Vinylbenziodoxol(on)es: Synthetic Methods and Applications

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Dedicated to Prof. Antonio Togni at the occasion of his retirement and 65th birthday.

Cyclic hypervalent iodine reagents are now frequently used in synthetic organic chemistry, either as oxidants or group-transfer reagents. Vinylbenziodoxol(on)es (VBXs) bearing alkene substituents have been less investigated than the corresponding trifluoromethyl or alkynyl reagents. Nevertheless, since 2016 the development of new synthetic methods to access VBXs has awaken the interest of the synthetic community, leading to new transformations highlighting their unique reactivity as electrophilic alkene synthons. In this review, an overview of the synthesis and applications of VBX reagents will be presented. The review is organized according to the two main classes of VBX reagents reported so far –simple alkyl/aryl-substituted VBXs and heteroatom (S, O, N, X)-substituted VBXs– as they differ significantly from the point of view of synthetic access.

Keywords: Hypervalent iodine • Benziodoxolones • Alkenes • Vinylation • Umpolung

1. Introduction

The carbon-carbon double bond is one of the most versatile functional groups in synthetic organic chemistry and it is of paramount importance in applied sciences.[1] Classical strategies such as elimination, carbonyl olefination[2] or olefin metathesis[3] enable efficient alkene synthesis. In addition, modern transition metal catalyzed cross coupling reactions and C-H bond functionalizations are routinely used to modify olefins. In this context, vinyl halides (or pseudohalides) have been applied as electrophilic vinyl partners for the creation of sp^2-sp^2 bond. However, vinyl halides can suffer from a lack of reactivity/selectivity in reactions with classical nucleophiles, radical intermediates and/or under metal-free conditions.

Hypervalent iodine (III) reagents are environmentally benign and possess enhanced reactivity in comparison to classical iodine (I) compounds.[4] The exceptional reactivity of iodine (III) derivatives originates from the weak three-center four-electron bond between the iodine atom and the two *trans* ligands associated to it: the *hypervalent bond* (Figure 1).

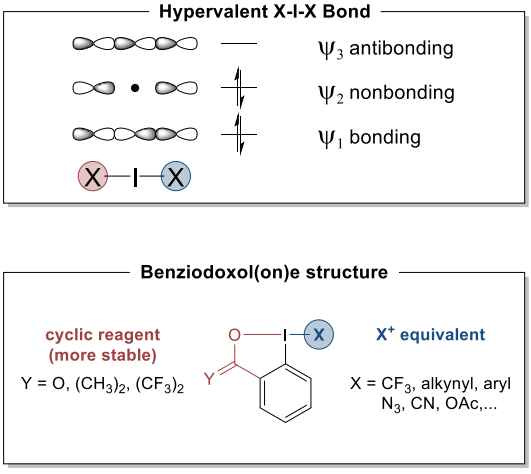


Figure 1. Hypervalent iodine bond and structure of benziodoxol(on)es.

Hypervalent iodine (III) compounds have become important functional-group transfer reagents in organic synthesis.[5] Among them, benziodoxol(on)e derivatives are exceptionally stable due to their rigid cyclic structure, and have gained in popularity over the acyclic iodonium salts.[6] Well-known benziodoxol(on)es such as Togni's reagent[7] and ethynylbenziodoxol(on)es (EBX)[8] are designed for the transfer of trifluoromethyl and alkynyl groups respectively. They are air and moisture tolerant and convenient to handle. Other benziodoxol(on)e-based reagents for the selective transfer of (hetero)aryl,[9] azide,[10] cyano,[11] and halogens[12] are also frequently used.

Taking advantage of the hypervalent bond, vinyliodonium salts have been utilized for the vinylation of various nucleophiles under mild conditions.[13] They have also been used as highly reactive partners in several metal-catalyzed cross-coupling reactions.[14] Nevertheless, their reactivity can be difficult to control and often lead to product mixtures.[15] They have been studied since several decades and have been the subject of specific reviews and book chapters.[16] In contrast, *vinylbenziodoxol(on)e* reagents (VBX) have emerged only recently as unique iodine (III) reagents for the selective transfer of vinyl groups (Figure 2). This review article will summarize the different syntheses of VBX reagents and then focus on their use as alkenylating reagents in new synthetic methods. Two classes of VBX will be differentiated and treated separately according to their substitution pattern: Compounds incorporating only C or H substituents on the olefin core will be referred as *VBXs* (section 2), while compounds having a hetereoatom conjugated to the olefin, will be identified as *hetero-VBXs* and abbreviated *X-VBXs* (with X = N, O, S,…) (section 3).

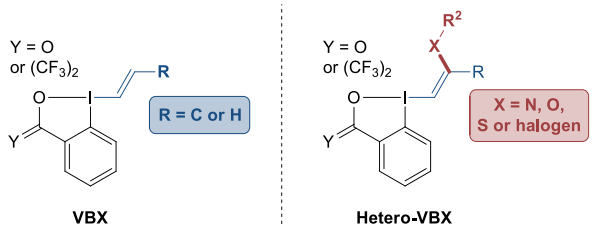
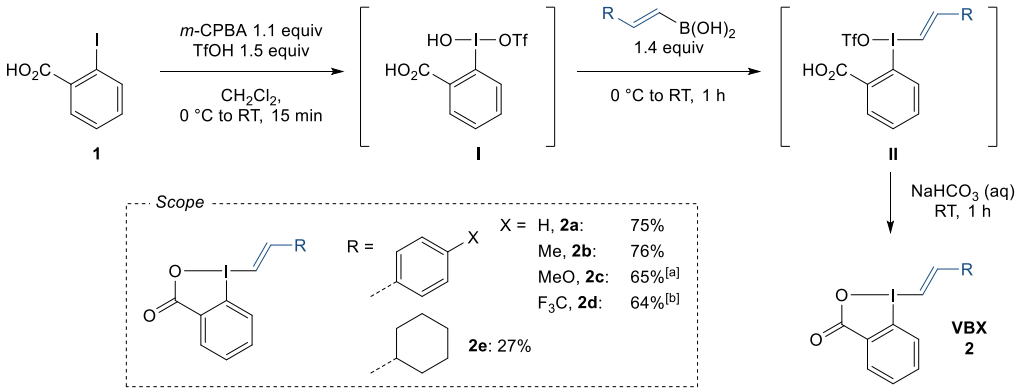


Figure 2. VBX reagents covered in this review article.

2. VBX

2.1. Synthesis

The first access to vinylbenziodoxolone reagents was reported in 2016 by the group of Olofsson.[17] The authors disclosed a practical one-pot synthetic procedure from 2-iodobenzoic acid (**1**) and coined the acronym *VBX* for the first time (Scheme 1). Oxidation of 2-iodobenzoic acid (**1**) with *m*-CPBA in presence of triflic acid forms the putative iodane intermediate **I**. Addition of vinylboronic acid then leads to iodonium salt **II**, which is then cyclized by mild basic treatment. The obtained VBX reagents **2** can be conveniently isolated by precipitation. However, the handling of hazardous dry *m*-CPBA[18] was necessary to maximize the reaction yield.

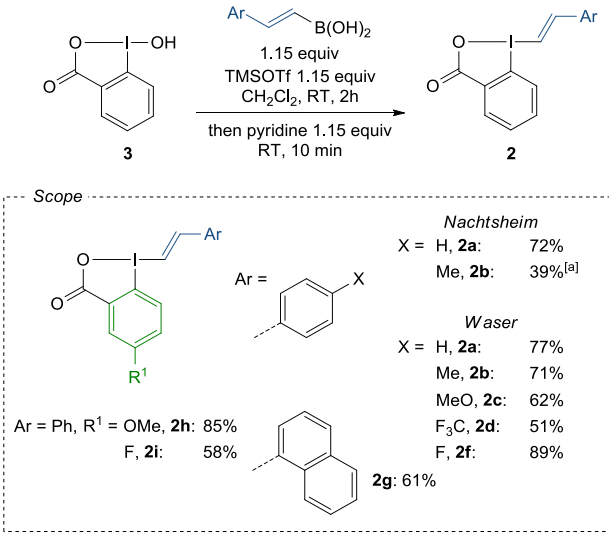


[a] TsOH instead of TfOH. [b] At 50 °C for 3 h.

Scheme 1. One-pot synthesis of VBX from 2-iodobenzoic acid (**1**).

The scope was essentially limited to aryl-substituted derivatives **2a-d**, and milder acidic conditions had to be employed for the more electron-rich **2c**. With a cyclohexyl substituent (**2e**), drastic diminution of the yield was observed. The structure of Phenyl-VBX (Ph-VBX, **2a**) was established by NMR, IR spectroscopy and X-ray crystallography. The VBX products are bench stable and can be kept in the dark at room temperature for prolonged time.

In 2017, an alternative route to access aryl-substituted VBX from pre-formed iodine (III) reagents was proposed by Nachtsheim (Scheme 2).[19] The procedure follows a common ligand exchange strategy used for the synthesis of vinyl(aryl)iodonium salts.[20] In this case, readily accessible hydroxybenziodoxolone (**3**) is first activated with TMSOTf, and then treated with vinylboronic acid. Final cyclization in presence of pyridine affords the corresponding VBX reagent **2**.

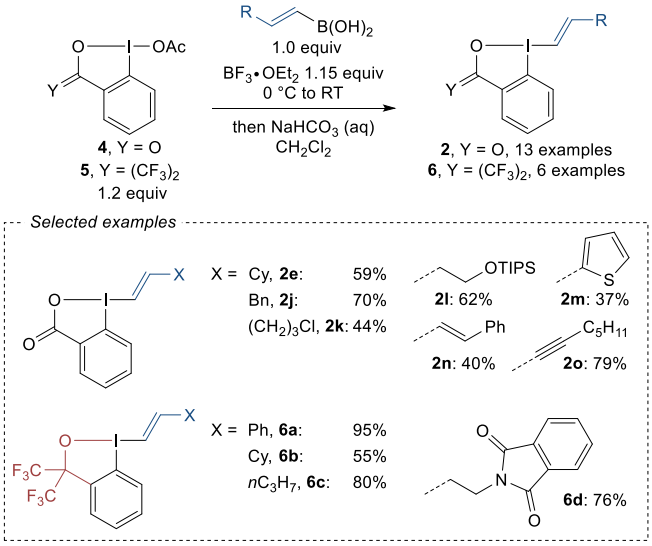


[a] Using a pinacol boronic ester as precursor.

Scheme 2. Synthesis of Ar-VBX **2** from hydroxybenziodoxolone (**3**).

