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Nickel-Catalyzed Enantioconvergent Borylation of Racemic Secondary Benzylic Electrophiles**

Zhaobin Wang, Shoshana Bachman, Alexander S. Dudnik, and Gregory C. Fu*

Abstract: Nickel-catalyzed cross-coupling has emerged as the most versatile approach to date for achieving enantioconvergent carbon–carbon bond formation using racemic alkyl halides as electrophiles. In contrast, there have not yet been reports of the application of chiral nickel catalysts to corresponding reactions with heteroatom nucleophiles to produce carbon–heteroatom bonds with good enantioselectivity. Herein, we establish that a chiral nickel/pybox catalyst can borylate racemic secondary benzylic chlorides to provide enantioenriched benzylic boronic esters, a highly useful family of compounds in organic synthesis. The method displays good functional group compatibility (e.g., unimpeded by the presence of an indole, a ketone, a tertiary amine, or an unactivated alkyl bromide), and both of the catalyst components ($\text{NiCl}_2\cdot\text{glyme}$ and a pybox ligand) are commercially available.

Enantioenriched benzylic boronic esters are an important family of target compounds in organic synthesis.^[1,2,3,4] From a practical perspective, boronic esters are attractive compared with organometallic reagents such as Grignard reagents and trialkylboranes due to their comparatively high air- and moisture-stability.^[5] Furthermore, the ability to transform the C–B bond of boronic esters, with stereochemical fidelity, into bonds such as C–C, C–N, C–O, and C–halogen render them highly versatile intermediates in organic chemistry.^[6] Due to these appealing features, an array of methods have been developed for the synthesis of enantioenriched benzylic boronic esters,^[1] including catalytic asymmetric processes such as the hydroboration of alkenes^[2] and the hydrogenation of alkenylboronic esters.^[3,4]

We and others have recently described a variety of nickel-catalyzed enantioconvergent cross-couplings of nucleophiles with racemic alkyl electrophiles; to date, progress in this area has been limited to the use of carbon-based nucleophiles to form C–C bonds (Figure 1a).^[7] Clearly, expanding the scope to include C–heteroatom bond construction would substantially enhance the usefulness of this strategy in synthesis. Aware of the importance of enantioenriched organoboron compounds, we chose to explore the possibility that a boron reagent might serve as the first effective heteroatom-based nucleophile in nickel-catalyzed enantioconvergent cross-couplings.^[8,9,10,11] Herein, we establish the viability of this approach (Figure 1b), specifically, we report a nickel/pybox-catalyzed borylation that provides enantioenriched boronic esters in good enantiomeric excess from an array of racemic secondary benzylic chlorides [Eq. (1)].

Nickel-catalyzed enantioconvergent cross-couplings:

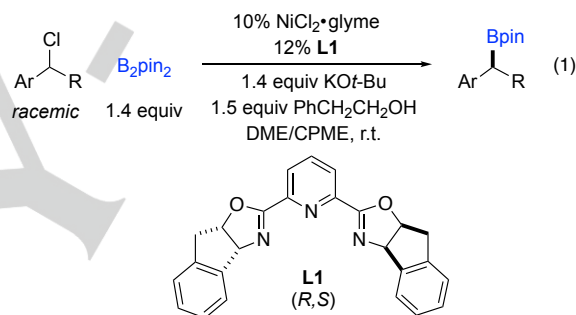
a) Previous work: Limited to C–C bond formation



b) This study: C–B bond formation



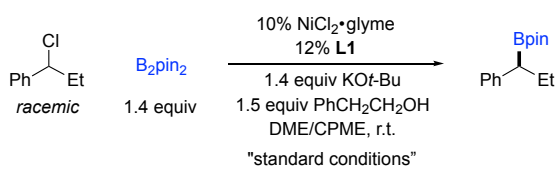
Figure 1. Nickel-catalyzed enantioconvergent cross-couplings of alkyl electrophiles.



Upon exploring a range of conditions, we determined that the enantioconvergent borylation of the racemic secondary benzylic chloride by B_2pin_2 that is illustrated in Table 1 can be achieved in 87% yield and 85% ee in the presence of a chiral nickel/pybox catalyst (entry 1); $\text{NiCl}_2\cdot\text{glyme}$, the pybox ligand **L1**, and B_2pin_2 are all commercially available. Essentially no C–B bond formation is detected if $\text{NiCl}_2\cdot\text{glyme}$ is omitted (entry 2), whereas a small amount is observed if pybox ligand **L1** or the primary alcohol is absent (entries 3 and 4).^[12] The use of pybox ligands **L2** and **L3**, rather than **L1**, leads to excellent yield but low enantioselectivity (entries 5 and 6), whereas bis(oxazoline) ligand **L4** provides poor yield and ee (entry 7). Lowering the temperature does not result in an enhancement in enantioselectivity (entry 8), and the use of a single solvent leads to a loss in yield with no change in ee (entries 9 and 10). Decreasing the catalyst loading (10%→5%) or the amount of nucleophile (1.4 equiv→1.1 equiv) has only a minor impact on the course of the reaction (entries 11 and 12). The enantioconvergent borylation is not highly water- or air-sensitive: even if it is conducted in the presence of a full equivalent of water or in a capped vial under air, a substantial amount of product is formed, in fairly good ee (entries 13 and 14).

