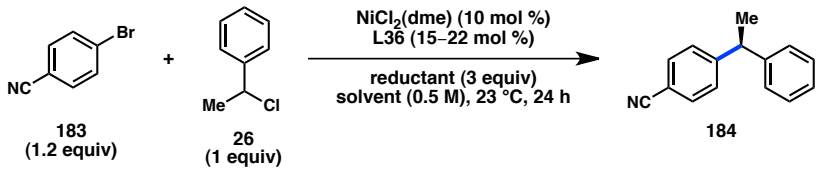
Other Ligand Scaffolds



We first chose to optimize reaction conditions with bis(oxazoline) **L36**. Unfortunately, reactions with **L36** were plagued with low yields and competitive homocoupling. The reaction also proved to be sensitive to ligand loading, with at least a 1.5:1 ligand/Ni ratio necessary for reproducible enantioinduction. Changing the solvent from DMA to THF reduced the yield and conversion but increased the ee of **184** to 58% (Table 5.2, entries 1 and 2). Using Zn^0 in place of Mn^0 provided complete conversion of benzyl chloride **26** and delivered diarylalkane **184** in 46% yield, albeit with near-

complete erosion of enantioinduction (entry 3). The loss of ee may result from in situ-generation of an organozinc reagent in the presence of Zn^0 as a reductant, altering the mechanism from a reductive coupling to a conventional Negishi cross-coupling.

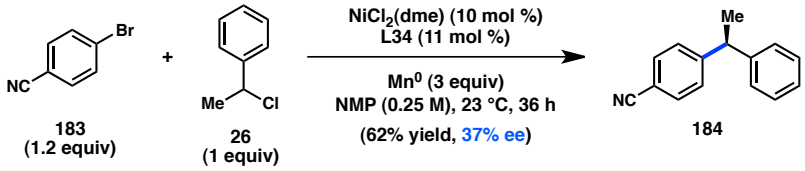
Table 5.2. *Bis(oxazoline) ligand in aryl-benzyl reductive cross-coupling.*



Entry	Reductant	Solvent	Conversion (%)	Yield (%)	ee (%)
1	Mn^0	DMA	100	24	48
2	Mn^0	THF	36	6	58
3	Zn^0	THF	100	46	5

We also studied diarylalkane generation mediated by benzyl-substituted bi(oxazoline) **L34**. Lowering the reaction concentration and employing a slight excess of aryl bromide **183** in NMP allowed product **184** to be formed in 62% yield (Scheme 5.4). Additional modifications to the reaction conditions did not increase the enantioselectivity of the transformation above 37% ee.

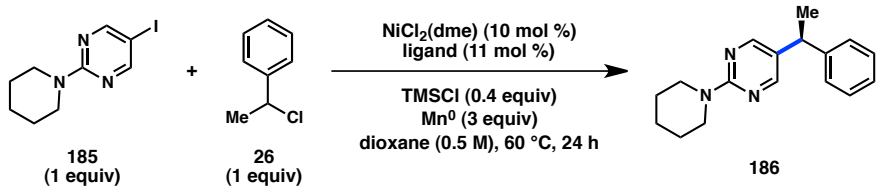
Scheme 5.4. *Bi(oxazoline) ligand in aryl-benzyl reductive cross-coupling.*



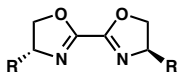
Approaching the transformation from a different direction, we decided to examine the cross-coupling between benzyl chloride **26** and heteroaryl halides. Pyrimidine **185** exhibited promising reactivity only when heated to 60 °C with additional activation by catalytic TMSCl. A screen of chiral scaffolds revealed that PHOX ligands gave moderate

yields but no enantioinduction and that Box ligands provided low reactivity. An analysis of bi(oxazolines) was more fruitful: **L34** (R = Bn) delivered diarylalkane **186** in 43% yield and 53% ee (Table 5.3, entry 3). The highest enantioselectivity was attained with **L119** (R = ^{s}Bu), furnishing **186** in 65% ee (entry 6). Additional optimization studies were performed with **L123** (R = ^{i}Bu), another promising ligand (entry 8).

