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Ni-Catalyzed Arylboration of Unactivated Alkenes: Scope and Mechanistic Studies

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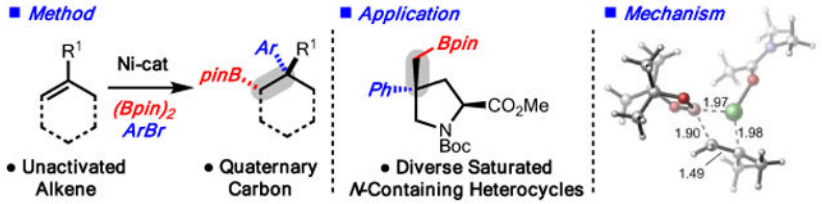
Abstract

A method for the Ni-catalyzed arylboration of unactivated monosubstituted, 1,1-disubstituted and trisubstituted alkenes is disclosed. The reaction is notable in that it converts highly substituted alkenes, arylbromides and diboron reagents to products that contain a quaternary carbon and a synthetically versatile carbon-boron bond with control of stereoselectivity and regioselectivity. In addition, the method is demonstrated to be useful for the synthesis of saturated nitrogen heterocycles, which are important motifs in pharmaceutical compounds. Finally, due to the unusual reactivity demonstrated, the mechanistic details of the reaction were studied with both computational and experimental techniques.

Graphical Abstract



INTRODUCTION:

The use of cross coupling reactions to forge C-C bonds has transformed the way in which molecules are constructed.[1] These reactions work particularly well for the synthesis of Csp^2-Csp^2 bonds, but the translation of these methods towards the preparation of Csp^3-Csp^2 bonds is considerably more challenging due to rapid β-hydride elimination of alkyl-metal intermediates and slower rates of transmetalation.1 Furthermore, the synthesis of quaternary carbons exacerbates the aforementioned challenges.[2,3,4,5]

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Supporting Information

Experimental procedures and analytical data for all compounds. This information is available free of charge via the Internet at http://pubs.acs.org/

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An emerging approach towards Csp^3-Csp^2 cross-coupling is to utilize alkenes as conjunctive reagents.[6] This strategy is attractive since the nucleophilic or electrophilic component does not need to be pregenerated, and widely available alkenes are employed. Our lab has been interested in the development of an approach that involves the cross coupling of aryl halides with Csp^3-alkyl metal intermediates that are catalytically generated by boryl metalation of alkenes.[7,8] These arylboration reactions are valuable as they allow for carbodifunctionalization by stereospecific transformation of the C-B bond to other functional groups.[9] Early work from our group and others focused on Pd/Cu, Ni/Cu and Pd-catalyzed arylboration of activated alkenes (Scheme 1A).7,[10,11]

Our group recently disclosed a Ni-catalyzed arylboration on challenging unactivated 1,2-disubstituted alkenes (Scheme 1B).[12,13,14] However, arylboration reactions on monosubstituted, 1,1-disubstituted, and trisubstituted alkenes were generally low yielding and poorly selective. Overcoming these challenges in the arylboration of 1,1-disubstituted and trisubstituted alkenes is particularly desirable as it leads to the construction of quaternary carbons. Carboboration of 1,1-disubstituted alkenes has only been demonstrated with select α-alkyl alkenylarenes, whereas reactions of trisubstituted alkenes are not known. [15] Additionally, selective 1,2-arylboration of monosubstituted alkenes has not yet been reported. Thus, the ability to carry out arylboration reactions of unactivated alkenes with various substitution patterns remains an unmet challenge.[16]

Herein we disclose a new method that overcomes the aforementioned challenges and allows for arylboration of unactivated monosubstituted, 1,1-disubstituted and trisubstituted alkenes (Scheme 1C). In the latter classes of substrates, the reaction involves stereospecific cross coupling of an *in situ-generated, stereodefined, tertiary alkyl-[Ni] complex*, resulting in vicinal alkene difunctionalization that displays complete stereochemical control. Moreover, the method outlined herein represents a new strategy for the synthesis of a diverse range of saturated nitrogen heterocycles, which are valuable building blocks in pharmaceutical synthesis (Scheme 1D).[17] Finally, a detailed analysis of the reaction mechanism is presented, with computational and experimental data that reveals the details of this unique reaction manifold.

RESULTS AND DISCUSSION: SCOPE

A key challenge identified in our initial report was the regioselectivity in the arylboration of terminal alkene substrates. For example, vinylcyclohexane (**1**) underwent 1,2-arylboration (product **2**) in moderate yield and with concomitant formation of 1,1-arylboration adduct **3** (Scheme 2). Based on preliminary mechanistic studies outlined in the initial report,12 the 1,2-arylboration product **2** likely arises via addition of a [Ni]-Bpin complex to the alkene, followed by capture of the subsequent alkyl-[Ni]-intermediate **4** with arylbromide. The formation of the 1,1-arylboration adduct 3 presumably arises by β-hydride elimination of the alkyl-[Ni]-intermediate followed by reinsertion and ArBr capture via **5**.[18]

To mitigate the formation of the 1,1-arylboration adduct **3**, ligands that occupy coordination sites and prevent the β-agostic interaction necessary for β-hydride elimination were investigated. However, traditional ligands such as amines or phosphines inhibited the

reaction. Since THF is likely coordinated to Ni during catalysis, other oxygen-derived Lewis basic additives were evaluated (Scheme 3). Early screens identified that amide additives suppressed the formation of the 1,1-arylboration product. Ultimately, 20 equiv of dimethylacetamide (DMA) was found to be optimal, both for suppressing formation of 1,1-arylboration product **3** and enhancing the yield of the desired 1,2-arylboration product **2**. Other related amides were inferior to DMA, and amides capable of bidentate coordination inhibited the reaction. Use of less than 20 equiv of DMA was slightly less effective, while increased quantities of DMA provided no additional benefit. A 4:1 mixture of THF:DMA, or approximately 20 equiv of DMA, was identified as optimal for reactivity and simple reaction setup.

