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Enantioselective assembly of chiral α-perfluoroalkyl boranes bearing vicinal boron/carbon stereogenic centers via copper catalysis

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Abstract

Enantioselective assembly of chiral α-perfluoroalkylated organoboron compounds is a significant challenge in synthetic chemistry. Herein, a copper-catalyzed asymmetric B-H insertion reaction was employed to couple 2-arylpyridine-boranes with α-aryl-α-perfluoroalkyl diazomethanes, delivering over 40 novel chiral α-perfluoroalkylated organoboron compounds bearing boron/carbon vicinal stereogenic centers. This protocol accommodates a range of perfluoroalkyl substituents, including CF_3, C_2F_5, C_3F_7, and C_4F_9. The reaction affords products in up to 85% yield, 99% ee, and dr > 20:1 for longer-chain perfluoroalkyl substrates. Mechanistic insights are provided by deuterium-labeling and KIE experiments, together with reference to previous related precedents. The scalability and further transformations of the reaction products demonstrate their potential usefulness in the synthetic community.

Keywords: B-H insertion, chiral organoboron, perfluoroalkylation, asymmetric catalysis, vicinal stereocenters

1. Introduction

Fluorine-containing organic compounds have significant potential for the development of pharmaceuticals and agrochemicals[1-5]. The incorporation of perfluoroalkyl moieties into pharmaceutical molecules can impart a variety of features, including enhanced membrane permeability, metabolism stability, and bioavailability[6-9]. Many bioactive molecules have perfluoroalkylated fragments, such as Flupoxam[10], Faslodex[11,12], KC-515[13,14], and G-29[15,16], which illustrates that perfluoroalkyl substitution is a powerful strategy to improve drug-like properties. The chiral perfluoroalkyl motif is an integral part of bioactive molecules such as Efavirenz[17,18] and Vilaprisan[19,20], further demonstrating the promise of chiral perfluoroalkylated compounds as drug candidates (Scheme 1a). Therefore, asymmetric perfluoroalkylation is a fascinating aspect of organofluorine chemistry. The strategies for the construction of chiral perfluoroalkyl compounds are relatively mature[21-24], including direct enantioselective introduction of the perfluoroalkyl groups through nucleophilic[25-30], electrophilic[31-38], and radical perfluoroalkylative reactions[39-49], or alternative approaches that use prefunctionalized fluoroalkyl substrates, including fluoroalkyl-substituted alkenes, amine, dienes, and carbon nucleophiles, to construct enantioenriched products[50-57]. However, the construction of chiral perfluoroalkyl compounds containing vicinal stereocenters is extremely limited[58,59]. To date, although elegant advances have been realized in the synthesis of boron-stereogenic compounds[60-62], a copper-catalyzed asymmetric B-H insertion method for accessing α-perfluoroalkylated organoboron compounds bearing vicinal boron/carbon stereogenic centers has not been reported. Given that such compounds can serve as versatile synthetic building blocks, the development of efficient asymmetric strategies to access these scaffolds represents a formidable challenge

