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Benziodoxole-Based Hypervalent Iodine Reagents for Atom-Transfer Reactions

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In the last decades, hypervalent iodine reagents have raised from chemical curiosities to mainstream reagents in organic synthesis. The use of benziodoxole-derived reagents has been especially successful in oxidation methods, whereas non-cyclic iodinanes have been used both for oxidation and atom-transfer reactions. On the other hand, the exceptional properties of benziodoxole reagents for atom-transfer reactions have only started to attract the attention of the synthetic community more recently. In this review, progress in the use of these compounds for C-X and C-C bond formations will be presented. In particular, recent breakthroughs in trifluoromethylation and alkynylation reactions have been realized since 2006 based on benziodoxole-derived reagents and these results are the main focus of this article.

1. Introduction

Hypervalent iodine compounds have always fascinated chemists, due to their non-classical bond character and exceptional reactivity.[1] Nevertheless, the research in this area has been mostly curiosity-driven for several decades, and it is only more recently that general synthetic applications have emerged. For example, the Dess-Martin periodinane (DMP) as a mild and non-toxic reagent is now one of the most often used oxidant in organic synthesis.[2] Structurally, it belongs to the benziodoxole-derived λ^5 iodine compounds, which are characterized by the inclusion of the iodine atom inside a ring.[3] This cyclic structure confers to the benziodoxole-derived reagents an exceptional stability when compared to other hypervalent iodines, and their use for oxidation reactions is now well-established.[4] A recent important progress in this field was the introduction of methods catalytic in iodine.[5]

Besides simple electron-transfer, the use of hypervalent iodine for oxidative atom transfer reactions is also emerging as a promising area, both for hetero- and carbon- atom transfer reactions.[6] In contrast to oxidation reactions, non-cyclic reagents have been used in the vast majority of cases. In fact, one may argue that the lower reactivity of benziodoxole-based reagents is an obstacle for their use as oxidative functionalization reagents. In the case of highly unstable structures or for the development of catalytic methods, less reactive reagents are desirable, however. Despite promising preliminary results mostly for heteroatom transfer, the number of benziodoxole-based reagents used in functionalization reactions other than simple oxidations constitutes only a fraction of the reported structures and most of them are based on the λ^3 iodine benziodoxolone structure (Figure 1). Whereas the formation of C-C bond using non-cyclic iodonium reagents has been very successful in the last decades,[6c] it is only in 2006 that Togni and co-workers reported the first use of benziodoxole-derived reagents **7** and **11** for CF_3 transfer.[7]

In 2009, our group introduced ethynylbenziodoxolone (EBX) reagents **8** for acetylene transfer reactions.[8] In these two recent works, key for success was the cyclic structure of the reagent, revealing for the first time the unique properties of benziodoxol(on)es for C-C bond formation.

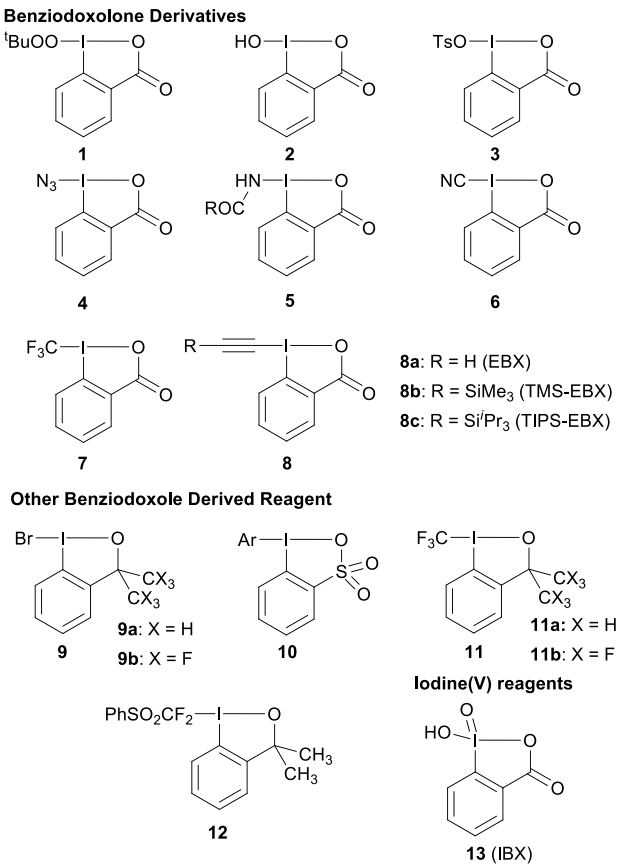


Figure 1: Benziodoxole-based reagents used in atom-transfer reactions.

The purpose of this review is to summarize recent results in the use of benziodoxole-based reagents for atom-transfer

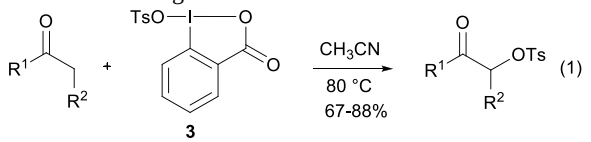
processes. Reactions involving isolated benziodoxole-based reagents will be treated in priority and methods with in situ formation or "pseudo-benziodoxole" structures with only weak intramolecular interactions will not be covered in details. As a review on benziodoxole-derived reagents has appeared in 2005,[3b] focus will be on the results obtained in the last five years. We will begin with heteroatom transfer reactions (Chapter 2) and then continue with reactions involving C-C bond formation (Chapter 3), with a particular focus on CF_3 (Section 3.1) and acetylene transfer (Section 3.2) reactions.

2. C-Heteroatom Bond Formation

A selection of early examples on the use of benziodoxole-derived reagents for heteroatom transfer reactions is presented in Scheme 1.[3b] *Tert*-butylperoxy benziodoxolone **1** was introduced by Ochiai and co-workers (**A**).[9] This reagent was efficient for the oxygenation of ethers, amines, sulfide and phenols. The peroxy group was conserved only in the case of phenols. The ammonium salt **14** of hydroxy benziodoxolone **2** has been used for the epoxidation of α,β-unsaturated ketones (**B**).[10] Tosyloxy benziodoxolone **3** has been applied for the iodotosylation of triple bonds in the presence of iodine (**C**).[11] Interestingly, a chiral pseudo benziodoxolone has also been reported for the asymmetric bis-tosylation of double bonds and the α-tosyloxylation of ketones.[12] Nitrogen-transfer reactions were especially studied by Zhdankin and co-workers.[13] Both the azidation (**D**) and amidation (**E**) of hydrocarbons was possible at high temperature via a radical pathway.

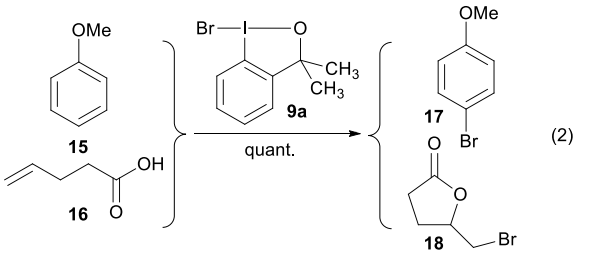
λ^5 iodanes have been mostly used for electron transfer. Nevertheless, IBX (**13**) has also emerged as an efficient reagent for the oxygenation of benzylic C-H bonds,[14] phenols[15] and the oxidative rearrangement of allylic alcohols (**F**).[16] Furthermore, several methods involving in situ formation of the active reagent have also been reported.[3b]