Application of the new conditions to a range of monosubstituted alkenes resulted in formation of the 1,2-arylboration products in good yields and suppressed 1,1-arylboration (Scheme 4).[19] Several points are noteworthy: 1) reaction of branched alkenes (products **2**, **6-8**, **13**) resulted in high regioselectivity (>10:1 rr). In particular, sterically demanding *t*-Bu-ethylene (product **7**) can participate in the reaction; however, in this case the 1,1-arylboration isomer formed in 11% yield. The increase in the amount of 1,1-arylboration in this case is likely due to a reduced rate of reaction of the alkyl-[Ni]-complex (analogous to **4**) with the arylbromide, which allows for β-hydride elimination to compete. 2) Reaction with non-branched alkenes led to product formation with good yield but modest regioselectivity (products **9-12**). 3) Reaction of allylbenzene formed only 1,2-arylboration product **12**, despite the potential for facile β-hydride elimination with the benzylic hydrogens.[16] 4) Ringopening products resulting from reaction of vinylcyclopropane were only formed in 3% yield (product **8**). 5) In several cases, 3.0 equiv PhBr (vs. 1.5 equiv PhBr) were necessary to obtain high yields, presumably resulting in faster trapping of the alkyl-Ni-complex and outcompeting β-hydride elimination or other decomposition reactions.

Given the remarkable effect of DMA on reactivity and selectivity, we desired to explore the reactivity of other classes of challenging alkenes. Selective 1,2-arylboration of 1,1-disubstituted alkenes was particularly difficult under previously reported conditions12 due to low yield and formation of the 1,1-arylboration regioisomer.[20] For these reactions to proceed, a sterically encumbered tertiary alkyl-[Ni]-complex must be generated and then undergo cross coupling with an ArBr faster than β-hydride elimination. Under the new conditions with DMA, alkenes with a variety of substitution patterns functioned well in the arylboration reaction (Scheme 5). Proximal functionalities, such as an ester (product **15**), acetal (product **18**), and Boc-protected amine (products **19-20**) functioned smoothly in the reaction. Sterically demanding substrates underwent the arylboration, albeit in slightly diminished yields (product **16-17**). Symmetric trisubstituted alkenes also perform well in the reaction and generate a single regioisomer in every case (products **20, 22-23**).

One of the most significant aspects of this study is the reaction of asymmetric trisubstituted alkenes, due to the opportunity for stereocontrol (Scheme 5). Reaction of *Z*- and *E*-alkenes led to the formation of different diastereomers resulting from a *syn*-arylboration in each case (products **24** and **25**, respectively). This process has also been extended to reaction of a cycloalkene to generate **26**. In all cases the reaction likely proceeds via the formation of stereodefined tertiary alkyl-[Ni]-complexes **27-29**. These Ni-complexes do not appear to

undergo epimerization or β-hydride elimination, thus highlighting their remarkable stability and reactivity.

A wide range of arylbromides was evaluated with alkene **30** (Scheme 6). In all cases, the reaction afforded a single observable regioisomer, and the undesired 1,1-arylboration product was not detected (with the exception of product **40**). Notably, aryl bromides bearing electron-donating (product **33**), electron-withdrawing (products **32**, **34-37**), and sterically demanding substituents (product **40**) function smoothly. In addition, functional groups such as an ester (product **35**), acetal (product **43**), primary alcohol (product **39**), tertiary amine, (product **42**), amide (products **41**, **44**), and select heterocycles (products **45-47**)[21] are tolerated. Finally, reaction with an alkenylbromide demonstrated that alkenylboration is a viable process (product **38**).

Substrates in which the arylbromide and alkene units are tethered were also examined (Scheme 7). In both cases (substrates **48** and **50**), the reaction formed products **49** and **51**, respectively, in accordance with formation of the more substituted alkyl-[Ni]-complex from borylnickelation. Furthermore, the formation of **51** in 20:1 dr (consistent with the starting alkene geometry isomeric ratio) represents the synthesis of a *N*-containing heterocycle.

Saturated nitrogen heterocycles, such as piperdine, pyrazine and pyrrolidine are among the top-ten ring systems in FDA approved drugs.17[a,b] Given the pharmaceutical industry's recent push to evaluate molecules with increased saturation, development of methods to access these motifs efficiently is highly relevant.17[c,d] We sought to apply the present arylboration to the synthesis of a diverse range of saturated nitrogen heterocycles from readily available unsaturated nitrogen heterocycles.

Under the optimized conditions, a variety of unsaturated nitrogen heterocycles underwent arylboration (Scheme 8). In the case of pyrrolidines with disubstituted and trisubstituted, endo- and exocyclic alkenes (**52**, **54**,[22] **58**, **60** and **70**) function well. In the case of stereoisomeric alkenes **58** and **60**, the products are formed from a *syn*-arylboration pathway. A similar range of piperidine ring systems was tolerated in the reaction (alkenes **62**, **64**, **66**, and **68**). In addition, an azetadine-based substrate was shown to function smoothly (alkene **56**).

The ability of the method to function well with chiral non-racemic substrates was also demonstrated with alkene **72** (prepared from commercially available *N*-Boc hydroxyproline methyl ester in two steps) (Scheme 9). In this case, reaction with bromobenzene delivered product **73** in 72% yield and 18:1 dr without epimerization of the C1 stereocenter. Based on the stereochemistry of the product, borylnickelation occurred from the least hindered face opposite the ester substituent according to the model (**74**) illustrated in Scheme 9

The method is also amenable to gram scale synthesis as illustrated in Scheme 10 (products **26** and **76**). As a demonstration of the robustness of the reaction conditions, the synthesis of **26** was achieved without the aid of a glovebox using standard Schlenk techniques.

The Bpin unit can easily be converted to other functional groups through various transformations such as oxidation (product **77**) and Matteson homologation (product **78**)

(Scheme 10). The homologation product could also be elaborated by Pd-catalyzed cross coupling to provide **79**.[23] Thus, through the sequence of arylboration and C-B bond transformation, elaboration of readily available starting materials can deliver diverse saturated nitrogen heterocycles.

RESULTS AND DISCUSSION: MECHANISM

Based on our prior observations, a Ni(I)-Ni(III) catalytic cycle was proposed (Scheme 11). **12** While both Ni(II) or Ni(0) pre-catalysts can be used, the formation of Ni(I)-complexes can occur through a comproportionation pathway.[24,25] The key step in the Ni(I)-Ni(III) cycle is the formation of a [Ni(I)]-Bpin complex followed by addition across an alkene. The resulting alkyl-[Ni(I)]-complex then undergoes reaction with the arylbromide, perhaps via an oxidative addition/reductive elimination sequence, to generate the product and regenerate [Ni(I)]-Br. The formation of the 1,1-arylboration adduct likely arises from β-hydride elimination of the alkyl-[Ni(I)]-complex followed by reinsertion and capture with the arylbromide.

