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Internal Delivery of Soft Chlorine and Bromine Atoms: Stereoselective Synthesis of (*E*)-β-Halogenovinyl(aryl)-λ^3-iodanes through Domino λ^3-Iodanation–1,4-Halogen Shift–Fluorination of Alkynes

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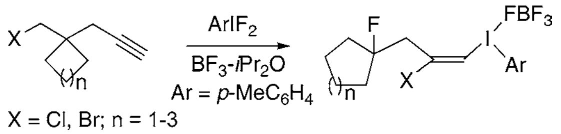
ABSTRACT



4-(Difluoroiodo)toluene-induced domino λ^3-iodanation–1,4-halogen shift–ring enlargement–fluorination reaction of 5-halopentynes with a four-, five-, or six-membered carbocycle afforded the ring-expanded (*E*)-δ-fluoro-β-halovinyl-λ^3-iodanes stereoselectively in high yields, probably via the intermediacy of five-membered halonium ions. Use of internal alkynes makes it possible to synthesize tetrasubstituted β-halovinyl-λ^3-iodanes with defined stereochemistry.

Hypervalent 1-alkenyl(phenyl)-λ^3-iodanes enjoy their rich chemistry in modern organic synthesis.[1] Because of the hypernucleofugality of phenyl-λ^3-iodanyl groups,[2] they undergo unusual vinylic S_N2 displacement by the reaction with a broad range of nucleophiles including halides, sulfides, carboxylic acids, amides, and thioamides.[3] They also serve as excellent progenitors for generation of free alkylidene carbenes:[4] for instance, (*Z*)-β-haloalkenyl(phenyl)-λ^3-iodanes (Cl, Br) undergo unique base-induced α-elimination of the phenyl-λ^3-iodanyl group with hypernucleofugality to generate reactive (α-haloalkylidene)carbenes, which afford 1-halocyclopentenes via intramolecular 1,5-carbon−hydrogen insertions and/or 1-haloalkynes through 1,2-shift of halogens.[5]

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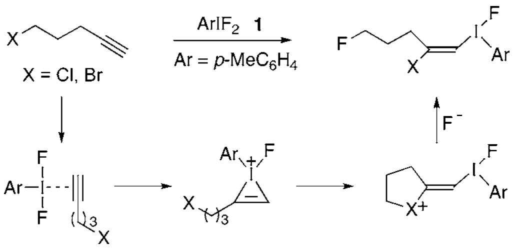
Methods available for the synthesis of β-chloro- and β-bromoalkenyl-λ^3-iodanes are very limited. A reported procedure involves Michael addition of a halide ion (Cl^- or Br^-) to 1-alkynyl(phenyl)(tetrafluoroborato)-λ^3-iodanes under acidic conditions, which proceeds in an exclusively stereoselective manner and affords (*Z*)-β-halovinyliodanes via anti addition of hydrogen halides in high yields.[6,7] The Michael addition procedure constitutes a general method of obtaining (*Z*)-β-halovinyl-λ^3-iodanes but cannot be applied to the synthesis of the *E*-isomers. We report herein for the first time the stereo- and regioselective synthesis of (*E*)-β-chloro- and (*E*)-β-bromoalkenyl-λ^3-iodanes through difluoroiodane-induced anti β-halogeno-λ^3-iodanation of terminal alkynes (Scheme 1).[8] In the reaction, a ω-halogen atom of 5-halo-1-alkynes (Cl or Br) rearranges regioselectively to the β-position by intramolecular 1,4-halogen shift via the intermediacy of five-membered halonium ions. A fluorine atom was also introduced to the terminal sp^3 carbon atom by the ring opening via bimolecular nucleophilic substitutions. This halogeno-λ^3-iodanation of alkynes was further extended to the domino λ^3-iodanation−halogen shift−alkyl shift−fluorination process, which was observed in the reaction of 4,4-dialkyl-5-halo-1-alkynes.

