

# Efficient Synthesis of Secondary Alkyl Fluorides via Suzuki Cross-Coupling Reaction of 1-Halo-1-fluoroalkanes

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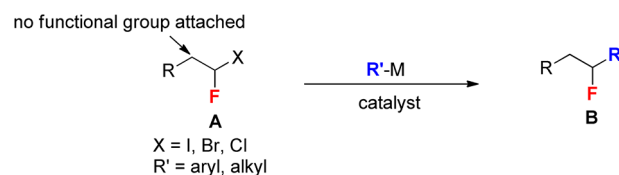
**S** Supporting Information

**ABSTRACT:** Organofluorine compounds have found extensive applications in various areas of science. Consequently, the development of new efficient and selective methods for their synthesis is an important goal in organic chemistry. Here, we present the first Suzuki cross-coupling reaction which utilizes dihalo compounds for the preparation of secondary alkyl fluorides. Namely, an unprecedented use of simple 1-halo-1-fluoroalkanes as electrophiles in  $C_{sp^3}-C_{sp^3}$  and  $C_{sp^3}-C_{sp^2}$  cross-couplings allows for the formal site-selective incorporation of F-group in the alkyl chain with no adjacent activating functional groups. Highly effective approach to the electrophilic substrates, 1-halo-1-fluoroalkanes, via iododecarboxylation of the corresponding  $\alpha$ -fluorocarboxylic acids is also presented. The conceptually new route to organofluorides was used for the facile preparation of biomedically valuable compounds. In addition, we demonstrated that an asymmetric version of the developed reaction for the stereoconvergent synthesis of chiral secondary alkyl fluorides is feasible.

Organofluorine compounds have found substantial applications in various areas of chemistry.<sup>1</sup> Especially, the ability of a fluorine-substituent to change the dipole moment, enhance metabolic stability, and improve target-binding affinity of a compound has made organic fluorides extremely important tools in drug discovery and biomedical investigations.<sup>2</sup> As such, considerable efforts have been directed toward the development of efficient synthetic strategies to prepare organofluorine compounds.<sup>3</sup> Notwithstanding, site-selective and general approaches to the preparation of aliphatic C-F bonds remain challenging. Although some approaches to secondary alkyl fluorides exist, the majority depends on specific reactivity enabling functional groups such as ketone, ester, nitrile, olefin for introduction of the fluoride substituent.<sup>3,4</sup> A general and effective method for the site-selective incorporation of F-group at any desired position in an alkyl chain would be a significant scientific advance and an important complement for the preparation of tailor-made secondary fluorides.

In this respect, geminal fluoro-haloalkanes **A** constitute highly attractive starting materials for such a method (Scheme 1). Indeed, a catalytic carbon-carbon bond formation via selective functionalization of the C-X bond of **A**, i.e., a cross-coupling reaction, would result in a facile and flexible synthesis of secondary alkyl fluorides **B**. If successful, it would allow for a formal site-selective fluorination of simple alkyl chain at the

## Scheme 1. Proposed Conversion of Geminal 1-Fluoro-1-Haloalkanes to Secondary Alkyl Fluorides



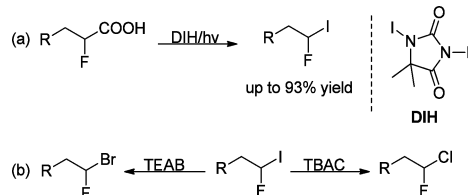
distant to functional groups positions. To the best of our knowledge, geminal fluoro-haloalkanes with no adjacent functional group and with  $\beta$ -hydrogens have not been utilized in cross-coupling chemistry previously.<sup>5</sup> One of the reasons might, apparently, be a need in reliable and efficient methods for their synthesis.<sup>6</sup>

