2. Alkynylation with Hypervalent Iodine Reagents

Jerome Waser, jerome.waser@epfl.ch, Laboratory of Catalysis and Organic Synthesis, EPFL SB ISIC LCSO, BCH 4306, 1015 Lausanne

Abstract

Alkynes are among the most versatile functional groups in organic synthesis. They are also frequently used in chemical biology and materials science. Whereas alkynes are traditionally added as nucleophiles into organic molecules, hypervalent iodine reagents offer a unique opportunity for the development of electrophilic alkyne synthons. Since 1985, alkynyliodonium salts have been intensively used for the alkynylation of nucleophiles, in particular soft carbon nucleophiles and heteroatoms. They have made especially a strong impact in the synthesis of highly useful ynamides. Nevertheless, their use has been limited by their instability. Since 2009, more stable ethynylbenziodoxol(on)e (EBX) reagents have been discovered as superior electrophilic alkyne synthons in many transformations. They can be used for the alkynylation of acidic C–H bonds with bases or aromatic C–H bonds using transition metal catalysts. They were also highly successful for the functionalization of radicals or transition metal-catalyzed domino processes. Finally, they allowed the alkynylation of a further range of heteroatom nucleophiles, especially thiols, under exceptionally mild conditions. With these recent discoveries, hypervalent iodine reagents have definitively demonstrated their utility for the efficient synthesis of alkynes based on non-classical disconnections.

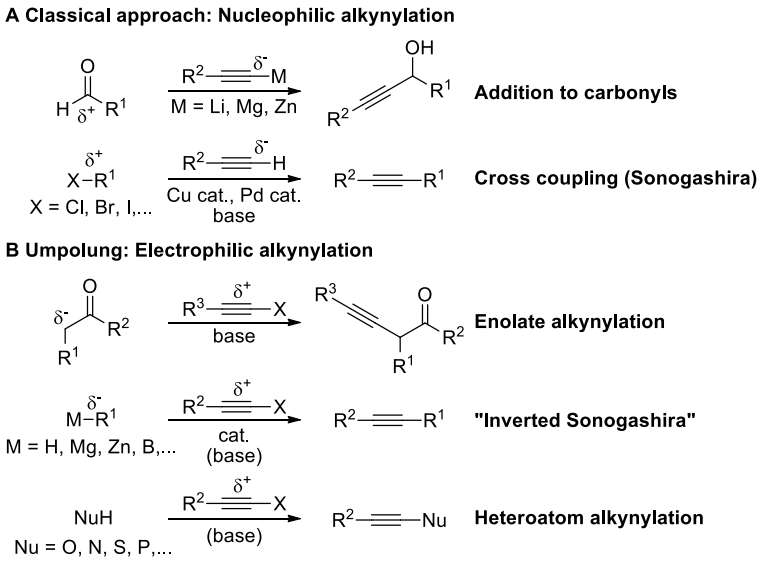
Keywords: Alkynes, Alkynyliodonium salts, Ethynylbenziodoxol(on)e (EBX) reagents.

Content

2.1 Introduction: the Umpolung of Alkynes

Alkynes are among the most versatile functional groups in organic chemistry [1]. This comes from the fact that the triple bond is stable under many conditions, yet can be easily transformed into a broad range of useful functional groups. In the last decades, alkynes have also found numerous applications in neighboring fields, such as chemical biology and materials science. For example, the [3+2] cycloaddition between alkynes and azides is now broadly applied in these fields, as it is bio-orthogonal, easy to perform and does not generate any waste (the paramount of a 'Click' reaction [2-3]). As linear π-systems, alkynes have also found broad applications in organic electronics or dyes for photovoltaics. To allow continued progress in synthetic and applied fields, new flexible and efficient methods to synthesize alkynes are urgently needed.

Most of the methods to access alkynes by transfer of a triple bond are based on nucleophilic alkynylation (Scheme 2.1, **A**). This is not surprising, as the terminal C–H bond of alkynes is highly acidic due to the sp-hybridization, and the formation of acetylide anions is consequently facile. Methods such as addition of acetylides to carbonyl compounds [4] or the Sonogashira cross coupling [5,6] are now routinely used for the synthesis of alkynes and are highly reliable. In stark contrast, the addition of alkynes onto nucleophiles requires an inversion of their inherent reactivity (an Umpolung, Scheme 2.1, **B**). This approach is more challenging and has been consequently less developed [7-9]. When considering the omnipresence of nucleophiles not only in synthetic organic chemistry, but also in chemical biology and materials science, this is an important shortcoming. Indeed, reactions such as the alkynylation of enolates, the "inverted Sonogashira" coupling of C–H or C–metal bonds or the direct alkynylation of heteroatoms are highly useful processes, which give access to molecular structures outside the reach of classical methods.



Scheme 2.1: Nucleophilic and electrophilic alkynylation.

Due to the high reactivity of the hypervalent bond, hypervalent iodine reagents have been intensively used in organic chemistry [10-15]. Among electrophilic alkynylation reagents, they occupy a central place, as they are ideally suited to allow overcoming the inherent nucleophilicity of alkynes (Figure 2.1). First successes were encountered by the use of arylalkynyliodonium salts [16], for which selective transfer of the alkyne group to nucleophiles was observed. More recently, the stability and selectivity issues often present with alkynyliodonium salts have been overcome by the introduction of more stable cyclic reagents, especially EthynylBenziodoXol(on)es (EBX) [17,18]. Due to their exceptional reactivity, hypervalent iodine reagents are often superior to less reactive reagents such as alkynyl halides [19] or sulfones [20-23]. On the other hand, they are more stable and less toxic than organometallic reagents, such as organolead compounds [24,25].

In this chapter, the use of hypervalent iodine reagents for alkynylation reactions will be covered. The most important results up to the last review in the field [9] will be summarized, followed by a more detailed presentation of the most recent works. The use of alkynyliodonium salts will be described first (Section 2.2) followed by the use of EBX reagents (Section 2.3). Each section will be divided according to the class of alkynylated nucleophile (carbon or heteroatom). The focus will be on reactions using well-defined hypervalent iodine alkynylation reagents.

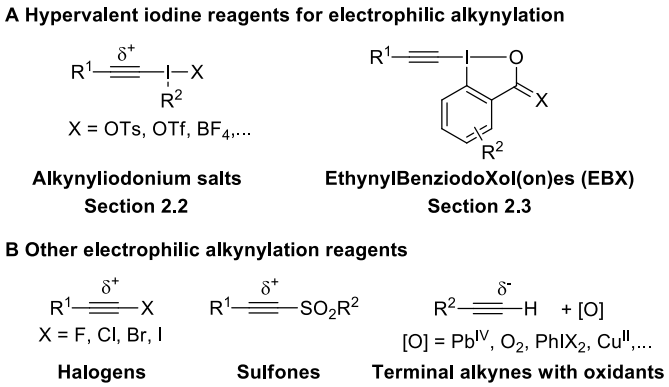
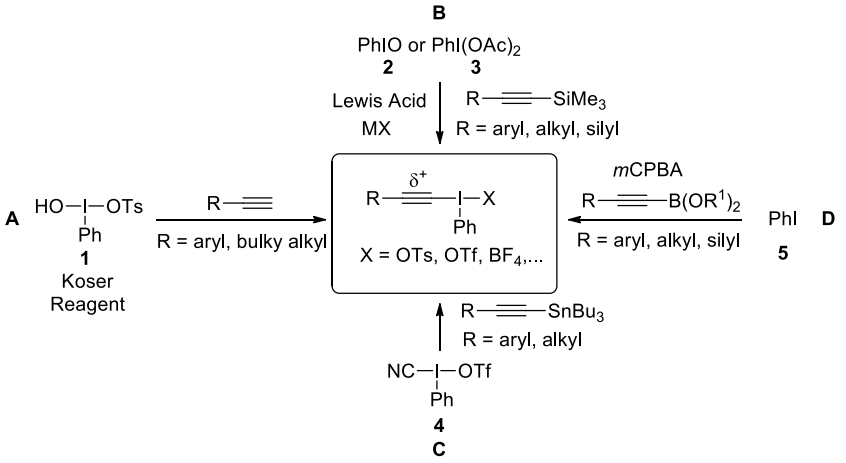


Figure 2.1: Electrophilic alkynylation reagents.

2.2 Alkynylation using Alkynyliodonium Salts

Alkynyliodonium salts are versatile reagents in organic chemistry, and their use goes far beyond alkynylation. For example, they can also be used in the synthesis of vinyliodonium salts, in cyclization reactions via carbene insertion or in cycloaddition reactions [16]. Several methods have been developed for their synthesis from different iodine precursors (Scheme 2.2). Early methods focused on the reaction of terminal alkynes with Koser reagent **1** [26], but this approach had a limited scope, as it worked only with aryl or bulky alkyl group on the alkyne (Scheme 2.2, **A**). More general methods were then developed by the reaction of iodosobenzene **2** with alkynylsilanes in the presence of Lewis acids and metal salts (Scheme 2.2, **B**) [27-29]. As the purity of iodosobenzene **2** can be highly batch dependent, an alternative protocol was developed starting from (diacetoxyiodo)benzene **3** by Kitamura and co-workers [30]. The broadest substrate scope was achieved starting from cyano(phenyl)iodonium triflate **4** by Stang and coworkers, but this approach required the use of more toxic alkynyl stannanes (Scheme 2.2, **C**) [31-32]. Finally, Olofsson and co-workers reported in 2012 a very practical one-pot oxidation-alkynylation protocol starting from iodobenzene **5** and using alkynyl boronic acid esters (Scheme 2.2, **D**) [33]. A limitation of this method is the use of the sometimes unstable and difficult accessible boronic acid esters.



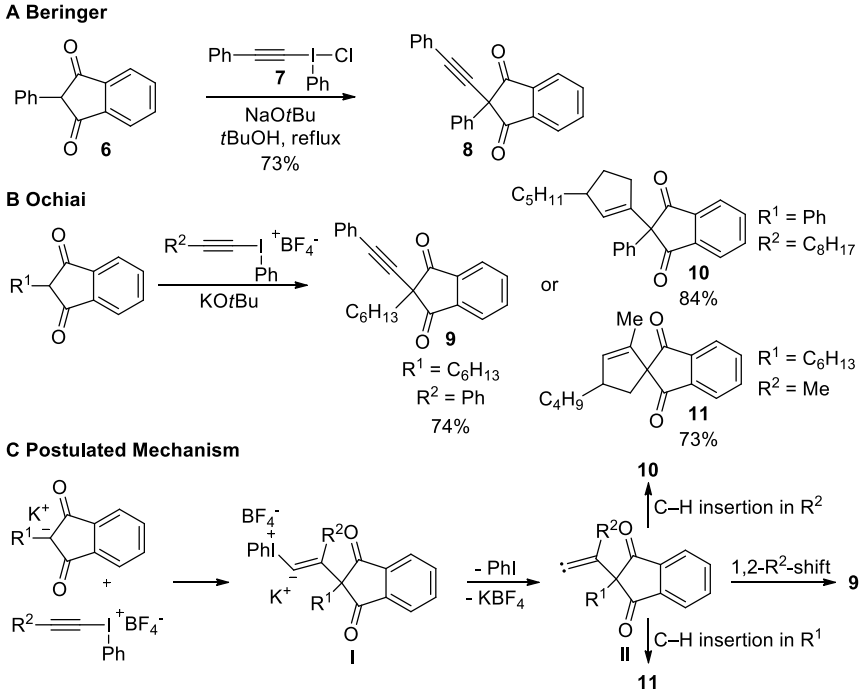
Scheme 2.2: Synthesis of alkynyliodonium salts.