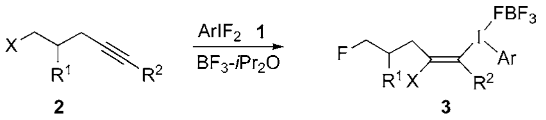
Scheme 1



Anti oxy-λ^3-iodanation of terminal alkynes with sulfonyloxy-λ^3-iodanes $PhI(OH)OSO_2R$ (R = Me, CF_3, *p*-MeC_6H_4) affords (*E*)-β-(sulfonyloxy)vinyl-λ^3-iodanes with high regio- and stereoselectivities, probably via the formation of three-membered-ring vinylenehalonium ions.[9] Analogous anti fluoro-λ^3-iodanation took place smoothly, when 1-decyne was treated with 4-(difluoroiodo)toluene (**1**) in the presence of $BF_3{-}iPr_2O$ in chloroform; (*E*)-β-fluoro-1-decenyl(*p*-tolyl)-λ^3-iodane was obtained in high yield (93%). Fluoro-λ^3-iodanation of terminal alkynes using a combination of difluoroiodane **1** and $Et_3N{\cdot}5HF$ was originally developed by Yoneda and Hara.[10] The methodology, however, does not seem to be applied to the synthesis of (*E*)-β-chlorovinyl-λ^3-iodanes because reaction of (dichloroiodo)benzene with aliphatic 1-alkynes has been shown to give predominantly (*E*)-1,2-dichloroalkenes via a radical mechanism, instead of the formation of β-chlorovinyliodanes.[11] Use of an external chloride anion as an additive was examined but found to be fruitless, thus when the BF_3-catalyzed reaction of 1-decyne with difluoroiodane **1** was carried out in the presence of Bu_4NCl (2 equiv), (*E*)-1,2-dichloro-1-decene (60%) was selectively produced with no evidence for formation of β-chlorovinyl-λ^3-iodane. Formation of the vicinal dichlorodecene probably reflects partial oxidation of the chloride anion to molecular chlorine by difluoro-λ^3-iodane **1** during the reaction and/or via ligand exchange on iodine(III) yielding dichloro(*p*-tolyl)-λ^3-iodane.[1a]

We found that internal delivery of a soft chlorine atom attached to a carbon atom makes it possible to synthesize β-chlorovinyl-λ^3-iodanes **3** (Table 1). Exposure of 5-chloro-1-pentyne (**2a**) to difluoroiodane **1** (1.2 equiv) in the presence of $BF_3{-}iPr_2O$ in chloroform solution at −60 °C to room temperature afforded (*E*)-2-chloro-5-fluoropentenyl-λ^3-iodane **3a** selectively in 55% yield, after treatment with a saturated aqueous $NaBF_4$ solution. Use of 2 equiv of **1** increased the yield of **3a** to 66%. 5-Chloro-4-methyl-1-pentyne (**2d**) similarly afforded (*E*)-β-chloro-ω-fluorovinyliodane **3d** regio- and stereoselectively via an intramolecular 1,4-chlorine shift from the terminal position to the β-acetylenic carbon atom. This process probably involves the intermediate formation of the five-membered 2-methylenetetramethyl-

Table 1. Stereoselective Synthesis of (*E*)-β-Chloro- and (*E*)-β-Bromovinyliodanes **3** via 1,4-Halogen Shift[a]



entry	**2** (R^1, R^2, X)	$ArIF_2$ **1**[b]	$BF_3{-}iPr_2O$[b]	**3** yield (%)[c]
1	**2a** (H, H, Cl)	1.2	1.2	**3a** 55
2	**2a** (H, H, Cl)	2	1.5	**3a** 66
3	**2a** (H, H, Cl)	2	1.5[d]	**3a** 29
4	**2a** (H, H, Cl)	2	1.5[e]	**3a** 64
5	**2b** (H, H, Br)	2	1.5	**3b** 80
6	**2c** (H, H, I)	2	1.5	**3c** −
7	**2d** (Me, H, Cl)	2	1.5	**3d** 74
8	**2e** (H, Me, Cl)	2	1.5	**3e** 83
9	**2f** (H, Et, Cl)	2	1.5	**3f** 92

[a] Reaction conditions: chloroform/−60 °C to room temperature over 5 h and then room temperature for 5 h/Ar. [b] Equivalents. [c] Isolated yields. [d] Room temperature for 5 h. [e] $BF_3{-}Et_2O$ was used.