In this paper, we report a novel and efficient method for a straightforward and general synthesis of secondary fluoroalkanes via unprecedented Suzuki cross-coupling reaction of geminal dihaloalkanes. We describe the utilization of 1-halo-1-fluoroalkanes in catalytic cross-coupling reaction, namely Suzuki alkylation ( $C_{sp^3}-C_{sp^3}$  bond construction) and arylation ( $C_{sp^3}-C_{sp^2}$  bond construction) processes, which allows for a site-selective fluorination of alkyl chain with no activating functional group neighboring to C-F unit. Moreover, we demonstrate that an asymmetric version of the developed reaction for the synthesis of highly enantiomerically enriched secondary alkyl fluorides starting from racemic 1-fluoro-1-haloalkanes is feasible. Facile and general synthesis of electrophilic substrates, geminal 1-fluoro-1-haloalkanes (RCHFX; X = I, Br, Cl), through the application of the iododecarboxylation reaction, recently developed in our group, to  $\alpha$ -fluorocarboxylic acids is also disclosed here.<sup>7</sup>

Recently, we reported an efficient, robust, and general synthesis of alkyl iodides from carboxylic acids through their simple treatment with commercially available diiododimethylhydantoin (DIH) under VIS irradiation (Scheme 2).<sup>7</sup> We now report that  $\alpha$ -fluorocarboxylic acids react smoothly with DIH in dichloroethane under VIS-irradiation to generate the corresponding 1-fluoro-1-iodoalkanes in high yields (Scheme 2a). The resulting geminal fluoro-iodoalkanes (not stable under chromatography conditions) can be isolated in an essentially pure form and in high yields after a simple aqueous workup of the reaction mixture.<sup>8</sup> These compounds can be converted to the corresponding more stable bromo/chloro-fluoroalkanes by nucleophilic displacement with tetraethylammonium bromide

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## Scheme 2. Generation of Geminal Fluoro-Haloalkanes via Iododecarboxylation Process



(TEAB) and tetrabutyl ammonium chloride (TBAC), respectively (Scheme 2b). All 1-fluoro-1-haloalkanes presented herein (Tables 2, 4, and 5) were prepared by this approach, starting from the corresponding  $\alpha$ -fluorocarboxylic acids, in a selective manner and high yields.<sup>8</sup> This method, for the first time, allows an access to 1-fluoro-1-haloalkanes from simple carboxylic acids.<sup>9</sup>

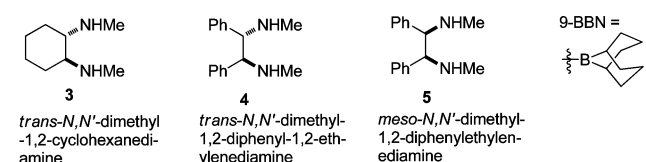
Having an efficient synthetic access to an array of geminal fluoro-haloalkanes in hand, we examined their use as electrophiles in the Suzuki cross-coupling reaction. We relied on the substantially different dissociation energy of C-X (X = I, Br, Cl) and C-F to enable selective activation of the C-X bond with an appropriate metal catalyst.<sup>10</sup> The seminal work of Fu et al. has made Suzuki  $\text{C}_{\text{sp}^3}\text{-C}_{\text{sp}^3}$  cross-couplings of alkyl halides a main-stay in contemporary organic chemistry.<sup>11</sup> Gratifyingly, adopting this chemistry and optimizing the reaction conditions for Suzuki cross-coupling of 1-fluoro-1-haloalkanes with alkyl BBN, we were able to prepare the desired secondary alkyl fluorides with high selectivity and yields.

Although useful for coupling reactions (*vide infra*), 1-fluoro-1-iodoalkanes are less stable than their bromo- and chloro-analogs. Therefore, optimization of the reaction parameters was carried out using 1-bromo-1-fluoroalkanes as starting materials. The optimal conditions for Ni-catalyzed cross-coupling of 1-bromo-1-fluoroalkanes with alkyl-9-BBN to generate secondary alkyl fluoride, as well as factors influencing this reaction, are presented in Table 1. We found that a Ni(II) catalyst and a diamine ligand are necessary for the cross-coupling process (compare entries 1–3). Utilizing other sources of Ni(II) or Ni(0) instead of  $\text{NiCl}_2\cdot\text{glyme}$  leads to somewhat lower yields (entries 5–7). While 4 is comparable to ligand 3 in terms of yield, ligand 5 proved to be less effective (entries 8 and 9). Using other solvents, e.g., diisopropyl ether or THF, results in slight decrease in yield (entries 10 and 11). The inferior yield is also observed when lower loadings of Ni catalyst and ligand, as well as changes in their ratio, are employed (entry 12).