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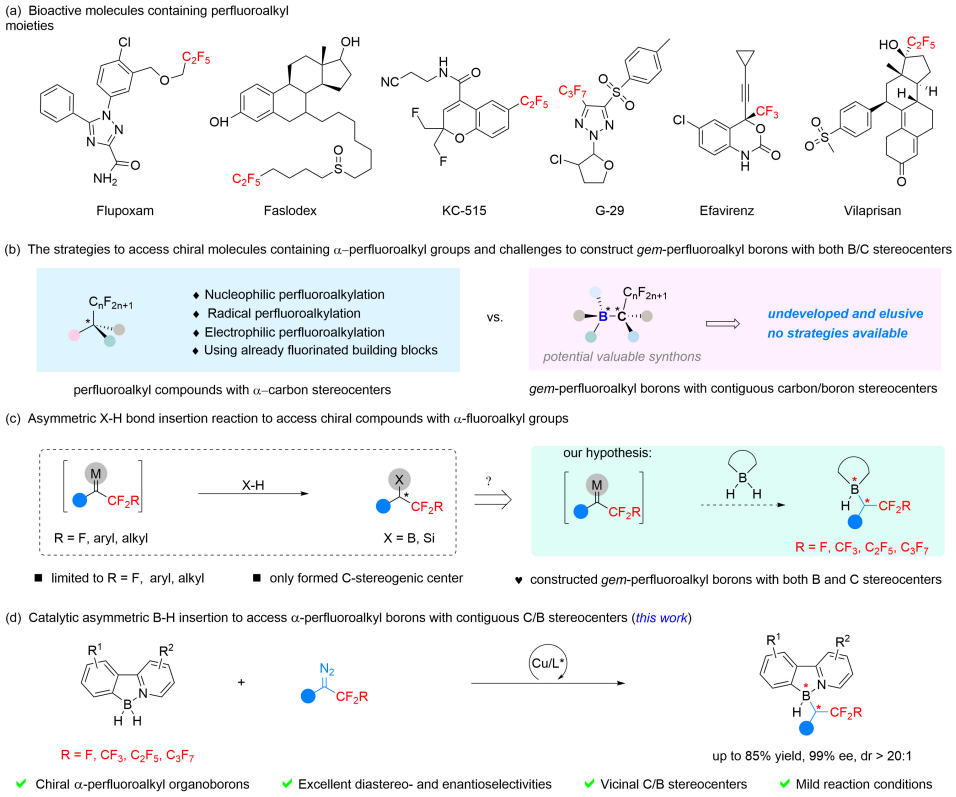
(Scheme 1b).



Scheme 1. Significance of chiral perfluoroalkyl containing compounds and their synthetic challenges.

In the past decades, the asymmetric insertion reaction with metal carbene intermediates has emerged as an effective and practical tactic to access various chiral compounds[63-67]. Correspondingly, asymmetric fluoroalkylation could be achieved through this strategy. Gouverneur and co-workers reported an example of copper-catalyzed asymmetric Si-H or B-H insertion, but the only chiral α-trifluoromethylated organoboron compound was isolated with moderate enantioselectivity[68]. Arnold and co-workers realized biocatalytic B-H bond insertion for the synthesis of chiral α-trifluoromethylated organoboron compounds with good enantioselectivity[69,70]. Zhu and co-workers disclosed that chiral *gem*-difluoroalkyl propargylic boron derivatives were constructed with good enantioselectivities (Scheme 1c, left)[71]. Likewise, chiral α-trifluoromethylated organoborons have been accessed through lithiation–borylation/1,2-boronate rearrangement, enantioselective 1,2-borotropic migration, and asymmetric organocatalytic homologation strategies[72-74]. The synthesis of chiral α-perfluoroalkylated organoboron compounds has attracted substantial research and attention due to its wide range of potential applications and unique chemical properties[75]. However, to the best of our knowledge, the types of chiral α-perfluoroalkylated organoboron compounds are very limited due to the complexity of organofluorine chemistry, and chiral organoboron compounds containing α-perfluoroalkyl groups are confined to the trifluoromethyl group and the carbon stereocenters. Recently, Xu's group and ours demonstrated the construction of carbon/boron vicinal stereocenters via B-H asymmetric insertion[76-79]. Even so, the construction of perfluoro-substituted compounds bearing carbon/boron vicinal stereocenters with high diastereo- and enantioselectivities remains a formidable challenge. Therefore, we speculated whether metal carbenes containing α-perfluoroalkyl motifs (e.g., R_f = CF_3, C_2F_5, C_3F_7, C_4F_9) could be acted as building blocks to construct α-perfluoroalkylated organoboron compounds with boron/carbon vicinal stereocenters via B-H asymmetric insertion (Scheme 1c, right). To achieve this reaction, we must overcome the challenges associated with introducing various perfluoroalkyl groups and constructing carbon/boron contiguous stereocenters. Herein, we present asymmetric B-H insertion for synthesizing α-perfluoroalkylated organoboron compounds with boron/carbon vicinal stereogenic centers. This methodology features mild reaction conditions, broad substrate scope and incredible perfluoroalkyl compatibility, providing a variety of chiral α-perfluoroalkylated organoboron compounds with contiguous boron/carbon stereogenic centers in moderate-to-excellent diastereoselectivities and excellent enantioselectivities (Scheme 1d).

