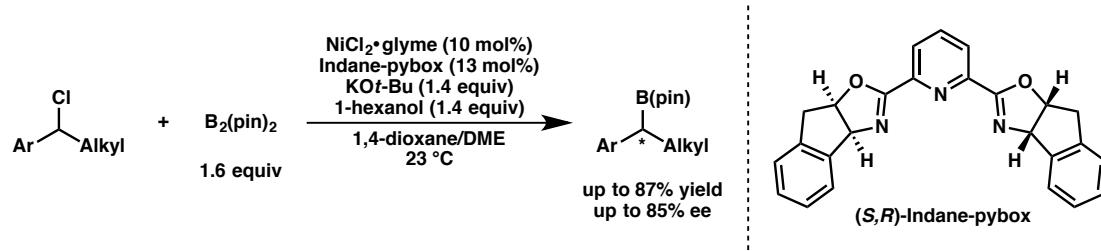


CHAPTER 3

Enantioselective Ni-Catalyzed Borylation of Secondary Benzylic Chlorides[†]

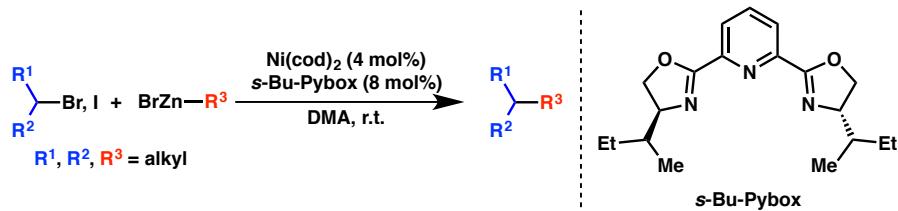


[†]This work was performed in collaboration with Dr. Alex Dudnik

3.1 Introduction

While palladium catalysis has been at the forefront of multiple advancements in cross coupling, nickel catalysis has recently proved to furnish complementary and equally powerful reactivity.¹ The broad expansion of nickel-catalyzed coupling reactions can be attributed to the utility imparted by the unique properties of nickel. For example, the accessibility of Ni(0), Ni(I), Ni(II), and Ni(III) oxidation states facilitates versatile modes of reactivity, including radical mechanisms.¹ In addition, β -hydride elimination is considered to be slower for nickel than for palladium.² These features have rendered Ni catalysts particularly efficient for cross coupling historically challenging substrates such as secondary alkyl halides.³ In 2003, the Fu group reported the first example of a Ni- or Pd- catalyzed cross coupling of β -hydrogen-containing, unactivated, secondary alkyl halides.⁴ The use of a Ni(COD)₂/s-Bu-Pybox catalyst system opened the door to the possibility of developing asymmetric variants (Scheme 3.1).

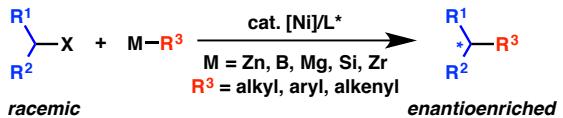
Scheme 3.1 Ni-catalyzed cross coupling of unactivated secondary alkyl halides



The Fu group has subsequently reported a variety of stereoconvergent, enantioselective Ni-catalyzed cross coupling reactions of both activated and unactivated racemic secondary alkyl halides with alkyl, aryl, and alkenyl

organometallic reagents (Scheme 3.2).³ These reactions and related systems are postulated to proceed through a single electron transfer pathway for cleavage of the alkyl halide C–X bond resulting in an alkyl radical intermediate.^{5,6,7,8,9}

Scheme 3.2 Stereoconvergent Ni-catalyzed cross coupling of secondary alkyl halides



In terms of an overall catalytic cycle, the enantioselective Negishi arylation of propargylic bromides is proposed to proceed via a bimetallic oxidative addition, radical chain pathway in which the catalyst resting state is an arylnickel(II) species (Figure 3.1).^{6a} In the case of unactivated alkyl halides, it has been postulated that the mechanism involves transmetallation followed by an inner-sphere electron transfer pathway for oxidative addition (Figure 3.2).¹⁰ It is likely that the reaction mechanism varies depending on the specific ligand, coupling partners, and reaction conditions.

