Enantioselective C(sp^3)–C(sp^3) Cross-Coupling of Non-activated Alkyl Electrophiles via Nickel Hydride Catalysis

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ABSTRACT: Cross-coupling of two alkyl fragments is an efficient method to produce organic molecules rich in sp^3-hydridized carbon centers, which are attractive candidate compounds in drug discovery. Enantioselective C(sp^3)-C(sp^3) coupling, especially of alkyl electrophiles without an activating group (aryl, vinyl, carbonyl) is challenging. Here we report a strategy based on nickel hydride addition to internal olefins followed by nickel-catalyzed alkyl-alkyl coupling. This strategy enables enantioselective cross-coupling of non-activated alkyl iodides with alkenyl boronates to produce chiral alkyl boronates. Employing readily available and stable olefins as pro-chiral nucleophiles, the coupling proceeds under mild conditions and exhibits broad scope and high functional group tolerance. Applications in late-stage functionalization of natural products and drug molecules, synthesis of chiral building blocks, and enantioselective formal synthesis of (*S*)-(+)-Pregabalin are demonstrated.

In drug discovery, it has been recognized that organic compounds with a greater 3-dimensitonal (3D) shape than flat aromatics have higher chances to succeed as drug candidates.(*1, 2*) The fraction of sp^3 carbons in a molecule is suggested as a descriptor for its 3D shape.(*1*) Because high-througput synthesis has become a standard practice in the pharmaceutical industry, methods introducing sp^3 carbons in a parallel manner such as cross-coupling of alkyl electrophiles(*3-6*) are highly valuable for drug development. Enantioselective cross-coupling of alkyl electrophiles, especially alkyl-alkyl coupling, remains challenging.(*3, 4, 7, 8*)

Enantioselective $C(sp^3)$-$C(sp^3)$ coupling may be achieved by enantioconvergent activation of racemic alkyl electrophiles followed by enantioselective alkyl-alkyl reductive elimination (Fig. 1A). In this process the newly created stereogenic center resides on the terminal carbon of the alkyl electrophile. Despite significant progress made by the group of Fu in this area, high yields and enantioselectivity are obtained for only a few specific combinations of electrophiles and nucleophiles.(*9-14*) For non-activated alkyl electrophiles, generally only Suzuki-Miyaura coupling of substrates containing a suitable directing group with alkyl-(9-BBN) reagents is efficient (Fig. 1A).(*9-11*) The scope of electrophiles is limited by the necessity for a directing group. The nucleophiles are organometallic reagents which are pre-functionalized and can be costly or sensitive. Terminal olefins were recently introduced as nucleophiles, however, the electrophiles are limited to activated alkyl halides (Fig. 1A).(*15, 16*)

An alternative strategy for enantioselective $C(sp^3)$-$C(sp^3)$ coupling consists of enantioselective metal hydride addition to an internal olefin to form a chiral M-alkyl intermediate, followed by stereospecific alkyl-alkyl coupling (Fig. 1B). This approach creates a stereogenic center at a carbon center of the olefin. While reports of stereoconvergent coupling of racemic α-zincated N-Boc-pyrrolidines with alkyl halides suggested the feasibility of this mode of alkyl-alkyl coupling,(*17, 18*) the challenge rests on the ability of a metal hydride catalyst to perform both enantioselective addition to an internal olefin and coupling with non-activated alkyl electrophiles. Cu-H catalyzed enantioselective functionalization of internal olefins is advancing rapidly in recent years,(*19-25*) but the coupling of the in-situ generated chiral organocopper intermediates with non-activated alkyl electrophiles remains elusive (Fig. 1B). Ni-H catalysis is more suited than Cu-H catalysis for coupling with alkyl electrophiles,(*15, 16, 26, 27*) however, Ni-H insertion into an internal olefin typically lead to chain-walking to form a terminal organonickel intermediate,(*28-33*) ablating the chirality generated in the initial insertion (Fig, 1B). A directing α-aryl or α-boryl group can stabilize a branched organonickel intermediate,(*27, 34-36*) but enantioselective coupling of such an intermediate with an alkyl electrophile has not been documented.