2. Methods

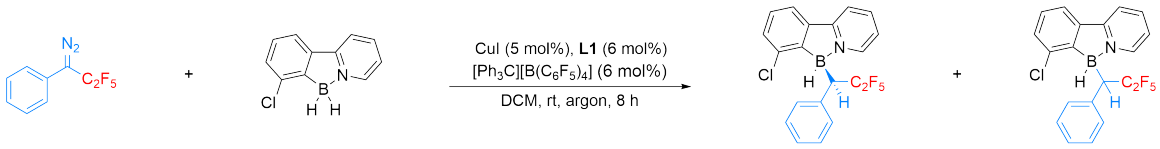
General procedure for asymmetric B-H insertion reactions. To a flame-dried Schlenk tube were added **1** (0.1 mmol, 1.0 equiv), **2** (0.12 mmol, 1.2 equiv), CuI (5 mol%), **L1** (6 mol%), $[Ph_3C][B(C_6F_5)_4]$ (6 mol%). The tube was evacuated and filled with argon for three cycles. Then, 1 mL of DCM was added under argon. The reaction was allowed to stir at rt for 8 hours. Upon completion, a proper

amount of silica gel was added to the reaction mixture. After removal of the solvent, the crude product was then purified by flash column chromatography.

3. Results and Discussion

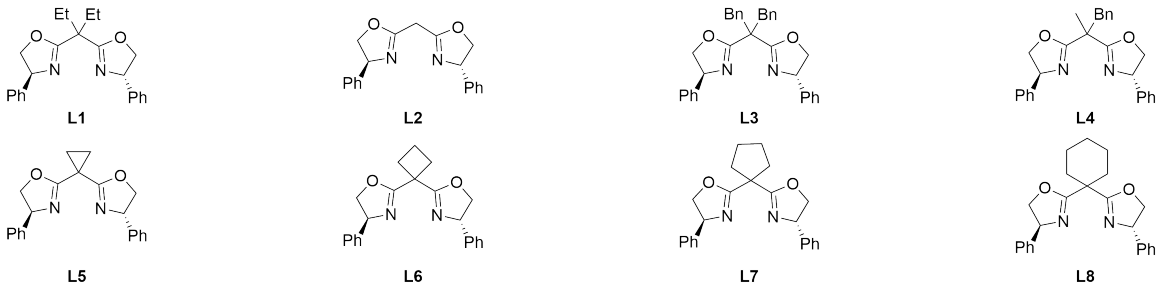
To validate our hypothesis, we started with 7-Cl 2-phenylpyridine-borane (**1a**) and (1-diazo-2,2,3,3,3-pentafluoropropyl)benzene (**2a**) as model substrates. Through a series of experiments, we found that the combination of CuI, **L1**, $[Ph_3C][B(C_6F_5)_4]$ as an additive in DCM at room temperature delivered the desired product **3aa** in 84% isolated yield with excellent diastereoselectivity (dr = 29:1) and enantioselectivity (99% ee) (entry 1, Table 1). When $Cu(MeCN)_4PF_6$ replaced CuI, yield, enantioselectivity and diastereoselectivity all decreased (Table 1, entry 2). When DCE was used instead of DCM, enantioselectivity was maintained, but both yield and diastereoselectivity were declined (Table 1, entry 3). When NaBArF and KBArF were used instead of $[Ph_3C][B(C_6F_5)_4]$, enantioselectivity and diastereoselectivity remained, but the yield decreased (Table 1, entry 4, 5). If there was no additive ($[Ph_3C][B(C_6F_5)_4]$) added to the system, only a trace amount of the product was detected (Table 1, entry 6). The change of substituents between the two oxazole rings showed that ethyl was the most suitable group to catalyze the reaction and that the substituents with less steric hindrance would reduce the diastereoselectivity (**L2**), while the substituents with more steric hindrance would gain better diastereoselectivity but would trim the product yield (**L3**, **L4**), and the effect of different cyclic substitutions was also evaluated and it turned out they were all not as good as that of ethyl groups (**L5**, **L6**, **L7**, **L8**).

Table 1. Optimization of Reaction Conditions[a].



