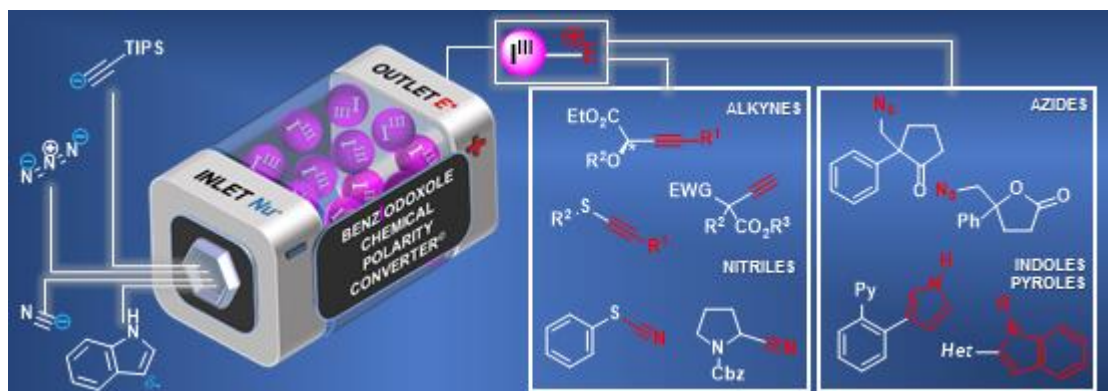# Cyclic Hypervalent Iodine Reagents: Enabling Tools for Bond Disconnection via Reactivity Umpolung.

Durga Prasad Hari[+], Paola Caramenti[+] and Jerome Waser*

Laboratory of Catalysis and Organic Synthesis, Ecole Polytechnique Fédérale de Lausanne, EPFL SB ISIC LCSO, BCH 4306, 1015 Lausanne, Switzerland.

The efficient synthesis of organic compounds is an important field of research, which sets the basis for numerous applications in medicine or materials science. Based on the polarity induced by functional groups, logical bond disconnections can be deduced for the elaboration of organic compounds. Nevertheless, this classical approach makes synthesis rigid, as not all bond disconnections are possible.

The concept of Umpolung has been therefore introduced: by inverting the normal polarity of functional groups, new disconnections become possible. Among the tools for achieving Umpolung, hypervalent iodine reagents occupy a privileged position. The electrophilicity of the iodine atom and the reactivity of the hypervalent bond allow access to electrophilic synthons starting from nucleophiles. Nevertheless, some classes of hypervalent iodine reagents can be too unstable for many applications, in particular involving metal catalysis. In this context, cyclic hypervalent iodine reagents, especially benziodoxolones (BXs) have been known since a long time to be more stable than their acyclic counterparts, yet their synthetic potential had not been fully exploited.

In this account, we report our efforts since 2008 in the use of BX reagents in the development of new transformations in organic synthesis, which showed for the first time their versatility as synthetic tools. Our work started with electrophilic alkynylation, as alkynes are one of the most important functional groups in organic chemistry, but are usually introduced as nucleophiles. We used ethynylbenziodoxolones (EBXs) in the direct alkynylation of nucleophiles, such as keto esters, thiols or phosphines. The reagents could then be applied to the gold- and palladium- catalyzed alkynylation of C-H bonds on (hetero)arenes, leading to a more efficient alternative to the Sonogashira reaction. More complex reactions were then developed with formations of several bonds in a single transformation. Gold- and platinum- catalyzed cyclization/alkynylation domino processes gave access to new types of alkynylated heterocycles. Multi-functionalization of olefins became possible through intramolecular oxy- and amino- alkynylations. (Enantioselective) copper-catalyzed oxy-alkynylation of diazo compounds led to stereocenters with perfect atom economy. Finally, EBXs were also used for the alkynylation of radicals generated under photoredox conditions.

Since 2013, we then extended the use of BX reagents to other transformations. Azidobenziodoxolo(ne)s (ABXs) were used in the azidation of keto esters, enol silanes and styrenes. New more stable derivatives were introduced. Cyanobenziodoxolones (CBXs) enabled the cyanation of stabilized enolates, thiols and radicals. Finally, new BX reagents were developed for the Umpolung of indoles and pyrroles. They could be used in metal-catalyzed directed C-H functionalizations, as well as in Lewis acid mediated oxidative coupling to give functionalized bi-(hetero)arenes.

In the last decade, our group and others have shown that BX reagents are not only "structural beauties", but also extremely useful reagents in synthetic chemistry. A toolbox of cyclic hypervalent iodine reagents is now available to achieve Umpolung-based disconnections. We are convinced that the field is still in its infancy, and many new reagents and transformations still remain to be discovered.

1. INTRODUCTION AND CONTEXT

Organic compounds have a deep impact on our everyday life as drugs, agrochemicals or materials. Over the last century, organic synthesis has matured as a craft and a science. Guidelines have been conceptualized to harness the fundamental properties of atoms, such as their electronegativity, to select adequate disconnections for bond formation.[1] For example, functional groups containing electronegative atoms, such as nitrogen, halogens, oxygens or sp^2 and sp^3 hybridized carbons are best introduced as nucleophiles onto

the carbon skeleton of organic compounds (Figure 1a). This approach is highly successful, but does not allow chemists to make all disconnections, as nucleophilic positions cannot be functionalized. To extend the versatility of organic synthesis, Seebach has introduced the concept of Umpolung (reversal of reactivity):[2] If the innate reactivity of synthons can be inverted, new disconnections become possible, leading to greater diversity and synthetic efficiency.

In this context, hypervalent iodine reagents have taken a privileged position based on the work of pioneers such as Beringer, Koser, Valvoglis, Moriarty, Zhdankin, Kita, Ochiai, and many others (Figure 1b).[3] Both iodanes and iodonium salts allow the Umpolung of many nucleophiles into electrophilic synthons. Even if the concept of hypervalency is still a subject of controversy,[4] it has been successfully used to rationalize the exceptional properties of hypervalent iodine reagents. However, their high reactivity can also lead to instability in presence of strong bases, transition metals or when heating. In this context, benziodoxol(on)es (BX, Figure 1c), a class of cyclic hypervalent iodine reagents, have shown increased stability due to the inclusion of the iodine atom into a heterocycle.[5,6] In particular, the groups of Ochiai and Zhdankin successively reported stable ethynyl (EBX),[7,8] azido (ABX)[9] and cyano (CBX)[10] benziodoxol(on)es. A further advantage of BX reagents is the modulation of their reactivity through the *trans*-effect in the hypervalent bond.[11] Derivatives bearing carboxy, isopropyl and hexafluoroisopropyl substituents have been most broadly used.

a) X⁻ Selected examples of nucleophiles for functional group transfer
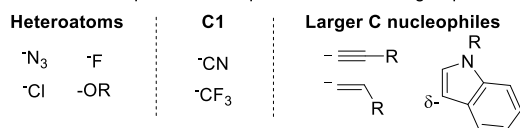
b) X⁺ Hypervalent iodine reagents for reactivity Umpolung: **low stability**
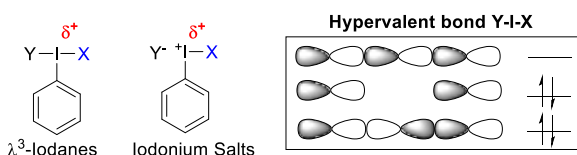
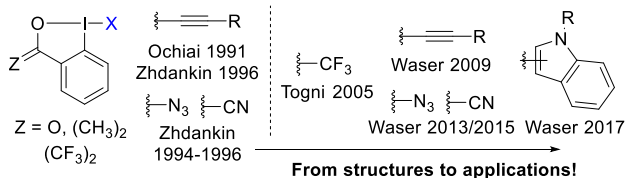c) X⁺ via benziodoxol(on)es: **Enhanced stability** and broad applications

Figure 1: Classical reactivity and Umpolung with hypervalent iodine reagents

For many years, structural studies on benziodoxolones have dominated the field, with few attempts in developing new synthetic applications. The situation changed in 2006, when Togni and coworkers reported the use of benziodoxol(on)es for trifluoromethylation.[12] The so-called Togni reagents are now broadly used for the introduction of pharmaceutically relevant trifluoromethyl groups in organic compounds.[13] Since 2008, our group has explored the potential of other BX reagents for group transfer reactions. We demonstrated that this class of reagents constitutes a unique toolbox for synthetic chemistry, which are superior to simple iodonium salts in many direct, transition metal- and photoredox- catalyzed transformations. After having focused on electrophilic alkynylation,[14] we moved to azidation and cyanation. In 2017, we introduced a new class of benziodoxolone reagents for the Umpolung of electron-rich heterocycles, in particular indoles and pyrroles. Many

other groups have since then used BX compounds in group-transfer reactions.[15,16] Herein, we will present an overview of our ten-year journey in the fascinating reactivity of these reagents

## 2. ELECTROPHILIC ALKYNYLATION

2.1 Alkynylation of acidic C-H bonds

We first encountered EBX reagents in 2010, when using alkynyliodonium salts for the alkynylation of enolates using reported methods.[17,18] We were facing serious issues of reproducibility and were not able to induce enantioselectivity under phase-transfer conditions. Building on the higher stability of EBX reagents,[7,8] we successfully used TMS-EBX (**1a**) and TBAF with stabilized enolates to give terminal alkynes **2a-f** in excellent yields (Scheme 1).[19] Asymmetric induction was now possible using Maruoka's phase transfer catalyst (**4**) (Scheme **2**).[20]

Scheme 1: Alkynylation of acidic C-H bonds using TMS-EBX (1a).
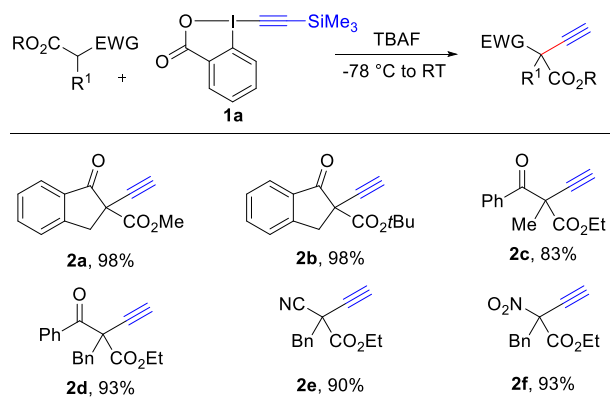

Scheme 2: Enantioselective alkynylation of *β*-keto esters using Maruoka's catalyst (4).
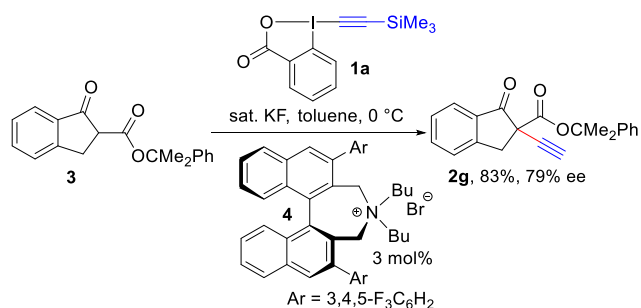

Two mechanisms can be envisaged (Scheme 3): Addition-elimination on the iodine atom (a) or conjugate addition to the alkyne, followed by reductive elimination and 1,2 shift (b). The use of ¹³C-labeled reagent **1b** led to product **9**,[19] which is in agreement with the 1,2 shift pathway.[17]

Scheme 3: Mechanism alternatives for the alkynylation of keto ester 5.
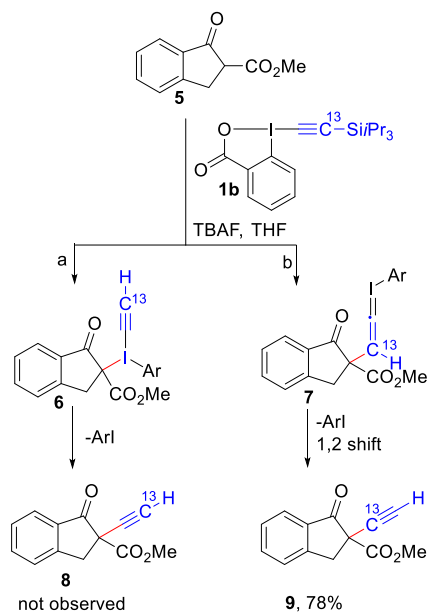
In 2014, as the phase-transfer approach was limited in both scope and enantioselectivity, we reported an alternative strategy to access quaternary stereocenters: Racemic alkynylation, followed by an enantioselective Tsuji-Trost allylation (Scheme 4).[21]

Scheme 4: Alkynylation/decarboxylative asymmetric allylic alkylation (DAAA) sequence.
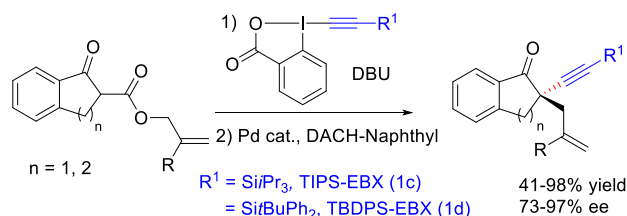

2.2 Alkynylation of heteroatoms

In 2013, we wondered if EBX reagents could also contribute to a more efficient synthesis of thioalkynes. These compounds are usually synthesized by addition of acetylides to oxidized thiol precursors.[22] Whereas only disulfides were obtained when the alkynylation was attempted with alkynyliodonium salts, a quantitative yield was realized using TIPS-EBX (**1c**) (Scheme 5a).[23,24] The reaction proceeded in five minutes at room temperature in an open flask with a wide range of EBX reagents and thiol substrates (products **10j-m**).

