

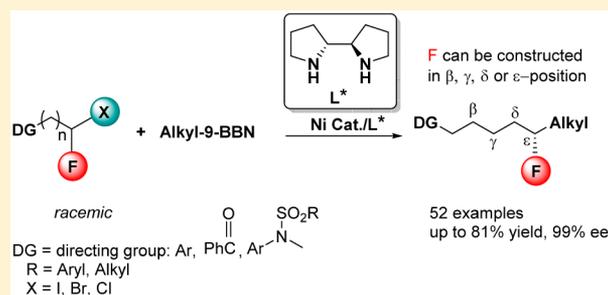
Enantioselective Suzuki Cross-Couplings of Unactivated 1-Fluoro-1-haloalkanes: Synthesis of Chiral β -, γ -, δ -, and ϵ -Fluoroalkanes

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S Supporting Information

ABSTRACT: The incorporation of fluorine atom into a stereogenic center is a highly challenging transformation with current methodologies offering access mainly to chiral α - and β -fluoroalkanes. In this article, the development of a novel general approach to construct β -, γ -, δ -, and ϵ -fluoroalkanes with good enantioselectivity is described. Different directing groups, such as benzyl, ketone, and sulfonyl, were shown to give good enantioselectivity under Suzuki cross-coupling conditions in the presence of a Ni catalyst and chiral diamine ligand. It includes the first examples of enantioselective synthesis of chiral fluorine-containing centers at as distant as δ or ϵ positions from the functional groups.

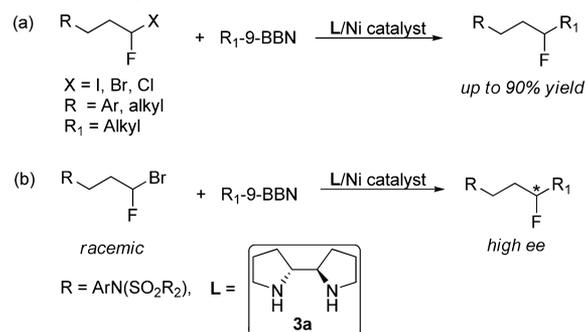


INTRODUCTION

Organic compounds bearing fluorine substituents have found wide and important applications in medicinal, pharmaceutical, and agricultural chemistries.^{1,2} Therefore, selective fluorination of organic molecules has rapidly become a field of great synthetic interest. Despite the existence of a number of synthetic strategies for the preparation of fluoroorganic compounds,³ the enantioselective construction of stereogenic centers bearing a fluorine substituent remains a challenging task in organic chemistry. Most of the advances have been described for the enantioselective fluorination of the position α to a carbonyl or other functional group (i.e., phenyl, alkene, enamine, hydroxyl).^{4–10} Reports describing enantioselective generation of chiral F-containing centers at nonactivated more distant positions are extremely rare.¹¹ To the best of our knowledge, no *general* efficient approach has been discovered for the formation of enantioenriched CHF-bearing stereocenters at the selected β , γ , δ , or even ϵ positions.

Recently, we developed an efficient and straightforward synthesis of geminal dihaloalkanes from carboxylic acids and initiated an active program on studies of these polyfunctional compounds in cross-coupling reactions.^{12,13} Thus, we discovered that 1-halo-1-fluoroalkanes are suitable electrophiles for selective and facile Suzuki cross-coupling reactions to produce secondary fluoroalkanes in excellent yields¹³ (Scheme 1a). This approach allows for selective installation of the fluorine substituent in a distant, unactivated position of the alkane chain. Importantly, we demonstrated the feasibility of extending this method to its asymmetric version once a suitable chiral catalyst is identified. We demonstrated that the racemic mixture of 1-bromo-1-fluoroalkanes bearing a *sulfonamide* moiety (Scheme 1b) can be converted to enantiomerically enriched alkyl fluorides upon stereoconvergent Suzuki cross-coupling.

Scheme 1. Synthesis of Secondary Fluoroalkanes via Suzuki Cross-Coupling of 1-Fluoro-1-haloalkanes



Employment of a Ni salt and chiral ligand **3a** provided high enantioselectivity, albeit with modest yields.

