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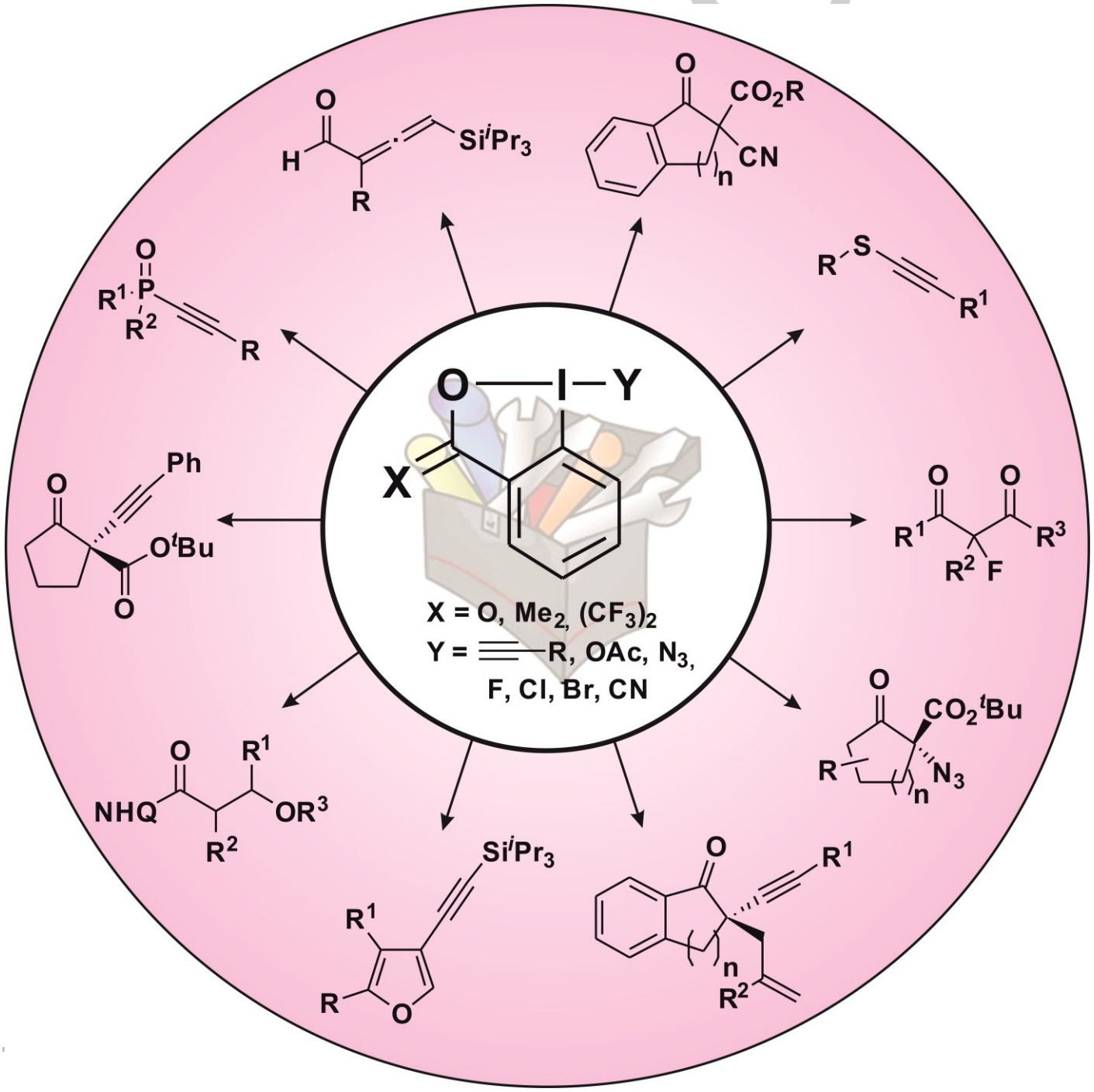
Cyclic Hypervalent Iodine Reagents for Atom Transfer Reactions: Beyond Trifluoromethylation

Yifan Li, Durga Prasad Hari, Maria Victoria Vita and Jerome Waser*[a]



Abstract: Hypervalent iodine compounds are privileged reagents in organic synthesis due to their exceptional reactivity. Among them, cyclic derivatives stand apart because of their enhanced stability. They have been broadly used as oxidants, but their potential for functional group transfer has only begun to be investigated recently. Whereas the use of benziodoxol(on)es for trifluoromethylation (Togni's reagents) is already largely recognized, other transformations have also attracted a strong interest recently. In this review, the development in the area since 2011 will be presented. After a short summary of synthetic methods to prepare benziodoxol(on)e reagents, their use to construct carbon-heteroatom and carbon-carbon bonds will be presented. In particular, the introduction of alkynes using EthynylBenziodoXol(on)es (EBX) reagents has been highly successful. Breakthroughs for the introduction of alkoxy, azido, difluoromethyl and cyano groups will be also described.

Yifan Li was born in Jinan, China in 1986. He obtained his bachelor diploma in material chemistry in 2008 at Jinan University and then moved to the University of Lyon 1 where he obtained is master degree in organic chemistry in 2011. Since 2012, he is carrying out his PhD at Ecole Polytechnique Fédérale de Lausanne (Switzerland) working on the development of new catalytic methods using hypervalent iodine reagents under the direction of Prof. Jérôme Waser.

Durga Prasad Hari was born in Jarajapupeta, Vizianagaram, A.P (India). He received his Master degree from IIT Madras and his PhD degree from the University of Regensburg under the supervision of Prof. Dr. Burkhard Koenig in 2014. Currently, he is working as post-doctoral fellow under the supervision of Prof. Jerome Waser at EPFL. His research interests focus on applications of hypervalent iodine reagents in organic synthesis. He was a finalist of Reaxys PhD prize 2012.

[a] Mr. Yifan Li, Dr. Durga Prasad Hari, Ms. Maria Victoria Vita and Prof. Dr. Jerome Waser
Laboratory of Catalysis and Organic Synthesis
Ecole Polytechnique Fédérale de Lausanne
EPFL SB ISIC LCSO, BCH 4306, 1015 Lausanne, CH
E-mail: jerome.waser@epfl.ch
Homepage: http://lcso.epfl.ch/

Maria Victoria Vita was born in Bologna, Italy. She did her undergraduate studies at the University of Bologna and then obtained her PhD in chemistry in 2015 from EPF Lausanne with Prof. Jérôme Waser.

((Author Portrait))

Jérôme Waser was born in Sierre, Valais, Switzerland in 1977. He obtained his chemistry Diploma at ETH Zurich in 2001. From 2002 to 2006, he was a PhD student at ETH Zurich with Prof. Erick M. Carreira. He then joined Prof. Barry M. Trost at Stanford University as a SNF postdoctoral fellow. From 2007 to 2014, he was an assistant professor at EPF Lausanne (EPFL). Since June 2014, he has been associate professor at EPFL. He is a recipient of the ERC Starting Grant 2013 and the Werner prize of the Swiss Chemical Society 2014.

1. Introduction

The development of new chemical transformations stands at the core of synthetic organic chemistry. With new reactions, known structures can be made more efficiently and uncharted region of the chemical space can be discovered. In this respect, hypervalent iodine reagents are very attractive, as they combine the high reactivity usually associated with metal reagents with the lower toxicity and costs of main group elements.[1] Key for their reactivity is the three-atom four-electron bond present in the reagents, which is weaker than a normal covalent bond (Figure 1). Considered first as "bonding curiosities" they have now plainly entered main stream synthetic chemistry and reagents like the Dess-Martin periodinane (**1**) (an iodine(V) reagent, also called λ-5 iodane) or iodobenzenediacetate (an iodine(III) reagent, λ-3 iodane) are nowadays routinely used. Whereas simple oxidation reactions have been established since decades, the excellent properties of hypervalent iodine reagents to act as electrophilic synthons of normally nucleophilic groups such as arenes, alkynes, halogens, acetate, trifluoromethyl, azides or cyanides (Umpolung of the reactivity) have been the focus of intense research more recently.

As for metal complexes, *trans*-effects can be used to influence the reactivity and stability of hypervalent iodine reagents.[2] On the other hand, cyclic hypervalent iodine reagents are more stable, especially when an aromatic ring is present to further

stabilize the electron-deficient iodine center by conjugation.[3] By far the most studied class of cyclic hypervalent iodine reagents are derived from 2-iodo benzoic acid or the corresponding dimethyl or bis(trifluoromethyl) alcohols. The two extensively used λ-5 iodane oxidants – the Dess-Martin periodinane (**1**) and IBX (**2**)- belong to this class of compounds (Figure 2, **A**). Cyclic λ-3 iodanes (the benziodoxol(on)es, Figure 2, **B** and **C**) are weaker oxidants and have been less used in synthesis, despite a very rich structural chemistry.

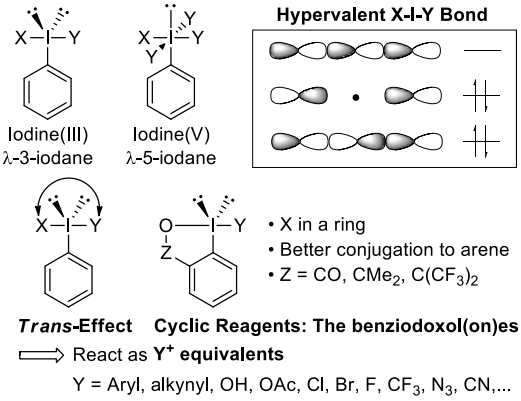


Figure 1. Structure and Bonding of Hypervalent Iodine Reagents.

In fact, up to 2005 most publications involving benziodoxol(on)e reagents were dedicated to structural studies, with only rare attempts towards synthetic applications.[3] In the last decade, the potential of benziodoxol(on)es for functional-group transfer has become the focus of intensive research. In a feature article in 2011, Waser and co-workers summarized the first important breakthroughs in this area,[4] involving especially the use of benziodoxolone reagents for trifluoromethylation (Togni reagents **4** and **12**)[5] and alkynylation (ethynylbenziodoxol(on)e (EBX) reagents such as TIPS-EBX (**5**)). Since 2011, the synthetic potential revealed in these preliminary results has become intensively investigated. This is apparent in comparing the number of reports before and after 2011 for the two most successful benziodoxolone reagents: Togni reagent **4** (13 and 80) and TIPS-EBX (**5**) (6 and 36) (Figure 2). The use of Togni reagents for trifluoromethylation reactions has been recently covered.[6] In this review, the use of benziodoxol(on)e reagents for the transfer of other functional groups will be presented. The focus will be on new results which appeared since 2011. Although the main part of the review will deal with alkynylation, new results involving the transfer of oxygen or nitrogen containing-groups as well as cyanides will also be presented.

The review will start with a short section on the synthesis and stability of benziodoxolone reagents, as those properties are essential to determine the utility of a reagent (section 2). We will then move to the formation of C-X bonds, either via introduction of a heteroatom on a carbon nucleophile, or the reverse approach (section 3). The last part of the review will deal with the formation of C-C bonds (section 4).