Table 5.3. *Bi(oxazoline) ligands in heteroaryl-benzyl reductive cross-coupling.*



Bi(oxazoline) Ligand Scaffold

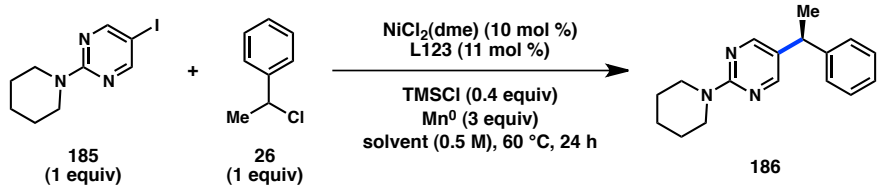


Entry	R	Ligand	Yield (%)	ee (%)
1	^{i}Pr	L113	2	26
2	^{t}Bu	L114	12	7
3	Bn	L34	43	53
4	Ph	L115	11	40
5	Cy	L118	30	55

Entry	R	Ligand	Yield (%)	ee (%)
6	^{s}Bu	L119	36	65
7	$CHPh_2$	L120	57	57
8	^{i}Bu	L123	44	58
9	CH_2(1-naph)	L121	58	47
10	CH_2(2-naph)	L122	46	55

Analysis of crude reaction mixtures revealed formation of benzyl homocoupling, aryl homocoupling, and hydrodehalogenation of aryl iodide **185**. A solvent screen was conducted to increase product yields and ee's (Table 5.4). THF led to a large reduction in enantioinduction, while the highest ee was still observed with dioxane (entries 1 and 2). In the absence of TMSCl, no desired product was formed (entry 7). Interestingly, only a trace of **186** was observed when Mn^0 was replaced with Zn^0 (entry 8). Future work on this coupling should focus on the scope of heteroaryl halide and investigate different cyclic benzyl chlorides that may enhance the enantioselectivity of the transformation.

Table 5.4. *Exploration of heteroaryl-benzyl reductive cross-coupling.*



Entry	Solvent	Yield (%)	ee (%)
1	dioxane	34	59
2	THF	55	8
3	DMA	67	44
4	DMPU	38	42
5	NMP	47	39
6	DMF	44	33
7[a]	dioxane	0	--
8[b]	dioxane	3	--

[a] No TMSCl. [b] Zn^0 used instead of Mn^0.

We next turned our attention to the coupling of vinyl bromide **156** and (chloro(phenyl)methyl)trimethylsilane (**187**) to form allylsilane **188** (Scheme 5.5).[15] Under our previously optimized conditions for vinyl couplings, no desired product was formed.[4] Undeterred, a ligand screen revealed that bis(oxazoline) ligands containing an isopropylidene linker were inefficient at imparting asymmetric induction (Figure 5.6, see Chapter 4 for comparison to chloride **26**). To our delight, cyclopropyl-linked ligand **L104** still furnished allylsilane **188** in 25% yield and 94% ee (entry 10). Bi(oxazoline) ligands delivered lower enantioinduction but sometimes provided higher yields of **188** (entries 11–14). Other ligand families did not perform better than bis(oxazoline) **L104**.

Scheme 5.5. *Initial attempt toward an allylsilane product.*

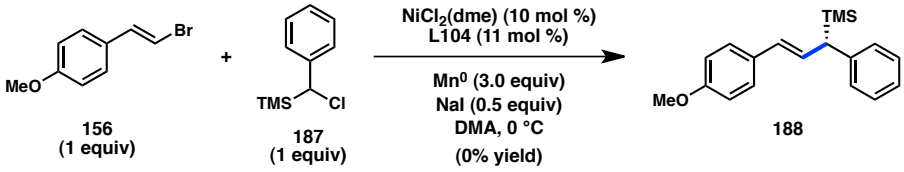
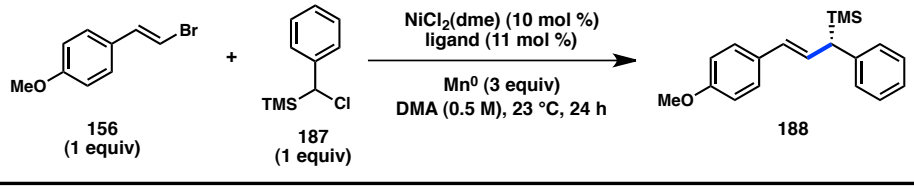
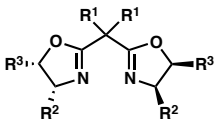


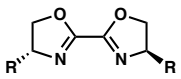
Figure 5.6. *Ligand evaluation for the preparation of allylsilanes.*