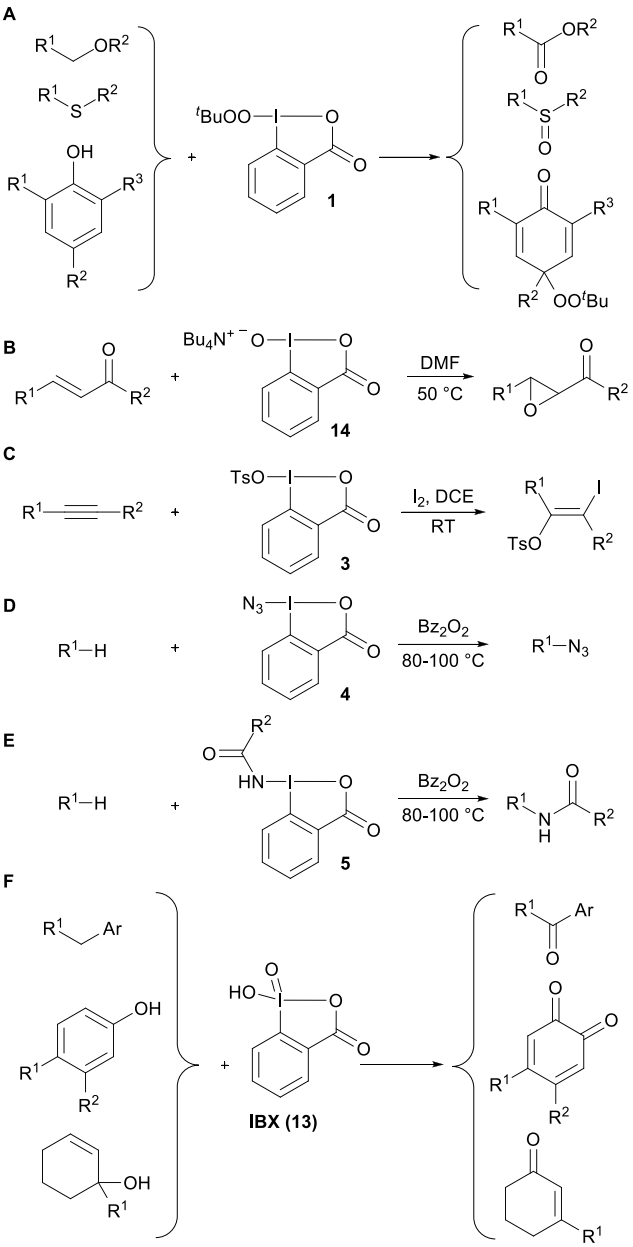
Since 2005, there are surprisingly few reports about the use of λ^3 iodanes for heteroatom transfer reactions. Karade and co-workers studied the tosyloxylation of ketones with reagent **3** in details (eqn 1).[17] Good yields were obtained for aromatic and aliphatic ketones, as well as for ketoesters. Several other examples of tosyloxylation reactions using λ^3 or λ^5-benziodoxole-based compounds were reported, but in these cases the active reagent was formed in situ.[18]



(1)

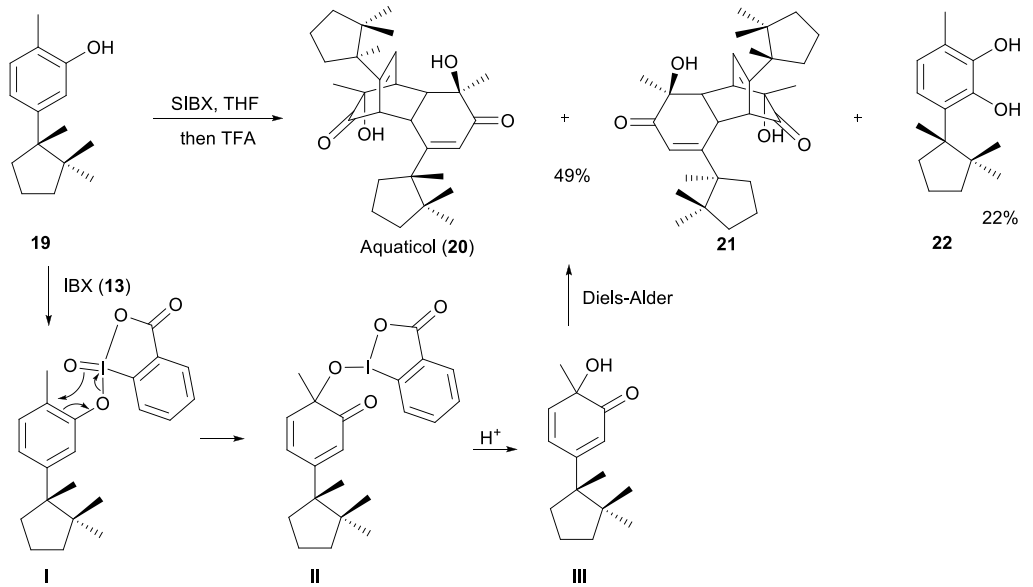
Based on earlier results of Martin and Amey,[19] Braddock and co-workers improved the synthesis of bromo benziodoxole **9a**.[20] They demonstrated that **9a** was an efficient source of bromonium ion for the bromination of anisole (**15**) and the bromolactonization of 4-pentenoic acid (**16**) (eqn 2).





Scheme 1: Selected examples of heteroatom-transfer reactions before 2005.

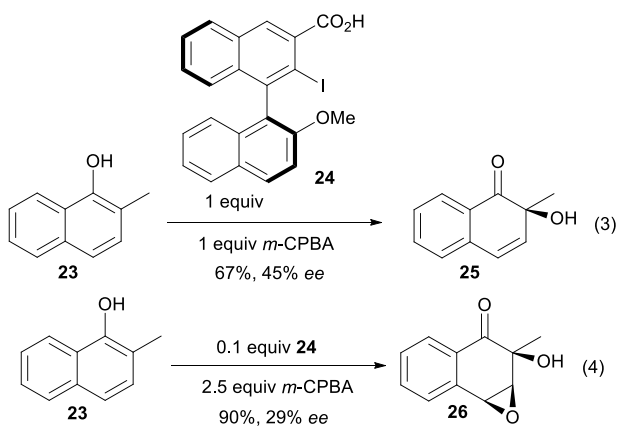
The use of IBX (**13**) for oxygen-transfer and oxidation of phenol has been further investigated.[4b,21] In particular, Quideau and co-workers used SIBX (a stabilized formulation of IBX (**13**))[22] in 2007 in a biomimetic synthesis of aquaticol (**20**) (Scheme 2).[21a]



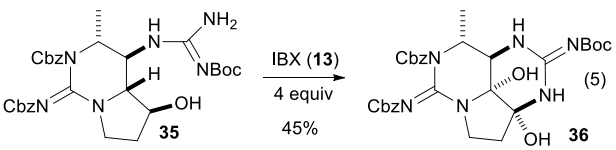
Scheme 2: Dearomatization-cycloaddition of phenols for the synthesis of aquaticol (**20**)

The treatment of (-)-hydroxycuparene (**19**) with SIBX led to oxidation via intermediates **I** and **II**. Due to the presence of the methyl group, further oxidation to the quinone was not possible, and a very reactive diene **III** was obtained, which dimerized via a Diels-Alder cycloaddition. The desired natural product **20** was obtained in 49% yield as a 1:1 mixture with diastereoisomer **21**. The main side product observed in the reaction was diol **22** resulting from the lack of regioselectivity in the oxidation step. A similar oxidative dimerization had been proposed for the biosynthesis of aquaticol (**20**).

In 2009, an important breakthrough was reported by Quideau and co-workers, who achieved asymmetric induction using a *in situ* generated chiral benziodoxolone reagent (eqn 3).[21e] When the reaction was run with 2-methyl naphthol (**23**), the oxidation product **25** was more stable, and dimerization did not occur. Interestingly, epoxy alcohol **26** was obtained in excellent yield when the reaction was run with a catalytic amount of iodide **24** and an excess of *m*-CPBA (eqn 4). Both a iodine (III) or an iodine (V) mechanisms were proposed for this reaction.[21e] In 2009, a similar approach based on an oxazolidinone pseudo-benziodoxole reagent has also been reported by Birman and co-workers.[23] These exciting preliminary results set the bases for further catalytic asymmetric reactions based on chiral benziodoxole-derived reagents.