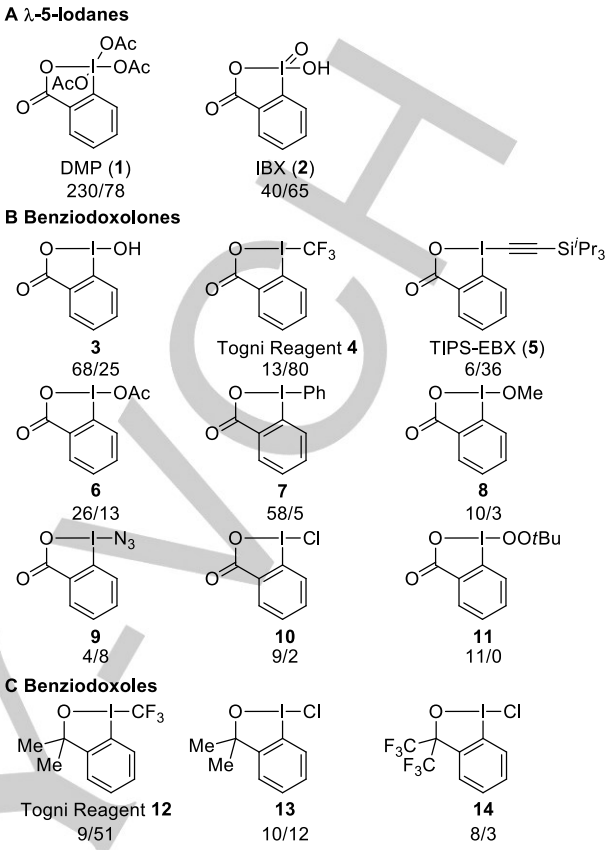


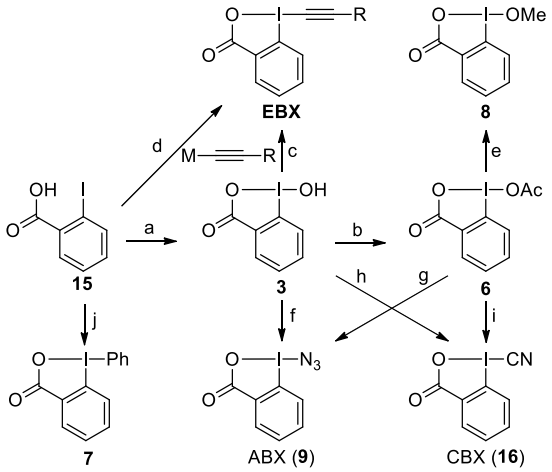
Figure 2. Cyclic hypervalent iodines which have been reported in more than ten different publications (according to a Reaxys structure search performed in July 2015, real report count may be much higher). The number of reports prior to/after 2011 are given below the compound number.

2. Synthesis and Stability of Benziodoxolone Reagents

The synthesis and structural characterization of benziodoxolones reagents has been already reviewed in details.[3] In this section, only the synthesis of the most relevant reagents for functional-group transfer will be described.

The preparation of benziodoxolones from cheap 2-iodo benzoic acid (**15**) is easy and scalable. Most synthesis starts with oxidation with sodium periodate to give hydroxy benziodoxolone **3**.[7] Care has to be taken when drying **3**, as a polymeric form can be formed by dehydration. For this reason, the use of acetoxy benziodoxolone **6**, a well-defined and crystalline compound obtained by the reaction of **3** with acetic anhydride,[5a] can be sometimes advantageous. EBX reagents can be accessed from **3** using different procedures.[8] Ochiai and co-workers reported the first synthesis in 1991 using alkynyl silanes and boron trifluoride etherate as Lewis acid.[8a] The procedure was improved by Zhdankin and co-workers in 1996 using TMSOTf as activator, followed by quenching with pyridine.[8b] This protocol was robust and could be scaled-up to the multi-gram scale by Waser and co-workers.[8c] In 2012, Olofsson and

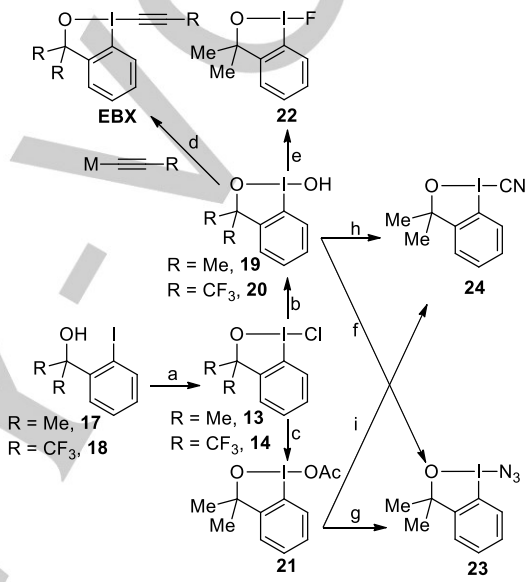
Bouma reported the first one-pot procedure for the synthesis of benziodoxolones starting from 2-iodo benzoic acid (**15**) and alkynyl boronic acid esters.[8d] Methoxy benziodoxolone **8** is accessed by methanolysis of reagent **6**.[5a] Azido[9] and cyano[9d,10] reagents **9** (ABX) and **16** (CBX) can be synthesized either from hydroxy benziodoxolone **3** or acetoxy benziodoxolone **6**. Finally, phenyl benziodoxolone reagent **7** can be synthesized efficiently using a multi-step protocol.[11a,b] More recently, Olofsson and Merritt, as well as Zhdankin and co-workers reported more convenient one-pot protocols.[11c,d]



Scheme 1. Synthesis of benziodoxolone reagents. Representative reaction conditions: a) $NaIO_4$, H_2O, CH_3CO_2H, reflux, 81%; b) Ac_2O, reflux, 90%; c1) M = $SiMe_3$, $BF_3{\bullet}OEt_2$, CH_2Cl_2, then MeOH, 60 °C, 10-31%; c2) M = $SiMe_3$, TMSOTf, CH_3CN, then pyridine or $NaHCO_3$, 30-85%; d) M = $B(OR^1)_2$, *m*CPBA, $TsOH{\bullet}H_2O$, CH_2Cl_2/TFE then $NaHCO_3$, 74-90%; e) MeOH, 63%; f) $TMSN_3$, CH_3CN, 94%; g) $TMSN_3$, TMSOTf, CH_2Cl_2, 75%; h) TMSCN, CH_3CN, 94%; i) TMSCN, CH_2Cl_2, 95%; j1) $K_2S_2O_8$, H_2SO_4, 0 °C to rt, then PhH, then aq. NH_3, 78%; j2) *m*CPBA, TfOH, PhH, CH_2Cl_2, 80 °C, then aq. NH_3, 66%; j3) Oxone, H_2SO_4, 5 °C, then PhH, CH_2Cl_2, 5 °C to RT, 88%.

Benziodoxoles are usually prepared from alcohols **17** and **18**. Alcohol **17** can be accessed by addition of methyl Grignard to 2-iodo benzoate methyl ester and **18** either from phenylhexafluoro isopropanol by iodination[12] or from 1,2-diiodobenzene by mono-metalation followed by reaction with hexafluoroacetone.[13] Hydroxy- and acetoxy derivatives **19**-**21** are key intermediates for the synthesis of other reagents. Most methods to access **19**-**21** involve the formation of chloride **13** and **14** by oxidation with *tert*-butyl hypochlorite[14] or cyanuric acid trichloride,[15] followed by hydrolysis[14,16] or acetolysis with silver acetate.[5a] EBX reagents bearing the trifluoromethyl groups can be accessed with Zhdankin's method using trimethylsilyl alkynes and trimethylsilyl triflate,[8b] whereas dimethyl-based reagents require the use of more reactive lithium acetylides.[17] Fluoro benziodoxole **22** can be accessed by reacting **19** with triethylammonium hydrofluoride.[18] Finally, azido and cyano reagents **23** and **24** can be synthesized using the same procedures as for the corresponding benziodoxolone reagents **9** and **16**.[9,10]

The cyclic structure of benziodoxol(on)e reagents results in a greatly enhanced thermal stability when compared to their non-cyclic counterpart. Nevertheless, they are high energy compounds which display a strongly exothermic decomposition, and have consequently to be manipulated with the adequate precautions.[19] Although there are no large difference of decomposition temperatures between benziodoxolones and benziodoxoles, the latter can in some cases such as azido reagents be less prone to explosive degradation.[19b] The moisture sensitivity of benziodoxol(on)es on the other hand is highly dependent on the functional group: very low for EBX reagents, but more pronounced for azido or cyano reagents.



Scheme 2. Synthesis of benziodoxole reagents. Representative reaction conditions (for R = Me/CF_3): a1) ^{t}BuOCl, CCl_4, 86%/43%; a2) Trichlorocyanuric acid, CH_3CN, 89%; b) KOH, H_2O/CH_2Cl_2, 89%/73%; c) AgOAc, CH_3CN, 89%; d1) R = Me, M = Li, TMSOTf, THF, -78 °C to rt, 86%; d2) R = CF_3, M = $SiMe_3$, TMSOTf, CH_3CN, then pyridine, 50-95%; e) $Et_3N{\bullet}3HF$, CH_2Cl_2, 94%; f) $TMSN_3$, CH_3CN, 87%; g) $TMSN_3$, TMSOTf, CH_2Cl_2, 96%; h) TMSCN, CH_3CN, 74%; i) TMSCN, CH_2Cl_2, 96%.

3. C-X Bond Formation

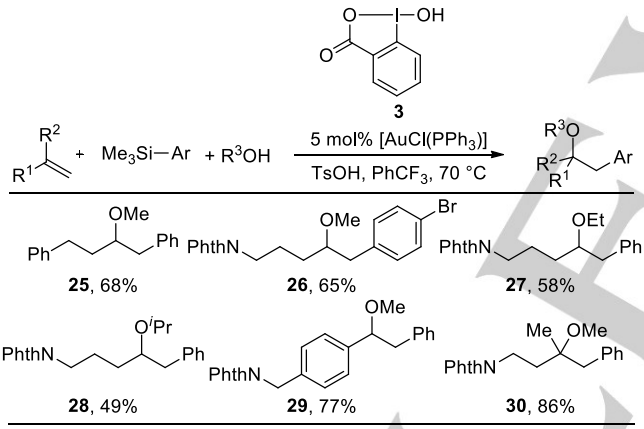
For the formation of C-X bonds, two approaches are possible: the use of heteroatom-substituted benziodoxol(on)e reagents with carbon nucleophiles, or the used of carbon-substituted benziodoxol(on)es with heteroatom nucleophiles. These two alternatives will be discussed in the following sections.

3.1. Reactions with the Heteroatom on the Hypervalent Iodine Reagent

3.1.1 C-O Bond Formation

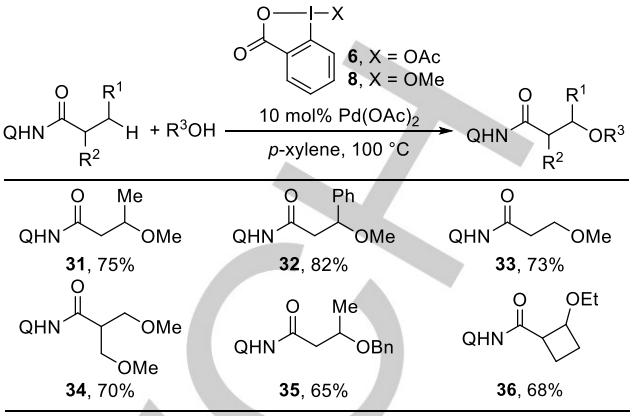
The formation of C-O bonds was one of the first areas of application of cyclic hypervalent iodine reagents for atom-transfer reactions. Early work with λ-3 iodanes focused on the

oxidation of C-H bond and sulfur atoms with *tert*-butylperoxy benziodoxolone **11**,[20] the epoxidation of olefins with ammonium salts of hydroxy benziodoxolone **3**,[21] and the tosyloxylation of alkynes and ketones.[22] Interestingly, IBX (**2**) has been early on demonstrated to be an excellent reagent for oxygen-transfer to C-H bonds or oxidative dearomatization reactions.[23] More recently, Kirsch and co-workers reported the efficient oxygenation of C-H bond α to carbonyl groups.[24] Quideau and co-workers harnessed the potential of dearomatization reactions for the synthesis of natural products.[25] They also achieved enantioselective dearomatization reactions by using chiral hypervalent iodine reagents based on a binaphthyl scaffold.[26,27] Two recent works indicated that benziodoxolone reagents can be superior to non-cyclic reagents in transition metal-catalyzed reactions. In 2012, Russell, Lloyd-Jones and Ball first reported the superiority of 2-hydroxy benziodoxole **3** for the gold-catalyzed methoxyarylation of olefins (Scheme 3).[28] The reaction worked well for non-activated terminal olefins (products **25**-**28**) and styrenes (product **29**). *gem*-Disubstituted olefins also gave good yields (product **30**), but the reaction was sluggish with β-substituted olefins. Benziodoxole **3** most probably allows accessing a highly reactive gold(III) intermediate, which then performs oxy-auration onto the olefin followed by arylation via reductive elimination.