2.2.1 Alkynylation of C-Nucleophiles

2.2.1.1 Alkynylation of Acidic C–H Bonds

The reactivity of alkynyliodonium salts was first discovered in the alkynylation of diketones (Scheme 2.3). In 1965, Beringer and Galton reported the alkynylation of diketone **6** with alkynyl iodonium chloride **7** in 73% yield (Scheme 2.3, **A**) [34]. However, alkynyliodonium chloride **7** is unstable and decomposes to form the corresponding chloroalkyne, which probably precluded more extensive synthetic use of this transformation. In 1986, Ochiai and co-workers reinvestigated this reaction with more stable alkynyliodonium tetrafluoroborate reagents (Scheme 2.3, **B**) [35]. They found that the result was highly dependent on the substituent of the reagent: with a phenyl group, alkyne products such as **9** were obtained, but with aliphatic groups, the formation of cyclopentenes such as **10** or **11** was observed. This result led Ochiai and co-workers to make a first mechanistic proposal for this transformation (Scheme 2.3, **C**). In contrast to many reactions with hypervalent iodine reagents, the initial attack of the nucleophile would not be on the iodine atom, but on the conjugate position of the triple bond. The resulting vinyl anion **I**, which can indeed be trapped by acids to form vinyliodonium salts, would then undergo α-elimination of iodobenzene to give carbene intermediate **II**. At this point, if the adjacent substituent has a strong migrating aptitude, as is the case for a phenyl moiety, a 1,2-shift occurs to give alkyne product **9**. With aliphatic groups, the migration is slow, and C–H insertion in either the substrate or the alkyne substituent is observed to give **10** or **11**. In the case of the alkynylation, the use of fast mi-

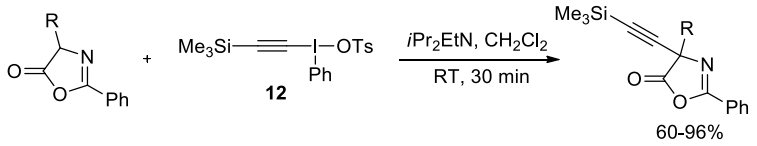
grating silyl or hydrogen substituents is especially relevant, as it gives access to versatile terminal acetylenes as products [36].



Scheme 2.3: Pioneering examples for the alkynylation of diketones and proposed mechanism.

After this seminal work, the alkynylation reaction with alkynyliodonium salts was applied to several classes of substrates, including diketones [36-38], ketoesters [36], malonates [36,39] and aminomalonates [40,41]. The latter class of compounds is especially interesting, as it was also successful in the case of alkyl substituted alkynes. This was probably made possible by an efficient 1,2-shift of the nitrogen heteroatom.

In 2014, Nachtsheim and co-workers reported the alkynylation of azlactones with trimethylsilyl alkynyliodonium salt **12** (Scheme 2.4, [42]). The obtained products were easily transformed into various amino acid derivatives. The reaction was also successful in the case of aliphatic substituted alkynes, although C–H insertion was observed as a minor pathway. Interestingly, the use of EBX reagents lead to exclusive formation of C–H insertion products, indicating that the same intermediate was not formed in both reactions.



Scheme 2.4: Alkynylation of azlactones.

2.2.1.2 Alkynylation of Organometallic Nucleophiles

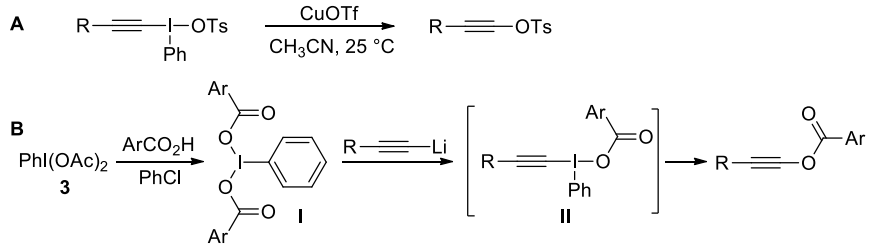
As alkynyliodonium salts decompose in the presence of strong bases, the alkynylation of organolithium or organomagnesium reagents is not possible. On the other hand, organocopper reagents react smoothly with alkynyliodonium tosylates. Through the right choice of the organometallic reagent (organocopper or cuprate), the reaction was successful on sp [43], sp^2 [44], and sp^3 [43,45] centers to give diynes, enynes and aliphatic alkynes as products. Due to their high reactivity, alkynyliodonium salts have also found applications in palladium- or copper-catalyzed alkynylation reactions such as carbonylation [46], Heck coupling [47-48], reactions with alkynes [49] and cross-coupling with organoboron/tin compounds [50]. However, their use in these transformations remains scarce, probably due their somewhat low stability in the presence of transition metals and the availability of more convenient alkyne sources.

2.2.2 Alkynylation of Heteroatoms

The alkynylation of heteroatoms is interesting, as it gives access to highly reactive and useful acetylene derivatives. Due to the nucleophilicity of heteroatoms, the Umpolung approach represented by alkynyliodonium salts is especially attractive. In several cases, evidence has been gathered that these reactions also proceed *via* a conjugated addition/α-elimination/1,2-shift mechanism.

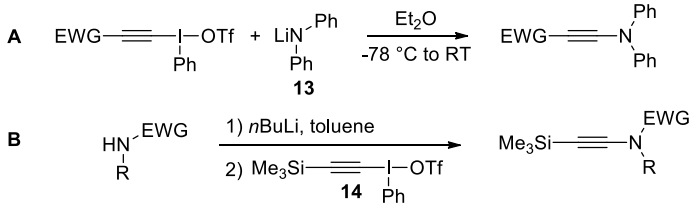
2.2.2.1 Alkynylation of Oxygen and Nitrogen Nucleophiles

As oxygen and nitrogen are often hard nucleophiles, their reaction with alkynyl iodonium salts is often difficult and can lead to decomposition. In 1987, Stang and co-workers reported that alkynyliodonium tosylates can be converted to the corresponding ynol tosylates in the presence of copper triflate (Scheme 2.5, **A** [51,52]). The rearrangement of alkynyliodonium carboxylates is even easier and occurs spontaneously in absence of any catalyst (Scheme 2.5, **B** [53,54]). In this case, the iodonium is best generated *in situ* by ligand exchange on (diacetoxyiodo)benzene **3** followed by addition of an alkynyl lithium reagent. The same approach could also be extended to ynol phosphates [53,55].



Scheme 2.5: Alkynylation of oxygen nucleophiles.

The synthesis of ynamines was investigated later. The first example was reported by Stang and co-workers in 1994, but this transformation was limited to the synthesis of push-pull ynamines (Scheme 2.6, **A** [56]). An important breakthrough was reported by Feldman and co-workers [57] and Witulski and co-workers [58], who demonstrated that alkynyliodonium triflates could be used for the synthesis of more stable ynamides (Scheme 2.6, **B**). The first efficient synthesis of this fascinating class of compounds allowed their widespread use in organic synthesis, especially in metal-catalyzed cycloisomerization and cycloaddition reactions [59]. The use of hypervalent iodine reagents is nowadays a classical method to access ynamides [60-68]. The method works especially well for the alkynylation of nitrogen bearing an electron-withdrawing group such as tosyl, acyl or carbamoyl [58, 60-65]. It works also for the alkynylation of heterocycles such as imidazole [66] or benzotriazole [67]. In 2012, Banert and co-workers also reported the first synthesis of azidoacetylene based on the reaction between an azide phosphonium salt and an alkynyliodonium tetrafluoroborate [68]. This highly unstable compounds decomposed with a half time of 17 h at –30 °C.

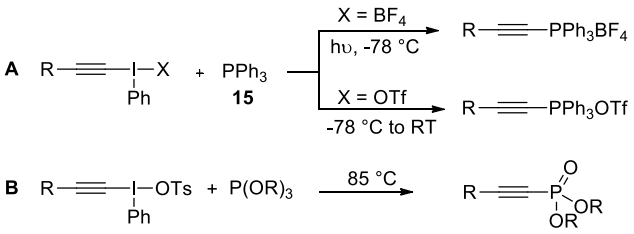


Scheme 2.6: Alkynylation of nitrogen nucleophiles.

2.2.2.2 Alkynylation of Phosphorus, Sulfur and other Nucleophiles

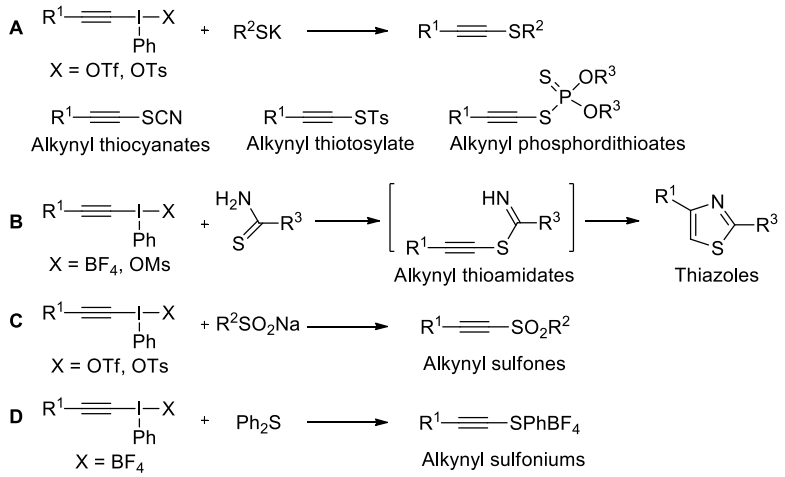
The alkynylation of phosphorus nucleophiles has been less investigated (Scheme 2.7). Ochiai and co-workers first demonstrated in 1987 that the alkynylation of triphenylphosphine was possible with alkynyliodonium tetrafluoroborate salts under light irradiation (Scheme 2.7, **A** [69]). The reaction most probably involves radical intermediates. In 1992, Stang and Critell showed that light irradia-

tion was not needed if alkynyliodonium triflates were used [70]. Later, this methodology could be extended to other triaryl- or alkyl phosphines [71-72]. In 1990, Koser and Lodaya also reported the synthesis of alkynylphosphonates by the Arbusov reaction of alkynyliodonium tosylates with trialkyl phosphites (Scheme 2.7, **B** [73]). Alternatively, the same compounds can be obtained by the reaction of alkynyliodonium tosylates with sodium phosphonate salts [74].



Scheme 2.7: Alkynylation of phosphorus nucleophiles.

The alkynylation of sulfur nucleophiles works well with alkynyliodonium tosylates and triflates as long as the sulfur atom is not too electron-rich, else oxidation reactions dominate. For example, alkynyl thiocyanates [38,39,75], thiotosylates [76] and phosphordithioates [77] can be accessed in good yields (Scheme 2.8, **A**). The alkynylation of thioamides is also possible, but in this case the obtained product is unstable and spontaneously cyclizes to give a thiazole (Scheme 2.8, **B** [78,79]). The alkynylation of sulfinates with alkynyliodonium triflates or tosylates gives an efficient access towards alkynyl sulfones (Scheme 2.8, **C** [80,81]). If C–H bonds are easily accessible, carbene C–H insertion products can also be observed in these transformations [82]. In 2014, Hamnett and Moran reported that the efficiency of alkynyl transfer can be increased by using 2-iodoanisole instead of 2-iodobenzoic acid as core of the hypervalent iodine reagent [83]. Finally, alkynylodonium salts can also be used to generate alkynyl sulfonium salts from diarylthioethers (Scheme 2.8, **D**, [84]).



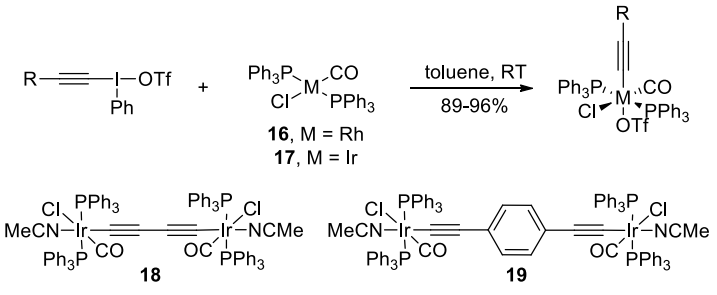
Scheme 2.8: Alkynylation of sulfur nucleophiles.

