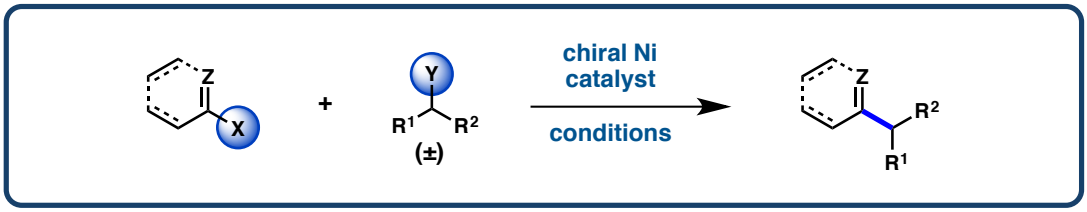
Chapter 5

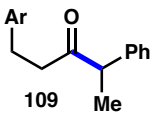
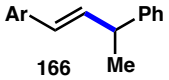
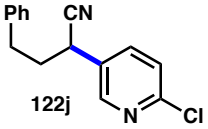
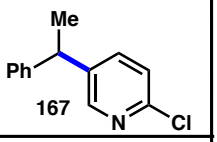
Preliminary Results Toward Novel Ni-Catalyzed Asymmetric Reductive Cross-Couplings

5.1 INTRODUCTION

As discussed in the previous chapters, the development of Ni-catalyzed asymmetric reductive cross-coupling has been a primary focus of research in our group for several years. This work has led to the successful development and publication of several such methods and opened the door to a new avenue of asymmetric catalysis. However, the pace of reaction development has suffered from significant difficulty in optimizing these transformations. Each new coupling requires a fresh assessment of reaction conditions and catalyst parameters, especially ligand structure. While some amount of this empirical evaluation is inevitable, a more general and reliable starting point for optimization would be advantageous, hastening the key later aspects of ligand design.

Table 5.1. *Cross-coupling substrates versus optimal conditions.*



Products / Conditions				
	109	166	122j	167
$NiCl_2$(dme), L32 Mn^0, DMBA, 3Å MS DMA/THF, rt	Control 79% yield, 93% ee	41% yield, 2% ee	22% yield, 24% ee	0% yield
$NiCl_2$(dme), L109 Mn^0, NaI DMA, 0 °C	0% yield	Control 91% yield, 93% ee	0% yield	0% yield
$NiCl_2$(dme), L89 Mn^0, TMSCl Dioxane, rt, 18 h	0% yield	0% yield	Control 78% yield, 85% ee	0% yield
$NiBr_2$(diglyme), L119 Mn^0, TMSCl Dioxane, rt, 18 h	0% yield	50% yield, 72% ee	7% yield, 80% ee	Control 85% yield, 79% ee

Recognizing this challenge, we were pleased to find that the cross-coupling of benzylic chlorides with (hetero)aryl iodides proceeded in high yield and ee under conditions very similar to those developed for the reductive (hetero)arylation of α-chloronitriles, differing only in ligand scaffold (see Chapters 3 and 4). This marked the greatest overlap in optimal reaction conditions we had developed and signaled a potential advance in generality. As shown in **Table 1**, a full survey of the reaction conditions developed in our group versus the substrate pairs for which they were optimal demonstrates the highly specific nature of our transformations. While the reaction parameters employed for reductive coupling of acyl chlorides provided modest yields of

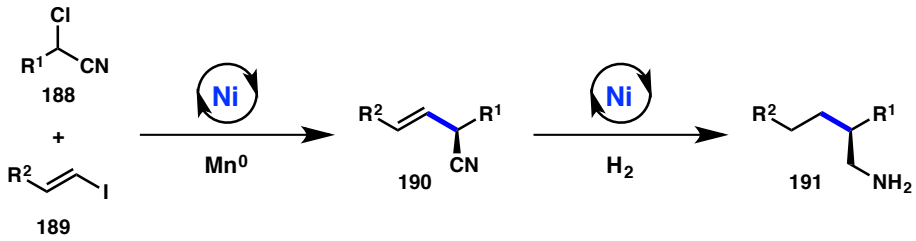
three of the products, only the model system gave promising enantioselectivity (Table 5.1, row 1). Conditions developed for the reductive coupling of vinyl bromides and benzylic chlorides were not tolerated in any other combination of electrophiles (Table 1, row 2). On the other hand, the conditions developed in Chapter 4 to afford diarylalkanes also furnished product in three of the reactions, and all above 70% ee (Table 1, row 4). Curiously, these were the only reaction conditions to succeed in the coupling to form diarylalkanes, suggesting that this transformation is perhaps uniquely challenging. While the conditions developed in Chapter 3 for the reductive coupling of α-chloronitriles and (hetero)aryl iodides were not tolerated by any other combination of electrophiles (Table 1, row 3), the similarity to the conditions for the formation of diarylalkanes, and the promising application of those conditions to other systems, suggests that dioxane/TMSCl may constitute a privileged solvent system for these reactions.