Additional data gathered in this study corroborates this mechanistic hypothesis. Key experiments are outlined in Scheme 12. 1) Radical intermediates are unlikely to be involved in the reaction pathway, as the reactions are stereospecific and ring opening of cyclopropane only occurs in minor quantities (Scheme 12A). 2) A pathway in which a bimetallic transmetalation between two different Ni species is unlikely as substrates in which the alkene and arylbromide units are tethered delivered the intramolecular arylboration product in good yield (Scheme 12B).[26] For a bimetallic reaction pathway of this type to function on these substrates, two different Ni-centers must react with the same molecule of substrate, which is highly unlikely. Moreover, crossover products that would arise from a bimetallic pathway via the intermediate shown in Scheme 12B were not observed in these intramolecular reactions in the presence of bromobenzene. 3) A linear free energy relationship between relative rate of reaction of various arylbromides and σ was observed (Scheme 3C). Due to the large positive ρ-value observed (2.6), electrophilic capture of the alkyl-Ni-intermediate occurs (either via oxidative addition or σ-bond metathesis).[27] 4) Determination of ^{13}C KIE at natural abundance revealed small, but statistically significant values for both carbons of the alkene (Scheme 12D).[28] The similar values and magnitude of the KIE suggests an early transition state with similar degrees of bond formation at both carbons of the alkene.

A catalytic cycle involving Ni(0) and Ni(II) intermediates was also considered (Scheme 13A). In this process, Ni(0) would undergo oxidative addition with the arylbromide to generate an Ar-[Ni(II)]-Br complex. Transmetalation with $(Bpin)_2$ would occur to provide Ar-[Ni]-Bpin which upon migratory insertion and reductive elimination would generate the product. The formation of the 1,1-arylboration adduct would arise from a similar β-hydride elimination sequence as shown in Scheme 11.

However, this catalytic cycle is inconsistent with two experiments outlined in Scheme 13. The first involves varying the equivalents of arylbromide (Scheme 13B). In particular, it was observed that the 1,1-arylboration regioisomer (*e.g.*, **81** and **83**) could be suppressed with

increased quantities of arylbromide. In the Ni(0)-Ni(II) catalytic cycle, the relative rates for the formation of the 1,1- and 1,2-arylboration products should be independent of arylbromide concentration (*i.e.*, arylbromide is only involved in oxidative addition, which precedes the divergence point for formation of the 1,1- and 1,2-arylboration products). In contrast, the data shown in Scheme 13B is consistent with the Ni(I)-Ni(III) catalytic cycle illustrated in Scheme 11, in which increased concentration of arylbromide results in more rapid capture of the alkyl-[Ni]-complex relative to β-hydride elimination and thus results in less 1,1-arylboration product formation. The second experiment examines the regioselectivity of intra vs. intermolecular arylboration reaction (Scheme 13C). For reaction of **84** and **87,** similar regioselectivity is observed, suggesting the formation of similar alkyl-[Ni]-intermediates prior to capture with an arylbromide, which is fully consistent with the Ni(I)-Ni(III) catalytic cycle. However, this is inconsistent with the Ni(0)-Ni(II) catalytic cycle in which the regioselectivity of migratory insertion from the Ar-[Ni]-Bpin complex **90** should be influenced by relative rate of ring forming reactions to form **91** and **92** and thus the regioselectivity should be different for reaction of substrates **84** and **87**. Furthermore, if the Ni(0)-Ni(II) pathway were operative it would seem likely that **90** would undergo insertion via a well established 5-exo-trig pathway to result in exclusive formation of **85** via **93**[29] (6-endo-trig cyclization, such as **94,** are very rare and only occur with specialized substrates).[30] However, since a significant amount of product **86** was observed, [Ni]-Ar migratory insertion is less likely than initial [Ni]-Bpin migratory insertion occurring first, followed by intramolecular trapping of the [Ni]-alkyl species with the arylbromide.

The experimental investigations outlined above have elucidated the overall features of the Ni(I)-Ni(III) catalytic cycle; however, several details remained unclear, specifically: 1) What is the nature of the [Ni]-Bpin and the alkyl-[Ni]-complexes? 2) What is the basis for the regioselectivity of migratory insertion? 3) How does the alkyl-[Ni]-complex undergo reaction with arylbromide? To address these questions, a computational investigation of the reaction was undertaken at the UM06/SDD–6-311+G(d,p)/SMD(THF)//UB3LYP/LANL2DZ–6-31G(d) level of theory.

The reaction between model substrate 2-methylprop-1-ene **95** and bromobenzene to afford product **96** was used as the model reaction in the calculations (Scheme 14). Under the experimental conditions with THF/DMA cosolvents, several possible ligands can potentially bind to the Ni(I)–Bpin, an active species in the catalytic cycle proposed in Scheme 11. These possible structures of the Ni-Bpin complex were probed computationally and a three-coordinate Ni-Bpin bound with a DMA and an alkene (**INT-1**, Figure 1) was found to be the most favorable structure (see Supporting Information for details). Alkene migratory insertion from **INT-1** occurred to generate the tertiary alkyl-Ni-complex **INT-2**. At this stage the regioselectivity of the reaction is determined, since the calculations indicate the alkene migratory insertion is irreversible. The computed regioselectivity ($\Delta\Delta G^{\ddagger}$ = 2.7 kcal/mol for **TS1** vs. **TS5**) is consistent with the experimental data (>20:1 regioselectivity) in that the insertion occurs to generate the less stable tertiary-Ni-complex **INT-2** as opposed to the more stable primary alkyl-Ni-complex **INT-11**. The primary factor in controlling the regioselectivity appears to be minimization of an unfavorable steric repulsion between the B-atom and the two methyl groups on the disubstituted alkene **95** in **TS5,** thus favoring **TS1**. It

should also be noted that the computed geometry of **TS1** is consistent with the observed ^{13}C KIE, as it is a synchronous four-membered cyclic transition state with nearly equal bond formation with the two alkene carbons. The insertion step was also determined to be turnover-limiting, with a barrier of $\Delta G^{\ddagger}$ = 7.4 kcal/mol, which is consistent with a reaction that occurs readily at 4 °C.

It was found that alkyl-Ni-intermediate **INT-2** is stabilized by a chelating coordination with the neighboring oxygen of the Bpin unit. We speculate that formation of a favorable five-membered chelation and occupying a coordination site are the primary factors in governing the stability of this unusual tertiary alkyl-Ni-complex. Reaction of **INT-2** with bromobenzene occurred readily through an oxidative addition/reductive elimination sequence via Ni(III)-complex **INT-4,** corroborating the observed linear free energy relationship (Scheme 12C). The rapid reductive elimination of this intermediate is a likely explanation for the formation of minimal byproducts in these reactions. Finally, turnover of the catalyst can occur through a series of ligand exchanges and transmetallation assisted by the alkoxide base via **TS4**. Additionally, the competition experiment between different arylbromides with bromobenzene was investigated computationally (Figure 2) and a good correlation was obtained between the experimental and DFT-computed relative rate data (R^2 = 0.873). Overall, the calculated catalytic cycle is wholly consistent with the experimental data.