Figure 3.1 Postulated radical chain mechanism for Ni-catalyzed Negishi arylation of propargylic bromides

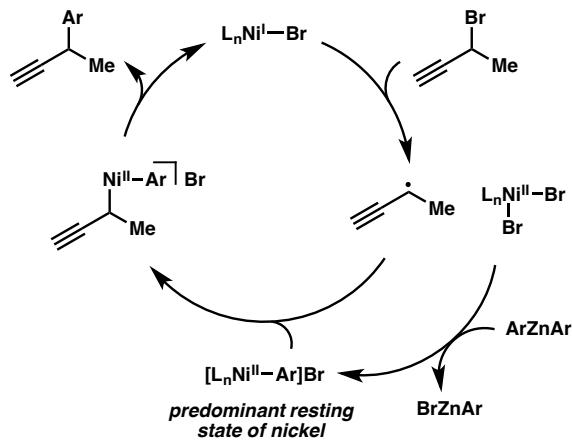
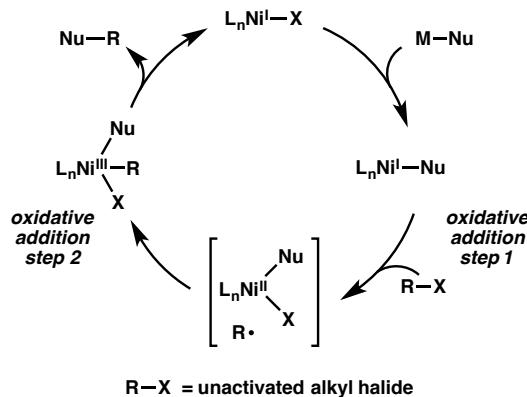


Figure 3.2 Outline of a possible mechanism for nickel-catalyzed coupling of unactivated alkyl halides

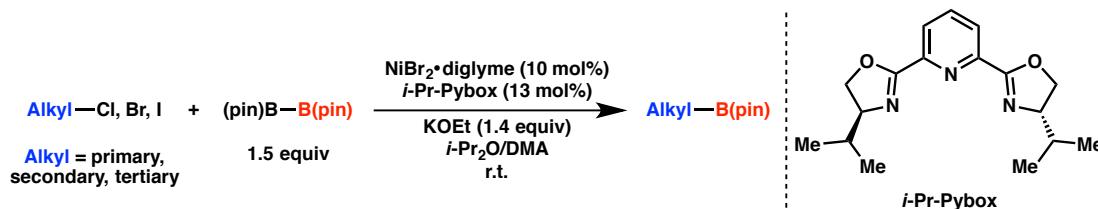


Several recent developments have focused on expanding the scope of these stereoconvergent cross coupling reactions to include new classes of electrophiles, including α -haloboronates,¹¹ α -halo- α -trifluoromethyl electrophiles,¹² and α -halo-sulfonamides and -sulfones.⁷ These enantioselective Ni-catalyzed coupling reactions of racemic secondary alkyl halides have been demonstrated with a variety of organometallic nucleophiles, including organozinc, -boron, -magnesium, -silicon, and

-zirconium reagents.³ Despite these advancements, an enantioselective coupling reaction of a secondary alkyl halide has yet to be established with a heteroatom nucleophile.

It has been reported that unactivated primary, secondary, and tertiary alkyl halides are effective coupling partners in Miyaura-type borylation reactions using a NiBr_2 •diglyme/*i*-Pr-Pybox catalyst system (Scheme 3.3).^{9a} A NiBr_2 •diglyme/achiral terpyridine catalyst system has also been shown to effect borylation of unactivated secondary alkyl bromides.¹³ Several other transition metals have been used to achieve Miyaura-type borylation of secondary alkyl halides, including copper,¹⁴ zinc,¹⁵ iron,¹⁶ manganese,¹⁷ and iridium;¹⁸ however, no catalytic asymmetric variant has been established.¹⁹

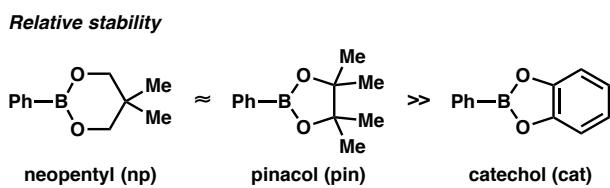
Scheme 3.3 *Ni*-catalyzed borylation of unactivated alkyl halides



Organoboron compounds are versatile intermediates in organic synthesis, serving as reaction partners in Suzuki couplings and as precursors to esters, alcohols, carboxylic acids, and amino acids.²⁰ The stability of alkylboronic esters to air, moisture, and retention of configuration renders them particularly valuable.²¹ Most boronic esters exhibit lower reactivity as compared to boronic acids and may be purified by column chromatography and dissolved in nonpolar organic solvents.

