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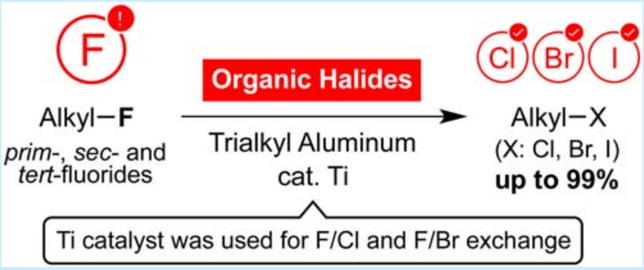
Halogen Exchange Reaction of Aliphatic Fluorine Compounds with Organic Halides as Halogen Source

Yuki Mizukami, Zhiyi Song, and Tamotsu Takahashi*

Catalysis Research Center and Graduate School of Life Science, Hokkaido University, Kita-ku, Sapporo 001-0021, Japan

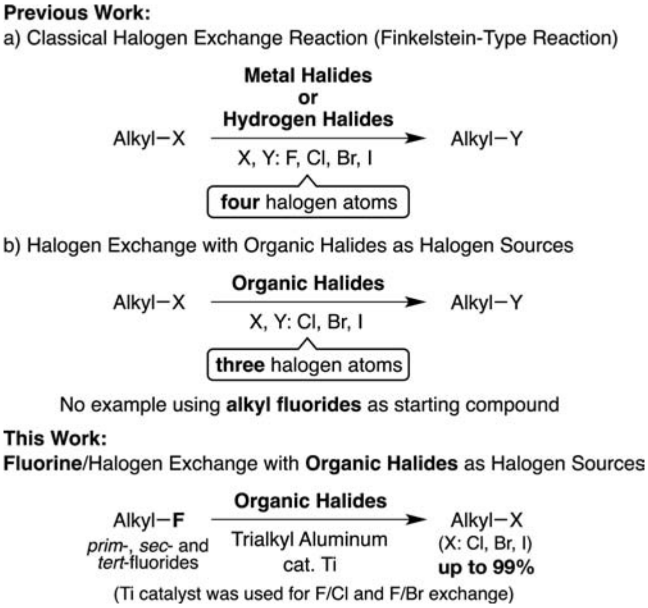
Ⓢ *Supporting Information*

ABSTRACT: The halogen exchange reaction of aliphatic fluorine compounds with organic halides as the halogen source was achieved. Treatment of alkyl fluorides (primary, secondary, or tertiary fluorides) with a catalytic amount of titanocene dihalides, trialkyl aluminum, and polyhalomethanes (chloro or bromo methanes) as the halogen source gave the corresponding alkyl halides in excellent yields under mild conditions. In the case of a fluorine/iodine exchange, no titanocene catalyst is needed. Only C−F bonds are selectively activated under these conditions, whereas alkyl chlorides, bromides, and iodides are tolerant to these reactions.



The halogen exchange of alkyl halides is a fundamental reaction in synthetic organic chemistry.[1−3] It is mainly used for preparing alkyl bromides or iodides, which are more reactive in organic synthesis. Finkelstein-type reactions have been well studied for the conversion of alkyl chlorides to the corresponding bromides or iodides and alkyl bromides to iodides (Scheme 1).[2] In contrast, the replacement of fluorine by chlorine, bromine, or iodine has been limited due to the thermodynamic stability and kinetic inertness of the carbon−fluorine bond.[3−5]

Scheme 1. Halogen Exchange Reaction of Alkyl Halides



Most halogen exchange reactions employ metal halides or hydrogen halides that promote the reaction and serve the halogen atoms. Several examples of fluorine/halogen exchange with metal halides or hydrogen halides have also been found. These halogen sources include $MoCl_5$,[3a] BX_3 (X = Cl, Br, or I),[3e] R_2AlCl,[3f] $AlCl_3$,[3g] and YbI_3,[3h] which are strong Lewis acids activating the C−F bond. On the other hand, organic halides have not been good candidates as the halogen source, mainly because the halogen interchange of two kinds of alkyl halides results in their equilibrium.[6b] Only two examples of halogen exchange with organic halides have been reported.[6] Pincock et al. developed halogen exchanges which occurred at the bridgeheads of norbornane, adamantane, and bicyclo[2.2.2]-octane derivatives in 1973.[6a] The other example was reported by Willy et al. in 1976.[6b] Conversion of primary alkyl halides was realized by a catalytic amount of inorganic halides and a large excess of organic halides. The organic halides were easily removed from the reaction mixture after serving halogen atoms, which leads to a shift in the equilibrium. Three kinds of alkyl halides such as alkyl chlorides, bromides, and iodides were converted into other alkyl halides by these methods. However, to the best of our knowledge, there is no report on halogen exchange of alkyl "fluorides" with an "organic" halogen source.