CONCLUSIONS

In summary, a strategy for the functionalization of a wide range of alkenes through arylboration is presented. Key to the development of a broadly applicable process was identification of dimethylacetamide as a key additive, which functions as a Lewis base to suppress side reactions. Notably, this method allows for the synthesis of quaternary carbons by cross coupling of readily available alkenes, arylbromides, and diboron reagents. The reactions proceed with high levels of regioselectivity and diastereoselectivity across a broad range of substrates. In addition, the reaction involves a rare cross coupling of a tertiary alkyl-[Ni], with control of stereochemistry in many cases. These advances allowed for development of a new strategy for the synthesis of saturated nitrogen-containing heterocycles, which are synthetically and pharmacologically valuable. Finally, the mechanistic details of this process were evaluated with computational and experimental techniques and provide insight into the details of this unique reaction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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18. If LiO*t*-Bu is used in place of NaO*t*-Bu, slightly higher regioselectivity is observed (3:1 rr vs. 1.3:1 rr) from ref 12 and as shown in Scheme 2, respectively). A synergistic combination of NaO*t*-Bu and DMA is observed and is required to observe 18:1 rr (**2:3**) as shown in Scheme 3.

19. The difference between NMR yields and yields of isolated product is due to, at times, a difficult separation by silica gel column chromatography.

20. For reactions of 1,1-disubstiuted and trisubstituted alkenes, it was found that 9:1 THF:DMA was sufficient as opposed to 4:1 THF:DMA that was optimal for monosubstituted alkenes.

21. 2-Substituted pyridyl bromides are required, likely to mitigate catalyst deactivation by coordination.

22. Arylboration reaction of **53** was previous reported and proceeds in similar yield. See ref 12.

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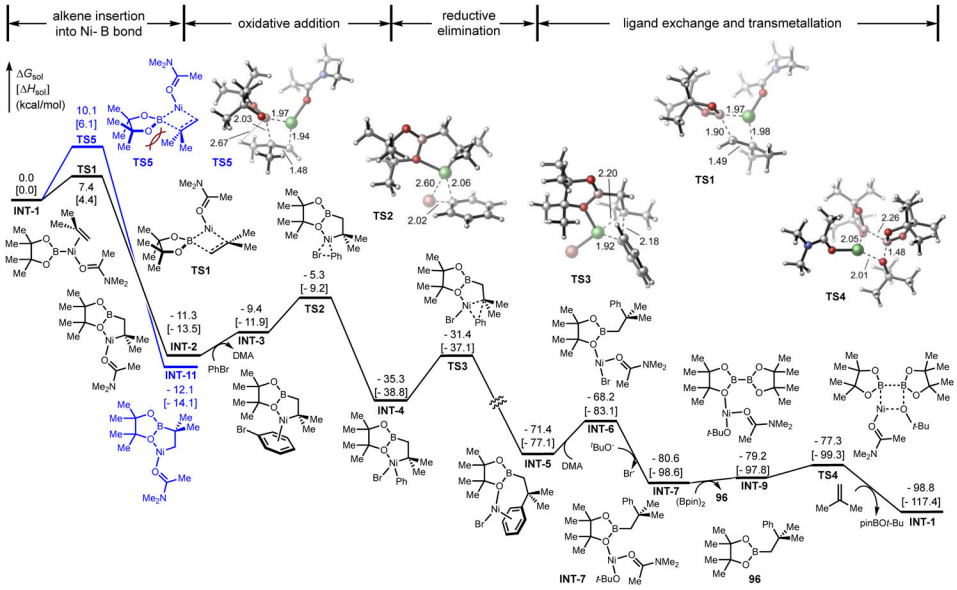


Figure 1:
Computed Energy Profile of the Arylboration Reaction.

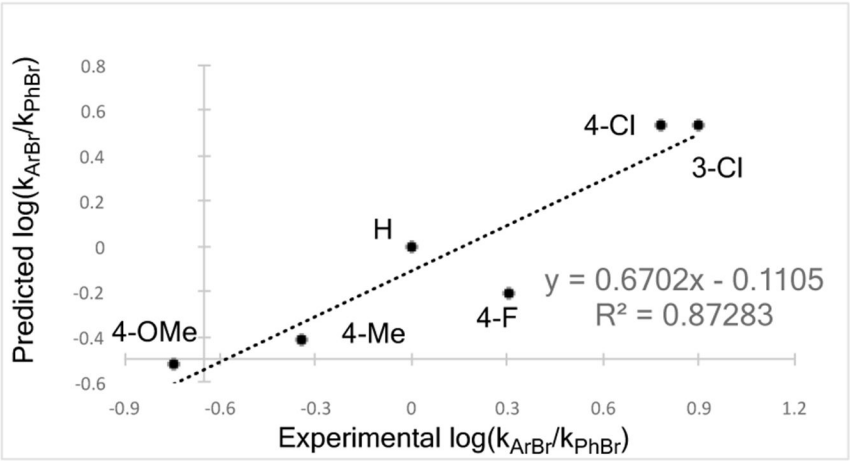
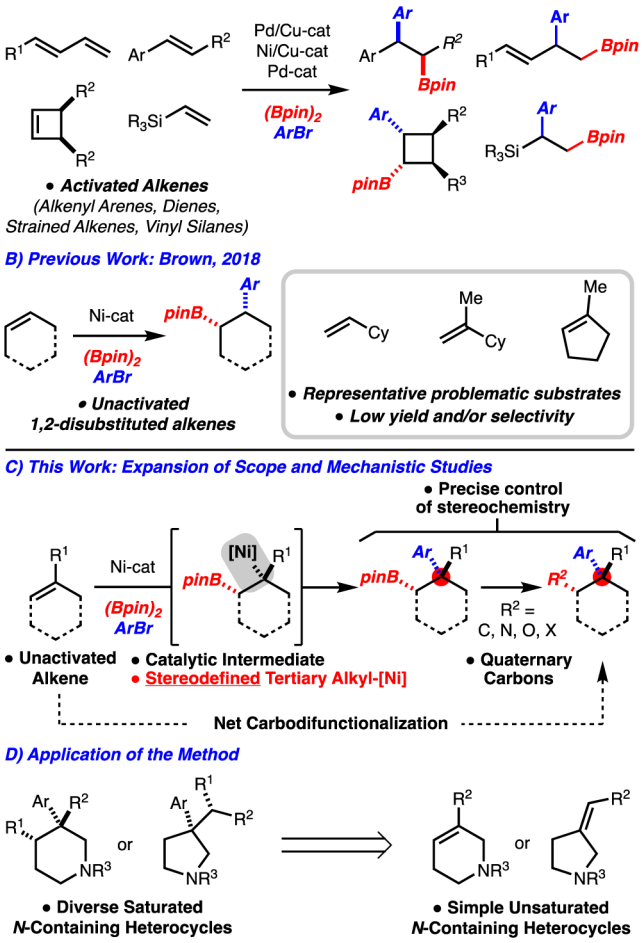
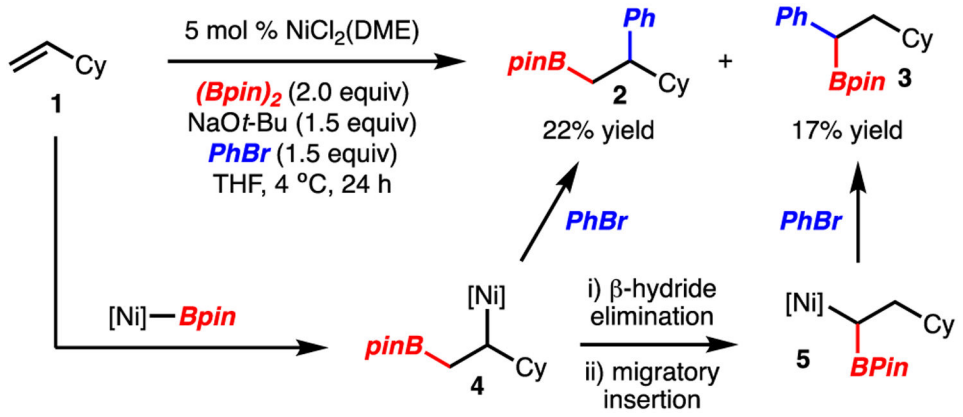