With these conditions in hand, we have launched preliminary explorations with a series of novel coupling partners. While none of the reactions described here have been optimized to any extent, they represent the ease with which new product scaffolds can be accessed under these conditions. While previous couplings have required significant effort simply to obtain even racemic product prior to parameter optimization, we anticipate that these reactions will yield to ligand and condition evaluation and enable faster successful development and publication.

5.2 VINYLATION OF α-CHLORONITRILES

Contemporaneously with the efforts described in Chapter 3 toward the heteroarylation of α-chloronitriles, we also conducted preliminary screens on the vinylation of these C(sp^3) electrophiles.[1] As with the corresponding arylation reaction, this reductive cross-coupling has not been reported in the literature, even in the racemic sense. These products (**190**) are particularly interesting targets for further development because of the opportunities for their derivatization. Simultaneous reduction of the nitrile and olefin functionalities under simple Raney Ni conditions should enable access to β-amino tertiary alkyl stereocenters (**191**) difficult to access convergently by other means (**Scheme 5.1**).

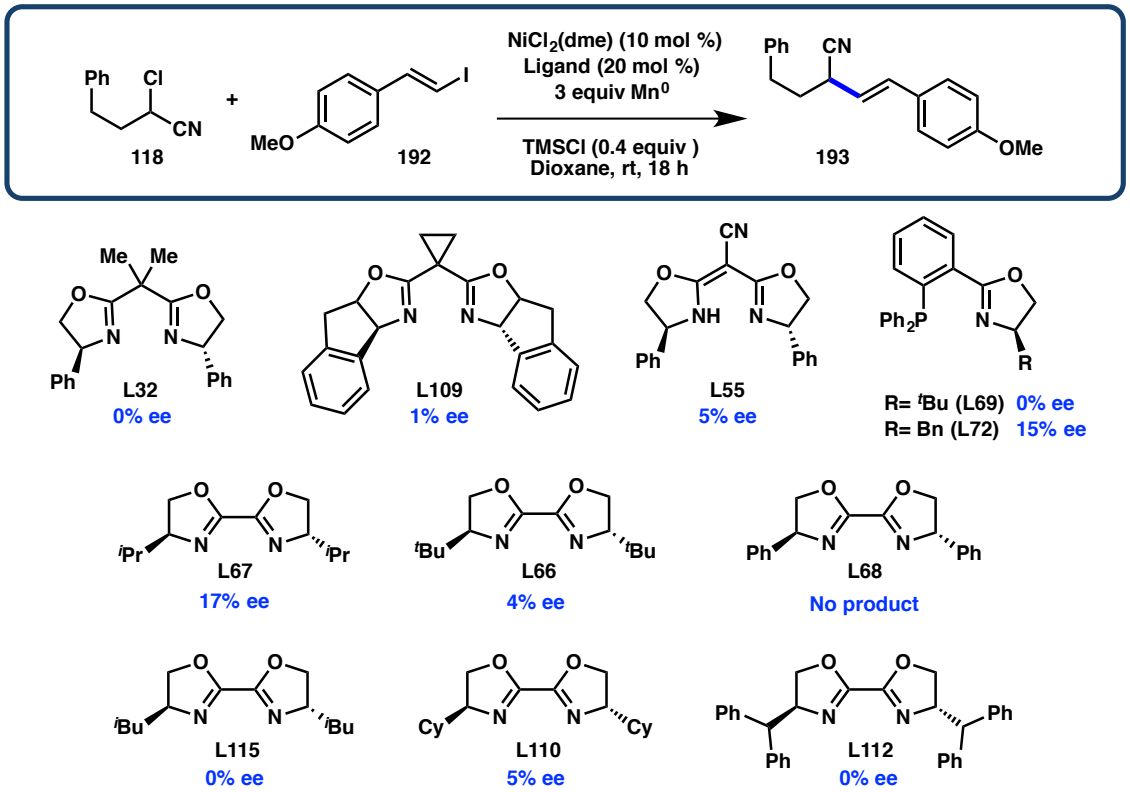
Scheme 5.1. *Reductive cross-coupling of chloronitriles with vinyl iodides.*



