Enantio- and Diastereoselective Construction of Vicinal C(sp^3) Centers via Nickel-Catalyzed Hydroalkylation of Alkenes

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ABSTRACT: In drug discovery, the proportion of aliphatic carbons (C(sp^3)) and the presence of chiral carbons in organic molecules are positively correlated to their chance of clinical success. Although methods exist for the synthesis of chiral C(sp^3)-rich molecules, they often are limited in scope, have poor modularity, or are unsuitable for stereoselective synthesis using racemic reagents. The stereocontrol of vicinal C(sp^3) centers is a particular challenge. Here we describe nickel-catalyzed enantio- and diastereoselective hydroalkylation of internal alkenes with racemic alkyl bromides to selectively form one of the four possible stereoisomers. Given its general and modular character as well as its high functional group tolerance, we expect this approach to have wide applications in the stereoselective synthesis of C(sp^3)-rich molecules.

Introduction.

Bonds between sp^3-hybridized carbons make up the majority of the backbones of most organic molecules. Recently the medicinal chemistry community has identified the proportion of sp^3-hybridized carbons centers and the presence of stereogenic centers as two descriptors of molecules' complexity. A higher level of complexity is correlated to improved physiochemical and pharmacokinetic profiles, leading to a higher chance of clinical success.(*1*, *2*) This emphasis of $C(sp^3)$-rich molecules calls for modular and convergent methods for stereoselective $C(sp^3)$-$C(sp^3)$ bond formation, which are still scarce.

Transition-metal-catalyzed $C(sp^3)$-$C(sp^3)$ cross-coupling (Fig. 1A) is an approach that fulfils the requirement of modularity and reliability in drug discovery. Rapid advances in nickel catalysis have enabled this coupling for a wider range of reaction partners, including enantioconvergent cross-coupling of various racemic alkyl electrophiles, and in a few cases, racemic alkyl nucleophiles.(*3*, *4*) However, these coupling reactions employ (over)stoichiometric amounts of pre-formed organometallic reagents as nucleophiles. Some of these reagents (e.g., Grignard and organozinc), are air- and moisture-sensitive and have limited functional group compatibility. Others (e.g., organoboron) might require multiple-step synthesis. To overcome these drawbacks while maintaining the inherent advantages of cross-coupling, nickel-hydride (Ni-H)-catalyzed hydroalkylation of alkenes has been developed.(*5*-*8*) In this approach, insertion of an alkene into a metal hydride species generates *in-situ* a metal alkyl species, which then cross-couples with an alkyl electrophile to form a new $C(sp^3)$-$C(sp^3)$ bond (Fig. 1A). These reactions use stable and readily available alkenes as pro-nucleophiles and typically have high functional group tolerance.

Controlling the stereochemistry of $C(sp^3)$-$C(sp^3)$ bond formation in Ni-H-catalyzed hydroalkylation is still a difficult task. In the last few years, several methods have emerged for either enantioconvergent cross-coupling of racemic alkyl electrophiles with alkenes (Fig. 1B) or enantioselective alkene hydroalkylation (Fig. 1B).(*9*-*19*) The former creates an enantioenriched $C(sp^3)$ center originating from the alkyl electrophile, whereas the latter creates an enantioenriched $C(sp^3)$ center originating from the alkene pro-nucleophile. However, a method to introduce two vicinal enantioenriched $C(sp^3)$ centers originating from both reaction partners had not been known (Fig. 1B). In previous reports where vicinal chiral carbons were created, the diastereoselectivity was typically very low, with a diastereomeric ratio (d.r.) of 1:1 to 2:1.(*9*, *13*, *16*). Notably, Lu, Fu (Y), and their co-workers reported improved, yet still modest, diastereoselectivity in eight examples of hydroalkylation of enamides with racemic α-haloboronates (d.r. = 2.5:1 to 8:1).(*15*) In addition, there is a single precedent for analogous doubly enantioconvergent $C(sp^3)$-$C(sp^3)$ cross-coupling, with propargylic halides and β-zincated amides as reaction partners.(*20*) Here we demonstrate that Ni-H catalysis can address the major remaining stereochemical challenge of hydroalkylation, namely, the simultaneous control of two vicinal $C(sp^3)$ stereocenters from two reaction partners (Fig. 1C).

Both chiral organoboranes and γ-lactams are versatile intermediates in organic synthesis.(*21*-*27*) Chiral lactams, lactones, and pyrrolidines (derived from lactams) are also commonly encountered structural motifs in pharmaceuticals and biologically active natural products (e.g., Fig. 1D). Stereoselective α-alkylation of lactams is difficult due to possible side reactions such as over-alkylation and epimerization.(*28*) Here we show Ni-catalyzed enantio- and diastereoselective hydroalkylation of alkenyl boronates with racemic 2-bromolactams or 2-bromolactone (Fig. 1C) can be used to produce a diverse set of compounds containing both enantioenriched alkyl boronate and enantioenriched alkyl lactam, lactone, or their derivatives.