Bis(oxazoline) Ligand Scaffold

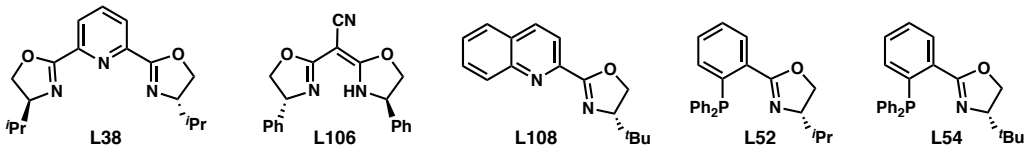
Entry	R^1	R^2	R^3	Ligand	Yield (%)	ee (%)
1	Me	^{i}Pr	H	L99	14	49
2	Me	Bn	H	L100	14	39
3	Me	Ph	H	L36	32	40
4	H	Ph	Ph	L43	14	17
5	H	Ph	H	L101	9	11
6	H	Bn	H	L124	34	7
7	H	^{t}Bu	H	L111	23	20
8	H	indanyl		L103	57	13
9	Me	indanyl		L51	14	28
10	$-CH_2CH_2-$	indanyl		L104	25	94



Bi(oxazoline) Ligand Scaffold

Entry	R	Ligand	Yield (%)	ee (%)
11	^{i}Pr	L113	27	36
12	^{t}Bu	L114	51	20
13	Bn	L34	51	31
14	Ph	L115	17	20

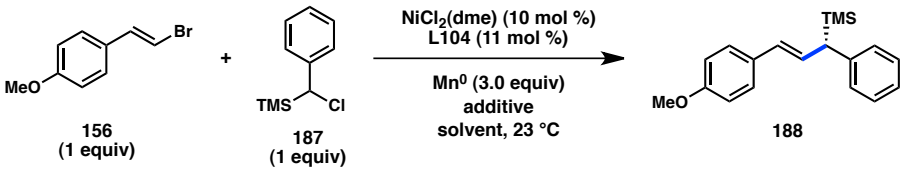
Other Ligand Scaffolds



Additional optimization of the reaction conditions demonstrated similar results for solvents DMA, NMP, and DMF, although both DMPU and THF failed to deliver product **188** (Table 5.5, entries 1–5). We were surprised to find that addition of 1 mol % cobalt(II) phthalocyanine (Co(Pc)) improved the yield of allylsilane **188** to 40% without affecting the ee (entry 6). Increasing the loading of Co(Pc) had little impact on the reaction yield, although changing the solvent to NMP delivered **188** in 49% yield and 96% ee (entry 9). While the role of Co(Pc) remains unclear, the compound is capable of

displacing halides in a two-electron fashion followed by homolytic cleavage of the resulting Co–C bond to generate a carbon-centered radical.[16] This strategy has been employed by Weix and coworkers for the coupling of benzylic electrophiles, wherein activation with cobalt and a mesylate leaving group prevents the high level of homocoupling observed with a chloride leaving group.[6] Follow-up studies are needed to elucidate the role of Co(Pc) and evaluate the generality of the allylsilane synthesis.

Table 5.5. *Optimization of reaction parameters for the preparation of allylsilanes.*



Entry	Solvent	Additive	Yield (%)	ee (%)
1	DMA	--	28	94
2	DMPU	--	0	--
3	NMP	--	32	94
4	DMF	--	18	90
5	THF	--	0	--
6	DMA	Co(Pc) (1 mol %)	40	95
7	DMA	Co(Pc) (3 mol %)	42	96
8	DMA	Co(Pc) (5 mol %)	42	95
9	NMP	Co(Pc) (2 mol %)	49	96

Co(Pc) = cobalt(II) phthalocyanine

5.4 CONCLUDING REMARKS

In conclusion, we have disclosed a model for cross-selectivity in the Ni-catalyzed reductive coupling of two distinct organohalide electrophiles. Improved yields can be achieved when a polar-type electrophile is combined with an electrophile that can stabilize formation of a transient radical. With respect to enantioinduction, electrophiles

that have a directing group or bear steric and electronic differences between both faces perform best. Several examples of promising cross-reactivity and enantioinduction have been presented, including couplings of α-halo carbonyls, benzyl chlorides, and α-silyl benzyl chlorides with C(sp^2)-hybridized coupling partners. Investigations to expand the substrate scope of enantioselective Ni-catalyzed reductive cross-couplings are currently underway in our laboratory.