Pinacol, neopentyl-, and catechol boronic esters are commonly used due to their relative stability, reactivity, and ease of preparation (Figure 3.3).²² Enantioenriched secondary and tertiary boronic esters have garnered recent interest as substrates for stereospecific coupling reactions.²³

Figure 3.3 Relative stability of commonly used boronic esters

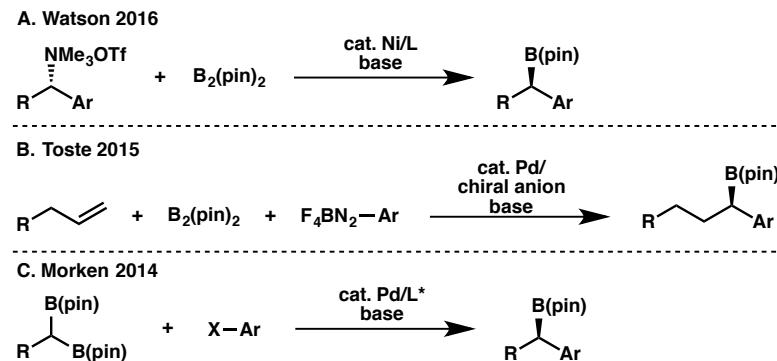


Among well-established strategies for synthesis of enantioenriched organoboronates are methods using stoichiometric chiral auxiliaries such as Brown's hydroboration²⁴ and Matteson's asymmetric homologation.²⁵ More recently developed catalytic enantioselective methods are focused on two approaches, borylation of organic functional groups (late-stage borylation), and the modification of boron-containing substrates (early-stage borylation). Catalytic enantioselective borylation reactions include hydroboration,²⁶ diboration,²⁷ allylic borylation,²⁸ and conjugate borylation.²⁹ State-of-the-art strategies include stereospecific Miyaura-borylations of enantioenriched electrophiles (Scheme 3.4A)³⁰ and the three-component coupling of olefins, aryl diazonium salts, and bis(pinacolato)diboron ($B_2\text{pin}_2$) via cooperative chiral anion phase transfer and Pd-catalysis (Scheme 3.4B).³¹

With respect to early-stage borylation, effective methods include the enantioselective conjugate addition of an organometallic or diboron reagent to a β -borylated substrates,³² enantioselective hydrogenation of vinyl boronates,³³ and

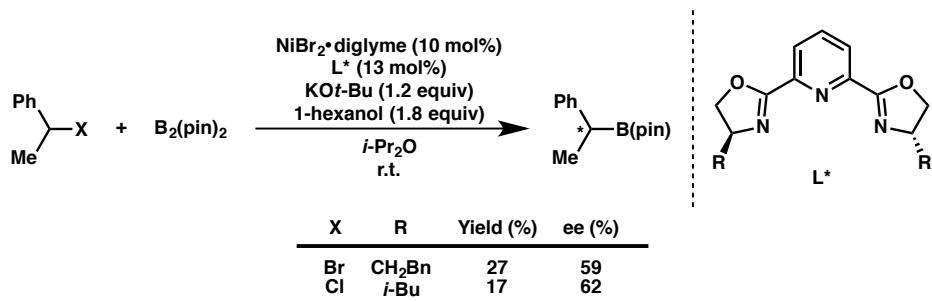
enantiotopic-group-selective Suzuki coupling of achiral germinal bis(pinacolboronates) (Scheme 3.4C).³⁴ Recent advances include the Fu group's stereoconvergent Ni-catalyzed cross coupling reactions of α -haloboronates.¹⁰

Scheme 3.4 Recent examples of stereoselective synthesis of benzylic boronic esters