Ph-VBX (**2a**) was efficiently synthesized employing this strategy, when only a moderate yield (39%) was obtained for tolyl-VBX **2b** using a pinacol boronic ester precursor instead of the acid. More recently, **2b** was accessed in good yield starting with the boronic acid precursor and additional examples of aryl-VBX **2c-2i** were disclosed by our group using this protocol.[21] Furthermore, we developed a new protocol based on Lewis acid activation for the synthesis of alkyl-substituted VBX reagents (Scheme 3). The combination of acetoxybenziodoxolone (**4**) and BF_3•OEt_2 was found optimal to access alkyl-VBX reagents such as **2e**, **2j-l** in better yields. This

protocol also gave access to other sensitive reagents, such as thiophene-substituted VBX **2m**, diene reagent **2n** and enyne reagent **2o**. In addition, the efficient preparation of benziodoxole-based reagents **6a-d**, having a hexafluoroisopropyl ligand backbone, was possible using these new reaction conditions starting from benziodoxole **5**.



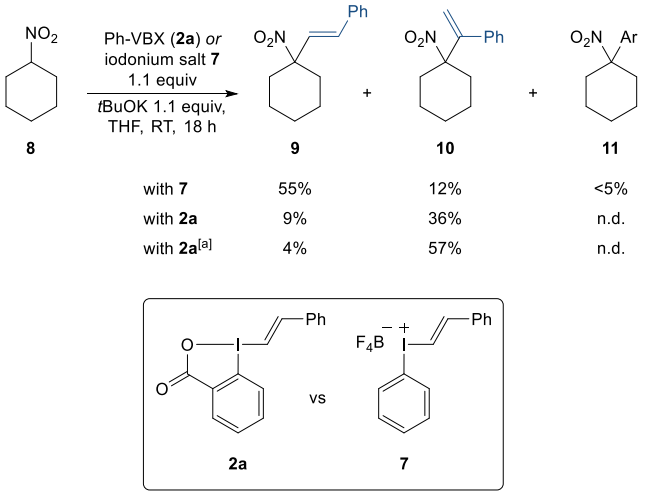
Scheme 3. VBX synthesis starting from acetoxybenziodoxol(on)es **4** and **5**.

Since the seminal work of Olofsson in 2016,[17] several syntheses of vinylbenziodoxol(on)e (VBX) have been therefore developed and allow a straightforward access to these cyclic iodine (III) reagents. A large array of functionalities ((hetero)aryl, alkyl, vinyl, alkynyl) are tolerated on the olefin, and the core structure of the reagents can be also modulated. However, major limitations need to be pointed out: The difficult handling of alkenyl boronic acids as vinyl source may restrain the scope and the practicability of the procedures, but efforts to use more practical precursors (silyl reagents or directly unsubstituted alkenes) were not successful so far. Efforts to synthesize the Z-isomer of VBXs have remained elusive, and these compounds might be unattainable based on previous reports on vinyl(aryl)iodonium salts indicating that both decomposition and isomerization are potential issues.[22]

2.2. Reactivity

Metal-free reactions

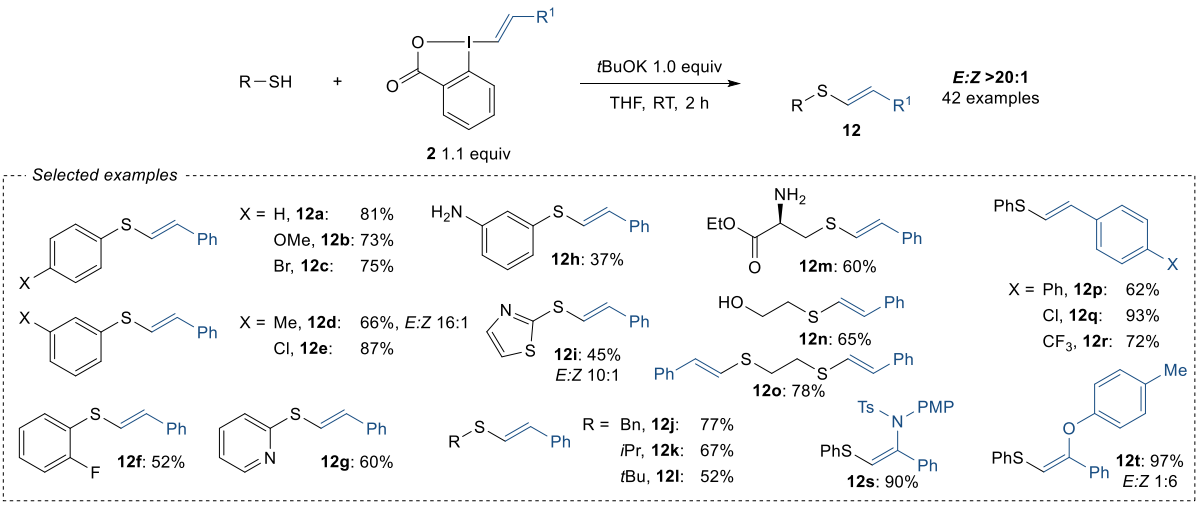
In addition to their synthetic protocol, Olofsson and coworkers made a comparative study of the reactivity of Ph-VBX (**2a**) and acyclic vinyl(phenyl)iodonium salt **7** for the *C*-alkenylation of nitrocyclohexane (**8**) under basic conditions (Scheme 4).[17] They observed the 1,1-disubstituted alkene **10** as major product in the case of Ph-VBX (**2a**), while the 1,2-disubstituted isomer **9** was obtained preferentially with iodonium salt **7**. No arylated product **11** was observed with VBX **2a**, which confirmed the complete chemoselectivity for vinyl transfer, whereas traces of side-product **11** were detected with **7**. The reaction was briefly optimized to increase the yield and the regioselectivity in favour of **10**.



[a] Optimized conditions: **2a**, 2.0 equiv, DME and 72 h were used. n.d. = not detected.

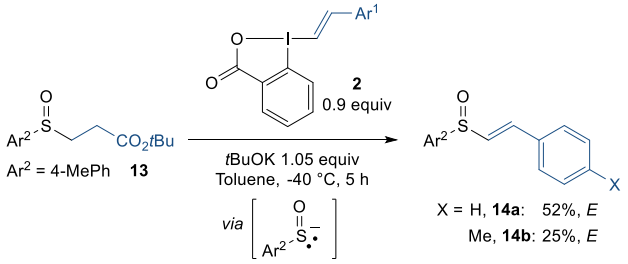
Scheme 4. Reactivity comparison between VBX **2a** and vinyliodonium salt **7**.

The same group applied VBX reagents to the electrophilic alkenylation of thiols under mild and transition metal-free conditions (Scheme 5).[23] After screening of several bases and solvents, *t*BuOK in THF was selected, allowing the formation of products **12** in good yield, excellent *trans* stereoselectivity and with minor formation of disulfide side products. The reaction was suitable for a large array of thiols, including aromatic (**12a-i**) and aliphatic thiols (primary (**12j**), secondary (**12k**) and tertiary (**12l**)). More challenging substrates possessing heterocycles (**12g** and **12i**) or further nucleophilic functions (**12m** and **12n**) were well tolerated, and the double functionalization of di-thiols could be achieved (**12o**). The scope in respect to VBX reagents was also investigated and allowed the introduction of various aryl-substituted vinyl groups having different electronic properties (**12p-r**). However, vinylation with Cy-VBX (**2e**) gave only modest yield and the scope of alkyl-VBXs was not further explored. Few examples of vinylations with N- and O-VBX were disclosed (**12s** and **12t**). The reaction of N- and S-VBX with sulphur nucleophiles had been already reported previously by our group[24] and the Miyake group[25] respectively (See section 3.2).



Scheme 5. Electrophilic vinylation of free thiols with VBX reagents.

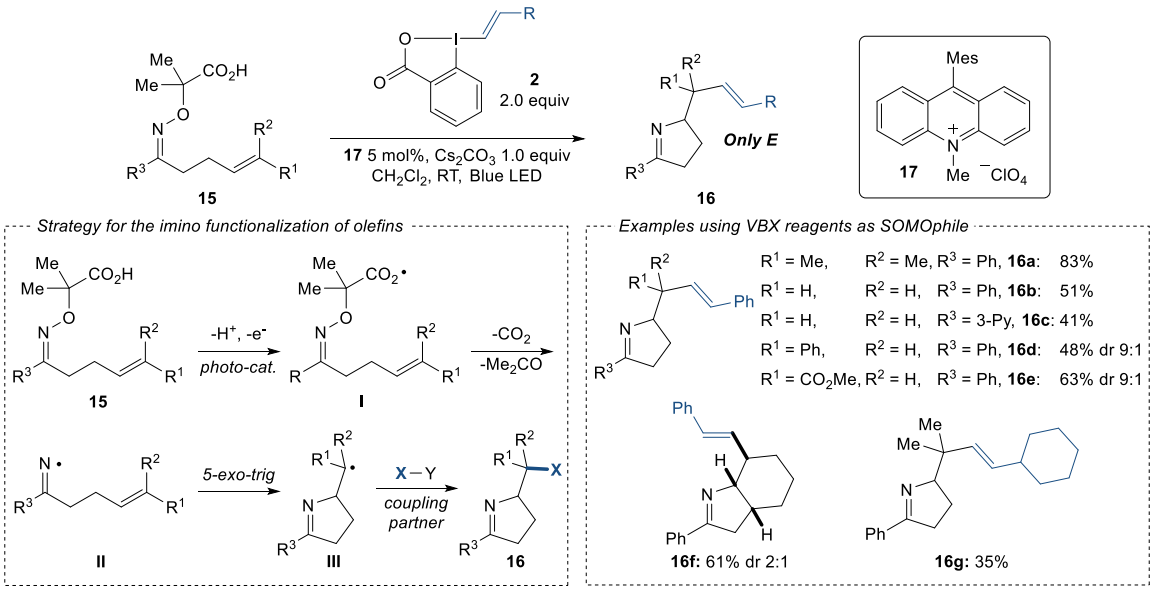
Our group reported the alkynylation of sulfenate anions, generated via retro-Michael addition from sulfanyl esters **13**, using EBX reagents in presence of *t*BuOK as base.[26] The transformation was successfully extended to the vinylation using Ar-VBX **2** without re-optimization of the experimental conditions (Scheme 6). Perfect conservation of the stereochemistry was observed in these two particular thio-vinylation cases, allowing access to valuable *E*-vinyl sulfoxides **14a** and **14b**.



Scheme 6. Vinylation of sulfenate anions generated *in situ* from sulfanyl esters **13**.