Scheme 3. Gold-catalyzed alkoxyarylation of olefins using hydroxy benziodoxolone reagent **3**.

In 2013, Rao and co-workers then reported the use of acetoxy and methoxy benziodoxolones **6** and **8** for the palladium-catalyzed alkoxylation of SP^3 C-H bonds (Scheme 4).[29] The reaction worked well for both alkyl and aryl substituents in β–position to the carbonyl (products **31** and **32**) and was also successful in the case of a primary C-H bond (product **33**). If several C-H bonds were accessible in γ position, bis-alkoxylation was observed (product **34**). Primary alcohols such as benzyl alcohol or ethanol (product **35** and **36**) also worked well in the reaction. Lower yields were obtained with secondary alcohols and tertiary alcohols could not be used. Interestingly, the transformation could also be applied to cyclic substrates (product **36**). In 2014, Rao and Zhong also extended this methodology to the synthesis of non-symmetrical acetals using two successive alkoxylations of primary C-H bonds.[30]



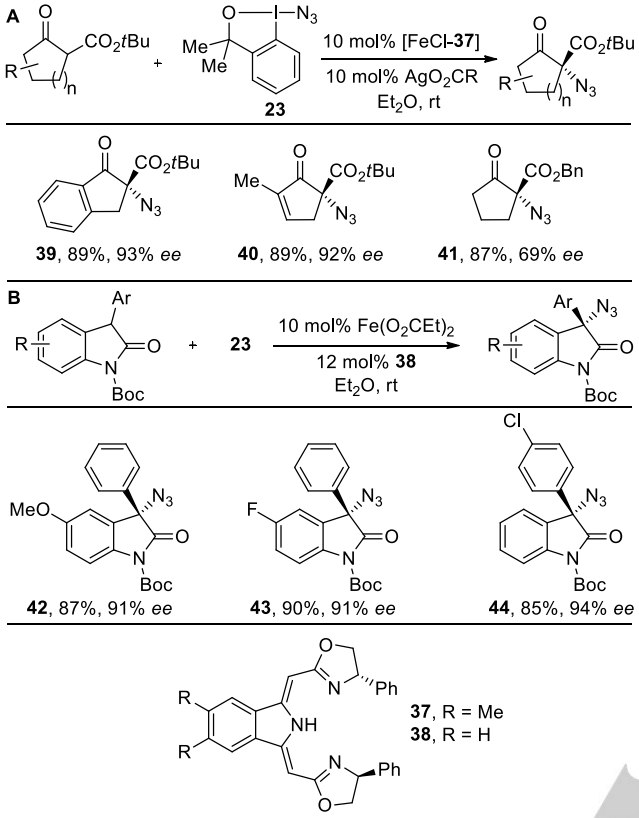
Scheme 4. Palladium-catalyzed C-H alkoxylation using benziodoxolone reagents **6** or **8**. Q = 8-amino-quinoline.

3.1.2 C-N Bond Formation

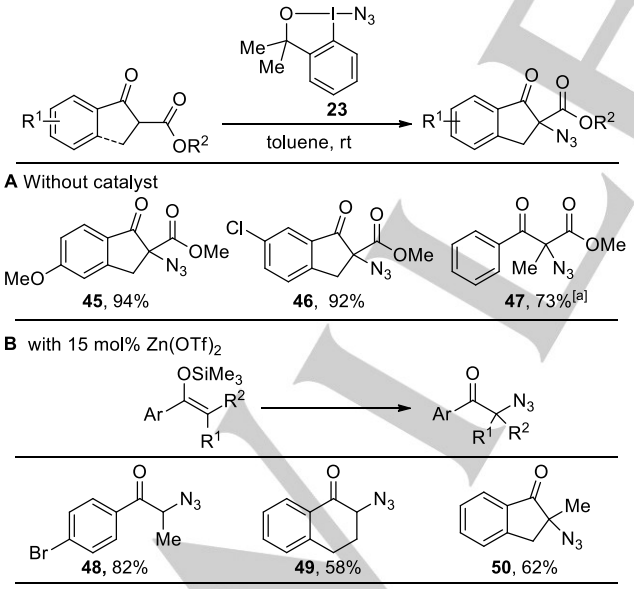
C-N bond formation with cyclic hypervalent iodine reagents was pioneered by Zhdankin and co-workers, who developed the azidation and amidation of radicals generated by C-H abstraction with benziodoxolone reagents.[9c,31] These methods were limited by the relatively harsh conditions needed for radical generation (high temperature, strong oxidants).

Surprisingly, no further work was done using these promising reagents until 2013, when the groups of Gade, Waser and Studer independently reported new transformations using azidobenziodoxol(on)es **9** and **23**.[32] Gade and co-workers developed a highly enantioselective iron-catalyzed azidation of β-ketoesters and oxindoles using benziodoxole reagent **23** (Scheme 5, **A** and **B**).[32a] Key for success was the use of the tridentate boxmi ligands **37** and **38**. High enantioselectivities and yields were obtained for ketoesters derived from indanone (products **39**) or cyclopentenone (product **40**). Lower enantioselectivities were observed for cyclopentanone derivatives (product **41**) and non-cyclic ketoesters could not be used. Under slightly modified conditions, azidated oxindoles **42**-**44** could also be obtained in high yields and enantioselectivities.

Waser and Vita reported a method to azidate in high yields β-ketoesters derived from indanone without the need of catalyst or base (Scheme 6, **A**, products **45-46**). Less reactive acyclic β-keto esters bearing an aromatic substituent were found to undergo azidation in good yield when using zinc triflate as catalyst (product **47**). The same catalyst was successful for the azidation of silyl enol ethers and secondary and tertiary azides **48-50** were obtained in good to excellent yield (Scheme 6, **B**).

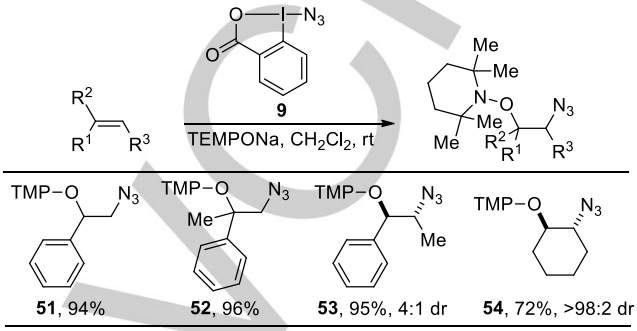


Scheme 5. Iron-catalyzed enantioselective azidation with benziodoxole **23**.



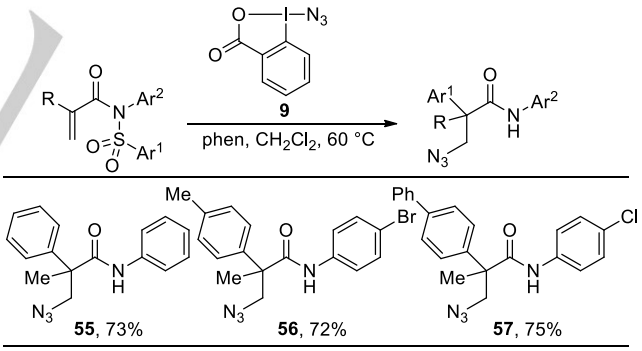
Scheme 6. Azidation of cyclic and acyclic β-ketoesters and silyl enol ethers. [a] With 30 mol% $Zn(OTf)_2$ as catalyst.

Also in 2013, Studer and Zhang reduced azidobenziodoxolone **9** with TEMPONa to form an azido radical, which was directly added to an olefin. The resulting alkyl radical recombined with TEMPO to give overall an oxyazidation of the alkene (Scheme 7).[32c] The reaction worked well for mono- and disubstituted styrene derivatives (products **51**-**53**). In the case of cyclic alkenes, high *trans* stereoselectivity was observed (product **54**).



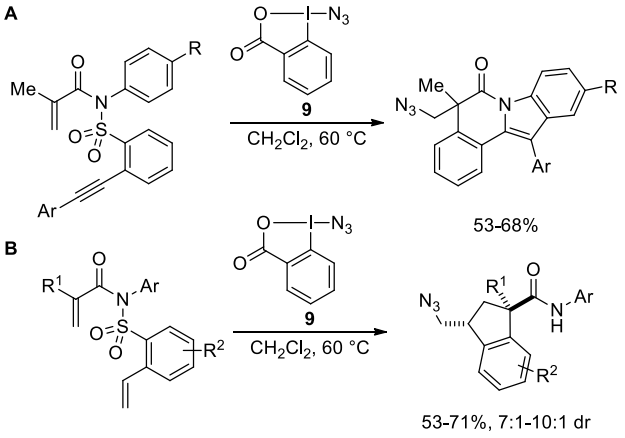
Scheme 7. Oxyazidation of olefins using azidobenziodoxolone **9**.

In 2014, Nevado and co-workers further exploited the potential of benziodoxolone **9** for the generation of azide radicals.[33] They developed the arylazidation of acrylamides based on the internal transfer of an aryl group on a sulfonamide (Scheme 8). β-Azido amides **55**-**57** bearing an all-carbon quaternary center in α-position were obtained in 72-75% yield.



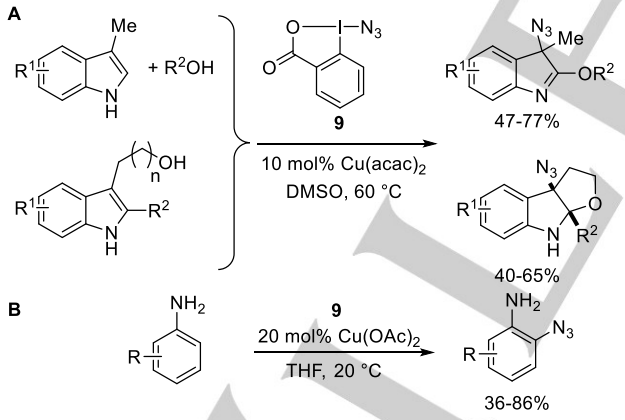
Scheme 8. Oxyarylation of olefins using azidobenziodoxolone **9**. Phen = phenanthroline.

In 2015, Nevado and co-workers increased the structural diversity accessible in this transformation by using a further C-N bond forming event and introducing unsaturation into the molecule allowing more complex cascade processes (Scheme 9).[34] The introduction of an *ortho*-alkynyl group on the arylsulfone allowed the formation of a tetracyclic heterocycle (Scheme 9, **A**).[34a] The addition of the azide radical could also be initiated on an alkene on the arylsulfone to generate a highly substituted indane product (Scheme 9, **B**).[34b]



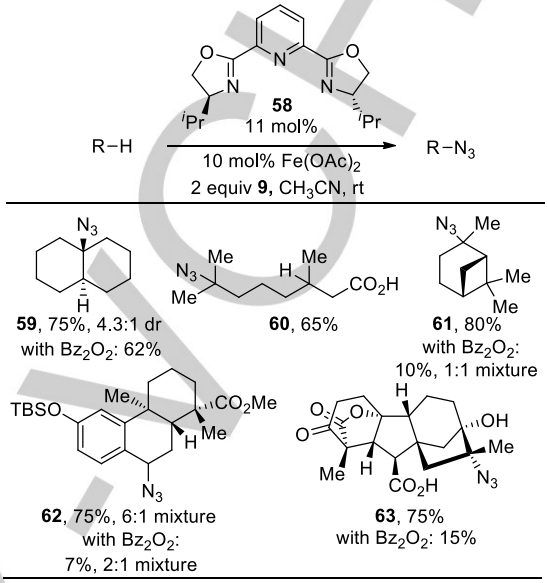
Scheme 9. More complex cascade azidoarylation processes using azidobenziodoxolone **9**.