Here we describe Ni-H catalyzed enantioselective $C(sp^3)$–$C(sp^3)$ cross-coupling of non-activated alkyl halides with alkenyl boronates (Fig. 1C). This coupling yields a diverse range of chiral alkyl boronic acid pinacol esters (Bpins), which are both versatile intermediates and important end points to bio-active molecules.(*37-40*) Previous methods for the synthesis of chiral alkyl boronates typically require substrates with a specific functional group at a specific position,(*41-43*) or stoichiometric chiral auxiliaries,(*44, 45*) or reactive organometallic reagents.(*43-46*) By using readily available and stable olefins as nucleophiles and mild conditions, our method provides notable advantages in reaction efficiency, substrate availability and scope, as well as functional group tolerance. In particular, applications in late-stage functionalization of many drug molecules and natural products are demonstrated.

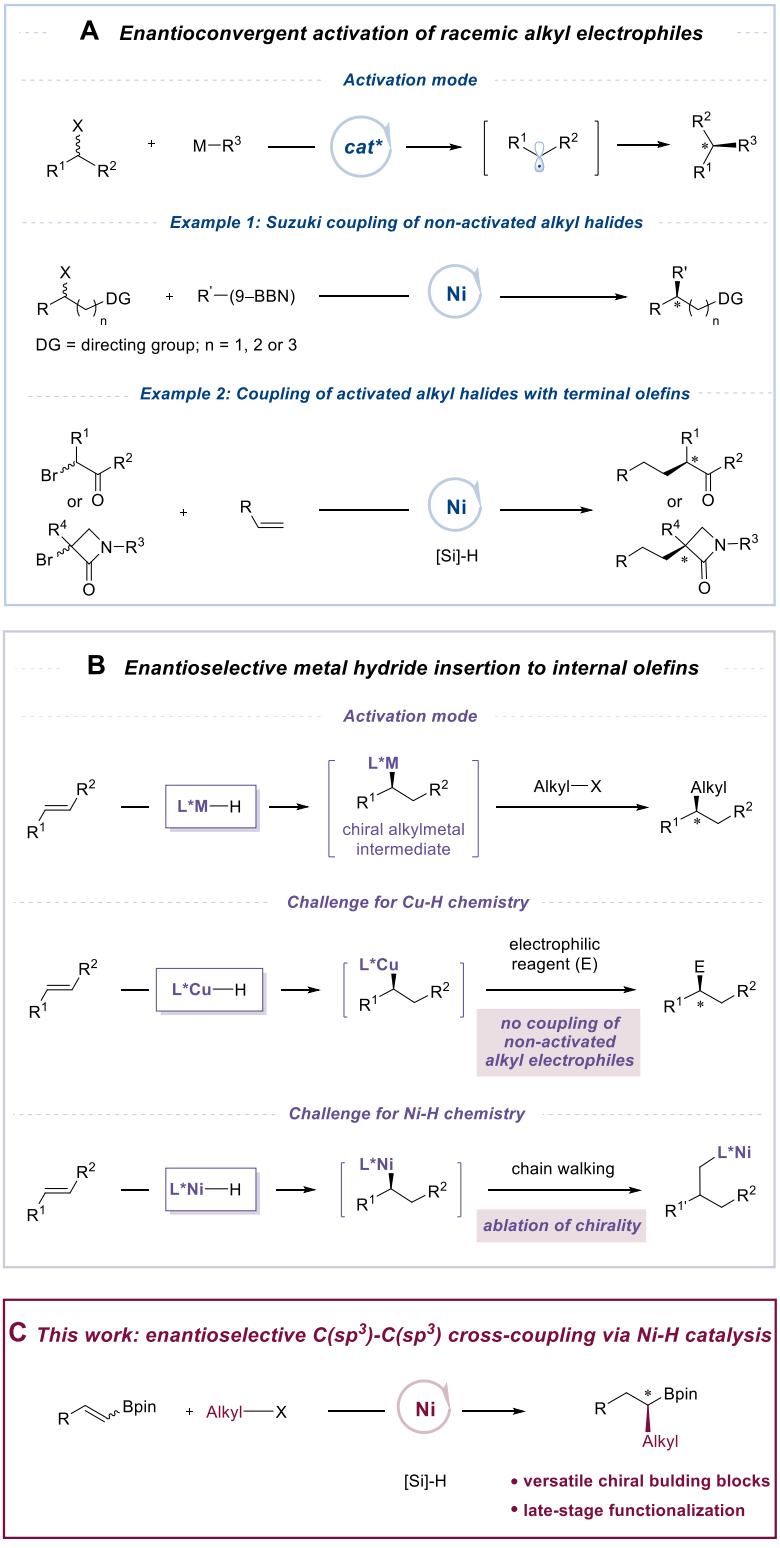
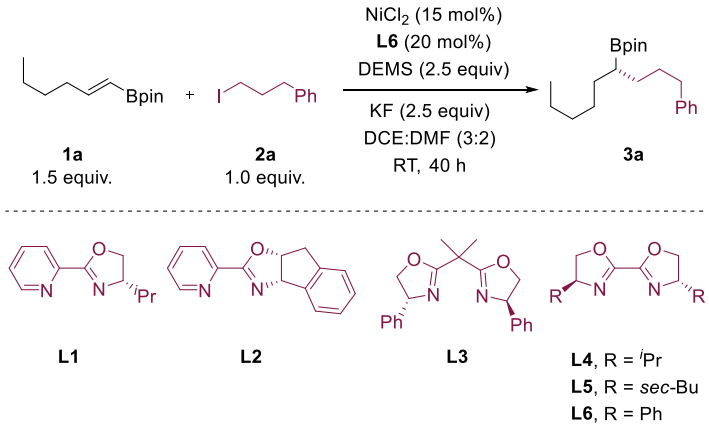


