Hypervalent Iodine Compounds

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Cyclic Hypervalent Iodine Reagents for Atom-Transfer Reactions: Beyond Trifluoromethylation

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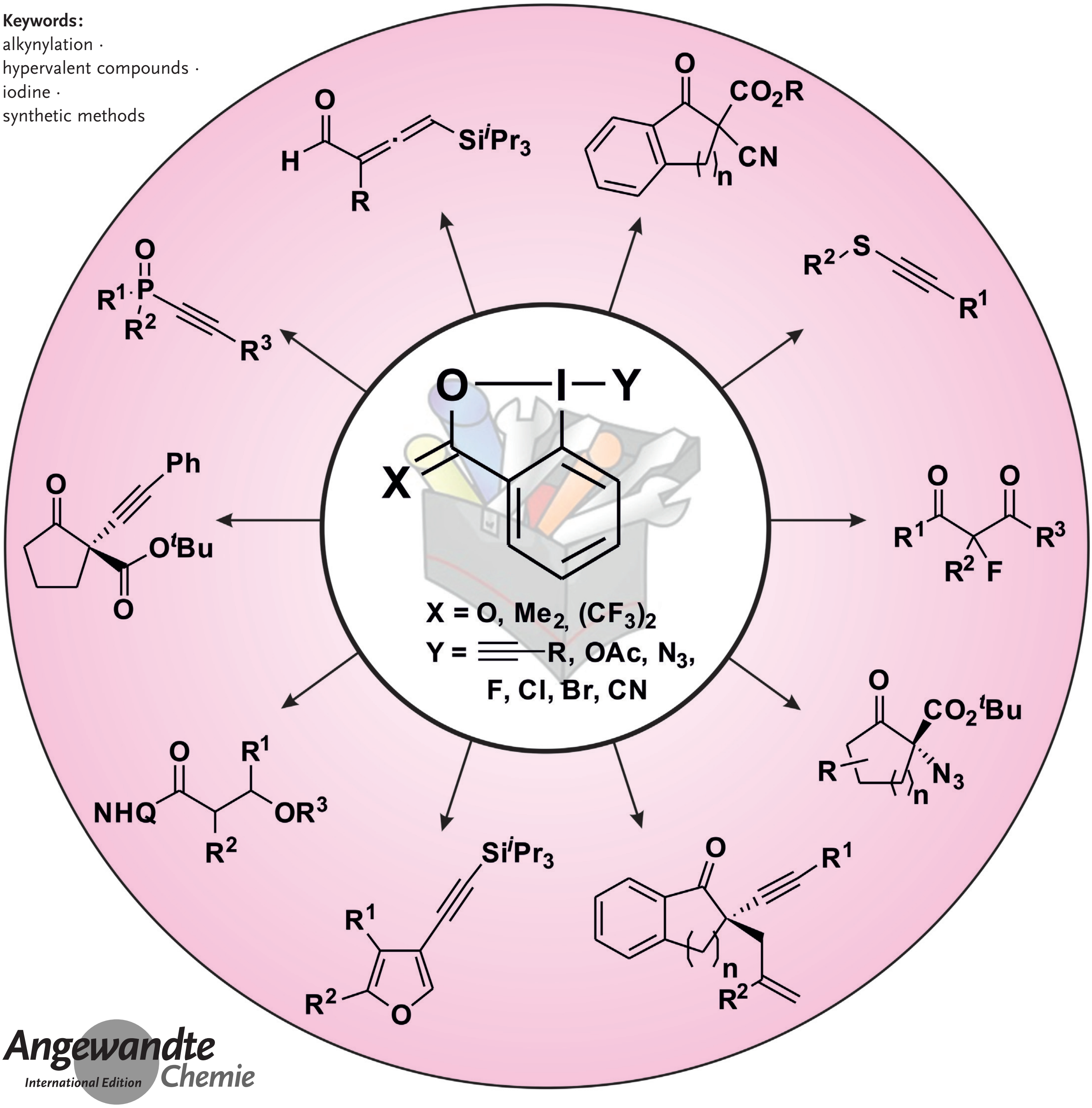

Hypervalent iodine compounds are privileged reagents in organic synthesis because of their exceptional reactivity. Among these compounds, cyclic derivatives stand apart because of their enhanced stability. They have been widely used as oxidants, but their potential for functional-group transfer has only begun to be investigated recently. The use of benziodoxol(on)es for trifluoromethylation (Togni's reagents) is already widely recognized, but other transformations have also attracted 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 by using ethynylbenziodoxol(on)e (EBX) reagents has been highly successful. Breakthroughs in the introduction of alkoxy, azido, difluoromethyl, and cyano groups will also be described.

From the Contents

1. Introduction

The development of new chemical transformations stands at the core of synthetic organic chemistry. New reactions allow known structures to be made more efficiently and uncharted regions of 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 become an established part of main stream synthetic chemistry, and reagents such as Dess–Martin periodinane (DMP, **1**); an iodine(V) reagent, also called λ-5-iodane) and iodobenzenediacetate (an iodine(III) reagent, λ-3-iodane) are nowadays used routinely. Whereas simple oxidation reactions have been established for 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, and cyanides (Umpolung of the reactivity) have been the focus of intense research more recently.

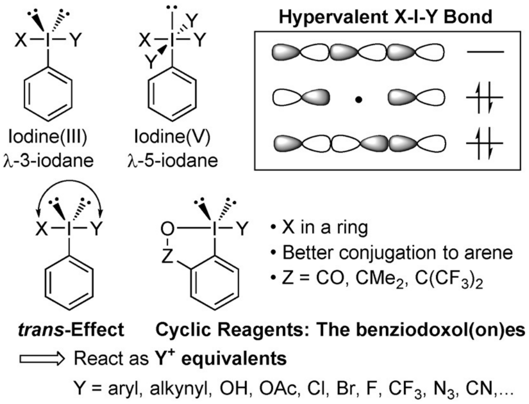

Figure 1. Structure and bonding of hypervalent iodine reagents.

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

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] which highlighted 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**, TIPS = triisopropylsilyl)). Since 2011, the synthetic potential revealed in these preliminary results has been intensively investigated. This is apparent on 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).

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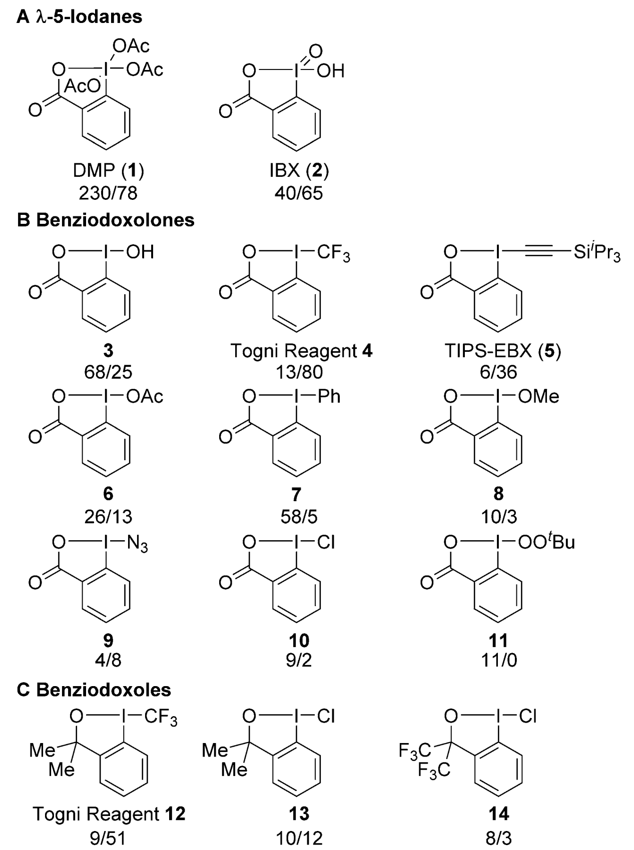

Figure 2. Cyclic hypervalent iodines which have been reported in more than ten different publications (according to a Reaxys structure search performed in July 2015; the real number of reports may be much higher). The numbers of reports prior to/after 2011 are given below the compound number.

The use of Togni reagents for trifluoromethylation reactions has recently been summarized.[6] In this current 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 have 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 through 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).