A catalytic enantioselective method for borylation of racemic alkyl halides would add to the breadth of work focused on synthesis of enantioenriched organoboronates. We hoped that the $\text{NiBr}_2\text{-diglyme}/i\text{-Pr-Pybox}$ catalyst system established by Dr. Alex Dudnik would provide a feasible starting point for the development of a Ni-catalyzed enantioselective borylation of secondary alkyl halides. Preliminary investigations by Dr. Alex Dudnik resulted in moderate ee (61%) and modest yield in the enantioselective borylation of a racemic benzylic halide (Scheme 3.5). The goal of this project is to improve upon these initial results and therein demonstrate the first example of an enantioselective Ni-catalyzed coupling of a racemic secondary alkyl halide with a heteroatom nucleophile.

Scheme 3.5 Enantioselective borylation of benzylic halides: preliminary studies

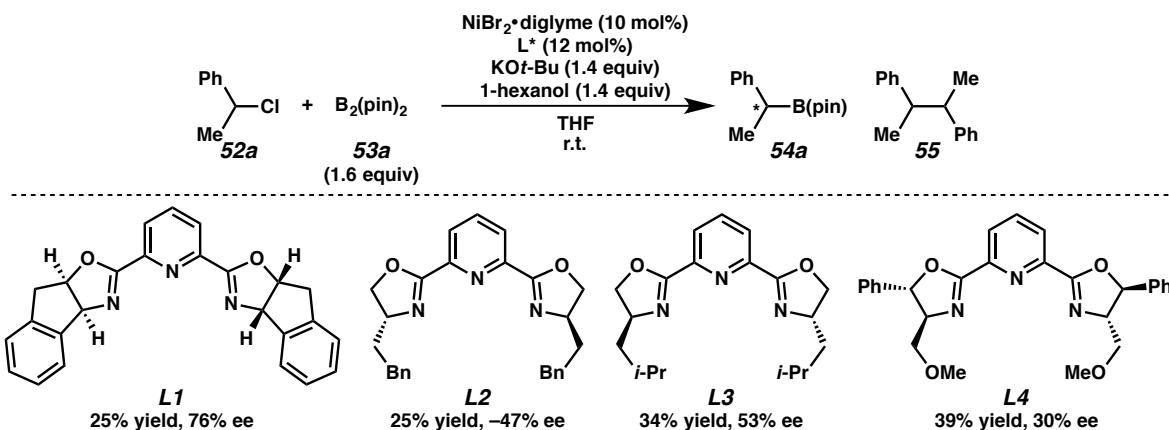


3.2 Results and Discussion

With Dr. Alex Dudnik's best conditions as a general starting point (Scheme 3.5), a variety of reaction parameters were explored in greater detail. Pyridine bis(oxazoline) (pybox) ligands resulted in superior ee values compared to other classes of ligands including bis(oxazoline), diamine, and quinoline oxazoline. It was found that other ethereal solvents than *i*-Pr₂O, such as THF or DME, resulted in greater ee values. Yields of the desired product were generally higher with an alkyl chloride than with an alkyl bromide.

Evaluation of a variety of pybox ligands for the coupling of benzylic chloride **52a** in THF revealed that indane-pybox **L1** resulted in a significant increase in enantioselectivity, although the desired product was formed in low yield due to electrophile homocoupling (**55**) (Scheme 3.6).

Scheme 3.6 Effect of pybox ligands on the borylation of a benzylic chloride



After a more detailed exploration of solvent effects, 1,4-dioxane was determined to provide a small increase in enantioselectivity. Increasing the steric demand of the benzylic chloride alkyl substituent from Me (**52a**) to Et (**52b**) improved yield but did not significantly affect enantioselectivity (Table 3.1).