Figure 1. Strategies for enantioselective C(sp^3)-C(sp^3) cross-coupling. (A) Enantioconvergent activation of racemic alkyl electrophiles. (B) Enantioselective metal hydride insertion to internal olefins. (C) This work: Ni-catalyzed enantioselective cross-coupling of non-activated alkyl halides with internal olefins.

We recently developed Ni-H catalyzed hydrocarbonation of alkenyl Bpins.(*27*) To achieve enantioselective C(sp^3)-C(sp^3) coupling based on this racemic reaction, we screened various chiral ligands and fine-tuned other reaction parameters. Our model reaction was the coupling of *trans*-1-hexenylboronic acid pinacol ester (**1a**) with 3-phenylpropyl iodide (**2a**) to give (*S*)-4,4,5,5-tetramethyl-2-(1-phenylnonan-4-yl)-1,3,2-dioxaborolane (**3a**) (Table 1). The optimized reaction conditions were established as the following: diethoxy-methylsilane (DEMS; 2.5 equiv.) as the hydride source, $NiCl_2$ (15 mol%) as the Ni source, Bi-Ox **L6** (20 mol%) as the ligand, KF (2.5 equiv) as the base, a (3:2) mixture of DCE/DMF as the solvent, room temperature, 40h. Under these conditions **3a** was obtained as a single regio-isomer in 72% GC yield (69% isolated yield) and 92% ee (entry 1, Table 1).

Table 1. Summary of the effects of reaction parameters on the reaction efficiency



Entry	Deviation from standard conditions	Yield (%)	ee (%)[b]
1	none	72 (69)[c]	92
2	**L1** instead of **L6**	73	52
3	**L2** instead of **L6**	76	42
4	**L3** instead of **L6**	31	36[d]
5	**L4** instead of **L6**	47	60
6	**L5** instead of **L6**	37	58
7	$NiBr_2$ instead of $NiCl_2$	52	80
8	$NiBr_2$.diglyme instead of $NiCl_2$	51	84
9[e]	CsF instead of KF	63	53
10	PMHS instead of DEMS	57	91
11	DMF as solvent	73	66
12	DCE as solvent	n.d.	n.d.

