Facilitating the Transmetalation Step with Aryl-Zincates in Nickel-Catalyzed Enantioselective Arylation of Secondary Benzylic Halides

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Abstract. A method for the highly enantioselective construction of fluoroalkyl-substituted stereogenic center by a nickel-catalyzed asymmetric Suzuki-Miyaura coupling of α-bromobenzyl trifluoro-/difluoro-/monofluoromethanes with a variety of lithium organoborate in the presence of 1.0 equivalent of $ZnBr_2$ was described. Preliminary mechanistic studies disclosed that reaction of lithium organoborate with $ZnBr_2$ generated a zincate $[Ph_2ZnBr]Li$, which facilitates the transmetallation step of the nickel-catalyzed cross-coupling reaction to enable high enantioselectivity.

INTRODUCTION

Over the past two decades, nickel-catalyzed asymmetric cross-coupling of secondary alkyl electrophiles with different nucleophiles has emerged as powerful methods for the construction of chiral tertiary carbon centers.[1-4] Since the seminar work by Fu and coworkers in 2005,[5] a number of activated racemic alkyl halides such as α-bromoamides,[5] α-bromoketones,[6] benzylic bromides and chlorides,[7-8] allylic chlorides[9] or 1-bromo-1-fluoroalkane[10] and unactivated racemic alkyl halides such as β- or γ-ether, amide or

sulfonyl-substituted alkyl bromides,[11-12] and α-haloboronates[13] were effectively employed as the coupling partners, while the choice of nucleophiles was originally mainly focused on alkyl zinc halides. Only recently, the nickel-catalyzed asymmetric couplings of racemic alkyl halides were successfully extended to other nucleophiles such as alkyl-9-BBN, aryl Grignard reagents, aryl zinc halides, aryl/vinyl silicates vinyl/alkynyl indium/zirconium/aluminum reagents.[6,14-19]

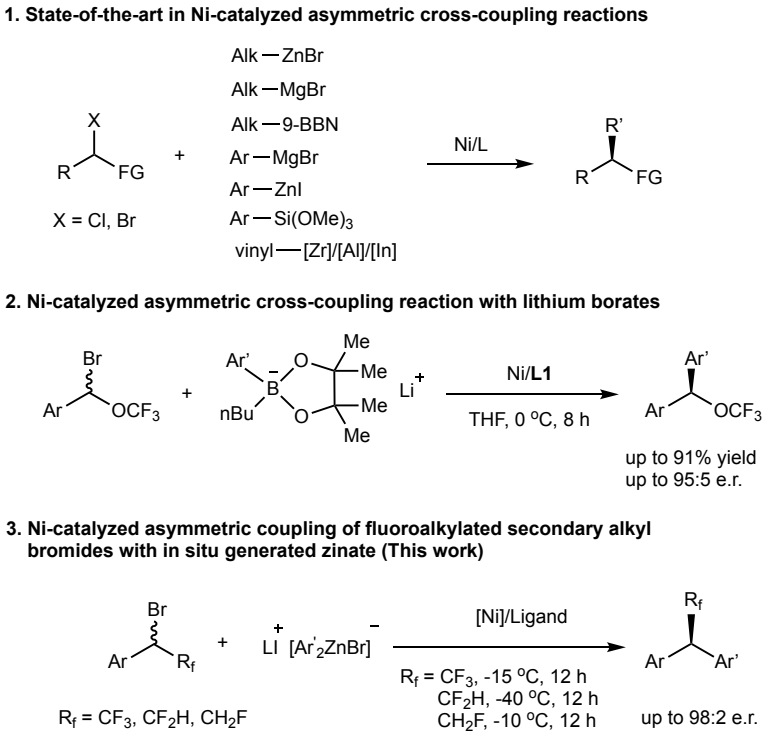


Figure 1. Ni-catalyzed asymmetric cross-coupling of racemic secondary alkyl halides.

Organoboron reagents are one of the most widely studied and applied reagents that allows for the efficient construction of carbon-carbon and carbon-heteroatom bonds.[20-22] Non-asymmetric couplings of secondary alkyl bromides with aryl boronic acids under nickel catalysis have been reported in early 2004.[23] Yet, mainly due to the slow transmetalation step of the aryl

boronic acid to the active nickel intermediate, theses reactions typically required 60 °C to occur to full conversion. To facilitate the transmetalation step, Fu and coworkers turned to alkyl-9-BBN and found that the reaction could be conducted at 5 °C-room temperature to ensure high enantioselectivity.[15] Nevertheless, alkyl boranes are generally air and moisture sensitive and should be prepared *in situ* by hydroboration of alkene before use, which hampered their widespread applications.

