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Stereocontrolled Synthesis of Halovinylbenziodoxoles via Hydro- and Iodochlorination of Ethynylbenziodoxoles**

Junliang Wu,* Xiaozhou Deng, and Naohiko Yoshikai*

Abstract: We report herein the synthesis of highly substituted and stereochemically well-defined vinylbenziodoxole (VBX) derivatives through hydrochlorination and iodochlorination of ethynylbenziodoxoles. The hydrochlorination is achieved using pyridine hydrochloride as an HCl source in an *anti*-fashion under mild, open-air conditions to afford a 2-chlorinated VBX product, which serves as a useful building block for the stereoselective synthesis of trisubstituted alkenes. Meanwhile, iodochlorination with iodine monochloride proceeds in an unusual *syn*-pathway, stereoselectively affording a tetrasubstituted VBX derivative.

Hypervalent iodine compounds bearing benziodoxol(on)e (BX) backbone have emerged as versatile electrophilic group-transfer agents in organic synthesis, as the cyclic BX moiety endows the reagents with well-balanced stability and reactivity suited under broad range of reaction conditions.[1] Among various BX-based group transfer reagents, ethynyl–BXs (EBXs) have found numerous applications in C–alkynyl and heteroatom–alkynyl bond formations since the pioneering work of Waser.[1a-d,2-4] Meanwhile, this class of compounds has also found unique synthetic applications beyond simple alkynyl group transfer, where the BX group does not act as a mere leaving group but as an integral part of the product.[5] In this context, EBXs have been found to serve as precursor to functionalized vinyl–BXs (VBXs), which would serve as novel alkenyl group transfer agents that are otherwise difficult to access. We disclosed palladium-catalyzed 1,1-hydrocarboxylation of various substituted EBXs via 1,2-iodine(III) shift, affording VBXs bearing enol carboxylate moiety (Scheme 1a).[6,7] Miyake reported *anti*-addition of phenols to aryl–EBXs under visible light irradiation (Scheme 1b), where the primary VBX product readily transforms into iodovinylether.[8] More recently, Waser has found simple conditions that allow for the *anti*-addition of sulfonamides and phenols to alkyl–EBXs with retention of the BX moiety in the products.[9,10] As highly functionalized VBX compounds hold promise as versatile synthetic building blocks for stereodefined alkenes,[11] further development of EBX-to-VBX transformations is highly desirable.

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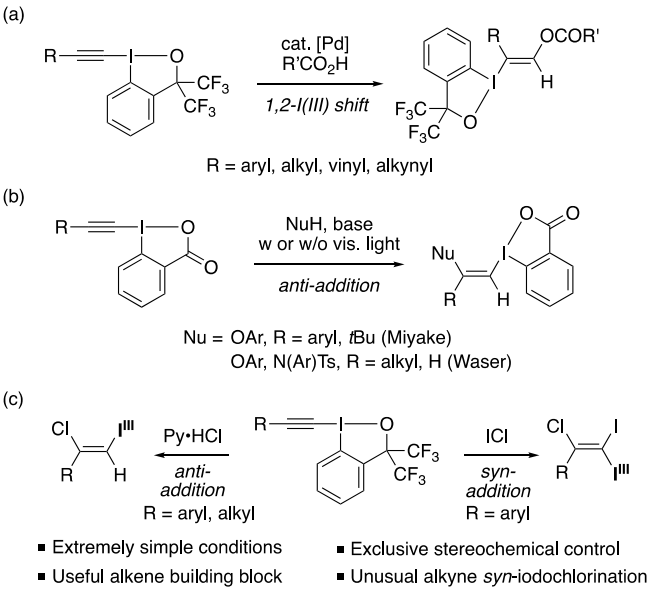
Herein, we report on stereoselective hydrochlorination and iodochlorination reactions of EBX, affording stereochemically well-defined halogenated VBX compounds (Scheme 1c). The former reaction was achieved using pyridine hydrochloride in an exclusive *anti* fashion, affording a useful building block for stereoselective synthesis of multisubstituted alkenes. The latter reaction using iodine monochloride features an unusual *syn*-addition pathway, affording an exotic tetrasubstituted VBX product.

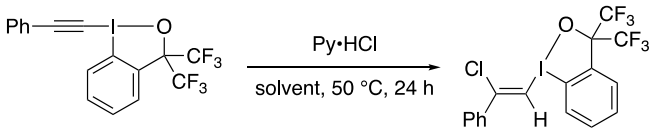


Scheme 1. Stereocontrolled synthesis of functionalized VBXs from EBXs.