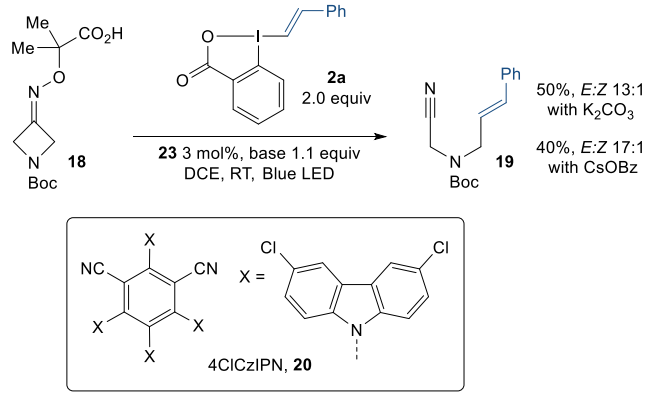
Vinylation of free radical

As several other hypervalent iodine transfer reagents,[27] VBXs proved to be good electrophilic radical acceptors. With the recent advent of photoredox catalysis several groups have started to apply VBX reagents under such conditions. In 2017, the group of Leonori reported the first use of VBX reagents as partners in a free-radical photoredox process mediated by acridinium dye **17** (Scheme 7).[28] A nitrogen-centred radical **II** was generated through a photoredox-initiated decarboxylation of oxime precursors **15** via carboxy radical **I**, followed by cyclization to give alkyl radical **III**, which is trapped to furnish nitrogen heterocycles **16**. Ph-VBX (**2a**) was effectively employed as radical trap without erosion of the olefin *E:Z* ratio to give products **16a-f**. Cy-VBX (**2e**) was also used in one example, furnishing the desired product **16g** in moderate yield.



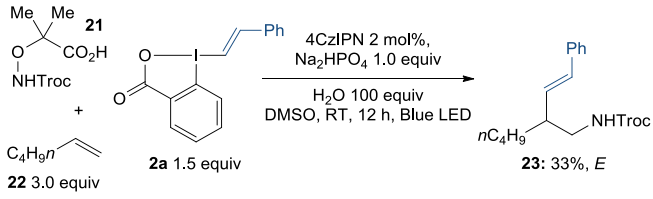
Scheme 7. Intramolecular photocatalyzed imino-vinylation of olefins with VBX **2**.

Our group has been particularly interested in merging hypervalent iodine chemistry and photoredox-catalyzed transformations. We reported the use of Ph-VBX (**2a**) as radical acceptor in a decarboxylation-fragmentation cascade of cyclic oxime **18** photocatalyzed by organic dye **20** to give nitrile **19** (Scheme 8).[29] In this example, partial isomerization of the double bond was observed. Isomerization could be minimized by using a milder base.



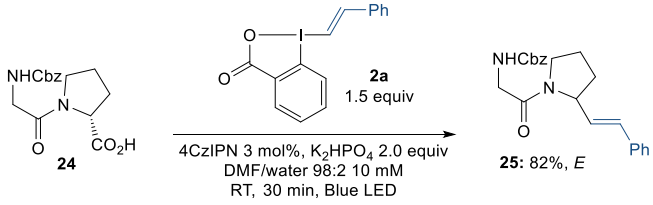
Scheme 8. Fragmentation of cyclic oxime **18** to give nitrile **19**.

A three-component radical difunctionalization of unactivated alkenes was reported by Studer and Jiang (Scheme 9).[30] In their methodology, an amidyl radical is generated by decomposition of α-amido-oxy acid precursor under organo-photoredox conditions. The authors reported the amido-alkenylation of 1-hexene (**22**), using **21** and Ph-VBX (**2a**). The expected three-component product **23** was obtained, albeit in low yield.



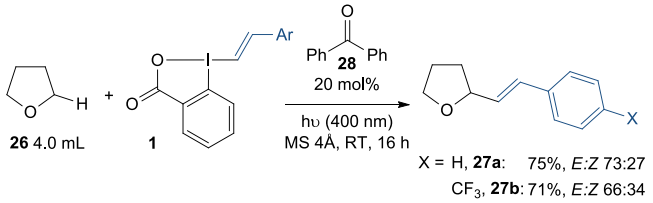
Scheme 9. Example of 1,2-amido-alkenylation of olefin **22** reported by Studer.

Recently, we disclosed a methodology for the *C*-terminus functionalization of peptides through a catalytic photoredox decarboxylation.[31] The work was directed towards alkynylation, but Ph-VBX (**2a**) could be also used for the selective vinylation of dipeptide **24** to give **25** in 82% yield (Scheme 10).



Scheme 10. Olefination at the *C*-terminus of dipeptide **24** using organo-photoredox catalysis.

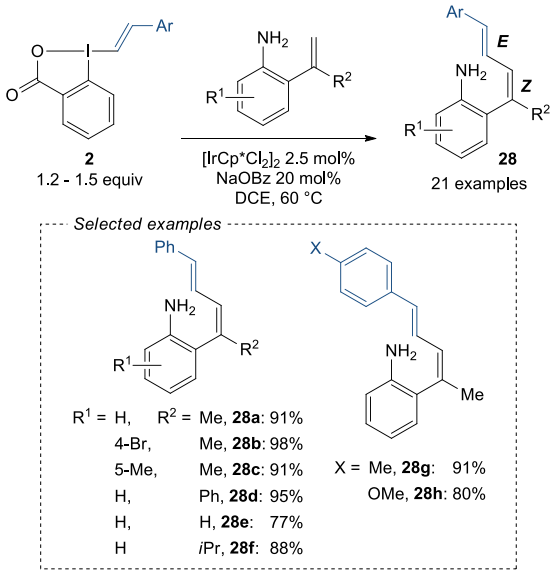
Nemoto and coworkers reported in 2020 the C(sp^3)-H olefination of THF (**26**) by using Ar-VBX reagents **2** in presence of benzophenone (**28**) as organic triplet-sensitizer at 400 nm (Scheme 11).[32] Good yields were obtained. However, the irradiating conditions led to isomerization of the double bond.



Scheme 11. Benzophenone (**28**) promoted vinylation of THF (**26**).

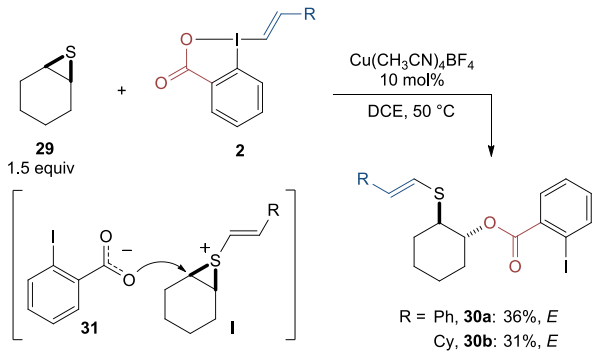
Metal-catalyzed transformations with VBX

Transition-metal-catalyzed activation of inert C(sp^2)-H bonds is a particularly active research area in organic synthesis.[33] An iridium-catalyzed direct C-H alkenylation of 2-vinylaniline derivatives with VBX reagents **2** was reported by the Nachtsheim group (Scheme 12).[19] The key deprotonation-metalation event was directed by the NH_2 group and VBXs showed superior reactivity compare to vinyliodonium salts. This method gave direct access to useful functionalized 1,3-dienes **28a-h** in excellent yields and with high to perfect (*Z*,*E*) stereoselectivity.



Scheme 12. Ir(III)-catalyzed C-H vinylation of 2-vinylanilines.

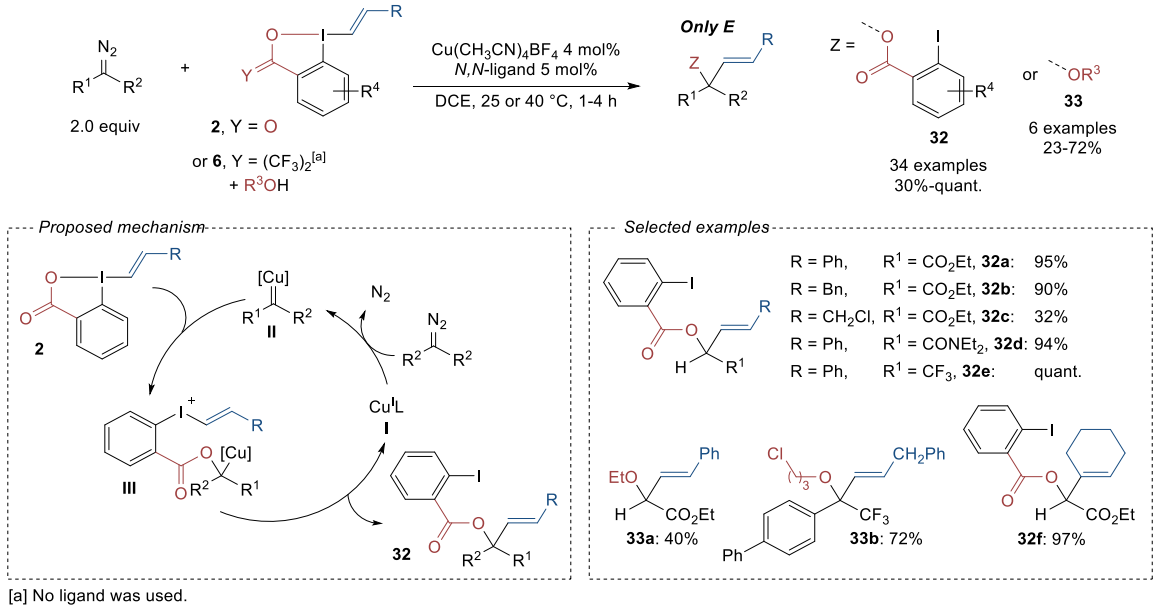
Finally, our group has studied the use of VBX reagents in copper catalysis. In our work for the difunctionalization of thiirane and thiethanes with hypervalent iodines reagents, we reported two examples of ring-opening reaction of cyclohexene sulfide (**29**) with Ph-VBX (**2a**) and Cy-VBX (**2e**) to access vinyl-thioethers **30a** and **30b** (Scheme 13).[34] The released benzoate **31** acts as a nucleophile, resulting in perfect atom economy, which is rare in hypervalent iodine chemistry.[35] The copper (I) catalyst is believe to activate the iodine (III) reagent and accelerate the formation of a reactive episulfonium intermediate **I**.



Scheme 13. Copper-catalyzed oxyvinylation of thiirane **29**.