[a] See the SI for experimental details; all reactions were carried out in 0.1 mmol scale with respect to **2a**; corrected GC yields using *n*-dodecane as an internal standard were reported. [b] The enantiomeric excesses (ees) were determined using HPLC analysis of the corresponding alcohol after stereospecific oxidation of the boronic ester (see SI for

details). [c] Isolated yield is shown in the parenthesis. [d] The opposite enantiomer was enriched. [e] Reaction time = 12h. DMF = Dimethylformamide; DCE = 1,2-Dichloroethane, RT = room temperature; h = hour. n.d. = not detected; PMHS = Polymethylhydrosiloxane; DEMS = Diethoxy-methylsilane.

The influence of different reaction parameter in the outcome of the reaction is described in Table S1–S5, SI. A concise summary of key observations is shown in Table 1. Structurally related Pyr-Ox (**L1** and **L2**) and Box (**L3**) ligands were inefficient in this transformation (entries 2-4, Table 1). Bi-Ox ligands with alkyl substituents gave lower yields or ees (entries 5 and 6, Table 1). The reacitons were sensitive to the substituents on the aryl units of the Bi-Ox ligands (Table S3, SI). Other nickel sources such as $NiBr_2$ and $NiBr_2$.diglyme afforded lower yields and enantioslectivities (entries 7 and 8, Table 1). Replaceing KF by CsF largely diminished the enantioselectivity (entry 9, Table 1). A reaction using PMHS (PMHS = polymethylhydrosiloxane) as hydride source had high enantioslectivity but a modest yield (entry 10, Table 1). The mixed solvent (DCE/DMF) turned out as the best solvent to achieve high enantioselectivity (entries 11 and 12, Table 1).

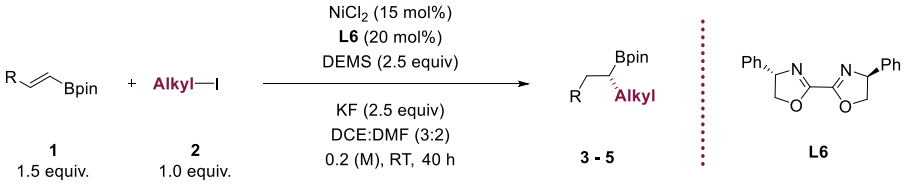
The scope of this enantioselective coupling method is broad (Table 2). In addition to an aryl group (**3a**, **3b**, **3h**), primary alkyl iodides containing a pendant ether (**3c**), ketone (**3d**), ester (**3e, 3i, 3j**), carbamate (**3f**), phthalimide (**3g**), and amine (**3k**, **3l**) group all reacted well. These data rules out the possibility of a specific group that directs the enantioselectivity of the coupling. A high level of functional group tolerance, unusual for cross-coupling of organometallic reagents, was achieved. For example, unprotected OH group was compatible (**3h**). Despite the ability of Ni to activated aryl chlorides, our method tolerated an Ar-Cl group (**3e**). Substrates containing medicinally relevant heterocycles such as furan (**3i**), thiophene (**3j**), indole (**3k**), piperidine (**3l**) were also viable. The coupling of alkyl bromides required an in-situ Br/I exchange and was slightly less efficient than the corresponding coupling of alkyl iodides. For example, coupling of *trans*-1-hexenylboronic acid pinacol ester (**1a**) with 3-phenylpropyl bromide gave **3a** in 50% yield and 86% ee in the presence of 40 mol% KI. By comparison, an analogous coupling using the corresponding alkyl iodide **2a** gave 69% yield and 92% ee.

Enantioselective coupling of two secondary alkyl fragments is challenging. Thus, it is noteworthy that the present method also works for the coupling of secondary alkyl iodides, including both acyclic and cyclic substrates, delivering the corresponding alkyl Bpins with good yields and high enantioselectivity (**4a**-**4i**). Medicinally interesting cyclic groups such as indane, oxetane and azeditine, were tolerated (**4d**-**4i**). No isomerization was observed in the alkyl fragments.