2. Synthesis and Stability of Benziodoxolone Reagents

The synthesis and structural characterization of benziodoxolone reagents has already been reviewed in detail.[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-iodobenzoic acid (**15**) is easy and scalable. Most syntheses start by oxidation with sodium periodate to give hydroxybenziodoxolone **3**.[7] Care has to be taken when drying **3**, as a polymeric form can be generated on dehydration. For this reason, the use of acetoxybenziodoxolone **6**, a well-defined and crystalline compound obtained from the reaction of **3** with acetic anhydride,[5a] can sometimes be advantageous. EBX reagents

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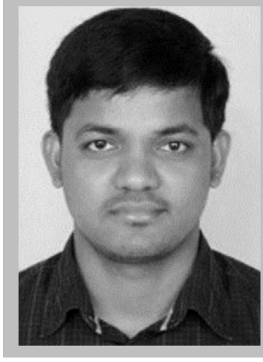
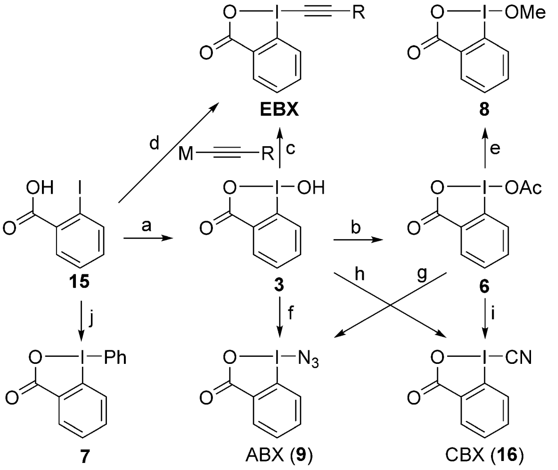


Durga Prasad Hari was born in Jarajapupeta, Vizianagaram, A.P (India). He received his Master degree from IIT Madras and his PhD from the University of Regensburg under the supervision of Prof. Dr. Burkhard Koenig in 2014. Currently, he is working as a postdoctoral fellow under the supervision of Prof.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

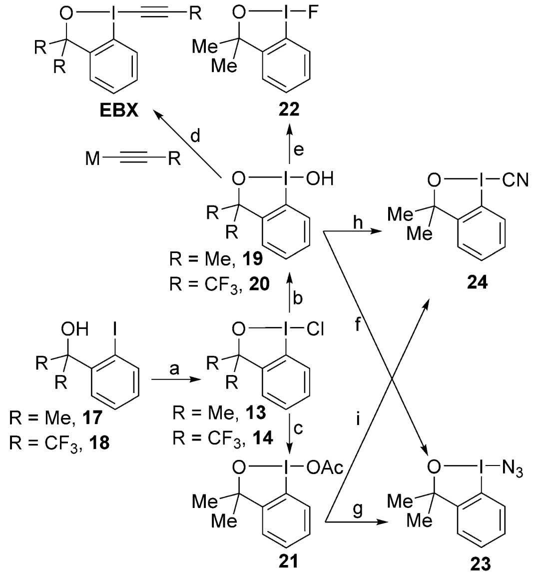
Jérôme Waser was born in Sierre, Valais (Switzerland) in 1977. He obtained his chemistry Diploma at ETH Zurich in 2001. From 2002 to 2006, he was a PhD student at ETH Zurich with Prof. Erick M. Carreira. He then joined Prof. Barry M. Trost at Stanford University as an SNF postdoctoral fellow. From 2007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

can be accessed from **3** by using different procedures.[8] Ochiai et al. reported the first synthesis in 1991 by using alkynyl silanes and boron trifluoride etherate as a Lewis acid.[8a] The procedure was improved by Zhdankin et al. in 1996 by using trimethylsilyltrifluoromethane sulfonate (TMSOTf) as activator, followed by quenching with pyridine.[8b] This procedure was robust, and Brand and Waser could scale it up to a multigram scale.[8c] In 2012, Bouma and Olofsson reported the first one-pot procedure for the synthesis of benziodoxolones starting from 2-iodobenzoic acid (**15**) and alkynyl boronic acid esters.[8d] Methoxybenziodoxolone **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 hydroxybenziodoxolone **3** or acetoxybenziodoxolone **6**. Finally, phenylbenziodoxolone reagent **7** can be synthesized efficiently by using a multistep procedure.[11a,b] More recently, Merritt and Olofsson, as well as Zhdankin and co-workers reported more convenient one-pot procedures (Scheme 1).[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 = $SiMe_3$, $BF_3{\cdot}OEt_2$, 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, $TsOH{\cdot}H_2O$, CH_2Cl_2/TFE 1:1 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→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→rt, 88 %. *m*CPBA = meta-chloroperbenzoic acid, OTf = trifluoromethanesulfonate, rt = room temperature, TFE = trifluoroethanol, TfOH = trifluoromethanesulfonic acid, TMS = trimethylsilyl, TsOH = *p*-toluenesulfonic acid.

Benziodoxoles are usually prepared from alcohols **17** and **18**. Alcohol **17** can be accessed by addition of methyl Grignard to 2-iodobenzoate methyl ester, and **18** either from phenylhexafluoro-2-propanol by iodination[12] or from 1,2-diiodobenzene by monometalation 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 trifluoromethyl groups can be accessed through Zhdankin's method by using trimethylsilyl alkynes and trimethylsilyl triflate,[8b] whereas dimethyl-based reagents require the use of more reactive lithium acetylides.[17] Fluorobenziodoxole **22** can be accessed by treating **19** with triethylammonium hydrofluoride.[18] Finally, azido and cyano reagents **23** and **24** can be synthesized by using the same procedures as for the corresponding benziodoxolone reagents **9** and **16** (Scheme 2).[9,10]



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→rt, 86 %; d2) R = CF_3, M = $SiMe_3$, TMSOTf, CH_3CN, then pyridine, 50–95 %; e) $Et_3N{\cdot}3\,HF$, 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 %.

The cyclic structure of benziodoxol(on)e reagents results in a greatly enhanced thermal stability compared to their noncyclic counterparts. Nevertheless, they are high-energy compounds which display a strongly exothermic decomposition, and have consequently to be manipulated with adequate precautions.[19] Although there are no large differences in the decomposition temperatures of 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.

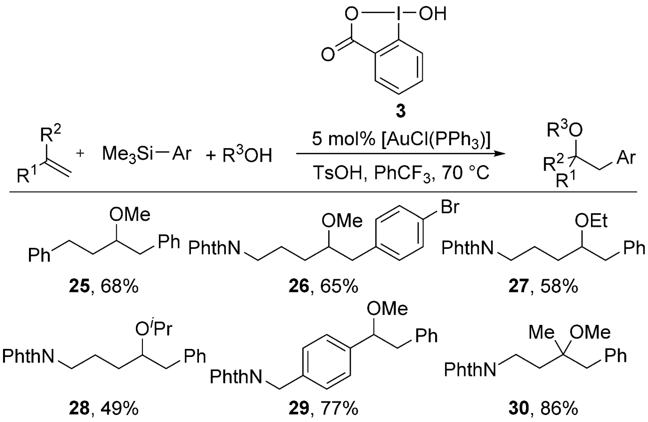
3. C–X Bond Formation

Two approaches are possible for the formation of C–X bonds: 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

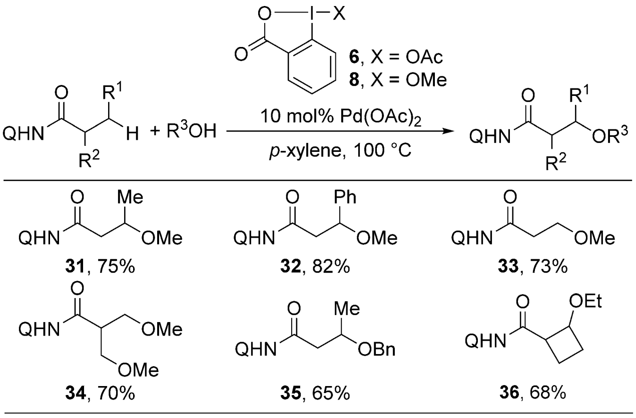
3.1.1. C–O Bond Formation

The formation of C–O bonds was one of the first areas in which cyclic hypervalent iodine reagents were applied for atom-transfer reactions. Early studies with λ-3-iodanes focused on the oxidation of C–H bonds and sulfur atoms with *tert*-butylperoxybenziodoxolone **11**,[20] the epoxidation of olefins with ammonium salts of hydroxybenziodoxolone **3**,[21] and the tosyloxylation of alkynes and ketones.[22] Interestingly, IBX (**2**) was demonstrated early on 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 bonds in the position 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 studies indicated that benziodoxolone reagents can be superior to noncyclic reagents in transition-metal-catalyzed reactions. In 2012, Ball, Lloyd-Jones, and Russell first reported the superiority of 2-hydroxybenziodoxolone **3** for the gold-catalyzed alkoxyarylation 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. Benziodoxolone **3** most probably allows access to a highly reactive gold(III) intermediate, which then performs oxyauration on the olefin followed by arylation through reductive elimination.



Scheme 3. Gold-catalyzed alkoxyarylation of olefins with hydroxybenziodoxolone reagent **3**. PhthN = phthaloyl.

In 2013, Rao and co-workers then reported the use of acetoxy- and methoxybenziodoxolones **6** and **8** for the palladium-catalyzed alkoxylation of $C(sp^3)$–H bonds (Scheme 4).[29] The reaction worked well for both alkyl and aryl substituents in positions β to the carbonyl group (products **31** and **32**) and was also successful in the case of a primary C–H bond (product **33**). Bisalkoxylation was observed if several C–H bonds were accessible in the γ position (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, while tertiary alcohols could not be used. Interestingly, the transformation could also be applied to cyclic substrates (product **36**). In 2014, Zong and Rao also extended this method to the synthesis of nonsymmetrical acetals by using two successive alkoxylations of primary C–H bonds.[30]

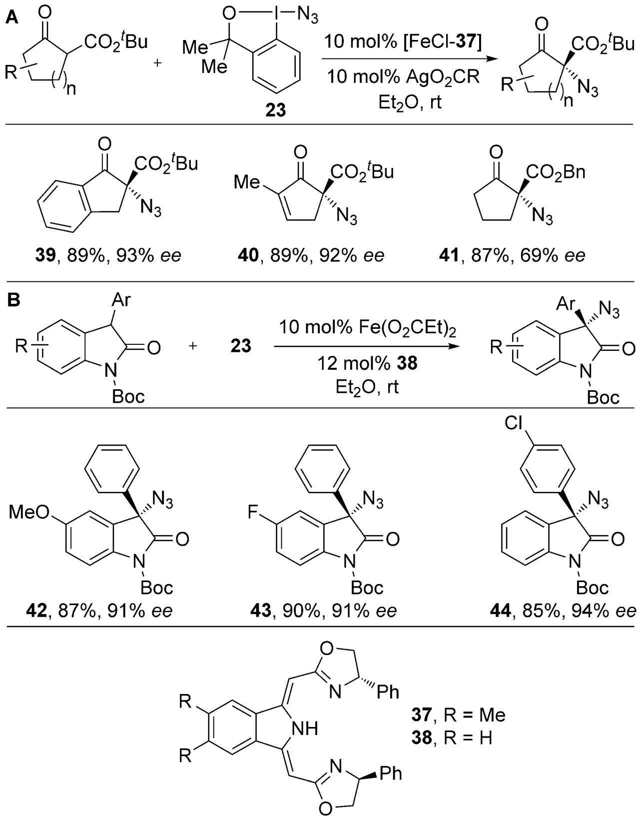


Scheme 4. Palladium-catalyzed C–H alkoxylation with benziodoxolone reagents **6** or **8**. Q = 8-aminoquinoline.