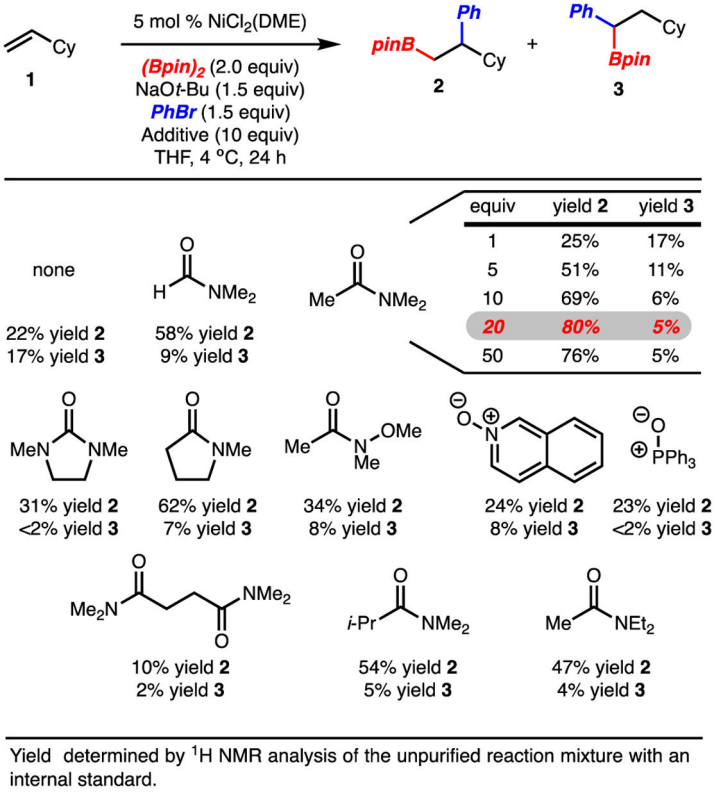
Figure 2.
Comparison of Predicted and Experimental LFER



Scheme 1.
Arylboration of Alkenes



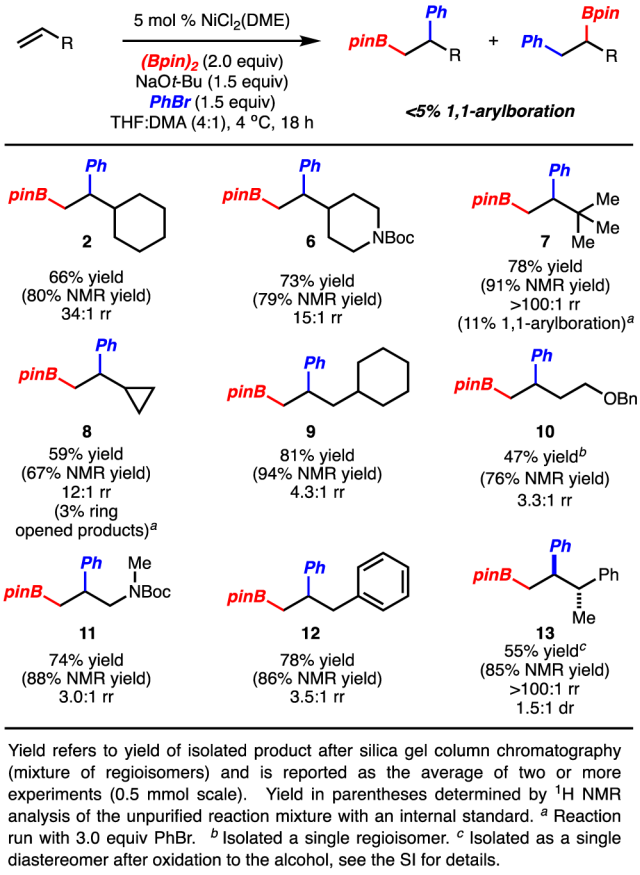
Scheme 2.
Initial Investigations



Yield determined by ^{1}H NMR analysis of the unpurified reaction mixture with an internal standard.