A mechanism for the thiol-alkynylation reaction was proposed based on computational studies (Scheme 6).[24] First, thiolate **I** could attack on the iodine atom of EBX to give **II**, which then undergoes reductive elimination to give the product. However, intermediate **II** was not observed in the computational studies. As alternative, conjugate addition of thiolate **I** to give vinyl benziodoxolone **III**, which undergoes α-addition followed by 1,2 shift leads to the product. This pathway was observed with a transition state energy of 23 kcal/mol. Nevertheless, a concerted pathway via asynchronous transition state **IV** with significant Hirshfeld charge separation was identified with a lower energy of 10.8 kcal/mol. In 2015, we further identified a four-atom transition state **V** leading to β-addition, which is favorable for alkyl groups on EBX, whereas α-addition is favored for electron withdrawing groups.[25]

Scheme 5: Alkynylation of thiols.

a) Alkynylation of thiols with TIPS-EBX (**1c**)

b) Alkynylation of thiols with R-EBX
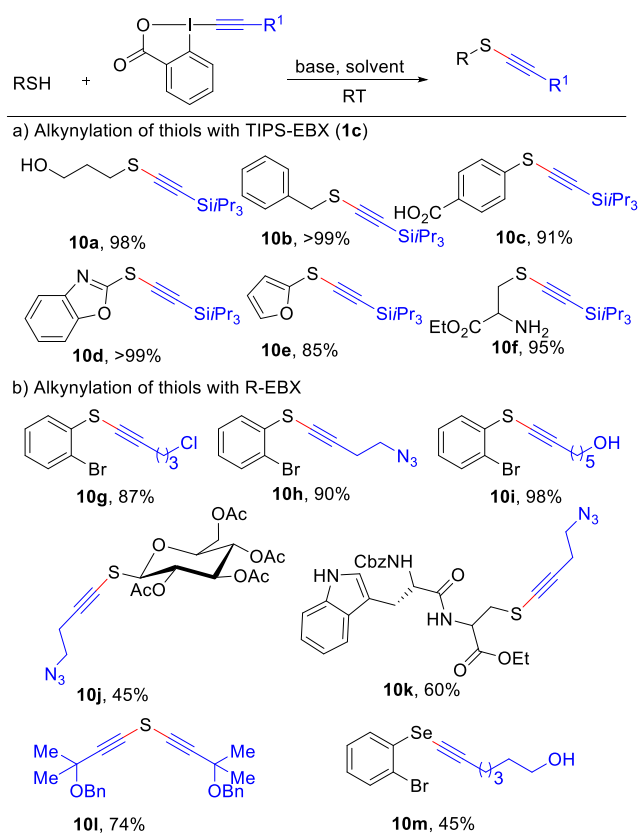
Scheme 6: Proposed mechanism for the alkynylation of thiols with Hirshfeld charge analysis on transition state IV.
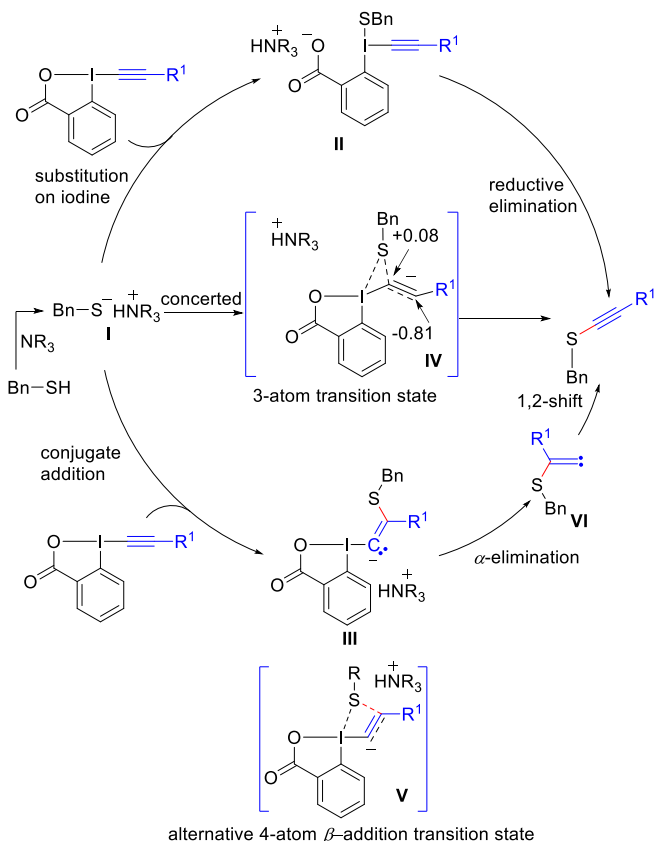
The very fast and selective reaction of EBX reagents with thiols under mild conditions motivated us to investigate applications in chemical biology. In 2015, Adibekian and our group reported a method for proteomic profiling of enzymes with hyperactive cysteines in living cells by using the azide-substituted EBX JW-RF-010 (**1e**) (Scheme 7).[26] The utility of the method was further demonstrated by identifying one target of curcumin in HeLa cells.
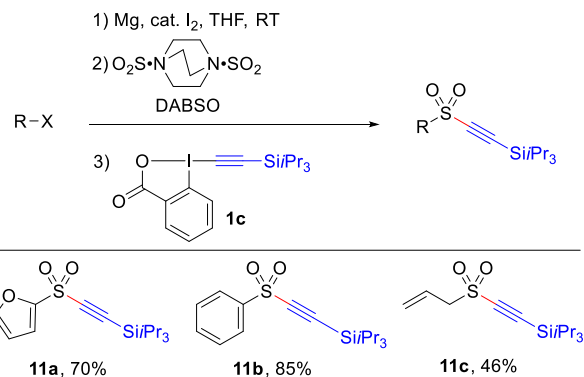
Scheme 7: Alkynylation of cysteine in complex proteomes.
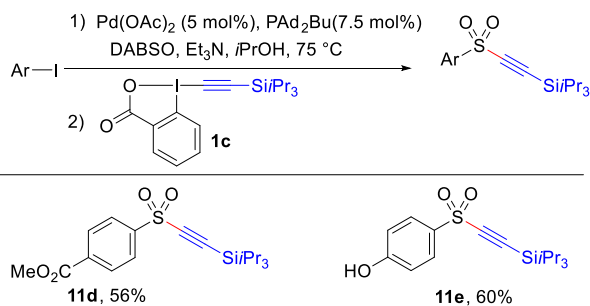

JW-RF-010 (1e)

PBS (pH = 7.4)
RT
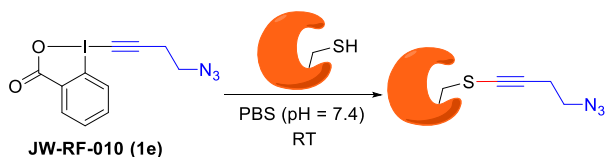
As a last effort in the area of heteroatoms functionalization, we further demonstrated the use of EBX reagents for the alkynylation of other sulfur and phosphorus nucleophiles. Sulfones **11a-e** were obtained from Grignard reagents or aryl iodides using DABSO (diazabicycloctane bis(sulfur dioxide)) as sulfur source (Scheme 8a and b)[27] and alkynyl phosphorous derivatives **12a-e** were synthesized from *H*-phosphi(na)tes and secondary phosphine oxides.[28]

Scheme 8: Alkynylation of sulfinates.

a) Alkynyl sulfone synthesis from Grignard reagents

1) Mg, cat. I$_2$, THF, RT

2) O$_2$S•N⌒N•SO$_2$
DABSO

R—X

3)

1c

11a, 70%   **11b**, 85%   **11c**, 46%

b) Palladium-catalyzed alkynyl sulfone synthesis form aryl iodides.

1) Pd(OAc)$_2$ (5 mol%), PAd$_2$Bu(7.5 mol%)
DABSO, Et$_3$N, *i*PrOH, 75 °C

Ar—I

2)   **1c**

11d, 56%   **11e**, 60%

Scheme 9: Alkynylation of *H*-phosphi(na)tes and secondary phosphine oxides.

DBU, THF
RT, 3 min

12a, 90%   **12b**, 91%   **12c**, 69%

12d, 86%   **12e**, 70% (1:1.3 dr)
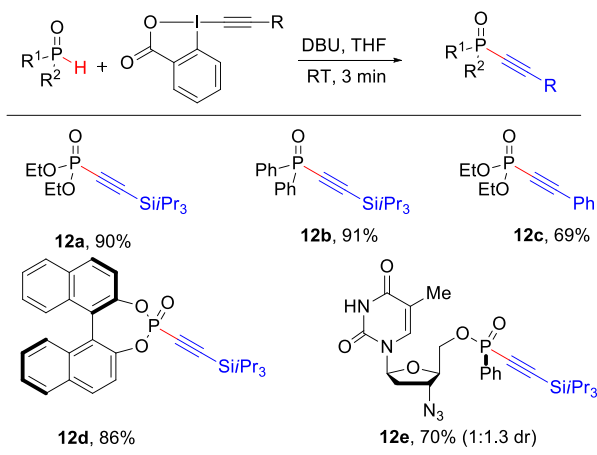
## 2.2 C-H Alkynylation of Hetero(arenes)

Our research on EBX reagents with simple nucleophiles had been highly successful, and we wondered if they could be also applied in the more complex settings of transition metal catalysis. Since 2007, using alkynyliodonium salts C-H functionalization had been a major project in our group, but without success, as the sensitive reagents constantly decomposed in the presence of the metal catalyst. In 2009, we had our first success with the direct alkynylation of indoles using TIPS-EBX (**1c**) and AuCl as catalyst (Scheme 10a).[29] C3 alkynylated indoles **13a-c** were obtained in good yields. The formation of C2-alkynylated indoles was observed when the C3 position was blocked (Scheme 10b, products **13d-e**).[30,31] The direct C-H alkynylation reaction was further extended to pyrroles (Scheme 10c, products **14a-c**),[32] thiophenes (Scheme 10d, products **15a-c**),[33] furans (Scheme 10e, products **16a-c**).[34] benzofurans (Scheme 10f, products **17a-c**),[35] and anilines and trimethoxy arenes (Scheme 11, products **18a-d**).[36]