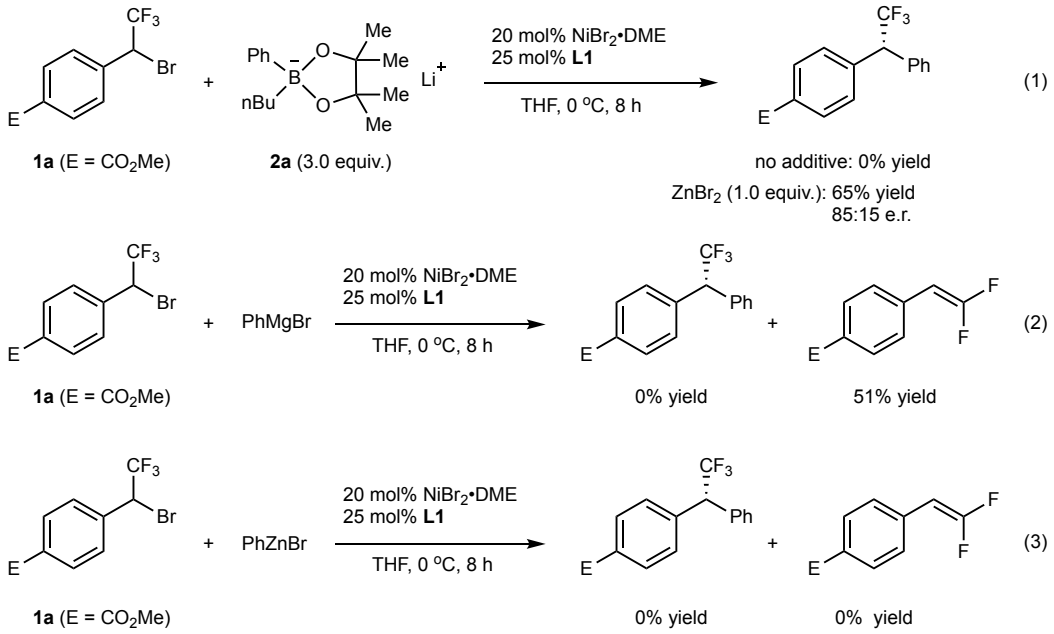
In 2017, we discovered that the transmetalation step in nickel-catalyzed asymmetric Suzuki-Miyaura coupling of CF_3O-substituted secondary benzylic bromide when easily available, air-insensitive lithium organoborate instead of aryl boronic acid was used as the nucleophile.[24] In this case, the reaction occurred smoothly at 0 °C to give the coupled product with a CF_3O-stustituted stereogenic center with excellent enantioselectivity. Inspired by this discovery and considering the fact that fluoroalkyl groups including trifluoromethyl (CF_3-), difluoromethyl (HCF_2-) and monofluoromethyl (CH_2F-) group are important structural motifs in refining the lead compound's selectivity and pharmacokinetics for new drug discovery,[25-28] we envisaged that the same strategy might work if a fluoroalkylated secondary benzylic bromide was allowed to react with lithium organoborate. One main problem for the transition-metal catalyzed coupling reactions of fluoroalkylated secondary benzylic bromides is the fluoride elimination from the fluoroalkylated secondary benzylic metal species if the subsequent transmetalation step is too slow.[29-30]

The key for the success of such a coupling reaction, therefore, is to accelerate the transmetalation step. Herein, we report a nickel-catalyzed highly enantioselective coupling reaction for the construction of the optically active fluoroalkylated benzhydryl derivatives from easily available prochiral α-bromobenzyl trifluoro-/difluoro-/monofluoromethanes and lithium organoborate. The presence of $ZnBr_2$ played a key role in promote the reaction by formation of a highly reactive zincate $[Ph_2ZnBr]Li$, which facilitates the transmetallation step of the nickel-catalyzed cross-coupling reaction.

RESULTS

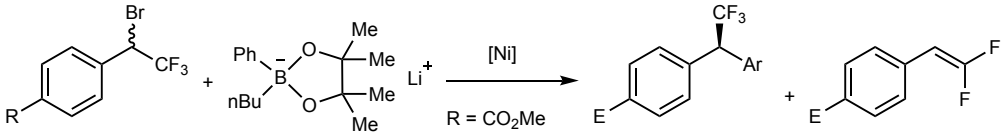
Screening of reaction conditions. Initially, we tried the reaction of prochiral trifluoromethylated benzylic bromide **1a** and lithium organoborate **2a** as a model reaction to optimize the reaction conditions. Surprisingly, the reaction did not take place at all when it was conducted in THF at 0 ^oC for 8.0 h using a combination of 20 mol% $NiBr_2$•DME and 25 mol% **L1** as the catalyst, which is the condition for the construction of trifluoromethoxylated stereogenic center (Eq 1). Notably, when 1.0 equivalent of $ZnBr_2$ was used as additive, the reaction occurred after 8 h at 0 ^oC to afford the coupled product in 65% yield with 85:15 e.r. (Eq 1). As a comparison, we studied the reaction of other nucleophiles such as Grignard reagent phenylmagnesium bromide or phenyl zinc bromide. As summarized in equation 2-3, reaction of substrate **1a** with phenyl magnesium bromide, under the identical conditions, mainly afforded the undesired defluorinated side product in 51% yield, while the reaction of

substrate **1a** with phenyl zinc bromide were slow and the formation of the coupled product was not observed.