Iodostyrene **192** was chosen as the initial model vinyl halide for this transformation, cross-coupling with standard chloronitrile **118** (**Scheme 5.2**). Employing the room temperature dioxane/TMSCl conditions, we were delighted to find modest to good conversions and yields that were not quantified in these initial screens (10-50% yields estimated). As in many of the reactions in **Table 5.1**, BiOx ligands (in particular **L67**) were found to be optimal for both conversion and ee, although only poor enantioselectivity was achieved. However, promising results were also obtained

employing BnPHOX **L72**, suggesting that either of these ligand classes may prove to be successful upon further optimization.

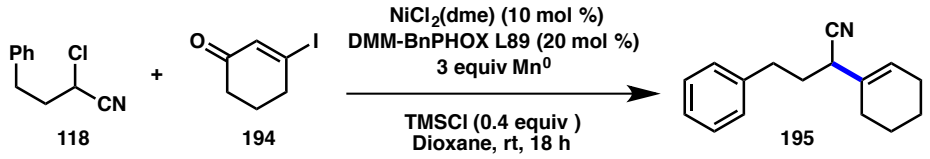
***Scheme 5.2**. Ligand screen for the vinylation of chloronitriles.*



Later in this development of the arylation chemistry discussed in Chapter 3, a second vinylation reaction was attempted, this time with β-iodocyclohexenone (**194**) (**Scheme 5.3**). This haloenone substrate was selected because of its resemblance to the best-performing heteroaryl iodides in the analogous cross-coupling. In that reaction, electron-deficient heteroaryl iodides were optimal substrates. Therefore we identified **194** as also being an electron-poor, cyclic, C(sp^2) electrophile. Unfortunately for the reaction at the time, this substrate behaves more like iodostyrene **192** than the heteroaryl halide series, affording **195** in only 15% ee when using optimal DMM-BnPHOX **L89**. It is

interesting to note that this coupling required $NaBF_4$ as an additive to observe modest yield, suggesting that this may be a crucial parameter to investigate moving forward.[2]

Scheme 5.3. *Condition screen for the coupling of chloronitriles with a haloenone.*



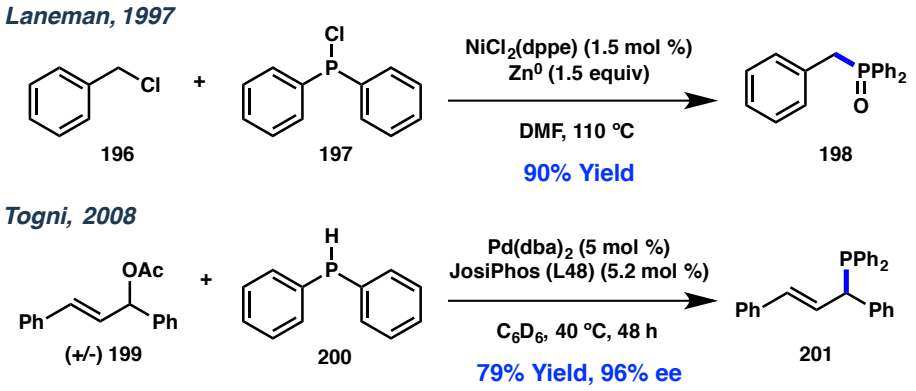
1 equiv 194	Trace Product
2 equiv 194	No Product
1 equiv 194 + $NaBF_4$	15% ee
2 equiv 194 + $NaBF_4$	1% ee

There are many important avenues of exploration remaining in the development of this vinyl cross-coupling. Some of these can be anticipated by looking to related cross-couplings in the literature. Firstly, it is likely that lower temperatures will be advantageous in this reaction. The asymmetric reductive vinylation of benzylic chlorides reported by Reisman and coworkers is the only such reaction to perform best at low temperature (0 ºC), while the asymmetric Negishi coupling of bromonitriles developed by Fu and coworkers proceeds at -60 ºC, the lowest they have observed.[3] Additives are also likely to be important, as shown by the effect of $NaBF_4$ in **Scheme 5.3** and the beneficial effect of NaI in Reisman's vinylation. Finally, based on our experiences in other methodology development campaigns, extensive exploration of ligand scaffolds is likely to be the most important variable. Interestingly, both BiOX and PHOX ligands perform adequately and similarly at this stage, providing ample space for optimization.