In 2014, two groups reported the combination of copper catalysis with benziodoxolone **9** for the azidation of electron-rich aromatic compounds (Scheme 10).[35] Jiao and co-workers developed the azidation of skatole derivatives in the presence of alcohols to give dehydroindole derivatives (Scheme 10, **A**).[35a] Intramolecular attack of an alcohol to give indoline derivatives was also possible. Hao and co-workers reported the *ortho* azidation of anilines at room temperature (Scheme 10, **B**).[35b] In 2014, Wang and co-workers reported that benziodoxolone **9** could also be used in the copper-catalyzed intramolecular oxyazidation of olefins to access isoxazolines.[36]



Scheme 10. Copper-catalyzed azidation of indoles and anilines using azidobenziodoxolone **9**.

The azidation method developed by Zhdankin was highly attractive for the functionalization of C-H bonds, yet its use was limited by the harsh conditions needed to generate the key alkyl radical intermediate. In 2015, Hartwig and Sharma were able to promote the C-H azidation process under milder conditions using iron(II) acetate as catalyst with PyBOX ligand **58** (Scheme 11).[37] Simple azide **59** was obtained in 75% yield already at room temperature. Azides **60**-**63** were obtained in greatly enhanced yield and selectivity when compared to the results in absence of iron catalyst.

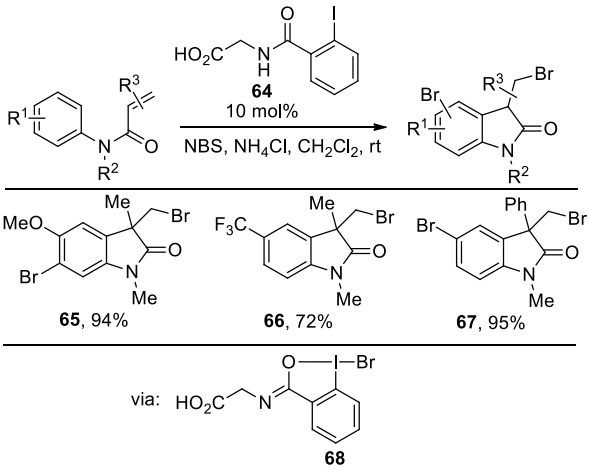


Scheme 11. Iron-catalyzed C-H azidation using azidobenziodoxolone **9**.

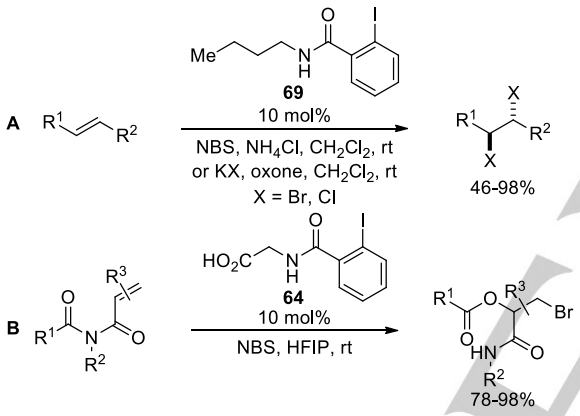
For the azidation of carbonyl compounds, Kirsch and co-workers also developed an alternative method based on the use of sodium azide and a cyclic λ-5 iodane, IBX-SO_3K.[38] This method was efficient for the azidation and diazidation of dicarbonyl compounds, as well as for the synthesis of α-triazido ketones.

3.1.3 C-Halogen Bond Formation

Early work by Martin and Amey, as well as Braddock and co-workers had demonstrated that bromobenziodoxole reagents could be used for the bromination of anisoles and bromolactonization reactions on olefins.[39] In 2012, Gulder and co-workers developed a new bromoarylation of olefins for the synthesis of oxindoles using a catalytic amount of iodine **64** and NBS as oxidant (Scheme 12).[40] The active bromination reagent was most probably benziodoxole derivative **68**. Oxindoles **65**-**67** could be obtained in 72-95% yield. In 2014, Gulder and co-workers further developed a general dibromination and dichlorination of olefins with catalyst **69** and either NBS or oxone as oxidant (Scheme 13, **A**).[41] In 2015, they reported an oxybromination of acrylamides based on the rearrangement of an acyl group on the amide (Scheme 13, **B**).[42]

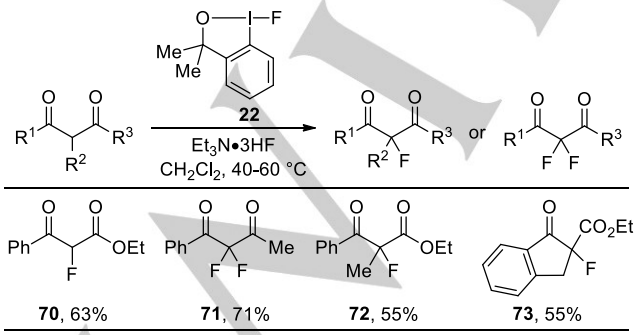


Scheme 12. Intramolecular bromoarylation of olefins.



Scheme 13. Dihalogenation and oxybromination of olefins.

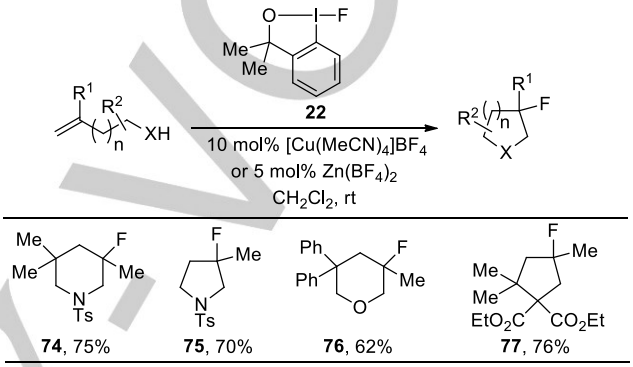
In 2013, Stuart and co-workers studied the reactivity of fluorobenziodoxole **22** in the fluorination of dicarbonyl compounds (Scheme 14).[18]



Scheme 14. Fluorination of activated carbonyl compounds.

Monofluorinated ketoester **70** was obtained in 63% yield, whereas difluorination was observed with diketones (product **71**). The reaction could also be used for the synthesis of acyclic or cyclic tertiary fluorides **72** and **73**.

In 2015, Szabo and Yuan reported the first fluorinative cyclization of alkenes using benziodoxole **22** (Scheme 15).[43] In this process, piperidine **74**, pyrollidine **75**, cyclic ether **76** and cyclopentane **77** could be obtained in 62-76% yield. In the case of amine and oxygen nucleophiles, zinc(II) tetrafluoroborate was used as catalyst, whereas a copper catalyst was better for carbon nucleophiles.



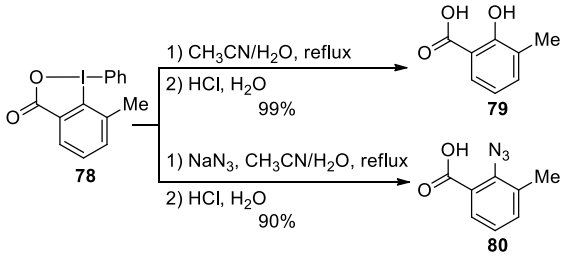
Scheme 15. Amino-, oxy- and carbofluorination with benziodoxole **22**.

In addition to C-halogen bond formation, Shen and co-workers reported very efficient methods for SCF_3 transfer to carbon nucleophiles.[44] They initially proposed that the active reagent was a benziodoxole derivative. However, Buchwald and co-workers later demonstrated that the reagent was in fact a thioperoxide.[45]

3.2. Reactions with the Heteroatom on the Substrate

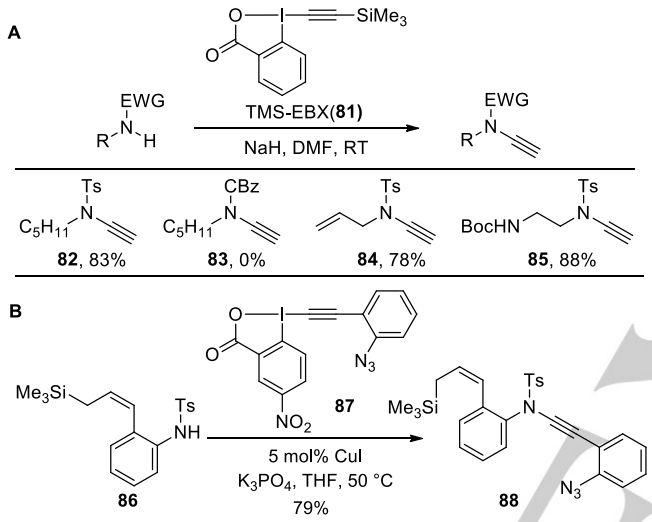
3.2.1 C-N and C-O Bond Formation

Arylation reactions with aryl benziodoxolone like **7** to form C-N or C-O bonds are well-established, with or without a metal catalyst.[46] They proceed with high selectivity for the transfer of the 2-carboxy benzoic acid group. In 2013, Zhdankin reported that *ortho*-substituted phenyl benziodoxolone **78** displayed enhanced reactivity, and could be easily transformed into 2-hydroxy or 2-azido benzoic acids **79** and **80** in high yields (Scheme 16).[11d]



Scheme 16. N- and O- arylation with reagent **78**.

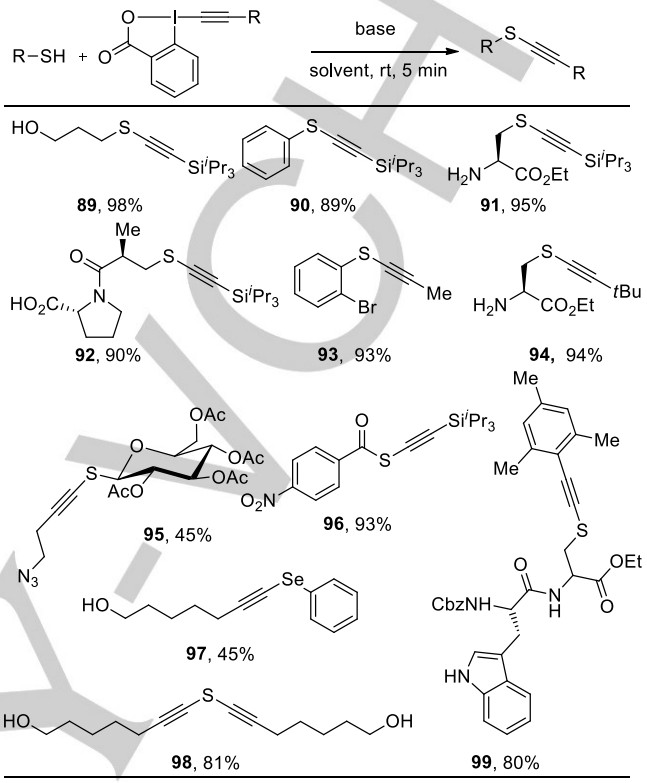
The alkynylation of nitrogen and oxygen nucleophiles on the other hand has been mostly achieved using alkynyliodonium salts.[47] In 2013, Cossy and Aubineau reported the alkynylation of sulfonamides with TMS-EBX (**81**) (Scheme 17, **A**).[48a] Ynamide **82** was obtained in 83% yield, whereas no product was obtained with carbamates. Selective functionalization of a sulfonamide in presence of a carbamate was also possible (product **85**). In 2014, Ohno and co-workers reported the copper(I)-catalyzed alkynylation of sulfonamide **86** with complex EBX reagent **87** (Scheme 17, **B**).[48b] Standard methods using alkynyl bromides did not work.