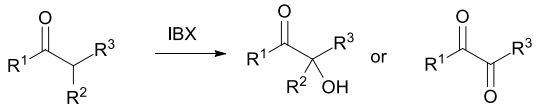


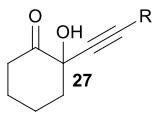
Several examples of the oxygenation of aliphatic C-H bonds using IBX (**13**) have also appeared since 2005.[24] In particular, Kirsch and co-workers studied the hydroxylation of acidic C-H bonds α to carbonyl groups.[24a-b] If a second activating group such as an alkyne or an ester was present, hydroxylation became favored over the oxidation to the conjugated system usually observed with IBX (**13**) (Table 1). Methyne groups were oxidized to the corresponding alcohols, whereas methylenes gave the fully oxidized carbonyls. Another example of α-hydroxylation of a ketone using IBX (**13**) was reported by Nagasawa and co-workers in the total synthesis of saxitoxin (eqn 5).[24c] In this case, the reaction was discovered serendipitously when attempting the oxidation of alcohol **35**. Hydroxylation happened immediately after oxidation of the alcohol to the ketone.



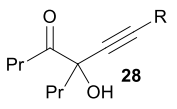
Other examples of the use of IBX for oxygen-transfer reactions include benzylic oxidation,[25] oxidation of oximes,[26] and an interesting oxidative rearrangement of homo-propargylic alcohols to give *Z*-enediones (Scheme 3).[27] This reaction was proposed to occur via oxidation to the corresponding ketone and α-hydroxylation, followed by a formal sigmatropic rearrangement to give the *Z*-enedione after release of hydroxy benziodoxolone **2**. The delivery of the proton to the less hindered face of allene intermediate **III** led selectively to the *Z* product.

Table 1: Selected examples of the α-hydroxylation of carbonyls

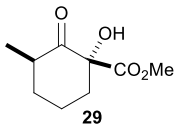




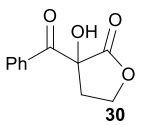
27a: R = Ph, 84%
27b: R = thienyl, 78%
27c: R = $(CH_2)_3OTHP$, 81%



28a: R = Ph, 77%
28b: R = TMS, 74%



78%



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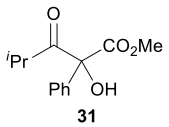

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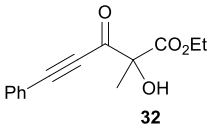

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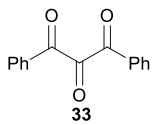

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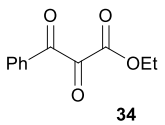

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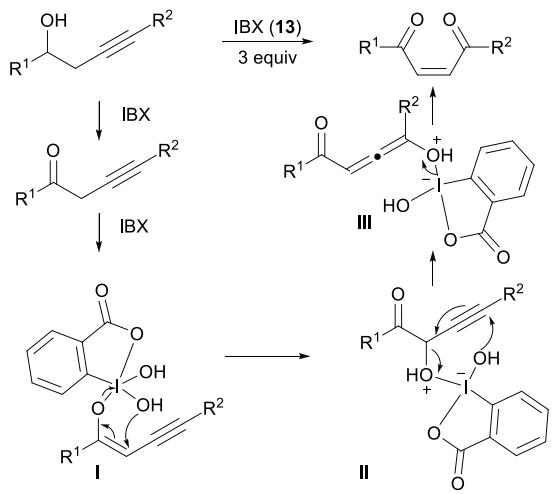
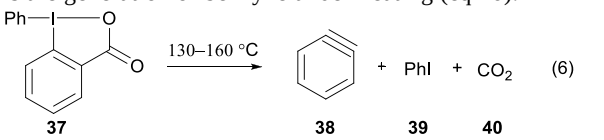


Scheme 3: Oxidative rearrangement of homopropargylic alcohols using IBX (**13**).

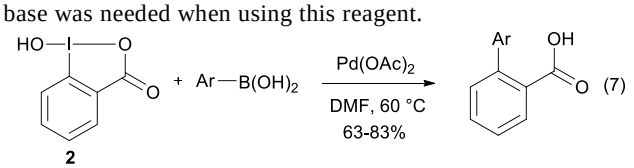
3. C-C Bond Formation

Benziodoxole-based reagents have been much less investigated for C-C bond formation than non-cyclic hypervalent iodine salts. In particular, important progress in direct C-H functionalization reactions has been achieved using aryliodonium salts.[6] A classical use of phenyl benziodoxolone **37** is the generation of benzyne under heating (eqn 6).[28]



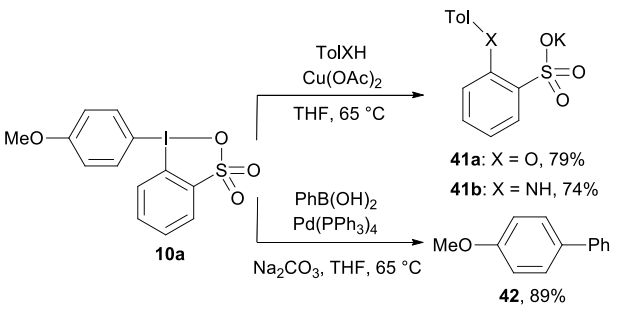
(6)

The use of hydroxy benziodoxolone **2** in Suzuki coupling has also been shortly examined (eqn 7).[29] Interestingly, no extra base was needed when using this reagent.



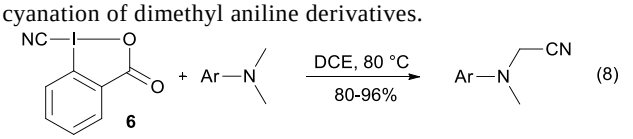
(7)

Preliminary results on the metal-mediated reactivity of the sulfur-analogous **10a** of aryl benziodoxolones have been reported by Justik and co-workers (Scheme 4).[30] The Cu-mediated reaction with oxygen or nitrogen nucleophiles led to the transfer of the sulfate-substituted aromatic ring, whereas the Pd-catalyzed reaction led to the formation of the biaryl product **42** incorporating the more electron-rich anisole ring. To the best of our knowledge, the reactivity of aryl benziodoxolones in classical cross-coupling reactions or direct C-H functionalization reactions has never been studied in details.



Scheme 4: Divergent reactivity of reagent **10a**.

The synthesis and use of cyano benziodoxolone **6** has been reported by Zhdankin and co-workers (eqn 8).[31] A radical-like behaviour was observed at high temperature, allowing the cyanation of dimethyl aniline derivatives.



(8)

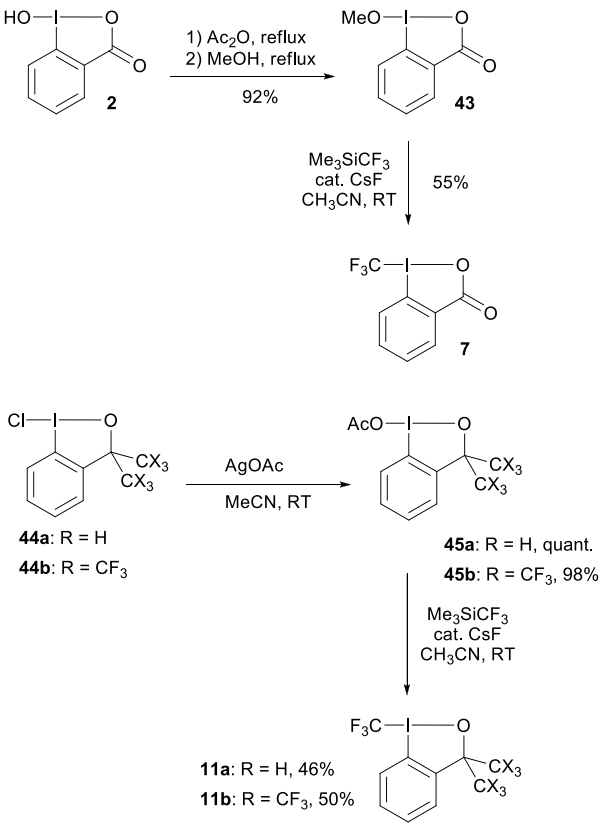
In fact, the rare and limited examples of cyano or aryl transfer using benziodoxole-derived reagents stand in contrast with the impressive results obtained with non-cyclic iodonium salts.[6] However, this situation is completely different when we consider CF_3-transfer reactions or direct alkynylations of heterocycles: for both reactions, the use of benziodoxole-derived reagents was essential for success. These two transformations will now be discussed in details.