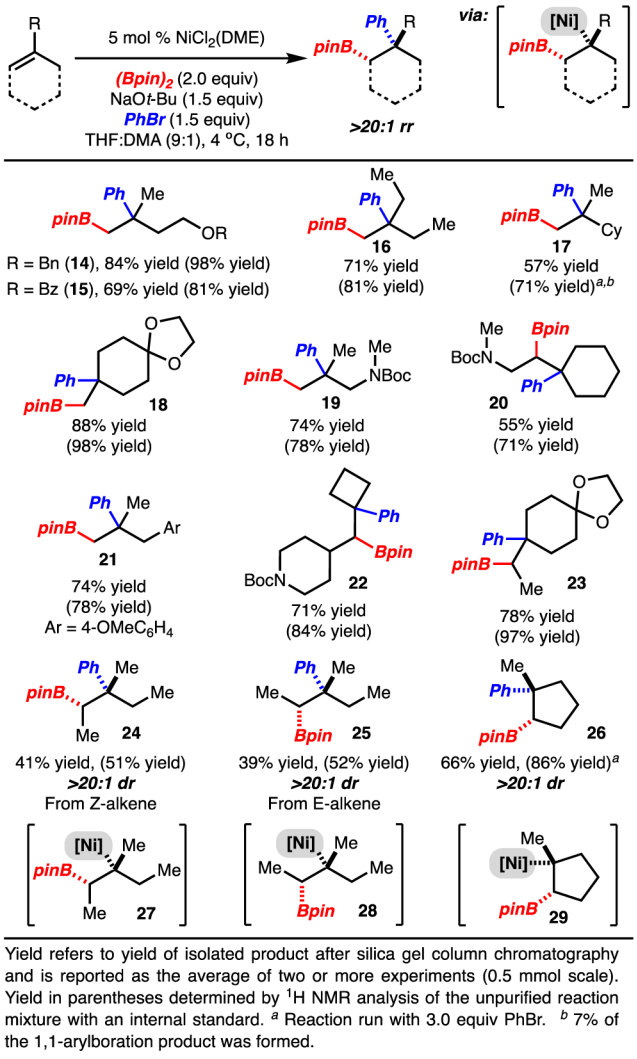
Scheme 3.

Evaluation of Lewis Basic Additives



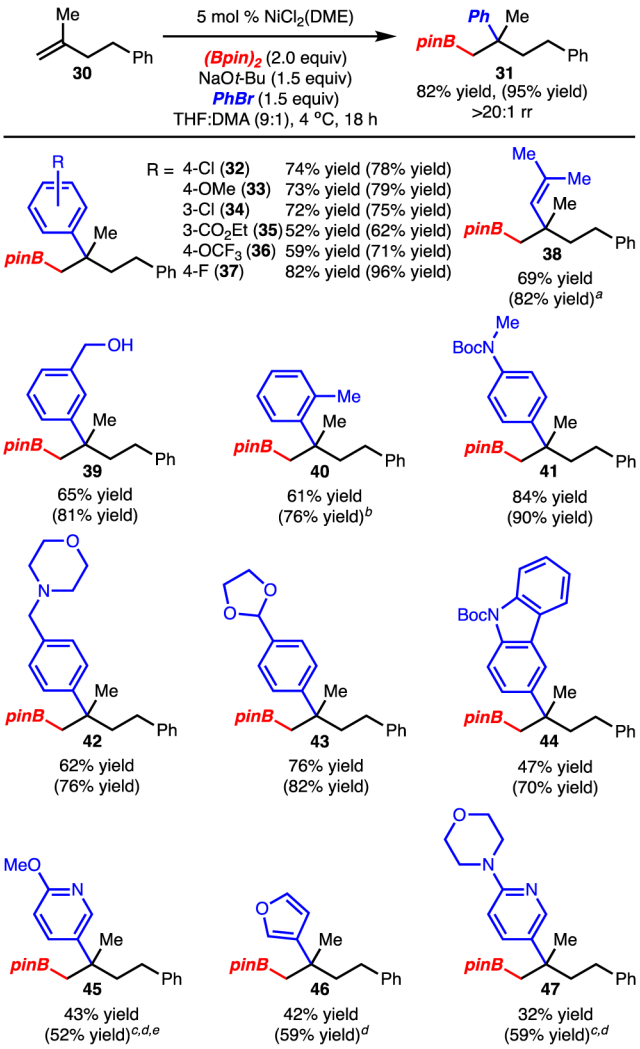
Yield refers to yield of isolated product after silica gel column chromatography (mixture of regioisomers) and is reported as the average of two or more experiments (0.5 mmol scale). Yield in parentheses determined by ^{1}H NMR analysis of the unpurified reaction mixture with an internal standard. [a] Reaction run with 3.0 equiv PhBr. [b] Isolated a single regioisomer. [c] Isolated as a single diastereomer after oxidation to the alcohol, see the SI for details.

Scheme 4.
Reaction with Monosubstituted Alkenes



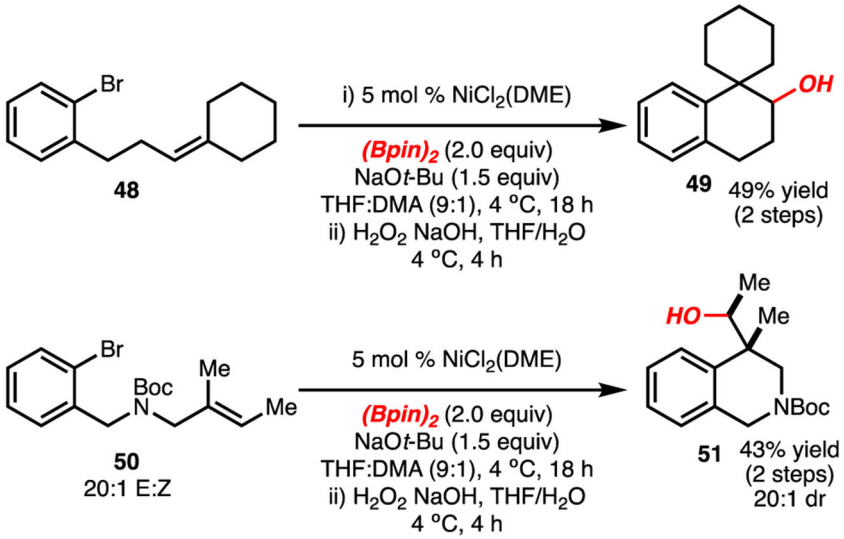
Yield refers to yield of isolated product after silica gel column chromatography and is reported as the average of two or more experiments (0.5 mmol scale). Yield in parentheses determined by ^{1}H NMR analysis of the unpurified reaction mixture with an internal standard. [a] Reaction run with 3.0 equiv PhBr. [b] 7% of the 1,1-arylboration product was formed.