Herein, we disclose our extended, comprehensive studies on *enantioselective* synthesis of nonactivated secondary fluoroalkanes by alkyl–alkyl Suzuki cross-couplings of geminal 1-halo-1-fluoroalkanes. We demonstrate that racemic 1-halo-1-fluoroalkanes bearing phenyl, keto, or sulfonamide substituents (as the directing groups) at various distant positions can efficiently participate in stereoconvergent enantioselective Suzuki reactions with alkylboranes. It establishes, for the first time, a universal efficient method for enantioselective construction of linear secondary fluoroalkanes bearing an F-containing stereocenter at β , γ , δ , and even ϵ positions from the functional group. The same chiral ligand (**3a**), which has been identified by us as an effective ligand for this type of reaction,

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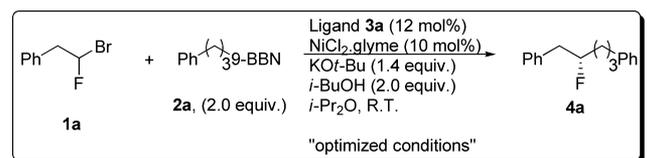
provides chiral recognition to the wide scope of substrates.¹⁴ Interestingly, employing haloalkanes wherein a keto directing group is responsible for ensuring an enantioselective cross-coupling has not previously been demonstrated. In addition, asymmetric cross-coupling reactions of alkyl halides bearing the directing groups at as distant as δ or even ϵ positions from the reaction center, as well as incorporation of a chiral CHF center at such distant positions, are largely unprecedented.¹⁵

RESULTS AND DISCUSSION

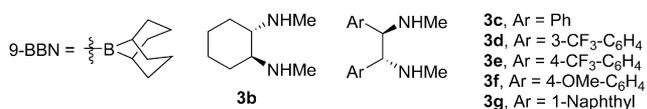
Recently, Fu et al. reported the first asymmetric Suzuki cross-coupling of unactivated secondary alkyl halides with organoboranes.^{15,16} In this seminal work, it was demonstrated that a functional group (e.g., phenyl, aniline, amide, carbamate, sulfonamide), usually located in the β or γ position from the reaction center of electrophiles, is necessary for ensuring good enantioselectivity, most likely due to a weak secondary interaction with the catalyst.

On the basis of these findings, we first investigated an enantioselective cross-coupling reaction of 1-bromo-1-fluoro-2-arylethanes with alkylboranes in order to generate fluoroalkanes bearing chiral F-containing centers β to the aryl unit. A representative example, cross-coupling of bromo(fluoro)alkane **1a** with alkyl-9-BBN **2a**, and its optimization studies are shown in Table 1. Most strikingly, we found that chiral ligands **3c** and **3d**, previously utilized in efficient enantioselective alkyl-alkyl Suzuki reaction of secondary alkyl halides,¹⁶ as well as their structural analogs **3e–g** proved inappropriate for geminal

Table 1. Optimization of Conditions for Enantioselective Cross-Coupling of 1-Bromo-1-fluoro-2-arylethane



Entry ^a	Variation from the "optimized conditions"	Yield (%) ^b	Ee (%)
1	none	76	99
2	no NiCl ₂ .diglyme	trace	-
3	no Ligand 3a	trace	-
4	no <i>i</i> -BuOH	trace	-
5	NiBr ₂ .diglyme instead of NiCl ₂ .diglyme	67	83
6	<i>n</i> -Hexanol instead of <i>i</i> -BuOH	72	86
7	45°C instead of R.T.	60	81
8	6 mol% NiCl ₂ .diglyme, 8 mol% Ligand 3a	56	82
9	PhMe instead of <i>i</i> -Pr ₂ O	53	73
10	Dioxane instead of <i>i</i> -Pr ₂ O	64	66
11	Hexane/Et ₂ O (1/1) instead of <i>i</i> -Pr ₂ O	57	80
12	3b instead of 3a	71	36
13	3c instead of 3a	80	-23
14	3d instead of 3a	78	-19
15	3e instead of 3a	75	-16
16	3f instead of 3a	77	-21
17	3g instead of 3a	74	-24