2a **1a** **3aa** **3aa'**

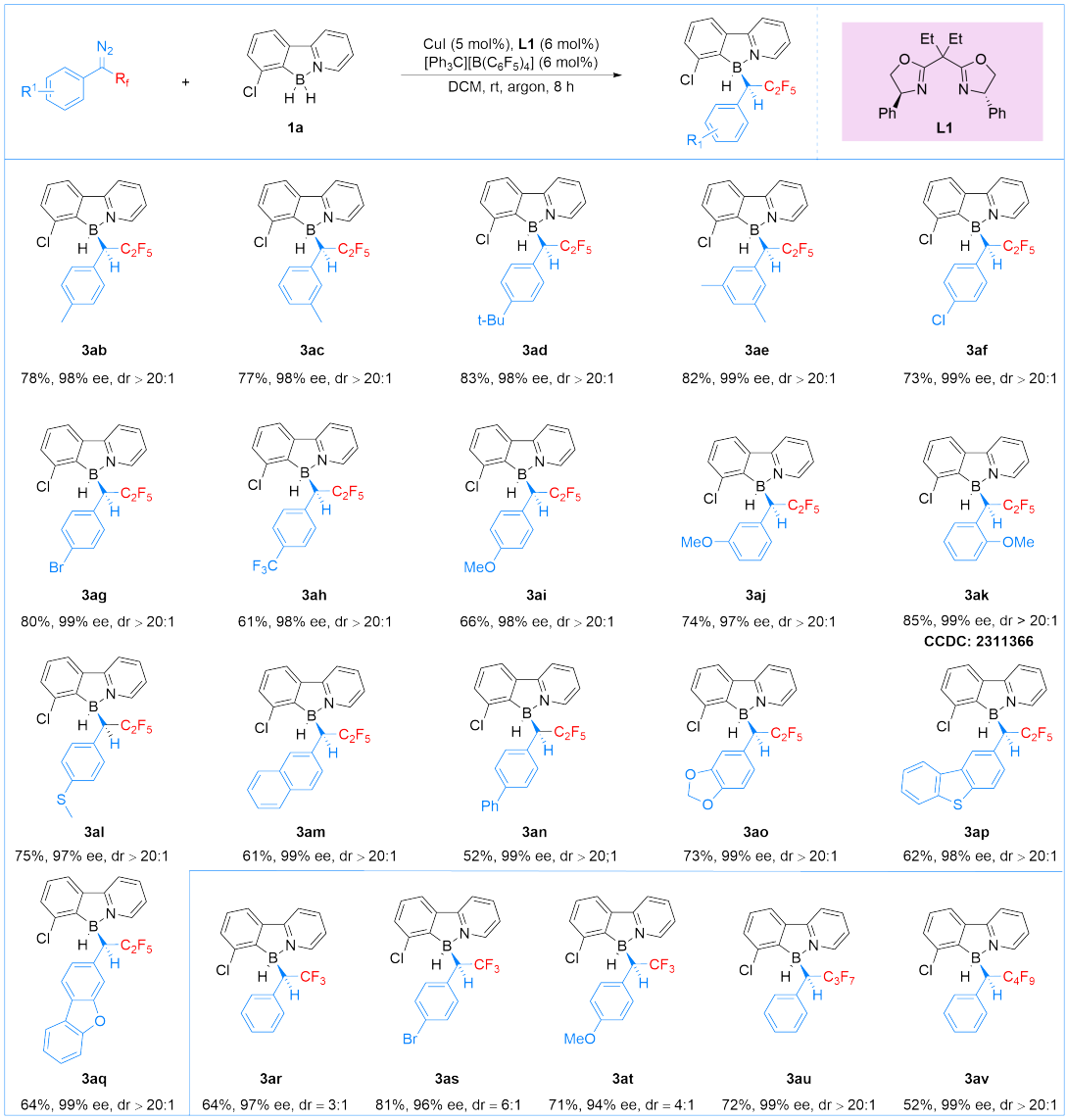
entry	variation	yield [%][b]	ee [%][d]	dr (**3aa**/**3aa'**)[b]
1	none	87(84)[c]	99	29:1
2	$Cu(MeCN)_4PF_6$ instead of CuI	70	94	12:1
3	DCE instead of DCM	80	99	20:1
4	$NaBAr_F$ instead of $[Ph_3C][B(C_6F_5)_4]$	75	99	28:1
5	$KBAr_F$ instead of $[Ph_3C][B(C_6F_5)_4]$	78	99	29:1
6	No $[Ph_3C][B(C_6F_5)_4]$	trace	-	-
7	**L2** instead of **L1**	84	98	13:1
8	**L3** instead of **L1**	65	99	30:1
9	**L4** instead of **L1**	73	99	25:1
10	**L5** instead of **L1**	76	99	18:1
11	**L6** instead of **L1**	74	95	18:1
12	**L7** instead of **L1**	70	99	20:1
13	**L8** instead of **L1**	67	94	6:1