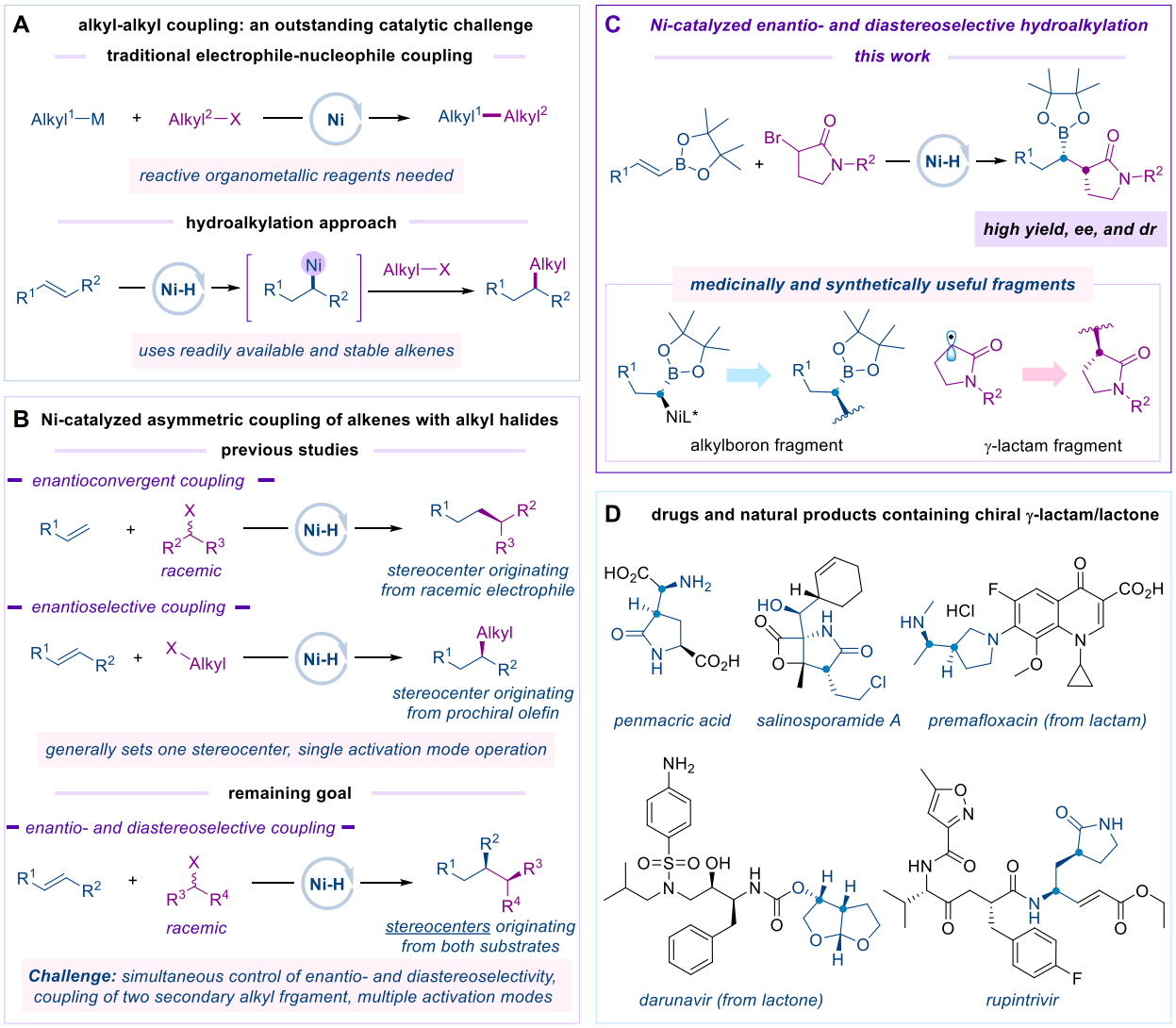


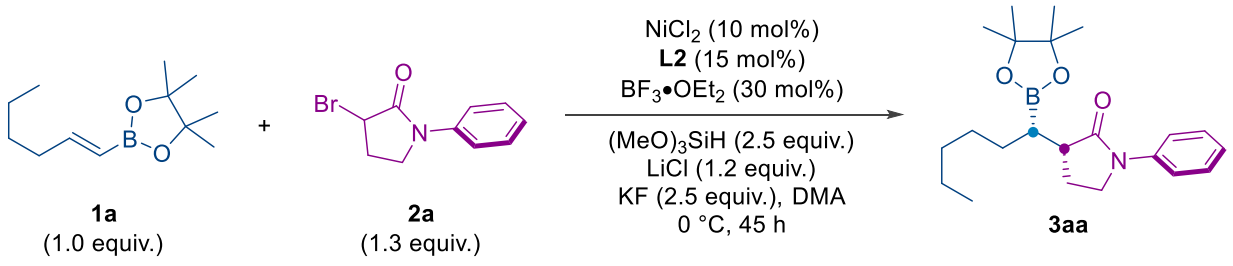
Figure 1. Stereoselective C(sp^3)-C(sp^3) cross-coupling. (A) Comparison of Ni-catalyzed traditional electrophile-nucleophile coupling and hydroalkylation of alkenes. (B) Previous achievements and a remaining challenge in Ni-catalyzed stereoselective hydroalkylation. (C) This work: Ni-catalyzed enantio- and diastereoselective hydroalkylation of alkenyl boronates with racemic alkyl halides. (D) Selected examples of drugs and natural products containing lactam/lactone derivatives with multiple stereocenters.

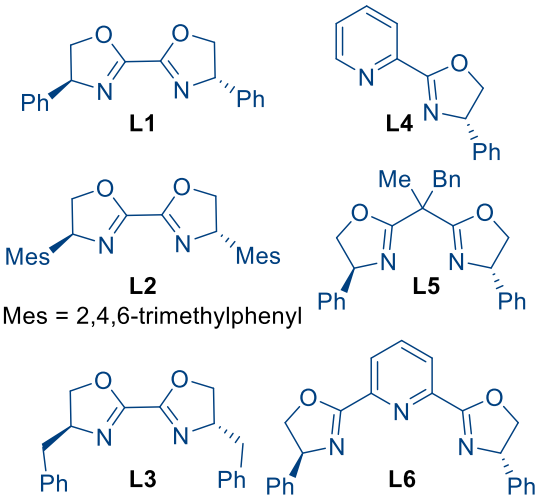
Results and Discussion.

We started our investigations by optimizing conditions for enantio- and diastereoselective hydroalkylation of an alkenyl boronic pinacol ester (Bpin) (**1a**) with α-bromo-γ-lactam (**2a**). We chose alkenyl boron compounds as pro-nucleophiles as we previously demonstrated enantioselective, but not diastereoselective, hydroalkylation of these substrates.(*13*) For electrophiles we first considered racemic α-bromocarbonyl substrates because several groups reported enantioconvergent hydroalkylation of alkenes using these substrates.(*10*, *11*) Through initial screening of various α-bromocarbonyls,(Table S1, SI) we identified **2a** as an appropriate

electrophile that would lead to promising diastereoselectivity. From the synthetic point of view, the substrates are either commercial or can be prepared in one-step, and the products are valuable synthons or end products. Upon investigating an array of reaction