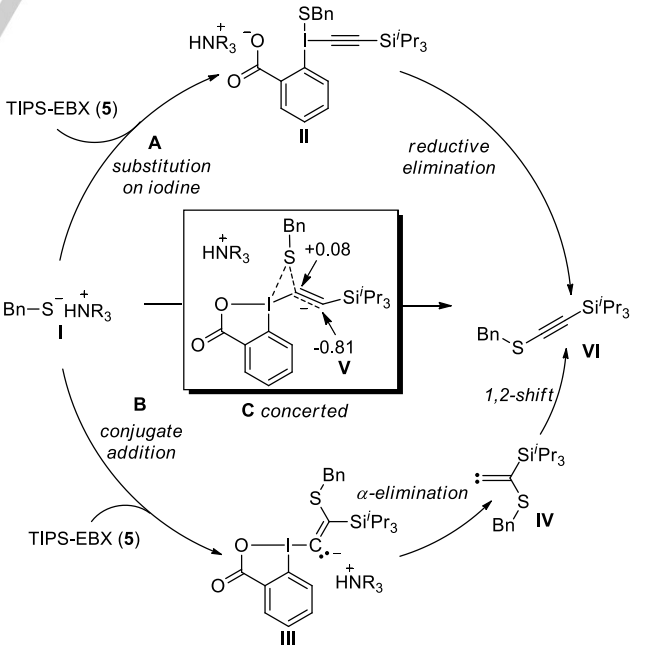
Scheme 17. N-alkynylation with EBX reagents.

3.2.2 C-S and C-P bond formation.

Alkynyliodonium salts can be used only for the alkynylation of relatively electron-poor sulphur and phosphorus nucleophiles, due to their strong oxidizing properties.[47] In 2013, Waser and Frei reported the alkynylation of thiols using TIPS-EBX (**5**) (Scheme 18).[49] The alkynylation reaction worked well for a broad range of substrates including phenolic, benzylic, heterocyclic, aliphatic, and peptidic thiols (products **89**-**92**). The alkynylation in the presence of a free amine gave the thiol alkynylated product **91** exclusively in 95% yield. In 2014, Waser and co-workers further reported the extension of the alkynylation reaction to alkyl and aryl functionalized EBX reagents.[50] The reaction tolerated a wide range of functional groups on the EBX reagent such as a chloro, an azido or a hydroxy group. The scope could also be extended to thioglycosides, thiocarboxylic acids, selenols, sulphide salts and dipeptides (products **95**-**99**). The authors proposed a mechanism for the alkynylation of thiols based on computational studies (Scheme 19). A first investigated pathway was attack of thiolate **I** on the iodine atom of TIPS-EBX (**5**) to give intermediate **II**, which undergoes reductive elimination to furnish product **VI** (pathway **A**).



Scheme 18. Alkynylation of thiols with R-EBX reagents.



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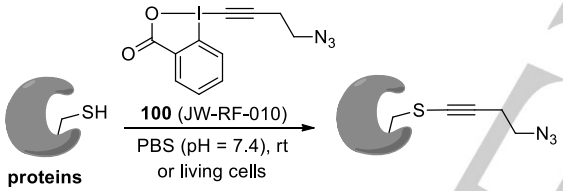
Scheme 19. Proposed mechanism for the alkynylation of thiols.

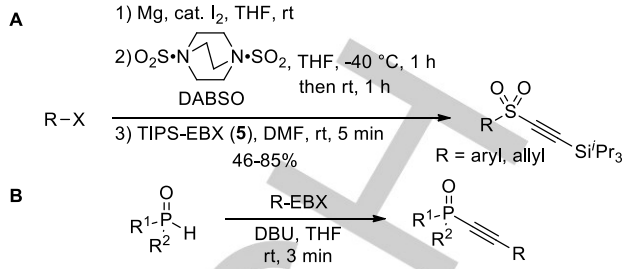
However, intermediate **II** could not be identified in the computational studies. A second possible mechanism would be the conjugate addition of thiolate **I** on TIPS-EBX (**5**) to give intermediate **III**, which undergoes α-elimination followed by 1,2 shift to give **VI** (pathway **B**). This pathway was indeed observed with a transition state energy of 23 kcal/mol for the addition step. Nevertheless, another unprecedented concerted pathway **C** was found with a lower energy of 10.8 kcal/mol. The obtained transition state **V** was distorted and polarized with a negative charge in α and a positive charge in β position to silicium.

In 2015, Adibekian, Waser and co-workers reported an efficient method for the proteomic profiling of cysteine residues in complex proteomes in both cell lysates and living cells using azide-functionalized alkynyl benziodoxolone **100** (Scheme 20).[51] The obtained thioalkyne adducts could be easily functionalized *via* copper-catalyzed cycloaddition of the azide with alkynes (CuAAC), either with fluorophores or biotin. Benziodoxolone **100** (JW-RF-010) was both more efficient and more selective than state-of-the-art reagents for cysteine functionalization, such as *N*-iodoacetamides, and allowed the identification of a different set of proteins. The methodology was used for the identification of the targets of curcumin in HeLa cells.



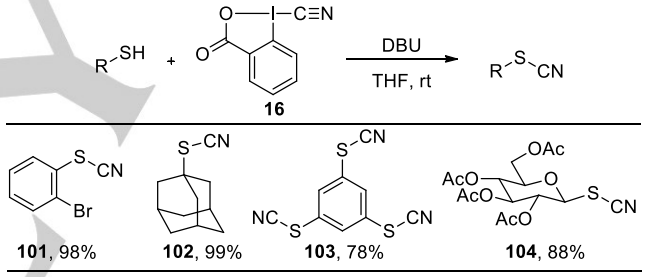
Scheme 20. Alkynylation of cysteine in complex proteomes using azide-EBX reagent **100**.

EBX reagents can also be used for the alkynylation of less nucleophilic sulphur and phosphorus derivatives. In 2015, Waser and Chen developed a new one-pot protocol for the preparation of arylalkynyl sulfones through the reaction of TIPS-EBX (**5**), diazabicycloctane-bis(sulphur dioxide) (DABSO), and organomagnesium reagents (Scheme 21, **A**).[52] Good yields were obtained with a broad range of aryl Grignard reagents. For base sensitive substrates, aryl iodides can be used as starting materials, together with a palladium catalyst, DABSO and TIPS-EBX (**5**). In 2014, Waser and Chen reported the use of EBX reagents for the alkynylation of *H*-phosphites, -phosphinates and phosphine oxides in the presence of a base (Scheme 21, **B**).[53] This reaction worked efficiently at room temperature in a few minutes and didn't require any transition metals.



Scheme 21. Synthesis of alkynyl sulfones and alkynyl phosphorus derivatives.

In 2015, Waser and co-workers reported the synthesis of thiocyanates starting from thiols using cyanobenziodoxol(on)e reagents CBX (**16**) or CDBX (**24**) at room temperature (Scheme 22).[54] The reaction tolerated a wide range of functional groups such as halogens, nitro, amide, ethers, and esters and could be applied to both aromatic and aliphatic thiols. Triple cyanation was also achieved in 78% yield (product **103**). The reaction could also be applied to more complex molecules such as thioglycosides (product **104**).



Scheme 22. Cyanation of thiols with CBX (**16**).

4. C-C Bond Formation

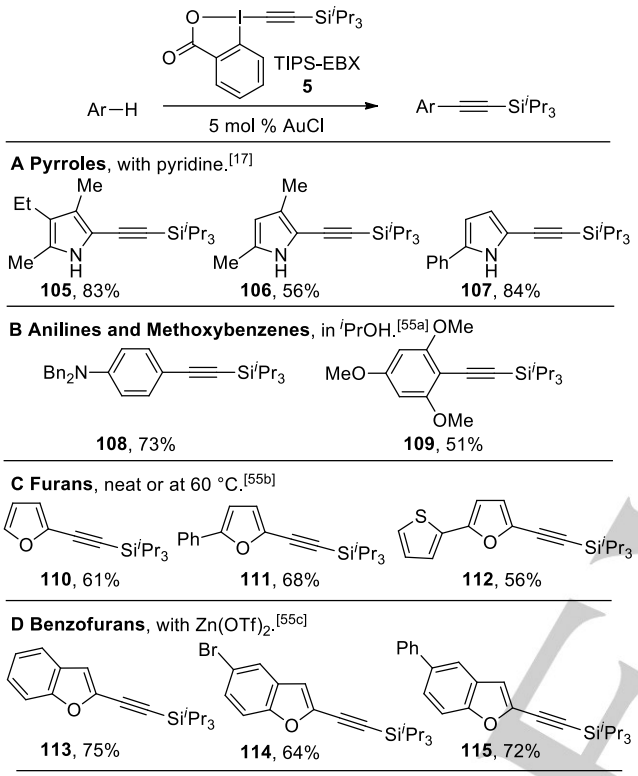
The formation of C-C bond using benziodoxole reagents has been mostly focused on alkynylation. A few rare examples of cyanation and arylation have also been reported.

4.1. Alkynylation

4.1.1 Transition Metal-Catalyzed C-H Bond Functionalization

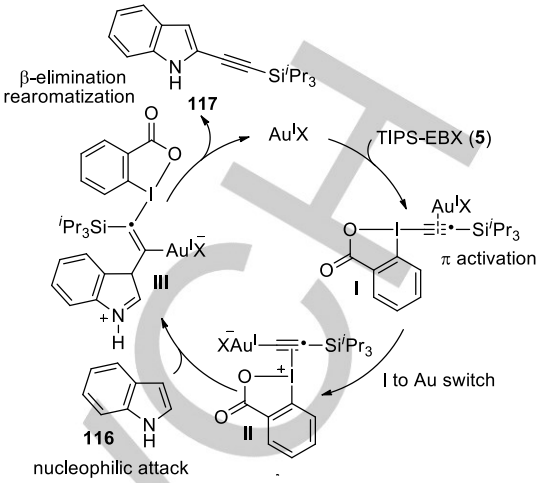
In 2009 and 2010, Waser and co-workers reported the first direct C-H alkynylation process on indoles, pyrroles and thiophenes respectively using a gold catalyst and TIPS-EBX (**5**) under mild conditions.[55] Further studies demonstrated that pyridine could be an efficient ligand to diminish the reactivity of AuCl in the presence of sensitive electron-rich pyrroles (Scheme 23, **A**, products **105**-**107**).[17] The alkynylation could be extended to less electron-rich substrates like anilines, trimethoxybenzenes, furans and benzofurans.[56] In the case of anilines, a moderate

bulky group on the nitrogen was essential for *para* selectivity (Scheme 23, **B**, product **108**). For furans, the reaction had to be performed under neat condition or at 60 ºC to achieve good yields (Scheme 23, **C**, products **110**-**112**). In 2013, Waser and Li reported that $Zn(OTf)_2$ was an efficient activating reagent for the direct C2 alkynylation of benzofurans (Scheme 23, **D**, products **113**-**115**). Waser and co-workers proposed either a π activation or an oxidative mechanism for the direct C-H alkynylation reaction.[17, 55a]



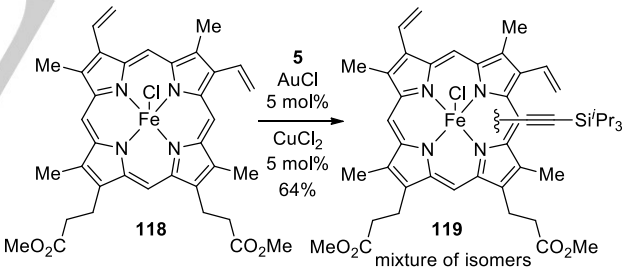
Scheme 23. Extension of the scope of the direct alkynylation of arenes.

In 2014, the mechanism of this transformation was examined by Ariafard using computational chemistry.[57] He found out that both the oxidative addition and the insertion/elimination mechanisms were too high in energy to rationalize the reaction rate. Instead, they proposed a new reaction pathway accessible at room temperature involving transfer of the alkyne from iodine to gold (from **I** to **II** in Scheme 24). Nucleophilic attack of indole (**116**) on intermediate **II**, followed by β-elimination and rearomatization would give the observed alkynylation product **117**.



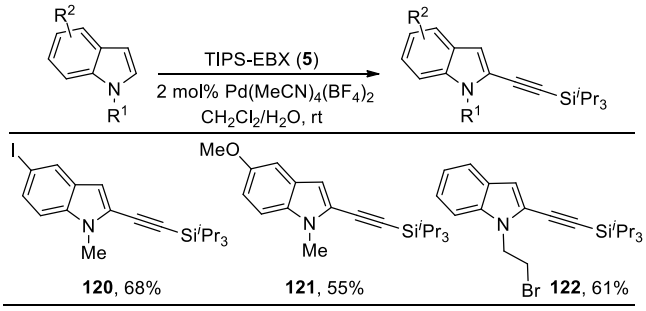
Scheme 24. New mechanism proposal for the alkynylation of indole (**116**).