3.1 CF_2X-Transfer

The introduction of fluorinated alkanes into organic compounds is an important field of research, due to the utility of these functional groups in medicinal chemistry.[32] In particular, electrophilic sources of perfluoroalkyls are rare.[33] Consequently, the discovery and development of electrophilic CF_2X-benziodoxol(on)e reagents constituted an important progress in this area.

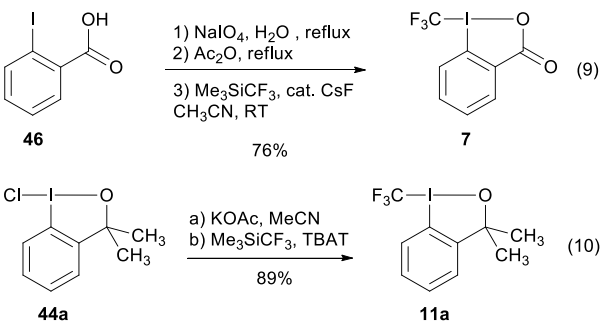
3.1.1 Trifluoromethylation

Togni and co-workers reported the first synthesis of trifluoromethyl benziodoxolone **7** and benziodoxole **11** in 2006 (Scheme 5).[34] The corresponding non-cyclic reagents were not stable and could not be isolated. The synthesis of both reagents involved formal substitution with nucleophilic CF_3 (generated in situ from Me_3SiCF_3) on activated benziodoxol(on)es **43** and **45**. This first generation synthesis gave access to reagents **7** and **11** in respectively three and five steps from 2-iodobenzoic acid (**46**).

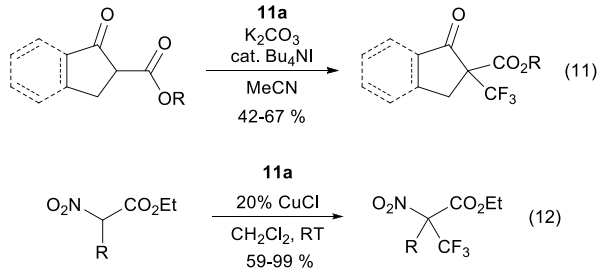


Scheme 5: First generation synthesis of **7** and **11**.

More practical syntheses were reported later. Benziodoxolone **7** was accessed in 76% yield over three steps from 2-iodo benzoic acid (**46**) (eqn 9).[35] An improved one pot synthesis of **11a** starting from benziodoxole **44a** was also developed, affording the desired product **11a** in 89% yield (eqn 10).[36]

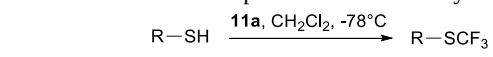


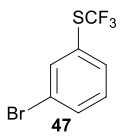
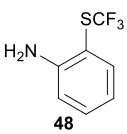
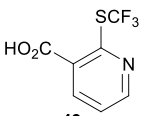
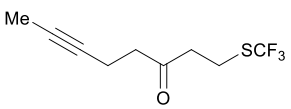
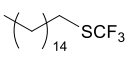
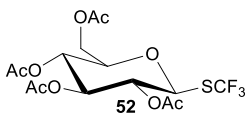
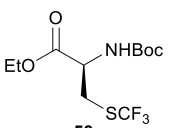
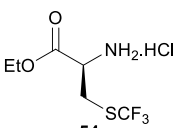
The use of reagent **11a** was first examined for the introduction of CF_3 group onto cyclic β-ketoesters under phase transfer conditions (eqn 11).[34,36] The reaction is also efficient without phase transfer catalyst, but more side reactions were observed. The reaction could be extended to α-nitro esters using CuCl as catalyst (eqn 12).[36] An important advantage of benziodoxole **11a** is the generation of the corresponding alcohol during the reaction, which can be recycled for the synthesis of **11a**.



Trifluoromethylation of thiols using reagent **11a** lead to a convenient access to the SCF_3 functionality (Table 2).[36] Both aromatic and aliphatic thiols were used successfully. The reaction was carried out at -78°C to avoid disulfide formation. A high tolerance towards functional groups was observed, including highly functionalized substrates such as thiosugars and cysteine. This method was further extended to the selective trifluoromethylation of cysteine in peptides using MeOH and water as solvent.[37]

Table 2: Selected examples of trifluoromethylation of thiols.

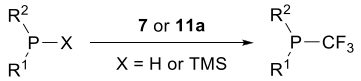


 **47**	82%	 **48**	82%
 **49**	95%	 **50**	53%
 **51**	51%	 **52**	90%
 **53**	82%	 **54**	99%

Trifluoromethylation of both secondary and primary phosphines was also investigated (Table 3).[38] Both benziodoxolone **7** and benziodoxole **11a** were efficient in this process, and **11a** was more reactive. Aromatic and aliphatic phosphines could be used. Steric hindrance on the phosphine was detrimental for the reaction with both **7** and **11a**. Interestingly, deprotonated phosphines ($MPPh_2$, M=Li or K) only afforded traces of product. This observation led the authors to exclude phosphides as intermediates in the reaction. When Cy_2PH was reacted with **7**, the formation of $CyP(CF_3)_2$

and $CyP(CF_3)H$ in trace amounts was observed in addition to the major product Cy_2PCF_3. The attack of CF_3-radical on Cy_2PH was proposed to lead to C-P homolytic cleavage in addition to C-H cleavage. Based on these results, the authors proposed a radical pathway for the trifluoromethylation of phosphines.

Table 3: Selected examples of trifluoromethylation of phosphines.



Substrate	Conditions	Product	Yield[a]
Ph_2PH (**55**)	**7**, RT	$Ph_2P(CF_3)$ (**56**)	78
Ph_2PH (**55**)	**11a**, -78°C to RT	$Ph_2P(CF_3)$ (**56**)	74
Ph_2PSiMe_3 (**57**)	**7**, RT	$Ph_2P(CF_3)$ (**56**)	92[b]
Ph_2PSiMe_3 (**57**)	**11a**, -78°C to RT	$Ph_2P(CF_3)$ (**56**)	69
$PhPH_2$ (**58**)	**7,** RT	$PhPH(CF_3)$ (**59**)	84[b]
$(o\text{-Tol})_2PH$ (**60**)	**7**, RT	$(o\text{-Tol})_2P(CF_3)$ (**61**)	48
$(o\text{-Tol})_2PH$ (**60**)	**11a**, -78°C to RT	$(o\text{-Tol})_2P(CF_3)$ (**61**)	50

[a] Isolated yield. [b] Conversion based on ^{19}F NMR with $PhCF_3$ as internal reference.

Togni and co-workers applied the developed methodology to the synthesis of a P-bis(trifluoromethyl) derivative **62** (Figure 2) of BINAP using reagent **11a**.[39] The addition of DBU was beneficial for the double trifluoromethylation. Unfortunately, ferrocene-derived ligands could not be functionalized, as they were too sensitive to oxidation.

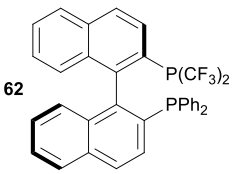
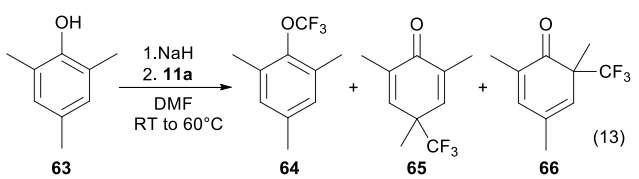


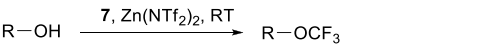
Figure 2: Bis-trifluoromethyl-BINAP **62**.