parameters (see SI, Table S2-S6) we found the optimized conditions. A concise summary of the effects of different parameters is shown in Table 1. The combination of $NiCl_2$ (10 mol%) and enantio-pure mesityl-Bi-Ox **L2** (15 mol%) as the precatalyst, $BF_3{\cdot}OEt_2$ (30 mol%) as a Lewis acid additive, $(MeO)_3SiH$ (2.5 equiv.) as the hydride source, KF (2.5 equiv.) as the base, and LiCl (1.2 equiv) as a further additive, DMA as solvent, and reaction at 0 °C for 45 hours delivered the best result (Table 1, entry 1). Under these conditions, the desired product **3aa** was isolated in 80 % GC yield (75% isolated yield) with 94% enantioselectivity (ee), 95:5 diastereoselectivity (dr), and complete regioselectivity.

Table 1. Optimization of the reaction conditions [a]





entry	*deviation*	*yield* (%)	*ee* (%)[b]	*dr*[b]
1[c]	*none*	80 (75)	94	95:5
2	**L1**	40	87	84:16
3	**L3**	22	0	40:60
4	**L4**	trace	n.d.	n.d.
5	**L5**	trace	n.d.	n.d.
6	**L6**	trace	n.d.	n.d.
7	w/o LiCl	73	86	88:12
8	w/o $BF_3{\bullet}OEt_2$	90	95	88:12
9	w/o LiCl + $BF_3{\bullet}OEt_2$	73	82	75:25
13	LiBr	69	86	87:13
14	BPh_3	16	96	95:5

[a] See the SI for experimental details; all reactions were carried out on 0.1 mmol scale with respect to **1a**; corrected GC yields using *n*-dodecane as an internal standard were reported. [b] The enantiomeric excess (ee) and diastereoselectivity (dr) were determined using chiral HPLC analysis of the product after column chromatography. [c] Isolated yield is shown in the parenthesis. DMA = *N*,*N*-Dimethylacetamide, h = hour. n.d. = not detected.