5.3 COUPLING OF BENZYL CHLORIDES WITH CHLOROPHOSPHINES

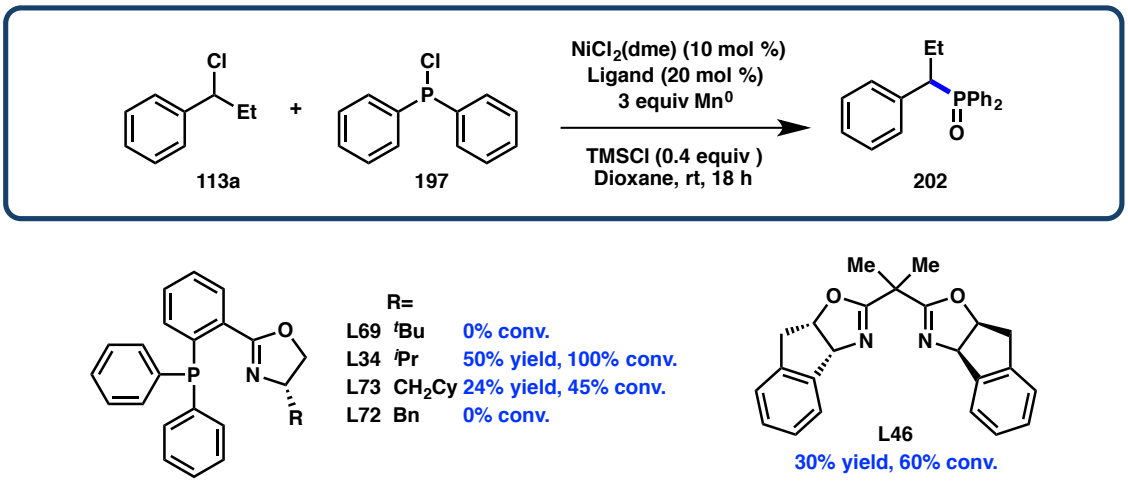
In the recent surge of reports on reductive cross-coupling (see **Chapter 1**), the focus has been exclusively on reactions to form C–C bonds. Indeed while Pd catalysis has been developed extensively to facilitate carbon–heteroatom bond formation, Ni has been employed much less often to this end. It is surprising then to note that some of the earliest work in Ni-catalyzed reductive cross-coupling employing chemical reductants (as opposed to electrochemical studies) is actually in the field of carbon–heteroatom bond formation, namely C–P coupling.[4] In 1997, Laneman and coworkers from Monsanto published a wide-ranging report on the cross-coupling of chloro(diphenyl)phosphine **197** with various C(sp^2) electrophiles, as well as C(sp^3) benzyl bromide **196** (**Scheme 5.4**).[5] Remarkably, the phosphine products are obtained in good yields when employing aryl, vinyl, or benzyl halides, including both bromides and triflates. No secondary alkyl halides are explored in this paper, and the benzyl product is reported to oxidize on work-up to phosphine oxide **198**. This report was followed by an electrochemical version in 1999 (suggesting that organo/phosphinozinc intermediates are unlikely)[6] and an expansion of the aryl halide scope in 2003.[7] While this reaction takes place under harsh conditions and no chiral products are reported, this presents an interesting entry to an unprecedented class of targets for asymmetric cross-electrophile coupling.