Scheme 5.
Reaction with Various Alkenes

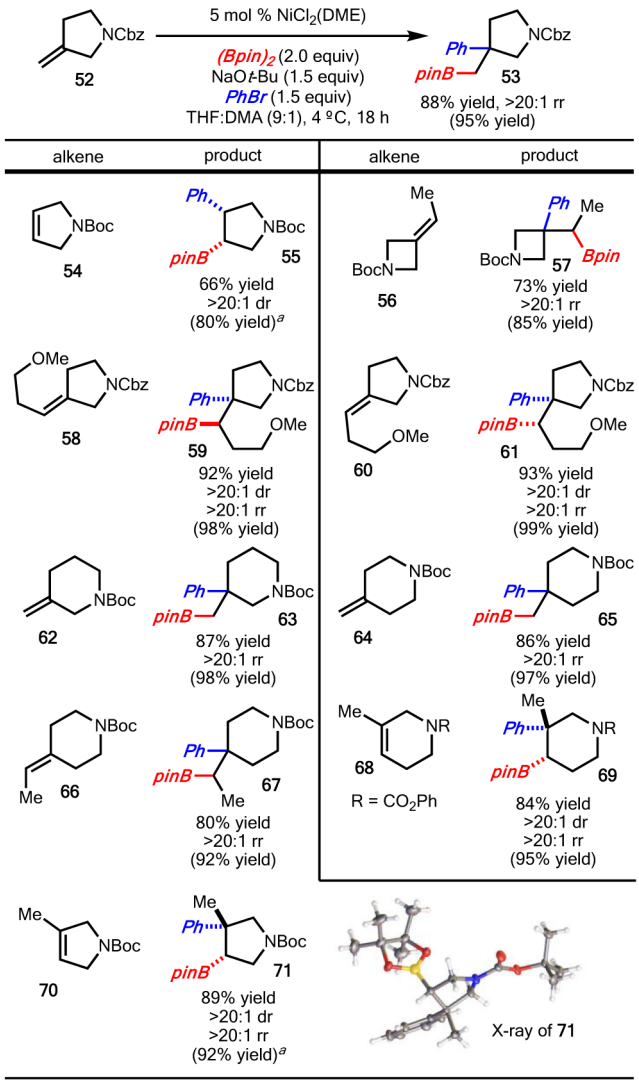


Yield refers to yield of isolated product after silica gel column chromatography and is reported as the average of two or more experiments (0.5 mmol scale). Yield in parentheses determined by ^{1}H NMR analysis of the unpurified reaction mixture with an internal standard. [a] Reaction run with 3 equiv. alkenylBr. [b] ~10% 1,1-arylboration generated. [c] Isolated as the corresponding alcohol after oxidation, see the SI for details. [d] Reactions run at 30 °C. [e] Reaction with 7.5 mol % $NiCl_2$(DME).

Scheme 6.
Reaction with Various (Het)Arylbromides

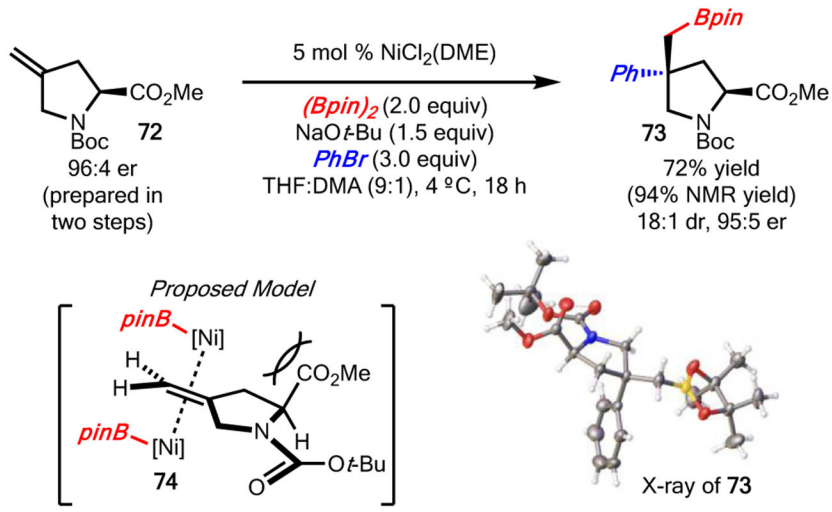


Scheme 7.
Intramolecular Variants

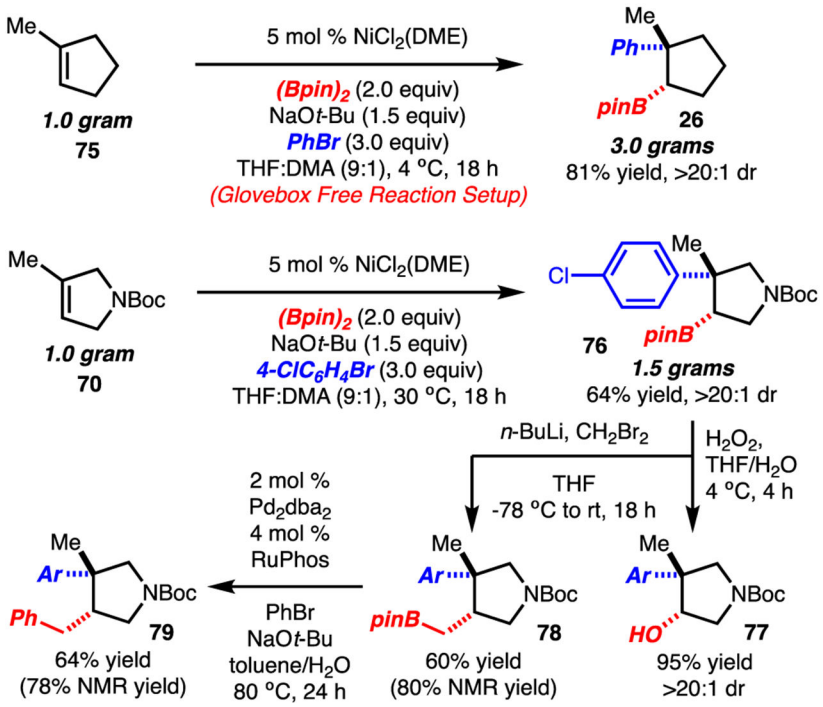


Yield refers to yield of isolated product after silica gel column chromatography and is reported as the average of two or more experiments (0.5 mmol scale).
[a] Reaction run with 3.0 equiv PhBr and at 30 °C.