3.1.2. C-N Bond Formation

The formation of C–N bonds by using cyclic hypervalent iodine reagents was pioneered by Zhdankin et al., 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 the generation of radicals (high temperature, strong oxidants).

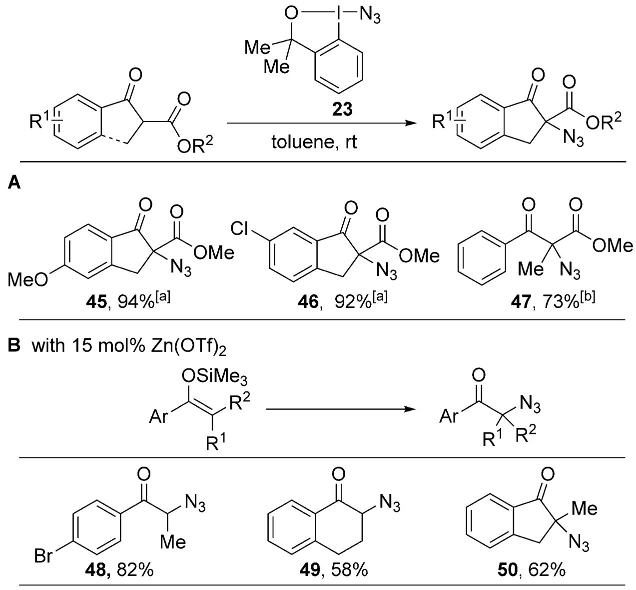
Surprisingly, no further work was done using these promising reagents until 2013, when the research groups of Gade, Waser, and Studer independently reported new transformations based on azidobenziodoxol(on)es **9** and **23**.[32] Gade and co-workers developed a highly enantioselective iron-catalyzed azidation of β-ketoesters and oxindoles by using benziodoxole reagent **23** (Scheme 5 A, 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 noncyclic ketoesters could not be used. Under slightly



Scheme 5. Iron-catalyzed enantioselective azidation with benziodoxole **23**. Bn = benzyl, Boc = *tert*-butoxycarbonyl.

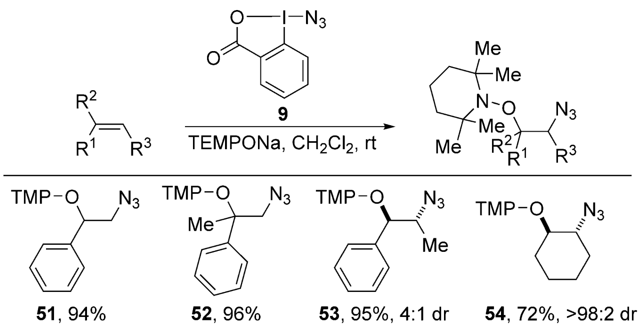
modified conditions, azidated oxindoles **42**–**44** could also be obtained in high yields and enantioselectivities.

Vita and Waser reported a method to azidate β-ketoesters derived from indanone in high yields without the need for a catalyst or base (Scheme 6 A, products **45** and **46**).[32b] Less-reactive acyclic β-keto esters bearing an aromatic substituent were found to undergo azidation in good yield when using zinc triflate as a 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 6B).



Scheme 6. Azidation of cyclic and acyclic β-ketoesters and silyl enol ethers. [a] Without catalyst. [b] 30 mol% $Zn(OTf)_2$ as catalyst.

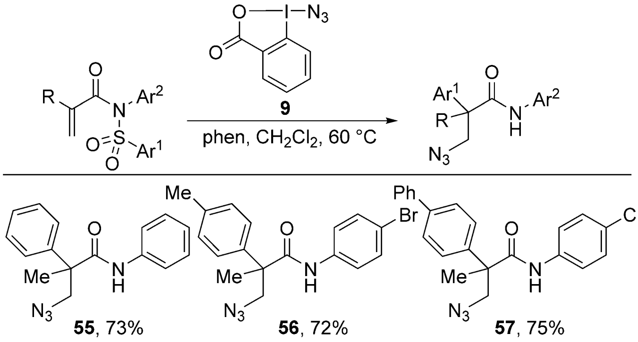
Also in 2013, Zhang and Studer reduced azidobenziodoxolone **9** with TEMPONa (TEMPO = 2,2,6,6-tetramethyl-1-piperidinoxyl) to form an azido radical, which was directly added to an olefin. The resulting alkyl radical recombined with TEMPO to give an overall oxyazidation of the alkene (Scheme 7).[32c] The reaction worked well for mono- and disubstituted styrene derivatives (products **51**–**53**). High *trans* stereoselectivity was observed in the case of cyclic alkenes (product **54**).



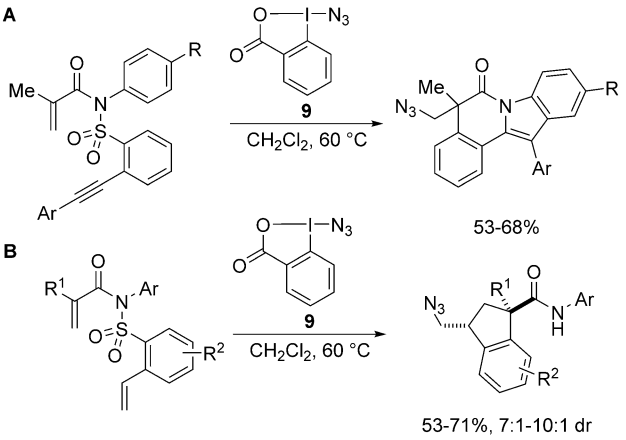
Scheme 7. Oxyazidation of olefins with azidobenziodoxolone **9**. TMP = tetramethylpiperidide.

In 2014, Nevado and co-workers further exploited the potential of benziodoxolone **9** for the generation of azide radicals.[33] They developed the aryl azidation 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 the α-position were obtained in 72–75 % yield.

In 2015, Nevado and co-workers increased the structural diversity accessible with this transformation by using a further C–N bond-forming event and introducing unsaturation into



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

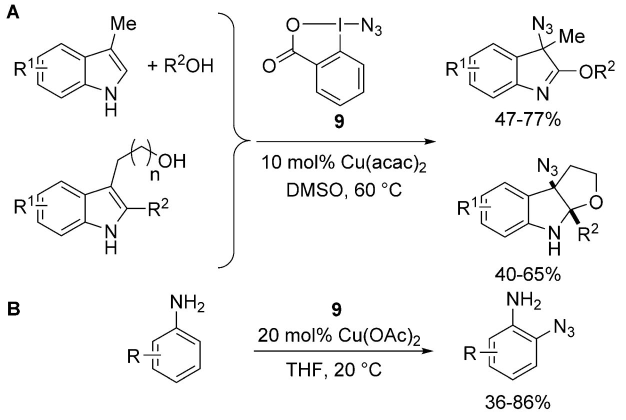


Scheme 9. More complex cascade azidoarylation processes with azidobenziodoxolone **9**.

the molecule, thereby allowing more complex cascade processes (Scheme 9).[34] The introduction of an *ortho*-alkynyl group on the aryl sulfone 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 aryl sulfone to generate a highly substituted indane product (Scheme 9 B).[34b]

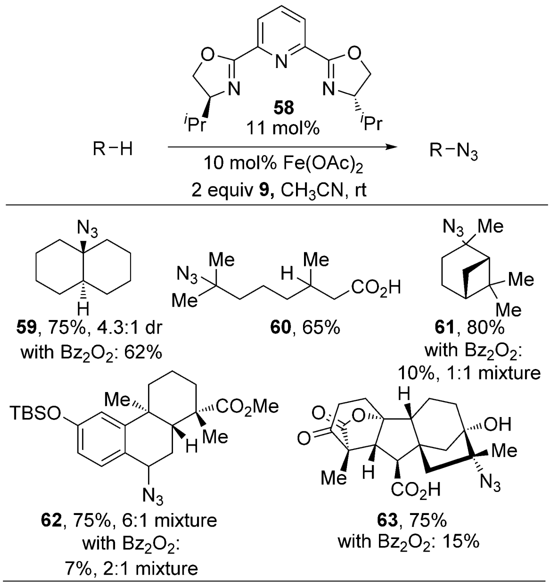
In 2014, two research groups reported the combination of copper catalysis with benziodoxolone **9** for the azidation of electron-rich aromatic compounds (Scheme 10).[35] Jiao and co-workers developed the azidation of skatole derivatives in the presence of alcohols to give dehydroindole derivatives (Scheme 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]

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



Scheme 10. Copper-catalyzed azidation of indoles and anilines by using azidobenziodoxolone **9**. acac = acetylacetonate.