Initially, we hypothesized two mechanisms involving either an oxidative mechanism or a π-activation for the C-H alkynylation (Scheme 12).[32] Oxidative addition of EBX on Au(I) would give Au(III) intermediate **I**. Electrophilic auration leads then to **II** and reductive elimination gives **13f**. The π-activation involves coordination of Au(I) to the triple bond to give **III**, followed by nucleophilic attack leading to **IV**. Finally, α-elimination followed by 1,2-shift gives **13f**. No silicon-shift was observed when C[13] labelled reagent **1b** was used. This result supports the oxidative mechanism. However, Ariafard found by computations that both the oxidative and π-activation mechanisms were too high in energy and proposed a iodine to gold shift on the alkyne to give intermediate **V**.[37] Indole addition to **V,** followed by β-elimination and rearomatization would lead to **13f**. Common to the three mechanisms is an electrophilic aromatic substitution step, which explains the high regioselectivity observed. In 2013, we also reported a palladium-catalyzed selective C2 alkynylation.[38] Other research groups later demonstrated that EBX reagents can be used for C-H alkynylation using a broad range of transition metal catalysts.[16]
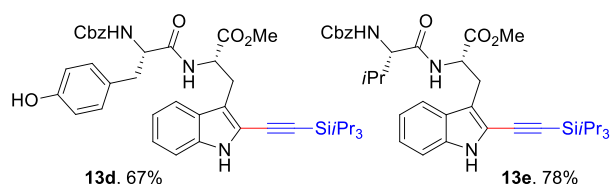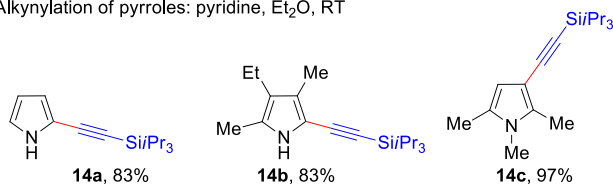
Scheme 10: Alkynylation of heteroarenes.
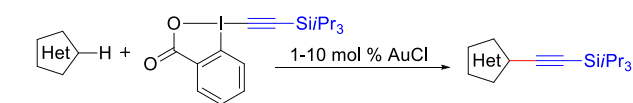
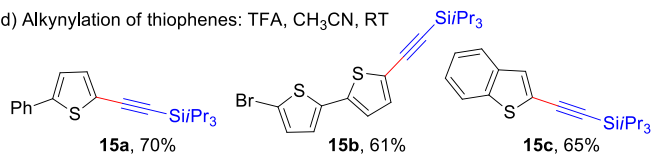a) C3 alkynylation of Indoles: Et₂O, RT

13a, 67%   **13b**, 82%   **13c**, 93%
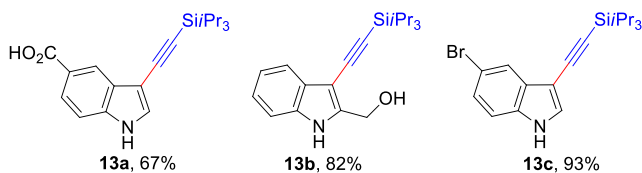
b) Alkynylation of tryptophan in peptides: CH₃CN, 40 °C

13d, 67%   **13e**, 78%

c) Alkynylation of pyrroles: pyridine, Et₂O, RT

14a, 83%   **14b**, 83%   **14c**, 97%

d) Alkynylation of thiophenes: TFA, CH₃CN, RT

15a, 70%   **15b**, 61%   **15c**, 65%

e) Alkynylation of furans: CH₃CN, RT-60 °C

16a, 73%   **16b**, 90%   **16c**, 56%
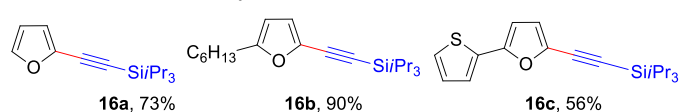
f) Alkynylation of benzofurans: Zn(OTf)₂, CH₃CN, RT

17a, 75%   **17b**, 64%   **17c**, 58%
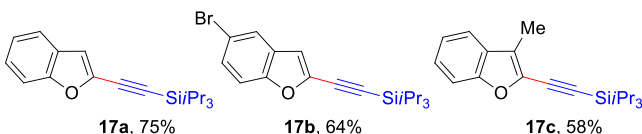
Scheme 11: Alkynylation of electron-rich anilines and trimethoxy arenes.

**18a**, 73%   **18b**, 85%

18c, 80%   **18d**, 79%
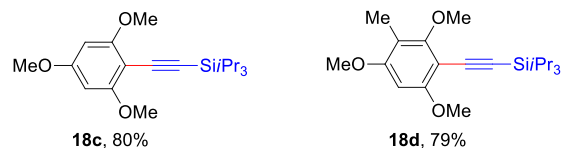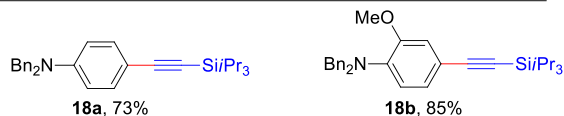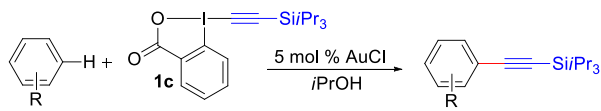
Scheme 12: Proposed mechanisms for the gold-catalyzed alkynylation.
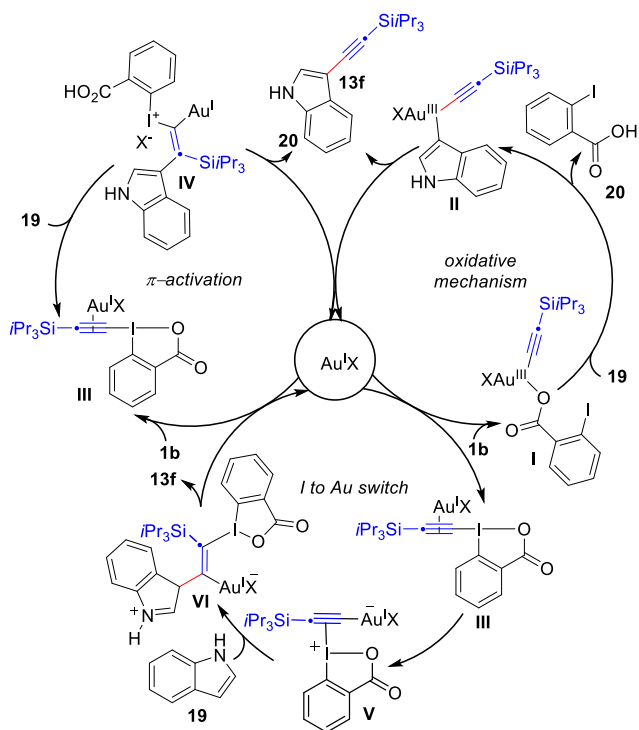

2.3 Alkynylation involving domino reactions

In our work on heterocycles, we had demonstrated that EBX reagents could be used for a single sp²-sp bond formation. We then investigated their used in domino reactions leading to the alkynylation of sp³ centers. We reported the first example of such a transformation with the palladium -catalyzed intramolecular oxy- and amino-alkynylation of olefins using phenols, carboxylic acids and imides as nucleophiles (Scheme 13a and b, products **21-22**).[39,40]

Scheme 13: Oxy-and amino-alkynylation of alkenes.
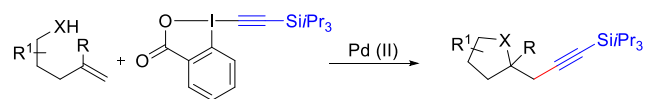
a) With phenols and carboxylic acids: Pd(hfacac)₂, CH₂Cl₂, RT

21a, 71%   **21b**, 70%   **21c**, 82%
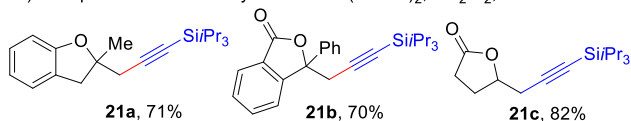
b) With tosyl imides: PdCl₂, LiCl, EtOH, RT

22a, 88%   **22b**, 57%   **22c**, 83%

22d, 79%   **22e**, 72% 83:17 dr, 2.4 g
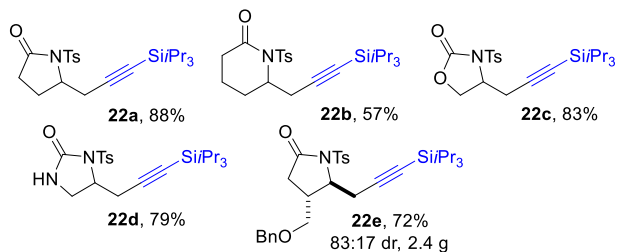
Initially, we proposed a mechanism involving a Pd(IV) intermediate **II** (Scheme 14).[39] Oxy/aminopalladation of the olefin gives intermediate **I**, which undergoes oxidative addition with TIPS-EBX

(**1c**) to give **II**, followed by reductive elimination. Ariafard proposed a different mechanism involving formation of palladium allenylidene intermediate **III** (in equilibrium with the iodine bound alkynyl palladium complex **IV**) based on computational studies.[41] 1,2-Shift followed by β-elimination of 2-iodobenzoic acid leads to the product.

**Scheme 14: Proposed mechanisms for the oxy- and amino-alkynylation of alkenes.**
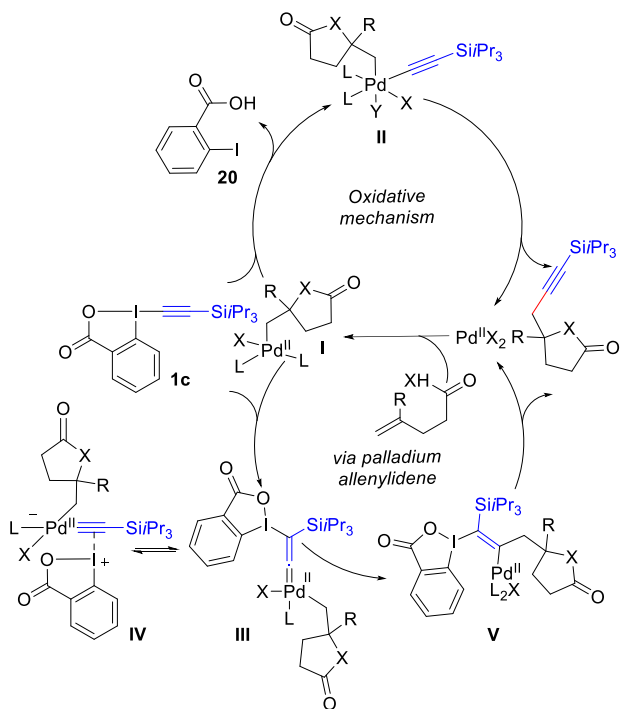
We then wondered then if domino processes could be also used for the synthesis of alkynylated heterocycles not accessible via C-H functionalization. As a proof of concept, we realized a one-pot synthesis of C3-alkynylated indoles **23a-c** upon reaction of anilines with TIPS-EBX (**1c**) using a gold catalyst (Scheme 15).[42]
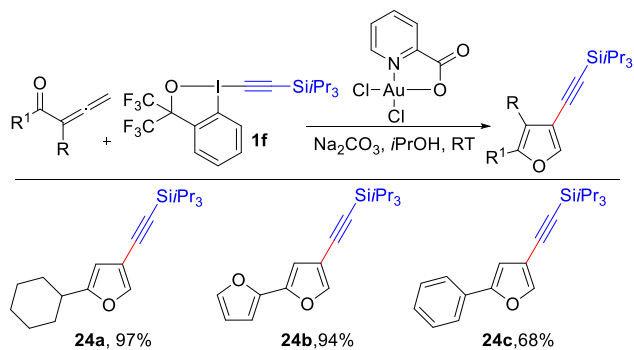
**Scheme 15: One-pot cyclization-alkynylation of *ortho*-alkynyl anilines.**
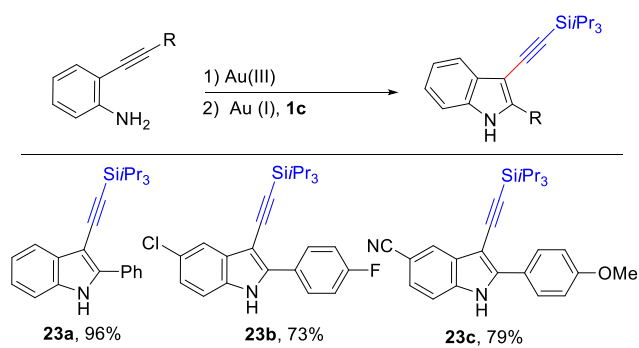
Nevertheless, such compounds can also be accessed via C-H functionalization. Therefore, we studied in 2013, the domino-cyclization-alkynylation of keto allenes into alkynyl furans using Au(III) picolinate as catalyst (Scheme 16).[34] C3 alkynylated furans **24a-c** were obtained in 68-97% yield, whereas C2 alkynylated furans are formed via C-H functionalization. In 2017, the reaction mechanism was studied by computational chemistry in collaboration with the Ariafard group (Scheme 17).[43] Allene **25** first reacts with **1g** and Au(III) to give iodonium **I** and Au(I) complex **II**. The later then reacts with allene **25** to give **III**. Cyclization to **IV** followed by

deprotonation with Na$_2$CO$_3$ gives **V**. Oxidative addition on **V** leading to **VII** and **VIII** is accelerated by the interaction of Au with the nitrogen atom (transition state **VI**). Au(III) complex **VIII** undergoes reductive elimination followed by ligand exchange with allene **25** to give product **24d** and close the catalytic cycle. These interesting results showed that the Au(III) complex was only a precursor of the active Au(I) catalyst.