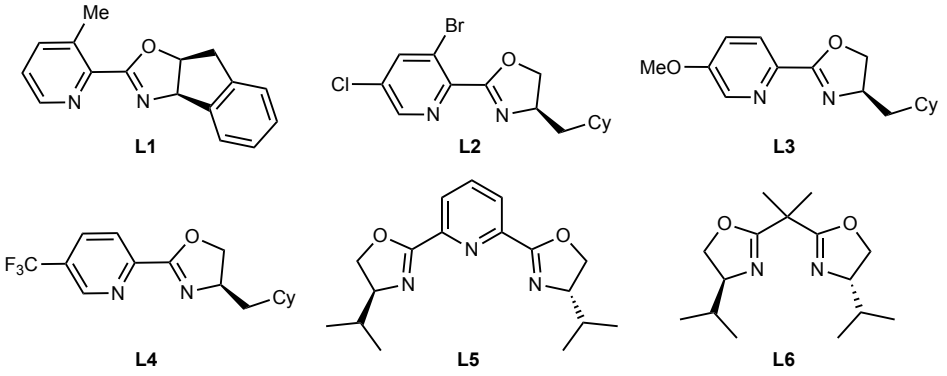


A quick further survey of the reaction conditions disclosed that a combination of $NiBr_2$•DME with ligand **L2** was the most efficient catalyst and the desired product **3a** was obtained in 62% yield with 95.5:4.5 e.r. along with the undesired defluorinated side product **3a'** in 5% yield when the reaction was conduct at -15 °C for 12 h (Scheme 2, entry 1). Switching the additive to $ZnCl_2$ gave slightly inferior results, while using $MgBr_2$ as additive was not effective at all (Scheme 2, entries 2-3). Further studied showed that reactions in DME or diglyme occurred in good yields with high enantioselectivity, while reactions in other solvents such as THF, DMA or DMF were less effective and reaction in toluene was completely shut down (Scheme 2, entries 4-8). Notably, using a combinaiton of DME/diglyme (v/v = 1/1) as the solvent gave slightly improved yield and enantioselectivity (Scheme 2, entry 9). The amount of $ZnBr_2$ was

Scheme 1. Optimization of the conditions for nickel-catalyzed asymmetric coupling of α-bromo-4-methoxycarbonylbenzyl trifluoromethyl 1a with lithium borate 2.[a,b]



entry	[Ni]	ligand	additive	solvent	temp (°C)	yield (%) 3	yield (%) 3'	e.r.
1	$NiBr_2$•DME	**L2**	$ZnBr_2$	DME	-15	62	5	95.5:4.5
2	$NiBr_2$•DME	**L2**	$ZnCl_2$	DME	-15	54	8	95:5
3	$NiBr_2$•DME	**L2**	$MgBr_2$	DME	-15	0	0	-
4	$NiBr_2$•DME	**L2**	$ZnBr_2$	diglyme	-15	78	0	95:5
5	$NiBr_2$•DME	**L2**	$ZnBr_2$	THF	-15	50	28	94.5:5.5
6	$NiBr_2$•DME	**L2**	$ZnBr_2$	toluene	-15	0	-	-
7	$NiBr_2$•DME	**L2**	$ZnBr_2$	DMA	-15	47	6	93:7
8	$NiBr_2$•DME	**L2**	$ZnBr_2$	DMF	-15	30	6	93:7
9	$NiBr_2$•DME	**L2**	$ZnBr_2$	DME/diglyme	-15	80	0	96:4
10	$NiBr_2$•DME	**L2**	$ZnBr_2$	DME/diglyme	rt	75	15	94:6
11	$NiBr_2$•DME	**L2**	$ZnBr_2$	DME/diglyme	-15	32	5	95.5:4.5 [c]
12	$NiBr_2$•DME	**L2**	$ZnBr_2$	DME/diglyme	-15	75	2	95.5:4.5 [d]
13	$NiCl_2$•DME	**L2**	$ZnBr_2$	DME/diglyme	-15	70	9	95.5:4.5
14	$Ni(OAc)_2$	**L2**	$ZnBr_2$	DME/diglyme	-15	71	6	96:4
15	$NiBr_2$•DME	**L1**	$ZnBr_2$	DME/diglyme	-15	70	15	88:12
16	$NiBr_2$•DME	**L3**	$ZnBr_2$	DME/diglyme	-15	81	0	94:6
17	$NiBr_2$•DME	**L4**	$ZnBr_2$	DME/diglyme	-15	30	50	90:10
18	$NiBr_2$•DME	**L5**	$ZnBr_2$	DME/diglyme	-15	0	0	-
19	$NiBr_2$•DME	**L6**	$ZnBr_2$	DME/diglyme	-15	24	0	58:42