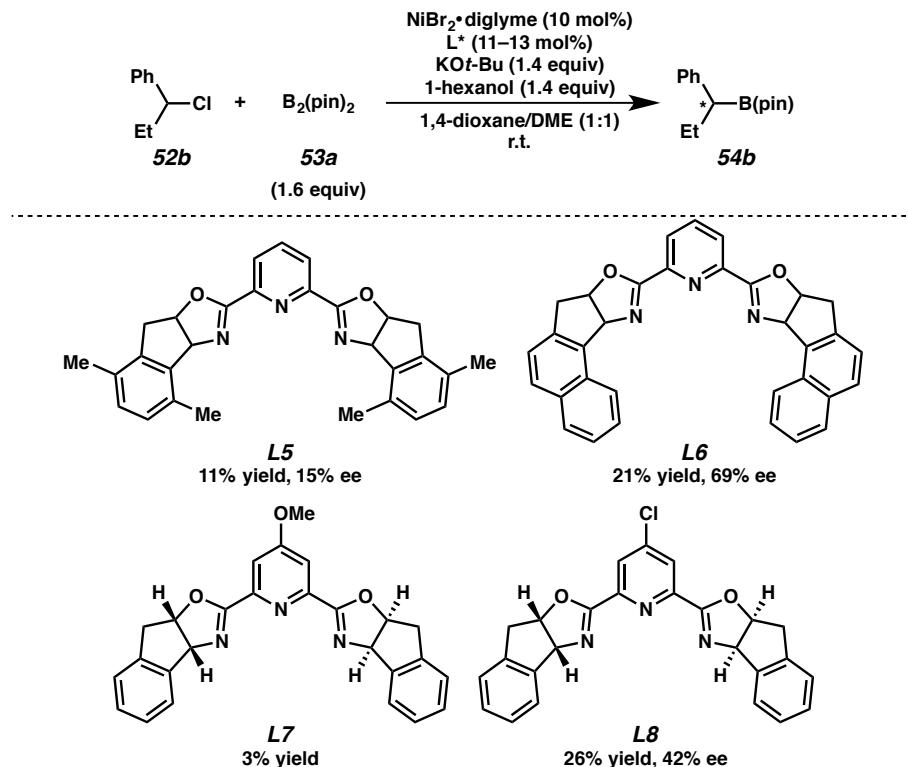
Table 3.1 Effect of various benzylic chloride alkyl substituents

		$\text{NiBr}_2 \bullet \text{diglyme (10 mol\%)} \\ \text{L1 (13 mol\%)} \\ \text{KO}t\text{-Bu (1.4 equiv)} \\ 1\text{-hexanol (1.4 equiv)} \\ 1,4\text{-dioxane} \\ \text{r.t.}$		
52a-c	53a	(1.6 equiv)		
		R	Yield (%)	ee (%)
52a → 54a	Me	38	82	
52b → 54b	Et	75	83	
52c → 54c	<i>n</i> -Bu	64 (uncalibrated)	80	

Other variations to the reaction conditions, such as using $\text{NiCl}_2 \bullet \text{glyme}$ instead of $\text{NiBr}_2 \bullet \text{diglyme}$, and using a mixture of 1,4-dioxane and DME, resulted in improved yields but unaffected enantioselectivity. Various indane-pybox derivatives were investigated (Scheme 3.7). Increasing the steric bulk or extending the π -system of the ligand (**L5** and **L6**, respectively) resulted in substantially decreased yields and

low to moderate enantioselectivity. Ligands with either an electron-donating or an electron-withdrawing substituent on the pyridine ring (**L7** and **L8**, respectively) were also detrimental to yield and/or enantioselectivity.

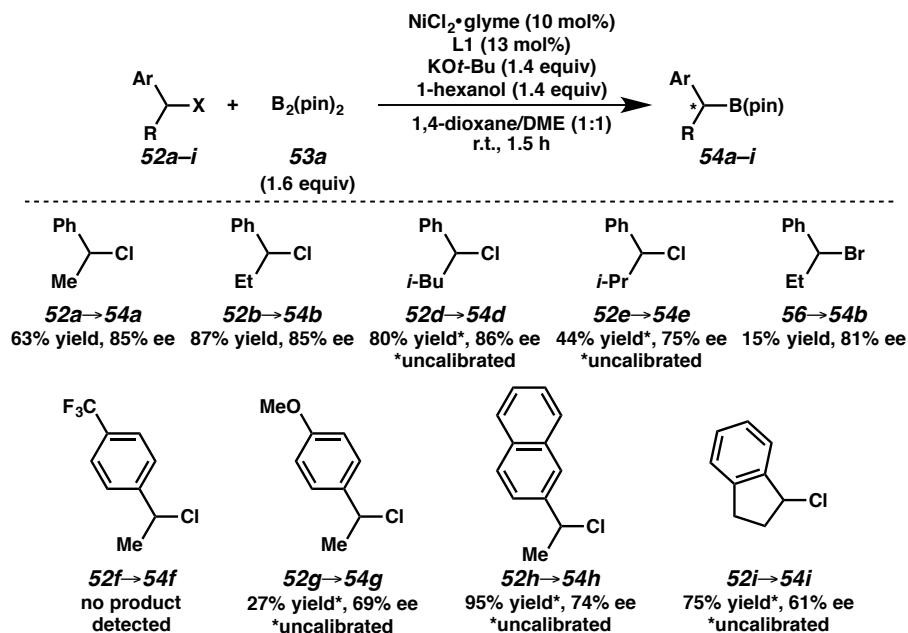
Scheme 3.7 Effect of indane-pybox derivatives on Ni-catalyzed borylation of a benzylic chloride