**Scheme 16: Gold-catalyzed domino-cyclization-alkynylation of keto allenes.**

Scheme 17: Proposed mechanism for the cyclization-alkynylation of allenes.
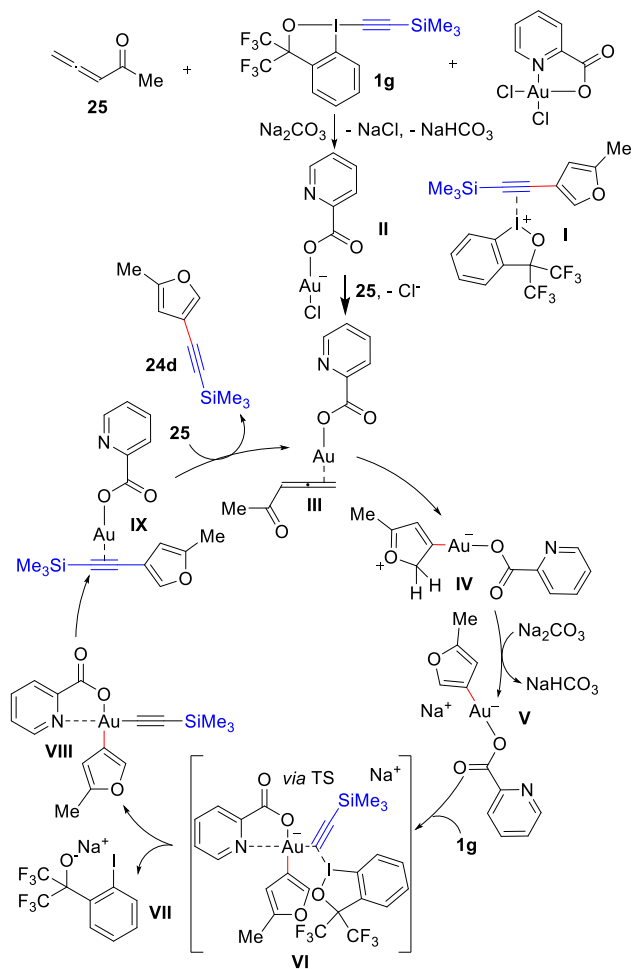
In 2015, we demonstrated that this strategy could also be used for the synthesis of indoles and carbazoles **26**-**29** alkynylated on the benzene ring (Scheme 18).[44] This platinum-catalyzed process started from from 2- or 3-substituted homopropargylic pyrroles.

The reaction probably proceeds via activation of the triple bond by platinum to give **I** (Scheme 19). Intramolecular attack of the most nucleophilic pyrrole C2 position gives then **II**. 1,2-Shift of the vinyl-platinum substituent via platinum carbene **III** then leads to **IV**. Finally, elimination of methanol and re-aromatization gives platinum aryl complex **V**, which then reacts with **1f** to deliver the product. In 2017, this mechanism was confirmed by Bi and co-workers based on computation.[45]

Scheme 18: Platinum-catalyzed domino cyclization-alkynylation for accessing 5- or 6-alkynylated indoles.
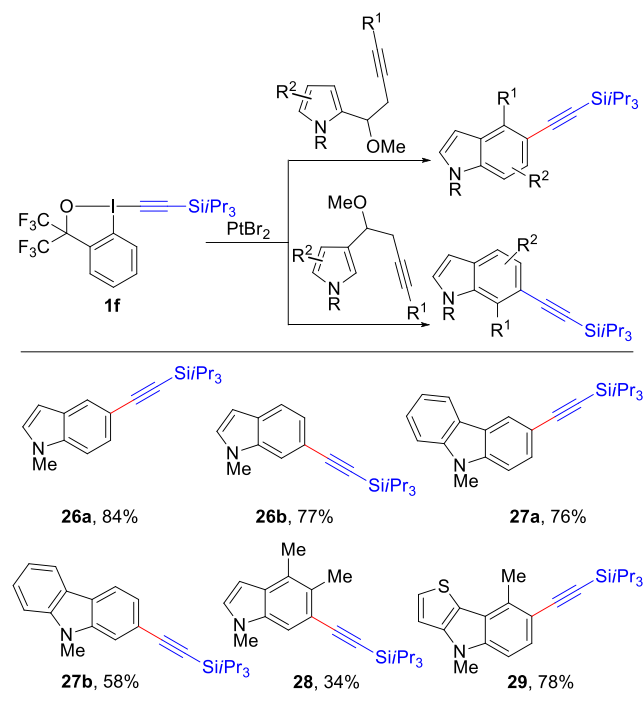
Highly conjugated hetereocycles are especially interesting as organic materials. In 2017, we used our strategy for the synthesis of C3-alkynylated benzofurans **30a-d** and benzothiophenes **31a-b** (Scheme 20).[46] The obtained alkynylated heterocycles were efficiently transformed into heterotetracene building blocks for organic materials.

Scheme 19: Proposed mechanism for the domino cyclization-alkynylation.
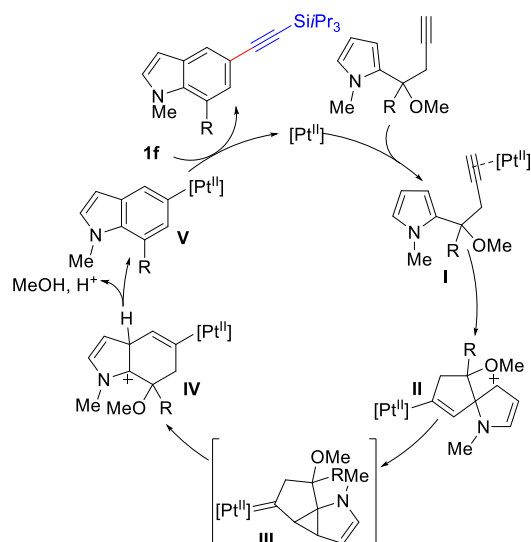
Alkynylations using EBXs usually releases 2-iodobenzoic acid. In 2016, we developed a copper-catalyzed oxyalkynylation of diazo compounds, in which the acid is incorporated in products **32a-f** (Scheme 21).[47] When vinyl diazo compounds were used, enynes **33a-c** were obtained as single geometric isomers (Scheme 21b). This example also demonstrate that the use of EBX reagent is not limited to precious metal catalysts, such as gold, platinum or palladium.

Scheme 20: Domino cyclization-alkynylation for accessing C3-alkynylated benzofurans and benzothiophenes.
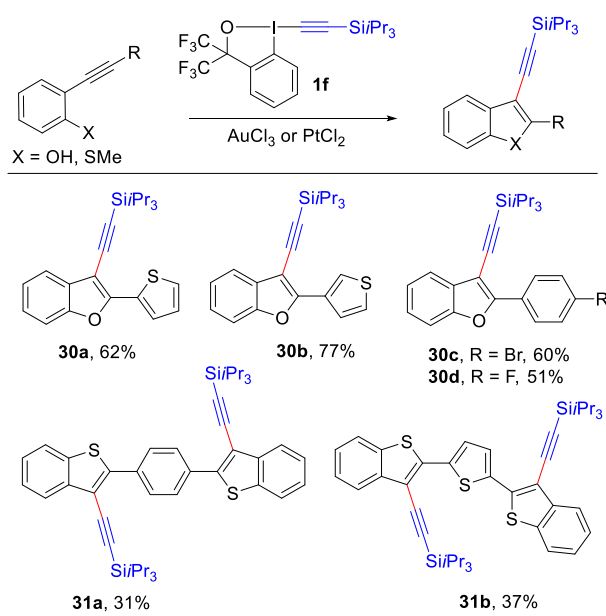
Scheme 21: Copper-catalyzed oxyalkynylation of diazo compounds.
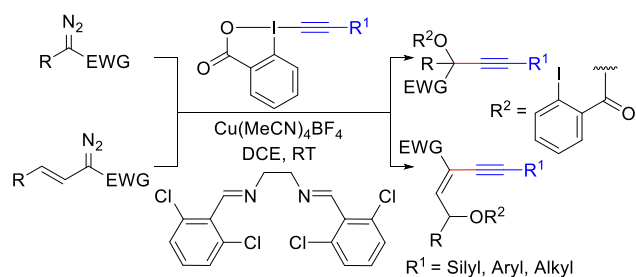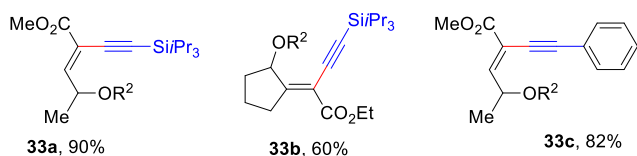
In 2017, we reported the enantioselective oxyalkynylation of diazo compounds using a copper catalyst and bisoxazoline (BOX) ligand **34** (Scheme 22, products **35a-i**).[48] Due to the high acidity of the propargylic hydrogen, these compounds cannot be accessed in enantiopure form via the addition of organometallic reagents onto the corresponding carbonyl compounds.

Scheme 22: Enantioselective oxyalkynylation of diazo compounds.