The optimized reaction conditions allow the efficient Suzuki cross-coupling of a wide variety of 1-bromo-1-fluoroalkanes with alkyl boranes (Table 2). Entries 1–4 show that by alternating the length of the alkyl unit in the substrate, the C-F motif can be selectively placed at any desired position in the chain of the product. This ability to introduce a C-F unit at a completely unactivated position in the alkyl chain underscores the power of this method. Remarkably, the reaction is efficient, despite the presence of potentially eliminable  $\beta$ -hydrogens in the starting material. The 1-bromo-1-fluoroalkanes can be decorated with a diverse array of functional groups. For instance, the reaction tolerates amides, sulfonamides, carbonyls, ethers, and esters (entries 7–11). In cases of amides and sulfonamides, catalyst  $\text{NiBr}_2\cdot\text{diglyme}$  gives higher yields than  $\text{NiCl}_2\cdot\text{glyme}$  (entries 10, 11). In all cases the secondary alkyl fluorides are obtained in high yields.

Table 1. Optimization of Cross-Coupling Conditions<sup>a</sup>

$\text{Ph-CH}_2\text{-CH}_2\text{-Br} + 9\text{-BBN} \xrightarrow[\text{Dioxane, r.t.}]{\begin{smallmatrix} 10 \text{ mol\% NiCl}_2\cdot\text{glyme} \\ 12 \text{ mol\% Ligand-3} \\ 1.4 \text{ equiv. KOt-Bu} \\ 2.0 \text{ equiv. } i\text{-BuOH} \end{smallmatrix}} \text{Ph-CH}_2\text{-CH}_2\text{-F}$		
Entry	Variation from the optimized condition	yield (%) <sup>b</sup>
1	none	90
2	no 3	n.r.
3	no Ni catalyst	n.r.
4	no <i>i</i> -BuOH	<10
5	$\text{NiBr}_2\cdot\text{glyme}$ instead of $\text{NiCl}_2\cdot\text{glyme}$	82
6	$\text{NiBr}_2\cdot\text{diglyme}$ instead of $\text{NiCl}_2\cdot\text{glyme}$	80
7	$\text{Ni(cod)}_2$ instead of $\text{NiCl}_2\cdot\text{glyme}$	67
8	4 instead of 3	89
9	5 instead of 3	50
10	<i>i</i> -Pr <sub>2</sub> O instead of Dioxane	87
11	THF instead of Dioxane	70
12	6 mol% $\text{NiCl}_2\cdot\text{diglyme}$ and 8 mol% 3, instead of 10%/12%	76



<sup>a</sup>1a (0.3 mmol), 2a (0.6 mmol),  $\text{NiCl}_2\cdot\text{glyme}$  (0.03 mmol), ligand (0.036 mmol), KOt-Bu (0.42 mmol), *i*-BuOH (0.6 mmol) in 3 mL solvent. <sup>b</sup>Isolated yield. n.r. = no reaction.

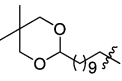
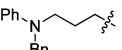
Table 2. Scope of Geminal Bromo-Fluoroalkanes for the Catalytic Synthesis of Secondary Alkyl Fluoride<sup>a</sup>

$\text{R-CH}_2\text{-CH}_2\text{-Br} + 9\text{-BBN} \xrightarrow[\text{optimized conditions}]{\text{Ph}} \text{R-CH}_2\text{-CH}_2\text{-F-Ph}$		
Entry	R	Product
1	Ph	6b
2	Bn	6c
3	$\text{Ph}(\text{CH}_2)_2$	6d
4	$\text{Ph}(\text{CH}_2)_3$	6e
5	2-Naphthyl	6f
6	$\text{CH}_3(\text{CH}_2)_{10}$	6g
7	$\text{Ac}(\text{CH}_2)_7$	6h
8	$\text{BnO}(\text{CH}_2)_2$	6i
9	$\text{EtOOC}(\text{CH}_2)_8$	6j
10 <sup>c</sup>		6k
11 <sup>c</sup>		6l

<sup>a</sup>1 (0.5 mmol), 2b (1.0 mmol),  $\text{NiCl}_2\cdot\text{glyme}$  (0.05 mmol), 3 (0.06 mmol), KOt-Bu (0.7 mmol), *i*-BuOH (1.0 mmol) in 5 mL solvent. <sup>b</sup>Isolated yield. <sup>c</sup> $\text{NiBr}_2\cdot\text{diglyme}$  as catalyst, 4 as ligand, *i*-Pr<sub>2</sub>O as solvent.