In addition to the alkynylation of second and third row main group heteroatoms, there are also a few examples of alkynylation of heavier elements including arsenic [85], selenium and tellurium [84, 86, 87].

2.2.3 Alkynylation of Metals

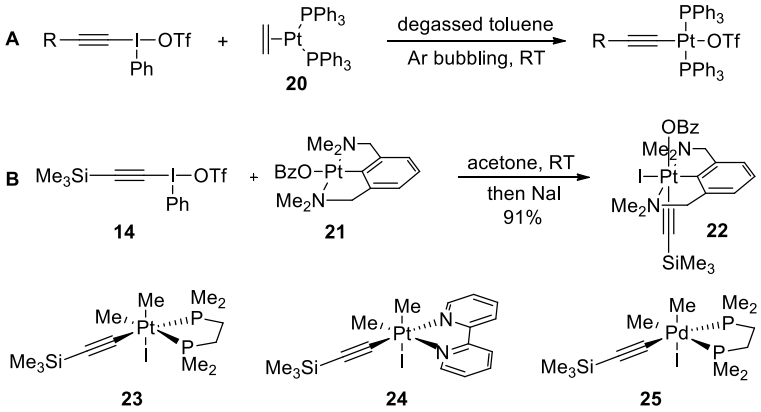
The reaction of alkynyliodonium salts with electron-rich transition metal results usually in an oxidative addition under formation of a metal-acetylide complex. Although this type of intermediates has been postulated in many catalytic reactions, this section will be limited to the cases in which the metal complexes could be isolated and characterized.

As a first interesting example, Stang and Critell reported in 1990 the alkynylation of Vaska complexes **16** and **17** with alkynyliodonium triflates as room temperature in excellent yield (Scheme 2.9) [88]. Using bis-alkynyliodonium salts, the method could be extended to the formation of binuclear complexes such as **18** and **19**, or even trinuclear systems [89-91]. These conjugated polymetallic complexes have great potential for applications in non-linear optics, organic conductors or liquid crystals.

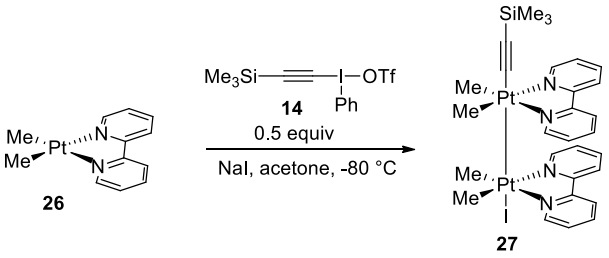


Scheme 2.9: Alkynylation of rhodium and iridium complexes.

Stang and co-workers also demonstrated that reaction of platinum(0) complex **20** with alkynyliodonium triflate yielded alkynyl platinum(II) complexes after careful optimization of the reaction conditions (Scheme 2.10, **A** [92]). Canty and co-workers then further used the strong oxidizing properties of alkynyliodonium salts to access alkynyl-metal complexes in high oxidation states [93-98]. They first demonstrated that platinum(II) pincer complex **21** could be oxidized to platinum(IV) alkynyl complex **22** in 91% yield using alkynyliodonium triflate **14** as reagent (Scheme 2.10, **B** [93]). They showed that the method could also be used to access platinum complexes **23** and **24** bearing a diphosphine and a bipyridine ligand, respectively [94]. The availability of these highly oxidized metal complexes allowed them to study elemental steps of catalytic cycles, in particular reductive elimination [95-97]. They were also able to synthesize the corresponding palladium(IV) complex **25** and characterize it at low temperature, as it decomposed readily at room temperature [94]. In 2009, Canty and co-workers were also able to characterize a rare Pt dimer complex **27** at –80 °C, obtained by reacting Pt(II) bipyridine complex **26** with half an equivalent of alkynylodonium triflate **14** (Scheme 2.11) [98]. In principle, **27** can be considered as either a Pt(III) or a Pt(II)-Pt(IV) dimer. The characterization of intermediate **27** is an important step on the way to better understand the mechanism of oxidation leading to high oxidation state metal complexes.



Scheme 2.10: Alkynylation of platinum and palladium complexes.



Scheme 2.11: Synthesis of Pt-dimer complex **27**.

2.2.4 Conclusion on the Use of Alkynyliodonium Salts

With the discovery and use of alkynyliodonium salts, a new class of electrophilic alkynylation reagents has emerged. Due to their impressive reactivity, they could be broadly used to introduce acetylenes on carbon nucleophiles, heteroatoms or metals. Nevertheless, with the exceptions of the alkynylation of nitrogen and new applications in the synthesis of alkynyl metal complexes, most research on alkynyliodonium salts has concentrated in the year 1985-1995, with rare more recent breakthroughs. In particular, very few applications using modern catalytic methods have appeared, in stark contrast to the use of aryliodonium salts in arylation reactions [99]. One of the possible reasons for this "drying out" of the field is the relatively low stability of alkynyliodonium salts, which makes their use often challenging.

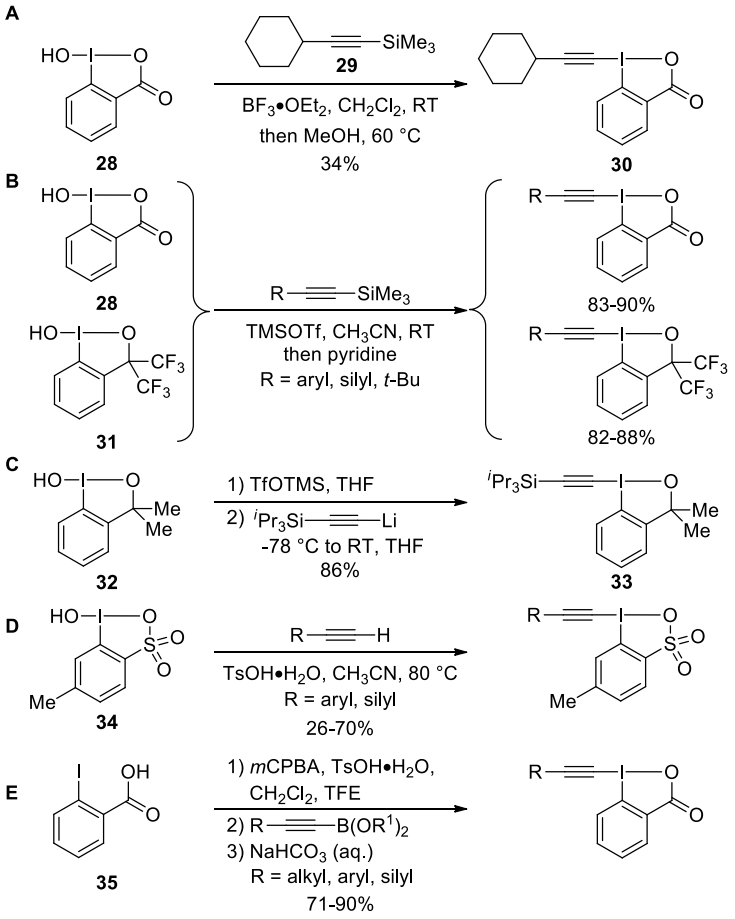
2.3 Alkynylation using Ethynylbenziodoxol(on)e (EBX) Reagents

One classical approach to enhance the stability of hypervalent iodine reagents is to incorporate the iodine atom into a cyclic structure fused to an aromatic ring (usually benzene [17,18]). Through the more rigid structure, the overlap of orbitals between the iodine atom and the benzene ring is further improved, which leads to increased stabilization. Furthermore, as the nucleophilic ligand of iodine (most often oxygen) is now part of the ring, reductive elimination and - in case of alkynyl reagents - conjugate addition is slowed down significantly. This has the advantage to further extend the range of substituents tolerated on the iodine atom. When considering the strong *trans*-effect in the hypervalent iodine bond [100], this can be very important to further modulate the reactivity of the reagents.

The first synthesis of a cyclic hypervalent iodine reagent was reported by Ochiai and co-workers in 1991 by the reaction of 2-hydroxy-benziodoxolone **28** with alkynyl trimethylsilane **29** in presence of boron trifluoride etherate (Scheme 2.12, **A** [101]). 1-[(Cyclohexyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one **30** (cyclohexyl-EBX) was obtained in 34% yield. In 1996, Zhdankin and co-workers significantly improved the synthesis of EBX reagents by the use of trimethylsilyl triflate as activator (Scheme 2.12, **B** [102]). This protocol was especially efficient in the case of aryl or silyl substituted alkynes, and could also be used to access bistrifluoro-

methyl-substituted benziodoxole derivatives. Waser and co-workers showed later that the protocol was highly useful for both, the synthesis of benzene-ring modified analogues and the synthesis of silyl-substituted EBX reagents on larger scale (up to 40 g [103,104]). The synthesis of dimethyl-substituted ethynylbenziodoxole reagents was reported by Waser and co-workers in 2012 where the use of a more reactive lithium acetylide as alkynylation reagent was required in the synthesis (Scheme 2.12, **C** [103]). Koser and co-workers already reported in 1993 that cyclic hypervalent iodine reagents bearing a more electron-withdrawing sulfonate group could be also easily accessed from the hydroxy derivative **34** using terminal acetylenes and toluene sulfonic acid as activator (Scheme 2.12, **D** [105]). Finally, Bouma and Olofsson developed in 2012 the first one-pot synthesis of EBX reagents starting directly from 2-iodobenzoic acid **35** (Scheme 2.12, **E** [33]). *meta*-Chloroperbenzoic acid was used as oxidant and alkynyl boronic acid esters as alkyne source. This protocol was general, allowing the synthesis of alkyl-, aryl- and silyl-substituted EBX reagents in 71-90% yield.

Surprisingly, the synthetic potential of cyclic hypervalent iodine reagents has been overlooked for a long time. Prior to 2009, only Kitamura and co-workers reported the use of an iodobenzoic acid based reagent, but in this case the protonated "open" form was used [38]. Since 2009, however, EBX reagents have been broadly applied in alkynylation reactions and have proven in many instances to be superior to the previously used alkynyliodonium salts.



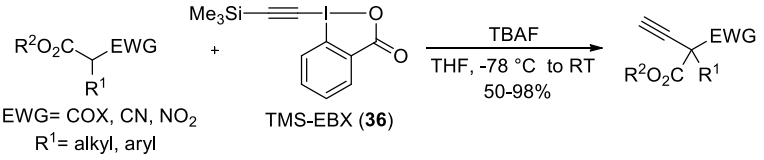
Scheme 2.12: Synthesis of cyclic alkynyl hypervalent iodine reagents.

2.3.1 Alkynylation of C-Nucleophiles

2.3.1.1 Alkynylation of Acidic C–H Bonds

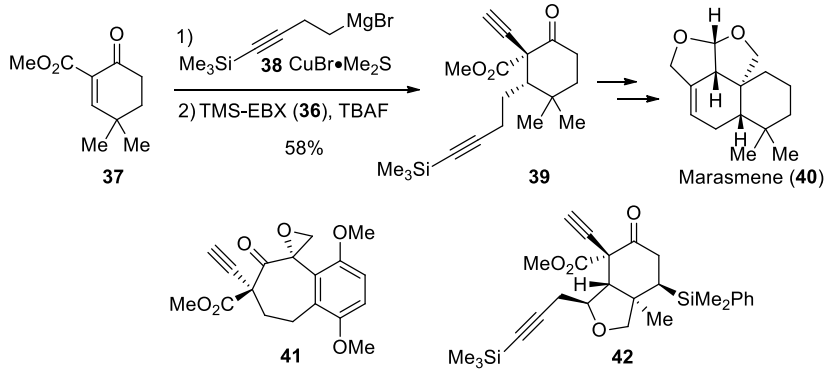
In 2010, Waser and co-workers reported the first study of the alkynylation of soft carbon nucleophiles using EBX reagents [106]. The alkynylation of ketoesters proceeded in nearly quantitative yields using TMS-EBX (**36**) and TBAF at low temperature to give directly the free acetylenes as products (Scheme 2.13). This method gave good yields not only for cyclic ketoesters, but also for non-cyclic keto-, cyano- and nitro- esters. *In situ* ^{1}H NMR experiments showed that the silyl group was first removed under these reaction conditions to give the very reactive

unsubstituted EBX reagent, which could be characterized at low temperature but decomposed at temperature higher than –20 °C. If the synthesis of aryl- or silyl-substituted alkynes is desired, good results were obtained using simply DBU as a base at room temperature [107].