Herein, we report the first example of halogen exchange between inactivated alkyl fluorides and organic halides in the presence of trialkyl aluminum and a catalytic amount of titanocene dihalide under mild conditions. Conversion of alkyl fluorides to chlorides or bromides was achieved under the above-mentioned conditions. Surprisingly, no titanocene catalyst is needed for the fluorine/iodine exchange.

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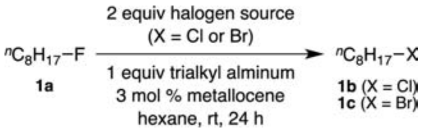
At the outset, we investigated efficient reaction conditions for the F/Cl and F/Br exchange reactions of the simple alkyl fluoride, 1-fluorooctane **1a** (Table 1). Halomethanes were employed as halogen sources due to their availability and ease of isolation of the product. A survey of different solvents revealed that hexane was optimal (see Table S1 in the Supporting Information). Trialkyl aluminum screening showed that ^{i}Bu$_3$Al was the most effective for the F/Cl exchange (entries 1−3). The starting compound was consumed, and 1-chlorooctane **1b** was obtained in 99% yield (entry 3). In contrast, a full conversion was not achieved and substitution of the fluorine atom with an alkyl group on the aluminum center occurred as a side reaction[7] when Me$_3$Al or Et$_3$Al was used (entries 1 and 2). For the F/Br substitution, Et$_3$Al and ^{i}Bu$_3$Al gave 1-bromooctane **1b** in 99% yield (entries 9−11). According to the titanocene-catalyzed C−F bond activation developed by Lentz et al.,[5b,c,e] we investigated the activity of [Cp$_2$TiF$_2$] as a catalyst for the reaction. However, a small amount of the starting material remained (entries 4 and 11). Compared with titanocene catalysts, zirconocene catalysts gave lower yields (entries 5 and 12). The reaction using trihalomethane and tetrahalomethane gave good results (entries 6, 7, and 13).

Table 1. Fluorine/Chlorine and Fluorine/Bromine Exchange Reaction of 1-Fluorooctane

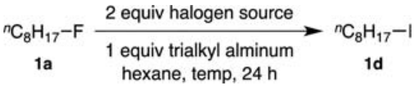


entry	halogen source	trialkyl aluminum	metallocene	yield (%)[a]
1	CH_2Cl_2	Me$_3$Al	Cp$_2$TiCl$_2$	29
2	CH_2Cl_2	Et$_3$Al	Cp$_2$TiCl$_2$	70
3	CH_2Cl_2	^{i}Bu$_3$Al	Cp$_2$TiCl$_2$	(99)
4	CH_2Cl_2	^{i}Bu$_3$Al	Cp$_2$TiF$_2$	77
5	CH_2Cl_2	^{i}Bu$_3$Al	Cp$_2$ZrCl$_2$	17
6	$CHCl_3$	^{i}Bu$_3$Al	Cp$_2$TiCl$_2$	87
7	CCl_4	^{i}Bu$_3$Al	Cp$_2$TiCl$_2$	99
8	CH_2Br_2	Me$_3$Al	Cp$_2$TiBr$_2$	69
9	CH_2Br_2	Et$_3$Al	Cp$_2$TiBr$_2$	(99)
10	CH_2Br_2	^{i}Bu$_3$Al	Cp$_2$TiBr$_2$	99
11	CH_2Br_2	Et$_3$Al	Cp$_2$TiF$_2$	92
12	CH_2Br_2	Et$_3$Al	Cp$_2$ZrBr$_2$	60
13	$CHBr_3$	Et$_3$Al	Cp$_2$TiBr$_2$	99

[a] NMR yields. The yields of isolated products are given in parentheses.

The F/I exchange was also examined (Table 2). Reactions with trialky aluminum reagents gave 1-iodooctane **1d** in good yields (entries 1−7). However, formation of an alkylated compound (*n*-decane) was observed when Et$_3$Al was used (entry 3).[7] A lower temperature at the beginning of the reaction suppressed the side reaction and afforded 1-iodooctane **1d** in 99% yield (entry 4). The reaction with ^{i}Bu$_3$Al and CH_2I_2 gave isobutyl iodide as an undesired byproduct even at low temperatute (entries 5 and 6).[8] Triiodomethane was effective as a halogen source (entry 7), while the use of iodomethane gave only 4% of product (entry 8).