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$_3$K.[38] This method was efficient for the azidation and diazidation of dicarbonyl compounds, as well as for the synthesis of α-triazido ketones.

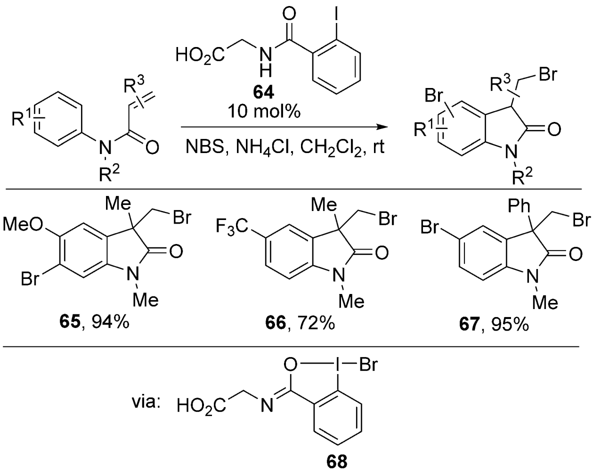


Scheme 11. Iron-catalyzed C$-$H azidation with azidobenziodoxolone **9**. Bz_2O_2 = dibenzoyl peroxide, TBS = *tert*-butyldimethylsilyl.

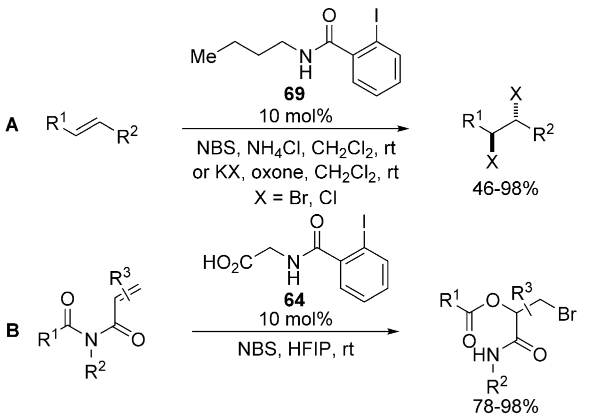
3.1.3. *Carbon–Halogen Bond Formation*

Early studies by Amey and Martin, as well as by Braddock et al., had demonstrated that bromobenziodoxole reagents could be used for the bromination of anisoles and the bromolactonization of olefins.[39] In 2012, Gulder and co-workers developed a new bromoarylation of olefins for the synthesis of oxindoles by using a catalytic amount of iodine **64** and *N*-bromosuccinimide (NBS) as the 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 the 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]

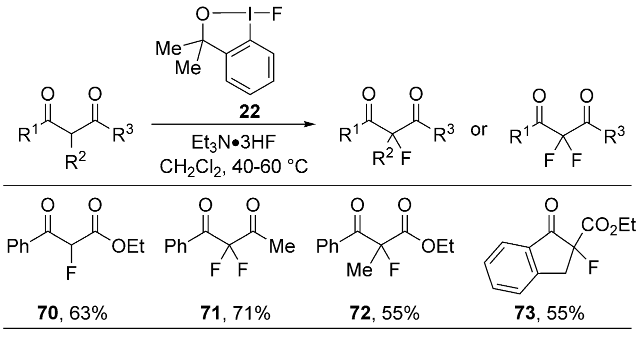
In 2013, Stuart and co-workers studied the reactivity of fluorobenziodoxole **22** in the fluorination of dicarbonyl compounds (Scheme 14).[18] Monofluorinated ketoester **70**



Scheme 12. Intramolecular bromoarylation of olefins.



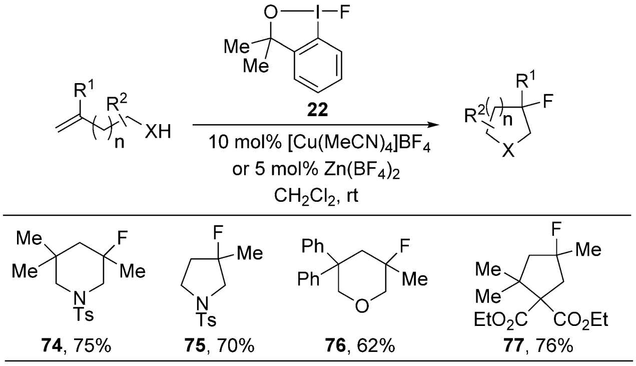
Scheme 13. Dihalogenation and oxybromination of olefins.



Scheme 14. Fluorination of activated carbonyl compounds.

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 2014, Szabó and co-workers reported the silver-mediated geminal difluorination of styrene derivatives using benziodoxole **22**.[43a] In 2015, they further extended the use of reagent **22** to the intramolecular aminofluorination of alkenes



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

(Scheme 15).[43b] In this process, piperidine **74**, pyrollidine **75**, cyclic ether **76**, and cyclopentane **77** could be obtained in 62–76 % yield. Zinc(II) tetrafluoroborate was used as a catalyst in the case of amine and oxygen nucleophiles, whereas a copper catalyst was better for carbon nucleophiles.

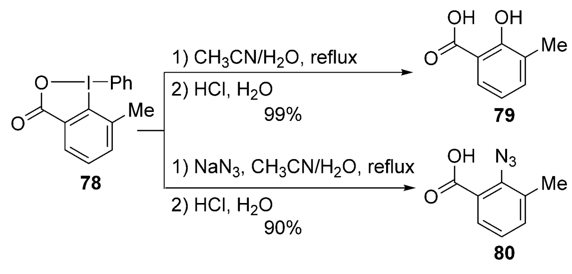
In addition to carbon–halogen bond formation, Shen and co-workers reported very efficient methods for transfer of SCF_3 groups to carbon nucleophiles.[44] They initially proposed that the active reagent was a benziodoxole derivative. However, Buchwald and co-workers later demonstrated that the reagent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

3.2. Reactions with the Heteroatom on the Substrate

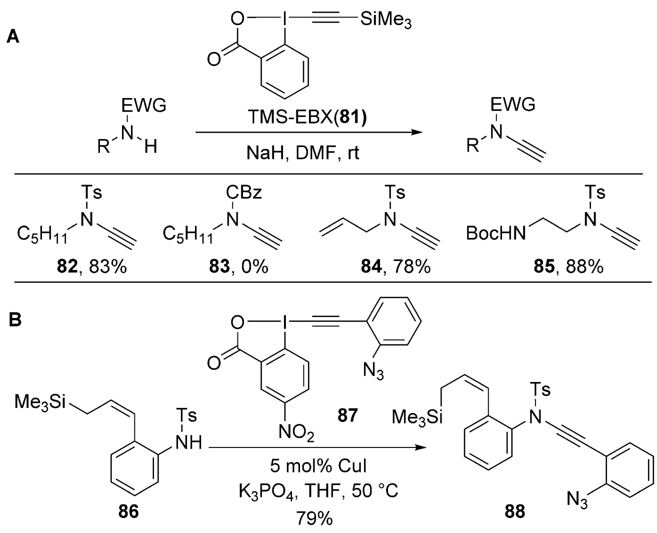
3.2.1. C–N and C–O Bond Formation

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

The alkynylation of nitrogen and oxygen nucleophiles has been mostly achieved by using alkynyliodonium salts.[47] In 2013, Aubineau and Cossy 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



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

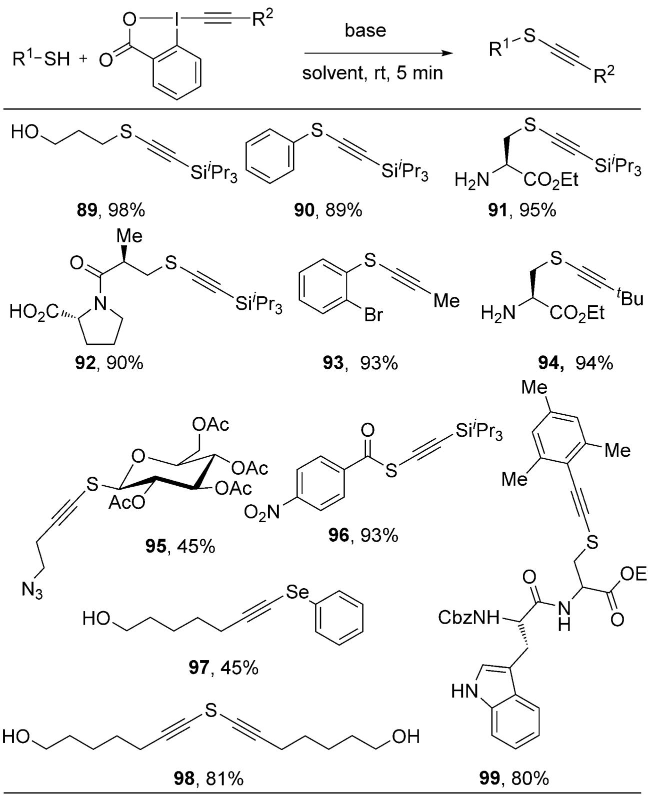


Scheme 17. N-Alkynylation with EBX reagents. EWG = electron-withdrawing group.

a sulfonamide in the 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 the complex EBX reagent **87** (Scheme 17B).[48b] Standard methods involving alkynyl bromides did not work.