In 2020, we disclosed the insertion of VBX reagents into diazo compounds using copper catalysis (Scheme 14).[21] Based on our previous experience on oxyalkynylation,[36] we identified VBX reagents **2** as privileged partners to realize the 1,1-oxyvinylation of transient copper-carbene intermediates.

This transformation cannot be performed using existing methodologies with vinyl halides.[37] The reaction was proposed to start with the nucleophilic attack of the carboxylate of VBX **2** onto the highly electrophilic copper-carbene **II** generated by reaction of the catalyst **I** with the diazo compound. Vinyl transfer from iodonium intermediate **III** would then give oxyvinylation product **32**. No isomerization of the transferred olefin was observed. Importantly, the reaction tolerated well the presence of various substituents on the alkene (products **32a-c** and **32f**), which motivated us to develop new functionalized VBX reagents (See section 2.1). Variation of the diazo compound was also possible (products **32d** and **32e**). In addition, the utilization of non-nucleophilic benziodoxole-based VBX **6** enabled the extension of the reaction to a three-component variant with external alcohol nucleophiles instead of the iodobenzoate (products **33a** and **33b**).



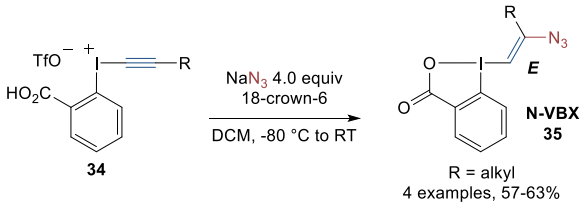
[a] No ligand was used.

Scheme 14. Copper-catalyzed 1,1-oxyvinylation of diazo compounds using VBX reagents **2** and **6**.

3. Hetero-VBX

3.1. Synthesis of hetero-VBX

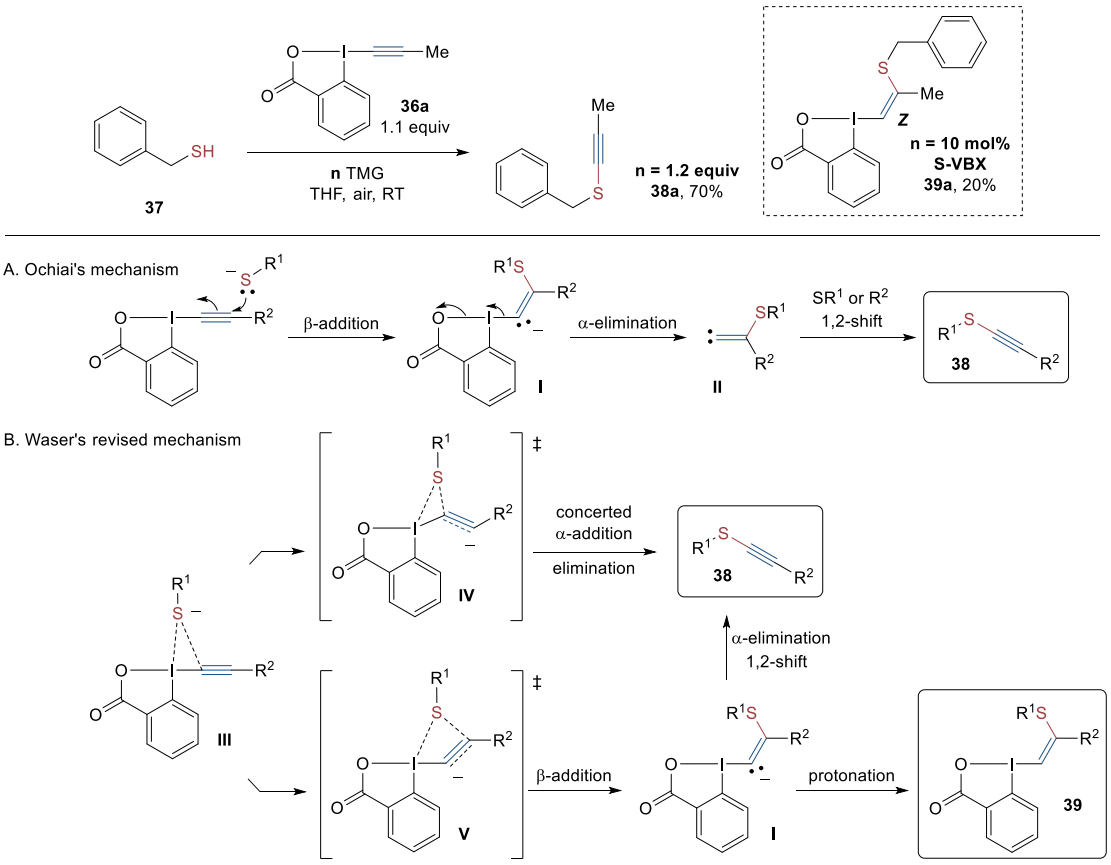
Among VBX reagents, hetero-substituted vinylbenziodoxolones (X-VBX, **2**) have been broadly studied since 2013. The first reported vinyl-substituted cyclic iodinanes **35** were discovered by the group of Fujiwara as early as 1996 (Scheme 15).[38] Iodinanes **35** were obtained from a Michael addition reaction of sodium azide on alkynyl-benzoic-iodonium triflates **34**. The unexpected *syn*-addition, leading to the *trans* olefin, contrasted with previous reactions of alkynyliodonium salts with azide nucleophiles that usually led to the *cis* isomer. Different N-VBX **35** bearing alkyl substituents from butyl to decyl could be obtained in moderate yields.



Scheme 15. First reported vinyl-substituted cyclic iodinanes **35**.

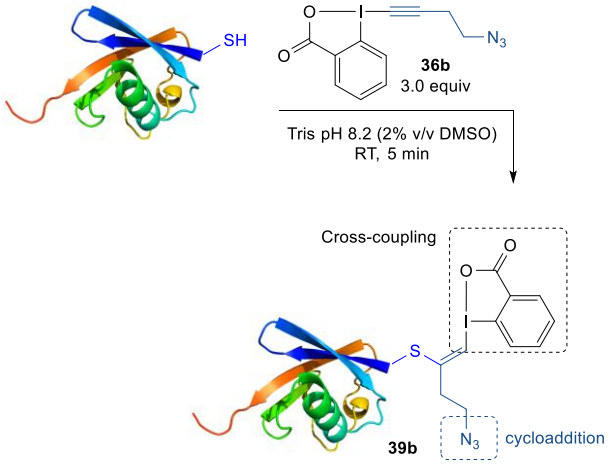
After this pioneering discovery, the study of X-VBX reagents remained latent for many years. In 2013, our group published a chemoselective thioalkynylation with TIPS-EBX.[39] The reaction proceeded at room temperature within five minutes, making the study of its mechanism particularly challenging. With Me-EBX (**36a**) thiovinyl benziodoxolone **39a** was observed as a side product in the synthesis of thioalkyne **38a** from benzyl thiol (**37**) (Scheme 16).[40] Interestingly, the use of a catalytic amount of base allowed to isolate **39a** in 20% yield as a single Z isomer. Its formation was first rationalized by protonation of the vinyl iodane **I**

generated by conjugate addition as proposed by Ochiai (Scheme 16A).[41] In contrast, alkynylation product **38** would be obtained via α-elimination to give carbene **II** followed by 1,2-migration. Computational studies by our group later uncovered two further reaction pathways: Starting from iodine-sulfur interaction complex **III**; both a concerted α-addition/elimination transition state **IV** and a β-addition transition state **V** with a sulfur-iodine interaction were located (Scheme 16B).[42] The latter pathway is favored for alkyl substituents and leads to the same vinyl iodane **I** as proposed by Ochiai, rationalizing the formation of **39**. The synthesis of S-VBX reagents was however not further optimized at this stage.



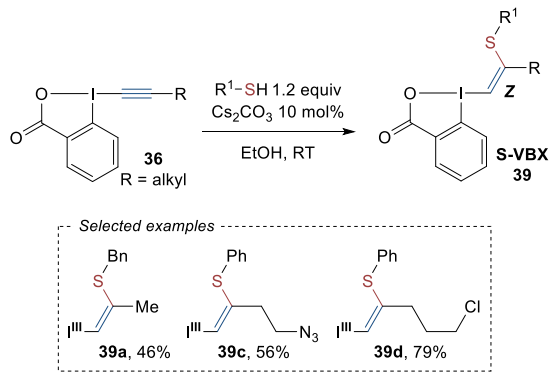
Scheme 16. Alkynylation of thiols with EBX reagents, isolation of S-VBX intermediate **39a** and proposed mechanisms.

In 2019, our group reported a cysteine bioconjugation methodology for the introduction of hypervalent iodine compounds onto biomolecules (Scheme 17).[43] Cysteine-containing peptides and proteins were engaged in a selective addition onto the alkynyl triple bond of EBX **36b**, resulting in stable VBX conjugates **39b**. The general cysteine labeling protocol demonstrate high efficiency, chemoselectivity, and functional-group tolerance under native conditions. The hypervalent iodine and the azide group could be then selectively modified (see section 3.2).



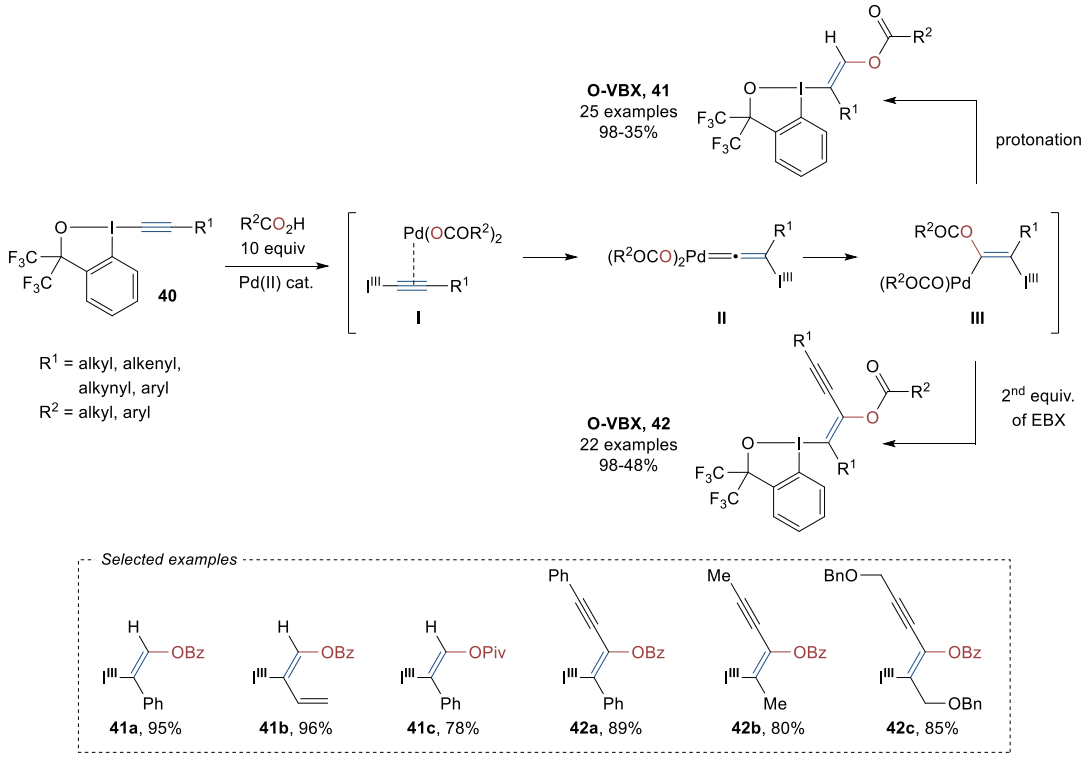
Scheme 17. Reaction of EBX **36b** with cysteine-containing biomolecules.