Table 2. Fluorine/Iodine Exchange Reaction of 1-Fluorooctane



entry	halogen source	trialkyl aluminum	temp (°C)	yield (%)[a]
1	CH_2I_2	Me$_3$Al	rt	(99)
2	CH_2I_2	Me$_3$Al	−40 to rt	(99)
3	CH_2I_2	Et$_3$Al	rt	94
4	CH_2I_2	Et$_3$Al	−40 to rt	(99)
5	CH_2I_2	^{i}Bu$_3$Al	rt	99
6	CH_2I_2	^{i}Bu$_3$Al	−40 to rt	99
7	CHI_3	Et$_3$Al	−40 to rt	99
8	CH_3I	Et$_3$Al	−40 to rt	4

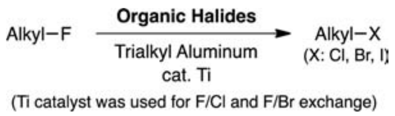
[a] NMR yields. The yields of isolated products are given in parentheses.

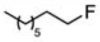
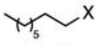
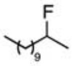
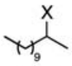
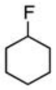
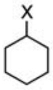
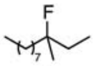
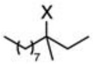
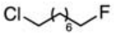
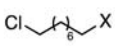
With the optimized conditions, the substrate scope for halogen exchange reaction of *primary*, *secondary*, and *tertiary* fluorides was investigated (Table 3). A variety of alkyl fluorides were effectively converted into the corresponding alkyl halides in good to excellent yields. Compared with *primary* alkyl fluorides, *secondary* and *tertiary* fluorides were more reactive. The reaction of these fluorides finished within 30 min. The reaction of *secondary* alkyl fluorides **2a**, diiodomethane, and Et$_3$Al gave minor products (entry 5). Cyclic compound **4a** afforded a mixture of halocyclohexane and an elimination side product (cyclohexene) (entries 6 and 7). In the case of the F/Br substitution of *tertiary* alkyl fluoride, a competing alkylation reaction[7] decreased the yields of halogenated products (entries 8 and 10). Notably, substrate **6a**, which possesses a fluorine and chlorine atom, did not undergo chlorine/halogen exchange and substitution of a fluorine atom occurred selectively (entries 12 and 13). The strong Lewis acidity and high fluoride affinity of an aluminum reagent enabled selective activation of the C−F bond. As a further demonstration of selectivity for alkyl fluorides, we carried out the reaction of three kinds of alkyl halides containing alkyl fluorides with an organic bromine or iodine source (Scheme 2). 100% conversion of 1-fluorooctane into the corresponding alkyl halides was observed, whereas less than 0.5% of the other halides were consumed.

To obtain mechanistic insight into the F/Cl and F/Br exchange, we carried out reactions without using the titanocene catalyst, trialkyl aluminum, or organic halide. The results were summarized in Scheme 3. First, we performed the reaction without using the titanocene catalyst. Only an alkylated product was obtained in 99% yield, and no brominated compound **7c** was observed.[7] This result shows that the halogen atom of the organic halogen source is not activated by a trialkyl aluminum and the titanocene catalyst is essential for transferring the halogen atom of an organic halide to the substrate. This is in sharp contrast to the F/I exchange reaction, where an organic halide such as CH_2I_2 is activated. Notably, activation of the C−F bond was observed due to the strong Lewis acidity of the aluminum reagent. Second, no reaction occurred under the conditions without a trialkyl aluminum. Third, the reaction without an organic halogen source gave a mixture of a hydrodefluorinated compound, an alkylated compound, and brominated compound **7c**. Clearly, the bromine atom of compound **7c** is derived from [Cp$_2$TiBr$_2$]. This result suggests that the halogen atom of organic halides is transferred to titanocene first, and then a substitution reaction of an alkyl fluoride with a halogen atom on titanocene affords the product.

To reveal how the halogen atom on organic halides is transferred to the substrate, we conducted the reaction of 1-fluorododecane with CH_2Br_2 (organic bromine source) and titanocene dichloride (chlorine source) in the presence of Et$_3$Al (Scheme 4). A mixture of 1-chlorododecane **7b** and 1-

Table 3. Halogen Exchange Reaction Using Various Alkyl Fluorides[a]

