Hypervalent Iodine Reagents

International Edition: DOI: 10.1002/anie.201503405
German Edition: DOI: 10.1002/ange.201503405

Ethynyl Benziodoxolone (EBX): Installing Alkynes the Reversed Way**

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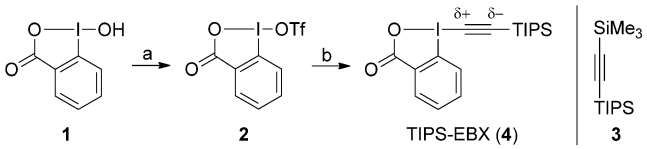
alkynes · C–H activation · EBX · hypervalent iodine reagents · rhodium

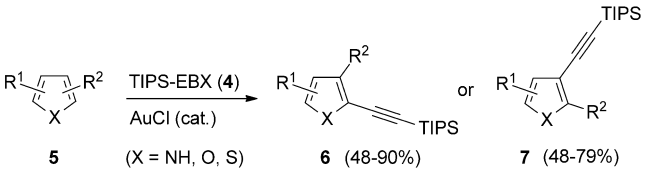
Hypervalent iodine compounds are powerful reagents for numerous organic transformations, such as oxidations, rearrangements, and single-electron-transfer and radical reactions, leading to the formation of carbon–carbon, carbon–heteroatom and heteroatom–heteroatom bonds.[1a] Although the preparation of an alkynyl-substituted member of this family of potent hypervalent iodine reagents, [(triisopropylsilyl)ethynyl]benziodoxolone (TIPS-EBX (**4**), Scheme 1), had



Scheme 1. Synthesis of TIPS-EBX (**4**). Reaction conditions: a) trimethylsilyl trifluoromethanesulfonate (TMSOTf; 1.1 equiv), CH_2Cl_2, 25 °C, 20 min; b) **3** (1.1 equiv), pyridine (1.1 equiv), MeCN, 25 °C, 20 min.

already been described by Zhdankin et al. in 1996,[1b] the chemical community had to wait until the year 2009 for its first striking applications. EBX reagents deliver an alkyne moiety with reversed polarity, thus allowing uncommon, but highly useful electrophilic alkynylation reactions.[2] Reagent **4** is readily available starting from 2-iodobenzoic acid; it is remarkably stable and highly reactive even at room temperature. In this Highlight, the most intriguing transformations that employ silyl-EBX and newly developed alkyl-EBX reagents are discussed.

The Waser group was the first to recognize the great potential of **4** and developed the first C–H alkynylation of pyrroles and indoles using this reagent. Key to success for these high-yielding transformations was the application of a gold(I) catalyst, which further increases the electrophilicity of the alkynyl unit by π-coordination to the triple bond.[3a] For the mechanism of the alkyne transfer, different scenarios have been discussed. Either π-activation leads to the formation of vinyl gold complexes with subsequent β-elimination, or the gold(I) species is oxidized to form a gold(III) complex, followed by arene metalation and reductive elimination.[3a] Further studies revealed that this method was also applicable to thiophenes, benzothiophenes,[3b] and furans,[3c] enabling the synthesis of a series of synthetically valuable 2- or 3-ethynylated heteroarenes (Scheme 2).



Scheme 2. Gold-catalyzed alkynylation of heteroarenes using TIPS-EBX, reported by Waser and co-workers. Reaction conditions: **4** (1.2 equiv), AuCl (5 mol%), Et_2O or MeCN, 25 °C or 60 °C, 12–60 h. For X = S, the addition of trifluoroacetic acid (TFA; 1.2 equiv) was required.

Inspired by this pioneering work, the Huang group exploited the combination of TIPS-EBX and a gold catalyst for the preparation of α-allenyl aldehydes **9**, γ-alkynyl allenyl aldehydes **10**,[4a] and ynones **12**[4b] from simple aliphatic aldehydes **8** (Scheme 3). The allene moiety arises from the rearrangement of the respective alkynyl group, which can only be installed in the α-position of the aldehyde, which in turn is activated by the pyrrolidine. In combination with oxygen, this additive was also crucial for the carbon–carbon bond cleavage that enables the synthesis of **12**. Mechanistically, an aerobic oxidation of alkynylated enamine **11** followed by breakdown of the four-membered 1,2-dioxetane intermediate was proposed for this transformation. The isolation of the side product pyrrolidine-1-carbaldehyde supported this assumption. Ynones **12** proved to be ideal precursors for cyclohexenones, pyrazoles, and pyrimidines whereas alkynylated allenals of type **10** were used for efficient syntheses of trisubstituted furans.[4]

Research groups dealing with the functionalization of electronically non-activated π-systems have also capitalized on the unique reactivity of **4**. Rh^{III} complexes proved to be the catalysts of choice for the desired transformations, which