Using modified conditions, thiols contained in small organic molecules could also be used for the synthesis of S-VBX reagents (Scheme 18). Derivatives **39a** and **39c-d** were obtained in moderate yield with complete *Z*-stereoselectivity.[43]



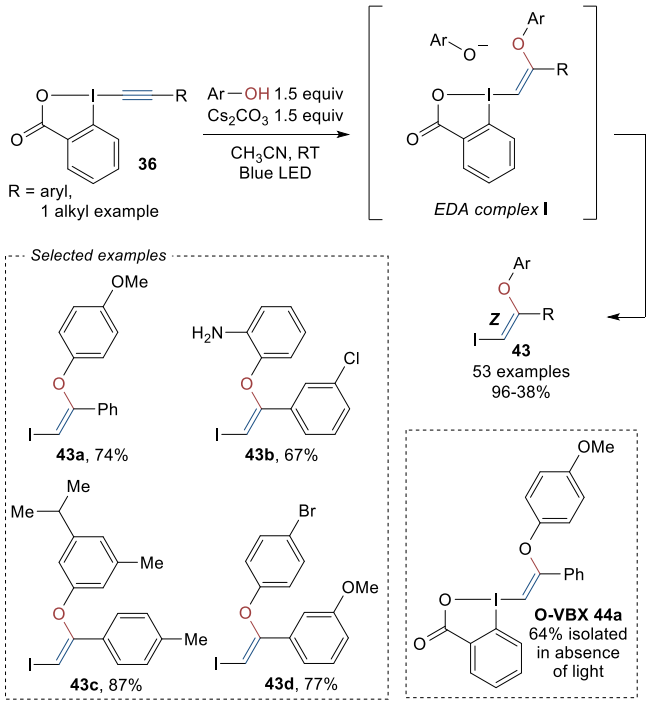
Scheme 18. Stereoselective synthesis of S-VBX reagents **39a** and **39c-d**.

The formation of O-VBXs **41** from EBX reagents **40** was firstly studied by Yoshikai and coworkers (Scheme 19). In 2016, they published the formation of *E*-alkenylbenziodoxoles **41** from the palladium-catalyzed addition of carboxylic acids to EBXs **40**.[44] Mechanistic experiments and computations suggested that the Pd(II) carboxylate-ligated alkynylbenziodoxole **I** undergoes a 1,2-I(III) shift to form **II**, followed by a migratory insertion of the vinylidene-Pd species (1,1-hydrocarboxylation) to give **III**. Finally protonation delivers the O-VBX reagent **41** with a *trans* geometry. The use of the COD ligand was critical to prevent decomposition. By changing the ligand to octahydrophenazine and increasing the equivalents of EBX **40**, alk-1-en-3-ynylbenziodoxoles **42** were obtained via interception of **III** with **40**, leading to a 1,1-carboxyalkynylation.[45] Both methods tolerated a variety of alkyl- alkenyl- alkynyl- and aryl(alkynyl)benziodoxoles and a series of alkyl- and arylcarboxylic acids, leading to hypervalent iodine reagents such as **41a-c** and **42a-c** in excellent yields. The reagents could be efficiently used as precursors in cross-coupling reactions (see section 3.2).



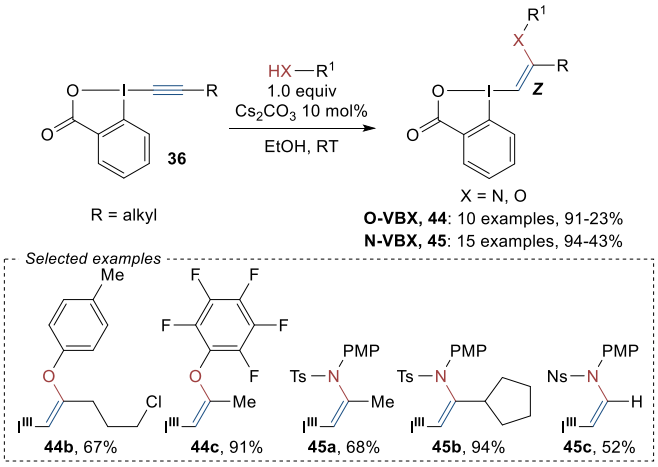
Scheme 19. Pd-catalyzed conversion of EBX **40** to functionalized O-VBX reagents **41** and **42** through 1,2-I(III) shift and 1,1-hydrocarboxylation or 1,1-carboxyalkynylation.

The addition of phenols on EBXs **36** was later reported by Miyake and coworkers, who developed a regio- and stereoselective synthesis of *Z*-2-iodovinyl phenyl ethers **43** under blue LED irradiation in presence of Cs_2CO_3 as a base (Scheme 20).[46] Several vinyl iodides such as **43a-43d** were obtained in good to excellent yields. The reaction is efficient with a broad range of phenols. In addition, different phenyl-substituted EBXs **36** can be used in the transformation, and one example is described with an EBX reagent **36** bearing an alkyl group. Interestingly, control experiments in absence of light led to the observation and isolation of O-VBX **44a**. Based on a series of experiments and computations, they proposed that the transformation proceeds through an electron donor-acceptor (EDA) complex **I**. In **I**, a photoinduced electron transfer is supposed to occur from the phenoxide donor to the O-VBX acceptor. DFT calculations support that this one-electron reduction of the VBX leads to spontaneous phenyl-iodine bond cleavage to provide the *Z*-2-iodovinyl phenyl ethers **43**. Using Cs_2CO_3, light was shown to be essential for the transformation. However, when the strong organic base 1,5,7- triazabicyclo[4.4.0]dec-5-ene (TBD) was used, no light was needed to promote the reaction. In this case, a thermal activation of the electron transfer was proposed.[47]



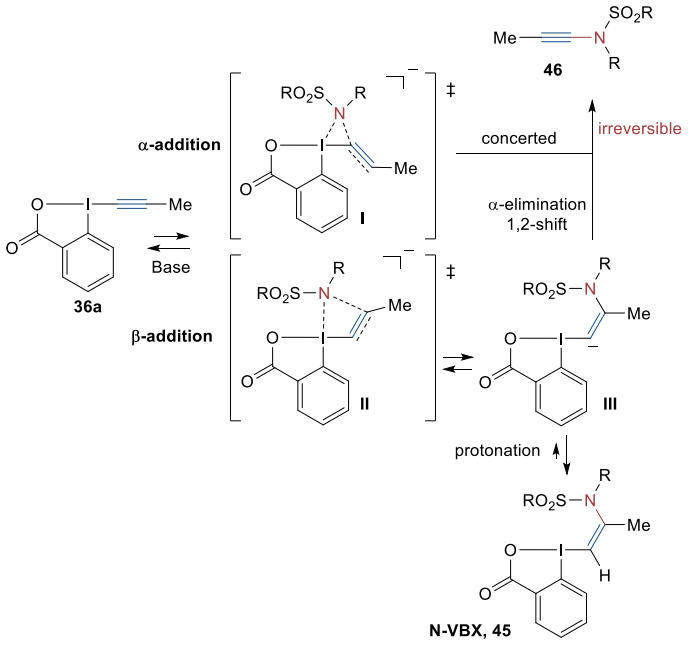
Scheme 20. Light-driven synthesis of *Z*-2-iodovinyl phenyl ethers **43** and isolation of O-VBX **44a**.

This work was an important breakthrough for the metal free addition of nucleophiles on EBX, however only two examples of VBX reagents were isolated. At the same time, our group was working on the synthesis of new O- and N-VBX reagents with focus on a protocol allowing to isolate them in good yields.[24] Based on the insights gained from the isolation of S-VBX **39a** in our previous work on the alkynylation of thiols,[40] optimized reaction conditions were developed (Scheme 21). *Z*-Enol ether and enamide-substituted benziodoxolones reagents **44**, and **45** were obtained by stereoselective addition of phenols and sulfonamides to EBXs **36** using a catalytic amount of Cs_2CO_3. The mild conditions developed tolerated numerous functional groups and the methodology could be used for modification of natural products and drugs. O- and N-VBXs such as **44b-c**, **45a-c** were obtained in good to excellent yields.



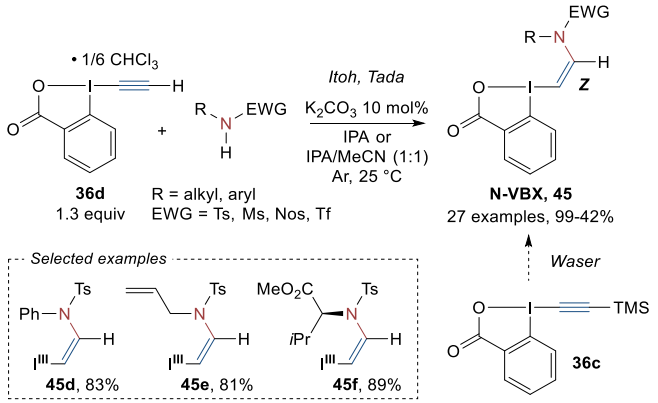
Scheme 21. Stereoselective synthesis of O- and N-VBX reagents **44b-c** and **45a-c**.

Nucleophilic addition of sulfonamides onto EBXs **36** had been previously reported by the group of Cossy, but this methodology, which involved a stoichiometric amount of base, led to the formation of the corresponding ynamides **46**.[48] To better understand the different reaction outcome when using a catalytic amount of base, computational studies were performed and an α and a β-addition transition state could be located (**I** and **II** in Scheme 22). The β-addition was shown to be favoured by about 10 kcal mol^{-1} to give **III**. Protonation of **III** was favoured by 15 kcal mol^{-1} compared to carbon-iodine bond breaking leading to **46**, giving **45** as the only product. However, in a presence of an excess of base, larger amounts of **III** are present in the reaction mixture, allowing for irreversible carbon-iodine cleavage.