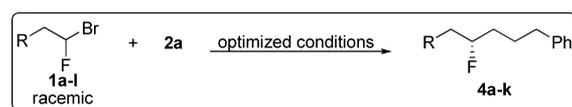


^aReactions were carried out with substrate **1a** (0.1 mmol), 9-BBN partner **2a** (0.2 mmol), Ni salt (0.12 mmol), ligand **3a** (0.16 mmol), KO^t-Bu (0.14 mmol), and *i*-BuOH (0.2 mmol) in *i*-Pr₂O (2 mL).
^bYields are isolated yields after chromatography.

bromo(fluoro)alkane substrates; all of them provided low enantioselectivity in the tested reaction (entries 12–17). After examination of different amine ligands, we were gratified to discover that employing (*R,R*)-2,2'-bispyrrolidine (ligand **3a**) in the presence of NiCl₂.glyme leads to formation of fluoroalkane **4a** in 76% isolated yield and 99% ee (entry 1). Any modifications of these reaction conditions led to deteriorated results. Thus, essentially no coupling product was obtained when the Ni salt, ligand, or *i*-BuOH is absent (entries 2–4). NiCl₂.glyme performs somewhat better compared to NiBr₂.diglyme under the optimized conditions (compare entries 1 and 5). Replacement of isobutanol with *n*-hexanol leads to lower enantioselectivity (entry 6). Carrying out the reaction at elevated temperature reduces both yield and ee (entry 7). Lower loadings of Ni salt and ligand provide inferior results (entry 8). Isopropyl ether proved superior in comparison to other examined solvents (entries 9–11).

Having these optimized conditions in hand, we explored numerous 1-bromo-1-fluoro-2-arylethanes in this reaction (Table 2). When the aryl group is a nonsubstituted phenyl or

Table 2. Scope of 1-Bromo-1-fluoroalkane Substrates Bearing Benzylic Directing Group



entry	R	product	yield, ee (%) ^b
1	Ph	1a	4a , 79, 99
2	2-naphthyl	1b	4b , 72, 90
3	3-OMe-C ₆ H ₄	1c	4c , 67, 98
4	4-OMe-C ₆ H ₄	1d	4d , 73, 50
5	4-CF ₃ -C ₆ H ₄	1e	4e , 66, 85
6	2-F-C ₆ H ₄	1f	4f , 71, 62
7	3-F-C ₆ H ₄	1g	4g , 68, 75
8	4-F-C ₆ H ₄	1h	4h , 69, 67
9	2-Me-C ₆ H ₄	1i	4i , 80, 57
10	3-Me-C ₆ H ₄	1j	4j , 66, 61
11	Bn	1k	4k , 67, 44

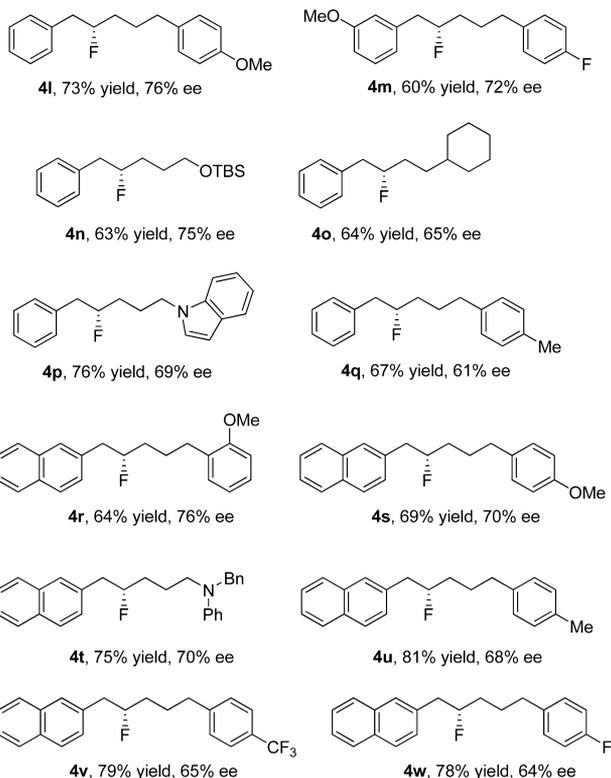
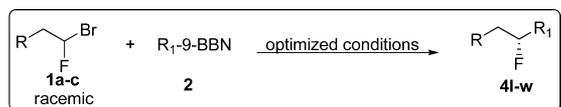
^aReactions were conducted with **1** (0.3 mmol), **2b** (0.6 mmol), Ni salt (0.03 mmol), **3a** (0.036 mmol), KO^t-Bu (0.42 mmol), and *i*-BuOH (0.6 mmol) in *i*-Pr₂O (6 mL).
^bYields are isolated yields after chromatography.