L1 **L2** **L3** **L4**

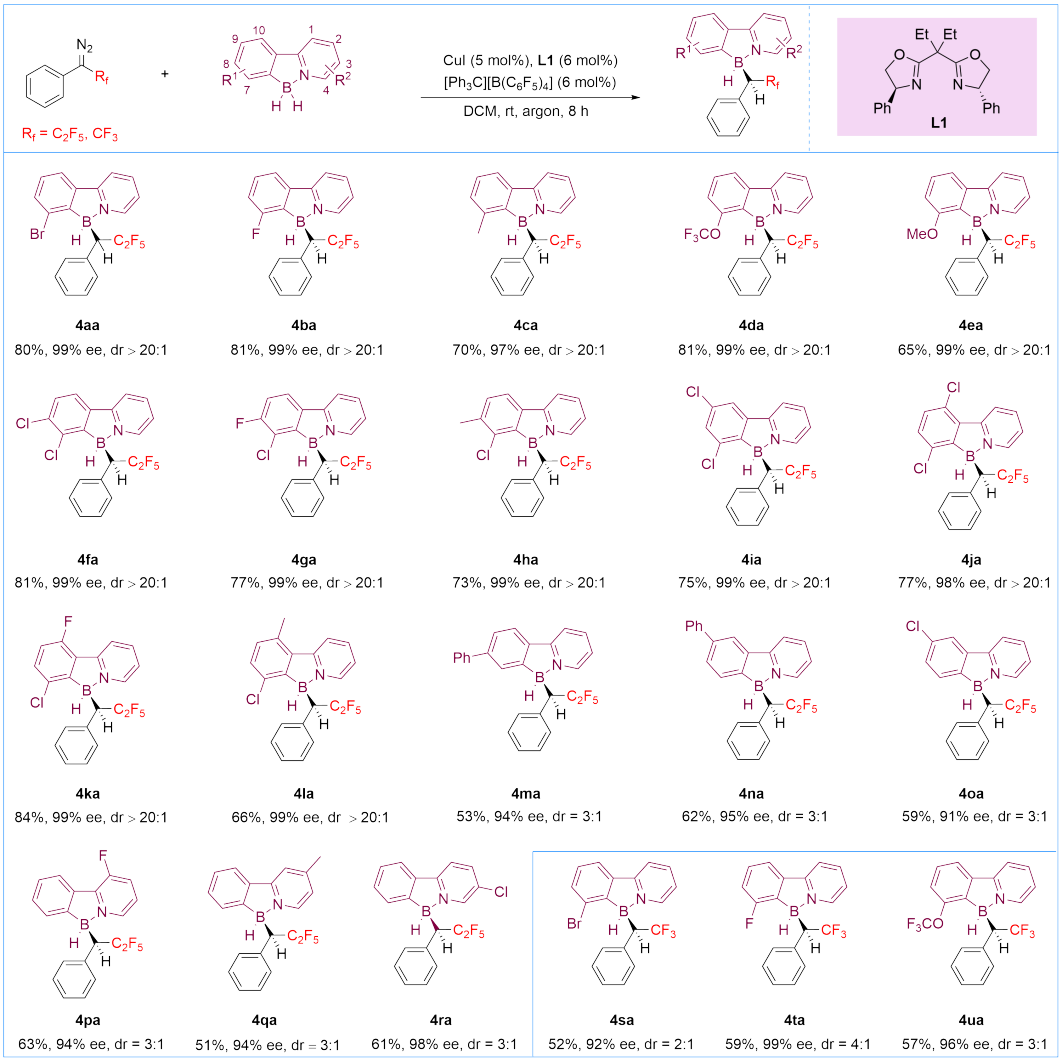
L5 **L6** **L7** **L8**

After the optimized conditions were obtained, the substrate range of α-aryl-α-perfluoroalky diazomethanes was explored with **1a** as borane (Scheme 2). When C_2F_5 was used as the perfluoroalkyl group, alkyl groups at different positions of the aryl rings were tolerated well, and the desired chiral α-perfluoroalkylated organoboron compounds (**3ab**-**3ae**) were obtained in 77-83% isolated yield with 98-99% ee and great dr values (> 20:1), respectively. To our delight, with electron-withdrawing groups like *para*-chloro (**3af**), *para*-bromo (**3ag**), *para*-trifluoromethyl (**3ah**) as well as electron-donating groups like a methoxy group at different positions (**3ai**-**3ak**), *para*-methylthioether (**3al**) of the aryl rings, the reactions proceeded smoothly and the corresponding products were achieved in good yields with excellent enantioselectivities (97-99% ee) and diastereoselectivities (dr > 20:1). The structure and absolute configuration of the compound **3ak** were confirmed by X-ray crystal analysis (CCDC 2311366, see Supporting Information (SI) for more details). When we investigated other polyphenylene or heterocycles such as naphthalene (**3am**), diphenyl (**3an**), 1,2-methylenedioxybenzene (**3ao**), dibenzofuran (**3ap**) and dibenzothiophene (**3aq**), the desired products were obtained in moderate yields (52-73%), yet with excellent enantioselectivities (98-99% ee) and diastereoselectivities (dr > 20:1). When we changed C_2F_5 into CF_3 as the perfluoroalkyl group, the corresponding products (**3ar**-**3at**) with various substituents on the aromatic rings were all rendered in good yields and high enantioselectivities, yet with poor diastereoselectivities. This might be due to the small steric hindrance of the CF_3 group. When C_3F_7 and C_4F_9 groups, which have larger steric hindrance, took the place of the C_2F_5 moiety as perfluoroalkyl groups, the target products (**3au**-**3av**) were delivered in excellent enantioselectivities and diastereoselectivities, but with the increase of steric hindrances, the yields decreased slightly. For instance, compound **3au** was obtained in 72% yield, while product **3av** was only achieved in 52% yield.



Scheme 2. Scope of *gem*-perfluoroalkyl aryl diazomethanes for the enantioselective B-H insertion reaction. Conditions: 7-Cl 2-phenylpyridine-borane (**1a**) (0.1 mmol, 1.0 equiv), α-aryl-α-perfluoroalkyl diazomethanes (**2**, 0.12 mmol, 1.2 equiv), CuI (5 mol%), ligand (6 mol%), $[Ph_3C][B(C_6F_5)_4]$ (6 mol%) and solvent (1 mL) at room temperature for 8 h.