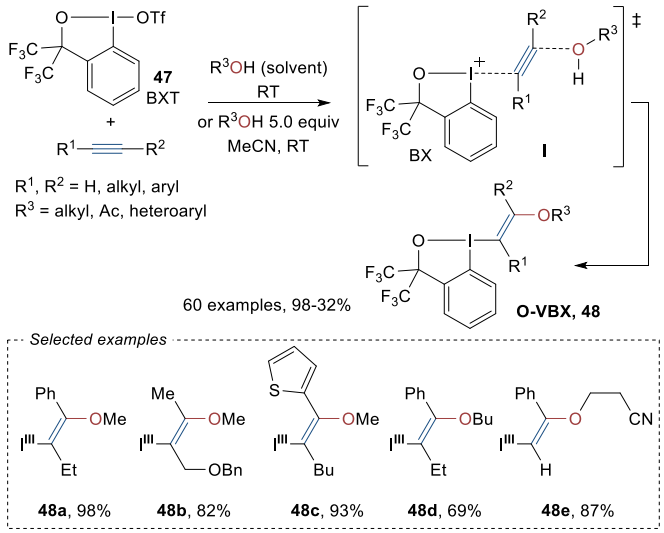
Scheme 22. Proposed mechanism for the selective formation of N-VBX reagent **45** over alkynylation product **46**.

During this work, one example of unsubstituted N-VBX **45** could be obtained from trimethylsilyl-EBX (**36c**), with *in situ* desilylation (Scheme 23). In 2019, Itoh, Tada and coworkers reported the synthesis of *cis*-β-amidevinyl benziodoxolones from an ethynyl-1,2-benziodoxol-3(1*H*)-one-chloroform complex (**36d**).[49] The reaction proceeded under mild conditions, in presence of a catalytic amount of base and sulfonamides derived from various amines, including amino acids, could be used as nucleophiles for the transformation. Hypervalent iodine reagents **45d-f** could be access in excellent yields. Furthermore, a synthetic approach for the synthesis of selectively deuterated N-VBX **45** was also developed.



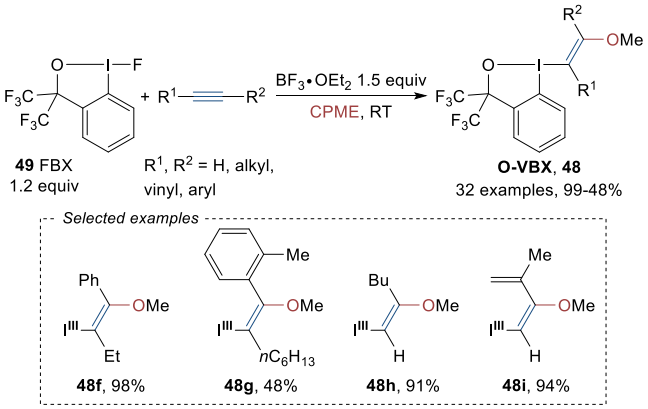
Scheme 23. Stereoselective synthesis of *cis*-β-amidevinyl benziodoxolones **45**.

Benziodoxolones are the starting material of choice for the stereoselective synthesis of hetero-VBX, by addition of phenol, sulphonamide and thiol nucleophiles. However, with the previously described methodologies, the addition of aliphatic alcohols could not be achieved. Yoshikai and coworkers answered this challenge with a regio- and stereoselective synthesis of highly substituted β-λ³-iodanyl vinyl ethers **48** achieved through *trans*-1,2-difunctionalization of alkynes with benziodoxole triflate (BXT, **47**) and alcohols (Scheme 24).[50] No base was required for the reaction to proceed and the mild conditions developed tolerated various internal and terminal alkynes, as well as a large range of alcohols, furnishing derivatives such as **48a-e** in high yields. In contrast to previously established methods, this approach did not require the preparation of a different EBX **40** for each O-VBX **48**. Supported by DFT calculations, the reaction was proposed to proceed through a stereoselective addition of alcohol via transition state **I**. Upon dissociation of triflate from BXT (**47**), a BX cation activate the alkyne, which triggers the nucleophilic addition of alcohol onto the triple bond with a Markovnikov-type selectivity. In the case of unsymmetrical dialkyl alkynes, the attack of alcohol was shown to occur on the sterically less hindered alkyne carbon. Such mechanism gives a *trans*-β-addition, contrary to the usual *cis*-β-addition observed for addition on EBX reagents.



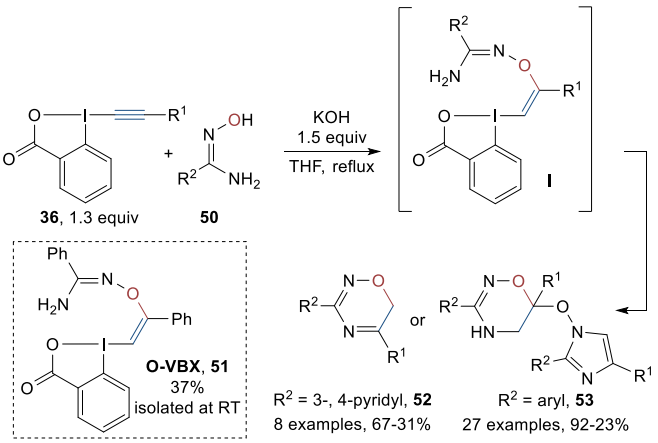
Scheme 24. Stereoselective synthesis of O-VBX **48** from BXT (**47**).

A combination of fluorobenziodoxole (FBX, **49**) and BF_3•OEt_2 in ethereal solvent was proposed as an alternative to generate the BX cation (Scheme 25).[51] The reaction proceeded with the same regio- and stereoselectivity as previously described, and after nucleophilic attack of cyclopentyl methyl ether (CPME), the oxonium intermediate undergo β-elimination to afford product **48**, HBF_4 and cyclopentene. Compounds such as **48f-i** could be synthesized in comparable to better yields than with the BXT (**47**)/alcohol system. A broad range of internal and terminal alkynes is again tolerated, but, compared to the previous methodology, the scope of alkoxy groups is limited to methoxy derived from the solvent CPME.



Scheme 25. Stereoselective synthesis of O-VBX **48** from FBX (**49**) and CPME.

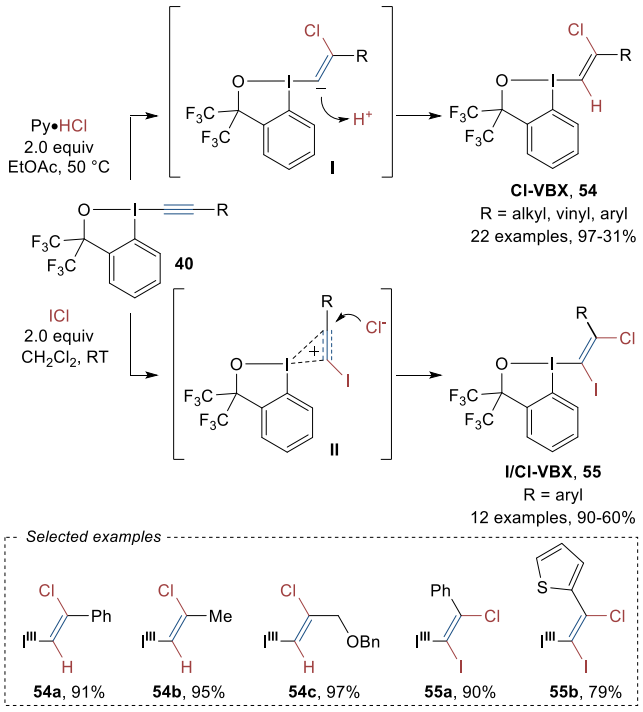
Li, Wen and coworkers reported a substituent-controlled synthesis of oxadiazine derivates from EBX **36** and amidoximes **50** (Scheme 26).[52] Under basic condition, the deprotonated amidoximes **50** attacks the β-carbon of EBX **36** to form a *Z*-vinylbenziodoxolone intermediate **I** that could be isolated at room temperature in the case of **51**. At higher temperature, VBX intermediate **I** can undergo either intramolecular cyclization to give **52** or a more complex addition/condensation cascade with a second equivalent of **36** and **50** resulting in heterocycle **53** depending on the substrate.



Scheme 26. Synthesis of oxadiazine derivatives **52** and **53** from EBXs **36** and amidoximes **50**.

Halovinylbenziodoxoles **54** and **55** were also synthesized by the group of Yoshikai who reported the stereoselective hydrochlorination and iodochlorination of EBX **40** (Scheme 27).[53] The reactions were achieved

under mild, open-air conditions. Highly substituted 2-chlorinated VBX **54a-c** were obtained by *anti*-hydrochlorination using pyridine hydrochloride as an HCl source. The procedure tolerates a variety of EBXs **40** derived from (hetero)aryl- and alkyl-acetylenes and the hydrochlorination could even be extended to ethynylbenziodoxolone and ethynyl(phenyl)iodonium tosylate. A narrower scope was observed for the iodochlorination and alkyl-EBXs **40** were not tolerated in the transformation. The reaction, which involved iodine monochloride, surprisingly afford the *syn*-iodochlorination products **55a-b**, contrasting with the *anti*-selectivity usually observed. Whereas the hydrochlorination is supposed to proceed through β-addition of a chloride ion to EBX **40**, followed by protonation of the resulting vinyl anion **I**, the iodochlorination follows a different mechanism. Based on DFT calculations, the authors proposed an electrophilic activation of EBX **40** by an iodine cation, followed by structural reorganization with formation of the new C-I bond and a new iodonium bridge with the BX cation (**II**). For steric reasons, the chloride anion would then approach from the opposite side of the BX group, leading to the *syn*-iodochlorination product **55**.



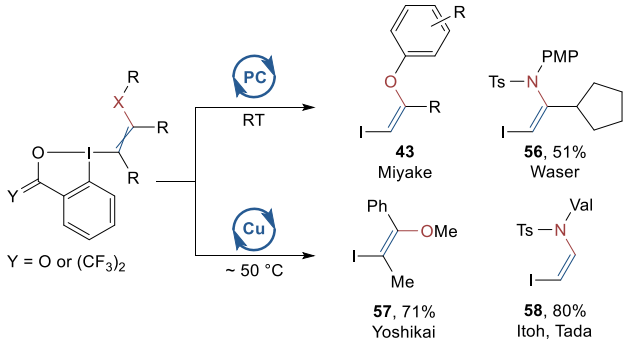
Scheme 27. Stereoselective hydrochlorination and iodochlorination of EBX **40**.