A structurally related Ph-Bi-Ox (**L1**) led to a modest yield with a lower dr and ee (Table 1, entry 2). A benzyl-substituted Bi-Ox (**L3**) gave a low yield and nearly no enantio- and diastereoselectivity. This result suggests that an aryl substituent in the Bi-Ox ligand was crucial to the stereoselectivity. Hydroalkylation did not occur when using other bi- and tridentate chiral nitrogen ligands such as Py-Ox (**L4**), Box (**L5**), and Py-Box (**L6**) (Table 1, entry 4-6). Both $BF_3{\cdot}OEt_2$ and LiCl additives increased diastereoselectivity, and LiCl also increased enantioselectivity (Table 1, entry 7-9). The use of LiBr instead of LiCl resulted in lower yield, ee, and dr (Entry 10). Replacing $BF_3{\cdot}OEt_2$ by BPh_3 did not change the ee or dr, but the yield was very

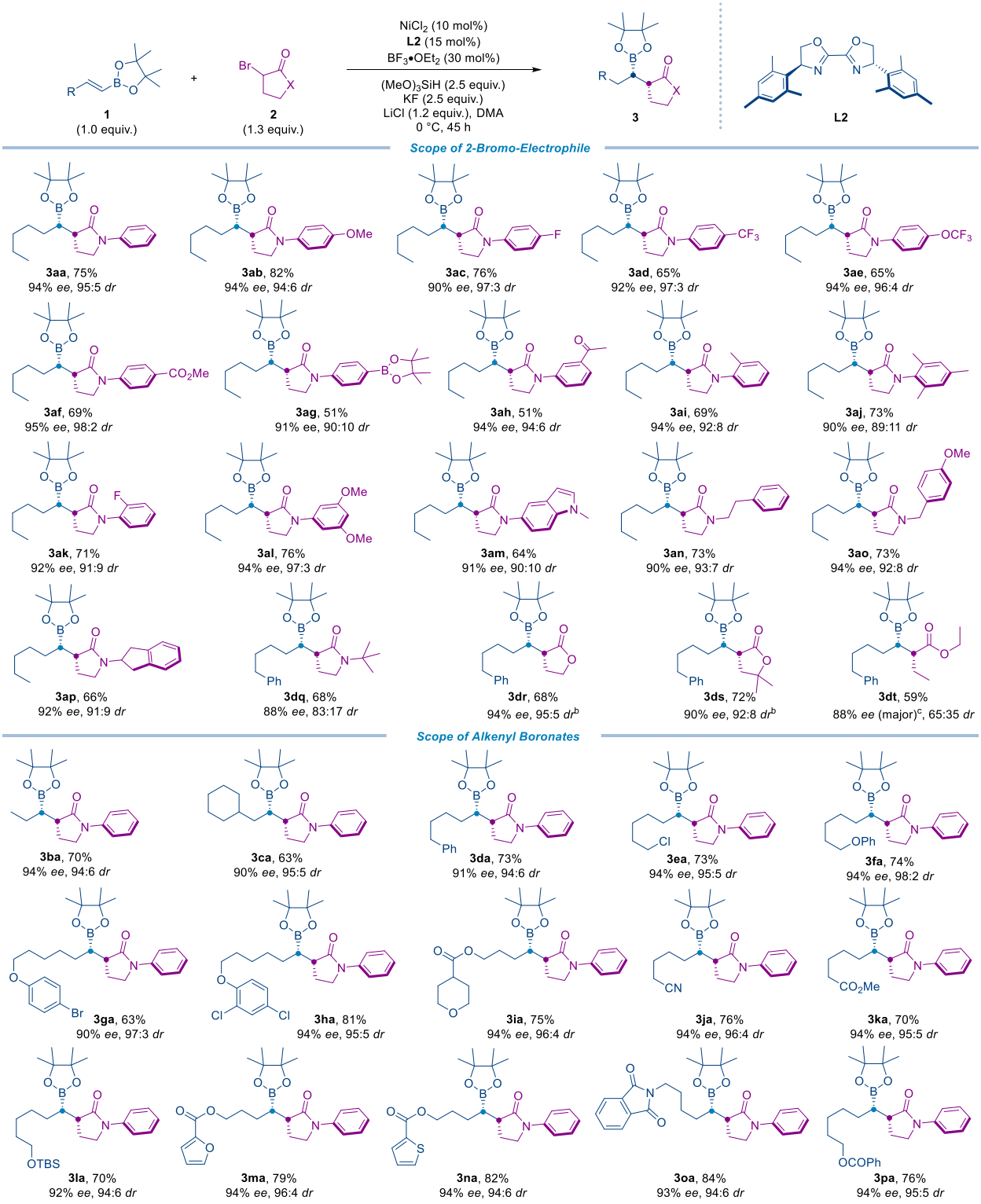
low (Entry 11). These results indicate that Li cations and Lewis acidic boron reagents enhance the stereocontrol. We propose $BF_3{\cdot}OEt_2$ coordinates to the carbonyl group of γ-lactam whereas Li^+ might bind to the O atoms of both the BPin and the carbonyl group. These interactions lead to a better differentiation of different stereoisomers, although the details remain unclear. Hall and co-workers suggested a similar coordination effect in Lewis acid-catalyzed addition of allylboronates to aldehydes.(*29*, *30*) Additionally LiCl increases the ionic strength of the reaction medium, which might influence the selectivity.(*31*, *32*)