Scheme 8.
Synthesis of Saturated Nitrogen Heterocycles

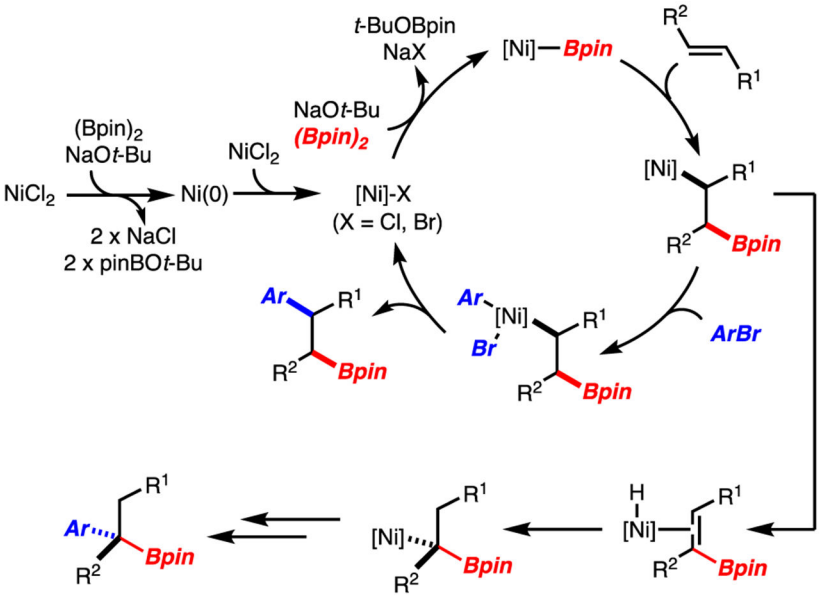


Scheme 9.
Diastereoselective Alkene Functionalization

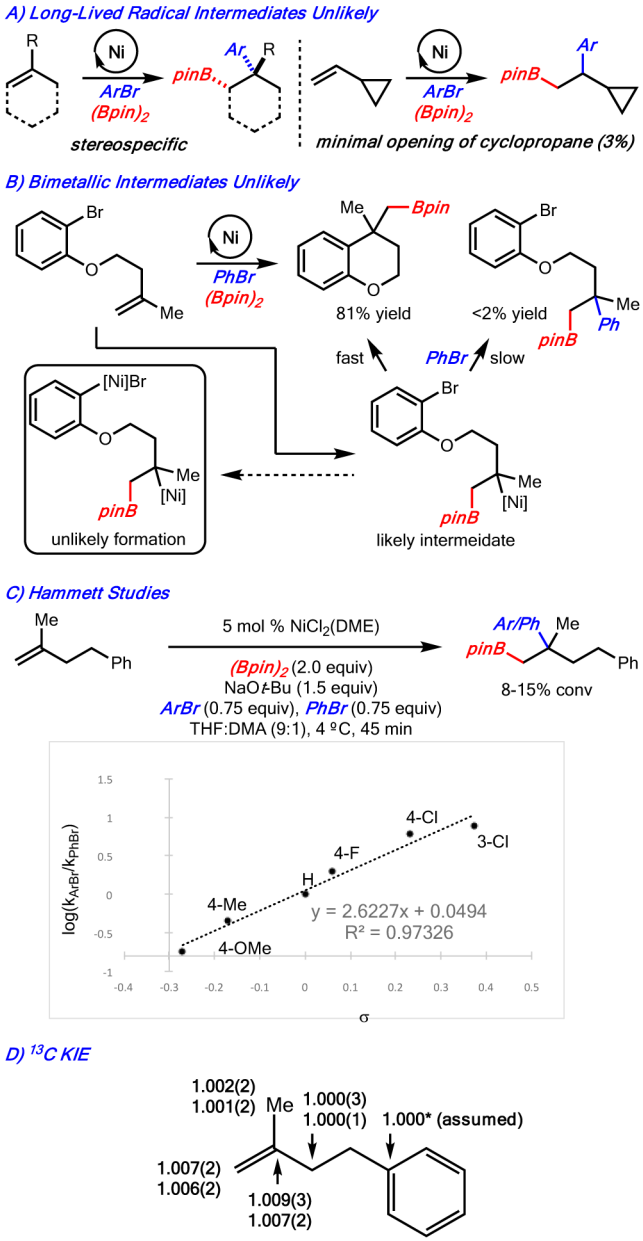


Scheme 10.

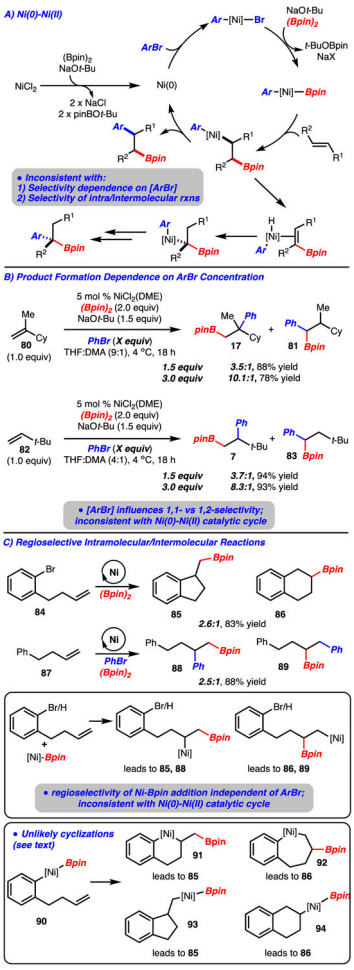
Gram Scale Reactions and Further Functionalization



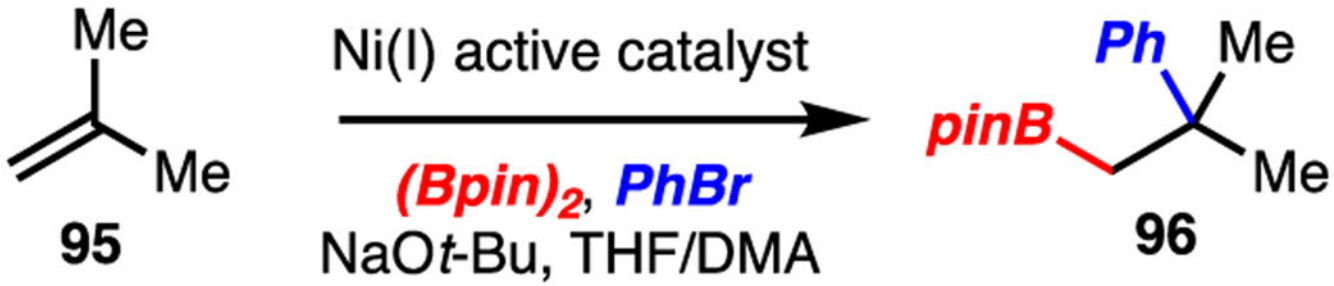
Scheme 11.
Proposed Catalytic Cycle



Scheme 12.
Mechanistic Investigations



Scheme 13.
Unlikely Ni(0)-Ni(II) Catalytic Cycle



Scheme 14.
Model Reaction Used in the Computational Studies