A wide range of alkyl boranes is compatible with our method, which provides an additional illustration of the versatility of this approach to fluoroalkanes (Table 3). While symmetrically substituted trialkylboranes proved highly efficient in the reaction (entry 7), we continued to focus on alkyl-9-BBN for obvious synthetic reasons. We found that 9-BBN-based alkyl nucleophiles bearing functional groups such as aryls, ethers, esters, and amines participated in the reaction to furnish the desired cross-coupling products in high yields (entries 2–6, 9–10). Interestingly, triaryl boranes are also compatible with this methodology, which provides access to formation of C-F units by

**Table 3. Scope of Organoboranes for the Catalytic Synthesis of Secondary Alkyl Fluorides<sup>a</sup>**

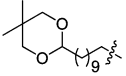
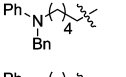
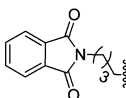
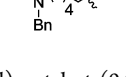
$\text{Ph-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-Br} + \text{R-9-BBN} \xrightarrow{\text{optimized conditions}} \text{Ph-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-F}$				
Entry	R	Product	Yield (%) <sup>b</sup>	
1	<i>n</i> -Octyl	<b>2a</b>	<b>6a</b>	90
2	2-OMeC <sub>6</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub>3</sub>	<b>2c</b>	<b>6m</b>	85
3	4-FC <sub>6</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub>3</sub>	<b>2d</b>	<b>6n</b>	81
4	Cyclohexyl(CH <sub>2</sub> ) <sub>2</sub>	<b>2e</b>	<b>6o</b>	74
5	TBSO(CH <sub>2</sub> ) <sub>5</sub>	<b>2f</b>	<b>6p</b>	84
6	MeOOC(CH <sub>2</sub> ) <sub>5</sub>	<b>2g</b>	<b>6q</b>	90
7 <sup>c</sup>	Et	<b>2h</b>	<b>6r</b>	90
8 <sup>c</sup>	Ph	<b>2i</b>	<b>6s</b>	89
9		<b>2j</b>	<b>6t</b>	83
10		<b>2k</b>	<b>6u</b>	86

<sup>a</sup>**1a** (0.5 mmol), **2** (1.0 mmol), catalyst (0.05 mmol), **3** (0.06 mmol), KO<sup>t</sup>-Bu (0.7 mmol), *i*-BuOH (1.0 mmol) in dioxane (5 mL). <sup>b</sup>Isolated yield. <sup>c</sup>R<sub>3</sub>B as organo borane source, **1b** as substrate, **4** as ligand, *i*Pr<sub>2</sub>O as solvent.

C<sub>sp</sub><sup>3</sup>-C<sub>sp</sub><sup>2</sup> bond formation. For example, Ph<sub>3</sub>B reacts smoothly with substrate **1b** to produce **6s** in 89% yield (entry 8).

The protocol is not limited to 1-bromo-1-fluoroalkanes as starting materials. 1-Fluoro-1-iodoalkanes (**7a–c**) and 1-chloro-1-fluoroalkanes (**8a–e**) can also serve as electrophiles to furnish, after cross-coupling, secondary fluoroalkanes in moderate to good yields (Table 4). We speculate that the lower yields observed for 1-fluoro-1-iodoalkanes, compared to their 1-fluoro-1-bromo-counterparts, may be due to trace amounts of iodine in