naphthyl ring highly enantioenriched products are obtained (entries 1 and 2). Interestingly, substitution of the phenyl ring in substrates **1** at the meta position with electronically different groups provides homobenzylic fluorides in good to excellent enantioselectivity (entries 3 and 7). However, the asymmetric induction for the corresponding para-substituted substrates is more variable (entries 4, 5, and 8).

An additional methylene group between the phenyl unit and the reaction center substantially decreases the ee value to 44% (substrate **1k**, entry 11), supporting the hypothetical importance of a secondary interaction between the catalyst and the CH₂Ar substituent for high enantiodiscrimination.^{16a}

We also examined the scope of this asymmetric cross-coupling of 1-bromo-1-fluoro-2-arylethane with respect to the nucleophile. As illustrated in Table 3, the broad range of 9-BBN-based alkyl nucleophiles bearing structural motifs such as aryls (with both electron-donating and -withdrawing substituents), heterocycles, ethers, and amines are compatible with

Table 3. Scope of Alkyl 9-BBN Coupling Partners



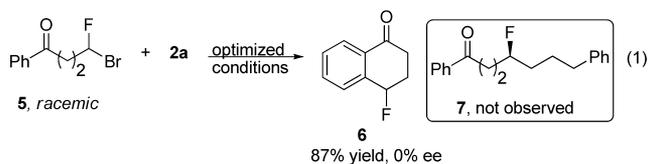
^aReactions were conducted with **1** (0.3 mmol), **2** (0.6 mmol), Ni salt (0.03 mmol), **3a** (0.036 mmol), KO^t-Bu (0.42 mmol), and *i*-BuOH (0.6 mmol) in *i*-Pr₂O (6 mL). ^bYields are isolated yields after chromatography.

this asymmetric cross-coupling and furnish the desired chiral fluoroalkanes in generally good yields and enantioselectivities (on average, 70% ee).

In order to conceptually expand the substrate scope of the geminal bromo(fluoro)alkane electrophiles, we sought additional functional elements that might serve as potential directing groups for enantioselective recognition. We selected a keto group as this motif is ubiquitous in valuable organic compounds or, alternatively, can be converted to a wide variety of other functionalities. Notably, while the carbonyl-containing functional groups amide and carbamate have been used as directing groups in the Suzuki reaction of secondary alkyl halides to generate all-carbon tertiary chiral centers,^{16c} employing ketone functionality is yet unreported in stereoconvergent alkyl-alkyl couplings.

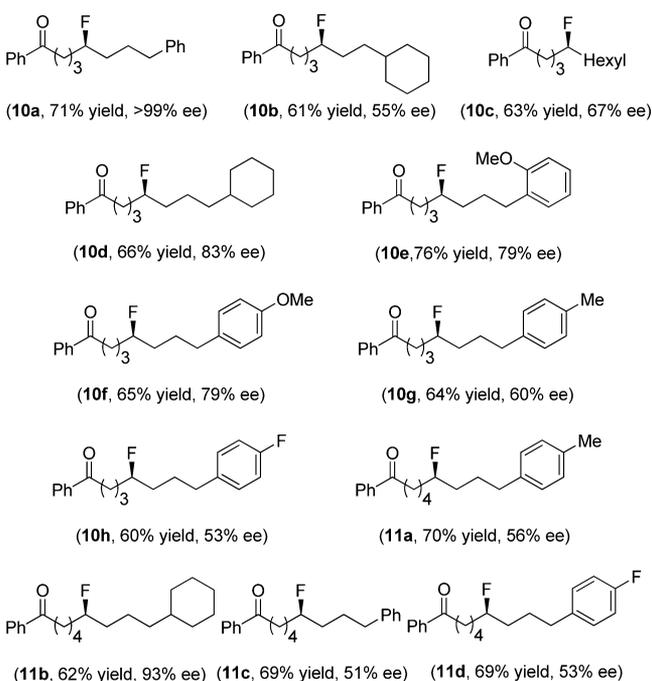
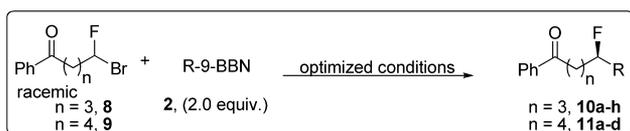
Interestingly, when 1-bromo-1-fluoro-3-phenylpropyl ketone **5** was subjected to the standard coupling reaction, no desired γ -fluoroketone **7** was observed. Instead, an intramolecular 6-membered cyclization took place to furnish a C-H-functionalized fluorinated product **6** in high yield, albeit as a racemic mixture (eq 1). This interesting reaction is being investigated, and the results will be reported elsewhere.