Metal-VBX complexes have also been proposed as intermediates of reactions in palladium-catalyzed condensation of *N*-aryl imines[54] and carboxyalkynylation of olefins[55] with hypervalent iodine reagent. However, these intermediates were not isolated and could not be characterized.

3.2 Reactivity of hetero-VBX

Hypervalent iodine reduction

Hypervalent iodine derivatives can be easily reduced to their monovalent form to deliver vinyl iodides. In the work of Miyake, the hypervalent iodine species **2** is reduced *in situ* by a photoinduced electron transfer to give **43** (Scheme 20 and 28).[46] Photoredox conditions were also used by our group to cleave the hypervalent bond of N-VBX **45**, delivering the monovalent compound **56**.[24] Copper-catalyzed reduction is another effective method used by the groups of Yoshikai and Itoh and Tada, to reduce the benziodoxol(on)es moiety without affecting the olefin stereochemistry.[49,50] Using a copper(I) reductant, iodine **57** and **58** were obtained in good yields at 50 °C.

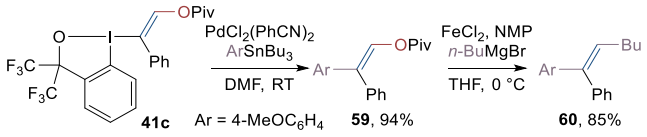


Scheme 28. Reduction of the hypervalent iodine bond in VBX**.**

Metal catalyzed C-C bond formation

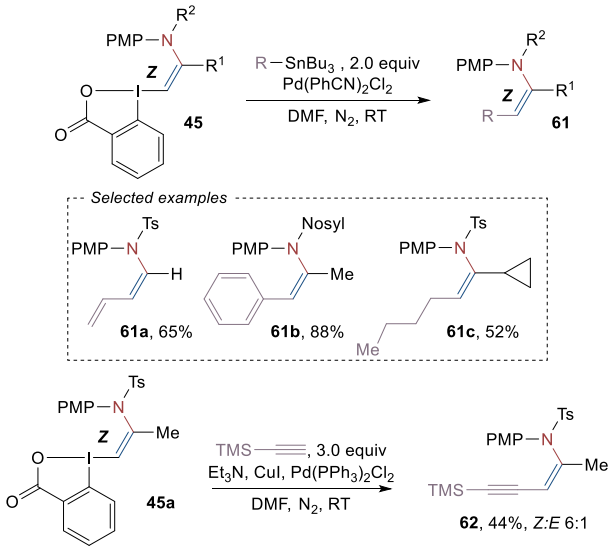
Transition-metal-catalyzed reactions often require high temperature for substrate activation. Hypervalent iodine reagents, with their enhanced reactivity, are ideal coupling partners for metal-catalyzed transformations at lower temperature. Therefore, X-VBXs have been broadly used in reactions such as the palladium-catalyzed Stille, Sonogashira and Suzuki-Miyaura cross-couplings. The reactions usually proceed at room temperature, with complete retention of the stereoselectivity.

Yoshikai and coworkers reported that O-VBX reagent **41c** could be used in a palladium-catalyzed Stille cross-coupling with aryl stannanes at room temperature, leading to stereodefined tri-substituted alkene **59** (Scheme 29).[44] The C-O bond on the alkene could be further functionalized by iron-catalyzed cross-coupling with butylmagnesium bromide to give **60**. Access to functionalized tetra-substituted enynes was possible using the products obtained from 1,1-carboxyalkynylation (Scheme 19) .[45]



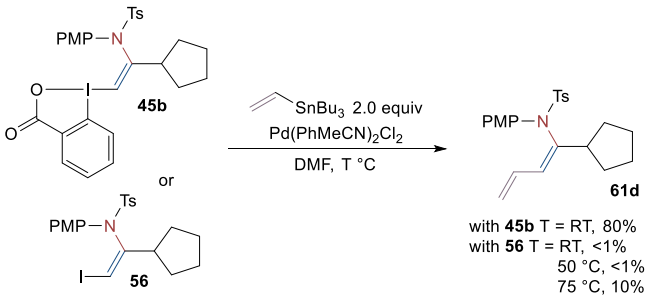
Scheme 29. Stille followed by iron-catalyzed cross-coupling of O-VBX reagent **41c.**

Similarly, our group used palladium-catalysis for the modification of O- and N-VBX **44** and **45**.[24] Coupling of aryl, vinyl and alkyl stannyl reagents were performed at room temperature with complete stereospecifity to give the *Z* products **61** (Scheme 30). Compounds **61a-c** were synthesized in 52-88% yields. A Sonogashira cross-coupling of **45a** with trimethysilyl acetylene could be also performed, with however a slight isomerization of the double bond, leading to **62** in 44% yield.



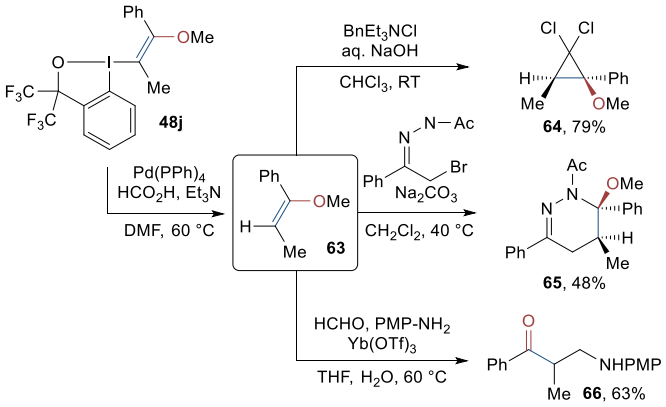
Scheme 30. Stille and Sonogashira cross-coupling of N-VBX reagent **45.**

A direct comparison of the reactivity of monovalent versus hypervalent iodine toward cross-coupling was performed by our group (Scheme 31).[24] N-VBX **45b** was synthesized from EBX **36** using the previously described conditions, and its monovalent analogue **56** could be obtained by reduction of **45b** using photoredox conditions.[46] Both reagents were engaged in a Stille cross-coupling with vinyl stannane. At room temperature, hypervalent iodine **45b** could be transformed into the vinyl product **61d** in 80% yield, whereas no conversion occurred with simple iodine **56**. When heating up to 75 °C, 10% of the desired product could be observed with **56**. This experiment highlighted the efficiency and synthetic utility of hypervalent iodine reagents in cross-coupling reactions.



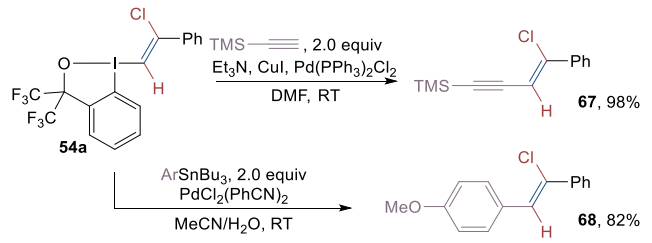
Scheme 31. Stille cross-coupling of hypervalent iodine **45b** versus monovalent iodine **56**.

Room temperature metal-catalyzed transformations were applicable to the highly substituted β-λ^3-iodanyl vinyl ethers **48** developed by Yoshikai and coworkers, for Sonogashira and Suzuki reactions, whereas higher temperature was required for Stille coupling of the reagents.[50] Their reagents could took part also in Rosenmund-von Braun cyanation, as well as palladium-catalyzed hydrodehalogenation of the BX moiety to give **63** (Scheme 32). Product **63**, generated *in situ*, could undergo cyclopropanation, inverse electron-demand Diels-Alder and ytterbium triflate catalyzed Mannich reaction, leading to products **64-66**.



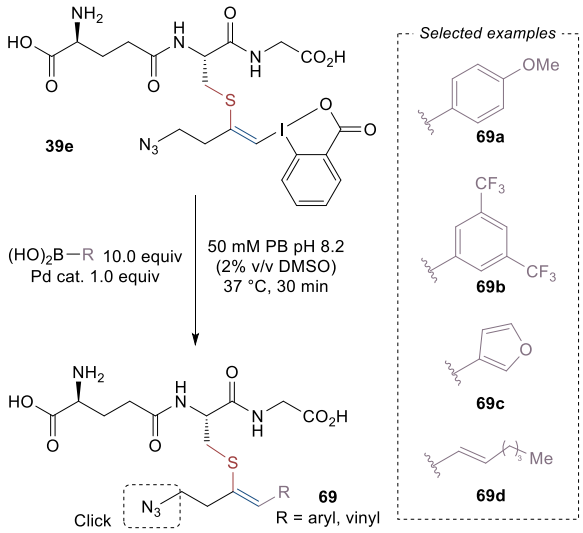
Scheme 32. O-VBX palladium-catalyzed hydrodehalogenation of **48j** and further functionalization of enol ether **63.**

Halovinylbenziodoxoles **54** displayed similar reactivity regarding metal-catalyzed reactions, and chloro-VBX **54a** was used in Stille and Sonogashira couplings with alkynes and stannanes at room temperature (Scheme 33). Cross-coupling of the hypervalent bond of iodochlorinated-VBXs **55** was not successful.[53]



Scheme 33. Stille and Sonogashira cross-coupling of Cl-VBX reagent **54a.**

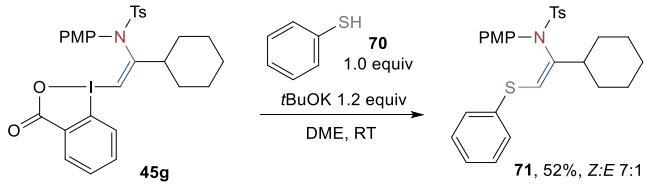
Our group developed a Suzuki-Miyaura cross coupling reaction of S-VBX reagent **36e** installed on glutathione with boronic acids to give alkenes **69a-d** (Scheme 34).[43] The reaction is selective for the vinyl hypervalent iodine bond and the biocompatible conditions could be applied to larger peptides and even proteins. In addition, the azide could be selectively functionalized by cycloaddition. The hypervalent iodine and the azide are therefore orthogonal in reactivity to each other and to existing natural functional groups in peptides and proteins, allowing applications for peptide and protein functionalization. For example, a triplet-state quencher and a fluorophore were introduced selectively, leading to extended fluorescence lifetime by suppressing photobleaching.