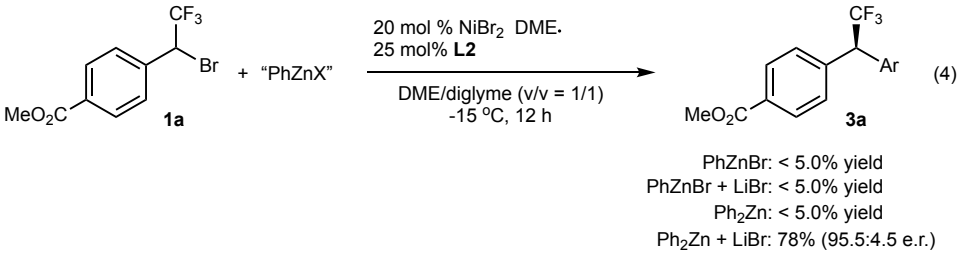
[a]Reaction conditions: compound **1a** (0.1 mmol), **2** (0.3 mmol) under conditions indicated in the scheme; [b]Yields were determined by ^{19}F NMR spectroscopy with trifluorotoluene as an internal standard; [c]0.5 equiv. of $ZnBr_2$ was used; [d]2.0 equiv. of $ZnBr_2$ was used.

also important for the reaction. While the reaction with 2.0 equivalents of $ZnBr_2$ gave comparative yield and enantioselectivity, reaction conducted with 0.5 equivalent of $ZnBr_2$ occurred in much lower yield decreased although the

enantioselectivity was high (Scheme 1, entries 11-12). We next studied the effect of different nickel precursors and ligands. It was found that reaction using different nickel precursors such as $NiCl_2$•DME or $Ni(OAc)_2$ had little effect on the efficiency of the reaction. Yet, the choice of the ligand plays a key role in delivering the high yields and high enantioselectivity. Pyridine-oxazoline ligand with either an electron-donating group (-OMe) or an electron-withdrawing group (-CF_3) at 5-position, as well as a methyl group at 3-position of the pyridyl moiety were less effective (Scheme 1, entries 13-17). Likewise, two commonly used dinitrogen ligands for nickel-catalyzed asymmetric coupling reaction were also ineffective under these conditions (Scheme 1, entries 18-19).

Mechanistic investigation. During the optimization of the reaction conditions, it was found that addition of 1.0 equivalent of $ZnBr_2$ dramatically accelerated the reaction rate. Presumptively, mixing lithium aryl borate with $ZnBr_2$ might generate several different arylated zinc species that could accelerate the transmetallation step and the overall catalytic reaction. To probe which arylated zinc species was involved in the reaction, we did several control experiments (Eq 4). First, reaction of compound **1a** with 3.0 equivalents of PhZnBr in the presence/absence of 3.0 equivalents of LiBr occurred under standard conditions in less than 5% yield of the coupled product. Likewise, reaction of compound **1a** with 3.0 equivalents of Ph_2Zn, again, gave the desired product in less than 5% yield. These results clearly excluded the

possibility of the involvement of PhZnBr and Ph_2Zn in the current reaction. Interestingly, addition of 3.0 equivalent of LiBr to the reaction of compound **1a** with Ph_2Zn led to full conversion of the starting material and gave the coupled compound **3a** in 78% yield with 95.5:4.5 e.r. These experimental results suggest that an anionic zincate $[Ph_2ZnBr]^-$ might involve in the reaction, consistent with the observation from Ingleson and co-workers that mixing 2.0 equivalents of lithium aryl borate with $ZnBr_2$ at room temperature generated an anionic $[Ph_xZnBr_y]^-$ (x + y = 3).[31]



To gain more support about the formation of lithium zincate from lithium aryl borate with $ZnBr_2$, we studied and compared the ^{13}C NMR spectra of the species generated from mixing lithium aryl borate with $ZnBr_2$ and Ph_2Zn with LiBr. As shown in Figure 2, mixing equimolar amount of Ph_2Zn with LiBr at room temperature in THF-d8 for 0.5 h cleanly generated $[Ph_2ZnBr]Li$, as evidence by a peak with a chemical shift at 161.0 ppm in ^{13}C NMR spectrum, which corresponds to the *ipso* carbon of the phenyl group in $[Ph_2ZnBr]Li$. Likewise, the same species was formed after 0.5 h at room temperature for the reaction of 3.0 equivalvents of lithium phenyl borate **2a** with $ZnBr_2$. These results clearly suggest anionic arylated zincate $[Ph_2ZnBr]Li$ would facilitate the

transmetallation step, and consequently, accelerates the overall catalytic reaction.