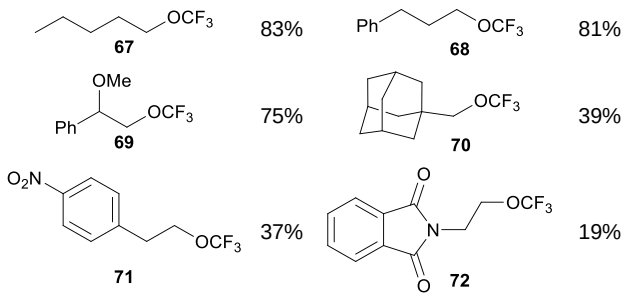
The trifluoromethylation of 2,4,6-trimethylphenol did not only afford the expected product **64**, but also the dearomatized products **65** and **66** along with other minor side products (eqn 13).[40] Unfortunately, it was not possible to optimize the selectivity of the reaction. Two type of mechanisms have been proposed to explain this result. The phenolate formed from **63** could first form a charge-transfer complex with **11a**, which then underwent single-electron transfer (SET). Radical recombination led then to the observed products. The second possible mechanism involved ligand exchange of benzoate with phenolate on I. CF_3 could then be released and attack the phenolate ring. Unfortunately, mechanism investigation did not allow to distinguish between these pathways.



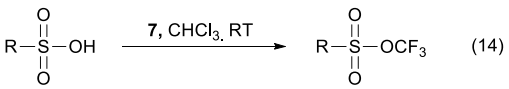
In order to extend the scope of trifluoromethylation reactions, Togni and co-workers examined the Lewis and Brønsted acid activation of benziodoxol(on)es more in details. The development of the trifluoromethylation of aliphatic alcohols catalyzed by zinc (II) salt resulted from these investigations (Table 4).[40] The zinc salts were used in stoichiometric amount compared to **7** together with an excess of alcohol. Catalytic amounts of zinc salts could be used, but they afforded lower yields. Togni proposed as a first step the ring opening of **7** with zinc salts to form complex **I** which was detected by ESI-MS (Scheme 6). The authors then proposed either a nucleophilic attack of ROH on **I**, followed by reductive elimination or a direct nucleophilic substitution to form complex **III**. Complex **I** is then regenerated by exchanging 2-iodobenzoic acid (**46**) for **7**. Interestingly, the authors showed that the reaction can also be catalyzed by a Brønsted acid (Tf_2NH) with lower efficiency.

Table 4: Selected examples of trifluoromethylations of alcohols.

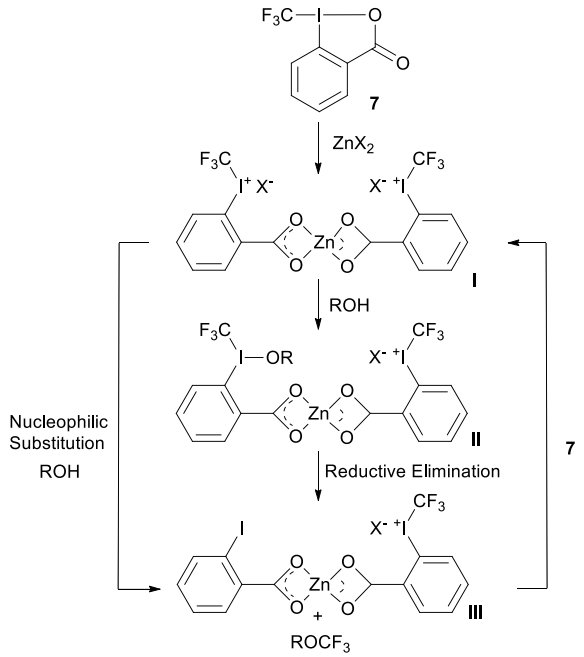




The Brønsted acid activation of **7** was further used by Togni for the trifluoromethylation of sulfonic acids (eqn 14).[41] Strong acids were required and the use of the toluenesulfonate salts failed to give the product. Interestingly, the Hammett plot showed that the substituent on the sulfonic acid had only a minor effect on the reaction rate. In addition, the tetrahydrofuran ring was opened and trifluoromethylethers were formed when benziodoxolone **7** was used in presence of Lewis or Brønsted acids in THF.[42]

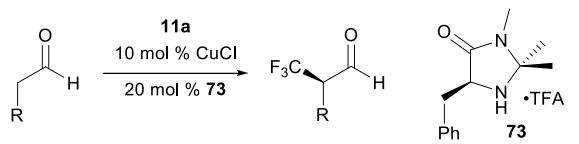


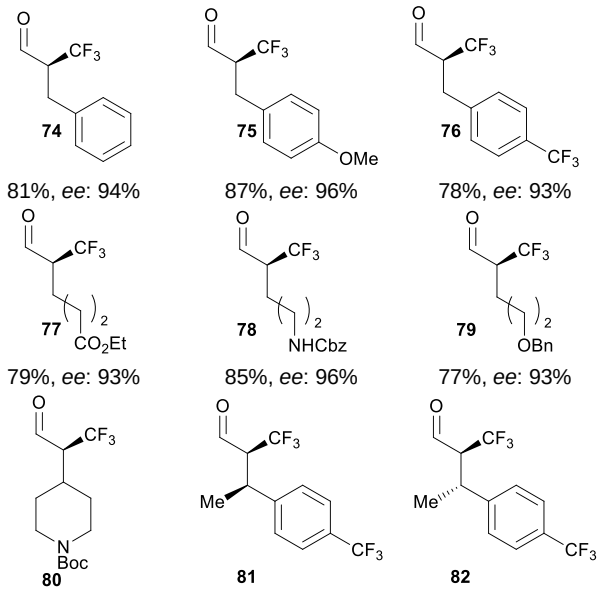
Mac Millan and co-workers recently reported the combination of organo- and Lewis acid- catalysis for the asymmetric α-trifluoromethylation of aldehydes using hypervalent iodine reagent **11a** (Table 5).[43] The use of Lewis acid was crucial to obtain the product in useful yield. A range of Lewis acids were efficient in the reaction. CuCl gave the best yield and enantioselectivity. The mechanism proposed included a Lewis acid mediated opening of the benziodoxole reagent **11a** (Scheme 7). The chiral enamine **I** formed from the aldehyde and imidazolidinone catalyst **73** then attacked the iodine atom. Reductive elimination finally led to C-C bond formation.

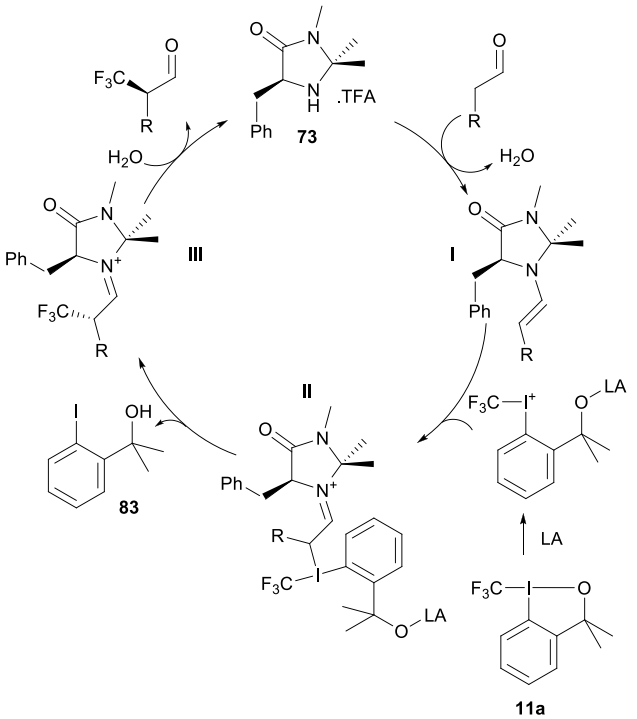


Scheme 6: Proposed mechanism for the trifluoromethylation of alcohols.

Table 5: Selected examples of enantioselective α-trifluoromethylation of aldehydes.