Scheme 2.13: Alkynylation of activated ester derivatives with TMS-EBX (**36**).

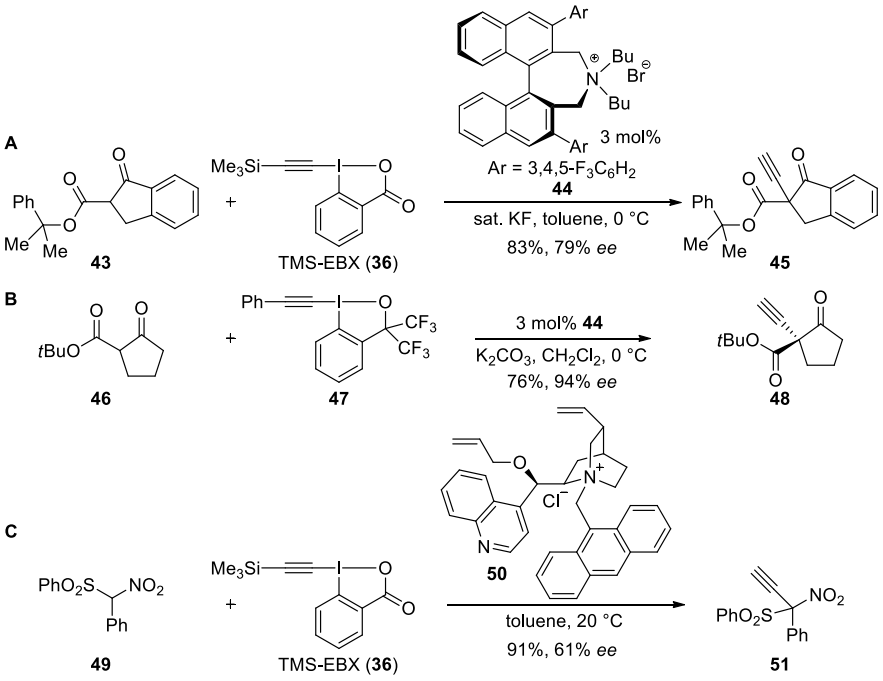
The robustness of the method was further demonstrated by Yang and co-workers, who used it first in the synthesis of drimane-type sesquiterpenoids such as marasmene (**40**, Scheme 2.14 [108]). In this case, the required ketoester was obtained via conjugate addition of an organocuprate onto Michael acceptor **37**. Later, Yang and co-workers also used the methodology for the synthesis of compounds **41** and **42** used in the total syntheses of (–)-lingzhiol and a fragment of azadirachtin, respectively [109-110].



Scheme 2.14: Applications of the alkynylation reaction in the total synthesis of natural products.

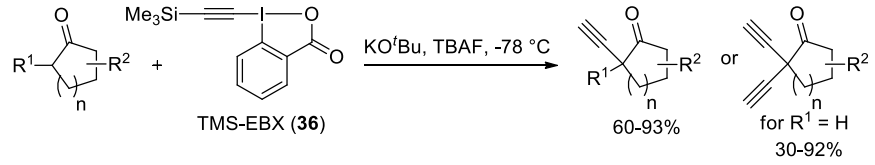
The enantioselective synthesis of compounds containing an all-carbon quaternary propargylic center would be highly desirable. In their first work, Waser and co-workers reported that a low enantioinduction was possible using cinchona-derived phase-transfer catalysts [106]. In 2013, they were further able to improve the enantiomeric excess by using the binaphthyl-based Maruoka phase transfer catalyst **44** (Scheme 2.15, **A** [111]). Although alkyne **45** could be obtained in 83% and 79% *ee*, the enantioinduction was lower for other substrates. In 2014, Maruoka and co-workers finally reported the first highly enantioselective asymmetric alkynylation using a hypervalent iodine reagent (Scheme 2.15, **B** [112]. Key to obtain high enantioinduction with ketoester **46** was the use of benziodoxole **47** instead of benziodoxolone reagents. The obtained products could be easily cyclized

to the corresponding spiro compounds by iodination or selenenylation. Finally, Vesely and co-workers showed in 2013 that the asymmetric alkynylation of α-nitro sulfone derivatives was also possible using cinchona-derived phase-transfer catalyst **50** (Scheme 2.15, **C** [113]). For example, alkyne **51** was obtained in 91% yield and 61% *ee*.



Scheme 2.15: Asymmetric alkynylation of ketoesters and nitrosulfones.

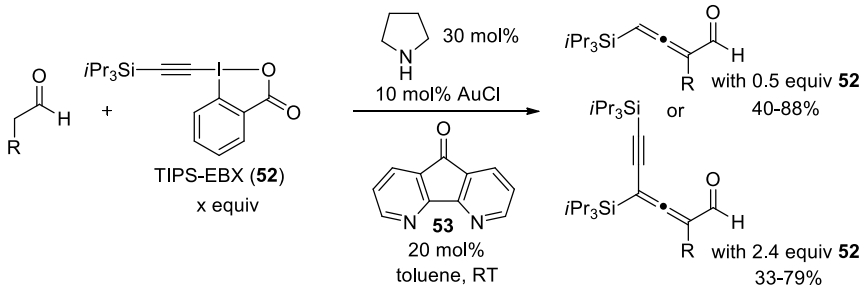
Recently, the scope of the alkynylation protocol has also been extended to other nucleophiles. Silva Jr. and co-workers reported the first alkynylation of simple aromatic ketones using TMS-EBX **36**, TBAF and potassium *tert*-butoxide as a base (Scheme 2.16 [114]). It is noteworthy that the alkynylation reaction is still highly efficient under these strongly basic conditions. Cyclic products could be obtained in 60-93% yield. In case of an unsubstituted α-position, diynes products were formed in 30-92% yield. Interestingly, the alkynylation was also successful with an aldehyde, which needed to be immediately reduced prior to isolation due to its instability.



Scheme 2.16: (Bis-)alkynylation of ketones and aldehydes

In 2015, Vesely and co-workers further extended the scope of the alkynylation for C–H acidic heterocycles [115]. Alkynylated pyrazolone, oxindole, rhodanine and azlactone could be obtained in good yields using TMS-EBX **36** and triethylamine as base in different solvents.

To extend the scope of the alkynylation of carbonyl compounds, the functionalization of aldehydes using enamine catalysis would appear as a logical choice. However, this transformation is still unknown. Nevertheless, Huang and co-workers reported in 2013 an important breakthrough in the area. The α-functionalization of aldehydes using pyrrolidine and a gold complex as co-catalyst became possible using TIPS-EBX **52** as reagent (Scheme 2.17 [116]). Although α-alkynylation was observed as minor pathway, the main products were the corresponding allenes. Increasing amounts of alkynes were obtained with increasing steric bulk in α-position of the aldehyde. Interestingly, the obtained allenes were still highly reactive under the reaction conditions and if an excess of TIPS-EBX **52** was used, a second alkynylation event took place to give enynes in 47-73% yield.

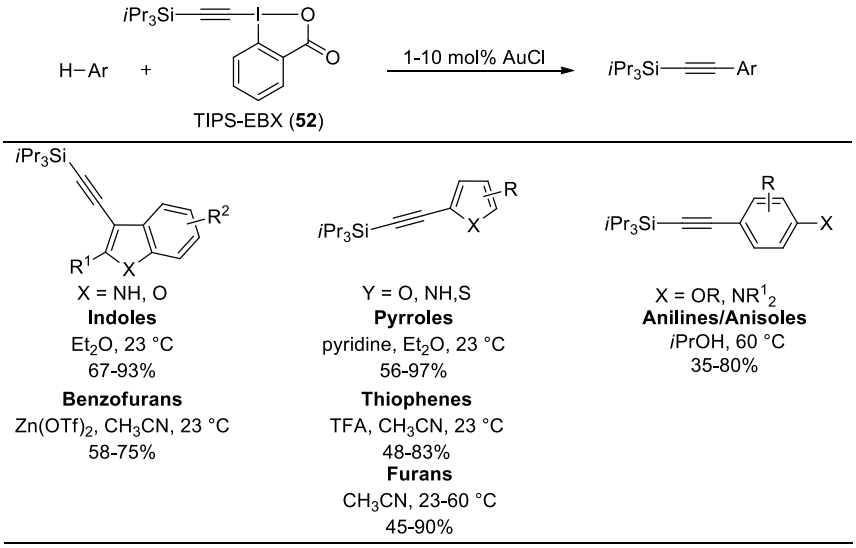


Scheme 2.17: Vinylidenation of aldehydes and cascade alkynylation.

2.3.1.2 Alkynylation of Aromatic and Vinylic C–H Bonds

In contrast to the alkynylation of acidic C–H bonds which can also be achieved using alkynyliodonium salts, the direct C–H functionalization of aromatic compounds or olefins has never been realized with this class of reagents so far. However, after several unfruitful attempts using palladium or copper catalysts and alkynyliodonium salts for the alkynylation of heterocycles, Waser and Brand reported in 2009 the first efficient alkynylation of indoles using TIPS-EBX **52** and AuCl as catalyst (Scheme 2.18 [117]). With indole, selective C3-alkynylation was obtained. The reaction was tolerant to many functional groups such as bromides, acids or alcohols. The method was already used in the synthesis of starting materi-

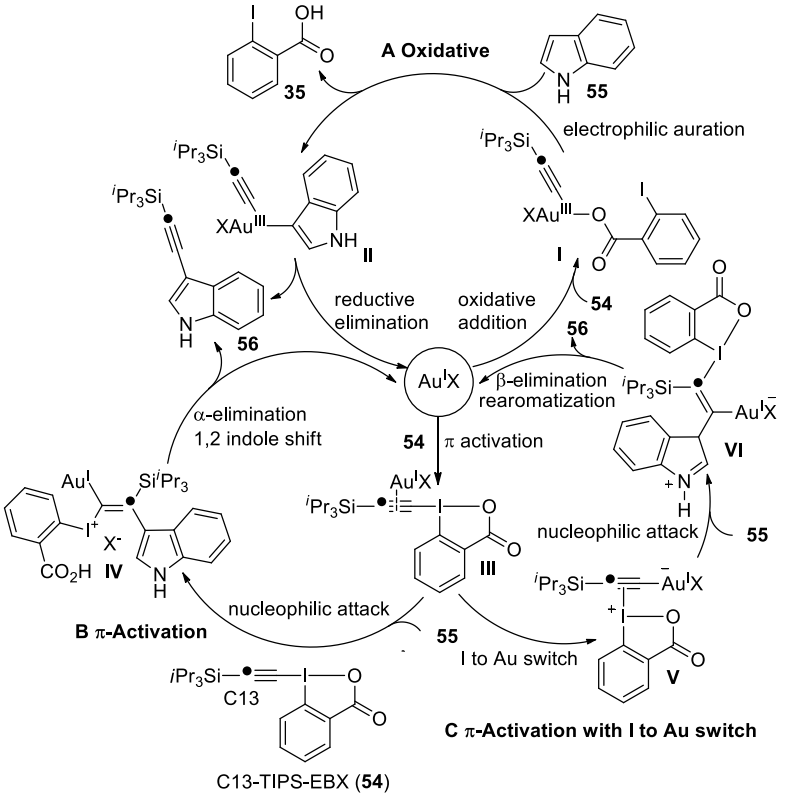
als for Friedel-crafts reactions of aminocyclopropanes [118] and for hydroamidation to access indole *cis*-enamides [119]. In 2010, Nevado and de Haro demonstrated that alkynylation was also possible using directly terminal propiolic ester derivatives and (diacetoxyiodo)benzene as co-oxidant [120].
Due to the high stability of TIPS-EBX **52** many reaction conditions are tolerated, which was important to optimize the alkynylation of other classes of aromatic compounds. For example, pyrroles were best functionalized in the presence of pyridine to avoid decomposition [103]. In this case, selective functionalization of the more electron-rich position was observed, unless it was blocked. In contrast, less reactive thiophenes required co-activation with a Brønsted acid catalyst, trifluoroacetic acid [121]. The obtained alkynyl thiophenes are interesting building blocks for the synthesis of organic materials. Furans could also be alkynylated in acetonitrile, sometimes at slightly higher temperature [122]. The alkynylation of less reactive benzofurans on the other hand required zinc triflate as co-activator [123]. Finally, the reaction was not limited to heterocycles. Electron-rich anilines or poly-methoxylated benzene rings could also be alkynylated at 60 °C in isopropanol [124]. Nevertheless, only highly electron-rich benzene rings could be functionalized with this method.