A wide range of alkenyl Bpins could be used as nucleophiles to deliver the corresponding enantiomerically enriched alkyl Bpins (**5a**-**5i**) (Table 2). The coupling was regioselective at the carbon α-to the Bpin group. The alkenes can contain functional group such as alkyl chloride (**5a**), ester (**5b, 5c**), ether (**5d**, **5e**, **5f**). Vinylboronate, a synthetically useful substrate posing a challenge in regioselectivity, was coupled in high enantioselectivity (90% ee) and regioselectivity (12:1 b/l). Coupling of a sterically demanding β,β′-disubstituted alkenyl Bpin was less efficient, giving the product in 30% yield.

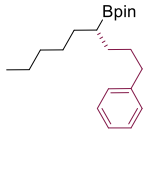
The Bpin group in product **4g** was stereospecifically oxidized to an alcohol group (**4g'**; SI, section 12). The X-ray crystal structure of **4g'** revealed the absoulte configuration of the chiral carbon center. By analogy, we assigned the corresponding absolute configurations to all products.

Table 2. Scope of Ni-H catalyzed enantioselective C(sp^3)-C(sp^3) coupling[a]



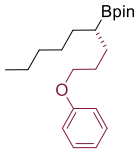
1 1.5 equiv. **2** 1.0 equiv. **3 - 5** **L6**

Primary alkyl iodides

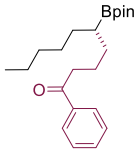


3a
69%, 92% *ee*
50%, 86% *ee*[b]

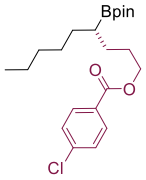
3b
80%, 90% *ee*



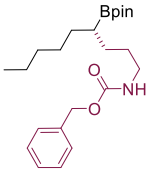
3c
72%, 89% *ee*



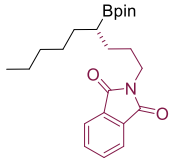
3d
67%, 92% *ee*



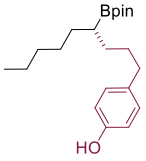
3e
64%, 90% *ee*



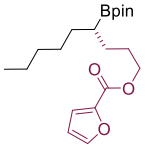
3f
70%, 88% *ee*



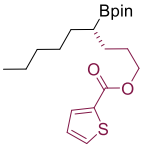
3g
75%, 90% *ee*



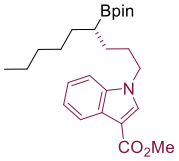
3h
55%, 93% *ee*



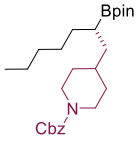
3i
71%, 90% *ee*



3j
60%, 90% *ee*

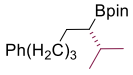


3k
50%, 91% *ee*

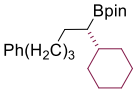


3l
79%, 92% *ee*

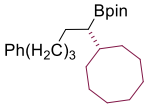
Secondary alkyl iodides[c]



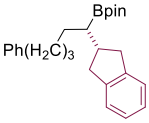
4a
70%, 93% *ee*



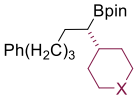
4b
67%, 93% *ee*



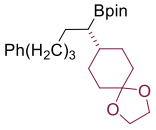
4c
78%, 90% *ee*



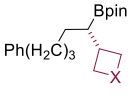
4d
69%, 91% *ee*



4e, X = O, 70%, 92% *ee*
4f, X = NBoc, 61%, 92% *ee*

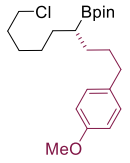


4g
63%, 92% *ee*

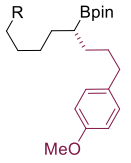


4h, X = O, 58%, 85% *ee*
4i, X = NBoc, 51%, 89% *ee*

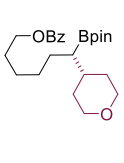
Alkenyl boronates



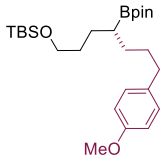
5a
61%, 91% *ee*



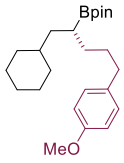
5b (R = CO_2Me), 57%, 90% *ee*
5c (R = OAc), 77%, 91% *ee*
5d (R = CH_2OPh), 69%, 90% *ee*