***Scheme 5.4**. Selected cross-couplings to afford alkyl(diaryl)phosphines.*



Therefore, we set out to explore the potential of these chlorophosphines as electrophiles in asymmetric reductive cross-coupling. Importantly, some interesting difficulties can be imagined in this proposed disconnection. For one, the desired products are chiral alkyl phosphines, strongly σ-donating ligands which may compete with the intended chiral ligand for binding to Ni, perturbing reactivity and selectivity. We were tentatively encouraged in this regard by a single report from Togni and coworkers, in which enantioenriched alkyl(diaryl)phosphines (**201**) are formed via asymmetric Pd catalysis using a JosiPhos ligand (**Scheme 5.4**).[8] While some mixed catalysis or even autocatalysis cannot be ruled out conclusively, this example at least suggests that highly enantioenriched phosphines can be obtained under such conditions. Second, Laneman and coworkers observed facile oxidation of their phosphine products upon workup. If observed, this may be avoidable by a rigorously air-free workup procedure, or perhaps the free phosphine can be complexed to a Lewis-acid such as borane, or protonated prior to workup, stabilizing it. Indeed, alkyl phosphine tetrafluoroborate salts can frequently be employed directly in catalysis with the addition of co-catalytic base, suggesting this is an approach worthy of consideration.[9]

***Scheme 5.5**. Ligand screen for coupling chlorophosphines and benzylic chlorides.*



As a preliminary exploration then, we subjected model benzylic chloride **113a** and chloro(diphenyl)phosphine **197** to the reductive cross-coupling conditions developed in Chapters 3 and 4 employing dioxane/TMSCl at room temperature, with a range of chiral ligands (**Scheme 5.5**). We were once again pleased to find moderate yields of the desired product in this first attempt, and with both PHOX and BOX ligand families. These results constitute the lowest-temperature Ni-catalyzed reductive C–P couplings by over 100 ºC, and are the first such reactions to employ 2º alkyl electrophiles. While these reactions still require substantial optimization to mitigate homocoupling and improve conversion, the potential impact of these transformations is clear even racemically. As we anticipated, the products are obtained as the phosphine oxides (distinguishable by polarity and ^{31}P NMR). However, further exploration of workup (as described above) is expected to enable isolation of the free phosphines or stable complexes thereof. Unfortunately, no attempts at this coupling employing achiral ligands (including bipyridines, diphosphines, and phenanthrolines) have been successful, precluding the development of separation

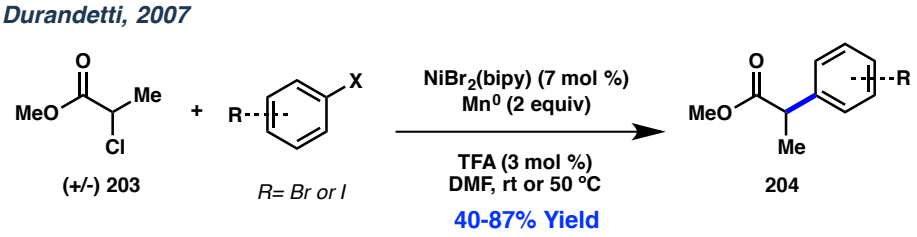
conditions to assay the ee of these products. At worst, this may be solved by employing scalemic chiral ligands, or preferably by identifying a compatible achiral ligand.

Moving forward, there are clearly many promising lines of inquiry with regard to this reaction. The usual reaction parameters of solvent, Ni source, and temperature should be examined. However, given the success observed under the initial conditions, a significant ligand screen of both BOX and PHOX classes should be conducted quickly to gauge the impact of ligand scaffold and substitution (especially once a suitable ee assay is developed). The more exciting aspect, however, is likely the substrate scope of this transformation. A wide range of diaryl- and dialkylchlorophosphines are commercially available (as well as chlorophosphites and diaminochlorophosphines), while the benzyl chloride partners are well-precedented in our laboratory. This disconnection would open the door to simple and convergent modular chiral phosphine synthesis. We anticipate that these products may prove useful as monodentate chiral ligands in transition metal catalysis, as well as in the field of nucleophilic catalysis where phosphines and NHCs find ample use.[10]