We then examined the scope of this reaction protocol (Table 2). A diverse array of 2-bromo-γ-lactams could be used as electrophiles to give the corresponding hydroalkylation products (**3aa**-**3aq**). The aryl substituents of the lactam nitrogen could contain both electron-donating and electron-withdrawing groups at the *para*-position, e.g., -OMe (**3ab**), -F (**3ac**), $-CF_3$ (**3ad**), $-OCF_3$ (**3ae**), $-CO_2Me$ (**3af**), -COMe (**3ah**). A transformable aryl-Bpin group was tolerated (**3ag**). Substitution at the *ortho*-position of the aryl group tended to slightly decreased the dr (**3ai**-**3ak**). *N*-Heteroaryl (**3am**) and *N*-alkyl (**3an**-**3dq**) substituted 2-bromo-γ-lactams were viable substrates as well. A tertiary alkyl substituent at the *N*-atom led to a substantially lower dr (83:17) (**3dq**). These results indicate the steric influence of the substituents of the lactam nitrogen on the diastereoselectivity of the reactions. In addition to 2-bromo-γ-lactams, 2-bromo-γ-lactones could be used as substrates to give hydroalkylation products in high yields, enantioselectivity, and diastereoselectivity (**3dr** and **3ds**). For these substrates, $BF_3{\cdot}OEt_2$ was no longer needed as an additive. The reaction with an acyclic 2-bromoester analogue had good yield and ee, but a low dr (**3dt**), indicating the importance of a cyclic substrate for the diastereocontrol. With a tertiary alkyl bromide, α-bromo-α-methyl-γ-butyrolactone, no hydroalkylation occurred, likely due to the large steric bulkiness of the substrate. We also attempted the reaction with a six-membered 2-bromo-*N*-phenyl-δ-valerolactam under the optimized conditions (see SI). The reaction had a low yield (27%) and diastereoselectivity (dr = 60:40). The enantioselectivity for the major and minor diastereomers were 89% and 52%, respectively.

A range of alkenyl Bpin reagents could be used as the pro-nucleophiles (**3ba**-**3oa**). Functional groups such as alkyl chloride (**3ea**), ether (**3fa**, **3ga**, **3ha**), TBS-ether (**3la**), ester (**3ia**, **3ka**, **3ma**, **3na**, **3pa**), alkyl nitrile (**3ja**), aryl (**3da**), phthalimide (**3oa**) in the alkenes were all tolerated. Substrates containing pharmaceutically relevant heterocycles such as furan (**3ma**), thiophene (**3na**), and pyran (**3ia**) reacted equally well. Aryl chloride and bromide groups remained intact (**3ga**, **3ha**), despite being susceptible to Ni-catalyzed cross-coupling.

The absolute stereochemistry of **3aa**, **3ab**, **3ad**, and **3af** was determined by single-crystal X-ray diffraction analysis. The absolute stereochemistry of other compounds was assigned based on analogy.

Table 2. Scope of Ni-catalyzed enantio- and diastereoselective hydroalkylation [a]



[a] All reactions were carried out on a 0.2 mmol scale w.r.t. alkenyl pinacol boronates (**1**). Conditions: $NiCl_2$ (10 mol%), ligand **L2** (15 mol%), $BF_3.OEt_2$ (30 mol%), **1** (0.20 mmol), **2** (0.26 mmol), $(MeO)_3SiH$ (0.50 mmol), KF (0.50 mmol), LiCl (0.24 mmol) and DMA (1.0 mL) at 0 °C for 45 hours. The enantiomeric excess (ee) and diastereomeric ratio (dr) were determined using chiral HPLC analysis (see SI for details). [b] conducted without $BF_3{\cdot}OEt_2$. [c] The minor diastereomer was formed with 47% *ee*.

We next applied this protocol for the functionalizations of drugs and natural product derivatives (Figure 2A). Reactions of alkenyl Bpins derived from drugs such as chlorambucil (a chemotherapy medication for the treatment of chronic lymphocytic leukemia), oxaprozin (a nonsteroidal anti-inflammatory drug (NSAID) for arthritis), probenecid (a drug used for gout treatment), and isoxepac (an anti-inflammatory drug) afforded hydroalkylation products (**4**–**7**) in good yields and high enantio- and diastereo selectivity. The estrone-derived alkenyl Bpin also reacted well to give **8**. A 2-bromo-γ-lactam substrate derived from an amine intermediate used in the synthesis of Lipitor® (*33*) was also transformed (**9**) in good yield and high diastereoselectivity.