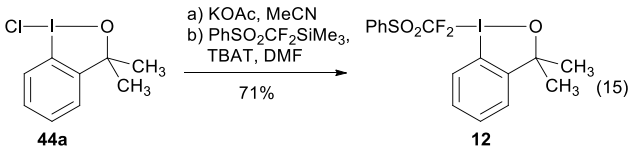


Scheme 7: Proposed mechanism for the organocatalytic trifluoromethylation of aldehydes.

In contrast to arylation reactions,[6] there are currently no successful examples of CF_3-transfer using Pd or Cu catalysts and hypervalent iodine reagents.[44]

3.1.2. (Phenylsulfonyl)difluoromethylation

Hu and coworkers reported the first synthesis of benziodoxole phenylsulfonyl difluoromethyl **12** using conditions analogous to Togni's procedure (eqn 15).[45] The reaction was used for the (phenylsulfonyl) difluoromethylation of thiols (Table 6). High yields were obtained for both aryl and alkyl thiols. The obtained products were subjected to reductive desulfonylation to form the corresponding difluoromethylated sulfides.



3.2 Acetylene Transfer

The chemistry of acetylenes has been intensively used in organic chemistry, material sciences and chemical biology.[46] Classical methods for acetylene-transfer reactions usually involve the formation of acetylide anions. In contrast, the reverse approach using electrophilic alkynyl synthons has been much less developed.[47] In this context, the use of alkynyl iodonium salts has been especially successful.[47d-e] Nevertheless, it had been limited to stoichiometric reactions with salts or organometallic reagents. We recently discovered that silyl-substituted ethynylbenziodoxolones (EBX (**8**)) are excellent acetylene transfer reagents, both in metal-free and metal-catalyzed reactions. These reagents are easily obtained in two steps from 2-iodo benzoic acid (**46**) on a 5-30 g scale (eqn 16).[48]

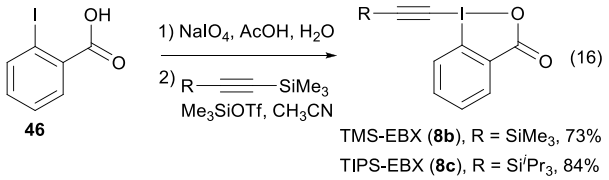
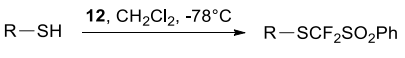
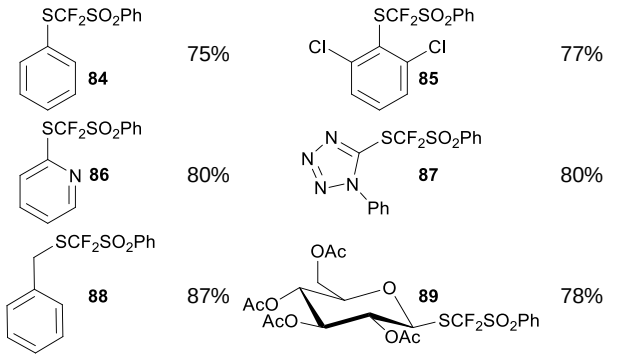


Table 6: Selected examples of (phenylsulfonyl)-difluoromethylation of thiols.

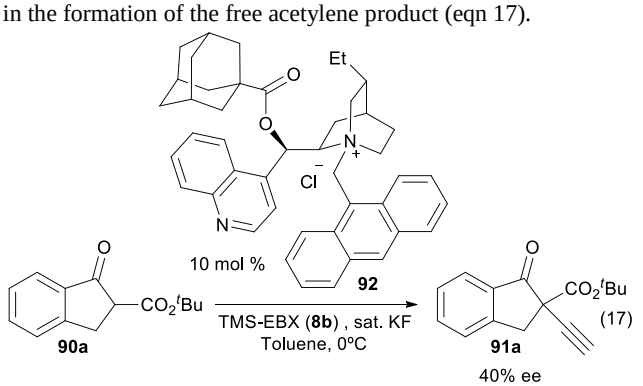




3.2.1 Alkynylation of Acidic C-H Bonds

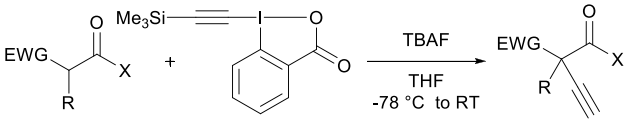
The alkynylation of tertiary acidic C-H bonds of α-substituted keto esters leads to the formation of all-carbon quaternary centers, which cannot be easily synthesized using classical acetylene chemistry. Prior to our work, this reaction was performed using alkynyliodonium salts in a two-steps procedure involving deprotonation with a strong base. Only a limited scope of substrates had been studied.[49]

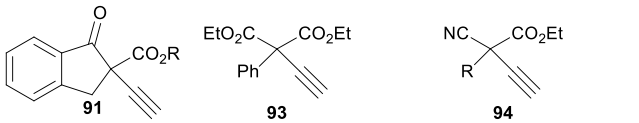
With the goal of developing an asymmetric alkynylation method, we initially examined phase transfer conditions developed by Jørgensen and co-workers[50] with non-cyclic alkynyliodonium salts.[51] However, low yields and no enantioselectivity were obtained in this case. In contrast, the use of TMS-EBX (**8b**) with KF as a base led to significant asymmetric induction (40% of *ee*) in the formation of the free acetylene product (eqn 17).



Unfortunately, further optimization of the enantioselectivity could not be achieved using this system, and we decided to investigate the racemic method more in details. Best yields were finally obtained using TBAF as a fluoride source in THF.[51] Under these conditions, efficient acetylene transfer was observed, and full conversion could be obtained even at -78 °C (Table 7).

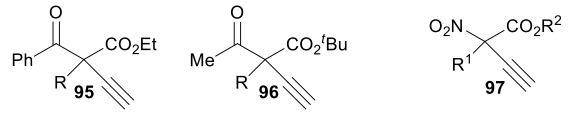
Table 7: Scope of the alkynylation of activated carbonyls.





91a: R = ^{t}Bu, 94% **93**: 95% **94a**: R = Bn, 90%

91b: R = Me, 98% **94b**: R = 4-Br-Bn, 75%



95a: R = Me, 83% **96a**: R = Me, 90% **97a**: R^1 = Me, R^2 = Et, 75%

95b: R = Bn, 93% **96b**: R = Et, 63% **97b**: R^1 = Bn, R^2 = Et, 93%

95c: R = allyl, 88% **96c**: R = Bn, 77% **97c**: R^1 = Ph, R^2 = Me, 80%

97d: R^1 = Ph, R^2 = ^{t}Bu, 85%

Cyclic keto esters and phenyl-diethylmalonate gave excellent yields in the alkynylation reaction. In contrast to cyclic substrates, linear keto-esters had never been investigated in the past. For these more challenging substrates, the desired acetylene products were obtained in 63-93% yield. Finally, the reaction could be extended to cyano and nitro esters, which are new classes of substrates for ethynylation reactions. When the reaction was followed by ^{1}H and ^{13}C NMR, a fast deprotection of TMS-EBX (**8b**) was observed and EBX (**8a**) was obtained. EBX (**8a**) could be characterized at low temperature, but it decomposed when the temperature was risen over -20 °C. The use of ^{13}C-labeled TIPS-EBX (**8c**) as reagent allowed us to observe a 1,2 shift of hydrogen in the product. This result indicated that a mechanism involving a conjugate addition to the alkyne, followed by α-elimination and 1,2- hydride shift via a carbene intermediate was probable. A similar mechanism had been proposed by Ochiai and co-workers in the case of alkynyliodonium salts.[49a]