5.4 COUPLING OF (HETERO)ARYL IODIDES AND α-CHLOROESTERS

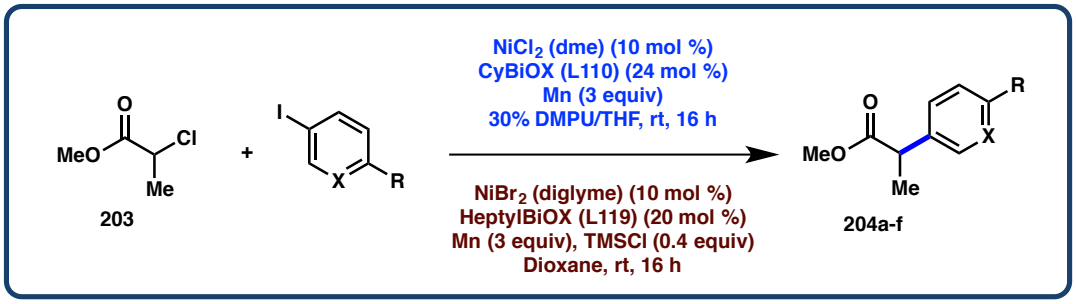
As a final example of the successful employment of these TMSCl/dioxane conditions on difficult asymmetric reductive cross-couplings, we include this entry. It is critical to note that all early work described in this section was carried out by Dr. Leah Cleary, while the new preliminary results were obtained by Kelsey Poremba. These results are included simply to further illustrate the robustness of dioxane/TMSCl as a solvent condition for the development of these reactions.

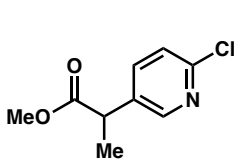
***Scheme 5.6**. Durandetti's reductive cross-coupling of α-chloroesters.*



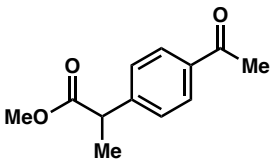
Also contemporaneously with the reaction development described in Chapter 3, significant work was conducted by our laboratory on the asymmetric reductive cross-coupling of α-haloesters with aryl iodides. As discussed in Chapter 1, this reaction was the first racemic reductive C–C bond-forming cross-coupling to be disclosed employing a chemical reductant (**Scheme 5.6**).[11] Therefore we imagined it may be amenable to asymmetric catalysis, expanding the scope of C(sp^3) electrophiles employable in this chemistry. To explore this reaction, we chose to study the coupling of commercially available methyl 2-chloropropionate (**203**) with various aryl iodides (**Scheme 5.7**). Importantly, the products of these couplings are chiral arylpropionates (**204**), a valuable pharmacophore present in a large family of nonsteroidal anti-inflammatory drugs such as Naproxen.[12] Extensive optimization was carried out on this system, including thorough evaluation of solvent, catalyst, additives, and ligands. Branched alkyl BiOx ligands were identified as providing optimal yield and ee. While moderate to good yields could be obtained for some substrates, synthetically useful ee's were never obtained during this effort and research on this project was temporarily suspended.

***Scheme 5.7**. Asymmetric reductive cross-couplings of α-chloroesters.*

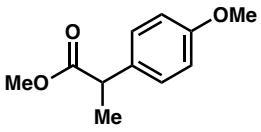




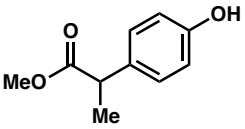
204a
21% yield
46% yield



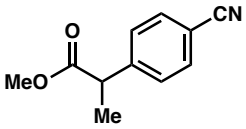
204b
85% yield, 73% ee
53% yield, 82% ee



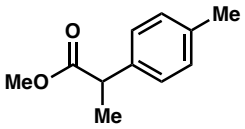
204c
51% yield, 66% ee
54% yield, 80% ee



204d
53% yield, 65% ee
77% yield, 59% ee



204e
19% yield, 74% ee
18% yield, 84% ee



204f
50% yield, 69% ee
15% yield, 60% ee

Recognizing the unique reactivity and selectivity, as well as generality afforded by the dioxane/TMSCl solvent system developed in Chapters 3 and 4, we decided to return to this reaction and assess the impact of these parameters. We were pleased to find that improved yields and ee's were obtainable for several substrates with no optimization whatsoever. Employing dioxane as solvent with TMSCl as an activator was successful in delivering several improved results over the previous conditions that had required more than a year to develop. This serves to illustrate the impact of highly general reaction parameters on optimization campaigns. We anticipate that beginning from this new result, a survey of BiOX ligand scaffolds and simple reaction parameters such as

concentration, Ni source, temperature, and substrate ratios may afford a high yielding and enantioselective transformation in comparatively short order.