2.4 Alkynylation of carbon radicals

EBX reagents are highly useful for the functionalization of carbon and heteroatom nucleophiles, as well as organometallic intermediates. The functionalization of radicals, which can be generate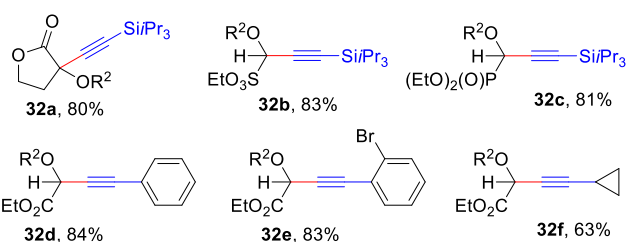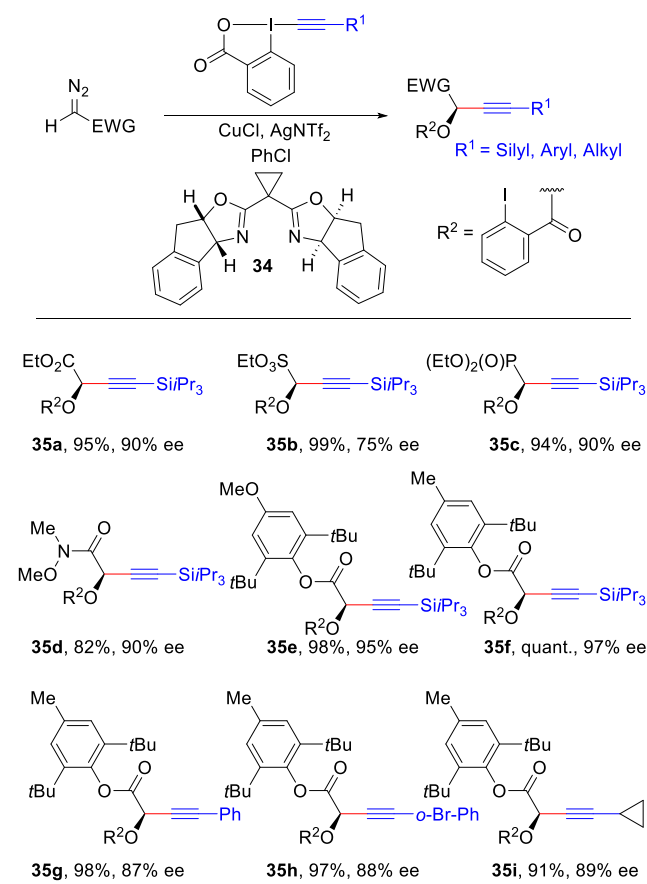d under neutral conditions, constitutes a further interesting area of applications. Li and co-workers were the first to report a decarboxylative alkynylation of carboxylic acids using EBX reagents and strong oxidants.[49] In 2015, we developed milder conditions for the synthesis of alkynes **36a-f** based on photoredox catalysis to avoid strong oxidants (Scheme 23).[50] Xiao and co-workers reported a similar transformation simultaneously.[51]

A mechanism for the decarboxylative alkynylation was proposed based on both experimental and computational studies (Scheme 24).[52] Single-electron oxidation of the carboxylate by the excited state of the Ir(III)-catalyst generates radical **I** after extrusion of CO_2. Addition to EBX then delivers the desired product and iodo radical **II**, which can then be reduced by Ir(II) to close the catalytic cycle. Concerning the radical addition step, two mechanisms very close in energy were proposed based on DFT calculations: a concerted α-addition via **III** or a β-addition via **IV**.

Scheme 23. Decarboxylative alkynylation of amino- and oxo- acids.
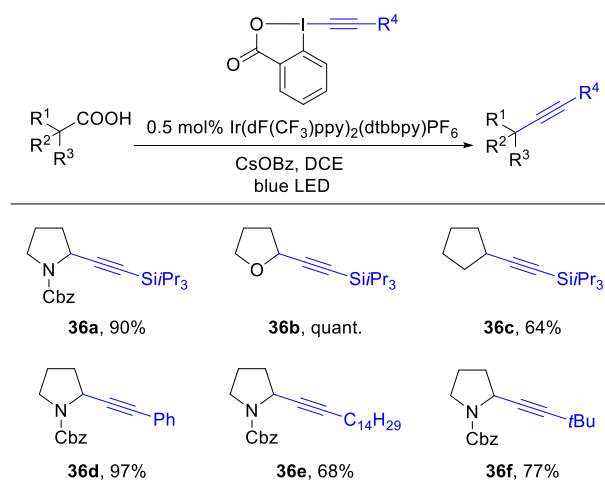
Scheme 24: Proposed mechanism for the decarboxylative alkynylation.
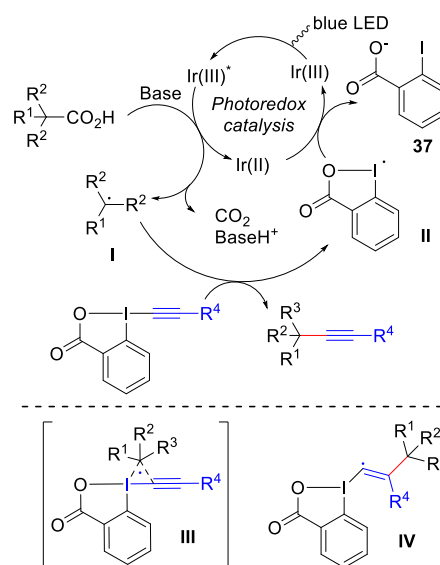
In 2018, we reported the alkynylation of nitrile-substituted alkyl radicals generated via oxidative ring fragmentation of cyclic oxime ethers (Scheme 25).[53] The use of organic dye **38c** with an increased reduction potential in the excited state compared to 4CzIPN (**38a**) led to the efficient fragmentation of both 4- and 5-membered cyclic oxime ethers to give the corresponding alkynylnitriles (**39a-f**). The reaction probably starts with the oxidation of the carboxylate by the excited photocatalyst. Fast decarboxylation followed by acetone extrusion leads to an imine radical. Fragmentation to an alkyl radical followed by alkynylation then gives the product.

Scheme 25: Fragmentation-alkynylation cascade of cyclic oxime ethers.

Scheme 26. Electrophilic azidation of keto esters and silyl enol ethers.
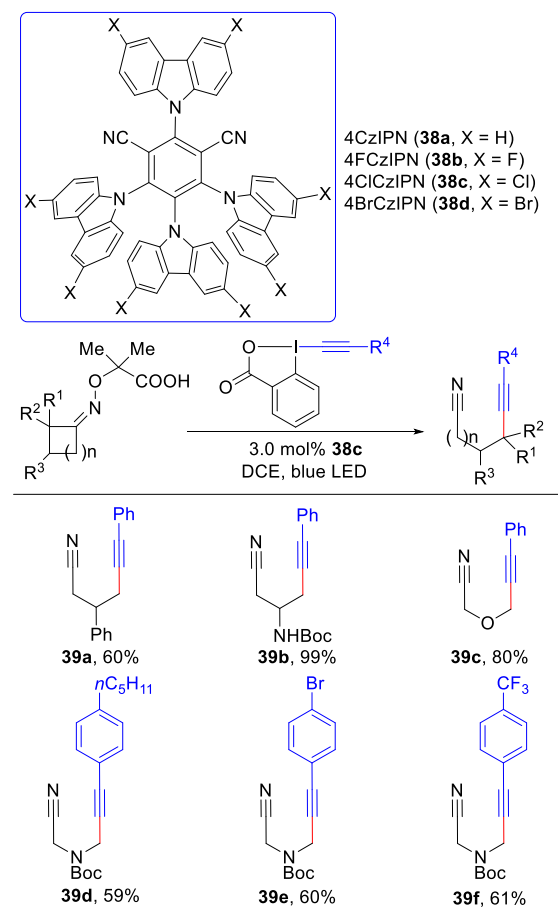
3. ELECTROPHILIC AZIDATION

Azides, as alkynes, are versatile functional groups, which are usually introduced as nucleophiles. Electrophilic azide sources allow other disconnections. Non-cyclic azide hypervalent iodine reagents are not stable and need to be prepared in situ. An important progress was realized when stable cyclic ABXs were introduced by Zhdankin and coworkers.[9] Nevertheless, new synthetic applications emerged only in 2013, with the independent reports of Gade and co-workers,[54] our group[55] and Studer and co-workers.[56] Since then, the field is in full expansion.[16]

3.1 Azidation of β-keto esters and silyl enol ethers

In 2013, we investigated the azidation of ketoester-derived enolates with ABXs as a proof-of-concept transformation. Such azidation had been realized with other hypervalent iodine reagents,[57] but had not been reported with ABXs when we started our investigations. A metal free protocol for cyclic indanones was developed 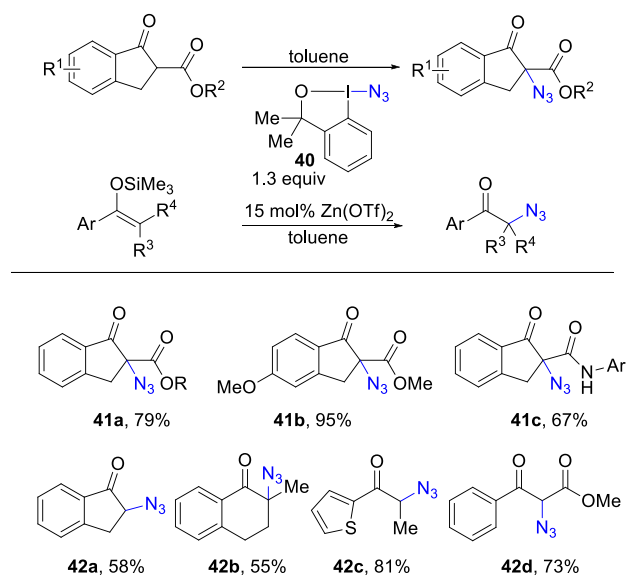using azidobenziodoxole **40** (**41a-c**, Scheme 26).[55] However, less reactive substrates such as silyl enol ethers and non-cyclic keto esters did not react with **40**. In this case, activation of the reagent with zinc triflate as catalyst was necessary to give products **42a-d**. In parallel to our work, Gade and co-workers reported an efficient enantioselective azidation of ketoesters using reagent **40**.[54]

We then re-investigated the Tsuji-Trost approach on allyl β-keto esters (Scheme 27). Homoallylic azides **43a-c** were obtained in good yields and excellent enantioselectivities.[58] Staudinger reduction and 1,3 cycloaddition gave then homoallylic amine **44** and triazole **45**.

Scheme 27. Decarboxylative allylation for the enantioselective synthesis of homoallylic azides.
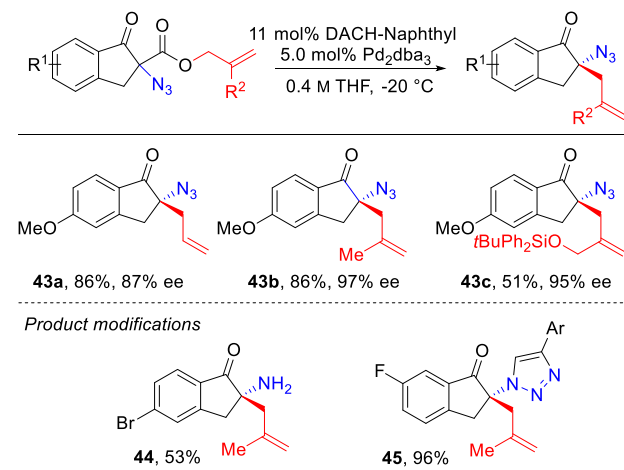
3.2 Generation of azido radicals: azido-lactonization and ring expansion

In 2017, our group became interested in using azidobenziodoxole(on)es reagents for the azido-lactonization of styrene derivatives in the context of extending the olefin functionalization reactions developed with oxyalkynylation (Scheme 28).[59] Photoredox activation of ABX **46** (Zhdankin reagent)[9] resulted in formation of an azido radical,[56,60] which reacted with the styrenes to form 1,2-azidolactones **47a-d**. No radical was formed from the weaker oxidizing **40**. In this case, the use of Pd(hfacac)$_2$ as Lewis acid gave 1,1-azidolactones **48a-d**, probably via a iodination, 1,2-aryl shift, azidation sequence, highlighting again the possibility to finely tune the reactivity of EBX reagents.

Following an accident due to the explosion of a sample of ABX **46**, we investigated its safety profile in collaboration with a specialized company, and discovered that it is both shock and friction sensitive.[61] However, the more stable azidobenziodazole **49** (ABZ), could also be used for the generation of radicals under photoredox

conditions in a new ring-expansion process to give cyclopenta-nones **50a-d** (Scheme 29), as well as in reported azidative transformations.[61]

Scheme 28. 1,2- and 1,1- azidolactonization of styrene derivatives.

47a, 81% **47b**, 94% **47c**, 54% **47d**, 87%

48a, 52% **48b**, 74% **48c**, 77% **48d**, 52%
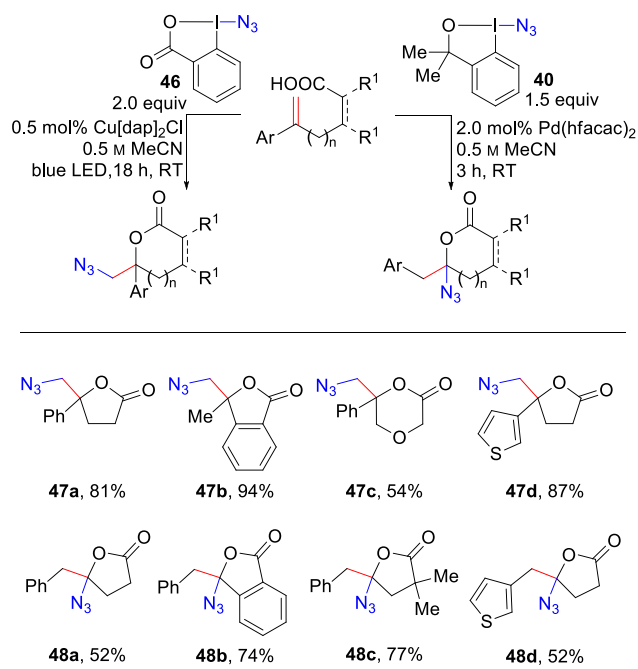
Scheme 29. Azidative ring expansion with ABZ (49).