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(7) For synthesis of (*E*)-β-chloroethenyl(chloro)(phenyl)-λ^3-iodane by the reaction of (*E*)-β-chloroethenylmercuric chloride with (dichloroiodo)benzene, see: (a) Brainina, E. M.; Freidlina, R. K. *Bull. Acad. Sci. URSS* **1947**, 623. (b) Freidlina, R. K.; Brainina, E. M.; Nesmeyanov, A. N. *Bull. Acad. Sci. URSS* **1945**, 647.

(8) For synthesis of (*E*)-β-chlorovinyl-λ^3-bromanes, see: Ochiai, M.; Nishi, Y.; Mori, T.; Tada, N.; Suefuji, T.; Frohn, H. J. *J. Am. Chem. Soc.* **2005**, *127*, 10460.

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enechloronium ion and the subsequent ring opening by the nucleophilic attack of the fluoride ion on the primary carbon C5. The strong C−Cl^+ bond at the sp^2 carbon C2 in the cyclic chloronium ion is resistant to the cleavage.

Evidence for 1,4-bromine participation was derived from the reaction of 5-bromopentyne **2b**, which afforded *trans*-β-bromopentenyliodane **3b** in 80% yield (Table 1, entry 5). In contrast, formation of (*E*)-2-iodopentenyliodane **3c** was not detected at all in the reaction of iodoalkyne **2c**:[12] this is probably due to the decreased thermal stability of **3c**, in which β-elimination of the iodine atom and the phenyl-λ^3-iodanyl group seems to be a rapid process.[6b] Facile oxidation of the iodine atom of **2c** by difluoroiodane **1** yielding a reactive (difluoro)alkyl-λ^3-iodane in preference to the addition reaction to the triple bond will be a possible alternative.[13]

λ^3-Iodanation of simple unsymmetrical internal alkynes generally produces a mixture of regioisomers of alkenyl-λ^3-iodanes.[14] We are pleased to find that the intramolecular neighboring group participation provides an excellent method for controlling the regio- and stereochemistry in λ^3-iodanation of internal alkynes, thus the reaction of 6-chloro-2-hexyne (**2e**) and 7-chloro-3-heptyne (**2f**) exclusively afforded the tetrasubstituted (*E*)-α-alkyl-β-chlorovinyl-λ^3-iodanes **3e** and **3f**, respectively, in high yields (Table 1, entries 8 and 9).[15] Structures of these rearranged vinyl-λ^3-iodanes **3d** and **3f** were unambiguously established by X-ray diffraction analyses (Figure 1).

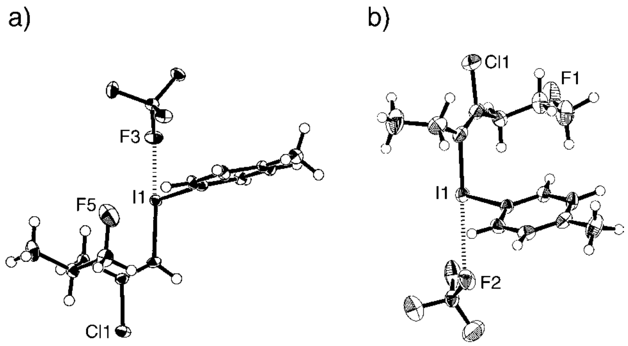
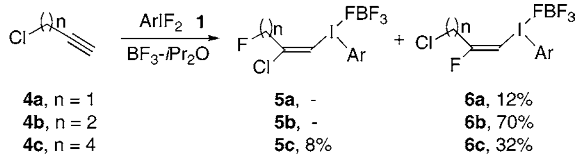


Figure 1. ORTEP drawing of (*E*)-β-chlorovinyl-λ^3-iodanes: (a) **3d** and (b) **3f**.