5.5 EXPERIMENTAL SECTION

5.5.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), and diethyl ether (Et_2O) were dried by passing through activated alumina columns. Anhydrous dimethylacetamide (DMA) was purchased from Aldrich and stored under inert atmosphere. Manganese powder (– 325 mesh, 99.3%) was purchased from Alfa Aesar. $NiCl_2$(dme) was purchased from Strem and stored in a glovebox under N_2 when not in use. Unless otherwise stated, chemicals and reagents were used as received. Triethylamine (Et_3N) was distilled over calcium hydride prior to use. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, CAM, or $KMnO_4$ staining. Flash column chromatography was performed as described by Still et al.[17] using silica gel (particle size 0.032-0.063) purchased from Silicycle. Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ^1H and ^{13}C NMR spectra

were recorded on a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), and are reported relative to internal $CHCl_3$ (^1H, $\delta = 7.26$) and $CDCl_3$ (^{13}C, $\delta = 77.0$). 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, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using 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. 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 OJ-H columns (4.6 mm x 25 cm) with visualization at 210, 254, and 280 nm. Analytical achiral GC-MS was performed with an Agilent 7890A GC and an Agilent 5975C VL MSD with triple axis detector utilizing an Agilent HP-5MS (30.0 m x 0.25 mm) column (0.4 mL/min He carrier gas flow).

5.5.2 Ni-Catalyzed Reductive Cross-Coupling

Acyl-Allyl Coupling (Table 5.1):

On a bench-top, to a 1/2 dram vial was added the appropriate ligand (0.006 mmol, 6 mol %), reductant (0.3 mmol, 3 equiv), $NiCl_2$(dme) (0.005 mmol, 5 mol %), and $MgCl_2$ (0.1 mmol, 1 equiv) if necessary. The vial was transferred into an N_2-filled glovebox and charged with the appropriate solvent (0.2 mL, 0.5 M) followed by cyclohexanecarboxylic acid (0.1 mmol, 1.0 equiv) and benzyl ether (internal standard). Allyl electrophile (0.2

mmol, 2 equiv) and pivalic anhydride (0.15 mmol, 1.5 equiv) were each added in one portion. The vial was sealed and removed from the glovebox. The mixture was stirred vigorously, ensuring that the reductant was uniformly suspended, at 23 °C for 24 h. The dark mixture was diluted with 10% ethyl acetate/hexane and passed through a plug of silica, using 10% ethyl acetate/hexane eluent. The solution was concentrated, and the crude reaction mixture was analyzed by ^{1}H NMR.

Aryl-Benzyl Coupling (Figure 5.5):

On a bench-top, to a 1/2 dram vial was added the appropriate ligand (0.011 mmol, 11 mol %), Mn^0 (0.3 mmol, 3 equiv), $NiCl_2$(dme) (0.01 mmol, 10 mol %), and 4-bromobenzonitrile (0.1 mmol, 1 equiv). The vial was transferred into an N_2-filled glovebox and charged with DMA (0.2 mL, 0.5 M) followed by (1-chloroethyl)benzene (0.1 mmol, 1.0 equiv) and benzyl ether (internal standard). The vial was sealed and removed from the glovebox. The mixture was stirred vigorously, ensuring that the reductant was uniformly suspended, at 23 °C for 24 h. The dark mixture was diluted with 20% ethyl acetate/hexane and passed through a plug of silica, using 20% ethyl acetate/hexane eluent. The solution was concentrated and the crude reaction mixture was analyzed by ^{1}H NMR and chiral SFC.

Heteroaryl-Benzyl Coupling (Table 5.3):

On a bench-top, to a 1/2 dram vial was added the appropriate ligand (0.0055 mmol, 11 mol %), Mn^0 (0.15 mmol, 3 equiv), $NiCl_2$(dme) (0.005 mmol, 10 mol %), and heteroaryl iodide (0.05 mmol, 1 equiv). The vial was transferred into an N_2-filled glovebox and

charged with DMA (0.1 mL, 0.5 M) followed by (1-chloroethyl)benzene (0.05 mmol, 1.0 equiv) and benzyl ether (internal standard). The vial was sealed and removed from the glovebox. The mixture was stirred vigorously, ensuring that the reductant was uniformly suspended, at 60 °C for 18 h. The dark mixture was diluted with 20% ethyl acetate/hexane and passed through a plug of silica, using 20% ethyl acetate/hexane eluent. The solution was concentrated and the crude reaction mixture was analyzed by ^{1}H NMR and chiral SFC.