Marletta and co-workers reported in 2014 the alkynylation of protoporphyrin IX (**118**) using the gold-catalyzed alkynylation with TIPS-EBX (**5**) (Scheme 25).[58] The product **119** was obtained as a mixture of regioisomers, but this was not a problem for biolabelling studies. The use of a copper co-catalyst was important to prevent the formation of gold nanoparticles, which led to decomposition of **118**. The gold-catalyzed alkynylation was also used in the synthesis of indole *cis*-enamides and substrates for Friedel-Crafts reactions with activated cyclopropanes.[59]



Scheme 25. Gold-catalyzed alkynylation of protoporphyrin IX (**118**).

In 2013, Waser and co-workers developed a palladium(II) catalysed C2 selective alkynylation of indoles (Scheme 26).[60] Functionalized indoles **120**-**122** were obtained in 55-68% yield at room temperature.

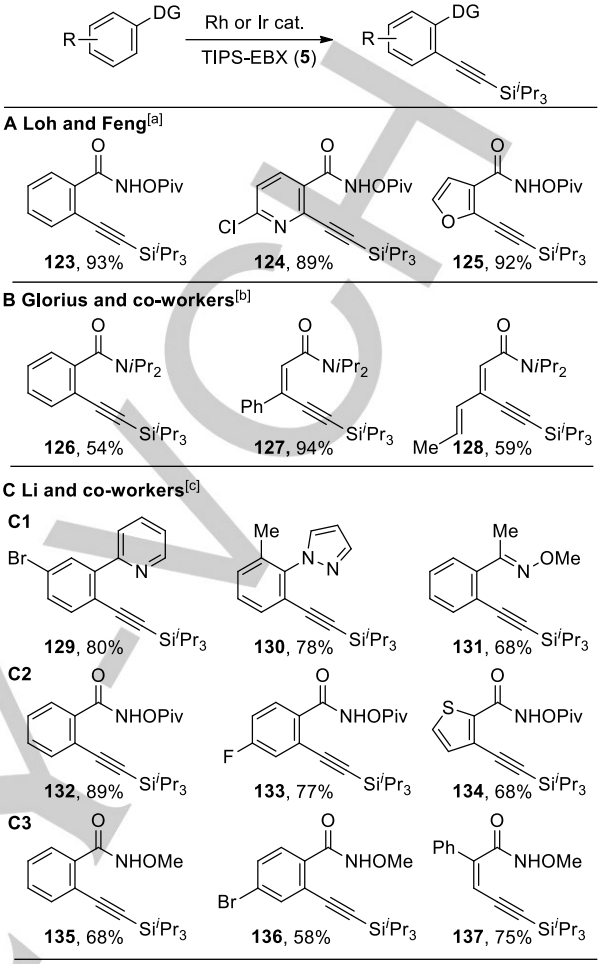


Scheme 26. C2 selective alkynylation of indoles.

In 2014, a breakthrough in the alkynylation of SP^2 C-H bonds using transition metal catalysts and EBX reagents was reported independently by three laboratories based on a directing group strategy.[61] Loh and Feng first reported the alkynylation of pivaloyl benzamides using a rhodium(III) catalyst and TIPS-EBX (**5**) (Scheme 27, **A**).[61a] Alkynylated benzenes **123** and heterocycles **124** and **125** were obtained in excellent yields at room temperature. Glorius and co-workers used a cationic rhodium(III) catalyst for the alkynylation of both benzamides and enamides (Scheme 27, **B**).[61b] Finally, Li and co-workers reported an extensive study on the alkynylation of arenes using TIPS-EBX (**5**) (Scheme 27, **C**).[61c] With a rhodium catalyst, they could use a broad range of directing groups such as pyridine, pyrazole or oximes (products **129**-**131**). Best results were again obtained with a pivaloylamide as directing group (products **132**-**133**). They also reported the first example of iridium-catalyzed alkynylation, which gave better results with a methoylamide directing group. This method could also be used for the synthesis of α-substituted ynamide **137**.

Since these three seminal reports, the directed C-H alkynylation using TIPS-EBX (**5**) and rhodium or iridium catalysts has been applied to a broad range of substrates. Loh and co-workers extended the rhodium-catalyzed alkynylation of olefins to both acrylamides and enamides.[62] Loh and co-workers, as well as Zhu and co-workers independently reported the rhodium-catalyzed C7- alkynylation of indolines, whereas Li and Zhou and co-workers used an iridium catalyst for the same transformation.[63] Chang and co-workers developed an efficient C8-alkynylation of quinoline-N-oxide using a cationic rhodium catalyst.[64] The efficiency of azomethine ylides as directing group was further demonstrated by Li and co-workers.[65] Finally, Hong and Kang developed two protocols for the selective C2 or C5 alkynylation of quinolones using either a rhodium or a ruthenium catalyst.[66]

Recently, the scope of rhodium-catalyzed alkynylation reactions with EBX reagents has been extended beyond simple arenes and alkenes.[67] Li and co-workers reported the alkynylation of the C-H bond of aromatic aldehydes (Scheme 28, **A**).[67a] Both alcohols and sulfonamides could be used as directing groups to get ynones in 36-92% yield. A similar procedure using different directing groups was later reported by Zhou and-coworkers.[67b]



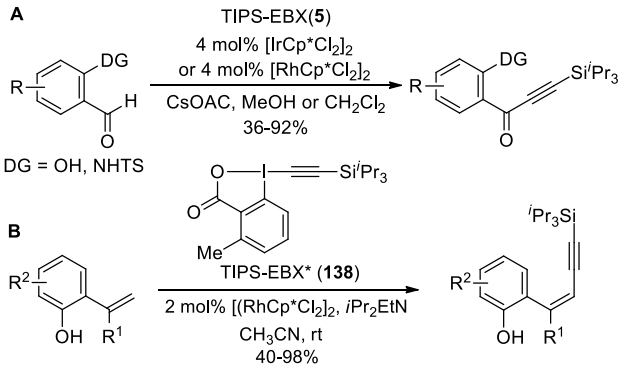
Scheme 27. Rhodium- and iridium-catalyzed alkynylation of arenes. Reactions conditions: [a] 2 mol% $[RhCp^*Cl_2]_2$, NaOAc, DCE, rt; [b] 10 mol% $[RhCp^*(MeCN)_3](SbF_6)_2$, CH_2Cl_2, 80 °C; [c] 2 mol% $[RhCp^*Cl_2]_2$, 10 mol% $Zn(OTf)_2$, DCE, rt-80 °C; or 2 mol% $[RhCp^*Cl_2]_2$, 20 mol% CsOAc, MeOH, rt; or 4 mol% $[IrCp^*Cl_2]_2$, 16 mol% $AgNTf_2$, DCE, 30 °C.

In 2015, Nachtsheim and co-workers reported the alkynylation of vinyl phenols (Scheme 28, **B**).[67c] Interestingly, the alkynylation occurred exclusively on the alkenes, probably via a less frequent six-membered rhodacycle intermediate. Enynes were obtained with very high *Z*-selectivity, but the reaction was successful only for terminally unsubstituted alkenes. Nachtsheim and co-workers used the more reactive TIPS-EBX* (**138**).[17] With **138**, the formation of contra-productive rhodacycle on the 2-iodobenzoic acid formed during the reaction is not possible, as the *ortho* position is blocked.

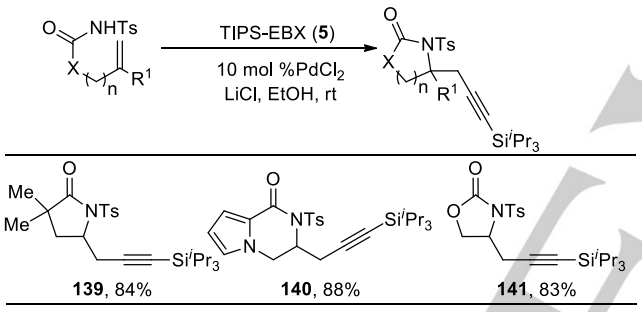
4.1.2 Alkynylation as Part of Domino Processes

In 2009, Waser and co-workers reported the palladium-catalyzed intramolecular oxyalkynylation of olefins with phenols and carboxylic acids and TIPS-EBX (**5**).[68a] In 2011, they expended this concept to the intramolecular aminoalkynylation

of terminal olefins (Scheme 29).[68b] Best results were obtained using a lithium palladate catalyst formed in situ from lithium chloride and palladium(II)chloride. This method was applied to synthesis of five-membered lactam **139**, ketopiperazine **140**, and oxazolidinone **141**.



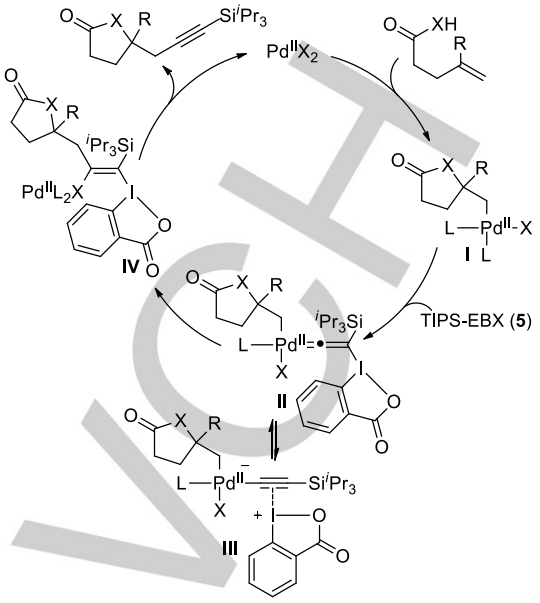
Scheme 28. Recent developments in rhodium-catalyzed C-H alkynylation.



Scheme 29. Aminoalkynylation of terminal olefins.

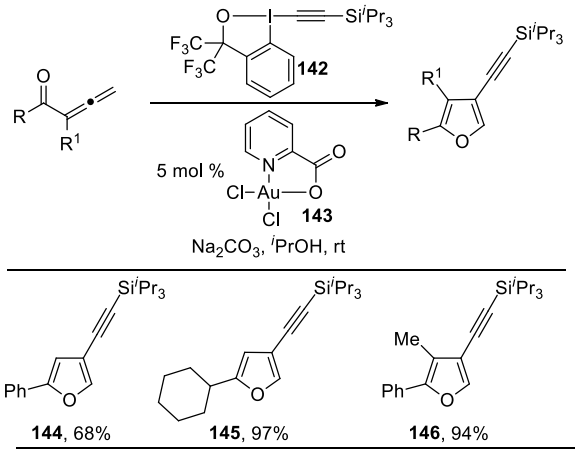
Originally, Waser and co-workers proposed a mechanism involving oxy- or amino- palladation, oxidative addition on TIPS-EBX (**5**) and reductive elimination. In 2014, Ariafard performed calculation on the oxyalkynylation process and discovered a more favorable pathway involving formation of palladium allenylidene intermediate **II** by reaction of intermediate **I** with TIPS-EBX (**5**) (Scheme 30).[69] **II** is in equilibrium with the less favorable palladium alkynyl complex **III**. From **II**, easy 1,2-shift of the alkyl group gives palladium alkenyl complex **IV**. Finally, simple β-elimination leads to the oxyalkynylation product.

Waser and co-workers then investigated other types of domino reactions with EBX reagents for the synthesis of (hetero)arenes. The initial attempt appeared in 2011 for the synthesis of 3-alkynylated indoles starting from anilines.[70] It was found that gold(III) could only perform the cyclization step from 2-ethynyl anilines and the addition of a gold(I) catalyst was required for alkynylation.



Scheme 30. Mechanism proposed by Ariafard for the oxyalkynylation reaction.