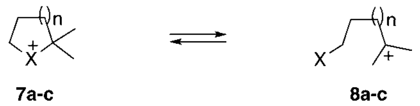
In these reactions, anti fluoro-λ^3-iodanation of alkynes **2** discussed above does not compete with the domino λ^3-iodanation−1,4-halogen shift−fluorination reaction yielding the vinyliodanes **3**. Both propargyl chloride (**4a**) and 4-chloro-1-butyne (**4b**), however, gave unrearranged fluoroiodanation products **6a** and **6b** exclusively (Scheme 2). A low yield of **6a** is attributed to the electron-deficient nature of the triple bond induced by a large inductive effect of the electronegative chlorine atom at the propargylic position. The attempted 1,3-chlorine shift in the reaction of **4b** seems to be a high-energy process because of a large ring strain of the four-membered chloronium ion.[16] The 1,5-chlorine shift can compete with a simple addition reaction, thus 6-chloro-1-hexyne (**4c**) produced a mixture of the rearranged (*E*)-β-chlorovinyliodane **5c** and the unrearranged **6c** in a ratio of 1:4. These results indicate that the rate of intramolecular chlorine shifts in λ^3-iodanation of ω-chloro-1-alkynes using difluoroiodane **1** decreases in the order 1,4- > 1,5- > 1,3-chlorine shifts.[17]

Scheme 2



It has been demonstrated that dimethyltetramethylenechloronium ion **7a** is more stable than the isomeric ring-opened carbocation **8a** at low temperature in nonnucleophilic media (Scheme 3).[18] The same holds true for the bromine analogue but with a greater preference for the five-membered bromonium ion **7b** because the bromine atom with lower electronegativity can accommodate positive charge more readily than the chlorine atom. On the other hand, with six-membered chloronium ion **7c**, the equilibrium is shifted to the open carbocation isomer **8c**.[19] These thermodynamic data are in a good agreement with our results shown in Table 1 and Scheme 2.

Scheme 3



a, n = 1, X = Cl; **b**, n = 1, X = Br, **c**, n = 2, X = Cl

Further evidence for halogen participation came from the reaction of 4,4-dialkylpentynes, in which 1,4-halogen shift was accompanied by an additional 1,2-shift of an alkyl group. Thus, the reaction of chlorodimethylpentyne **9** with difluoro-λ^3-iodane **1** afforded (*E*)-2-chloro-4-fluoro-4-methylhexenyl-

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[12] Neighboring 1,4-participation tendencies of chlorine, bromine, and even iodine atoms have been evaluated in the reaction of 5-halo-1-pentynes with trifluoroacetic acid at 60 °C. See: (a) Peterson, P. E.; Bopp, R. J.; Ajo, M. M. *J. Am. Chem. Soc.* **1970**, *92*, 2834. (b) Peterson, P. E.; Duddey, J. E. *J. Am. Chem. Soc.* **1966**, *88*, 4990.

[13] For facile oxidation of alkyl iodides with aryl-λ^3-iodanes, see: (a) Gallos, J.; Varvoglis, A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1999. (b) Zefirov, N. S.; Zhdankin, V. V.; Kozmin, A. S. *Izv. Akad. Nauk SSSR* **1983**, 1682.

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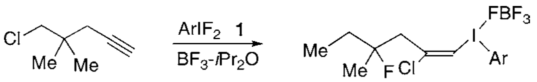
[18] (a) Henrichs, P. M.; Peterson, P. E. *J. Am. Chem. Soc.* **1973**, *95*, 7449. (b) Larsen, J. W.; Metzner, A. V. *J. Am. Chem. Soc.* **1972**, *94*, 1614.

[19] Henrichs, P. M.; Peterson, P. E. *J. Org. Chem.* **1976**, *41*, 362.

λ^3-iodane **10** in 84% yield most likely via the domino λ^3-iodanation−1,4-chlorine shift−1,2-methyl shift−fluorination sequence (Scheme 4).