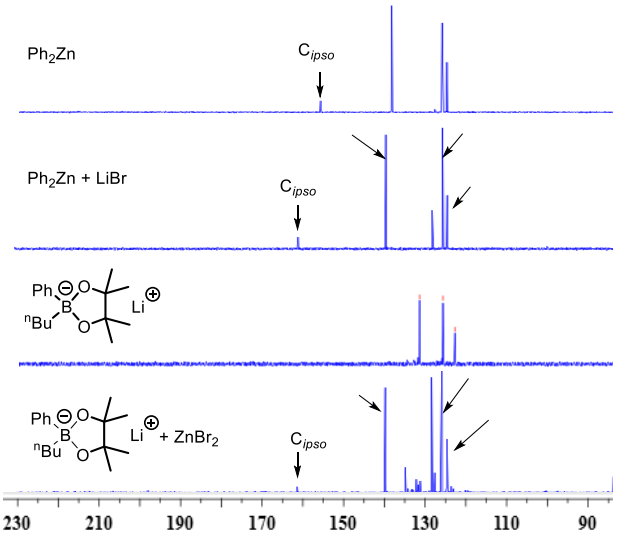
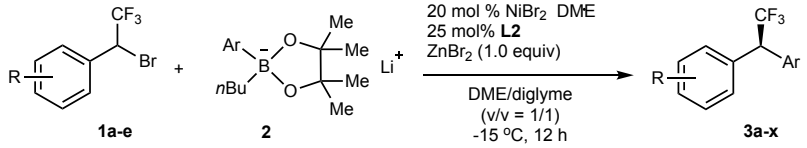


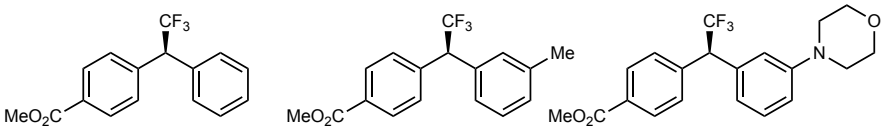
Figure 2. ^{13}C NMR spectra of Ph_2Zn, Ph_2Zn+LiBr, 2a and 2a+$ZnBr_2$ in THF-*d8*.

Substrate Scope Investigation. Having identified the role of $ZnBr_2$, we next investigated the generality of the nickel-catalyzed coupling reaction for the preparation of enantio-enriched benzhydryl trifluoromethane derivatives. As summarized in Scheme 2, in general, lithium aryl borates **2a-f** with different substituted groups reacted smoothly to give the corresponding compounds **3a-f** in good yields and high enantioselectivities. For example, reaction of α-bromo-4-methoxycarbonylbenzyl trifluoromethyl **1a** with lithium aryl borate **2c** occurred under standard conditions in 43% yield with 94:6 e.r. (Scheme 2, 3c). Furthermore, trifluoromethylated benzylic bromides (**1b-e**) with electron-withdrawing substituted groups such as cyano, nitro, trifluoromethyl or trifluoromethoxy group reacted smoothly with lithium phenyl borates 2a to afford the coupled products in high yields and high enantioselectivities

Scheme 2. Scope of nickel-catalyzed asymmetric coupling of α-bromo-benzyl trifluoromethane with lithium aryl borates. [a,b]



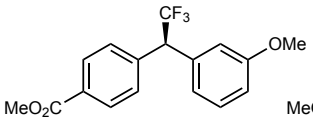
1a-e **2** **3a-x**



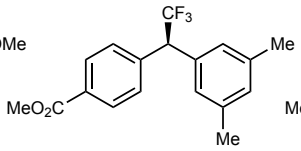
3a, 77% yield
96:4 e.r.

3b, 56% yield
95:5 e.r.

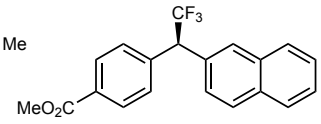
3c, 43% yield
94:6 e.r.



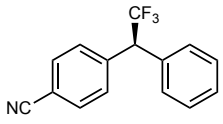
3d, 66% yield
95:5 e.r.



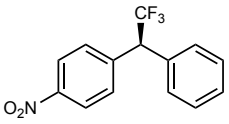
3e, 62% yield
94:6 e.r.



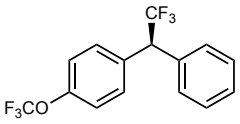
3f, 67% yield
92:8 e.r.



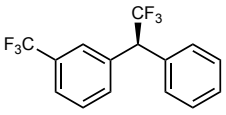
3g, 77% yield
94:6 e.r.



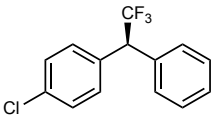
3h, 53% yield
96:4 e.r.



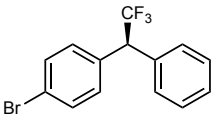
3i, 68% yield
95:5 e.r.



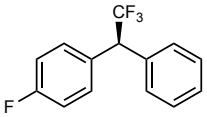
3j, 75% yield
97:3 e.r.



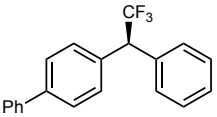
3k, 65% yield
96:4 e.r.



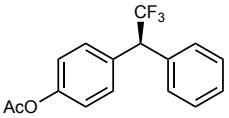
3l, 68% yield
95:5 e.r.



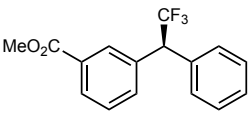
3m, 52% yield
96:4 e.r.