50a, 90% **50b**, 96% **50c**, 86% **50d**, 58%

4. ELECTROPHILIC CYANATION

4.1 Synthesis of homoallylic nitriles

As for alkynes or azides, we expected CBXs[10] to serve as electrophilic cyanide sources. In fact, CBX (**51**) could be used for the cyanation of allylic β keto esters, which were engaged in an enantioselective Tsuji-Trost process (Scheme 30, products **52a-c**).[58] The nitrile group could be then either reduced to amine **53**, or hydrated to amide **54**.

Scheme 30. Decarboxylative allylation for the enantioselective synthesis of homoallylic nitriles.

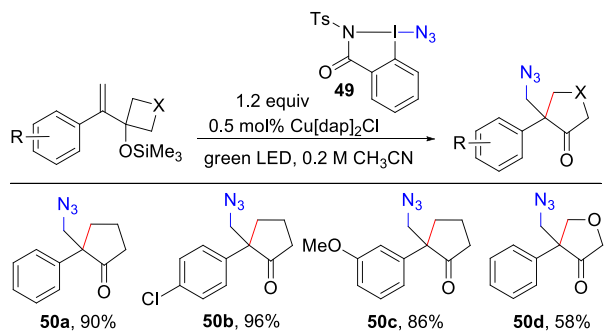**52a**, 91%, 80% ee **52b**, 81%, 78% ee **52c**, 75%, 92% ee

Product modifications

53, 41% **54**, 83%
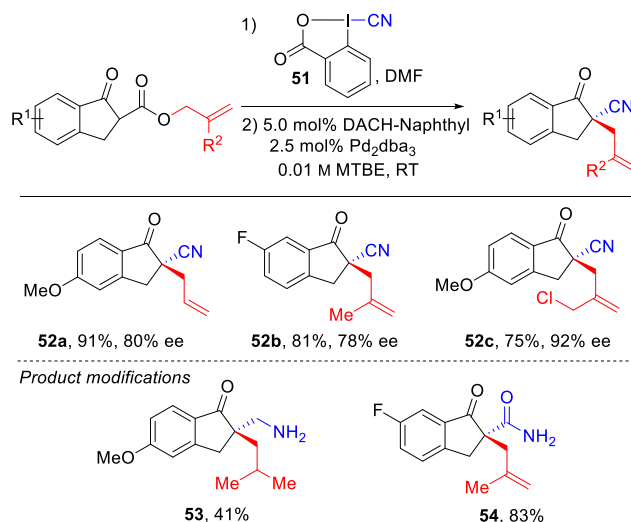
4.2 Synthesis of thiocyanates from thiols

Inspired by our results in thio-alkynylation (Scheme 5), we reported the use of CBX (**51**) for the cyanation of thiols (Scheme 31).[62] Aromatic and aliphatic thio- and seleno- cyanates **55-58** were obtained in excellent yields. Interestingly, hypervalent sulfur reagents were later developed by Alcarazo and co-workers to perform similar reactions.[63]

Scheme 31. Cyanation of thiols with CBX (51).

55a, 90% **55b**, 94% **55c**, 94%

56a, 88% **56b**, 97%

57, 88% **58**, 88%
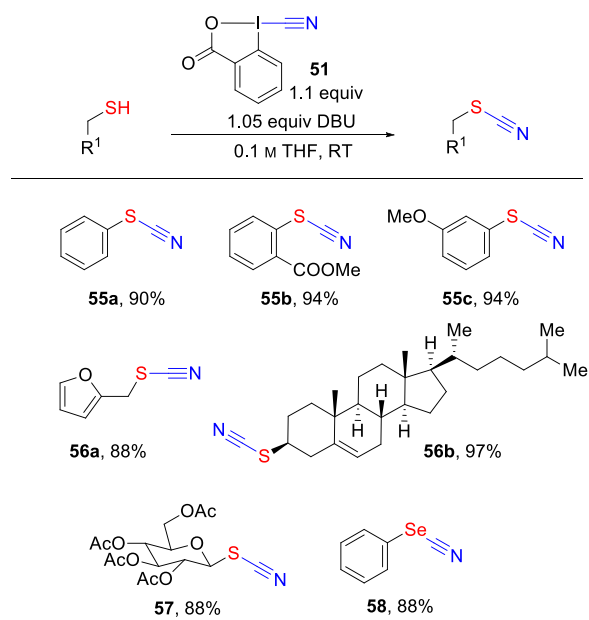
4.3 Decarboxylative cyanation of carboxylic acids

Our work in the photoredox-catalyzed decarboxylative alkynylation was extended to decarboxylative cyanation using CBX (**51**) to give nitriles **59-60** (Scheme 32).[52]

Scheme 32. Decarboxylative cyanation of amino- and oxo-acids.
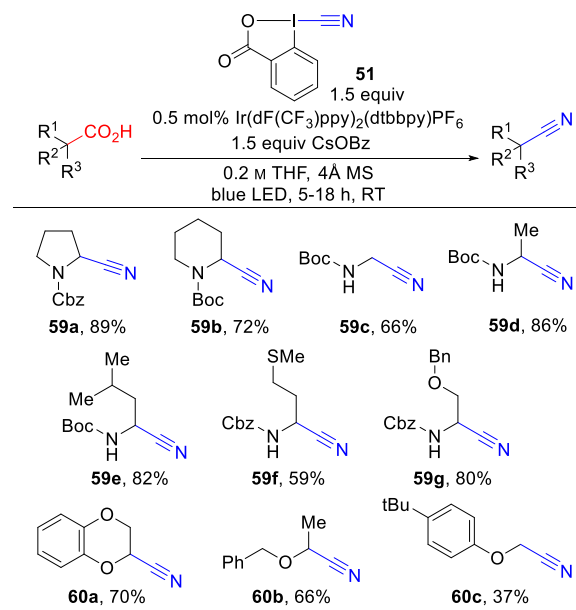
In contrast to alkynylation, cyanation was shown through experiments and DFT calculations to proceed via carbocationic intermediates (Scheme 33). CBX (**51**) being a stronger oxidant than EBX (**1**), it is able to reduce radical **I,** formed under photoredox conditions, to give stabilized carbocation **II** and radical anion **III** (Single Electron Transfer, SET). The later collapses into radical **IV** and cyanide anion (**61**). Recombination of **II** and **61** gives the product, whereas **IV** can re-enter the photoredox cycle (Scheme 24).

Scheme 33. Proposed single electron transfer (SET) mechanism for the cyanation reaction.

5. ELECTROPHILIC INDOLES AND PYRROLES

5.1 Synthesis of new indole- and pyrrole- BX reagents

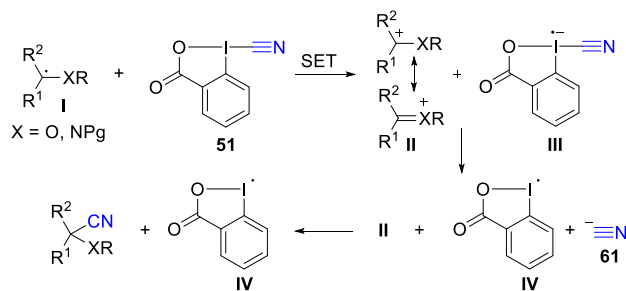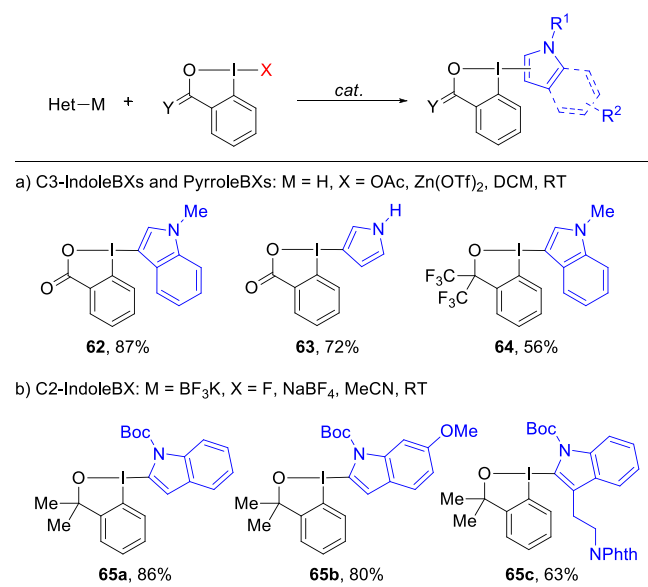In 2017, we reported the serendipitous discovery of a novel class of stable cyclic Indole- and Pyrrole- based BX reagents.[64-66] C3-substituted-indole and pyrrole BX reagents **62**-**64** were accessed from the heterocycles by the Lewis Acid-catalyzed addition to acetoxybenziodoxol(on)es (Scheme 34a).[64-65] C2-substituted indole BX reagents **65a-c** were obtained by reaction of trifluoroborate salts with fluorobenziodoxole (Scheme 34b).[66]

Scheme 34. Synthesis of Indole- and Pyrrole-BXs.

a) C3-IndoleBXs and PyrroleBXs: M = H, X = OAc, Zn(OTf)$_2$, DCM, RT

b) C2-IndoleBX: M = BF$_3$K, X = F, NaBF$_4$, MeCN, RT

5.2 Metal-catalyzed C-H functionalization with IndoleBXs and PyrroleBXs

In most metal-catalyzed C-H arylation processes, electron-rich heterocycles are used as nucleophilic partners, leading often to regioselectivity and reactivity issues. Our electrophilic reagents allowed an Umpolung approach in the Rh(III)- and Ru(II)-catalyzed directed C-H functionalization of arenes (Scheme 35a-b). The desired heteroarylated products were obtained in good yields as single regiosiomers using either pyridines (**66a-c**) or methoxamides (**67a-c**) directing groups.[64-65] Heteroarylated 2- an 4- pyridones **68** and **69** and quinoline *N*-oxide **70** could also be accessed (Scheme 35c).[67] Finally, the method could be extended to *ortho*-hydroxy and amido benzaldehydes using either a Rh(III) or an Ir(III) catalyst (Scheme 35d, products **71**-**73**).[68] None of these transformations was successful using the corresponding aryl iodides or iodonium salts.

5.3 Metal-free oxidative cross-coupling for the synthesis of mixed bi-heterocycles

In 2018, we reported a metal-free oxidative cross coupling using TMSCl and HFIP as activators for the synthesis of mixed bi-indoles **74a-c** and other mixed heteroaryls **75**-**77** (Scheme 36).[66] This method allowed the synthesis of bi-heterocycles with complete regioselective installation of functional groups in either one of the two reacting partners. The reasons for the exclusive transfer of the indole heterocycle and the observed high regioselectivity are not well understood at this stage and will require further mechanistic studies.