Gratifyingly, introducing one more methylene unit between the carbonyl group and the reaction center gave the desired results, namely, cross-coupling of 1-bromo-1-fluoro-4-phenyl-



propyl ketone **8** with alkyl-9-BBN results in enantioenriched δ -fluoroketones **10** possessing stereogenic CHF center (Table 4).

Table 4. Enantioselective Suzuki Cross-Coupling of 1-Bromo-1-fluoroalkanes Bearing Ketone as a Directing Group



^aReactions were carried out with substrate **8** or **9** (0.2 mmol), 9-BBN partner **2** (0.4 mmol), Ni salt (0.24 mmol), ligand **3a** (0.32 mmol), KO^t-Bu (0.28 mmol), and *i*-BuOH (0.4 mmol) in *i*-Pr₂O (4 mmol). ^bYields are isolated yields after chromatography.

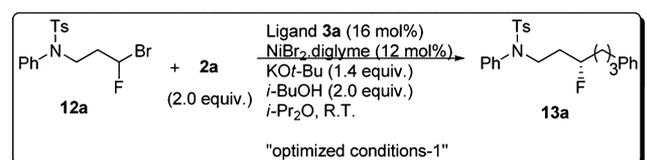
We used the same catalyst system (NiCl₂/ligand **3a**) and reaction conditions that were developed for homobenzylic electrophiles **1**. The process is sensitive to the stereoelectronic parameters of the nucleophilic alkyl moiety: while some alkyl 9-BBN lead to high ee values (79–99% ee, examples **10a**, **10d**, **10e**, and **10f**), others give moderately enantioenriched products (**10b**, **10c**, **10g**, and **10h**).

Remarkably, the keto group can be located even five carbons away from the reaction center, and chiral recognition still occurs. Thus, we were pleased to find that ϵ -bromo(fluoro)-ketones **9** can undergo asymmetric Suzuki coupling under our standard conditions to give a chiral ϵ -fluoroketone with moderate to excellent enantioselectivity (Table 4, **11a–d**). Examples of alkyl electrophiles bearing a directing group at a distance of four or five carbons away from the reaction center and which are nevertheless able to deliver an appreciable enantiodiscrimination in cross-coupling reactions are largely

unreported. Most importantly, enantioselective installation of the fluorine substituent at such distant positions from any functional group to result in chiral δ - and ε -fluoroalkanes, to the best of our knowledge, is unprecedented.

Our further investigations focused on introduction of a sulfonamide directing group to the geminal bromo(fluoro)-alkane substrates for stereoconvergent Suzuki coupling. Since sulfonamides are a potent structural motif for development of antibacterial,¹⁷ antitumor,¹⁸ and anti-HIV¹⁹ agents, the resulting selectively fluorinated chiral sulfonamides could be of significant interest to biomedical research. When 1-bromo-1-fluoro-3-sulfonamide **12a** was subjected to the coupling reaction with alkylborane **2a** under similar conditions that were developed for aforementioned geminal dihaloelectrophiles (**1**, **8**, and **9**) the desired γ -fluoroalkane **13a** was obtained in 27% yield and 79% ee. Optimization studies slightly improved the outcome of this process (Table 5). The most striking