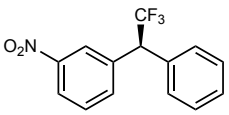
3n, 53% yield
95:5 e.r.



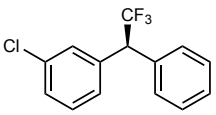
3o, 55% yield
94:6 e.r.



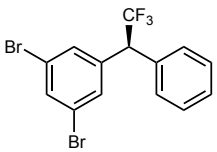
3p, 56% yield
96:4 e.r.



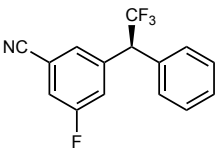
3q, 49% yield
96:4 e.r.



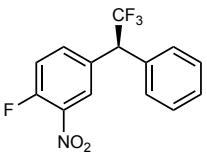
3r, 86% yield
95:5 e.r.



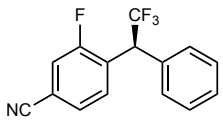
3s, 58% yield
96:4 e.r.



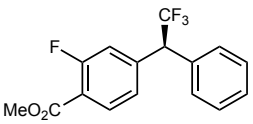
3t, 71% yield
94:6 e.r.



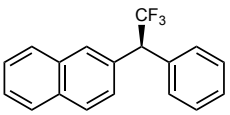
3u, 60% yield
93:7 e.r.



3v, 71% yield
98:2 e.r.



3w, 65% yield
92:8 e.r.



3x, 51% yield
95:5 e.r.

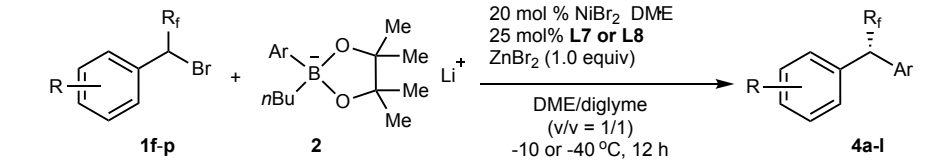
[a]Reaction conditions: compound **1** (0.3 mmol), phenylboronic pinacol ester **2** (0.9 mmol), $NiBr_2$•DME (20 mol%), ligand **L2** (25 mol%) and $ZnBr_2$ (0.3 mmol) in DME/diglyme (v/v = 1/1) at -15 °C for 12 h; [b]Isolated yields.

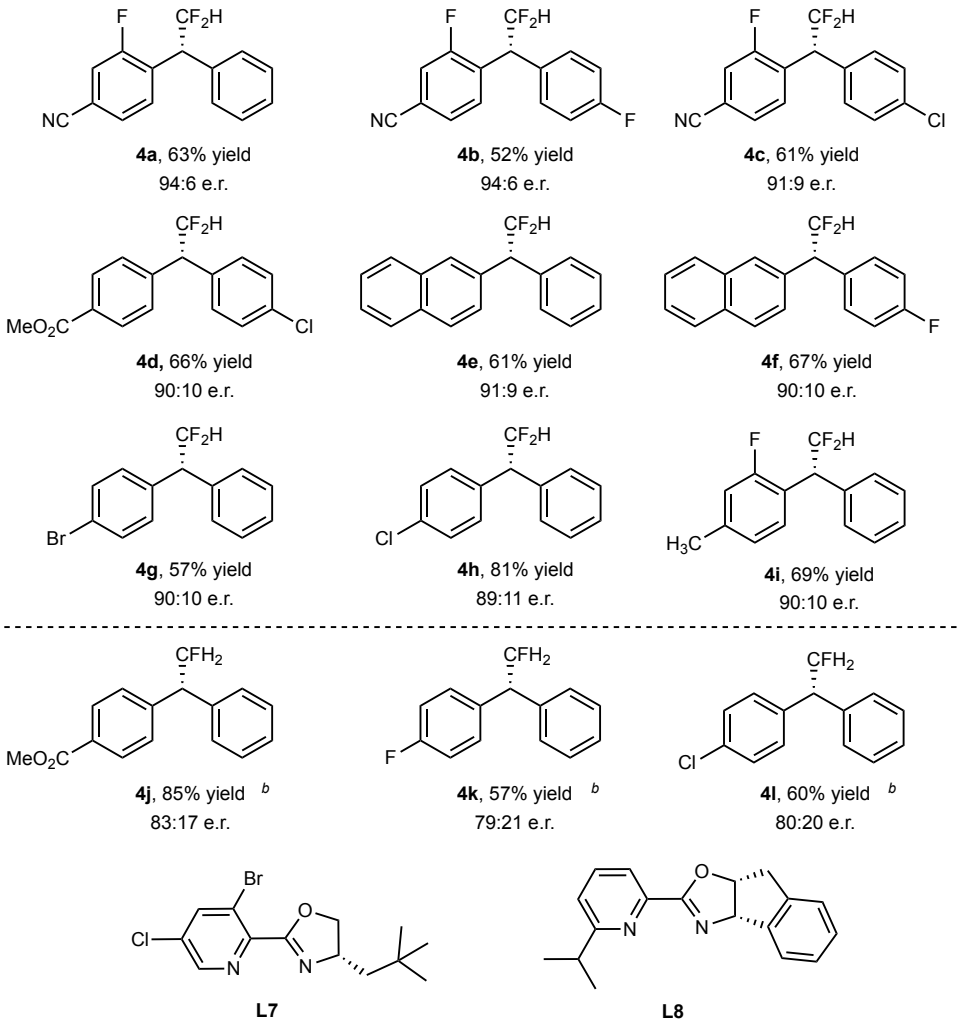
(Scheme 2, **3g-i**). For example, reactions of both α-bromo-4-nitrobenzyl trifluoromethane and α-bromo-3-trifluoromethyl benzyl trifluoromethane with lithium phenyl borates **2a** gave the corresponding products **3h** and **3j** in 53% and 75% yields with excellent enantioselectivities 96:4 and 97:3 e.r., respectively (Scheme 2, **3h, 3j**). Notably, trifluoromethylated benzylic bromides with a halogen group such as chloride, bromide, fluorine, were compatible and reacted with lithium phenyl borates **2a** to give the corresponding products **3k-m** in 65%, 68%, and 52% yields, with 96:4, 95:5 and 96:4 e.r., respectively (Scheme 2, **3k-m**). Furthermore, α-bromobenzyl trifluoromethyl with *para*-, *meta*-, and *ortho*-substituents are all compatible coupling partners, affording the desired products in good yields and high enantioselectivities. For example, both α-bromo-3,5-dibromide benzyl trifluoromethane and α-bromo-2-fluorine-4-cyano benzyl trifluoromethane reacted to afford compounds **3s**, **3v** in 58 and 71% yield with 96:4 and 98:2 e.r., respectively (Scheme 2, **3s**, **3v**). Previously reported method for the preparation of enantio-enriched benzhydryl trifluoromethane derivatives typically required to use optically secondary α-(trifluoromethyl)benzyl tosylates to react with various aryl boronic acids in the presence of a palladium catalyst.[29, 32-37] Thus, the current method provided an alternative, more efficient method to access this family of compounds.