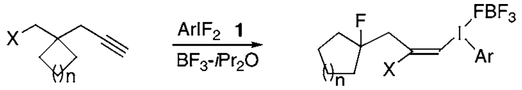
Scheme 4

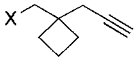
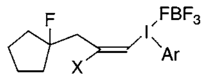
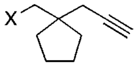
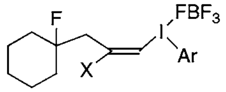
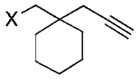
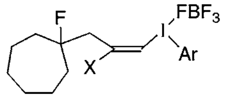


9 **10**

When the domino reaction was applied to 5-chloropentyne **11a** with a four-membered carbocycle, a ring enlargement to the cyclopentane skeleton occurred and the fluorinated (*E*)-3-cyclopentyl-2-chloropropenyliodane **12a** was obtained stereoselectively in a high yield (Table 2, entry 1). In the same manner, bromoalkyne **11b** afforded the ring-expanded (*E*)-λ^3-iodane **12b** with a cyclopentyl group, whereas the attempted 1,4-iodine shift with a ring expansion of iodoalkyne **11c** was again found to be fruitless (Table 2, entries 2 and 3). Chloro- and bromopentynes **11d** and **11e** with a cyclopentyl group resulted in the formation of fluorocyclohexanes **12d** and **12e**, respectively, in high yields. Furthermore, the domino reaction of halopentynes **11f** and **11g** possessing a cyclohexyl group afforded (*E*)-cycloheptylpropenyl-λ^3-iodanes **12f** and **12g** stereoselectively. The solid-state structure of **12a** shown in Figure 2 clearly indicates the formation of a rearranged fluorocyclopentyl moiety.

Table 2. Domino λ^3-Iodanation−1,4-Halogen Shift−Ring Enlargement−Fluorination[a]



entry	**11** (X)	**12**	yield (%)[b]
			
1	**11a** (Cl)	**12a**	87
2	**11b** (Br)	**12b**	89[c]
3	**11c** (I)	**12c**	-
			
4	**11d** (Cl)[d]	**12d**	90
5	**11e** (Br)	**12e**	92
			
6	**11f** (Cl)	**12f**	84
7	**11g** (Br)	**12g**	85

[a] Reaction conditions: Iodane **1** (2 equiv)/BF_3−$i$$Pr_2O$ (1.5 equiv)/chloroform/−60 °C to room temperature over 5 h and then room temperature for 5 h/Ar. [b] Isolated yields. [c] Contaminated with a small amount of impurity. [d] Iodane **1** (2 equiv)/BF_3−$i$$Pr_2O$ (2.2 equiv)/chloroform/−60 °C for 2 h/Ar.

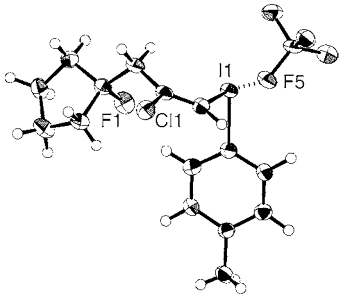
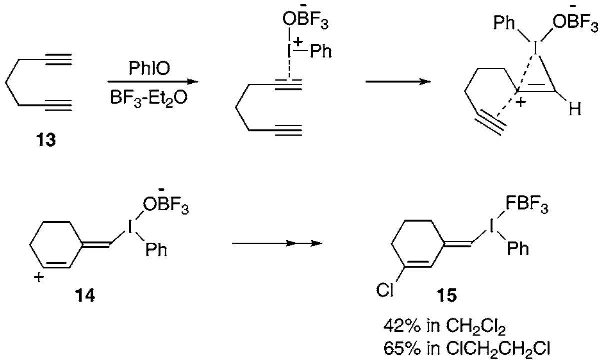


Figure 2. ORTEP drawing of ring-expanded vinyl-λ^3-iodane **12a**.

We found that intermolecular delivery of a soft chlorine atom attached to a carbon atom also took place efficiently under appropriate conditions. Exposure of 1,6-heptadiyne (**13**) to iodosylbenzene in the presence of BF_3−Et_2O in dichloromethane at room temperature afforded the cyclized δ-chlorodienyl-λ^3-iodane **15** in 42% yield (Scheme 5). The reaction probably involves an initial λ^3-iodanation of a terminal alkyne, followed by a neighboring group participation of another triple bond with formation of a cyclic vinyl cation **14**, and finally a delivery of a soft chlorine atom from the solvent dichloromethane. In fact, use of a more nucleophilic solvent dichloroethane increased the yield of dienyl-λ^3-iodane **15** to 65%.

Scheme 5



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Supporting Information Available: Typical experimental procedures, spectral data for new compounds, and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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