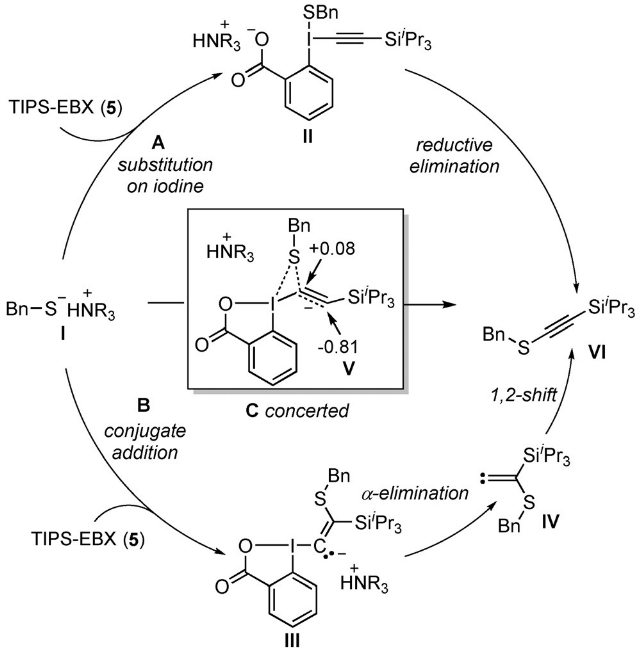
3.2.2. C–S and C–P Bond Formation

Alkynyliodonium salts can be used only for the alkynylation of relatively electron-poor sulfur and phosphorus nucleophiles, because of their strong oxidizing properties.[47] In 2013, Frei and Waser 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 exclusively the thiol-alkynylated product **91** 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, sulfide salts, and dipeptides (products **95**–**99**).



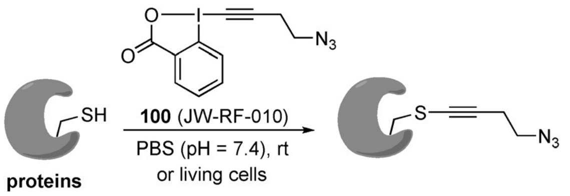
Scheme 18. Alkynylation of thiols with R-EBX reagents. Cbz = benzyloxycarbonyl.

The authors proposed a mechanism for the alkynylation of thiols on the basis of 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). 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 a 1,2-shift to give **VI** (pathway B). This pathway was indeed observed with a transition-state energy of 23 kcal mol^{-1} for the addition step. Nevertheless, another unprecedented concerted pathway C was found with a lower energy of 10.8 kcal mol^{-1}. The obtained transition state **V** was distorted and polarized with a negative charge at the α position and a positive charge at the β position to the silicium center.



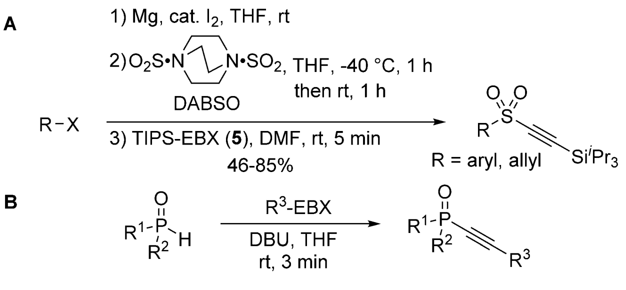
Scheme 19. Proposed mechanism for the alkynylation of thiols.

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 by using azide-functionalized alkynyl benziodoxolone **100** (Scheme 20).[51] The obtained thioalkyne adducts could be easily functionalized by 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 method was used for the identification of the targets of curcumin in HeLa cells.



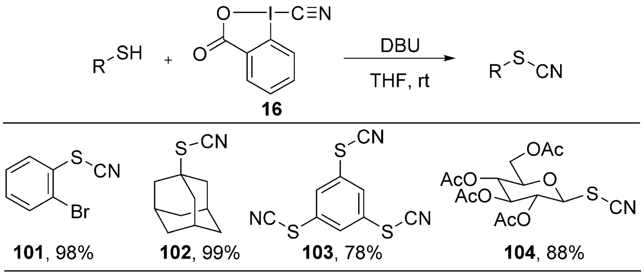
Scheme 20. Alkynylation of cysteine in complex proteomes with azide-EBX reagent **100**. PBS = phosphate-buffered saline.

EBX reagents can also be used for the alkynylation of less nucleophilic sulfur and phosphorus derivatives. In 2015, Chen and Waser developed a new one-pot procedure for the preparation of arylalkynyl sulfones through the reaction of TIPS-EBX (**5**), diazabicyclooctane bis(sulfur 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, Chen and Waser 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 by 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

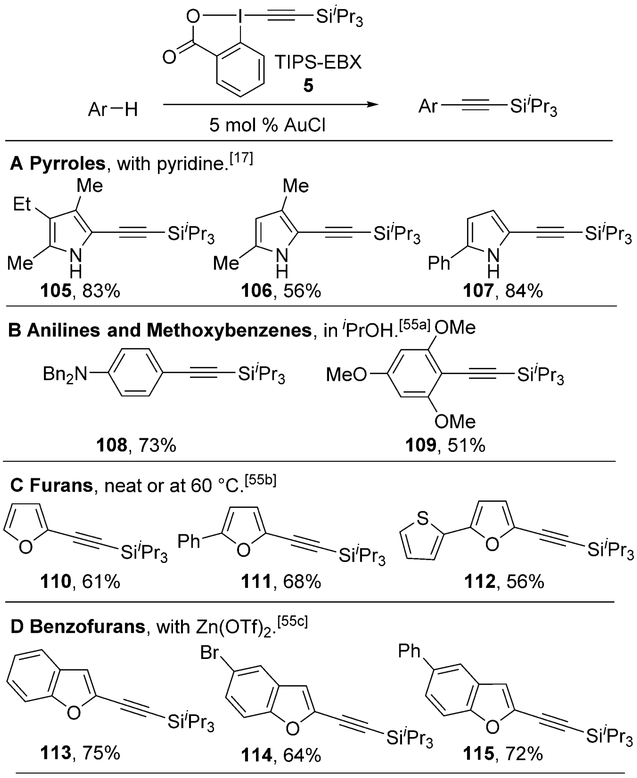
The formation of C–C bonds by using benziodoxole reagents has been mostly focused on alkynylation. A few rare examples of cyanation and arylation have also been reported.

4.1. Alkynylation

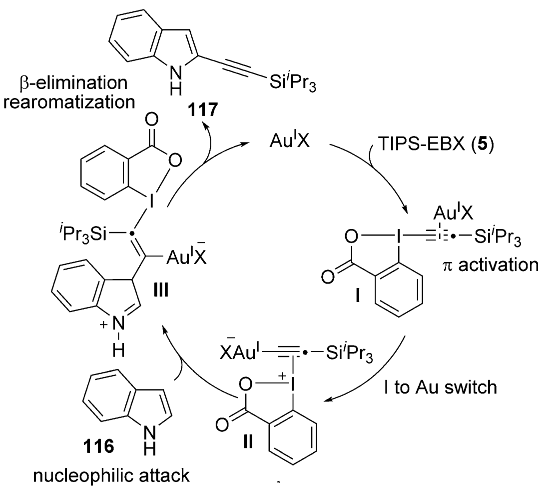
4.1.1. Transition-Metal-Catalyzed Functionalization of C–H Bonds

In 2009 and 2010, Waser and co-workers reported the first direct C–H alkynylation process on indoles, pyrroles, and thiophenes by 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 such as anilines, trimethoxybenzenes, furans, and benzofurans.[56] In the case of anilines, a moderate bulky group on the nitrogen atom was essential for *para* selectivity (Scheme 23 B, product **108**). In the case of furans, the reaction had to be performed under neat conditions or at 60 °C 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**).[56c] Waser and co-workers proposed either a π-activation or an oxidative mechanism for the direct C–H alkynylation reaction.[17,55a]

In 2014, the mechanism of this transformation was examined by Ariafard by 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, he proposed a new reaction pathway that was accessible at room temperature and involved transfer of the alkyne from the iodine to the gold center (from **I** to **II** in Scheme 24). Nucleophilic attack of indole (**116**) on intermediate **II**, followed by β-elimination

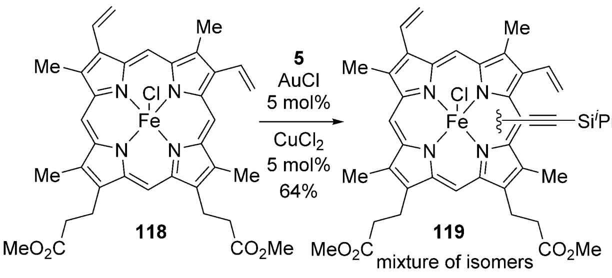


Scheme 23. Extension of the scope of the direct alkynylation of arenes.