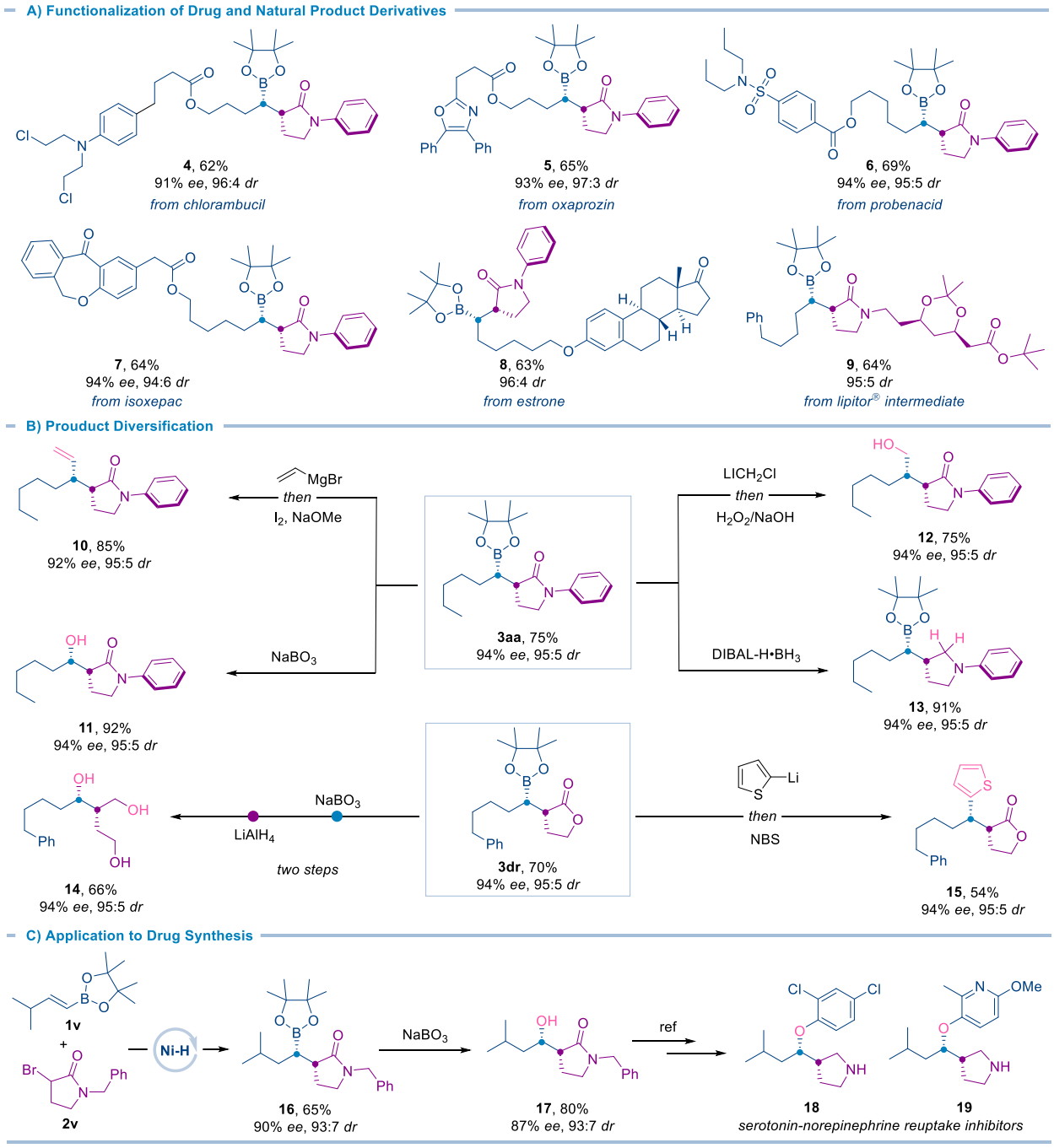


Figure 2. Synthetic application.