Hydrochlorination of haloalkynes offers straightforward approach toward synthetically useful 1,2-chlorohaloalkenes. Zhu and Xu independently achieved *anti*-hydrochlorination of haloalkynes with LiCl/HOAc using palladium and gold catalysts, respectively,[12] which likely involved *anti*-chlorometalation of the C≡C bond as a key step.[13] Ochiai reported a transition metal-free *anti*-hydrochlorination of alkynyl(phenyl)iodonium tetrafluoroborate using LiCl/HOAc or HCl/MeOH, while the scope of the reaction was demonstrated for only a handful iodonium salts.[14,15] By contrast to these precedents, the present *anti*-hydrochlorination, found during our study on the Pd-catalyzed 1,1-hydrocarboxylation,[6] was achieved under extremely simple conditions. Thus, the reaction between Ph-EBX **1a** and pyridine hydrochloride (Py•HCl, 2 equiv) proceeded smoothly in EtOAc at 50 °C under air, affording the VBX product **2a** in quantitative yield exclusively as a *cis* isomer (Table 1, entry 1). The compound **2a** is stable under ambient conditions and can be purified by routine chromatography with minimal loss. The stereochemistry of **2a** was unambiguously established by X-

ray crystallographic analysis.[16] The reaction also took place in ethereal solvents (entries 2 and 3) or chlorinated solvents (entries 4–6), while substantial decrease in the yield was observed in some cases. We found that the combination of LiCl (10 equiv) and HOAc solvent was also effective for the *anti*-hydrochlorination, albeit in a modest yield. Note that the use of pyridine hydrobromide caused decomposition of **1a** and failed to promote the desired hydrobromination, while the hydrobromination product was observed when using LiBr and HOAc (data not shown).

Table 1. Effect of solvents on hydrochlorination.[a]



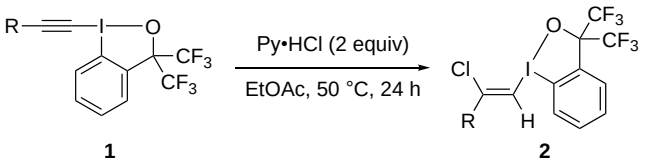
1a **2a**

Entry	Solvent	Yield [%][b]
1	EtOAc	99 (97)
2	1,4-dioxane	88
3	DME	87
4	DCE	91
5	CH_2Cl_2	68
6	$CHCl_3$	54
7[c]	HOAc	70

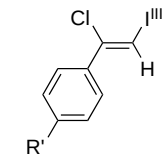
[a] The reaction was performed using 0.1 mmol of **1a** and 0.2 mmol of Py•HCl in 1 mL solvent at 50 °C for 24 h. [b] Determined by ^{19}F NMR using 1,4-bis(trifluoromethyl)benzene as an internal standard. The yield of the isolated product is shown in the parentheses. [c] The reaction was performed using LiCl (10 equiv) instead of Py•HCl at room temperature.

Table 2 summarizes the scope of the *anti*-hydrochlorination of EBXs. For EBXs derived from a variety of (hetero)arylacetylenes, the reaction proceeded smoothly to afford the desired VBX products **2a**–**2o** in moderate to excellent yields. A gram-scale reaction of **1a** (2.35 g) afforded **2a** in excellent yield (2.30 g, 91%). We observed significant effect of the substituent on the aryl group on the efficiency of the hydrochlorination. Thus, electron-withdrawing groups, such as halogen, aldehyde, ester, and cyano groups, at the *para*-position typically led to high yields (see **2b**–**2f**, 73–91%), while EBX bearing an electron-donating *para*-methoxy group underwent substantial decomposition, affording the desired product **2i** only in 31% yield. Aryl–EBXs bearing ortho substituents afforded the desired products **2l**–**2n** in apparently lower yields (42–68%), most likely due to the steric effect. 2-Thienyl–EBX afforded the desired product **2o** in excellent yield regardless of the electron-rich nature of the thienyl group. EBXs derived from alkylacetylenes and enyne were also amenable to hydrochlorination, producing the products **2p**–**2s** in good to excellent yields. Interestingly, a bis-EBX substrate underwent exclusive hydrochlorination on only one of the alkyne moieties even in the presence of excess Py•HCl (4 equiv) to afford **2t**, for unknown reasons. Notably, the present hydrochlorination could be extended to ethynylbenziodoxolone and ethynyl(phenyl)iodonium tosylate, affording the desired products **2u** and **2v**, respectively, in high yields.