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

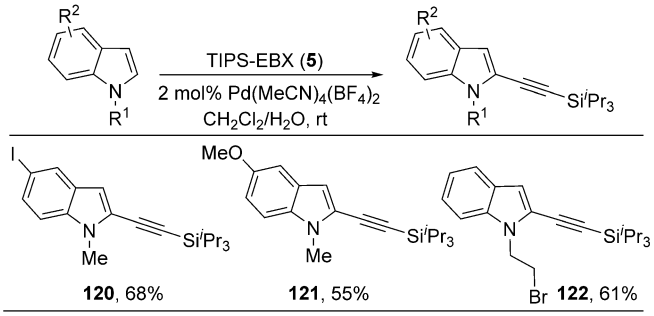
and rearomatization would give the observed alkynylation product **117**.



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

Nierth and Marletta reported in 2014 the alkynylation of protoporphyrin IX (**118**) by using a 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 biolabeling 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]

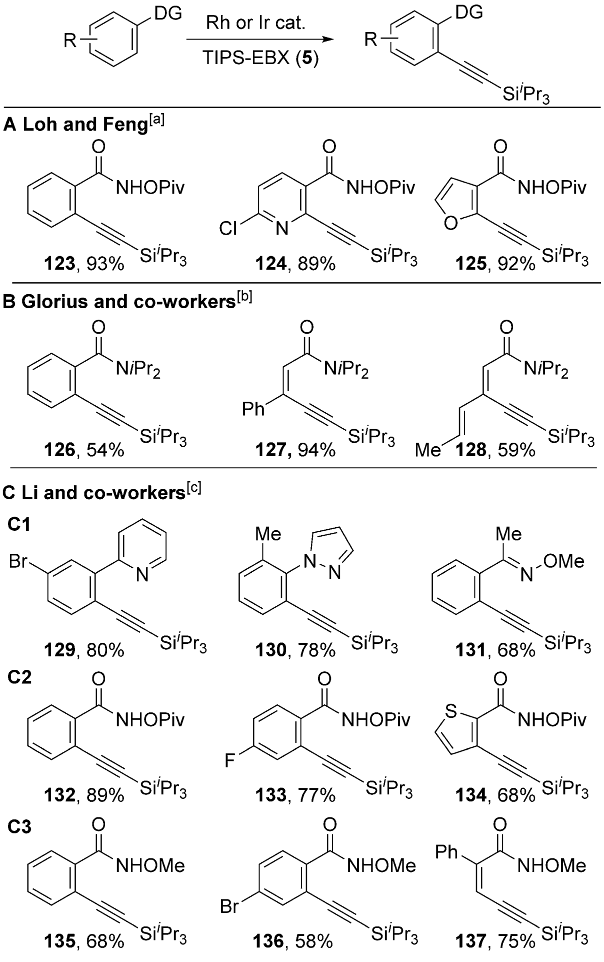
In 2013, Waser and co-workers developed a palladium(II) catalyzed C2-selective alkynylation of indoles (Scheme 26).[60] Functionalized indoles **120–122** were obtained in 55–68 % yield at room temperature.



Scheme 26. C2-Selective alkynylation of indoles.

In 2014, a breakthrough in the alkynylation of C(sp^2)–H bonds by using transition-metal catalysts and EBX reagents and based on a directing-group strategy was reported independently by three research groups.[61] Feng and Loh first reported the alkynylation of pivaloyl benzamides by 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 27B).[61b] Finally, Li and co-workers reported an extensive study on the alkynylation of arenes using TIPS-EBX (**5**; Scheme 27 C).[61c] By using a rhodium catalyst, they could use a broad range of directing groups such as pyridine, pyrazole, or oximes (products **129–131**). The best results were again obtained with a pivaloylamide as a 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**.

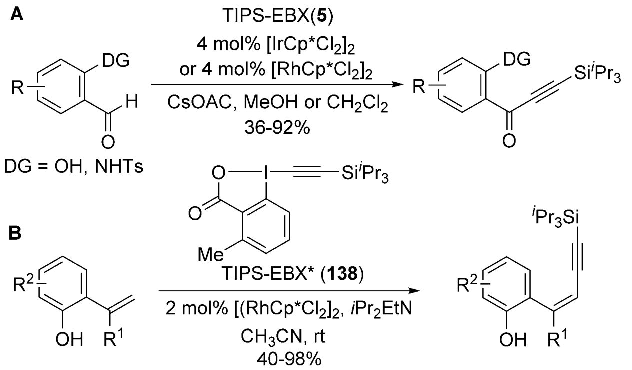
Since these three seminal reports, directed C–H alkynylation using TIPS-EBX (**5**) and rhodium or iridium catalysts has been applied to a broad range of substrates. Loh and co-



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. Cp* = pentamethylcyclopentadienyl, DCE = 1,2-dichloroethane, DG = directing group, Piv = pivaloyl.

workers extended the rhodium-catalyzed alkynylation of olefins to both acrylamides and enamides.[62] Loh et al. as well as Zhu and co-workers independently reported the rhodium-catalyzed C7-alkynylation of indolines, whereas Li, 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 by using a cationic rhodium catalyst.[64] The efficiency of azomethine ylides as the directing group was further demonstrated by Li and co-workers.[65] Finally, Kang and Hong developed two procedures for the selective C2- or C5-alkynylation of quinolones by 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] Alcohols and sulfonamides could both be used as directing groups to obtain ynones in 36–92 % yield. A similar procedure using different directing groups was later reported by Zhou and co-workers.[67b]

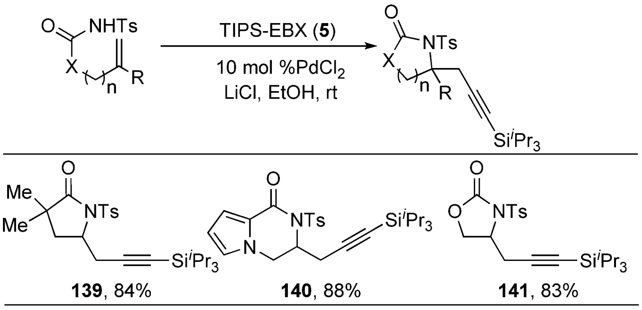


Scheme 28. Recent developments in rhodium-catalyzed C–H alkynylation.

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 the contraproductive rhodacycle on the 2-iodobenzoic acid formed during the reaction is not possible, as the *ortho* position is blocked.

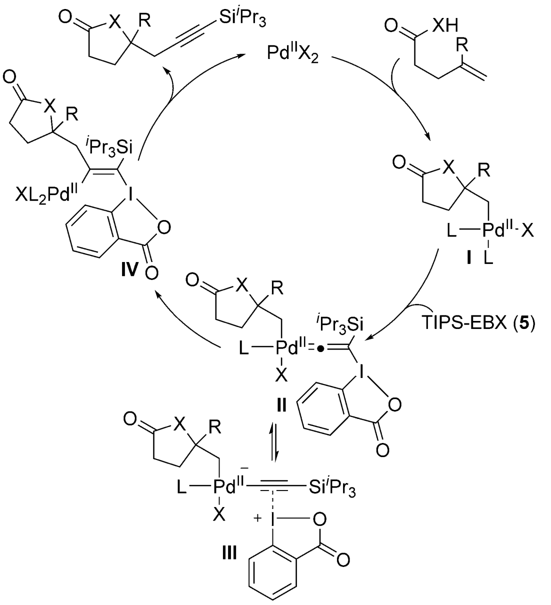
4.1.2. Alkynylation as Part of Domino Processes

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



Scheme 29. Aminoalkynylation of terminal olefins.

Originally, Waser and co-workers proposed a mechanism involving oxy- or aminopalladation, oxidative addition on TIPS-EBX (**5**), and reductive elimination. In 2014, Ariafard performed calculations 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] Intermediate **II** is in equilibrium with the less-favorable palladium-alkynyl complex **III**. From **II**, an easy 1,2-shift of the alkyl group gives palladium-alkenyl complex **IV**. Finally, simple β-elimination leads to the oxyalkynylation product.

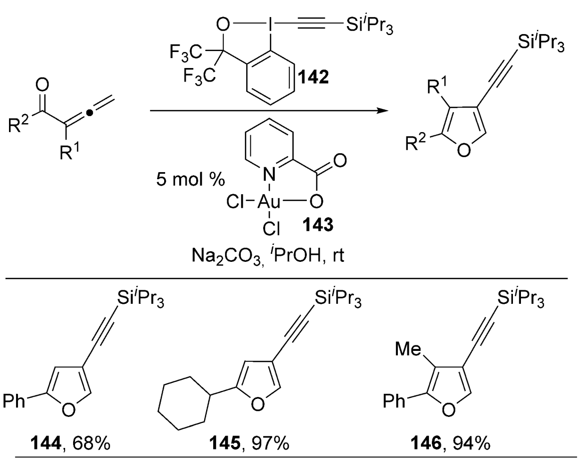


Scheme 30. Mechanism proposed by Ariafard for the oxyalkynylation reaction.

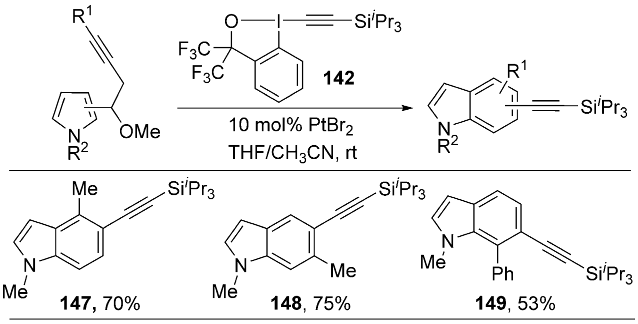
Waser and co-workers then investigated other types of domino reactions with EBX reagents for the synthesis of (hetero)arenes. A first attempt was made in 2011 for the synthesis of 3-alkynylated indoles starting from anilines.[70] It was found that gold(III) could only perform the cyclization step from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

In 2013, Waser and co-workers reported the first cyclization–alkynylation domino reaction of keto allenes by 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 by direct C–H alkynylation. This reaction most probably proceeds through gold-catalyzed cyclization of the keto allene to form a C3-aurated furan, which is then alkynylated by **146**.