5e
79%, 90% *ee*[c]

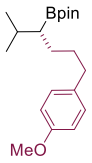


5f
56%, 92% *ee*



5g
54%, 91% *ee*

5h
68%, 90% *ee*[d]



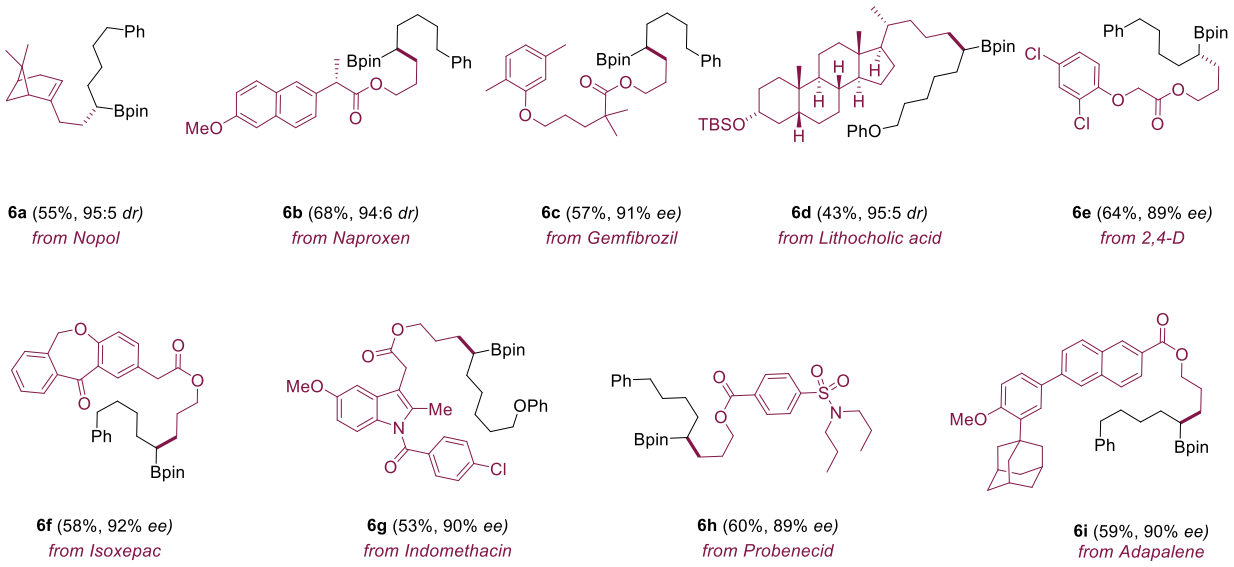
5i
30%, 91% *ee*[d]

[a] All reactions were carried out with $NiCl_2$ (15 mol%), ligand **L12** (20 mol%), **1** (0.15 mmol), **2** (0.10 mmol), DEMS (0.25 mmol), KF (0.25 mmol) and DCE:DMF (0.5 mL) at room temperature for 40 hours. The enantiomeric excesses

(ees) were determined using HPLC analysis (see SI for details). [b] Alkyl bromide with 40 mol% KI was used. [c] **1** (0.1 mmol) and **2** (0.15 mmol) were used. [d] Reactions were conducted in 0.2 mmol scale with respect to **2**.

Late-stage functionalization of drug molecules and natural products typically require mild reaction conditions and high functional group tolerance. The present method is well suited for this purpose. Indeed, the method could be used to synthesize an array of chiral alkyl Bpins bearing a complex or bio-active alkyl fragments derived from drugs and natural products (Table 3). Alkyl iodides bearing multiple stereocenters derived from nopol, a chiral terpinol (**6a**), naproxen (**6b**), a nonsteroidal anti-inflammatory drug, and a lithocholic acid derivative (**6d**) were all viable electrophiles, yielding potentially valuable products in synthetically useful yields and high diastereoselectivity. In addition, alkyl iodides derived from drugs such as gemfibrozil (**6c**), isoxepac (**6f**), indomethacin (**6g**), probenecid (**6h**) and adapalene (**6i**) as well as from a herbicide 2,4-D (**6e**) were transformed into the corresponding chiral alkyl Bpins with ease.