Table 5. Enantioselective Suzuki Cross-Coupling of 1-Bromo-1-fluoroalkanes Bearing Sulfonamide Directing Group



entry ^a	variation from the "optimized conditions-1"	yield (%) ^b	ee (%)
1	none	35	83
2	no NiBr ₂ ·diglyme	trace	
3	no ligand 3a	trace	
4	no <i>i</i> -BuOH	trace	
5	NiCl ₂ ·glyme instead of NiBr ₂ ·diglyme	27	79
6	<i>n</i> -hexanol instead of <i>i</i> -BuOH	24	78
7	45 °C instead of room temperature	trace	
8	10 mol % NiBr ₂ ·diglyme, 12 mol % ligand 3a	22	80
9	PhMe instead of <i>i</i> -Pr ₂ O	30	73
10	dioxane instead of <i>i</i> -Pr ₂ O	19	58
11	hexane/Et ₂ O instead of <i>i</i> -Pr ₂ O	30	80
12	3b instead of 3a	16	36
13	3c instead of 3a	67	-45
14	3d instead of 3a	68	-31
15	3e instead of 3a	64	-41
16	3f instead of 3a	61	-46
17	3g instead of 3a	69	-21

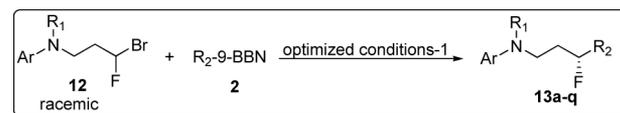
^aReactions were carried out with substrate **12a** (0.1 mmol), 9-BBN partner **2** (0.2 mmol), Ni salt (0.12 mmol), ligand **3a** (0.16 mmol), KOt-Bu (0.14 mmol), and *i*-BuOH (0.2 mmol) in *i*-Pr₂O (2 mL).

^bYields are isolated yields after chromatography.

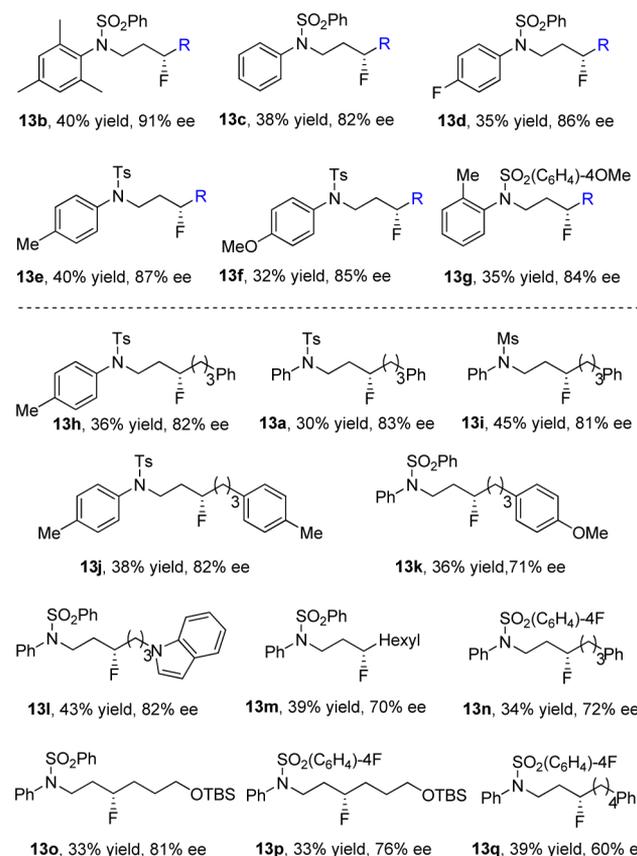
conclusions from these optimization studies are (a) NiBr₂·diglyme outperforms NiCl₂·diglyme for this type of electrophile, providing **13a** in 35% yield and 83% ee (entry 1), and (b) ligand **3a** proved superior also for sulfonamide-decorated geminal bromo(fluoro)alkanes; although other tested secondary diamine ligands **3b–g** can substantially improve yield, they provide the product with low enantioselectivity (entries 12–17). As anticipated, in the absence of Ni salt, ligand **3a**, or *i*-BuOH the coupling product is not formed (entries 2–4). In addition, performing the reaction at elevated temperature resulted in only trace amounts of **13a** (entry 7).