Scheme 34. Aqueous Suzuki-Miyaura cross coupling reaction of S-VBX **39e.**

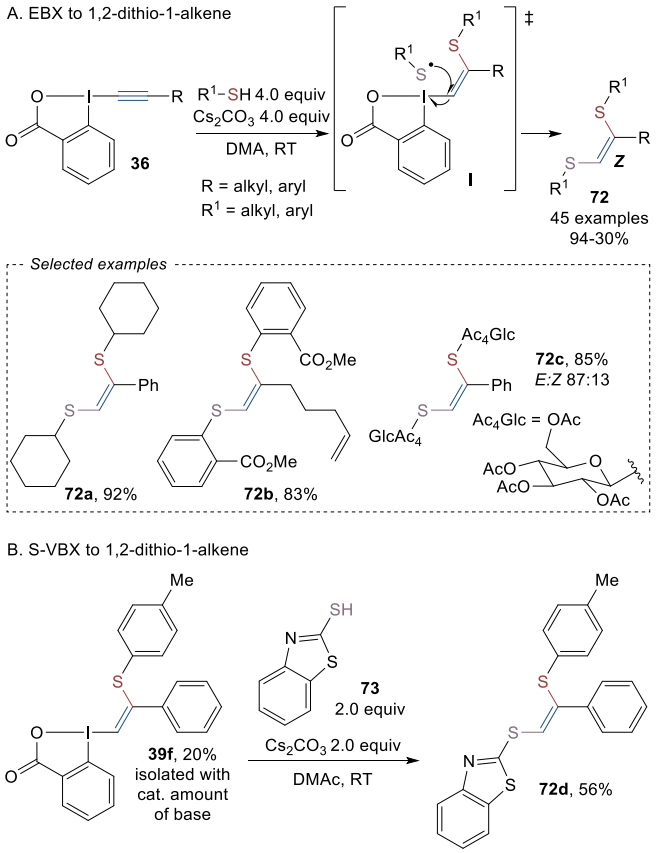
Metal-free C-X bond formation

Iodonium salts are known to react as vinyl cation equivalents in presence of nucleophiles.[56] Hetero-vinylbenziodoxol(on)es have been shown to display similar reactivity. Our group was able to transform N-VBX reagent **45g** into thioenamide **71**, using thiophenol (**70**) in presence of an excess of base (Scheme 35).[24] The mechanism of the reaction was not studied but the slight isomerization observed suggest an addition-elimination pathway.



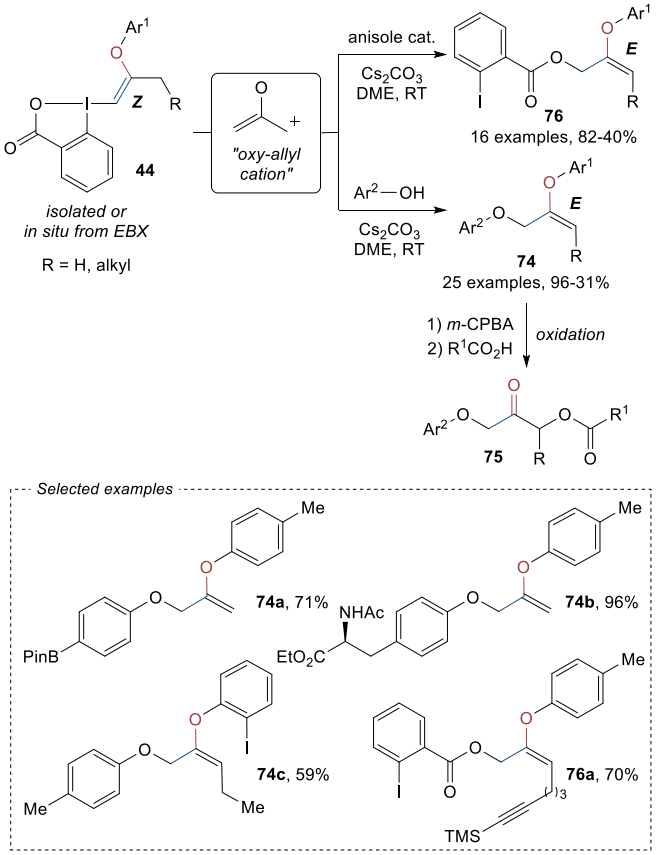
Scheme 35. Addition of thiophenol (**70**) onto N-VBX **45g**.

Thiol nucleophiles were also used by the group of Miyake for the synthesis of 1,2-dithio-1-alkenes **72** (Scheme 36A).[25] In presence of an excess of nucleophile and base, the addition of two thiol equivalents to the C-C triple bond of EBX **36** was observed, leading to *Z*-1,2-dithio-1-alkene **72** with loss of the hypervalent bond. A number of aliphatic and aromatic thiols, as well as thioglycosides are compatible with the reaction conditions. Compounds **72a-c** were obtained in excellent yield and high stereoselectivity. Experimental and computational mechanistic studies revealed that the *cis* regioselectivity observed in the *Z*-1,2-bisthiolated alkene product is explained by the combination of two steps: *cis*-selective nucleophilic thiol addition to the β-position of EBX **36**, leading to an S-VBX intermediate, followed by a *cis*-specific radical addition of a second equivalent of thiol (**I**). Using a catalytic amount of base, S-VBX intermediate **39f** could be isolated and then converted to the dithiolated product **72d** in presence of an excess of Cs_2CO_3 (Scheme 36B). Phenyl-VBX (**2a**) could also be transformed to vinyl sulfides under the reported conditions, which is consistent with the work later published by the group of Olofsson on electrophilic vinylation of thiols with VBX (See section 2.2).[23]



Scheme 36. Reaction of EBX **36** and S-VBX **39f** with thiol nucleophiles.

Nucleophilic addition onto O-VBX reagents **44** was studied by our group. Surprisingly, the O-VBXs **44** displayed an oxy-allyl cation-like behaviour, rather than the expected vinyl cation reactivity (Scheme 37).[57] This new mode of reactivity was observed in presence of an excess of cesium carbonate and is most efficient with phenols as nucleophiles, affording aryl enol ethers products **74** with *E* stereoselectivity. Few examples were also presented with carbon and nitrogen nucleophiles. The obtained ether derivatives **74** could be transformed into α-difunctionalized ketones **75** under oxidative conditions in presence of acid. In absence of external nucleophiles, the 2-iodobenzoate group of the O-VBX reagent is transferred, leading to aryl enol esters substrates **76.** For example, both the ether products **74a-c** and the ester product **76a** could be obtained in good to excellent yields. The reaction was proposed to proceed through isomerization of VBX **44** to an allyl iodinane intermediate, followed by either a S_N1 pathway, with α-elimination of the aryl iodide to deliver an oxy-allyl cation species, or a S_N2 mechanism, with direct reaction of the nucleophile with the allylic hypervalent iodine intermediate.



Scheme 37. O-VBX reagents **44** as oxy-allyl cation synthetic equivalents.

Summary and Outlook

The quest for new vinyl cation surrogates for enabling effective olefination methods has drawn important research efforts in organic chemistry. Benziodoxolone-based transfer reagents have recently emerged has privileged reagents to reach this goal due to their high reactivity combined with sufficient stability. Both VBX and hetero-VBX reagents have attracted significant attention since 2016.

Convergent methods for the preparation of VBXs, essentially from boron precursors, have been explored and accommodate well various kind of substitutions ((hetero)aryl, alkyl, alkenyl, alkynyl) on the double bond. Although important progress has been achieved, the development of synthetic routes from more readily available starting materials remain desirable to popularize the use of VBXs within the organic chemist community. Since their introduction by Olofsson in 2016, VBXs as electrophilic alkene synthons have enabled unprecedented transformations in different domains such as transition-metal catalysis, radical chemistry or classical ionic chemistry. Different outcome when compared to vinylhalides and acyclic vinyl iodonium salts have been often observed.

Hetero-VBX possess an extra hetero-atom (N, O, S or halogen) conjugated to the alkene, which influences considerably the electronics of the later. X-VBX reagents have been obtained mostly through the addition of soft nucleophiles onto well-established EBX reagents, which need nevertheless to be first synthesized. In this respect, the new difunctionalization of alkynes from simple iodane precursors and alcohols developed by Yoshikai and coworkers constitutes an important progress.[50] The formation of X-VBX proceeds usually with high stereoselectivity and gives access to highly functionalized reagents with defined geometry, a challenging task for enols and enamines. The high reactivity of the hypervalent bond serves as basis for cross-coupling reactions under mild conditions to further diversify the products.

Vinylbenziodoxolones have been surprisingly inexistent in the hypervalent iodine transfer reagent tool box until 2015 and have emerged only very recently. This may be due to the well-developed chemistry of electrophilic alkene synthons, especially halides. In contrast, electrophilic alkyne synthons were less developed, which led to a faster rise of EBX reagents. Nevertheless, the results obtained in the last five years with VBX reagents demonstrated their unique reactivity, especially for the Umpolung of nucleophilic olefins such as enol ethers and enamides. It is clear that their synthetic potential has just started to be investigated. We hope that our overview of the current state of the art will stimulate and inspire the synthetic community to further develop the synthetic access and new applications of VBX reagents.

Acknowledgements

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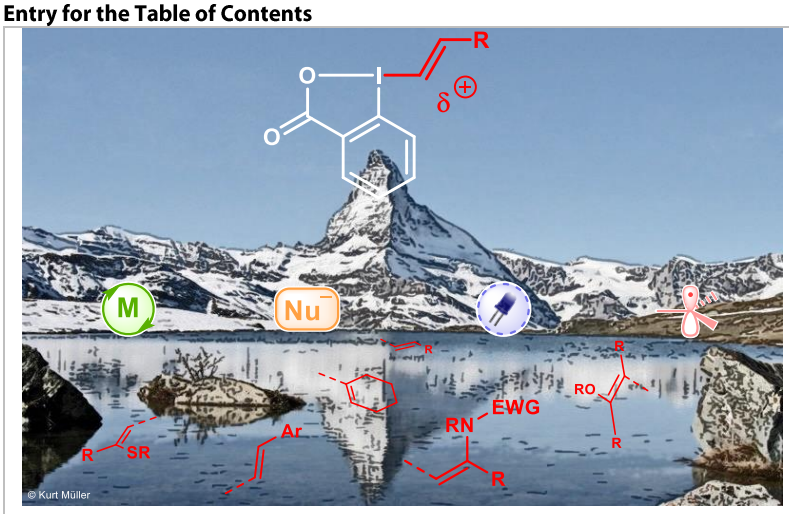

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