In 2015, Li and Waser 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 31. Gold-catalyzed cyclization–alkynylation of keto allenes.



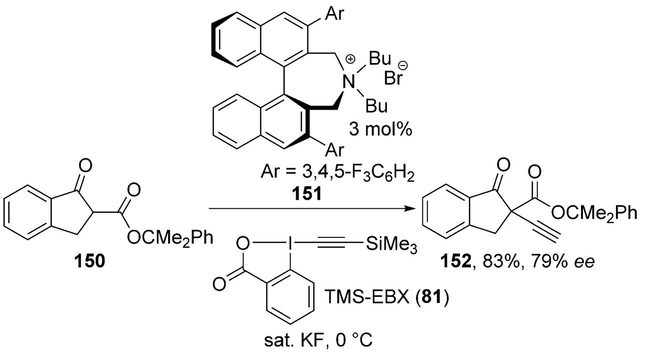
Scheme 32. Platinum-catalyzed cyclization–alkynylation domino reaction to access 5- or 6-alkynylated indoles.

4.1.3. *Direct Alkynylation of Carbon Nucleophiles*

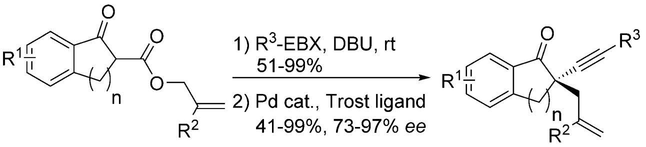
In 2010, Waser and co-workers reported the efficient ethynylation of α-cyano, α-oxo, and α-nitro β-ketoesters by using TMS-EBX (**81**) at low temperature in the presence of TBAF, and reported preliminary results of asymmetric induction on using cinchona-based phase-transfer catalysts.[72] In 2013, they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

In 2014, Waser and co-workers developed an indirect approach to access α-alkynyl indanones and tetralones with high enantiopurities through an alkynylation/palladium-catalyzed decarboxylative asymmetric allylic alkylation (DAAA) sequence (Scheme 34).[73] α-Alkynyl β-allyl keto esters were obtained in high yields on using diazabicyclo[5.4.0]undec-7-ene (DBU) or tetramethylguanidine (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% ee.

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] Alkynes **153**, **154**, and **155**, used in the synthesis of marasmene, (−)-



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



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

lingzhiol, and a fragment of azadirachtin, respectively, could be obtained in good yield by using this method.[74a–c] In 2015, it was also applied to the total synthesis of the core of retigeranic acid A.[74d]

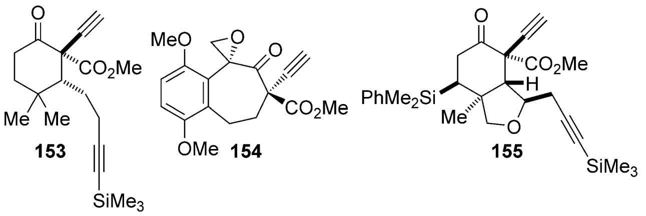
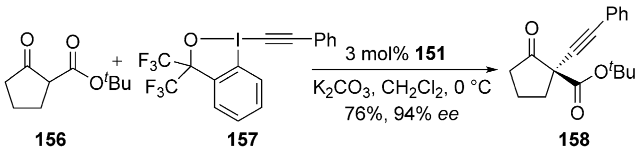


Figure 3. Alkyne building blocks for the synthesis of natural products accessed using TMS-EBX (**81**).

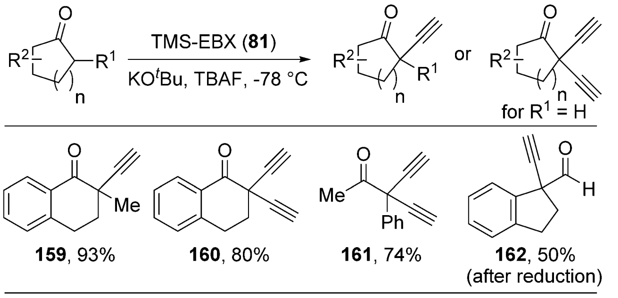


Scheme 35. Enantioselective alkynylation using phase-transfer catalyst **151** and benziodoxole reagent **157**.

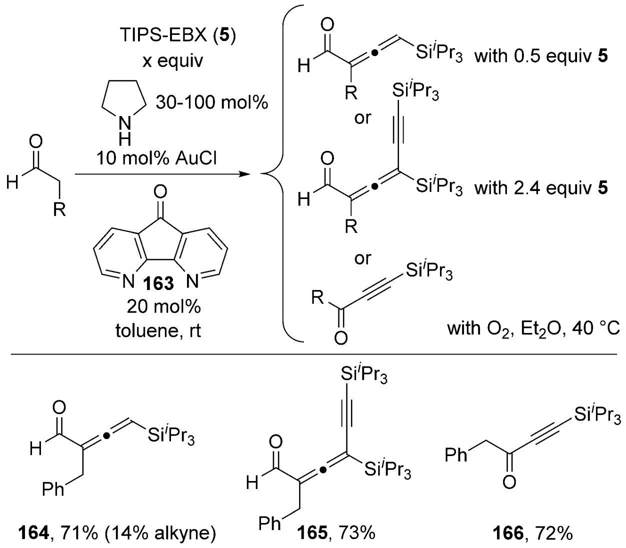
In 2014, Maruoka and co-workers reported the first alkynylation of ketoesters that proceeded with more than 90% *ee* (Scheme 35).[75] Key for success with phase-transfer catalyst **151** was the use of phenylbenziodoxole **157** instead of TMS-EBX (**81**).

The scope of nucleophiles in the alkynylation reaction was further extended by Veselý and co-workers.[76] Alkynylated nitrosulfones, pyrazolones, oxindoles, rhodanines, and azlactones were obtained in good yield using TMS-EBX (**81**) and mild bases. The use of a cinchona-derived phase-transfer catalyst allowed the formation of alkynylated nitrosulfones with up to 61% *ee*. In 2014, Silva Jr. et al. reported the first successful alkynylation of aromatic ketones by using TMS-EBX (**81**; Scheme 36).[77] Cyclic derivatives such as tetralone **159** were obtained in very good yield. Dialkynylation was obtained (products **160** and **161**) when the starting material contained secondary α positions. Interestingly, the first example of the alkynylation of an aldehyde was also reported in this study (product **162**).

The alkynylation of aldehydes activated as enamines was studied by Wang, Li, and Huang (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



Scheme 36. Alkynylation of ketones with TMS-EBX (**81**). TBAF = tetrabutylammonium fluoride.

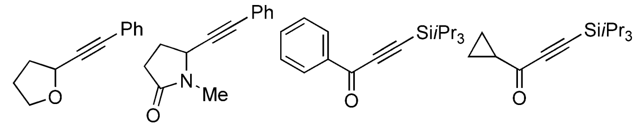


Scheme 37. Reactions of TIPS-EBX (**5**) with aldehydes under amine/gold catalysis.

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 the catalyst, thereby precluding the development of enantioselective reactions.

4.1.4. Alkynylation of Carbon Radicals

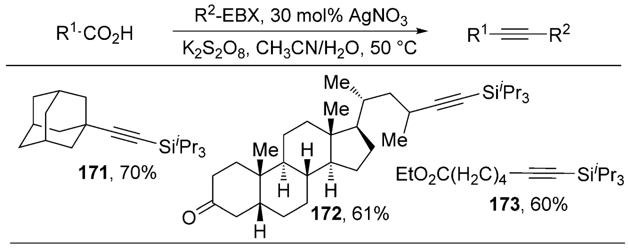
The alkynylation of radicals generated using classical C–H abstraction methods with EBX reagents has been studied only recently (Figure 4).[79] In 2014, Yu, Chen, and co-workers reported that alkynylation of the position α to heteroatoms was possible using *tert*-butylhydroperoxide (TBHP) or di-*tert*-butylperoxide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



167, 79% TBHP, 60 °C
168, 50% TBHP, 60 °C
169, 91% DTBP, 130 °C
170, 52% TBHP, 80 °C

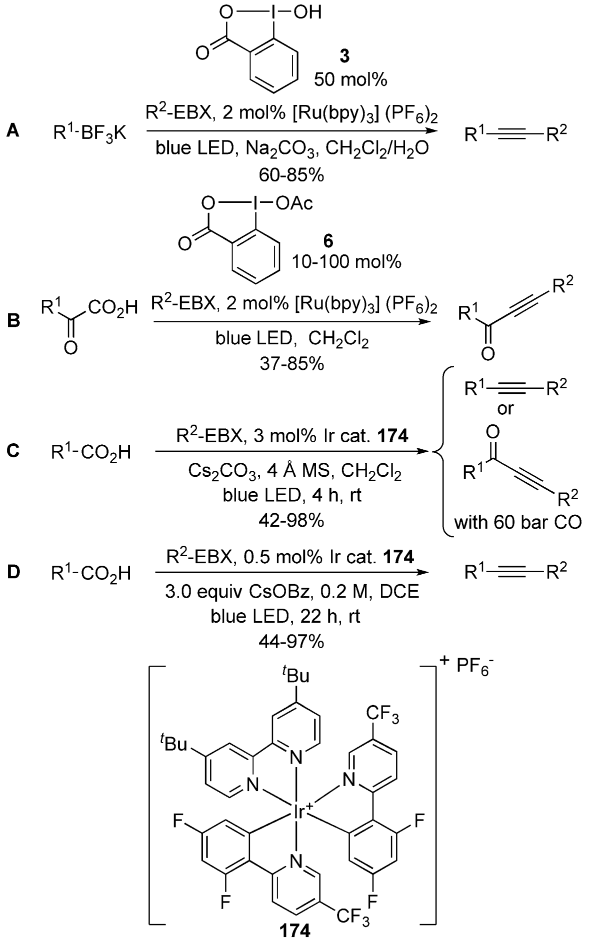
Figure 4. Alkynes obtained by oxidative C–H abstraction.