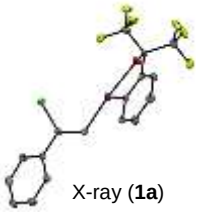
Table 2. *anti*-Hydrochlorination of EBXs.[a]



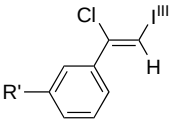
1 **2**



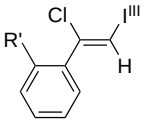
2a (R' = H), 91%[b]
2b (R' = Br), 73%
2c (R' = Cl), 89%
2d (R' = CHO), 86%
2e (R' = CO_2Et), 91%
2f (R' = CN), 81%
2g (R' = Me), 93%
2h (R' = $SiMe_3$), 61%
2i (R' = OMe), 31%



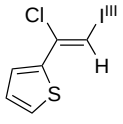
X-ray (**1a**)



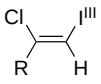
2j (R' = OMe), 91%
2k (R' = CF_3), 80%



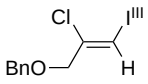
2l (R' = F), 68%
2m (R' = CF_3), 58%
2n (R' = Me), 42%



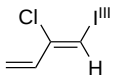
2o, 94%



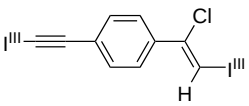
2p (R = Me), 95%
2q (R = Bu), 93%



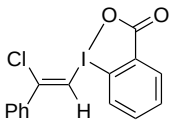
2r, 97%



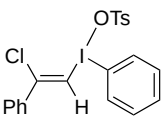
2s, 69%



2t, 83%[c]



2u, 95%



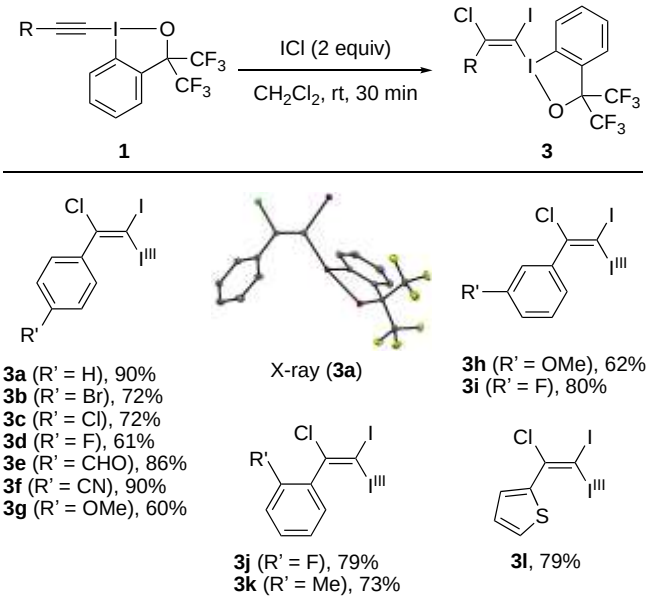
2v, 93%

[a] The reaction was performed on a 0.1 mmol scale under the conditions in Table 1, entry 1. The symbol I^{III} in the product structure refers to the benziodoxole moiety. [b] The reaction was performed on a 5 mmol scale. [c] 4 equiv of Py•HCl was used.

Iodochlorination of alkynes with iodine monochloride or equivalent reagents comprised of electrophilic iodine source and chloride anion has been explored as an approach to 1,2-iodochloroalkenes.[17] The reaction typically occurs with *anti* selectivity,[18] which can be easily rationalized by a mechanism involving formation of a cyclic iodonium species and subsequent *anti*-addition of a chloride anion. Iodochlorination of haloalkynes was also achieved using the Barluenga reagent ($I(Py)_2•BF_4$) and LiCl, featuring *anti* selectivity.[19] Given this background, we were surprised to find that the reaction of **1a** with ICl in CH_2Cl_2 completed quickly within 30 min under open air to afford the *syn*-iodochlorination product **3a** in high yield, whose stereochemistry was unambiguously confirmed by X-ray crystallographic analysis (Table 3).[16] A variety of aryl–EBXs also underwent iodochlorination to afford the products **3b**–**3l** as single stereoisomers in moderate to good yields. The reaction was particularly high-yielding with aryl–EBXs bearing aldehyde and