We demonstrated the synthetic utility of the hydroalkylation products (Figure 2B). The boryl group could be stereospecifically converted into an ethenyl group (**10**), an alcohol group (**11**), a methyl alcohol group (**12**), or a thiophene group (**15**). All these transformations went smoothly without erosion in ee and dr. The lactam moiety in **3aa** was reduced to the medicinally relevant pyrrolidone group (**13**) without racemization. The lactone ring in **3aq** was opened through stereospecific oxidation of the boryl group followed by a $LiAlH_4$ reduction to give a chiral acyclic tri-alcohol (**14**) in high yield and with stereochemical retention. We applied the hydroalkylation method for the synthesis of key intermediate to several antidepressant drug molecules that belong to the serotonin-norepinephrine reuptake inhibitors (SNRI) family (**18** and **19**, Figure 2C).(*34*) Reaction of readily available alkenyl Bpin (**1v**) and lactam (**2v**) under the standard hydroalkylation conditions described above afforded the product (**16**) in a good yield and with high ee and dr. The latter was stereospecifically oxidized by $NaBO_3$ to give the chiral alcohol (**17**), which is a known key intermediate to these drug molecules.(*34*)

We performed a preliminary mechanistic study. When a radical clock substrate, ethyl 2-bromo-2-cyclopropyl ester, was subjected to the standard reaction conditions, the product originating from ring-opening of the cyclopropyl group was observed (Fig. 3A). The reaction was completely shut down in the presence of a radical scavenger, TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxyl) (Fig. 3B). Meanwhile an alkyl-TEMPO adduct (**22**) was found. These results indicate the intermediacy of alkyl radicals formed after activation of the alkyl halides. The diastereoselectivity of the product **3aa** and the enantiomeric excess of the recovered 2-bromo-γ-lactam substrate (**2a**) as a function of time were monitored (Fig. 3C). The enantiomeric excess of the unreacted **2a** remained zero throughout the course of the reaction. No change in diastereoselectivity (dr) of the product **3aa** was found (dr remained 95:5 throughout the course of the reaction). These data indicate that the reaction proceeds through an enantioconvergent process for the racemic alkyl halides, instead of a kinetic resolution process. The reaction of a deuterated-alkenyl Bpin substrate gave the product (**23**) as a single diastereomer, indicating the insertion of alkene into Ni-H as the enantio-determining step (Fig. 3D). The diastereoselectivity is increased with the $BF_3{\cdot}OEt_2$ additive. It is possible that $BF_3{\cdot}OEt_2$ or another species formed during the reaction catalyzes the isomerization of the minor diastereomer to the major diastereomer. However, a control experiment excluded this possibility as no change in dr and ee was observed when the product **3aa** (with 87% ee and 75:25 dr) was subjected to the standard reaction conditions which contained $BF_3{\cdot}OEt_2$ and other active species (Fig. 3E).

Based on these data and those on previously reported analogous hydroalkylation reactions, (*9*, *14*, *15*, *35*) we consider that two catalytic cycles based on $Ni^{I}/Ni^{II}/Ni^{III}$ redox transformations might be operating (Fig. 3F). In path-I, a Ni^{I}-Cl (**A**) species activates the alkyl bromide through a single-electron transfer to a Ni^{II} bis(halide) species (**B**) and the α-carbonyl alkyl radical. Species B is converted into a Ni^{II}-H (**C**), which inserts into the alkene substrate to form a Ni^{II}-α-boryl-alkyl intermediate (**D**). The latter traps the α-carbonyl alkyl radical to form a Ni^{III}-bis(alkyl) species (**E**). Reductive elimination from **E** releases the coupling product and regenerates the starting Ni^{I}-Cl species (**A**). In an alternative pathway (path-II), the Ni^{I}-Cl (**A**) is proposed to react faster with the hydrosilane than with the alkyl halide, yielding a Ni^{I}-H species (**F**). The latter inserts into the alkene substrate to form a Ni^{I}-α-boryl-alkyl species (**G**). Species **G** activates the alkyl halide to give the Ni^{II}-α-boryl-alkyl intermediate (**D**) and an α-carbonyl alkyl radical. Re-combination of these two species yields the Ni^{III}-bis(alkyl) intermediate (**E**), which reductively eliminates the coupling product and regenerates the starting Ni^{I}-Cl catalyst (**A**). For both catalytic cycles, we

propose that the stereoselectivity originates from initial enantioselective hydrometallation to give a chiral Ni-α-boryl-alkyl moiety, followed by diastereoselective reductive elimination from the Ni^{III}-bis(alkyl) intermediate. The latter step is preceded by reversible Ni-C bond homolysis of the Ni-α-boryl-alkyl moiety to induce the enantioconvergent process. The main difference between the two catalytic cycles is the species that activate the alkyl electrophile, which is a Ni^{I}-Cl species (**A**) in path-I and a Ni^{I}-α-boryl-alkyl species (**G**) in path-II. To distinguish these two possibilities, isolation and reactivity studies of the corresponding intermediates are warranted.