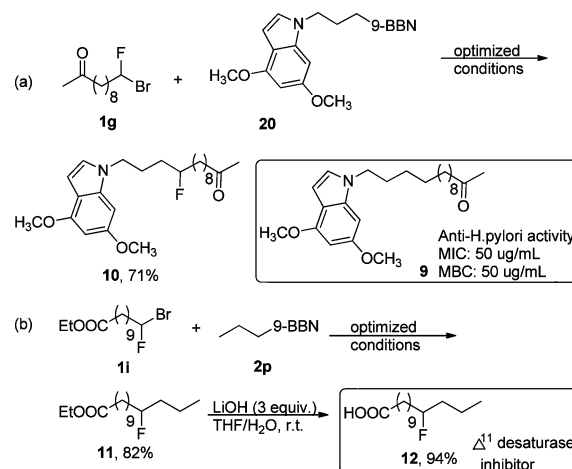
**Table 4. 1-Fluoro-1-Iodo/Chloroalkanes in the Catalytic Synthesis of Secondary Alkyl Fluorides<sup>a</sup>**

$\text{R-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-X} + \text{R}_1\text{-9-BBN} \xrightarrow{\text{optimized conditions}} \text{R-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-F}$				
X = I, <b>7a–c</b> X = Cl, <b>8a–e</b>				
Entry	R	R <sub>1</sub>	Product	Yield (%) <sup>b</sup>
1	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>10</sub>	<b>7a</b>	C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>3</sub> <b>2b</b>	<b>6g</b> 62
2	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>10</sub>	<b>8a</b>	2-OMeC <sub>6</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub>3</sub> <b>2c</b>	<b>6v</b> 73
3	Ac(CH <sub>2</sub> ) <sub>7</sub>	<b>7b</b>	C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>3</sub> <b>2b</b>	<b>6h</b> 58
4	BnOCH <sub>2</sub>	<b>7c</b>	C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>3</sub> <b>2b</b>	<b>6i</b> 66
5	C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>2</sub>	<b>8b</b>	<i>n</i> -Hexyl <b>2l</b>	<b>6w</b> 69
6	C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>2</sub>	<b>8b</b>	<i>n</i> -Octyl <b>2a</b>	<b>6a</b> 68
7	C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>2</sub>	<b>8b</b>	C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>3</sub> <b>2b</b>	<b>6d</b> 70
8	C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>2</sub>	<b>8b</b>	2-OMeC <sub>6</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub>3</sub> <b>2c</b>	<b>6m</b> 77
9	C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>2</sub>	<b>8b</b>	4-FC <sub>6</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub>3</sub> <b>2d</b>	<b>6n</b> 73
10	C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>2</sub>	<b>8b</b>	Cyclohexyl(CH <sub>2</sub> ) <sub>2</sub> <b>2e</b>	<b>6o</b> 66
11	C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>2</sub>	<b>8b</b>	TBSO(CH <sub>2</sub> ) <sub>5</sub> <b>2f</b>	<b>6p</b> 60
12	Ph	<b>8c</b>	2-OMeC <sub>6</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub>3</sub> <b>2c</b>	<b>6x</b> 75
13	EtOOC(CH <sub>2</sub> ) <sub>6</sub>	<b>8d</b>	C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>3</sub> <b>2b</b>	<b>6y</b> 70
14	C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>2</sub>	<b>8b</b>		<b>2j</b> <b>6t</b> 70
15	C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>2</sub>	<b>8b</b>		<b>2m</b> <b>6z</b> 66
16		<b>8e</b>		<b>2m</b> <b>6z'</b> 61

<sup>a</sup>**1** (0.5 mmol), **2b** (1.0 mmol), catalyst (0.05 mmol), **4** (0.06 mmol), KO<sup>t</sup>-Bu (0.7 mmol), *i*-BuOH (1.0 mmol) in 5 mL *i*Pr<sub>2</sub>O. <sup>b</sup>Isolated yield.

the starting material that partially poisons the Ni catalyst (entries 1–3). Indeed, employment of 1-fluoro-1-bromoalkane in this reaction with controllable addition of the trace amounts of iodine leads to the reduced yields. In the case of the 1-fluoro-1-chloroalkanes, the difficulty of cleaving the stronger C-Cl bond may account for the slightly lower yield (entries 2, 5–16).<sup>12</sup>

The present method can be applied to the synthesis of biochemically valuable fluorinated compounds. For example, spiroaxine derivative **9** is reported to exhibit antibacterial activity.<sup>13</sup> We prepared its fluorinated analog **10**, in a facile manner by Ni-catalyzed cross-coupling of the 1-fluoro-1-bromoalkane **1g** and alkyl-BBN **2o** in 71% isolated yield (Scheme 3a). We arbitrarily choose to introduce the fluorine at

**Scheme 3. Syntheses of 10 and 12**

C(4) of the alkyl chain of **9**. However, all other possible fluorinated analogues of **10** should be accessible using the same strategy. Consequently, this method constitutes a strategic entry to prepare biologically active compounds that are fluorinated at preselected alkyl positions.