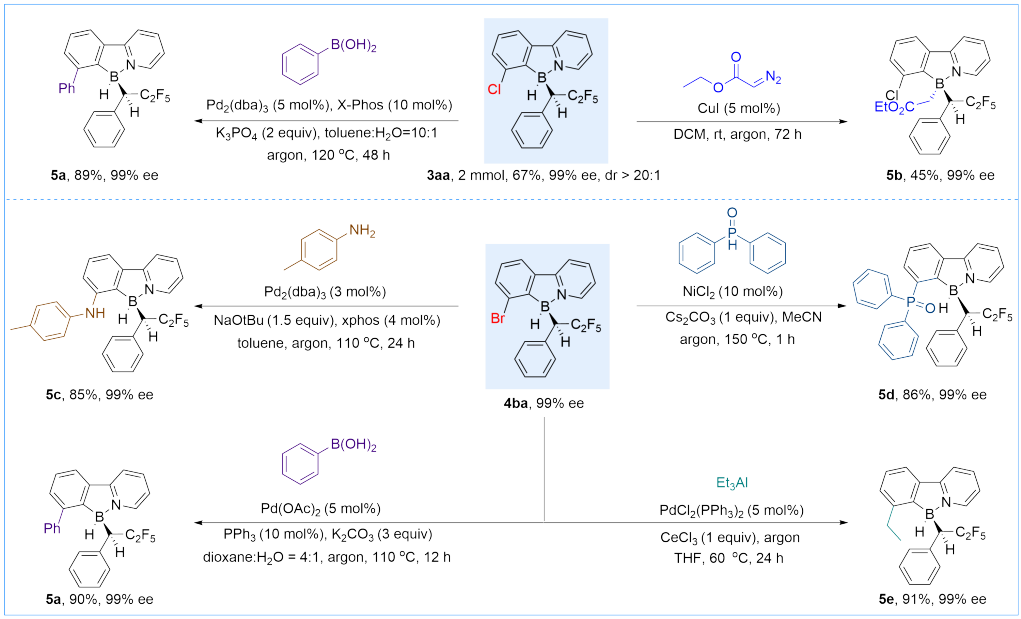
Next, we examined the scope of the 2-arylpyridine-borane derivatives. As shown in Scheme 3, when (1-diazo-2,2,3,3,3-pentafluoropropyl)benzene (**2a**) was used as the diazo substrate, a wide array of 7-substituted 2-arylpyridine-boranes was tolerated well, leading to the corresponding enantio-enriched α-perfluoroalkylated organoboron compounds bearing boron and carbon vicinal stereogenic centers in moderate to high yields with excellent diastereo- and enantioselectivities (**4aa**-**4la**, 65-84% yields, 97-99% ee, dr > 20:1). We found that the aromatic rings of 2-arylpyridine-borane substrates bearing groups like halogen substituents (**4aa**, **4ba**), methyl groups (**4ca**), and electron-withdrawing groups such as trifluoromethoxy (**4da**), electron-donor groups methoxy (**4ea**) were well-tolerated, resulting in high enantioselectivities (97-99% ee) and diastereoselectivities (dr > 20:1), with excellent yields for compounds **4aa**-**4da** and moderate yield for compound **4ea**. The disubstituted 2-arylpyridine boranes could react smoothly with **2a**, producing the expected products **4fa**-**4la** in 66-84% yields with excellent enantioselectivities (98-99% ee) and very good diastereoselectivities (dr > 20:1). We also expanded the range of substrates to 2-phenylpyridine-boranes without substituents at position 7. Compared to the 7-position substituted boranes, the boranes with substituents at other positions rendered the target products (**4ma**-**4ra**) in lower