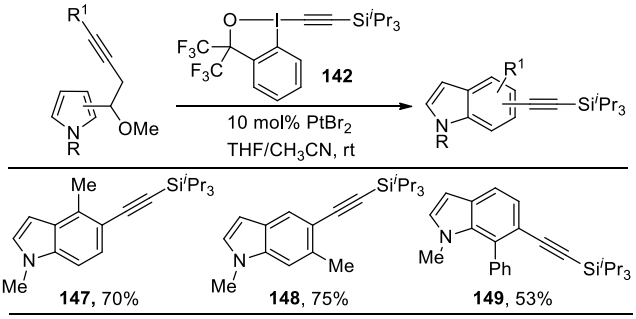
In 2013, Waser and co-workers reported the first cyclization-alkynylation domino reaction of keto allenes using ethynylbenziodoxole reagent **142** and gold(III) catalyst **143** (Scheme 31).[56b] This transformation gave access to alkyl- and aryl-substituted 3-alkynylated furans **144**-**146**, which could not be accessed via direct C-H alkynylation. This reaction most probably proceeds via gold-catalyzed cyclization of the keto allene to form a C3-aurated furan, which is then alkynylated by **146**.



Scheme 31. Gold-catalyzed cyclization-alkynylation of keto allenes.

In 2015, Waser and co-workers reported another domino reaction to synthesize 5- or 6- alkynylated indoles (Scheme

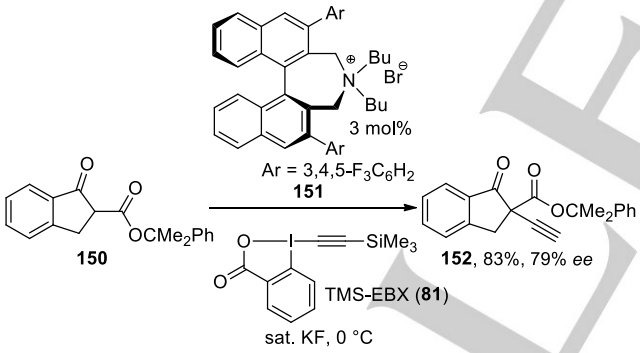
32).[71] This transformation could not be catalyzed by either gold(I) or gold(III), but a platinum(II) catalyst was successful. Starting from 2- or 3- homopropargylic pyrroles 5- and 6-alkynylated indole derivatives **147**-**148** and **149** were obtained selectively.



Scheme 32. Platinum-catalyzed cyclization-alkynylation domino reaction to access 5- or 6-alkynylated indoles.

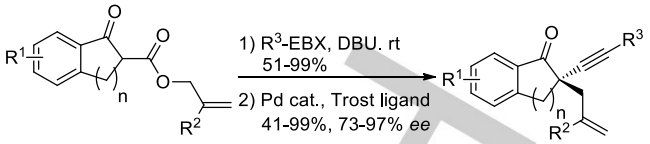
4.1.3 Direct Alkynylation of Carbon Nucleophiles.

In 2010, Waser and co-workers reported the efficient ethynylation of α-cyano, α-oxo and α-nitro β-ketoesters using TMS-EBX (**81**) at low temperature in presence of TBAF and reported preliminary results of asymmetric induction using *cinchona*-based phase transfer catalysts.[72] In 2013, they reported an improved procedure using Maruoka's catalyst (**151**) affording ketoester **152** in 79% *ee* (Scheme 33).[19a]



Scheme 33. Enantioselective alkynylation using Maruoka's catalyst (**151**).

In 2014, Waser and co-workers developed an indirect approach to access α-alkynyl indanones and tetralones in high enantiopurities through an alkynylation/palladium-catalyzed decarboxylative asymmetric allylic alkylation (DAAA) sequence (Scheme 34).[73] Alpha alkynyl β-allyl keto esters were obtained in high yields using DBU or TMG as stoichiometric bases with TIPS-EBX (**5**) or TBDPS-EBX. The silyl protected α-alkynyl β-allyl ketoesters were then subjected to palladium catalysis using the Trost ligand naphthyl-DACH to yield α-alkynyl α-allyl ketones with up to 97% enantioselectivity.



Scheme 34. Alkynylation-decarboxylative asymmetric allylic alkylation sequence for the synthesis of quaternary propargylic centers.

Yang and co-workers demonstrated the versatility of the alkynylation of ketoesters with TMS-EBX (**81**) in the synthesis of terpene natural products (Figure 3).[74] Alkyne **153**, **154** and **155** used in the synthesis of marasmene, (-)-lingzhiol and a fragment of azadirachtin respectively, could be obtained in good yield using this methodology.[74a-c] In 2015, it was also applied to the total synthesis of the core of retigeranic acid A.[74d]

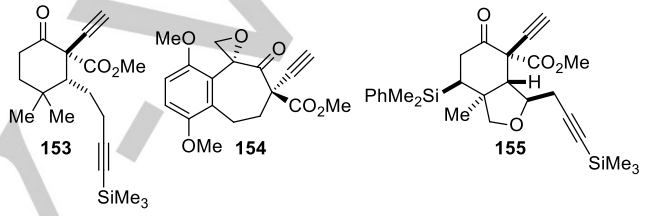
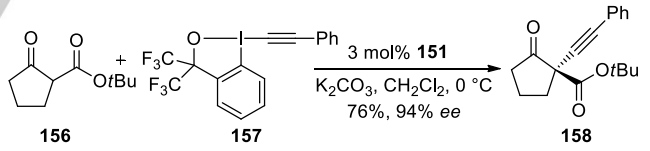


FIgure 3. Alkyne building blocks for the synthesis of natural products accessed using TMS-EBX (**81**).

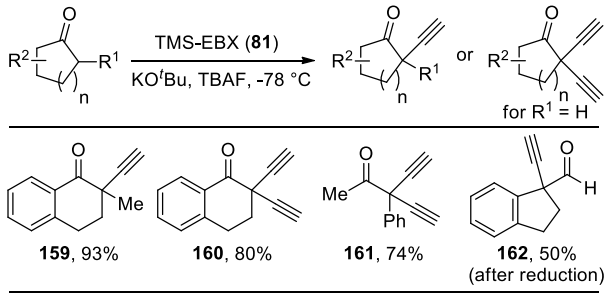
In 2014, Maruoka and co-workers reported the first alkynylation of ketoesters proceeding with more than 90% *ee* (Scheme 35).[75] Key for success with phase-transfer catalyst **151** was the use of phenylbenziodoxole **157** instead of TMS-EBX (**81**).



Scheme 35. Enantioselective alkynylation using phase-transfer catalyst **151** and benziodoxole reagent **157**.

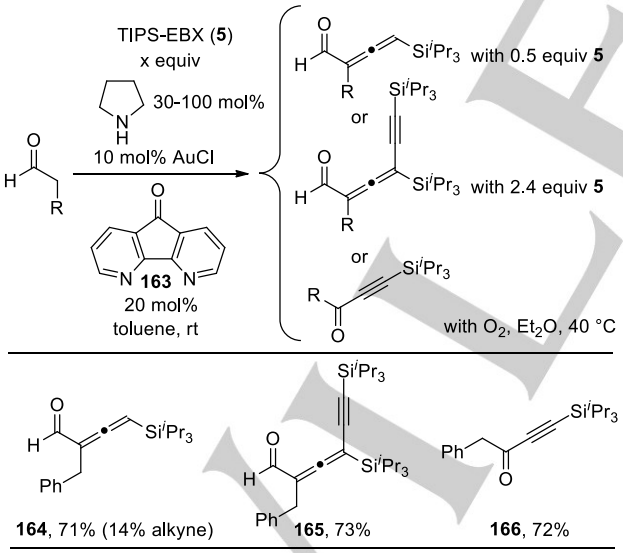
The scope of nucleophiles in the alkynylation reaction was further extended by Vesely and co-workers.[76] Alkynylated nitro-sulfones, pyrazolones, oxindoles, rhodanines and azlactones were obtained in good yields using TMS-EBX (**81**) and mild bases. The use of a *cinchona*-derived phase-transfer catalyst allowed the formation of alkynylated nitro-sulfones with up to 61% *ee*. In 2014, Silva Jr. and co-workers reported the first successful alkynylation of aromatic ketones using TMS-EBX (**81**) (Scheme 36).[77] Cyclic derivatives such as tetralone **159** were obtained in very good yield. With secondary α positions, dialkynylation was obtained (products **160** and **161**).

Interestingly, the first example of alkynylation of an aldehyde was also reported in this work (product **162**).



Scheme 36. Alkynylation of ketones with TMS-EBX (**81**).

The alkynylation of aldehydes activated as enamines was studied by Huang and Wang (Scheme 37).[78] The formation of the enamine was not enough to promote the reaction with TIPS-EBX (**5**), but the use of a gold co-catalyst gave full conversion. However, the main product was not an alkyne, but an allene such as **164**. If an excess of TIPS-EBX (**5**) was used, a second alkynylation took place to give enynes such as **165**. Interestingly, when the reaction was performed under oxygen, oxidative cleavage of the formed enamine was observed to give ynone **166**. A current limitation of this method is that it works only with unsubstituted pyrrolidine as catalyst, precluding the development of enantioselective reactions.



Scheme 37. Reactions of TIPS-EBX (**5**) with aldehydes using amine/gold catalysis.

4.1.4 Alkynylation of Carbon Radicals.

The alkynylation of radicals generated using classical C-H abstraction methods with EBX reagents has been studied only recently (Figure 4).[79] In 2014, Yu and Chen and co-workers reported that alkynylation α- to heteroatoms was possible using *tert*butylhydroperoxide (TBHP) or di*tert*butylperoxide (DTBP) as oxidant at 60 °C (products **167** and **168**).[79a] Similar conditions could be then applied for the generation of ynones starting from aldehydes (products **169** and **170**).[79b,c]

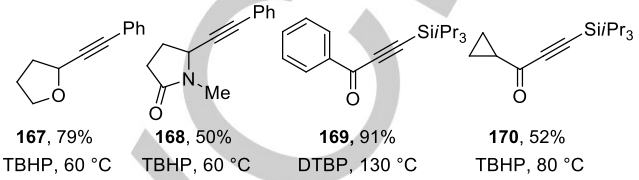
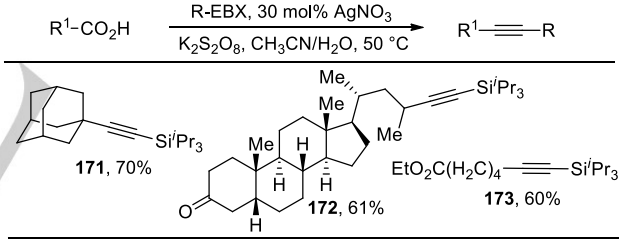


Figure 4. Alkynes obtained via oxidative C-H abstraction.

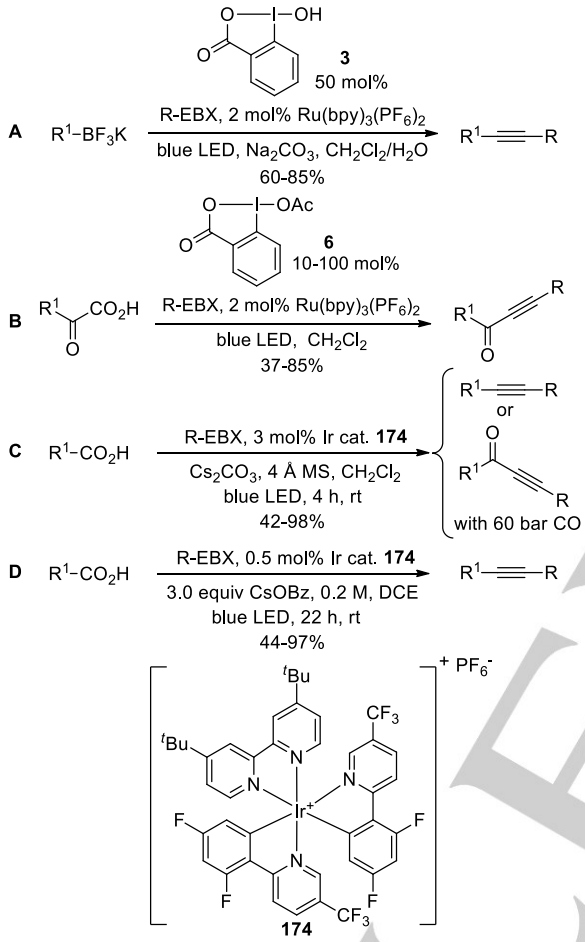
To generate radicals under milder and more selective conditions, Li and co-workers used a decarboxylation reaction (Scheme 38).[80] Using potassium persulfate as oxidant and a silver catalyst, alkynes **171**, **172** and **173** derived from tertiary, secondary and primary carboxylic acids could be accessed in 60-70% yield. Aryl benziodoxolones could also be used. In 2015, Duan and co-workers reported that this method could be extended to α-keto-acids to generate ynones.[81]



Scheme 38. Decarboxylative alkynylation of carboxylic acids.