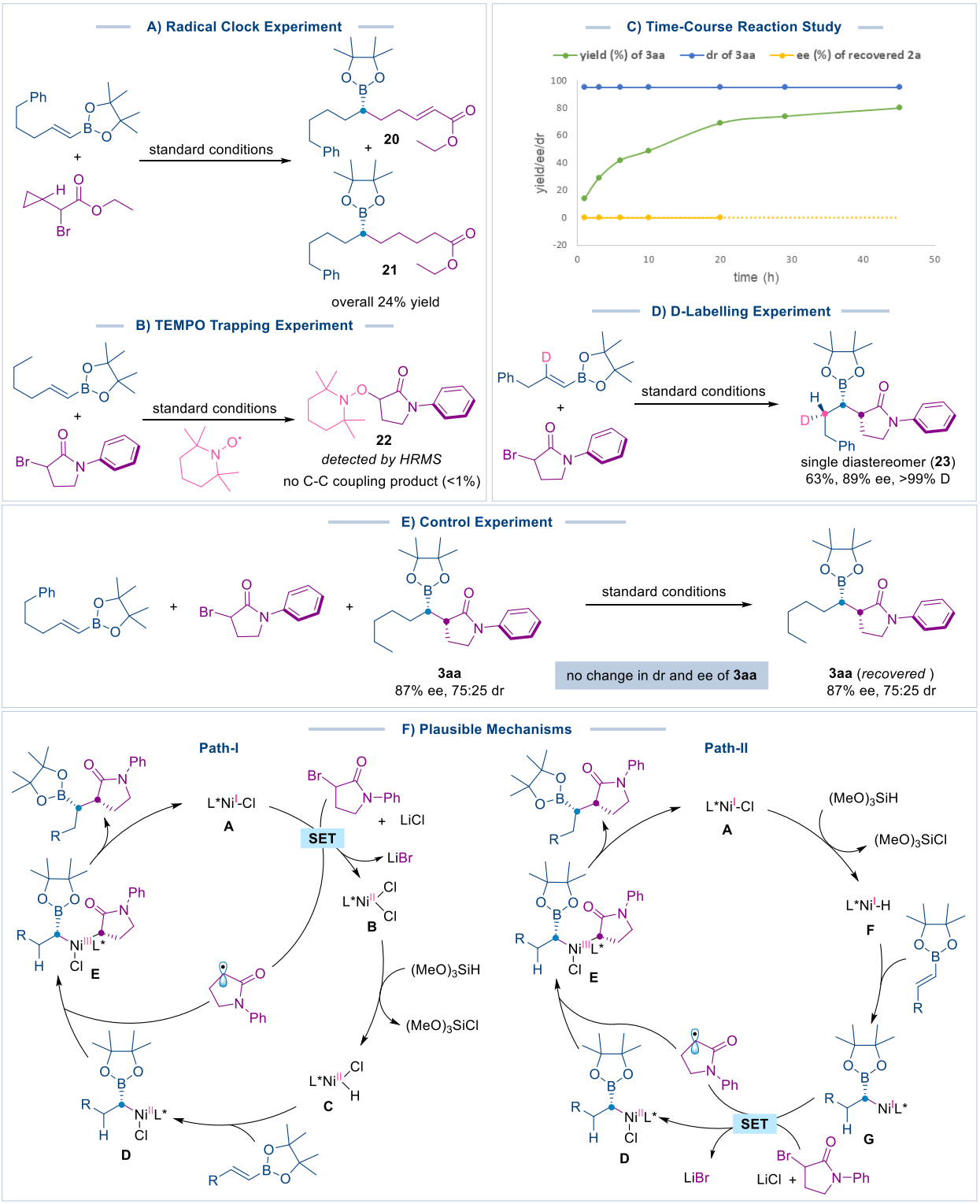


Figure 3: Mechanistic study

Conclusion.

In summary, using asymmetric Ni-H catalysis, we achieve stereoselective C(sp^3)-C(sp^3) bond formation where the stereochemistry of both vicinal C(sp^3) centers originating from two different reaction partners is controlled. The method is general and modular, providing a streamlined access to C(sp^3)-rich molecules with several stereogenic centers. Efforts to expand the scope of the reaction partners to include other classes of alkenes and alkyl electrophiles, as well as to elucidate the mechanism of the catalysis, are underway. We expect these efforts to open up new avenues in stereoselective synthesis.

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Author Contributions: S.B. and X.H. conceived the project. S.B. designed, optimized, and studied the scope and mechanism of the synthetic method. C.F. contributed to the study of synthetic applications as well as some characterization of the compounds. S.B. and X.H. prepared the manuscript, with input from C.F.

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Competing interests: The authors declare no competing interests.

Data Availability: Crystallographic data for **3aa**, **3ab**, **3ad** and **3af** have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 2165076 (**3aa**), CCDC 2165081 (**3ab**), CCDC 2118223 (**3ad**), and CCDC 2118224 (**3af**). Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk. All other data supporting the findings of this study, including experimental procedures and compound characterization, NMR, HPLC and X-ray analyses are available within the Article and its Supplementary Information. Raw NMR and HPLC data are also freely available in Zenodo: DOI: 10.5281/zenodo.6797372.

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