Scheme 2.18: Gold-catalyzed alkynylation of aromatic compounds.

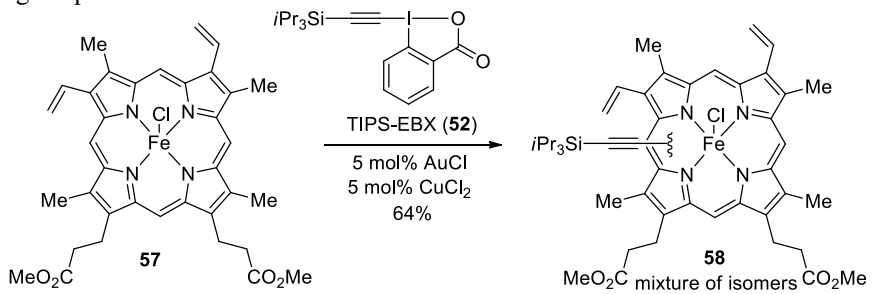
Mechanistically, this new transformation is highly intriguing. Unfortunately, gold catalysts bearing phosphine or carbene ligands were not active for the reaction, which made the isolation of well-defined gold complexes impossible. Furthermore, the formation of gold particles was also observed during the reaction. Initially, two mechanisms were proposed as shown in Scheme 2.19 [103, 117]. 1) an oxidative mechanism involving oxidative addition of the reagent on the gold(I)

catalyst to give a gold(III) intermediate **I**, followed by electrophilic auration to give **II** and final reductive elimination (Scheme 2.19, **A**) or 2) a π-activation mechanism proceeding via coordination of the gold catalyst to give intermediate **III** followed by nucleophilic addition leading to **IV** (Scheme 2.19, **B**). Finally, *α*-elimination and 1,2-shift would lead to the product. When the reaction was performed with C13 labelled reagent **54**, no shift of the silicium group was observed. For these reasons, the oxidative mechanism appeared more probable at this time, as a less favorable indole 1,2-shift would have to be proposed in the case of the π-activation mechanism. In 2014, Ariafard studied the mechanism in more detail by computational investigations [125]. Interestingly, it was found that both mechanisms **A** and **B** were too high in energy for a room temperature reaction. They proposed a novel pathway involving iodine to gold shift on the alkyne to give iodine-activated gold acetylide intermediate **V** (Scheme 2.19, **C**). Addition of indole **55** followed by *β*-elimination and rearomatization would lead also to product **56** without silicium shift. It would be interesting in the future to design experiments which investigate this unprecedented mechanism.



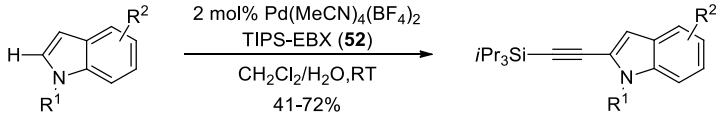
Scheme 2.19: Speculative mechanisms for the gold-catalyzed alkynylation.

An impressive extension of the gold-catalyzed method was reported by Marletta and co-workers in 2014. They developed the direct alkynylation of protoporphyrin IX **57** using TIPS-EBX **52** and AuCl as catalyst (Scheme 2.20 [126]). Protoporphyrin IX **57** is one of the most important heme cofactors and the availability of alkyne-tagged derivatives would be highly useful for studying biological processes. Interestingly, the use of $CuCl_2$ as co-catalyst was important to prevent the formation of gold nanoparticles which led to decomposition. The product **58** was obtained as a mixture of four isomers, but this was not an issue for studying biological processes.



Scheme 2.20: Alkynylation of protoporphyrin IX **57**.

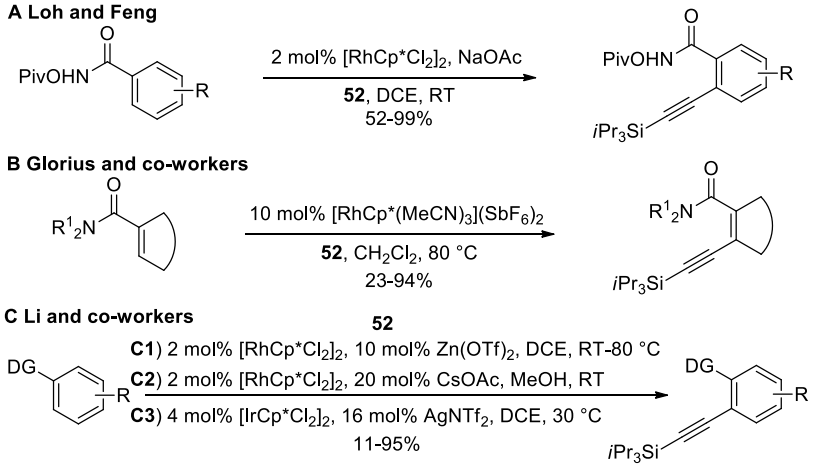
The gold-catalyzed alkynylation of heterocycles allowed the functionalization of the most electron-rich position. Nevertheless, this is a limitation if the synthesis of other alkyne regioisomers is desired. In 2013, Waser and co-workers reported that the C2-selective alkynylation of indoles was possible using a palladium catalyst (Scheme 2.21 [127]). A current limitation of this approach is the requirement for an alkyl substituent on the nitrogen atom.



Scheme 2.21: Palladium-catalyzed C2-alkynylation of indoles.

Up to 2014, the alkynylation via C–H functionalization of non-activated aromatic rings using hypervalent iodine reagents was unknown. In 2014, the groups of Li, Loh and Glorius reported nearly simultaneously a directing group strategy for the alkynylation of arenes using rhodium catalysis (Scheme 2.22). The work of Loh and Fang used a pivaloyl benzamide protecting group together with a rhodium(III)-Cp* catalyst and TIPS-EBX **52** as reagent (Scheme 2.22, **A** [128]). A major advantage in comparison to previously reported C–H alkynylation methods is that the reaction could be performed at room temperature giving excellent yields of products and tolerating many functional groups. Glorius and co-workers reported the alkynylation of benzamides using a cationic rhodium(III) complex (Scheme 2.22, **B**, [129]). In this case, the transformation could be also extended to olefins,

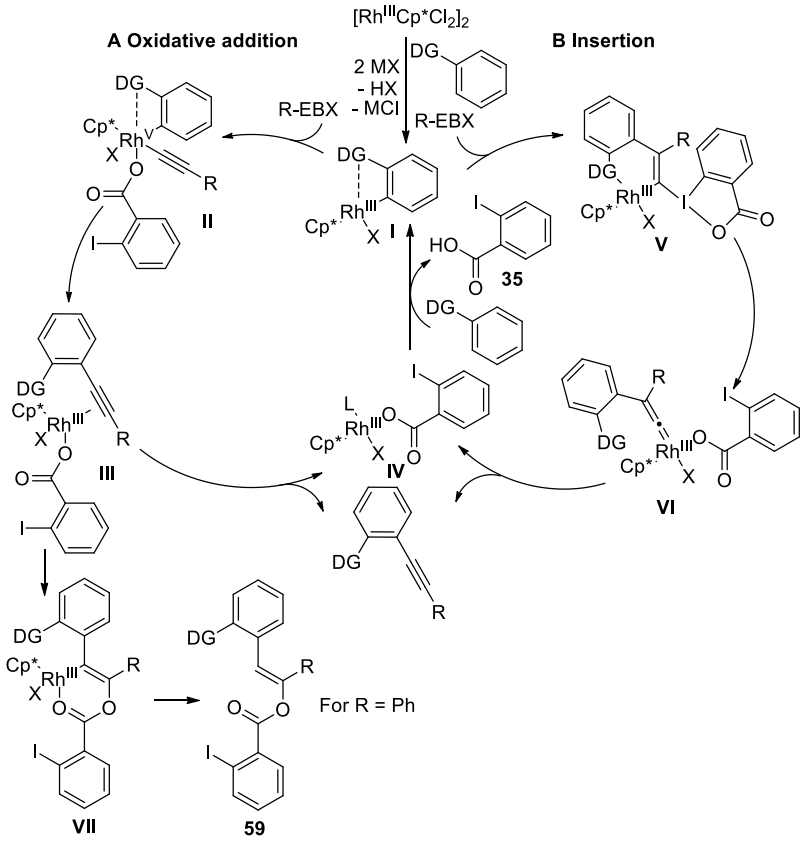
giving β-disubstituted products containing either a benzene ring, a heterocycle or an alkene. Li and co-workers reported a very complete study on the C–H alkynylation of arenes using TIPS-EBX **52** and either rhodium or iridium catalysts (Scheme 2.22, **C** [130]). Using a rhodium(III)-Cp* catalyst activated by zinc triflate, a broad range of heterocycles such as pyridine, pyrimidine or pyrazole could be used as directing groups (**C1**). The pyrimidine ring was not only successful in the case of benzenes, but also for the functionalization of indoles. This methodology has also been used by Zhou and co-workers to alkynylate a more functionalized indole substrate [131]. Non-aromatic directing groups such as oximes, nitrones, nitrosoanilines, azo- or azoxy-groups and simple amides could also be used. For pivaloyl benzamides, they used conditions very similar to the ones reported by Loh and Fang (**C2**). They also reported the first example of C–H alkynylation catalyzed by an iridium(III)-Cp* complex activated by silver bistriflimide (**C3**). Methoyl benzamides were the best substrates in this case and the products were obtained in similar yields as with the rhodium catalyst.



Scheme 2.22: Rhodium-catalyzed directed C–H alkynylation of arenes and olefins.