Encouraged by the high enantioselectivity in nickel-catalyzed coupling of α-bromo-benzyl trifluoromethane with lithium aryl borates, we next tried to extend this reaction to other fluoroalkyl substituted benzyl bromides. After a quick screen of the reaction conditions, it was found that when a more sterically-hindered ligand **L7** was used as the ligand and the reaction temperature was decreased to -40 °C, good to excellent enantioselectivities could be achieved (Scheme 2). For example, reactions of 4-(1-bromo-2,2-difluoroethyl)-3-fluorobenzonitrile with lithium phenyl borate **2a** and lithium 4-fluorophenyl borate **2f** occurred smoothly after 12 h to afford the corresponding products in 94:6 e.r. (Scheme 2, **4a**,**b**). Since few methods for the construction of difluoromethyl-substituted stereogenic carbon center have been reported previously,[38-39] the current method represents an attractive approach for the preparation of optically active difluoromethylated benzhydryl derivatives.

On the other hand, reaction of monofluoromethylated substrates were much more challenging. After carefully screening of the combination of nickel salts and ligands, it was found that using a combination of $NiBr_2$•DME with ligand **L8** could catalyze the reactions of 4-(1-bromo-2,2-difluoroethyl)-arenes with lithium phenyl borate **2a** to give the corresponding coupled products 4j-k after 12 h at -10 °C in moderate enantioselectivities (79:21 ~83:17 e.r.).

Scheme 3. Scope of nickel-catalyzed asymmetric Suzuki-coupling of α-bromo-benzyl di-/mono-fluoromethane with lithiun aryl borates. [a,b]





L7 L8

[a]Reaction conditions: compound **1** (0.3 mmol), phenylboronic pinacol ester **2** (0.9 mmol), $NiBr_2$•DME (20 mol%), ligand **L7** or **L8** (25 mol%) and $ZnBr_2$ (0.3 mmol) in DME/diglyme (v/v = 1/1) at -10 or -40 °C for 12 h; [b]Isolated yields.

Synthetic application. To showcase the applicability of the nickel-catalyzed asymmetric coupling reaction of prochiral trifluoromethylated benzylic bromide with lithium organoborate, we applied this protocol for the synthesis of trifluoromethylated mimic of an inhibitor for the histone lysine methyltransferase enhancer of Zeste Homolog 2 (EZH2).[40] As shown in Figure

4, compound **5** was generated in 55% overall yield with 94:6 e.r. via a four-step transformation from easily available α-bromo-4-*tert*-butoxybenzyl trifluoromethane.