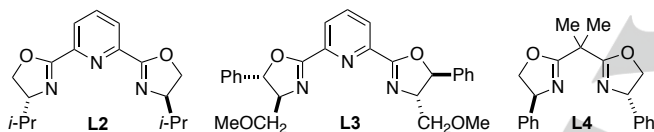
[*] Z. Wang, S. Bachman, A. S. Dudnik, Prof. G. C. Fu
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Table 1. Enantioconvergent borylation of a racemic benzylic chloride: effect of reaction parameters.^[a]


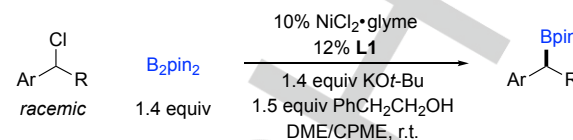
entry	variation from the "standard conditions"	yield (%) ^[b]	ee (%) ^[c]
1	none	87	85
2	no NiCl ₂ ·glyme	<2	–
3	no L1	16	–
4	no PhCH ₂ CH ₂ OH	24	73
5	L2, instead of L1	95	<2
6	L3, instead of L1	98	–40
7	L4, instead of L1	17	–6
8	0 °C, instead of r.t.	52	84
9	DME only	80	84
10	CPME only	61	84
11	5% NiCl ₂ ·glyme, 6% L1	78	80
12	1.1 equiv B ₂ pin ₂ , 1.1 equiv KOt-Bu, 1.2 equiv PhCH ₂ CH ₂ OH	79	84
13	1.0 equiv H ₂ O	58	79
14	under air in a closed vial	47	80

[a] All data are the average of two experiments. [b] The yield was determined through GC analysis with *n*-dodecane as an internal standard. [c] A negative value for ee signifies that the major product is the R enantiomer.



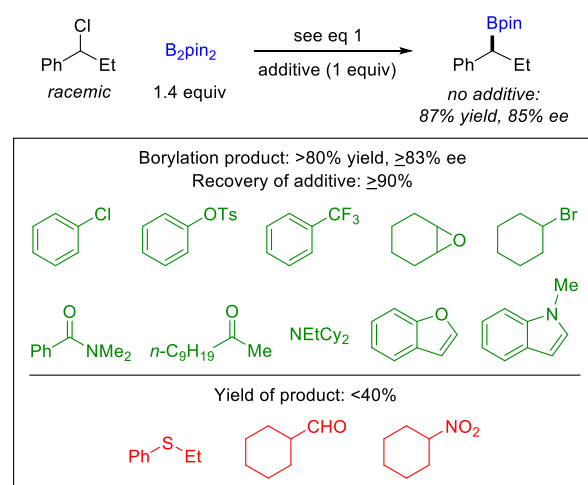
Next, we explored the scope of this new method for the catalytic asymmetric synthesis of enantioenriched benzylic boronic esters (Table 2). We have determined that the alkyl group (R) of the electrophile can vary in steric demand from Me to Cy (entries 1–5), although the presence of a bulky cyclohexyl substituent leads to somewhat lower yield and ee (entry 5). Functional groups such as an ether, an ester, and an unactivated primary alkyl chloride are compatible with the borylation conditions (entries 7–9). With regard to the aryl substituent, it may be substituted in the para, meta, or ortho position (entries 10–14), and it can be a 1-naphthyl group (entry 15); however, if it is a 6-dibenzofuryl substituent, the reaction proceeds in good yield but moderate ee (entry 16). The method can be applied not only to an acyclic, but also to a cyclic, benzylic chloride (entry 17). On a gram-scale (1.42 g of product), the borylation illustrated in entry 3 proceeds in 85% yield and 88% ee.

By conducting an enantioconvergent borylation in the presence of a variety of additives, we have further examined the functional-group tolerance of the method (Figure 2). We have determined that an aryl chloride, aryl tosylate, epoxide, unactivated secondary alkyl bromide, tertiary amide, ketone, tertiary amine, benzofuran, and indole have little or no impact on C–B bond formation, and the additive can be recovered virtually quantitatively at the end of the reaction (>90%). On the other hand, the presence of a thioether, aldehyde, or nitroalkane impedes the borylation.