Scheme 35. Rh(III), Ru(II) and Ir(III)- catalyzed C-H heteroarylation.
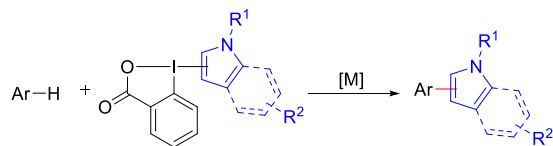
a) Aryl-pyridines: [RhCp*Cl$_2$]$_2$, NaOPiv, AgSbF$_6$, DCE, 50-100 °C

66a, 59%   **66b**, 79%   **66c**, 92%
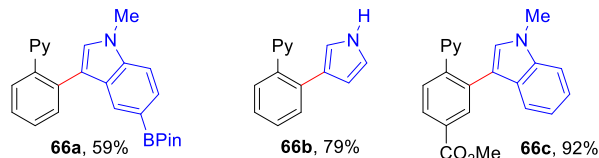
b) Aryl-methoxamides: Ru[p-cymene(AdCO$_2$)$_2$], TFE, 60 °C

67a, 75%   Br **67b**, 84%   **67c**, 79%
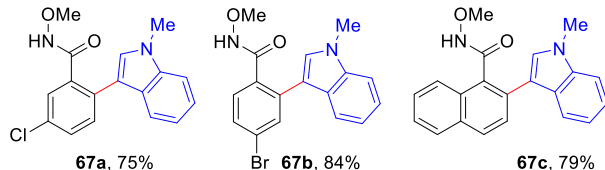
c) Heteroarenes: [RhCp*Cl$_2$]$_2$, Zn(OTf)$_2$, AgSbF$_6$, MeOH, 80 °C

68, 86%   **69**, 57%   **70**, 60%
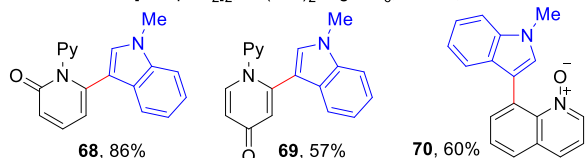
d) Benzaldehydes: [RhCp*Cl$_2$]$_2$ or [IrCp*Cl$_2$]$_2$, KOAc, MeOH, RT or 40 °C

71, 94%   **72**, 88%   **73**, 90%

Scheme 36. Synthesis of mixed bi-heteroarenes.

Ar(Het)—H   1.0 equiv TMSCl, 10 equiv HFIP, DCM, r.t.

74a, 51%   **74b**, 45%   **74c**, 51%

75, 70%   **76**, 28%   **77**, 94%
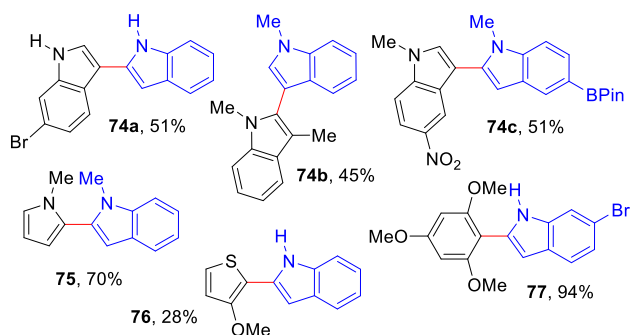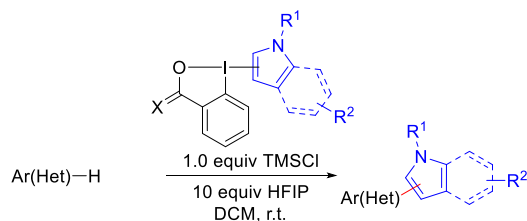
6. CONCLUSION

Since 2008, our group has exploited the reactivity of benziodoxol(on)es reagents in organic synthesis. The basis for this work had been set by synthetic and structural studies by pioneers in the field of hypervalent iodine chemistry, such as Martin, Ochiai and Zhdankin among others. The potential of these reagents for fine chemical synthesis via "Umpolung disconnections" was first demonstrated extensive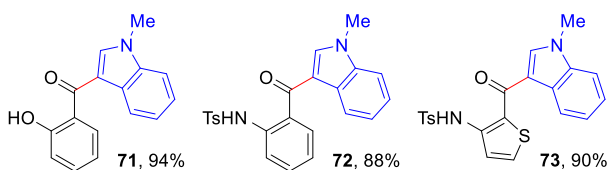ly by Togni and coworkers in trifluoromethylation and our group in alkynylation. Our work on Ethynylbenziodoxolone (EBX) reagents showed for the first time their exceptional properties in the electrophilic alkynylation of nucleophiles, radicals and organometallic intermediates. We then demonstrated that azidobenziodoxolones (ABX) and cyanobenziodoxolones (CBX) were equally useful for electrophilic azidation and cyanation. Finally, we introduced new reagents for the Umpolung of indoles and pyrroles. Nowadays, many research groups around the world are using cyclic hypervalent iodine reagents to develop new transformations. The reason for the success of BX reagents may reside in the exceptional reactivity of hypervalent iodine, combined with the extra stability and modularity of the cyclic structure. We expect that the "synthetic treasure" of benziodoxol(on)es has just started to be exploited, and many more reagents and transformations still remain to be discovered.

AUTHOR INFORMATION

Corresponding author

*E-Mail: jerome.waser@epfl.ch

Author contribution

[+]D. P. H. and P. C. contributed equally.

ORCID

Durga Prasad Hari: 0000-0002-0734-8427

Paola Caramenti: 0000-0002-8523-8944

Jerome Waser: 0000-0002-4570-914X

Notes

The authors declare no competing financial interest.

Biographical Information

Durga Prasad Hari 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. He worked as postdoctoral fellow under the supervision of Prof. Jerome Waser at EPFL from 2014 to 2018. Currently, he is a postdoctoral fellow in the group of Prof. Varinder Aggarwal at the University of Bristol. His research interests focus on applications of hypervalent iodine reagents in organic synthesis. He was a finalist of Reaxys PhD prize 2012.

Paola Caramenti received her Master degree in 2014 at Università Statale di Milano, under the guidance of Prof. Francesca Clerici. She then joined the group of Prof. Jerome Waser at EPFL to pursue her PhD studies. Her current research topic involves the synthesis of novel hypervalent iodine reagents and their application.

Jerome Waser studied chemistry at ETH Zurich (PhD degree in 2006 with Prof. Erick M. Carreira). He then joined Prof. Barry M. Trost at Stanford University as SNF postdoctoral fellow. From

2007 to 2014, he was an assistant professor at EPFL. Since 2014, he is associate professor at EPFL, focusing on the use of hypervalent iodine reagents in synthesis, cyclopropane chemistry and tethered reactions. He received the ERC starting (2013) and consolidator (2017) grants, the Werner prize of the Swiss Chemical Society 2014 and the Springer Heterocyclic Chemistry Award 2016.

ACKNOWLEDGMENTS

REFERENCES

(1) Corey, E. J.; Cheng, X. M. *The Logic of Chemical Synthesis*; John Wiley & Sons, Inc., New York, 1995.

(2) Seebach, D., Methods of Reactivity Umpolung. *Angew. Chem., Int. Ed.* **1979**, *18*, 239-258.

(3) Yoshimura, A.; Zhdankin, V. V., Advances in Synthetic Applications of Hypervalent Iodine Compounds. *Chem. Rev.* **2016**, *116*, 3328-3435. And references therein.

(4) Stirling, A., Assessing Hypervalency in Iodanes. *Chem. Eur. J.* **2017**, *24*, 1709-1713.

(5) Zhdankin, V. V., Benziodoxole-Based Hypervalent Iodine Reagents in Organic Synthesis. *Curr. Org. Synth.* **2005**, *2*, 121-145.

(6) Sun, T.-Y.; Wang, X.; Geng, H.; Xie, Y.; Wu, Y.-D.; Zhang, X.; Schaefer III, H. F., Why does Togni's Reagent I exist in the High-Energy Hypervalent Iodine Form? Re-Evaluation of Benziodoxole Based Hypervalent Iodine Reagents. *Chem. Commun.* **2016**, *52*, 5371-5374.

(7) Ochiai, M.; Masaki, Y.; Shiro, M., Synthesis and Structure of 1-Alkynyl-1,2-Benziodoxol-3(1H)-Ones. *J. Org. Chem.* **1991**, *56*, 5511-5513.

(8) Zhdankin, V. V.; Kuehl, C. J.; Krasutsky, A. P.; Bolz, J. T.; Simonsen, A. J., 1-(Organosulfonyloxy)-3(1H)-1,2-benziodoxoles: Preparation and Reactions with Alkynyltrimethylsilanes. *J. Org. Chem.* **1996**, *61*, 6547-6551.

(9) Zhdankin, V. V; Krasutsky, A. P.; Kuehl, C. J.; Simonsen, A. J.; Woodward, J. K.; Mismash, B.; Bolz, J. T. Preparation, X-Ray Crystal Structure, and Chemistry of Stable Azidoiodinanes Derivatives of Benziodoxole. *J. Am. Chem. Soc.* **1996**, *118*, 5192–5197.

(10) Zhdankin, V. V.; Kuehl, C. J.; Krasutsky, A. P.; Bolz, J. T.; Mismash, B.; Woodward, J. K.; Simonsen, A. J., 1-Cyano-3-(1H)-1,2-Benziodoxols: Stable Cyanoiodinanes and Efficient Reagents for Direct N-Alkyl Cyanation of N,N-Dialkylarylamines. *Tetrahedron Lett.* **1995**, *36*, 7975-7978.

(11) Ochiai, M.; Sueda, T.; Miyamoto, K.; Kiprof, P.; Zhdankin, V. V., *Trans* Influences on Hypervalent Bonding of Aryl λ3-Iodanes: Their Stabilities and Isodesmic Reactions of Benziodoxolones and Benziodazolones. *Angew. Chem., Int. Ed.* **2006**, *45*, 8203-8206.

(12) Eisenberger, P.; Gischig, S.; Togni, A., Novel 10-I-3 Hypervalent Iodine-Based Compounds for Electrophilic Trifluoromethylation. *Chem. Eur. J.* **2006**, *12*, 2579-2586.

(13) Charpentier, J.; Frueh, N.; Togni, A., Electrophilic Trifluoromethylation by Use of Hypervalent Iodine Reagents. *Chem. Rev.* **2015**, *115*, 650-682.

(14) Waser, J., Alkynylation with Hypervalent Iodine Reagents. In *Hypervalent Iodine Chemistry*, Wirth, T., Ed. Springer International Publishing: Cham, 2016; pp 187-222.

(15) Kaschel, J.; Werz, D. B., Ethynyl Benziodoxolone (EBX): Installing Alkynes the Reversed Way. *Angew. Chem., Int. Ed.* **2015**, *54*, 8876-8878.

(16) Li, Y.; Hari, D. P.; Vita, M. V.; Waser, J., Cyclic Hypervalent Iodine Reagents for Atom-Transfer Reactions: Beyond Trifluoromethylation. *Angew. Chem., Int. Ed.* **2016**, *55*, 4436-4454.

(17) Beringer, F. M.; Galton, S. A. Acetylenic and Ethylenic Iodonium Salts and Their Reactions with a Carbanion. *J. Org. Chem.* **1965**, *30*, 1930–1934.

(18) Zhdankin, V. V.; Stang, P. J. Alkynyliodonium Salts in Organic Synthesis. *Tetrahedron* **1998**, *54*, 10927–10966.

(19) Fernández González, D.; Brand, J. P.; Waser, J. Ethynyl-1,2-Benziodoxol-3(1 H)-One (EBX): An Exceptional Reagent for the Ethynylation of Keto, Cyano, and Nitro Esters. *Chem. Eur. J.* **2010**, *16*, 9457–9461.

(20) Fernández González, D.; Brand, J. P.; Mondière, R.; Waser, J. Ethynylbenziodoxolones (EBX) as Reagents for the Ethynylation of Stabilized Enolates. *Adv. Synth. Catal.* **2013**, *355*, 1631–1639.

(21) Vita, M. V.; Mieville, P.; Waser, J. Enantioselective Synthesis of Polycyclic Carbocycles via an Alkynylation–Allylation–Cyclization Strategy. *Org. Lett.* **2014**, *16*, 5768–5771.

(22) Werz, D. B.; Gleiter, R.; Rominger, F., Cyclic Tetra- and Hexaaynes Containing 1,4-Donor-Substituted Butadiyne Units: Synthesis and Supramolecular Organization. *J. Org. Chem* **2004**, *69*, 2945-2952.

(23) Frei, R.; Waser, J. A Highly Chemoselective and Practical Alkynylation of Thiols. *J. Am. Chem. Soc.* **2013**, *135*, 9620–9623.