5.5 CONCLUDING REMARKS

We have begun to evaluate the application of the reaction conditions developed in Chapters 3 and 4 to novel reductive cross-coupling transformations. This solvent system consisting of dioxane and substoichiometric TMSCl has been shown to be remarkably general in these reactions, enabling the generation of cross-coupled products with no optimization. First, the coupling of vinyl iodides with α-chloronitriles proceeds with modest yields and poor enantioselectivity, but with multiple ligand classes. Development of this reaction should enable the synthesis of chiral β-tertiary primary amines via short, convergent sequence. Second, the mildest reductive C–P bond-forming reductive cross-coupling to date was demonstrated. This is also the first such transformation to employ 2º alkyl electrophiles. We hope that development of this asymmetric reaction will enable the convergent preparation of chiral monodentate phosphines useful as ligands or nucleophilic catalysts. Finally, recent work from our group was discussed involving the coupling of α-chloroesters with (hetero)aryl iodides. Reaction conditions employing a dioxane/TMSCl solvent system gave comparable and frequently improved results to previous reaction conditions that had been extensively optimized. Further ligand screening based on these results is expected to enable a highly asymmetric cross-coupling. These results suggest an unprecedented generality under these conditions that should facilitate more rapid method development as we seek to expand the scope of Ni-

catalyzed asymmetric reductive cross-coupling. Work on these reactions and more is ongoing in our laboratory.

5.6 EXPERIMENTAL SECTION

5.6.1 *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) and 1,4-dioxane were 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. $NiBr_2$(diglyme) was purchased form Sigma Aldrich and stored in a glovebox under N_2. Unless otherwise stated, chemicals and reagents were used as received. 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. 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, δ = 7.26) and $CDCl_3$ (^{13}C, δ = 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. 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.

5.6.2 *Vinyl iodide/α-chloronitrile cross-coupling (Schemes 5.2, 5.3)*

In a glovebox, to a 1 dram vial was added the appropriate ligand (0.01 mmol, 20 mol %), reductant (0.3 mmol, 3 equiv), $NiCl_2$(dme) (0.005 mmol, 10 mol %), and vinyl iodide substate (if solid, 0.05 mmol, 1 equiv). The vial was charged with the 1,4-dioxane (0.14 mL, 0.37 M) followed by vinyl iodide substrate (if liquid, 0.05 mmol, 1 equiv), benzyl chloride substrate (0.05 mmol, 1.0 equiv), TMSCl (0.02 mmol, 0.4 equiv), and benzyl ether (internal standard). The vial was sealed and removed from the glovebox. The mixture was stirred vigorously at 500 rpm, ensuring that the reductant was uniformly suspended, at 23 °C for 24 h. The reaction mixture was diluted with 10% 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.

5.6.3 *Chlorophosphine/benzyl chloride cross-coupling (Scheme 5.5)*

In a glovebox, to a 1 dram vial was added the appropriate ligand (0.01 mmol, 20 mol %), reductant (0.3 mmol, 3 equiv), and $NiCl_2$(dme) (0.005 mmol, 10 mol %). The vial was charged with the 1,4-dioxane (0.14 mL, 0.37 M) followed by chlorophosphine substrate (0.05 mmol, 1 equiv), benzyl chloride substrate (0.05 mmol, 1.0 equiv), TMSCl (0.02 mmol, 0.4 equiv), and benzyl ether (internal standard). The vial was sealed and

removed from the glovebox. The mixture was stirred vigorously at 500 rpm, ensuring that the reductant was uniformly suspended, at 23 °C for 24 h. The reaction mixture was diluted with 10% ethyl acetate/hexane and passed through a plug of silica, using 40% ethyl acetate/hexane eluent. The solution was concentrated, and the crude reaction mixture was analyzed by ^{1}H and ^{31}P NMR.

5.6.4 *(Hetero)aryl iodide/α-chloroester cross-coupling (Scheme 5.7)*

In a glovebox, to a 1 dram vial was added the appropriate ligand (0.01 mmol, 20 mol %), reductant (0.3 mmol, 3 equiv), and $NiBr_2$(diglyme) (0.005 mmol, 10 mol %). The vial was charged with the 1,4-dioxane (0.14 mL, 0.37 M) followed by α-chloroester substrate (0.05 mmol, 1 equiv), aryl iodide substrate (0.05 mmol, 1.0 equiv), TMSCl (0.02 mmol, 0.4 equiv), and benzyl ether (internal standard). The vial was sealed and removed from the glovebox. The mixture was stirred vigorously at 500 rpm, ensuring that the reductant was uniformly suspended, at 23 °C for 24 h. The reaction mixture was diluted with 10% 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.

5.7 NOTES AND REFERENCES

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