A disadvantage of the method developed by Li and co-workers is the requirement for a stoichiometric strong oxidant. Recently, several research groups have made use of photoredox catalysis to avoid this issue (Scheme 39).[82] In 2014, Chen and co-workers reported the alkynylation of trifluoroborates salts using a ruthenium catalyst and aryl, alkyl and silyl EBX reagents (Scheme 39, **A**).[82a] The use of hydroxybenziodoxolone **3** as additive was required, probably to initiate the catalytic cycle by oxidation of the ruthenium(II) catalyst. In 2015, Chen and co-workers developed the first decarboxylative alkynylation under photoredox conditions for the synthesis of ynones starting from carboxylic acids (Scheme 39, **B**).[82b] Acetoxy benziodoxolone **6** was required as a catalyst. Finally, Xiao, Lu and co-workers[82c] and Waser and co-workers[82d] independently reported the first decarboxylative alkynylation of carboxylic acids working for a

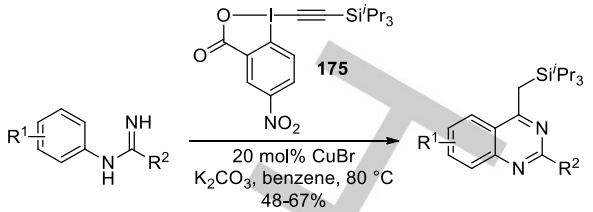
broad range of substrates without the need for further oxidative additive (Scheme 39, **C** and **D**). Key for success was the use of iridium(III) catalyst **174**. Xiao, Lu and co-workers focused on aryl EBX as reagents and also reported the formation of ynones when the reaction was performed under CO pressure. Waser and co-workers on the other hand developed an efficient protocol for the transfer of synthetically versatile silyl alkynes.



Scheme 39. Alkynylation reactions using photoredox catalysis.

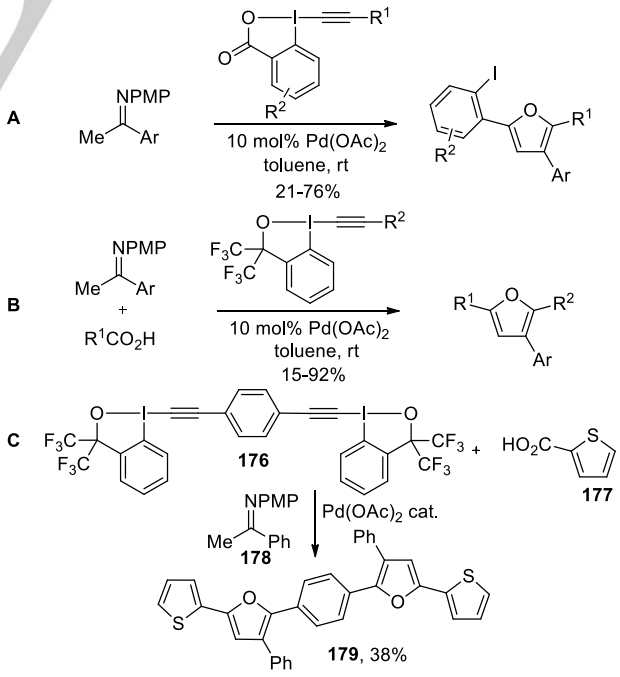
4.2. Other Transformations

Other transformations than alkynylation have still not been broadly investigated. Arylation for example remained limited to a few examples of cross-coupling reactions.[46h, 83] EBX reagents have been used for other transformations than simple alkynylation. Ohno, Fujii and co-workers reported in 2010 the copper-catalyzed synthesis of quinazolines starting from amidines and using benziodoxolone reagent **175** (Scheme 40).[84] The introduction of the nitro group in reagent **175** led to an increase in yield compared to TIPS-EBX (**5**).

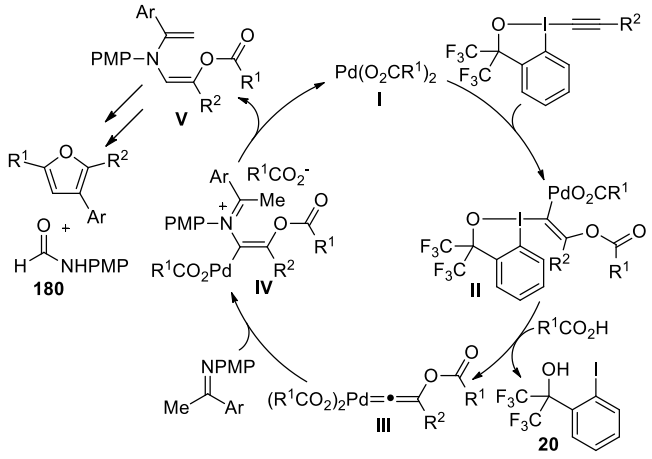


Scheme 40. Synthesis of quinazolines with EBX reagent **175**.

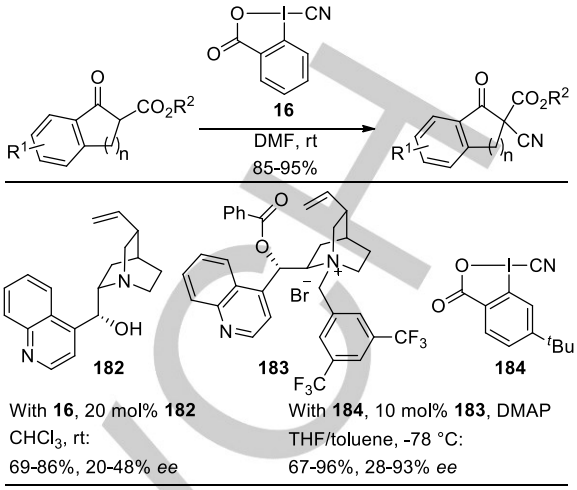
A new type of palladium-catalyzed transformation involving EBX reagents was reported by Yoshikai and co-workers.[85] When EBX reagents were reacted with ketimines, furans incorporating the iodoaryl group of the reagent were obtained (Scheme 41, **A**).[85a] A three-component reaction involving a carboxylic acid as third partner could then be developed by using a benziodoxole reagent (Scheme 41, **B**).[85b] Particularly impressive was the reaction of new bisbenziodoxole reagent **176** with thiophene carboxylic acid **177** and ketimine **178** to give polyaromatic compound **179** in 38% yield (Scheme 41, **C**). The reaction was proposed to be initiated by insertion of a palladium carboxylate complex **I** into the triple bond to give **II** (Scheme 42). α-Elimination of aryl iodide **20** and ligand exchange with the carboxylic acid would lead then to palladium allenylidene intermediate **III**. Nucleophilic attack of the imine followed by protodemetallation would give enamine **V** and regenerate active catalyst **I**. From **V**, a series of bond formation/breaking events finally would lead to the furan, as well as to formamide **180**, which could be isolated.



Scheme 41. Palladium-catalyzed synthesis of furans using EBX reagents.

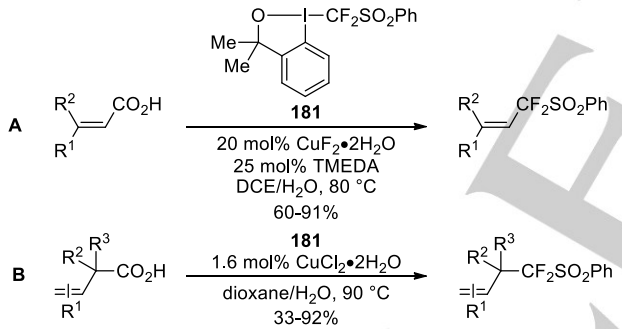


Scheme 42. Speculative mechanism for furan synthesis.



Scheme 44. Cyanation of ketoesters with benziodoxolone reagents.

To develop an alternative for difluoromethylation, Hu and co-workers introduced benziodoxole reagents **181**.[86] They first reported the difluoromethylation of thiols using reagent **181** in 2008.[86a] In 2012, they further developed the copper-catalyzed difluoromethylation of vinyl and allyl carboxylic acids with benziodoxole **181** (Scheme 43, **A** and **B**).[86b,c]



Scheme 43. Copper-catalyzed difluoromethylation of carboxylic acids.

In 2015, Chen and co-workers reported the first cyanation of cyclic ketoesters in high yield using cyanobenziodoxolone **16** (Scheme 44).[87a] Waser and co-workers then reported the use of *cinchona* alkaloid **182** as catalyst for enantioselective cyanation with up to 48% ee.[87b] Finally, Zheng and co-workers developed the first highly enantioselective cyanation of ketoesters using modified *cinchona* phase-transfer catalyst **183** and benziodoxolone **184**.[87c] The introduction of the *tert*-butyl group in **184** was essential to increase its solubility and allow performing the reaction at low temperature to enhance enantioselectivity.

5. Summary and Outlook

Cyclic hypervalent iodine reagents are known for a long time, but their use had been limited mostly to simple oxidation reactions. In the last decade, their potential for more complex functional group transfer reactions has begun to be exploited. Whereas trifluoromethylation using Togni reagents has had the largest impact, alkynylation using EBX reagents has been increasingly investigated. The alkynylation of thiols under mild conditions has been developed, leading to first application in biology. The alkynylation of heteroaromatic C-H bonds using gold or palladium catalysts, or of arene rings using a directing group and rhodium or iridium catalysts was successful. EBX reagents are also ideally suited for the alkynylation of carbon nucleophiles and radicals.

Whereas trifluoromethylation and alkynylation with benziodoxol(on)e reagents have now attracted the full interest of the research community, other transformations have remained scarce. Exciting preliminary results obtained since 2013 with azidation, cyanation or oxygen-transfer reactions indicate that this situation will change soon. It is our conviction that the synthetic potential of benziodoxolone reagents has just begun to be investigated, and that with time they will rise to be one versatile toolbox for organic and medicinal chemists.

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Keywords: Hypervalent Iodine • Alkynylation • Synthetic Methods • Reagents • Benziodoxol(on)es

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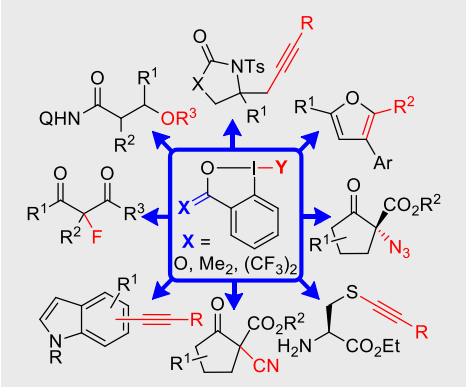
REVIEW

A New Toolbox: Hypervalent iodine compounds are privileged reagents in organic synthesis due to their exceptional reactivity. Among them, cyclic derivatives stand apart due to their enhanced stability. Whereas the use of benziodoxol(on)es for trifluoromethylation (Togni's reagents) is now largely recognized, other transformations have also attracted a strong interest recently. In this review, the progress in the area since 2011 will be presented.



*Yifan Li, Durga Prasad Hari, Maria Victoria Vita and Jerome Waser **

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