Under the optimized conditions, the scope of the reaction was explored with respect to the alkyl halide coupling partner (Scheme 3.8). Benzylic chlorides with a methyl (**52a**), ethyl (**52b**), isobutyl (**52d**), or isopropyl (**52e**) α -substituent undergo Ni-catalyzed borylation in moderate to good enantioselectivity. Benzylic bromide **56** results in high enantioselectivity but low yield of the desired boronic ester **54b**. The yield and enantioselectivity of the reaction are sensitive to the electronics of the aryl substituent; an electron-poor benzylic chloride (**52f**) results in no detectable

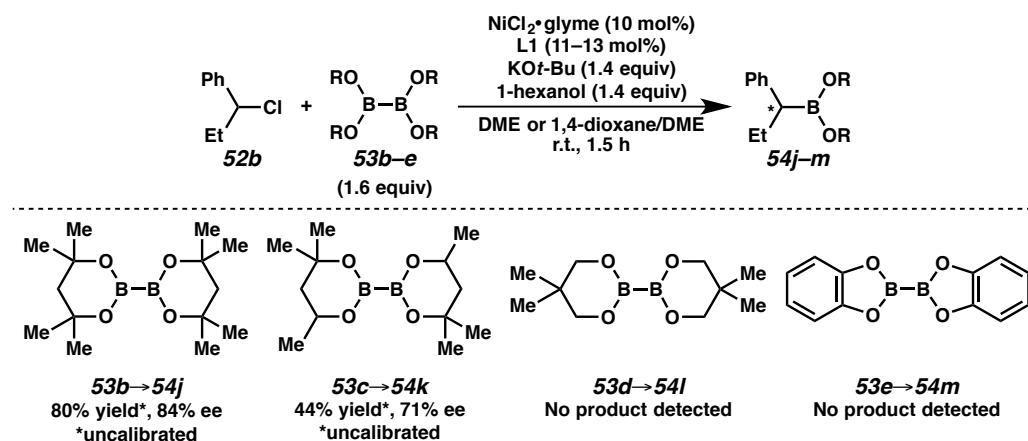
borylation, while an electron-rich benzylic chloride (**52g**) furnishes the boronic ester in low yield and moderate enantioselectivity. Decreased enantioselectivity is also observed in the case of a benzylic chloride with a naphthyl substituent (**52h**) and 1-chloroindane (**52i**).

Scheme 3.8 Effect of electrophile structure on yield and enantioselectivity under optimized conditions



The reaction is also sensitive to the structure of the boron-containing reagent. For example, bis(hexylene glycolato) diboron (**53b**) results in lower enantioselectivity, while bis(neopentylglycolato)diboron (**53d**) and bis(catecholato)diboron (**53e**) do not result in any product formation (Scheme 3.9). In addition, pinacolborane and tetrahydroxydiboron do not yield the desired product under similar conditions.