diastereoselectivities and moderate yields, but enantiomeric selectivities remained good. The introduction of a substituent at 7-position of 2-arylpyridine-boranes was conducive to the stereocontrol of this transformation. Similar results were obtained when (1-diazo-2,2,2-trifluoroethyl)benzene (**2r**) was used as the diazo substrate. No matter whether electron-withdrawing groups like halogen substituents (**4sa**, **4ta**) or electron-donor groups (**4ua**) were present on the aromatic ring of the boranes, excellent enantioselectivities were obtained, yet yields and diastereoselectivities were relatively low.



Scheme 3. Substrate scope of 2-arylpyridine-boranes for the enantioselective B–H insertion reaction. Conditions: 2-arylpyridine-borane (**1**) (0.1 mmol, 1.0 equiv), α-aryl-α-perfluoroalkyl diazomethanes (**2**, 0.12 mmol, 1.2 equiv), CuI (5 mol%), ligand (6 mol%), $[Ph_3C][B(C_6F_5)_4]$ (6 mol%) and solvent (1 mL) at room temperature for 8 h.

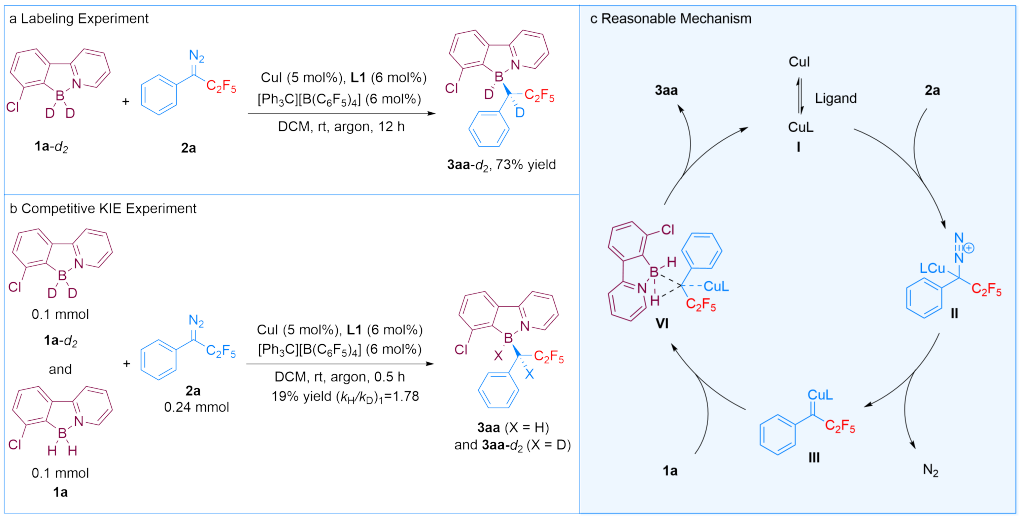
To demonstrate the synthetic utility of this enantioselective desymmetric B-H bond insertion reaction, we first performed an amplification reaction (Scheme 4). To our delight, the product **3aa** was successfully obtained when the reaction was amplified to 2 mmol by halving the catalyst; the enantioselectivity and diastereoselectivity remained unchanged, with a moderate yield of 67%. In addition, the derivatizations of **3aa** were also conducted to further showcase the synthetic utility. Suzuki coupling between chloride