Vinyl-Benzyl Coupling (Figure 5.6):

On a bench-top, to a 1/2 dram vial was added the appropriate ligand (0.0055 mmol, 11 mol %), Mn^{0} (0.15 mmol, 3 equiv), $NiCl_2$(dme) (0.005 mmol, 10 mol %), and vinyl bromide (0.05 mmol, 1 equiv). The vial was transferred into an N_2-filled glovebox and charged with DMA (0.1 mL, 0.5 M) followed by (chloro(phenyl)methyl)trimethylsilane (0.05 mmol, 1.0 equiv) and benzyl ether (internal standard). The vial was sealed and removed from the glovebox. The mixture was stirred vigorously, ensuring that the reductant was uniformly suspended, at 23 °C for 18 h. The dark mixture was diluted with 20% ethyl acetate/hexane and passed through a plug of silica, using 20% ethyl acetate/hexane eluent. The solution was concentrated and the crude reaction mixture was analyzed by ^{1}H NMR and chiral SFC.

5.6 NOTES AND REFERENCES

(1) Reviews on reductive cross-couplings: (a) Everson, D. A.; Weix, D. J. *J. Org. Chem.* **2014**, *79*, 4793. (b) Knappke, C. E. I.; Grupe, S.; Gärtner, D.; Corpet, M.; Gosmini, C.; Jacobi von Wangelin, A. *Chem. Eur. J.* **2014**, *20*, 6828. (c) Moragas, T.; Correa, A.; Martin, R. *Chem. Eur. J.* **2014**, *20*, 8242.

(2) (a) Netherton, M. R.; Fu, G. C. *Adv. Synth. & Catal.* **2004**, *346*, 1525. (b) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674. (c) Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656. (d) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417.

(3) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 7442.

(4) Cherney, A. H.; Reisman, S. E. *J. Am. Chem. Soc.* **2014**, *136*, 14365.

(5) Cui, X.; Wang, S.; Zhang, Y.; Deng, W.; Qian, Q.; Gong, H. *Org. Biomol. Chem.* **2013**, *11*, 3094.

(6) Ackerman, L. K. G.; Anka-Lufford, L. L.; Naodovic, M.; Weix, D. J. *Chem. Sci.* **2015**, *6*, 1115.

(7) For a related stereoconvergent transformation: Tellis, J. C.; Primer, D. N.; Molander, G. A. *Science* **2014**, *345*, 433.

(8) (a) Wotal, A. C.; Weix, D. J. *Org. Lett.* **2012**, *14*, 1476. (b) Wotal, A. C.; Ribson, R. D.; Weix, D. J. *Organometallics* **2014**, *33*, 5874. (c) Wu, F.; Lu, W.; Qian, Q.; Ren, Q.; Gong, H. *Org. Lett.* **2012**, *14*, 3044. (d) Yin, H.; Zhao, C.; You, H.; Lin, K.; Gong, H. *Chem. Commun.* **2012**, *48*, 7034. (e) Zhao, C.; Jia, X.; Wang, X.; Gong, H. *J. Am. Chem. Soc.* **2014**, *136*, 17645.

(9) Durandetti, M.; Gosmini, C.; Périchon, J. *Tetrahedron* **2007**, *63*, 1146.

(10) (a) Wang, S.; Qian, Q.; Gong, H. *Org. Lett.* **2012**, *14*, 3352. (b) Anka-Lufford, L. L.; Prinsell, M. R.; Weix, D. J. *J. Org. Chem.* **2012**, *77*, 9989. For a Co-catalyzed method: (c) Gomes, P.; Gosmini, C.; Périchon, J. *Org. Lett.* **2003**, *5*, 1043.

(11) Dai, Y.; Wu, F.; Zang, Z.; You, H.; Gong, H. *Chem. Eur. J.* **2012**, *18*, 808.

(12) Gooßen, L. J.; Ghosh, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 3458.

(13) Yonova, I. M.; Johnson, a. G.; Osborne, C. A.; Moore, C. E.; Morrissette, N. S.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2014**, *53*, 2422 and references cited therein.

(14) Do, H. Q.; Chandrashekar, E. R. R.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 16288.

(15) For a related Kumada–Corriu coupling: (a) Hayashi, T.; Konishi, M.; Ito, H.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4962. (b) Hayashi, T.; Konishi, M.; Okamoto, Y.; Kabeta, K.; Kumada, M. *J. Org. Chem.* **1986**, *51*, 3772.

(16) K. Takai, K. Nitta, O. Fujimura, K. Utimoto, *J. Org. Chem.* **1989**, *54*, 4732.

(17) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923.