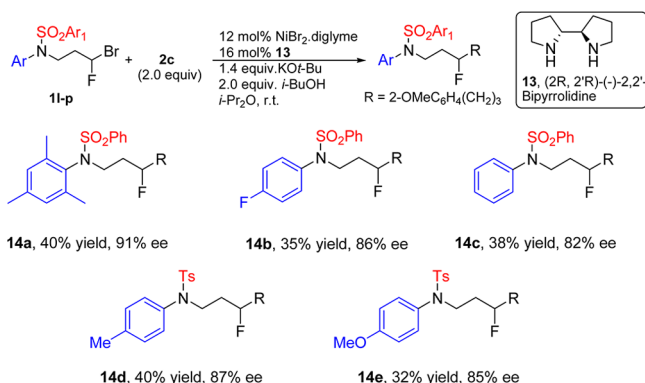
As an additional example of the utility of our method, we have prepared 11-fluorotetradecanoic acid **12** which exhibit inhibitory activity of Δ<sup>11</sup> desaturase.<sup>14</sup>

This compound is straightforwardly and efficiently synthesized by catalytic cross-coupling of 1-bromo-1-fluoroester **1i** and propyl BBN followed by a subsequent hydrolysis of the resulting ester **11** (Scheme 3b).

The secondary alkyl fluorides described above were all prepared as racemic mixtures. However, a stereoconvergent synthesis of enantiomerically enriched secondary alkyl fluorides may be envisioned if a suitable chiral catalyst is identified. Delightfully, preliminary studies show that this is feasible. Thus, we were able to prepare the chiral secondary alkyl fluorides **14** possessing stereogenic C-F center by the cross-coupling of racemic sulfonamides **1l–p** and organoborane **2c** using Ni catalyst and chiral ligand **13** with high enantioselectivity (91% ee), albeit with modest yield (Table 5). Further studies are required in order to improve efficiency and extend a scope of this transformation.

In conclusion, we have established the first Suzuki cross-coupling reaction that utilizes geminal dihaloalkanes as starting materials for the efficient and general synthesis of secondary fluoroalkanes. Moreover, we have demonstrated, for the first time that simple 1-fluoro-1-haloalkanes with no adjacent functional groups can be powerful electrophiles for the cross-coupling



**Table 5. Enantioselective Catalytic Synthesis of Secondary Alkyl Fluoride<sup>a</sup>**

<sup>a</sup>Reactions were carried out with substrate **1** (0.2 mmol), **2c** (0.4 mmol), Ni catalyst (0.024 mmol), ligand **13** (0.032 mmol), KOt-Bu (0.28 mmol), *i*-BuOH (0.4 mmol) in *i*-Pr<sub>2</sub>O (4 mL). Yields are isolated yields after chromatography.

processes. A wide array of 1-fluoro-1-haloalkanes is now available by the efficient methodology for their synthesis, which is reported in this work. The developed cross-coupling method employing these geminal dihalo compounds represents a conceptually new approach for the preparation of a variety of secondary alkyl fluorides possessing  $\beta$ -hydrogens and having no adjacent activating functional groups. Using this approach, site-selectively fluorinated analogs of bioactive molecules as well as known C-F containing compounds with interesting biomedical properties can be facilely prepared. Direct asymmetric catalytic stereoconvergent synthesis of enantioenriched secondary alkyl fluorides from the racemic mixture of 1-fluoro-1-haloalkanes proved feasible and is currently under further investigation in our laboratories.

## ■ ASSOCIATED CONTENT

### ■ Supporting Information

Experimental details and 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.

## ■ ACKNOWLEDGMENTS

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