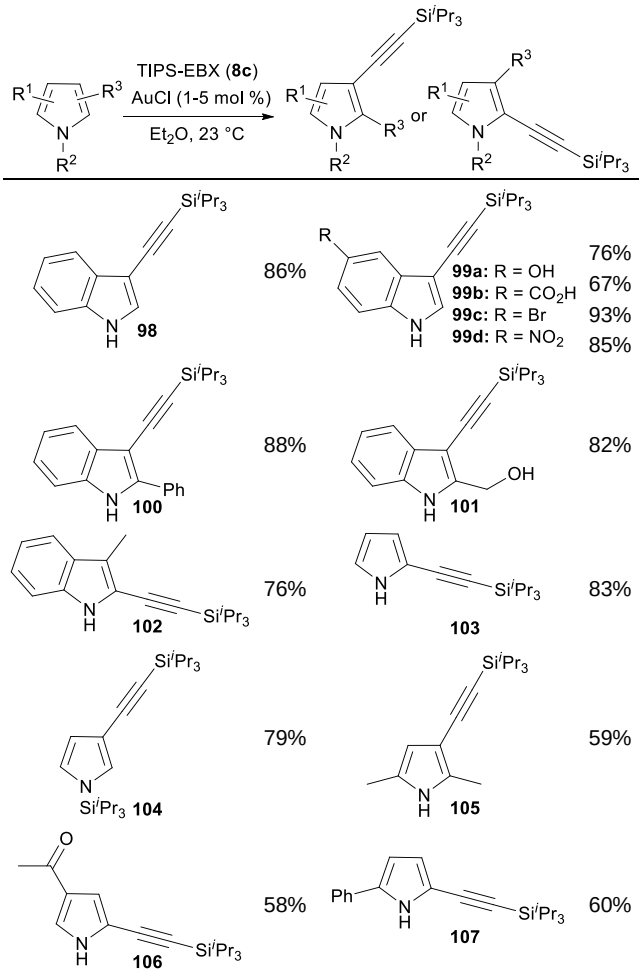
3.2.2 C-H Alkynylation of Heterocycles

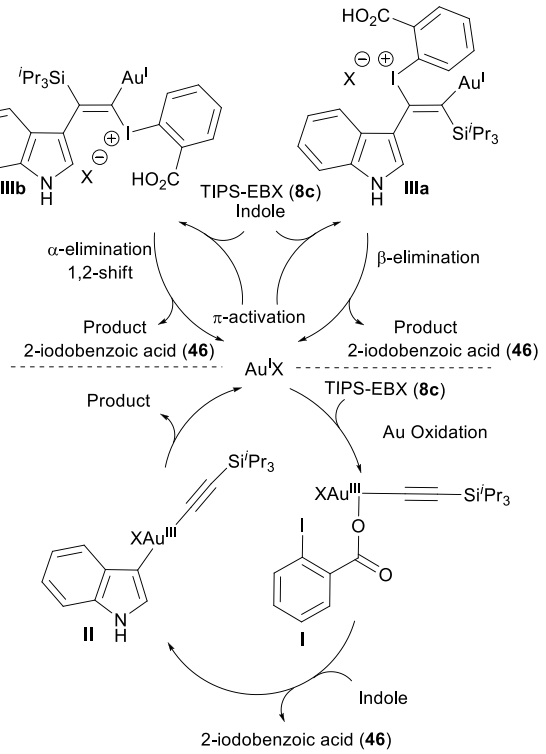
In contrast to the direct arylation and vinylation of heterocycles,[52] direct alkynylation has been only scarcely investigated up to 2009.[53] The field has attracted more interest since then and several direct alkynylations of heterocycles have been reported.[47f,54] In 2009, we reported the use of TIPS-EBX (**8c**) in the gold-catalyzed direct alkynylation of indoles and pyrroles (Table 8).[55] The reaction was run at room temperature under air and did not require dry solvents. Moreover, the 2-iodobenzoic acid (**46**) formed during the alkynylation reaction could be easily recovered via basic work-up and reused for the synthesis of TIPS-EBX (**8c**). The reaction was in general regioselective for the more electron-rich unsubstituted position of the heterocycles. The method was highly tolerant towards functionalities. Even highly reactive groups such as carboxylic acids, phenols or alcohols led to products in high yields. Importantly, the method was also orthogonal to classical cross-coupling, as halogen

substituents were tolerated. The use of 2-substituted indoles was successful except for electron-withdrawing groups. In addition, pyrroles could also be alkynylated despite their high sensitivity. In case of pyrroles, the regioselectivity of the reaction could be inverted by the use of the bulky TIPS protecting group on the nitrogen to give 3-substituted pyrrole **104**. Interestingly, the corresponding alkynyl iodonium salts did not afford any products, demonstrating the unique properties of the benziodoxolone structure.

At least two mechanisms could be envisaged, in which Au acts either as a redox active metal or via π-activation (Scheme 8). The oxidative mechanism would include as a first step an oxidative addition of Au^{I} on TIPS-EBX (**8c**) to form Au^{III} complex **I**. A ligand exchange with indole followed by reductive elimination would then give the alkynylation product. The π-activation mechanism would go through a gold catalyzed attack of indole on the triple bond of TIPS-EBX (**8c**). Depending on the regioselectivity of this process, either a β-elimination from **IIIa** or a α-elimination/1,2-shift from **IIIb** would lead to the product. A mechanism involving substitution and reductive elimination at iodine appeared less probable at this stage. Unfortunately, preliminary investigations did not allow to distinguish between these pathways.

Table 8: Selected examples of direct alkynylation of indoles and pyrroles.

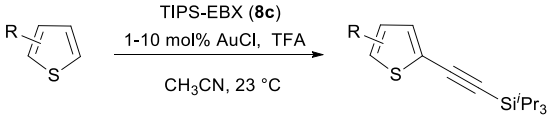


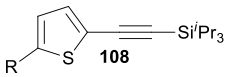


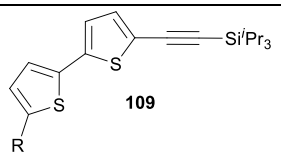
Scheme 8: Proposed mechanisms for the alkynylation of indole.

Both thiophenes and acetylenes are of utmost interest in organic materials. However, there are no methods for the direct alkynylation of thiophenes. The extension of the scope towards these heterocycles was consequently investigated. Unfortunately, previously developed conditions led to low yields and conversions, which is in accordance with the reported lower nucleophilicity of thiophenes. Nevertheless, we were delighted to discover that the addition of TFA (one equivalent compared to TIPS-EBX (**8c**)) gave good yields with a broad range of thiophenes (Table 9).[56] This represented the first cooperative gold-Brønsted acid activation of alkynyl hypervalent iodine reagents. The reaction was tolerant towards a broad range of functional groups, except for electron-withdrawing groups directly attached to thiophene. Bithiophenes, phenylthiophenes and 3,4-ethylenedioxythiophene, which are important in material sciences, could also be alkynylated. Finaly, 3-methylbenzothiophene was also used successfully in the reaction.

Table 9: Selected examples of direct alkynylation of thiophenes.

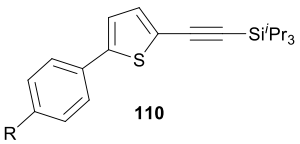




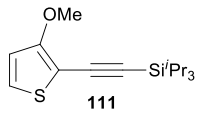


108a: R = C_6H_{13}, 83%
108b: R = H, 73%
108a: R = CH_2NHCbz, 81%

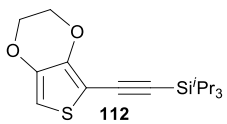
109a: R = C_6H_{13}, 68%
109b: R = Br, 61%



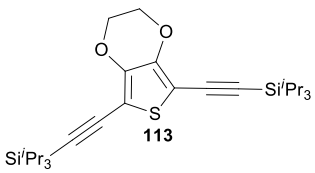
110a: R = H, 70%
110b: R = Br, 67%
110c: R = OMe, 67%