Table 3. Late-Stage functionalization of natural product and drug derivatives.



6a (55%, 95:5 *dr)* *from Nopol*

6b (68%, 94:6 *dr)* *from Naproxen*

6c (57%, 91% *ee)* *from Gemfibrozil*

6d (43%, 95:5 *dr)* *from Lithocholic acid*

6e (64%, 89% *ee)* *from 2,4-D*

6f (58%, 92% *ee)* *from Isoxepac*

6g (53%, 90% *ee)* *from Indomethacin*

6h (60%, 89% *ee)* *from Probenecid*

6i (59%, 90% *ee)* *from Adapalene*

Chiral alkyl Bpins are powerful intermediates in asymmetric organic synthesis because the C–B moiety can be easily transformed into a C–X moiety (X = C or heteroatom) with conservation of chirality at the α-C center. We provide several illustrative examples in Figure 2A for the transformation of one coupling product **4e**. C–C, C–O, and C–Br bond formation reactions proceeded cleanly, affording chiral organic compounds (**7**-**10**) without erosion in enantiomeric excess. We also applied our method for the enantioselective formal synthesis of the drug (*S*)-(+)-Pregabalin (Figure 2B).(*47*) Coupling of *trans*-3-methyl-1-butenyl boronic acid pinacol ester (**1m**) with *tert*-butyl(2-iodoethoxy)diphenylsilane (**2e'**) provided **11** in 42% yield with 90% ee. Stereospecific homologation of **11**, amination and silyl ether-deprotection provided the amino alcohol intermediate **12** in 43% overall yield from **11**. Conversion of **12** to pregabalin was previously reported.(*48*) A 2.0 mmol-scale reaction of *trans*-5-phenyl-1-pentenyl boronic acid pinacol ester (**1b**) with 4-iodotetrahydro-*2H*-pyran (**2q)** yielded **4e** in 68% yield and 92% ee (eq 1, Figure 2C). A one-pot reaction sequence consisted of hydroboration of 1-hexyne to give alkenyl Bpin **1a** in-situ, followed by cross-coupling with **2b** without isolating **1a**, yielded **3b** in 74% yield

and 90% ee (eq. 2, Figure 2D). These results further showcase the preparative utility of the coupling.