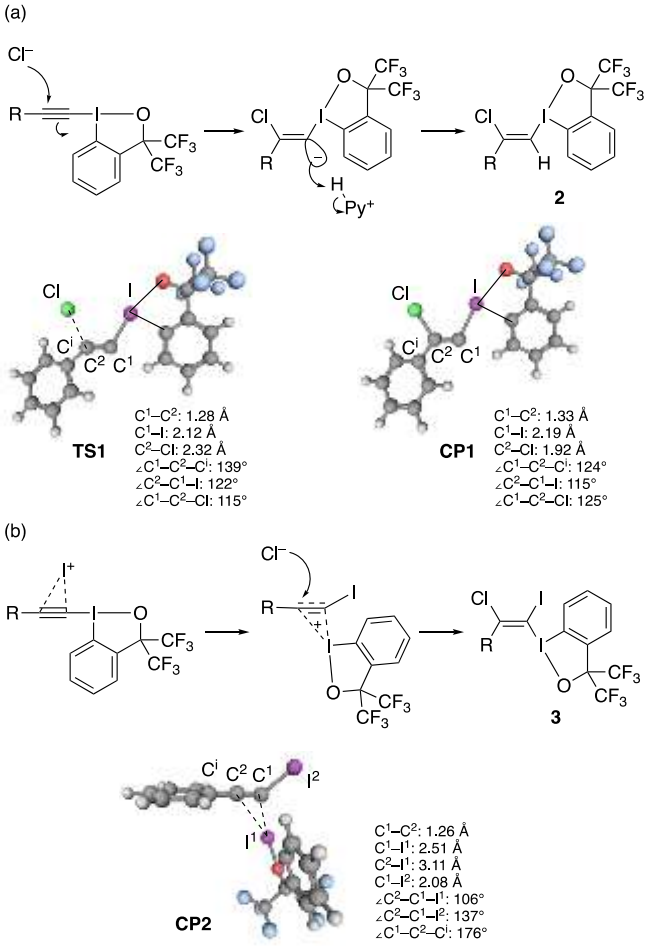
cyano groups (**3e** and **3f**), while it became somewhat sluggish with those bearing fluorine (**3d**) and methoxy (**3g** and **3h**) substituents. Unfortunately, alkyl–EBXs decomposed under the reaction conditions and failed to give the desired products.

Table 3. *syn*-Iodochlorination of EBXs.[a]



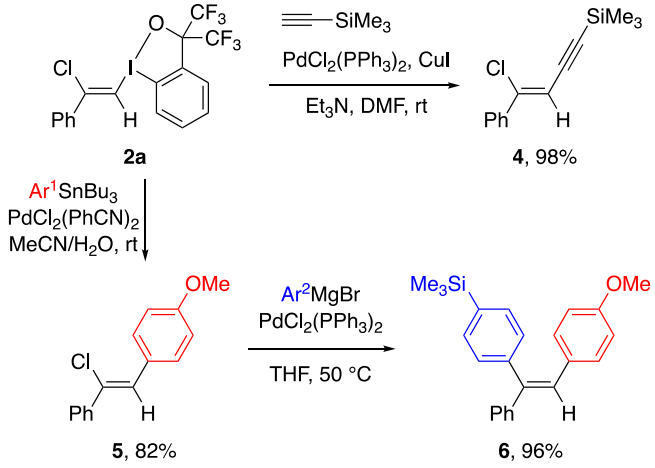
[a] The reaction was performed on a 0.1 mmol scale. The symbol I^{III} in the product structure refers to the benziodoxole moiety.