Scheme 3.9 Effect of diboron structure on yield and enantioselectivity under optimized conditions



3.3 Conclusion

We have developed, to the best of our knowledge, progress toward the first example of enantioselective Ni-catalyzed cross coupling of racemic alkyl halides and *heteroatom* nucleophiles. Specifically, the borylation of secondary benzylic chlorides with $\text{B}_2(\text{pin})_2$ can be achieved in up to 87% yield and 85% ee using a $\text{NiCl}_2 \bullet \text{glyme}/\text{indane-pybox}$ catalyst system. This is the first method for catalytic enantioselective Miyaura-type borylation of alkyl halides. This $\text{C}(\text{sp}^3)\text{–B}$ coupling reaction occurs under mild conditions (room temperature) with commercially available, air-stable reagents: $\text{NiCl}_2 \bullet \text{glyme}$, indane-pybox, and $\text{B}_2(\text{pin})_2$. Although the substrate scope with respect to both the benzylic chloride and diboron coupling partners remains modest, we have established a valuable proof-of-concept that enantioselective Ni-catalyzed cross coupling of racemic alkyl halides can be extended beyond C–C bond formation.

3.4 Experimental Procedures

3.4.1 General Information

The following reagents were purchased and used as received: $\text{NiCl}_2 \cdot \text{glyme}$ (Aldrich), ligand **L1** (Aldrich), 1,4-dioxane (anhydrous, 99.8%; Aldrich), DME (anhydrous, 99.5%, inhibitor-free; Aldrich), $\text{KO}t\text{-Bu}$ (Strem), 1-hexanol (anhydrous, $\geq 99\%$; Aldrich). Diboron reagents were purchased from Frontier Scientific or Combi-Blocks. Benzylic chlorides³⁵ and bromides^{6b} were prepared from the corresponding alcohols according to literature procedures. All reactions were carried out in oven-dried glassware under an atmosphere of nitrogen.

¹HNMR spectroscopic data were collected on a Varian 500 MHz spectrometer at ambient temperature. GC analyses were obtained on an Agilent 6890 Series GC system with a DB-1 column (length 30 m, internal diameter 0.25 mm). HPLC analyses were carried out on an Agilent 1100 Series system with Daicel CHIRALPAK columns (internal diameter 4.6 mm, column length 25.0 cm, particle size 5 μm).

3.4.2 Ni-Catalyzed Borylation of Benzylic Chlorides

General procedure for evaluating benzylic chloride scope on a small-scale: To a 4-mL vial **A** open to air was added $\text{NiCl}_2\text{-glyme}$ (2.2 mg, 0.010 mmol, 0.10 equiv) and **L1** (5.2 mg, 0.013 mmol, 0.13 equiv). Vial **A** was then brought into a nitrogen-filled glovebox and 0.5 mL dioxane were added. (Note: Due to the poor solubility of **L1** in ethereal solvent, a stock solution of Ni/L1 cannot be made. The procedure for **A** was repeated n times for the number of reactions in the screen.) The Ni/L1 solution was then stirred for 45 min. A stock solution of diboron reagent and base was then prepared in a separate 4-mL vial **B**. To vial **B** was added $\text{KO}t\text{-Bu}$ ($15.7n$ mg, 0.140 n mmol, 1.40 n equiv), 1-hexanol ($17.5n$ μL , 0.140 n mmol, 1.40 n equiv), and 0.2 n mL DME. The contents of **B** were stirred for 1 minute, then a solution of B_2pin_2 (40.6 n mg, 0.160 n mmol, 1.60 n equiv) in 0.2 n mL DME was added. The contents of **B** were then stirred for 45 min, after which the solution was diluted to a total volume of 0.5 n mL with DME. To vial **A** was then added the benzylic chloride (0.100 mmol, 1.00 equiv) followed by 0.5 mL of the stock solution in vial **B**. Vial **A** was then sealed with a PTFE-lined cap and removed from the glovebox. After 1.5 h, the vial was opened to air and dodecane (17.0 mg, 0.100 mmol, 1.00 equiv) was added. The mixture was then filtered through a small silica plug, eluting with diethyl ether. An aliquot of the eluate was then removed for GC determination of the yield with respect to dodecane as an internal standard. The remaining eluate was then concentrated by rotary evaporator and oxidized with $\text{NaBO}_3\text{-4H}_2\text{O}$ (~20 mg) in 1:1 $\text{H}_2\text{O/THF}$ (2 mL) at room temperature for 30 min. The mixture was extracted with Et_2O , the combined organic phases were dried over Na_2SO_4 and concentrated by

rotary evaporator, and the residue was purified by preparative TLC (Et₂O/hexanes). The purified alcohol was then dissolved in hexanes for HPLC analysis on a CHIRALPAK OD column (2–3% IPA/hexanes, 1.0 mL/min).

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