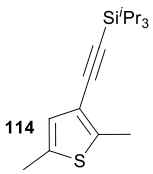
63%



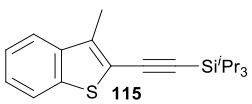
70%



70%



48%



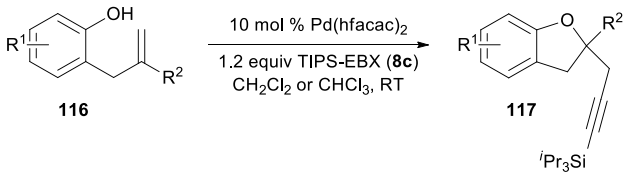
73%

3.2.3 Intramolecular Oxyalkynylation of Olefins

The encouraging results obtained with the alkynyl benziodoxolones motivated us to further explore their applicability in the field of Pd catalysis. In particular, the Wacker cyclization has been known as an effective method to generate O- and N-containing heterocycles starting from non-activated alkenes for nearly forty years.[57] More recently, cascade reactions involving oxidative functionalizations of the key Pd-alkyl intermediate have been developed for C-C, C-X, C-O or C-N bond formation.[58] Several of these processes have been proposed to proceed via a Pd^{IV} intermediate. The oxidative transfer of acetylene had never been realized using this approach, although Canty reported the use of alkynyliodonium salts to generate a Pd^{IV}-acetylene complex.[59] Our group recently described the first example of Pd-catalyzed intramolecular oxyalkynylation of non-activated olefins using TIPS-EBX (**8c**).[60] Pd hexafluoroacetyl acetonate was identified as the best catalyst for this process. TIPS-EBX (**8c**) was required for the reaction. Only very low yields were observed when using alkynyliodonum salts or less hindered silyl group on the acetylene.

Good to very good yields were obtained with a broad range of *o*-allyl phenols (Table 10). Substrates bearing an electron-withdrawing group on the benzene ring afforded the highest yields. On the other hand, electron-donating groups were not tolerated. This could be due to the lower acidity of these substrates or their higher oxidation sensitivity.

Table 10: Scope of the alkynylation of *o*-allylphenols.



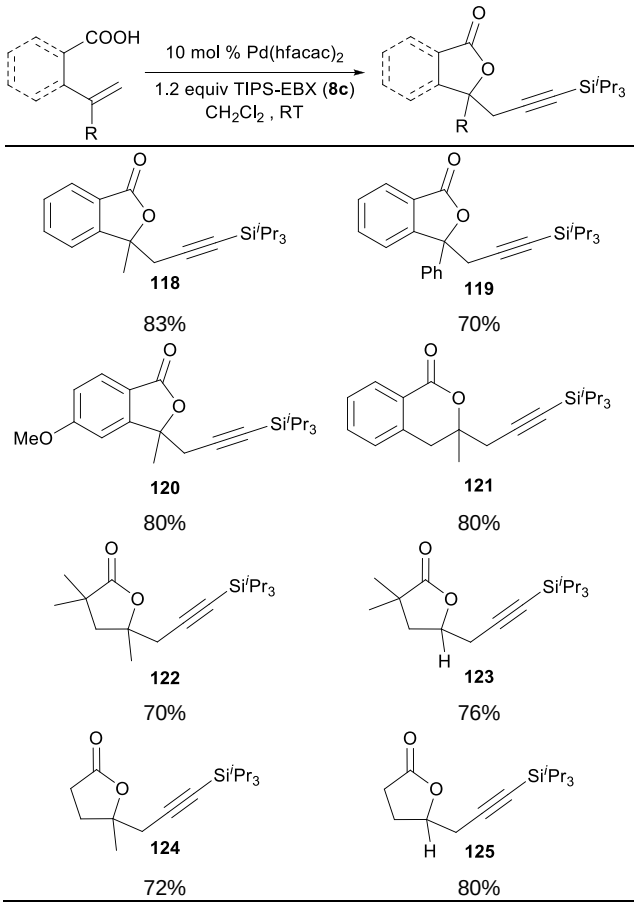
116 **117**

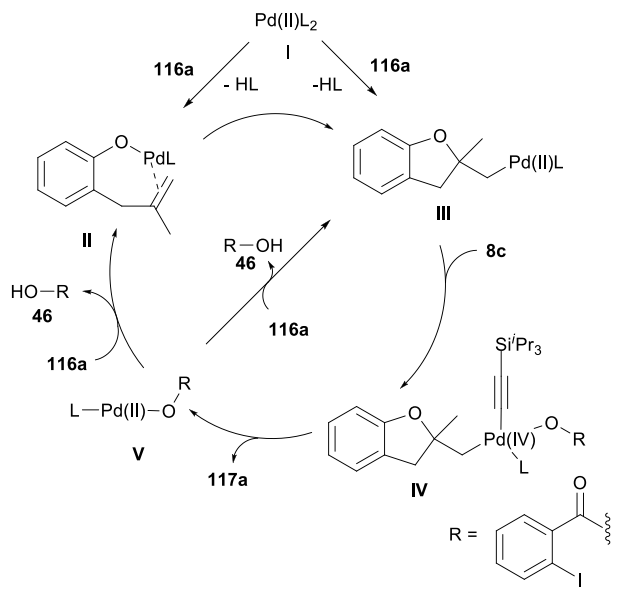
R^1 =	R^2 =	Yield
H (**116a**)	Me (**117a**)	73%
4-Br (**116b**)	Me (**117b**)	68%
4-CN (**116c**)	Me (**117c**)	76%
4-NO_2 (**116d**)	Me (**117d**)	72%
4-MeCO (**116e**)	Me (**117e**)	87%
3-Br (**116f**)	Me (**117f**)	66%
2-Br (**116g**)	Me (**117g**)	52%
H (**116h**)	H (**117h**)	41%

Indeed, it was found that carboxylic acids, which are more acidic and not oxidation sensitive, are good substrates for the reaction (Table 11). Aromatic γ- and δ-lactones could be obtained in good yields. Moreover, it was possible to extend our method to aliphatic carboxylic acids. To our delight, C-C bond formation was faster than β-hydride elimination in the case of 4-pentenoic acids and the alkynylation proceeded in good yield to give lactones **123** and **125**.

The first steps of the catalytic cycle are probably olefin activation and nucleophilic addition to generate Pd^{II} alkyl σ-complex **III** (Scheme 9). These steps could proceed either via direct double bond activation or first via ligand exchange with the phenol to give Pd-alkoxide **II**. Complex **III** would then react with TIPS-EBX (**8c**), to afford Pd^{IV} complex **IV**. Reductive elimination would then occur with release of the product and formation of Pd^{II} complex **V**. In the last step, a ligand exchange is proposed to allow double bond activation.

Table 11: Scope of the alkynylation of carboxylic acids.





Scheme 9: Proposed mechanism for the oxyalkynylation of olefins.

4.Conclusions

In the field of hypervalent iodine chemistry, the use of benziodoxole-derived reagents has been mostly limited to oxidation reactions in the past. Functionalization reactions involving atom transfer from the reagent have been mostly limited to non-cyclic iodinanes. Despite promising results for hetero-atom transfer, it is only very recently that the unique properties of benziodoxole-derived reagents have been used for C-C bond formations, especially for the introduction of fluorinated alkanes and acetylenes. These promising preliminary results open new opportunities for the use of hypervalent iodine reagents in challenging oxidative functionalization reactions. The field is still in its infancy, and further work is required to develop new reactions based on benziodoxole-derived reagents. Particularly challenging will be the development of asymmetric methods or the use of processes catalytic in iodine with in situ formation of the active reagent.

5. Addendum (July 26, 2010)

During the reviewing process of this manuscript, a new overview article on electrophilic trifluoromethylation methods including hypervalent iodine reagents has appeared.[61] Togni and co-workers have published a structural study of several new benziodoxole-based reagents.[62] Furthermore, they have reported a detailed study on the trifluoromethylation of arenes.[63] A broad scope of aromatic compounds was tested, including pyrroles, indoles, imidazoles, pyridines, phenols, anisoles and anilines. A positive effect of additives such as Zn salts or tris(trimethylsilyl)silyl chloride was observed. This work constitutes the broadest study of the electrophilic trifluoromethylation of arenes so far and demonstrated further the high potential of benziodoxole-based reagents. Nevertheless, the yields were highly dependent on the substrate structure, and further improvements will be needed to develop a truely general trifluoromethylation method for arenes.

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Notes and references

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