Scheme 2 illustrates proposed reaction pathways for the present hydrochlorination and iodochlorination reactions. The hydrochlorination may proceed through β-addition of a chloride ion to EBX and subsequent protonation of the resulting vinyl anion by pyridinium proton (Scheme 2a).[9,14,15] Preliminary DFT calculations on a model system (B3LYP/SDD for I, 6-31+G(d) for other atoms) allowed us to locate a transition state of chloride addition (**TS1**), which adopts a substantially bent structure and leads to a vinyl anion **CP1** (see the Supporting Information for more detail). **CP1** has *cis* arrangement of the Cl and BX groups, and its protonation would afford the *anti*-hydrochlorination product. By contrast to the hydrochlorination, it would be reasonable to assume that the iodochlorination is initiated by electrophilic activation of EBX by I^+ (Scheme 2b). DFT optimization of a complex between Ph-EBX and I^+ spontaneously converged to **CP2**, with essentially complete formation of the new C–I bond (2.08 Å compared to 2.13 Å in the product) and substantial elongation of the C–I^{III} bond (2.51 Å compared to 2.12 Å in the starting material). This barrierless structural reorganization would be due to the intrinsic weakness of the C–I^{III} bond. Thus, **CP2** may be better regarded as alkynyl iodide activated by BX cation rather than EBX activated by I cation. As such, a chloride anion would approach from the opposite side of the BX group to avoid steric hindrance, thus ensuring the *syn*-iodochlorination stereochemistry.



Scheme 2. Proposed reaction pathways of *anti*-hydrochlorination and *syn*-iodochlorination of EBX, and DFT-optimized structures.

The present hydrochlorination products would serve as versatile building blocks for the stereoselective synthesis of multisubstituted alkenes, as illustrated in Scheme 3. The product **2a** was readily converted to enyne **4** in a quantitative yield by Sonogashira coupling. A triarylethene **6** was stereoselectively prepared by a sequence of Stille and Kumada couplings in good overall yield. Meanwhile, to date, our attempts on using the iodochlorination products in the cross-coupling chemistry have been largely unsuccessful.[20] Nonetheless, further exploration is ongoing on their potential use as building blocks for tetrasubstituted alkenes and also as functionalized vinylidene-type synthons.[19a]



Scheme 3. Product transformations.

In summary, we have reported *anti*-hydrochlorination and *syn*-iodochlorination of EBXs for the synthesis of highly functionalized VBXs. Both the reactions are achieved using extremely simple reagents under mild, open-air conditions with high stereoselectivity. The 2-chloro VBXs synthesized by the hydrochlorination serve as versatile building blocks for the stereoselective synthesis of trisubstituted alkenes. The iodochlorination features a unique *syn*-selective addition pathway, and the utility of the unusual trihalogenated alkene products is currently under investigation.

Acknowledgements

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Keywords: hypervalent iodine compounds • alkyne • hydrohalogenation • dihalogenation • cross-coupling

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[16] CCDC 1900632 (**2a**) and 1900633 (**3a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[18] For *syn*-iodochlorination of silyl-substituted alkynes, see: K. C. Sproul, W. A. Chalifoux, *Org. Lett.* **2015**, *17*, 3334-3337.

[19] a) J. Barluenga, M. A. Rodríguez, P. J. Campos, G. Asensio, *J. Am. Chem. Soc.* **1988**, *110*, 5567-5568; b) J. Barluenga, M. A. Rodríguez, P. J. Campos, *Tetrahedron Lett.* **1990**, *31*, 2751-2754; c) J. Barluenga, M. A. Rodríguez, P. J. Campos, *Synthesis* **1992**, 270-272.

[20] Sonogashira coupling between **3a** and trimethylsilylacetylene (2 equiv) under typical conditions ($PdCl(PPh_3)_2$, CuI, Et_3N) afforded the double

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alkynylation product via cleavage of both the C–I bonds in a modest yield (45%). Further studies on chemoselective and iterative coupling are currently underway.

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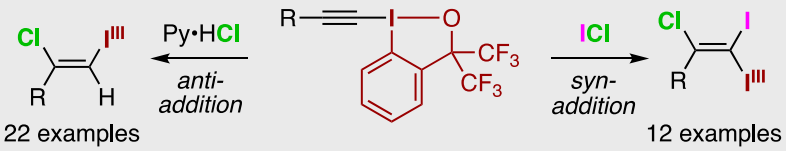

We report herein the synthesis of highly substituted and stereochemically well-defined vinylbenziodoxole (VBX) derivatives through hydrochlorination and iodochlorination of ethynylbenziodoxole (EBX). The hydrochlorination is achieved using pyridine hydrochloride as an HCl source in an *anti*-fashion under mild conditions, while the iodochlorination with iodine monochloride proceeds in an unusual *syn*-pathway.

Junliang Wu, Xiaozhou Deng, and Naohiko Yoshikai**

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Stereocontrolled Synthesis of Halovinylbenziodoxoles via Hydro- and Iodochlorination of Ethynylbenziodoxoles