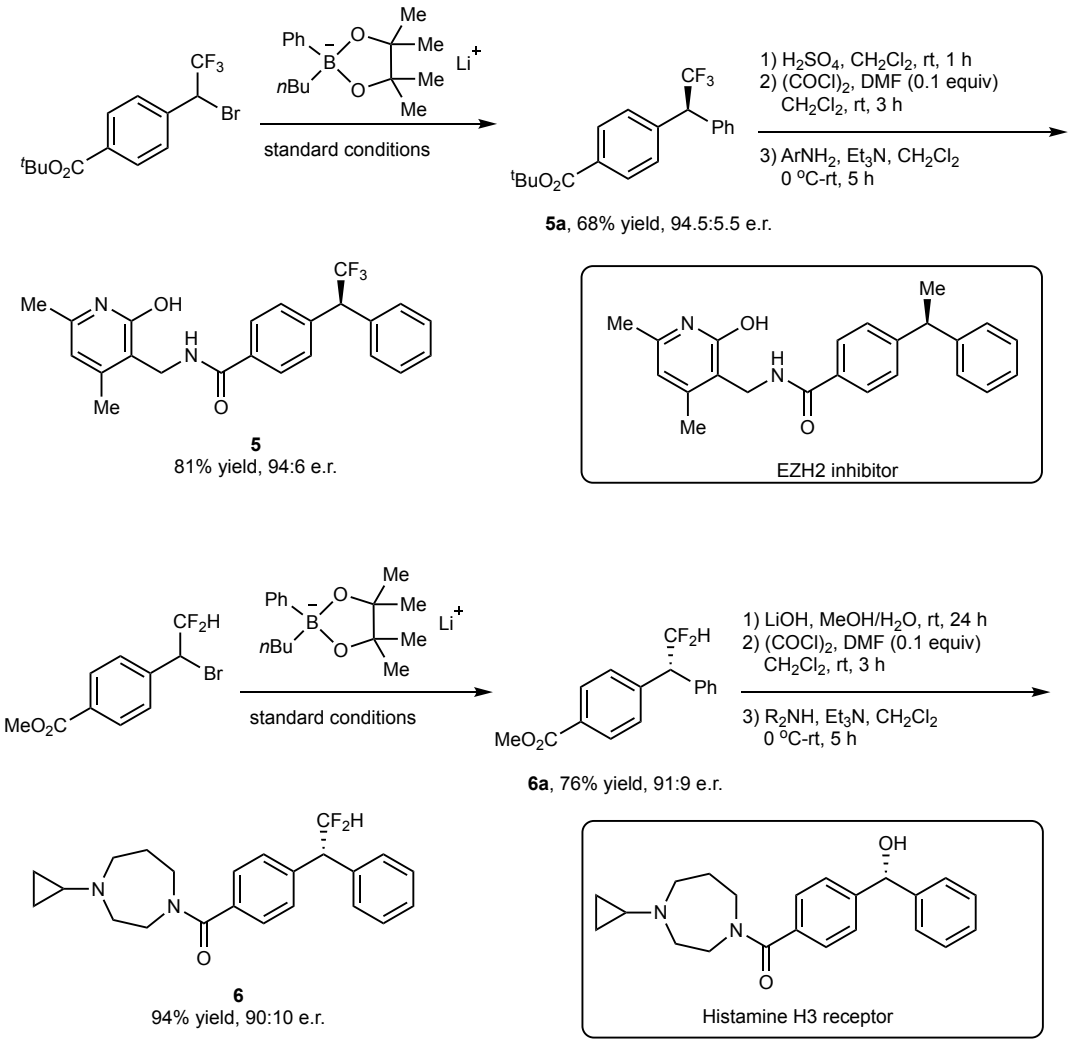


Figure 4. Preparation of trifluoromethylated/difluoromethylated derivatives of drug candidates.

Due to the slightly acidic proton in the difluoromethyl group which allows it to act as a lipophilic hydrogen-bond donor, the difluoromethyl group (CHF_2) was generally considered as a bioisostere for a hydroxy goup (-OH).[41] Replacement of a hydroxy group of a drug molecule with a

difluoromethyl group may result in a Me-too or Me-better drug molecule. Consequently, a difluoromethylated compound **6**, which is a mimic of histamine H3 receptor,[42] was synthesized in 71% overall yield and 90:10 e.r. after four steps.

CONCLUSION

In summary, we developed a highly enantioselective nickel-catalyzed coupling of easily available α-bromobenzyl fluooalkanes with a variety of lithium aryl borates in the presence of stiochiometric amount of $ZnBr_2$. Preliminary mechanistic studies disclosed that a highly reactive zincate $[Ph_2ZnBr]Li$ is generated, which facilitates the transmetallation step of the nickel-catalyzed cross-coupling reaction. Thus, the protocol may serve as a versatile, efficient, and convenient approach for the rapid access of chiral benzhydryl fluoroalkane derivatives. The application of the high reactive lithium aryl zincate $[Ar_2ZnBr]Li$ in other transition metal-catalyzed cross-coupling reactions are undergoing currently in our laboratory.

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