Table 2. Enantioconvergent borylations of racemic benzylic chlorides: scope.^[a]


entry	Ar	R	yield (%) ^[b]	ee (%)
1	Ph	Et	81	86
2	Ph	Me	64	82
3	Ph	<i>n</i> -Bu	80	88
4	Ph	CH ₂ -C(Me) ₂ -Me	82	88
5	Ph	Cy	61	78
6	Ph	Bn	79	83
7	Ph	(CH ₂) ₅ -OBn	66	80
8	Ph	(CH ₂) ₅ -OBz	74	83
9	Ph	(CH ₂) ₅ -Cl	82	86
10	<i>p</i> -tolyl	Et	64	82
11	<i>m</i> -tolyl	Et	77	82
12	<i>m</i> -anisyl	Et	69	80
13	<i>o</i> -tolyl	Et	88	86
14	<i>o</i> -fluorophenyl	Et	85	81
15	1-naphthyl	Et	90	83
16	6-dibenzofuryl	Et	86	51
17	cyclohexyl	Cl	81	81

[a] All data are the average of two experiments. [b] Yield of purified product.

**Figure 2.** Enantioconvergent borylation of a racemic benzylic chloride: functional-group compatibility. Each additive was examined individually.

As mentioned at the outset, enantioenriched benzylic boronic esters are versatile intermediates in organic synthesis that can be converted with high stereochemical fidelity into other useful

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families of compounds; several representative examples are provided in Figure 3. Thus, the illustrated boronic ester can be aminated, hydroxymethylated, and arylated (a variety of bioactive compounds include tertiary stereocenters that bear two different aryl substituents^[13]) without erosion in enantiomeric excess.^[6]

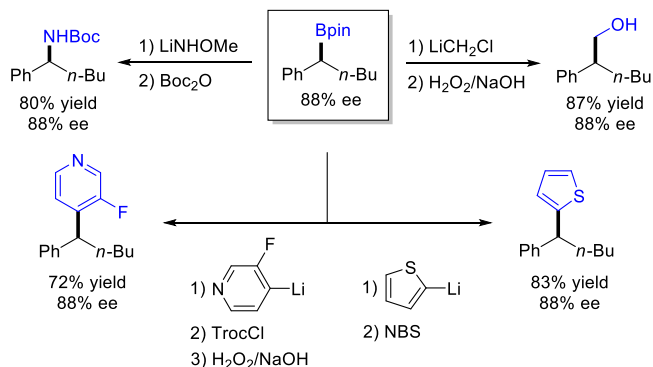
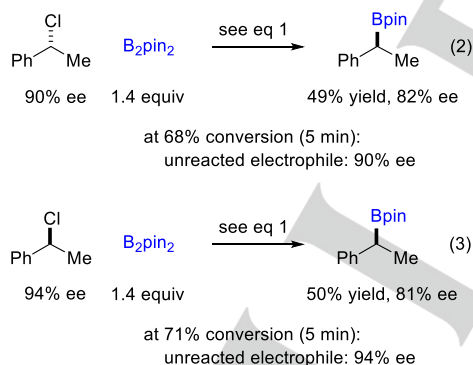


Figure 3. Representative transformations of an enantioenriched benzylic boronic ester.

We have determined that, with a given enantiomer of catalyst, nickel-catalyzed borylation proceeds with essentially identical yield and enantioselectivity, regardless of the original configuration of the electrophile, establishing that the stereochemistry of the borylation is fully controlled by the chiral catalyst [Eq. (2) and (3)]. Furthermore, at partial conversion, the ee of the electrophile is unchanged, indicating that the chiral catalyst reacts with the two enantiomers of the electrophile at essentially identical rates, that the electrophile does not undergo racemization under the reaction conditions, and that C–Cl cleavage by the catalyst is irreversible.^[14]



In summary, we have enlarged the scope of nickel-catalyzed stereoconvergent cross-couplings of alkyl electrophiles to include C–heteroatom bond construction for the first time, specifically, transforming racemic benzylic chlorides into enantioenriched benzylic boronic esters, a useful family of compounds in organic synthesis. The method displays good functional-group compatibility, and both of the catalyst components (NiCl₂·glyme and pybox ligand **L1**) are commercially available. Investigations of other C–heteroatom bond-forming processes, including enantioconvergent reactions, as well as mechanistic studies, are underway.

Keywords: asymmetric catalysis • boron • cross-coupling • nickel

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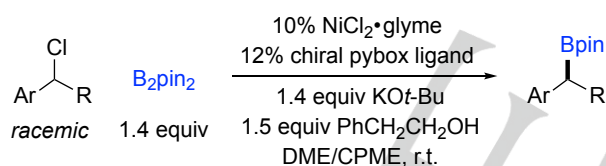
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**Nickel-Catalyzed Enantioconvergent
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Layout 2:

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