Preliminary mechanistic investigations were made my both Loh and Fang and Li and co-workers leading to two speculative mechanisms, either *via* initial oxidative addition or *via* insertion (Scheme 2.23, **A** and **B**). Both mechanisms start with activation of the rhodium(III)-chloride complex with different metal salts followed by formation of a rhodium(III)-metalacycle **I** with the substrate including the directing group (most probably with a concerted metalation-deprotonation mechanism). Intermediate **I** could then reacts with the EBX reagent either via oxidative addition to give rhodium(V) intermediate **II** (**A**), or via insertion to give rhodium(III) intermediate **V** (**B**). For the latter, high regioselectivity is expected for the insertion due to the high polarization of the triple bond in EBX reagents. From **II**, reductive elimination gives rhodium(III) intermediate **III**. Decomplexation of the product and re-formation of the rhodium(III) metalacycle **I** with probably the ben-

zoate acting as a base then closes the catalytic cycle. From **V**, α-elimination of the iodonium reagent will lead to rhodium(III) allenylidene complexe **VI**. 1,2-aryl shift and product decomplexation then gives intermediate **IV**. Interestingly, Li and co-workers also observed the formation of product **59** if Ph-EBX was used as reagent. They proposed that **59** was formed from intermediate **III** via insertion into the alkyne to give **VII**, followed by protodemetalation. In support of this mechanism, Li and co-workers were indeed able to isolate rhodium(III) complexes corresponding to intermediates **I** and **VII** (but with a *tert*-butyl instead of the phenyl group for the latter). Furthermore, they argued that the insertion mechanism was less probable, due to the high reactivity of rhodium(III) allenylidene intermediate **VI**, for which side reactions would have been expected, especially with nucleophilic directing groups.

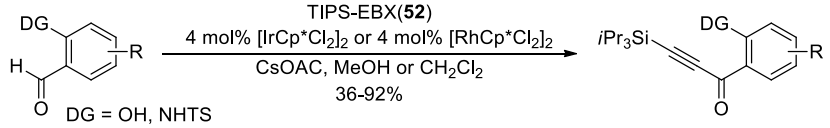


Scheme 2.23: Speculative mechanisms for the rhodium catalyzed alkynylation.

With these three reports, the basis was set for a broader use of EBX reagents in rhodium catalysis. Loh and co-workers continued their work and reported the alkynylation of acryl tosyl imides and enamides [132-133]. The reaction with acryl

imides proceeded also with disubstituted alkenes and allowed to extend the scope of this transformation. The alkynylation of enamides led to very useful enynamides as products, but was limited to α-substituted alkenes. Loh and co-workers also demonstrated that the methodology could be extended to the C7-alkynylation of indolines using a pyridine directing group on the nitrogen [134]. Interestingly, this reaction was also possible with Ph-EBX as reagent. The products can be easily oxidized to the corresponding indole derivatives. Zhu and co-workers reported the use of acetyl as directing groups and Zhou and Li and co-workers a pyrimidyl directing group with an iridium catalyst to achieve the same transformation [135,136]. In 2014, Chang and co-workers developed the first C8-alkynylation of quinolone *N*-oxide using a rhodium catalyst [137]. The oxygen atom could be easily removed by reduction. The same year, Li and co-workers reported that azomethine ylides were also excellent directing group for the alkynylation of benzene rings [138]. Finally, in 2015 Hong and Kang described the selective C–H alkynylation of quinolones [139]. In the absence of a directing group on the nitrogen and using a rhodium catalyst, C5-alkynylation was achieved selectively. Using a pyrimidyl directing group and, for the first time, a ruthenium catalyst, the C2-alkynylated products could be obtained.

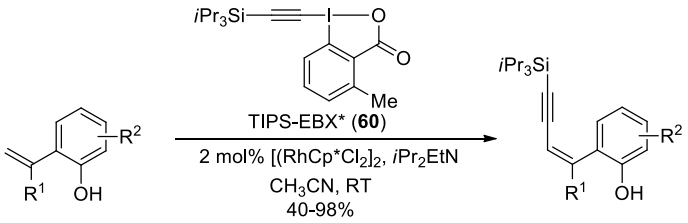
Recently, attempts have been made to extend the scope of rhodium-catalyzed C–H alkynylation beyond olefins and arenes functionalization *via* a classical five-membered metalacycle. Li and co-workers developed the directed C–H alkynylation of benzaldehydes (Scheme 2.24 [140]). Both alcohols and sulfonyl amines could be used as directing groups. With alcohols, an iridium catalyst in methanol was used giving ynones in good yields. With sulfonyl amines the best results were obtained with a rhodium catalyst in dichloromethane.



Scheme 2.24: Directed C–H alkynylation of benzaldehydes.

In 2015, Nachtsheim and co-workers investigated the directed alkynylation of ortho-vinyl phenols with EBX reagents (Scheme 2.25 [141]). As only moderate yields were obtained using TIPS-EBX **52**, the more reactive TIPS-EBX* **60**, introduced by Waser and co-workers [103], was used. Apart of its enhanced reactivity, the *ortho*-methyl group in **60** also blocked pathways leading to C–H activation side products. Exclusive formation of the *Z*-enyne was observed, without alkynylation of the benzene ring. The best yields were obtained for α- alkyl or aryl substituted vinyl phenols. Unsubstituted products could be isolated in moderate yields, but no products were obtained for *β*-substituted vinyl phenols. Mechanistically, this reaction is interesting, because it proceeds *via* the formation of a less frequent six-membered rhodium metalacycle. From this intermediate, the inser-

tion-elimination-shift mechanism was proposed, although the oxidative addition pathway could also be operative.



Scheme 2.25: Directed C–H alkynylation of *ortho*-vinyl phenols.

For the synthesis of ynones, an alternative approach to metal catalysis was recently reported by Wei and Zhu and co-workers [142]. Instead of the generation of an acyl-metal bond, they speculated that an acyl radical generated by C–H abstraction under oxidative conditions could also react with EBX reagents. Indeed, this was the case using either *tert*-butyl hydroperoxide (TBHP) or di-*tert*-butyl peroxide (DTBP) as oxidant at 80-130 °C. Although the reaction required a stoichiometric oxidant and elevated temperature, it has the advantage to be highly general, allowing reactions of aromatic, heteroaromatic and aliphatic aldehydes. Yields were generally higher with aromatic aldehydes, but the reaction worked only with silyl EBX reagents. Aliphatic aldehydes were obtained in moderate yields, but the transformation could also be used for aryl EBX reagents.

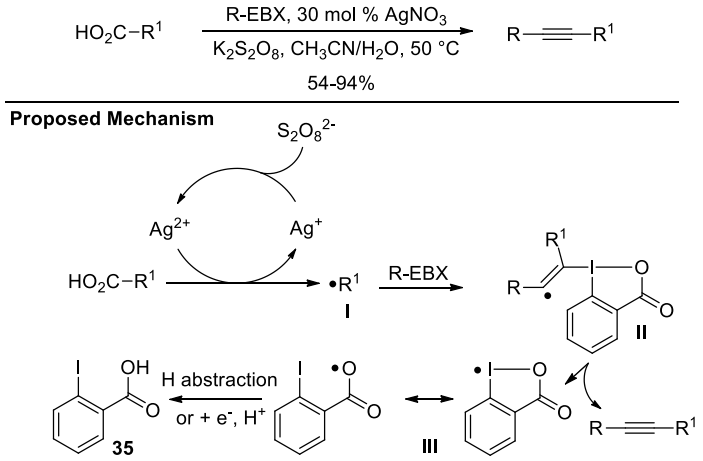
2.3.1.3 Alkynylation of Aliphatic C–H Bonds

The alkynylation of sp^3-C–H bonds has been in general much less developed than of sp^2-C–H bonds. Metal-mediated methods have been limited to the use of alkynyl bromides [143], whereas radical approaches have been dominated by alkynyl sulfones [21-22]. Nevertheless, Yu and Chen and co-workers reported recently that aromatic EBX reagents were highly efficient for the interception of radical generated in α-position to heteroatoms [144]. Silyl EBX could also be used. The inherent limitations of this radical-mediated approach are the requirement for a large excess of substrate and the formation of mixtures of products when several C–H bonds are of similar strength.

2.3.1.4 Alkynylation of C–C and C–B Bonds

The alkynylation of C–H bonds is a very attractive method from the point of view of synthetic efficiency, but it presents a serious issue of selectivity if no directing groups or polarizing heteroatoms are present. The use of pre-installed functional groups can be advantageous in this context, provided that the starting

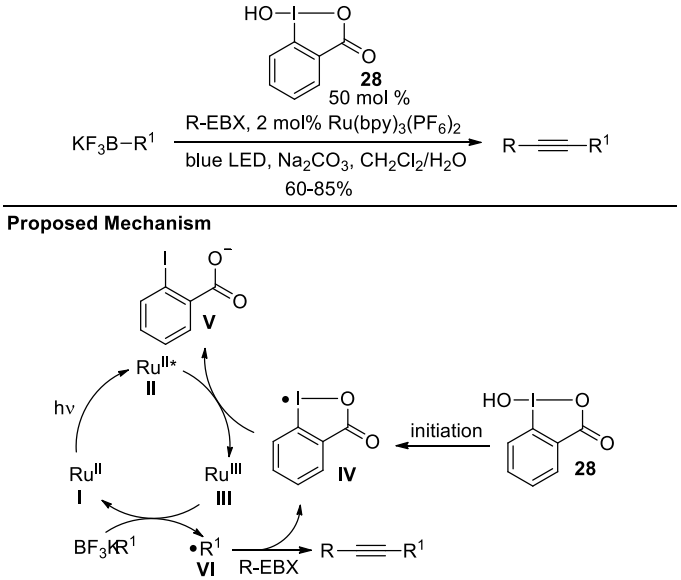
materials are commercially available or easily accessible. In this context, Li and co-workers reported in 2012 the oxidative decarboxylative alkynylation of carboxylic acids as shown in Scheme 2.26 [145]. Starting from broadly available carboxylic acids, aliphatic aromatic and silyl alkynes could be obtained in good yields. Impressively, the reaction was successful for the functionalization of tertiary, secondary and primary acids. It also tolerated numerous functional groups like bromine, esters or imides. The reaction was proposed to proceed *via* the silver mediated oxidation of the carboxylate to form a carboxyl radical, which immediately loses carbon dioxide to give an alkyl radical **I**. The active silver(II) oxidant would be generated by oxidation of silver(I) by persulfate, allowing to use silver nitrate as a catalyst. The alkyl radical would then add to the triple bond of the EBX reagent to give intermediate **II**. β-Elimination of iodo radical **III** then gives the product. Radical **III** is then most probably further reduced to the carboxylate and protonated to give **35**, or alternatively, **35** is directly formed via C–H abstraction. Addition of the radical on the EBX reagent with reversed regioselectivity followed by an α elimination-1,2-shift sequence could also be considered.



Scheme 2.26: Oxidative decarboxylative alkynylation of aliphatic carboxylic acids.

In 2014, Chen and co-workers reported an alternative method based on the oxidative alkynylation of trifluoroboronate salts using a photoredox catalyst, substoichiometric amounts of hydroxybenziodoxolone **28** and EBX reagents (Scheme 2.27 [146]). The reaction worked well for the transfer of aryl, silyl and alkyl alkynes. Primary, secondary, and tertiary boronate salts were all successfully alkynylated. The reaction tolerated functional groups such as ketones, bromides, alcohols and azides. Interestingly, the authors were also able to perform the alkynylation in buffered water solutions in presence of several amino acids, demonstrating its potential for the functionalization of biomolecules. Concerning the reaction mechanism, the author proposed that light activation of the rutheni-

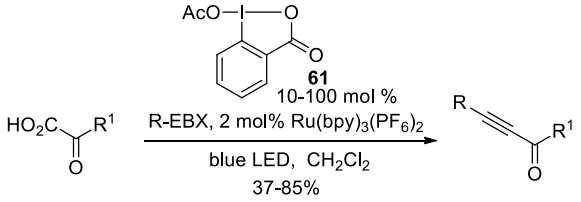
um(II) catalyst **I** generates a strongly reductive complex **II**, which is able to reduce radical **IV** (or hydroxybenziodoxole **28**). The obtained ruthenium(III) complex **III** is now a strong oxidant able to generate an alkyl radical **VI** from the boronate salt. As shown by Li and co-workers, radical **VI** then reacts with the EBX reagent to give the product and a further molecule of radical **IV**. In principle, a small amount of initiator would be enough to start a catalytic cycle. Nevertheless in practice a relatively large amount (50 mol%) of hydroxybenziodoxole **28** is needed for an efficient transformation. The possibility of a reaction proceeding *via* a catalyst-independent radical chain reaction was excluded by a light on/off experiment, showing that light was always needed to observe conversion.