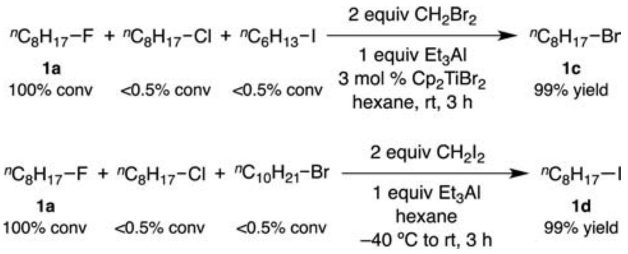


entry	substrate	reaction conditions	product	X	yield (%)[b]
1	 **1a**	A	 **1b-d**	Cl (**1b**)	(99)
2	1a	B		Br (**1c**)	(99)
3	1a	C		I (**1d**)	(99)
4[c,d]	 **2a**	B	 **2c-d**	Br (**2c**)	(99)
5[d,e]	2a	C		I (**2d**)	91
6[c,d]	 **3a**	B	 **3c-d**	Br (**3c**)	78
7[d,e]	3a	C		I (**3d**)	94
8[c,d]	 **4a**	B	 **4c-d**	Br (**4c**)	trace
9[d,h]	4a	C		I (**4d**)	93
10[c,d]	 **5a**	B	 **5c-d**	Br (**5c**)	80
11[d,h]	5a	C		I (**5d**)	(99)
12	 **6a**	B	 **6c-d**	Br (**6c**)	(99)
13	6a	C		I (**6d**)	(99)

[a]Reaction conditions: (A) CH_2Cl_2 (2 equiv), Cp_2TiCl_2 (3 mol %), $^iBu_3Al$ (1 equiv), hexane, rt, 24 h; (B) CH_2Br_2 (2 equiv), Cp_2TiBr_2 (3 mol %), Et_3Al (1 equiv), hexane, rt, 24 h; (C) CH_2I_2 (2 equiv), Et_3Al (1 equiv), hexane, −40 °C to rt, 24 h. [b]NMR yields. The yields of isolated products are given in parentheses. [c]5 mol % of catalyst was used. [d]Reaction time was 30 min. [e]Reaction temperature was −30 °C. [f]3-Iodododecane and 2-dodecene were obtained as a minor product. [g]Alkylated compound (1-ethyladamantane) was obtained as minor product. [h]Reaction temperature was 0 °C.

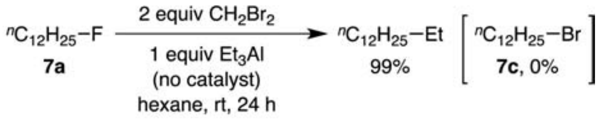
bromododecane **7c** was obtained in 22% and 77% yield, respectively. This result revealed that the organic halogen source provides the halogen atom to the titanocene catalyst first and then the halogen atom on titanium is transferred to the substrate. The halogen atom transfer from the organic halide to titanocene is regarded as regeneration of the catalyst.

Scheme 2. C−F Selective Halogen Exchange of Alkyl Halides

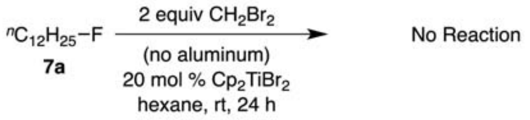


Scheme 3. Control Experiments for F/Br Exchange Reaction

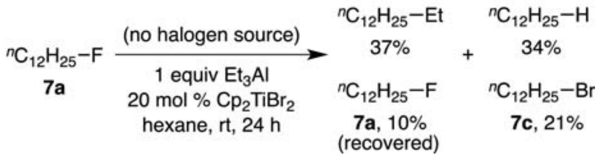
a) A reaction without titanocene catalyst



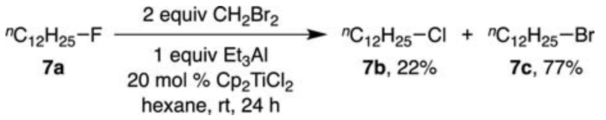
b) A reaction without trialkyl aluminum



c) A reaction without organic halogen source



Scheme 4. Halogen Exchange Reaction with Two Kinds of Halogen Sources



In order to elucidate the mechanism of the halogen exchange, we must await further investigation. However, we assume that the dialkyl aluminum halide, which was used in the halogen exchange of alkyl fluorides reported by Terao, Kambe and co-workers,[7] or the equivarent of this, is formed as the active species. The results shown in Schemes 3 and 4 indicate that the active species for the F/Cl and F/Br exchange is generated by the reaction of titanocene dihalides with the trialkyl aluminum.[8] For the F/I substitution, the active species may be generated from polyiodomethane and trialkyl aluminum.[9]

In summary, we developed the first example of a halogen exchange reaction of aliphatic fluorine compounds with organic halogen sources. A halogen atom on organic halides (polyhalomethane) was transferred to alkyl fluoride substrates by a titanocene catalyst, which is used in F/Cl and F/Br exchange, and a trialkyl aluminum. The titanocene catalyst accepts the halogen atom on organic halogen sources. The trialkyl aluminum activates the C−F bond of the substrate, the halogen atom on the titanocene catalyst, and polyiodomethane. Further mechanistic studies and expansion of the substrate scope are ongoing.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02589.

Detailed synthetic procedures, characterization, ^{1}H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: tamotsu@cat.hokudai.ac.jp.

Notes

The authors declare no competing financial interest.

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