3aa or bromide **4ba** with phenyl boronic acid both delivered the same compound **5a** in excellent yields and enantioselectivities. It was worth noting that the B-H bond of product **3aa** could be further inserted with ethyl diazoacetate to obtain the corresponding product **5b** at a yield of 45%, without affecting stereoselectivity. Moreover, **4ba** could be connected to various functional groups through a series of coupling reactions, for instance, compound **5c** was obtained through Buchwald-Hartwig amination reaction. When **4ba** coupled with diphenyl phosphate to form organophosphorus **5d**, what makes us happy is that even at 150 °C the reaction product **5d** was still not racemized. When reacted with triethylaluminum, **4ba** was converted into compound **5e**. Gratifyingly, after a series of transformations, the enantioselectivities and diastereoselectivities could be completely saved and remain unchanged, and the yields were also good.



Scheme 4. Synthetic transformations.

We performed labeling experiments to demonstrate this hydrogen transfer process. The deuterium atom from **1a**-d_2 was transferred to the α-carbon of the boron-stereogenic product **3aa**-d_2 (Scheme 5a). Competitive kinetic isotope effect experiments ($(k_H/k_D)_1$ = 1.78) and parallel kinetic isotope effect experiments ($(k_H/k_D)_2$ = 1.38; for experimental details, see Section 1.6c in the Supporting Information) showed that the hydrogen transfer step might not be involved in a turnover-limiting step (Scheme 5b)[77-80]. Based on labeling experiments, a plausible mechanism is proposed to explain this insertion reaction (Scheme 5c). In these transformations, the initial coordination of the box ligand (**L1**) with CuI yields chiral copper **I**, diazo compound **2a** is activated by copper **I** to form intermediate **II**, and a molecule of nitrogen is extruded to form highly active carbene intermediate **III**. The subsequent reaction of carbene intermediate **III** with borane **1a** will undergo a ternary ring transition state **VI**, resulting in the final product **3aa**.



Scheme 5. Mechanistic experiments and a plausible mechanism.

4. Conclusions

In summary, we disclose a copper-catalyzed enantioselective and diastereoselective B-H insertion reaction to assemble chiral α-perfluoroalkylated organoboron compounds. The structure of the products is unique, combining a boron stereogenic center with a carbon stereogenic center containing perfluoroalkyl groups into the same molecule, realizing the combination of organoboron chemistry and organofluorine chemistry. The reaction portrays unique product structures with vicinal boron and carbon stereogenic centers, valuable products with both chiral boranes and chiral perfluoroalkanes, mild reaction conditions with excellent enantioselectivities and moderate-to-excellent diastereoselectivities. The potential values of the products were demonstrated by synthetic utilities and applications. The reaction provides an avenue to access chiral *gem*-perfluoroalkylated organoborons which contain contiguous carbon and boron stereogenic centers for the first time, will enrich both organofluorine chemistry and organoboron chemistry, and expand the range of both chiral organoborons and chiral organofluorine compounds.

Supplementary materials

The supplementary material for this article is available at: Supplementary materials.

Declarations

Authors contribution

Song Q: Conceptualization, supervision, writing-original draft, writing-review & editing.
Cai X: Methodology, investigation, writing-original draft, writing-review & editing.
Jia J, Feng B, Zhang G, Li L: Investigation, data curation, formal analysis, writing-review & editing.
Zhu BH: Investigation, data curation, formal analysis, writing-original draft, writing-review & editing.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The data and materials could be obtained from the corresponding author.

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