Scheme 2.27: Alkynylation of aliphatic trifluoroborate salts.

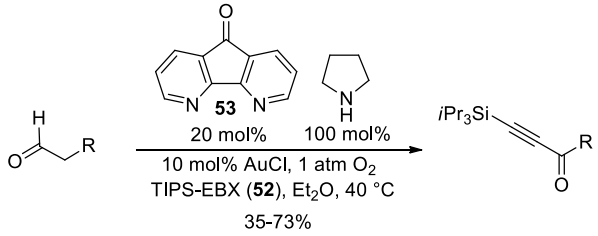
In 2015, Chen and co-workers reported an extension of the photoredox strategy for the synthesis of enones based on the decarboxylation of α-keto acids using EBX reagents and acetoxy benziodoxolone **61** as additive (Scheme 2.28 [147]). The reaction worked again best with aryl EBX reagents, but silyl or alkyl-substituted alkynes could still be obtained in moderate yields. Aromatic, heteroaromatic and aliphatic ynones were obtained in good yields. Interestingly, the methodology was not limited to the synthesis and ketones, but could also be applied to access amides and esters. A similar catalytic cycle as for the alkynylation of boronates salts was proposed with oxidative generation of an acyl radical. The key difference resides in the way the radical is formed. The authors proposed the formation of a covalent adduct between the carboxylate and benziodoxolone **61**, which would facilitate oxidation by ruthenium(III) to give the radical. In this pro-

cess, **61** is not reduced and could be therefore used in catalytic amounts. Indeed, with only 10 mol% of **61**, the alkynylation product was still isolated in 56% yield.



Scheme 2.28: Decarboxylative alkynylation of α-carbonyl-substituted carboxylic acids.

Finally, Huang and co-workers reported in 2014 a fundamentally different approach to access ynones using EBX reagents [148]. During their work on the α-vinylidenation of aldehydes, using cooperative catalysis between an amine and a gold catalyst [116], they observed the formation of one carbon atom shorter ynones when oxygen was not carefully excluded. By performing the reaction under 1 atm of oxygen and optimizing the reaction conditions, they were able to obtain the ynones as major products (Scheme 2.29). The reaction worked well for the synthesis of primary and secondary aliphatic ynones. Interestingly, the formation of one ynamide was also reported. The authors proposed that the first step of this reaction is similar to the α-vinylidenation with the formation of an enynamide. However, under oxygen atmosphere this highly nucleophilic intermediate is oxidatively cleaved *via* the formation of a dioxetane ring. Indeed, pyrroldine-2-carboxaldehyde was observed as a side product.

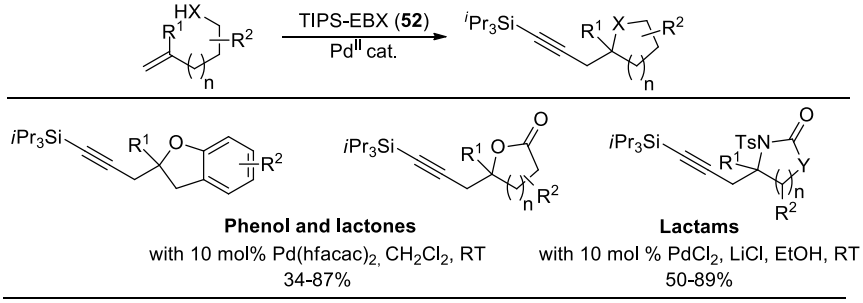


Scheme 2.29: Ynones synthesis from aldehydes via C–C bond cleavage.

2.3.1.5 Alkynylation as Part of Domino Processes

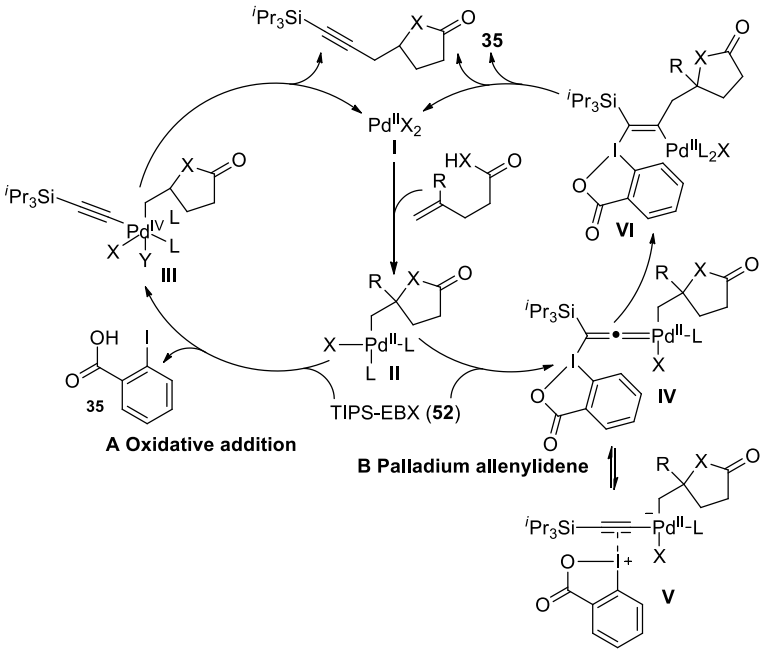
In domino processes, several new bonds are formed in a single transformation, leading to a more efficient synthesis [149]. The introduction of an alkyne group during domino processes would be highly desirable when considering the versatile reactivity of the triple bond. Nevertheless, alkynyliodonium salts were not used in such transformations, probably because they are often unstable in the presence of transition metal catalysts.

In 2010, Waser and co-workers reported the first example of intramolecular palladium-catalyzed oxyalkynylation of alkenes leading to the successive formation of a C–O and a C–alkyne bond (Scheme 2.30, **A** [150]). Whereas the use of alkynyl iodonium salts led to the formation of the desired product in trace amount only, good yields could be obtained using TIPS-EBX **52** with phenols as nucleophiles and palladium(II)bishexafluoroacetylacetonate as catalyst. Only electron-neutral or poor phenols could be used in this process, as electron-rich substrates decomposed. Aliphatic alcohols could not be used. On the other hand, acids gave lactones with a broader scope. In this case, both aromatic and aliphatic acids could be used. In 2011, Waser and co-workers were able to extend the method to the synthesis of lactams using tosylimides as nucleophiles [151]. In this case, best results were obtained with palladium(II) chloride as catalyst in ethanol. The reaction worked well for the synthesis of γ-lactams, oxazolidinones and imidazolidinones. It was also easily scalable to the gram scale and was used in the total synthesis of the pyrrolizidine alkaloid trachelanthamidine. Finally, the method could be also applied to the synthesis of δ-lactams in moderate to high yields depending on the rigidity of the substrates.



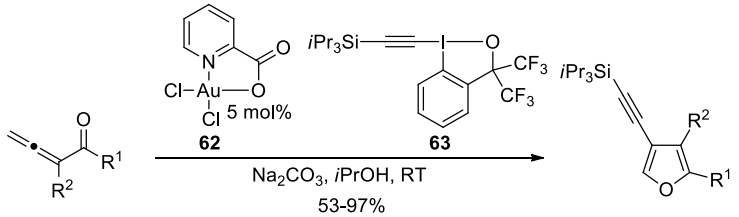
Scheme 2.30: Oxy- and amino-alkynylation of alkenes.

Originally, Waser and co-workers proposed a mechanism involving a palladium(IV) intermediate **III** (Scheme 2.31, **A** [149]). Complex **III** would be accessed by either *syn*- or *anti*- oxy/aminopalladation of the olefin to give **II**, followed by oxidative addition of TIPS-EBX **52**. Reductive elimination would then give the observed product and regenerate the palladium(**II**) catalyst. This proposal was based on the work of Canty and co-workers, who were able to characterize palladium(IV) alkynyl complexes [94]. However, Ariafard reported calculations in 2014 that gave a very high energy for this reaction mechanism [152]. They found a lower energy pathway leading to palladium allenylidene intermediate **IV**, which was in equilibrium with an iodine bound alkynyl palladium complex **V**, with **IV** being the major species. From **IV**, a facile α-insertion of the alkyl group give palladium(II) vinyl intermediate **V**. Finally β-elimination of 2-iodobenzoic acid **35** would lead to the observed product.



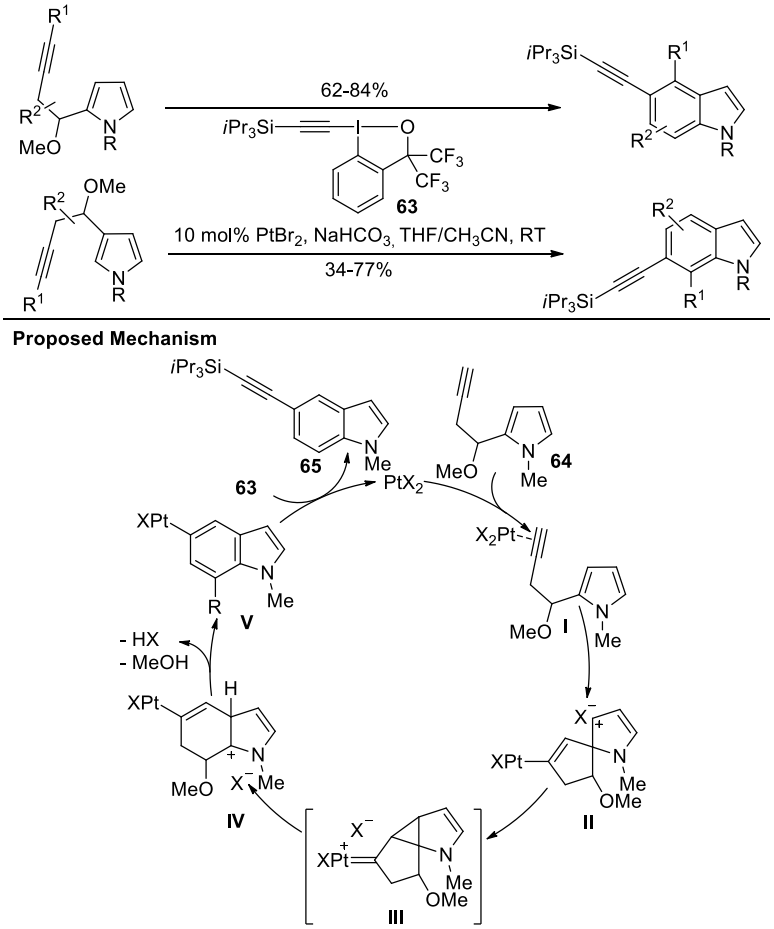
Scheme 2.31: Speculative mechanisms for the oxy- and aminoalkynylation reactions.

After having successfully developed a domino process involving C(sp^3)-C(sp) bond formation as terminating event, Waser and co-workers investigated if domino processes could also be used to make a C(sp^2)-C(sp) bond. Preliminary studies focused on the synthesis of indoles directly from *ortho*-alkynyl anilines [153]. A one-pot process could indeed be developed, but not a true domino transformation, as a gold(III) catalyst was required for cyclization and a gold(I) catalyst for alkynylation. A further limitation of this early work is that it gave access to products which are easily synthesized *via* direct C-H alkynylation. To overcome these limitations, Waser and co-workers decided to develop a domino reaction based on the gold-catalyzed cyclization of allene ketones to form furans reported by Hashmi and co-workers [154]. In this transformation, a C3-metallated furan is formed, which could be then alkynylated to give the electronically unfavored regioisomer. In 2013, they reported the first example of such a true domino reaction using gold(III) picolinate catalyst **62** and ethynylbenziodoxole **63** as reagent (Scheme 2.32 [122]). The reaction was efficient with electron-neutral and rich aromatic rings on the allene, but could not be used in the case of electron-poor substituents due to decomposition. It was particularly efficient with alkyl substituents.