(24) Frei, R.; Wodrich, M. D.; Hari, D. P.; Borin, P.-A.; Chauvier, C.; Waser, J. Fast and Highly Chemoselective Alkynylation of Thiols with Hypervalent Iodine Reagents Enabled through a Low Energy Barrier Concerted Mechanism. *J. Am. Chem. Soc.* **2014**, *136*, 16563–16573.

(25) Wodrich, M. D.; Caramenti, P.; Waser, J. Alkynylation of Thiols with Ethynylbenziodoxolone (EBX) Reagents: α- or β- π-Addition? *Org. Lett.* **2016**, *18*, 60–63.

(26) Abegg, D.; Frei, R.; Cerato, L.; Hari, D. P.; Wang, C.; Waser, J.; Adibekian, A. Proteome-Wide Profiling of Targets of Cysteine Reactive Small Molecules by Using Ethynyl Benziodoxolone Reagents. *Angew. Chem., Int. Ed.* **2015**, *54*, 10852–10857.

(27) Chen, C. C.; Waser, J. One-Pot, Three-Component Arylalkynyl Sulfone Synthesis. *Org. Lett.* **2015**, *17*, 736–739.

(28) Chen, C. C.; Waser, J. Room Temperature Alkynylation of H-Phosphi(na)tes and Secondary Phosphine Oxides with Ethynylbenziodoxolone (EBX) Reagents. *Chem. Commun.* **2014**, *50*, 12923–12926.

(29) Brand, J. P.; Charpentier, J.; Waser, J. Direct Alkynylation of Indole and Pyrrole Heterocycles. *Angew. Chem., Int. Ed.* **2009**, *48*, 9346–9349.

(30) Tolnai, G. L.; Brand, J. P.; Waser, J. Gold-Catalyzed Direct Alkynylation of Tryptophan in Peptides Using TIPS-EBX. *Beilstein J. Org. Chem.* **2016**, *12*, 745–749.

(31) Hansen, M. B.; Hubálek, F.; Skrydstrup, T.; Hoeg-Jensen, T. Chemo- and Regioselective Ethynylation of Tryptophan-Containing Peptides and Proteins. *Chem. Eur. J.* **2016**, *22*, 1572–1576.

(32) Brand, J. P.; Chevalley, C.; Scopelliti, R.; Waser, J. Ethynyl Benziodoxolones for the Direct Alkynylation of Heterocycles: Structural Requirement, Improved Procedure for Pyrroles, and Insights into the Mechanism. *Chem. Eur. J.* **2012**, *18*, 5655–5666.

(33) Brand, J. P.; Waser, J. Direct Alkynylation of Thiophenes: Cooperative Activation of TIPS–EBX with Gold and Brønsted Acids. *Angew. Chem., Int. Ed.* **2010**, *49*, 7304–7307.

(34) Li, Y.; Brand, J. P.; Waser, J. Gold-Catalyzed Regioselective Synthesis of 2- and 3-Alkynyl Furans. *Angew. Chem., Int. Ed.* **2013**, *52*, 6743–6747.

(35) Li, Y.; Waser, J. Zinc–Gold Cooperative Catalysis for the Direct Alkynylation of Benzofurans. *Beilstein J. Org. Chem* **2013**, *9*, 1763–1767.

(36) Brand, J. P.; Waser, J. *Para*-Selective Gold-Catalyzed Direct Alkynylation of Anilines. *Org. Lett.* **2012**, *14*, 744–747.

(37) Ariafard, A. A Density Functional Theory (DFT) Mechanistic Study of Gold(I)-Catalyzed Alkynylation of the Indole and Pyrrole Substrates, Using a Hypervalent Iodine Reagent. *ACS Catal.* **2014**, *4*, 2896–2907.

(38) Tolnai, G. L.; Ganss, S.; Brand, J. P.; Waser, J., C2-Selective Direct Alkynylation of Indoles. *Org. Lett.* **2013**, *15*, 112-115.

(39) Nicolai, S.; Erard, S.; Fernández González, D.; Waser, J. Pd-Catalyzed Intramolecular Oxyalkynylation of Alkenes with Hypervalent Iodine. *Org. Lett.* **2010**, *12*, 384–387.

(40) Nicolai, S.; Piemontesi, C.; Waser, J. A Palladium-Catalyzed Aminoalkynylation Strategy towards Bicyclic Heterocycles: Synthesis of (±)-Trachelanthamidine. *Angew. Chem., Int. Ed.* **2011**, *50*, 4680–4683.

(41) Ariafard, A. Computational Mechanistic Study of Palladium(II)-Catalyzed Carboxyalkynylation of an Olefin Using an Iodine(III) Oxidant Reagent. *Organometallics* **2014**, *33*, 7318–7324.

(42) Brand, J. P.; Chevalley, C.; Waser, J. One-Pot Gold-Catalyzed Synthesis of 3-Silylethynyl Indoles from Unprotected o-Alkynylanilines. *Beilstein J. Org. Chem.* **2011**, *7*, 565–569.

(43) Ghari, H.; Li, Y.; Roohzadeh, R.; Caramenti, P.; Waser, J.; Ariafard, A. Gold-Catalyzed Domino Cyclization–Alkynylation Reactions with EBX Reagents: New Insights into the Reaction Mechanism. *Dalton. Trans.* **2017**, *46*, 12257–12262.

(44) Li, Y.; Waser, J. Platinum-Catalyzed Domino Reaction with Benziodoxole Reagents for Accessing Benzene-Alkynylated Indoles. *Angew. Chem., Int. Ed.* **2015**, *54*, 5438–5442.

(45) Man, X. P.; Jiang, Y. Y.; Liu, Y. X.; Bi, S. W., Mechanistic Study on Platinum-Catalyzed Domino Reaction of Benziodoxole and Pyrrole Homopropargylic Ethers for Indole Synthesis. *Organometallics* **2017**, *36*, 2843-2852.

(46) Li, Y.; Gryn'ova, G.; Saenz, F.; Jeanbourquin, X.; Sivula, K.; Corminboeuf, C.; Waser, J. Heterotetracenes: Flexible Synthesis and in Silico Assessment of the Hole-Transport Properties. *Chem. Eur. J.* **2017**, *23*, 8058–8065.

(47) Hari, D. P.; Waser, J. Copper-Catalyzed Oxy-Alkynylation of Diazo Compounds with Hypervalent Iodine Reagents. *J. Am. Chem. Soc.* **2016**, *138*, 2190–2193.

(48) Hari, D. P.; Waser, J. Enantioselective Copper-Catalyzed Oxy-Alkynylation of Diazo Compounds. *J. Am. Chem. Soc.* **2017**, *139*, 8420–8423.

(49) Liu, X.; Wang, Z.; Cheng, X.; Li, C., Silver-Catalyzed Decarboxylative Alkynylation of Aliphatic Carboxylic Acids in Aqueous Solution. *J. Am. Chem. Soc.* **2012,** *134*, 14330-14333.

(50) Le Vaillant, F.; Courant, T.; Waser, J. Room-Temperature Decarboxylative Alkynylation of Carboxylic Acids Using Photoredox Catalysis and EBX Reagents. *Angew. Chem., Int. Ed.* **2015**, *54*, 11200–11204.

(51) Zhou, Q. Q.; Guo, W.; Ding, W.; Wu, X.; Chen, X.; Lu, L. Q.; Xiao, W. J., Decarboxylative Alkynylation and Carbonylative Alkynylation of Carboxylic Acids Enabled by Visible-Light Photoredox Catalysis. *Angew. Chem., Int. Ed.* **2015**, *54*, 11196-11199.

(52) Le Vaillant, F.; Wodrich, M. D.; Waser, J. Room Temperature Decarboxylative Cyanation of Carboxylic Acids Using Photoredox Catalysis and Cyanobenziodoxolones: A Divergent Mechanism Compared to Alkynylation. *Chem. Sci.* **2017**, *8*, 1790–1800.

(53) Le Vaillant, F.; Garreau, M.; Nicolai, S.; Gryn'ova, G.; Corminboeuf, C.; Waser, J. Fine-Tuned Organic Photoredox Catalysts for Fragmentation-Alkynylation Cascades of Cyclic Oxime Ethers. *Chem. Sci.* **2018**, *9*, 5883–5889.

(54) Deng, Q.-H.; Bleith, T.; Wadepohl, H.; Gade, L. H. Enantioselective Iron-Catalyzed Azidation of β-Keto Esters and Oxindoles. *J. Am. Chem. Soc.* **2013**, *135*, 5356–5359.

(55) Vita, M. V.; Waser, J. Azidation of β-Keto Esters and Silyl Enol Ethers with a Benziodoxole Reagent. *Org. Lett.* **2013**, *15*, 3246–3249.

(56) Zhang, B.; Studer, A. Stereoselective Radical Azidooxygenation of Alkenes. *Org. Lett.* **2013**, *15*, 4548–4551.

(57) Harschneck, T.; Hummel, S.; Kirsch, S. F.; Klahn, P., Practical Azidation of 1,3-Dicarbonyls. *Chem. Eur. J.* **2012,** *18*, 1187-1193.

(58) Vita, M. V.; Caramenti, P.; Waser, J. Enantioselective Synthesis of Homoallylic Azides and Nitriles via Palladium-Catalyzed Decarboxylative Allylation. *Org. Lett.* **2015**, *17*, 5832–5835.

(59) Alazet, S.; Le Vaillant, F.; Nicolai, S.; Courant, T.; Waser, J. Divergent Access to (1,1) and (1,2)-Azidolactones from Alkenes Using Hypervalent Iodine Reagents. *Chem. Eur. J.* **2017**, *23* , 9501–9504.

(60) Fumagalli, G.; Rabet, P. T. G.; Boyd, S.; Greaney, M. F., Three-Component Azidation of Styrene-Type Double Bonds: Light-Switchable Behavior of a Copper Photoredox Catalyst. *Angew. Chem., Int. Ed.* **2015,** *54*, 11481-11484.

(61) Alazet, S.; Preindl, J; Simonet-Davin, R.; Nicolai, S.; Nanchen, A.; Meyer, T.; Waser J. Cyclic Hypervalent Iodine Reagents for Azidation: Safer Reagents and Photoredox Catalyzed Ring Expansion. *J. Org. Chem.* **2018**, *83*, 12334–12356. Preprint on *ChemRXiv* **2018**, https://doi.org/10.26434/chemrxiv.6946058.v1.

(62) Frei, R.; Courant, T.; Wodrich, M. D.; Waser, J. General and Practical Formation of Thiocyanates from Thiols. *Chem. Eur. J.* **2015**, *21*, 2662–2668.

(63) Talavera, G.; Pena, J.; Alcarazo, M., Dihalo(imidazolium)sulfuranes: A Versatile Platform for the Synthesis of New Electrophilic Group-Transfer Reagents. *J. Am. Chem. Soc.* **2015,** *137*, 8704-8707.

(64) Caramenti, P.; Nicolai, S.; Waser, J. Indole- and Pyrrole-BX: Bench-Stable Hypervalent Iodine Reagents for Heterocycle Umpolung. *Chem. Eur. J.* **2017**, *23*, 14702–14706.

(65) Caramenti, P.; Waser, J. Bench-Stable Electrophilic Indole and Pyrrole Reagents: Serendipitous Discovery and Use in C–H Functionalization. *Helv. Chim. Acta* **2017**, *100*, e1700221.

(66) Caramenti, P.; Nandi, R. K.; Waser, J. Metal-Free Oxidative Cross Coupling of Indoles with Electron-Rich (Hetero)arenes. *Chem. Eur. J.* **2018**, *24*, 10049–10053.

(67) Grenet, E.; Das, A.; Caramenti, P.; Waser, J. Rhodium-Catalyzed C–H Functionalization of Heteroarenes Using indoleBX Hypervalent Iodine Reagents. *Beilstein J. Org. Chem.* **2018**, *14*, 1208–1214.

(68) Grenet, E.; Waser, J. Iridium- and Rhodium-Catalyzed Directed C–H Heteroarylation of Benzaldehydes with Benziodoxolone Hypervalent Iodine Reagents. *Org. Lett.* **2018**, 20, 1473-1476.