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



Scheme 38. Decarboxylative alkynylation of carboxylic acids.

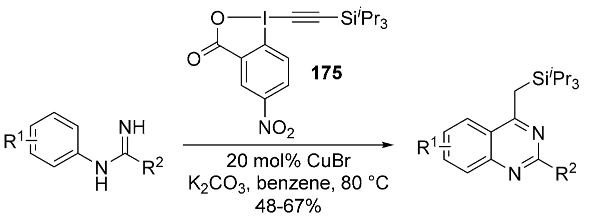
A disadvantage of the method developed by Li and co-workers is the requirement for a stoichiometric strong oxidant. Recently, several research groups have made use of photoredox catalysis to avoid this issue (Scheme 39).[82] In 2014, Chen and co-workers reported the alkynylation of trifluoroborates salts by using a ruthenium catalyst and aryl, alkyl, and silyl-EBX reagents (Scheme 39 A).[82a] The use of hydroxybenziodoxolone **3** as an 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] Acetoxybenziodoxolone **6** was required as a catalyst. Finally, Xiao, Lu, and co-workers[82c] as well as Waser and co-workers[82d] independently reported the first decarboxylative alkynylation of carboxylic acids that worked for a broad range of substrates without the need for further oxidative additive (Scheme 39 C,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 procedure for the transfer of synthetically versatile silyl alkynes.



Scheme 39. Alkynylation reactions using photoredox catalysis. bpy = 2,2’-bipyridine.

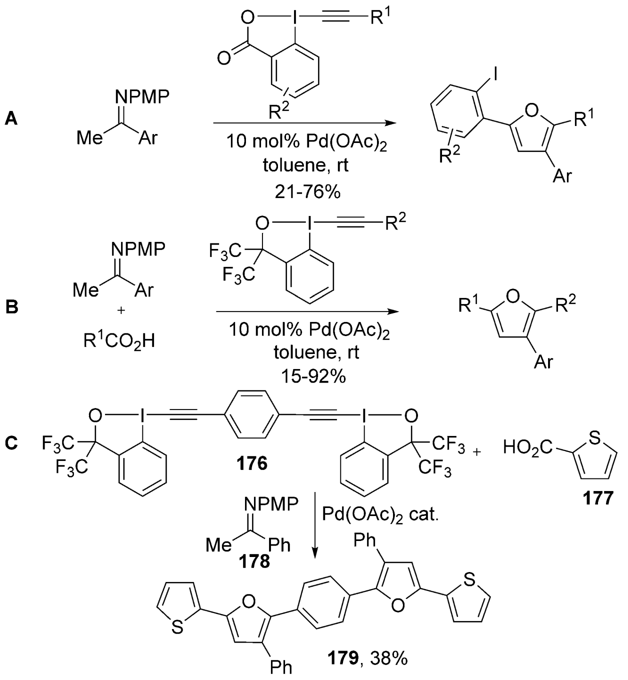
4.2. Other Transformations

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

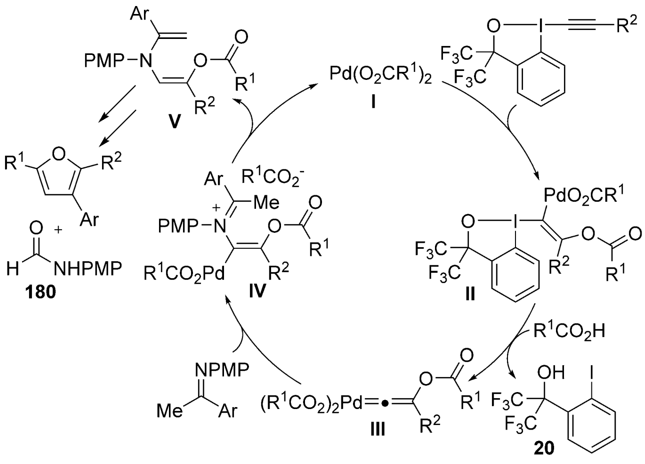


Scheme 40. Synthesis of quinazolines with EBX reagent **175**.

A new type of palladium-catalyzed transformation involving EBX reagents was reported by Yoshikai and co-workers.[85] Furans incorporating the iodoaryl group of the reagent were obtained when EBX reagents were treated with ketimines (Scheme 41 A).[85a] A three-component reaction involving a carboxylic acid as a third partner was then developed by using a benziodoxole reagent (Scheme 41 B).[85b] Particularly impressive was the reaction of the 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 then lead to palladium-allenylidene intermediate **III**. Nucleophilic attack of the imine followed by protodemetalation would give enamine **V** and regenerate active catalyst **I**. From **V**, a series of bond-formation/breaking events would finally lead to the furan, as well as to formamide **180**, which could be isolated.

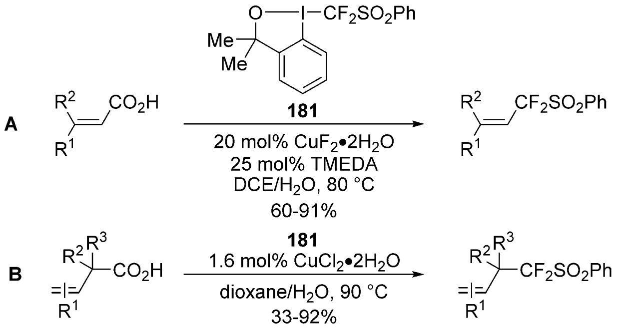


Scheme 41. Palladium-catalyzed synthesis of furans with EBX reagents. PMP = *p*-methoxyphenyl.



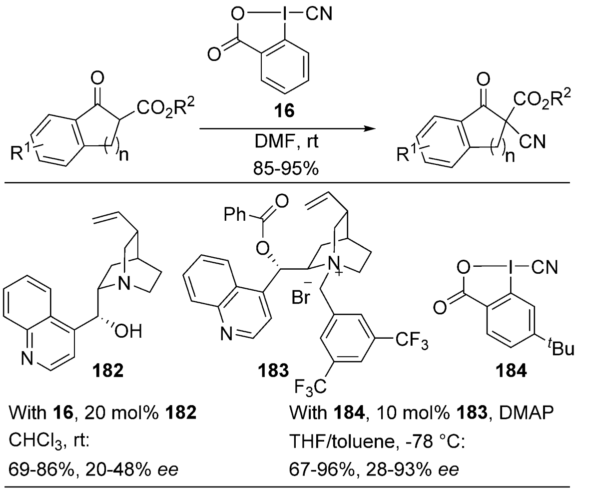
Scheme 42. Speculative mechanism for furan synthesis.

To develop an alternative for difluoromethylation, Hu and co-workers introduced benziodoxole reagents **181**.[86] They first reported the difluoromethylation of thiols by using **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,B).[86b,c]



Scheme 43. Copper-catalyzed difluoromethylation of carboxylic acids. TMEDA = *N*,*N*,*N'*,*N'*-tetramethylethylenediamine.

In 2015, Chen and co-workers reported the first cyanation of cyclic ketoesters in high yield by using cyanobenziodoxolone **16** (Scheme 44).[87a] Waser and co-workers then reported the use of cinchona alkaloid **182** as the catalyst for enantioselective cyanation in up to 48 % *ee*.[87b] Finally, Zheng and co-workers developed the first highly enantioselective cyanation of ketoesters by 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 the reaction to be performed at low temperature to enhance the enantioselectivity.



Scheme 44. Cyanation of ketoesters with benziodoxolone reagents. DMAP = 4-dimethylaminopyridine.

5. Summary and Outlook

Cyclic hypervalent iodine reagents have been known for a long time, but their use had mostly been limited to simple oxidation reactions. In the last decade, their potential for more complex functional group transfer reactions has begun to be exploited. Although trifluoromethylation using Togni reagents has had the largest impact, alkynylation using EBX reagents has been increasingly investigated. Alkynylation of thiols under mild conditions has been developed, which has led to the first application in biology. The alkynylation of heteroaromatic C–H bonds in the presence of gold or palladium catalysts, or of arene rings by 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 rare. Exciting preliminary results obtained since 2013 regarding azidation, cyanation, or oxygen-transfer reactions indicate that this situation will change soon. It is our belief that the synthetic potential of benziodoxolone reagents has just begun to be investigated, and that with time they will rise to be a versatile tool for organic and medicinal chemists.

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