Scheme 2.32: Domino cyclization-alkynylation of allene ketones.

After this work, the more challenging synthesis of arene-alkynylated indoles were investigated. Due to the enhanced reactivity of the pyrrole ring, the direct functionalization of indoles on the benzene ring is highly challenging. A domino process to access these compounds would be therefore highly useful. They were able to develop a platinum catalyzed method starting from homopropargylic pyrrole derivatives and benziodoxole reagent **63** (Scheme 2.33) [155]. Gold catalysts could not be used in this process. Starting from C2-substituted pyrroles, C5-alkynylated indoles were obtained, whereas C3-substituted pyrroles gave C6-functionalized products. Mechanistically, this reaction much probably proceeds via activation of the triple bond in pyrrole **64** by the platinum catalyst (intermediate **I**), followed by intramolecular attack of the most nucleophilic pyrrole C2 position to give key intermediate **II**. 1,2 shift of the vinyl-platinum substituent via a possible platinum carbene intermediate **III** then gives complex **IV**. Interestingly, shift of the ether substituent had been observed with gold catalysts for the simple cyclization process [156]. At this point, elimination of methanol and re-aromatization would give a platinum aryl complex **V**, which would then react with benziodoxole **63** to give the observed product **65**. The mechanism of this last step is not clear at this stage. In case of C3 substituted pyrroles, C2 attack would give directly the desired six-membered ring without the need for 1,2-shift.



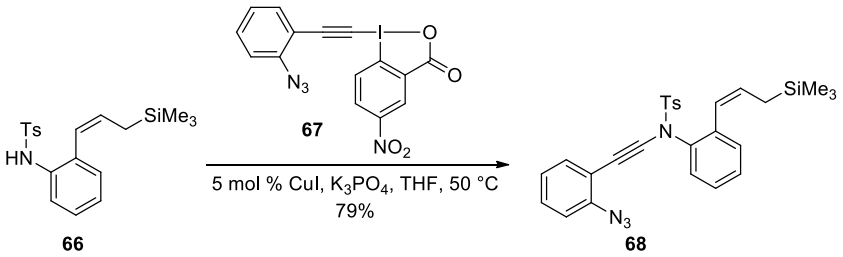
Scheme 2.33: Domino cyclization-alkynylation for the synthesis of arene-alkynylated indoles.

2.3.2 Alkynylation of Heteroatoms

2.3.2.1 Alkynylation of Oxygen and Nitrogen Nucleophiles

Up to now, no efficient alkynylation of oxygen nucleophiles with EBX reagents has been reported. Also in the case of nitrogen nucleophiles, alkynyliodonium salts remain the reagents of choice. Nevertheless, Cossy and co-workers reported in 2013 that the alkynylation of sulfonamides was possible with TMS-EBX **36** [157]. Interestingly, no alkynylation was observed in the case of carbamates, although these substrates are readily alkynylated with alkynyliodonium salts. Se-

lective alkynylation of the tosyl amide in presence of a carbamate was possible. This selectivity was exploited for the synthesis of tetrahydropyrazine heterocycles. In 2014, Ohno and co-workers reported the synthesis of the more complex ynamides **68** based on the copper-catalyzed alkynylation of tosyl amide **66** using aryl EBX reagent **67** (Scheme 2.34 [158]). Interestingly, this constituted the first example of a copper-catalyzed reaction with an EBX reagent in which the alkyne group is kept in the product. Although alkynyl bromides have been traditionally used in copper catalysis for the synthesis of ynamides, they were not successful in this case.

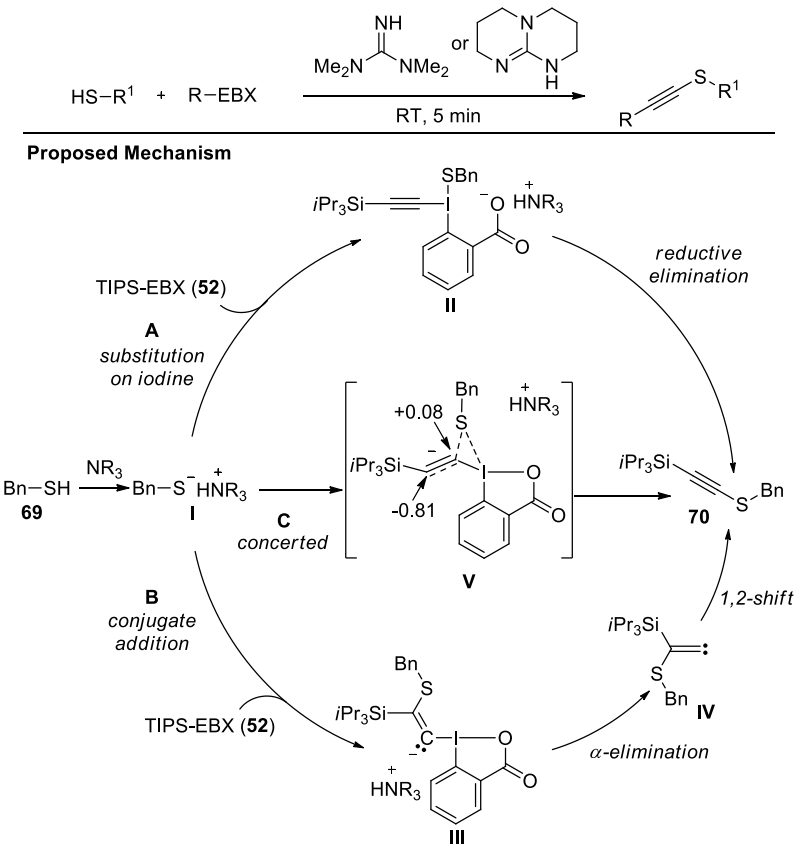


Scheme 2.34: Copper-catalyzed alkynylation of tosyl amide **66** with EBX reagent **67**.

2.3.2.2 Alkynylation of Phosphorus, Sulfur and other Nucleophiles

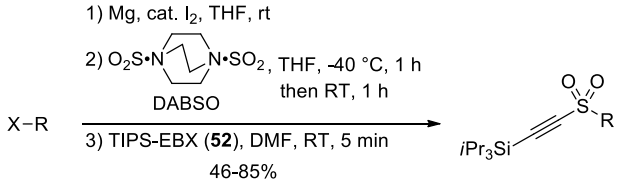
The alkynylation of numerous heteroatom nucleophiles has been highly successful with alkynyliodonium salts. Nevertheless, the alkynylation of omnipresent simple thiols had never been reported, probably because the oxidation of thiols to disulfide is readily promoted by alkynyliodonium salts. In 2013, Waser and co-workers demonstrated that the alkynylation of thiols was possible with TIPS-EBX **52** in high yields in less than one minute reaction time at room temperature (Scheme 2.35 [159]). Key for success was the use of tetramethylguanidine (TMG) as a base. The scope of the reaction was very broad, as it included aliphatic thiols, thiophenols, heteroaromatic thiols, cysteine and peptides. The transformation was tolerant to many functional groups, such as halogens, alcohols, acids, amides, anilines and even the free amino group of cysteine. The obtained thioalkynes could be easily deprotected and reacted in a [3+2] cycloaddition with azides. In 2014, they further reported the extension of the scopes to glycosides, thioacids and sulfide salts [160]. Furthermore, the use of not silyl-substituted alkynes was also highly successful for all substrates classes. In some cases, the use of triazabicyclodecene (TBD) as base gave superior results. The exception were thioacids, as the products were too instable to be isolated in this case. Importantly, functional groups such as chloride, alcohol or azide incorporated on the EBX reagent were also tolerated.
The fact that the reaction was successful for a broad scope of EBX reagents was surprising, as side reactions were dominating in the case of alkyl substituted alkynyliodonium salts (see Section 2.2.1.1). Waser and co-workers turned to calcu-

lations to gain a better understanding of the reaction mechanism [160]. Deprotonation of the thiol was proposed as required step as no reaction occurred in the absence of base. A first possibility would be then attack of the thiolate **I** on TIPS-EBX (**52**) to give intermediate **II**, followed by reductive elimination (**A**). However, intermediate **II** was not observed in the calculations. A more probable mechanism involves conjugate addition to give **III**, followed by α-elimination and 1,2-shift to give **70** (**B**). This pathway was indeed found by calculations with a relatively low transition state of 23 kcal/mol leading to **III**, followed by a barrierless elimination/1,2-silyl shift to give product **70**. However, a third unprecedented pathway was also found by calculations: a concerted three-atom transition state mechanism leading directly to **70**, with an energy as low as 10.8 kcal/mol. The transition state **V** itself was distorted and showed a strong polarization, with the negative charge in α-position and the positive charge in β-position to silicium. The difference between the two pathways was much smaller for an alkyl substituent, probably due to the silyl effect.



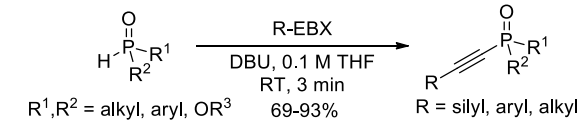
Scheme 2.35: Alkynylation of thiols with EBX reagents.

The reaction of sulfinates with alkynyl iodonium salts was successful, as these substrates are less easy to oxidize. Nevertheless, Waser and Chen demonstrated that EBX reagents can be also useful to synthesize alkynyl sulfones, as they allow a new one-pot procedure starting directly form Grignard reagents (Scheme 2.36 [161]). In this protocol, DABSO (DABCO•SO_2) is added after formation of the Grignard reagent. Addition of DMF and TIPS-EBX **52** gives aryl alkynyl sulfones in 46-85% yield. For base sensitive substrates, it was also possible to start from aryl iodides and use a palladium catalyst.



Scheme 2.36: One-pot synthesis of alkynyl sulfones.

In 2014, Waser and Chen also reported that EBX reagents could be used in the alkynylation of phosphites (Scheme 2.37 [162]). The reaction also worked well for the alkynylation of phosphinates and secondary phosphine oxides.



Scheme 2.37: Alkynylation of phosphorus nucleophiles with EBX reagents.

2.3.3 Conclusion on the Use of EBX Reagents

In contrast to alkynyliodonium salts, which have been used in organic synthesis for decades, EBX reagents have been used intensively only in the last five years. However, they have already made a strong impact in the synthesis of alkynes, as they allowed new transformations which were not accessible before. They were especially successful in transition metal catalysis, where they allowed the development of new C–H functionalization and domino reactions. They also demonstrated important advantages for the functionalization of acidic C–H bonds or carbon centered radicals. Alkynyliodonium salts allowed new transformations with heteroatoms, such as the alkynylation of thiols, or presented distinct enough properties to be highly useful, for example in the alkynylation of tosyl amides, sulfinates or phosphorus nucleophiles.

2.4 Conclusions

The importance of alkynes in organic chemistry cannot be overstated. They are now also increasingly useful for chemical biology and materials science. The introduction of alkynes as nucleophiles into molecules is currently the method of

choice, but it limits the range of disconnections possible. As one of the best electrophilic alkyne synthons, alkynyliodonium salts have attracted strong interest since the mid 80's. Even if very successful, their utility has been limited by their lower stability, especially in the presence of transition metals. Nowadays, their main routine use resides in the synthesis of ynamides. The introduction of more stable ethynylbenziodoxolone (EBX) reagents, first synthesized by Ochiai and Zhdankin, has initiated a renaissance of the use of hypervalent iodine reagents for alkynylation reactions. A broad range of mild reactions has become now available to introduce alkynes onto both carbon nucleophiles and heteroatoms, with the potential to revolutionize the way to disconnect this versatile functional group. As research is increasing pace in the area, many more exciting transformations can be expected to be discovered in the future.

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