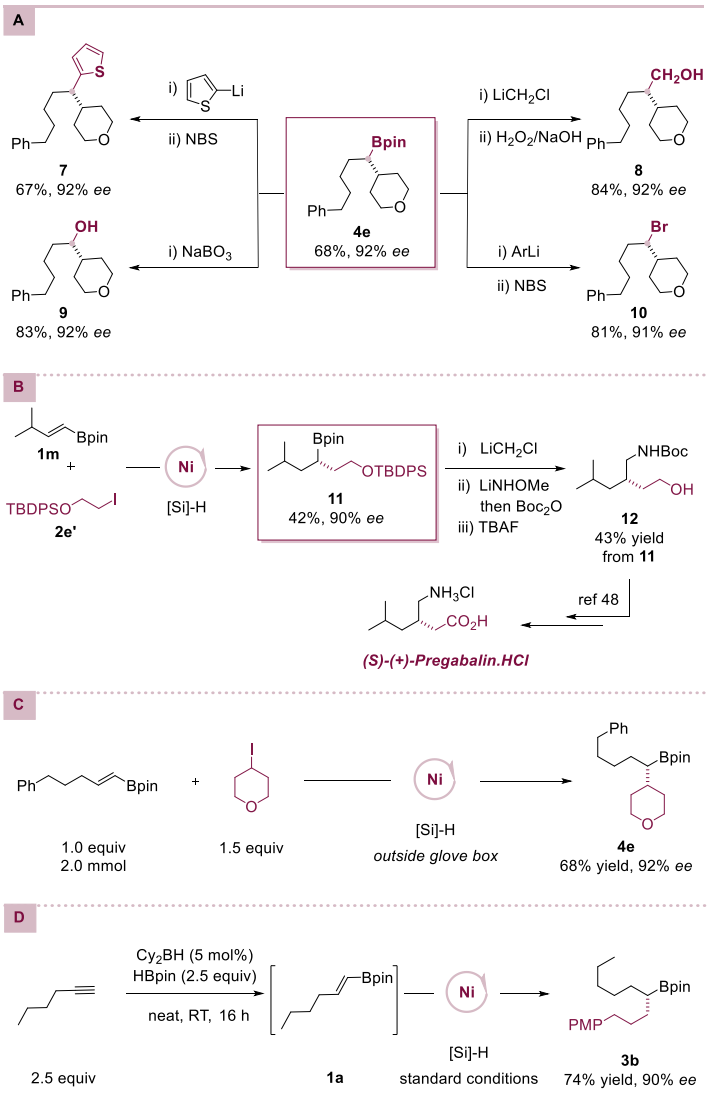


Figure 2. (A) Chiral alkyl Bpins as versatile intermediates. (B) Synthesis of **12**, a key intermediate of (*S*)-(+)-Pregabalin. (C) A large scale experiment. (D) One-pot asymmetric hydroalkylation without isolation of alkenyl Bpin.

The mechanism of this Ni-H catalyzed enantioselective C(sp^3)-C(sp^3) cross-coupling is proposed in Figure 3. Under reaction conditions, a chiral L*Ni-X (X = Cl or I) species (**A**) is formed as the actual catalyst. Reaction of **A** with a hydrosilane generates a Ni-H species L*Ni-H (**B**), which inserts into the alkene moiety of an alkenyl Bpin. The insertion is regioselective at the carbon α- to the boryl group. The resulting Ni-alkyl intermediate (**C**) cross-couple with an alkyl iodide to furnish the product. We propose the stereoselective step is the insertion of a chiral Ni-H into the olefin. Consistent with this hypothesis, reaction of a *cis*-alkenyl Bpin (**1l**) gave a product (**3b**)

identical to the reaction of its *trans* analogue (SI, section 11). The possibilty of reversible Ni-alkyl homolysis followed by stereoselective reductive elimination,(*49*) however, cannot be ruled out at this moment. The reaction profile excludes a kinetic resolution process (SI, section 11). The oxidation state of relevant Ni species as well as the details of the activation of alkyl iodide are subject to future study.

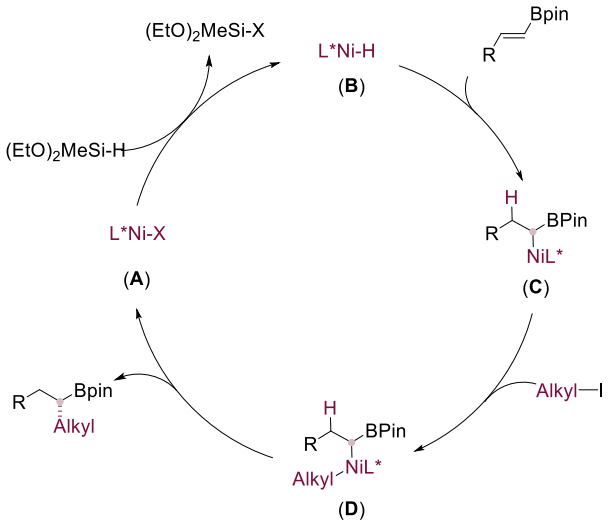


Figure 3. A proposed mechanism. X = Cl or I

In summary, we have developed Ni-H catalyzed enantioselective C(sp^3)-C(sp^3) coupling of non-activated alkyl iodides with alkenyl Bpins. By employing readily available and stable olefin as nucleophiles, this coupling enables streamlined synthesis of chiral alkyl Bpins under mild conditions, with previously unattained scope and functional group tolerance. Examples in late-stage functionalization and chiral syntheses demonstrate the potential utility of this method in drug discovery.

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Data availability: All data are available upon request.

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