The optimized conditions proved general for the synthesis of a wide variety of chiral γ -fluoroalkanes bearing a sulfonamide moiety in high enantioselectivity, albeit with moderate yield (Table 6). The reaction tolerates varied substitutions of both

Table 6. Scope of Cross-Coupling Reaction of 1-Bromo-1-fluoroalkanes Bearing Sulfonamide Directing Group



R = 2-OMeC₆H₄(CH₂)₃



^aReactions were carried out with substrate **12** (0.2 mmol), 9-BBN partner **2** (0.4 mmol), Ni salt (0.24 mmol), ligand **3a** (0.32 mmol), KOt-Bu (0.28 mmol), and *i*-BuOH (0.4 mmol) in *i*-Pr₂O (4 mL).

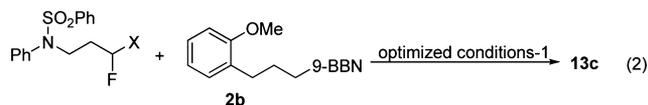
^bYields are isolated yields after chromatography.

the *N*-aryl and the *N*-sulfonyl moieties of the amine group in the racemic electrophile **12** as well as a variety of alkyl-9-BBN nucleophiles to provide product **13** with generally high ee values (up to 91% ee).

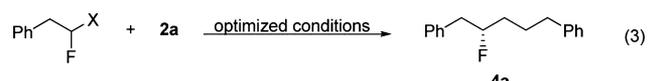
We found that the unreacted substrate **12** (recovered after reaction) is racemic. It rules out a kinetic resolution mechanism, although the yields are below 50%. The moderate yield in the stereoconvergent C–C coupling of **12** with **2** could conceivably be the result of a relatively strong interaction between the catalyst and the sulfonamide moiety, which inhibits the catalytic cycle. Further ligand modifications are apparently required in order to improve the yield of this particular reaction.

It should be mentioned that racemic 1-iodo-1-fluoro-alkanes and 1-chloro-1-fluoroalkanes bearing phenyl, ketone, or

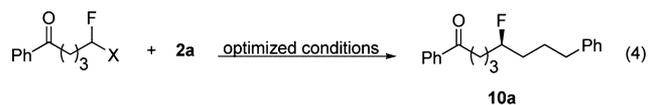
sulfonamide directing groups can also be employed in the developed asymmetric Suzuki reaction to produce the corresponding chiral secondary fluoroalkanes with good ee; however, the analogous 1-bromo-1-fluoroalkanes gave better results in terms of yield and enantioselectivity under the same conditions (eqs 2–4). We presume that the inferior results



X	yield (%)	ee(%)
I	30	75
Br	38	82
Cl	20	74



X	yield (%)	ee(%)
I	66	85
Br	79	99
Cl	54	83



X	yield (%)	ee(%)
Br	71	>99
Cl	37	89

observed for 1-iodo-1-fluoroalkanes, compared to their 1-bromo-1-fluoro counterparts, may be due to the comparative instability of the former. This may lead to release of trace amounts of iodine in the starting material that partially poisons the Ni catalyst.¹³ In the case of the 1-chloro-1-fluoroalkanes, the difficulty of cleaving the stronger C–Cl bond may account for the slightly poorer results.

CONCLUSIONS

We established a novel general method for efficient catalytic preparation of β -, γ -, δ -, and ϵ -fluoroalkanes bearing a distant chiral CHF center at the selected position.²⁰ It includes the first examples of enantioselective synthesis of chiral fluorine-containing centers at as distant as δ or ϵ positions from the directing functional groups. Our approach is general in a sense that the generation of a F-bearing stereogenic center at all these positions implies the same strategy, namely, a stereoconvergent cross-coupling of the corresponding racemic 1-halo-1-fluoroalkanes with alkylboranes. Moreover, the same commercially available chiral ligand, which was identified by us for the asymmetric cross-couplings of geminal dihaloalkanes, is used in all cases. We demonstrated that phenyl, keto (for the first time), or sulfonamide substituents can be used as directing groups for chiral recognition in the alkyl–alkyl cross-couplings to generate unactivated fluoroalkanes with good enantioselectivity. Although our approach opened a door for unprecedented synthesis of chiral fluoroalkanes with distant chiral CHF centers, the yield or enantioselectivity is moderate in some cases. Therefore, further studies on ligand design for the improvement of both efficiency and substrate scope of this reaction is underway in our laboratories.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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