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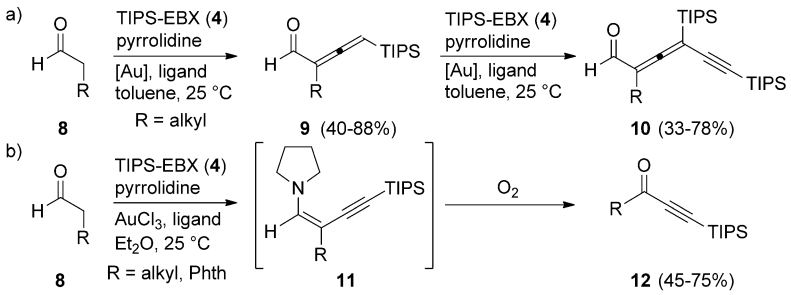
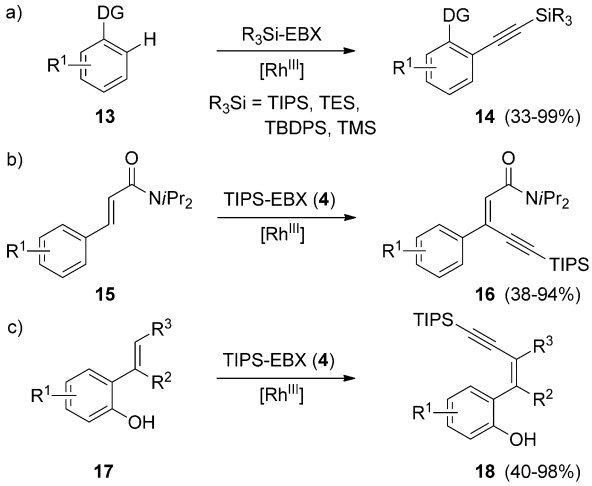
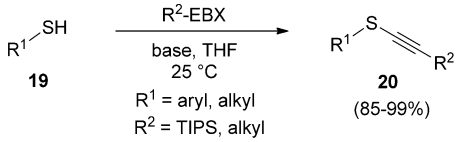
[**] We are grateful to the German Research Foundation (DFG, postdoctoral fellowship to J.K. (2014–2015)) and the Fonds der Chemischen Industrie (Dozentenstipendium to D.B.W.).



Scheme 3. Studies of the Huang group on the α-alkynylation of aldehydes. Reaction conditions: a) **4** (1.0 equiv), pyrrolidine (20 mol%), AuCl or $AuCl_3$ (10 mol%), ligand (20 mol%; 2,2′-bipyridine or phenanthroline), 24 h; b) **4** (1.0 equiv), pyrrolidine (1.0 equiv), $AuCl_3$ (10 mol%), 4,5-diazafluoren-9-one (20 mol%), O_2, 40 °C, 10 h. Phth = phthaloyl.



Scheme 4. Alkynylation reactions of unactivated arene and styrene derivatives. Reaction conditions: a) **4** (1.1 equiv), $[\{RhCp^*Cl_2\}_2]$ (2 mol%), NaOAc (1.1 equiv), DCE, 25 °C, 12 h;[5a] or R_3Si-EBX (1.1 equiv), $[\{RhCp^*Cl_2\}_2]$ (2 mol%), $Zn(OTf)_2$ (10 mol%), DCE, 25 °C, 16 h;[5b] or **4** (2.0 equiv), $[RhCp^*(MeCN)_3](SbF_6)_2$ (10 mol%), CH_2Cl_2, 80 °C, 16 h (same for b).[5c] c) **4** (1.2 equiv), $[\{RhCp^*Cl_2\}_2]$ (2.5 mol%), diisopropylethylamine (DIPEA; 1.5 equiv), MeCN, 25 °C, 2 h.[5d] DCE = 1,2-dichloroethane, TBDPS = *tert*-butyldiphenylsilyl, TES = triethylsilyl.

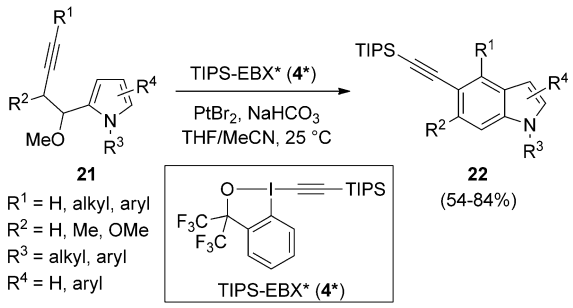


Scheme 5. Alkynylation of thiols. Reaction conditions: R^2-EBX (1.1 equiv), 1,1,3,3-tetramethylguanidine (1.2 equiv), 5 min.

proceeded under mild reaction conditions and tolerated a large number of functional groups (Scheme 4).[5] Among others, oximes, nitrones, 2-pyridines, 2-pyrimidines, and amides could be used as directing groups (DGs). For the terminal alkynylation of styrenes, a neighboring hydroxy group as in **17** was indispensable.[5d] A plausible mechanistic scenario involves the formation of rhodacycles through a metalation–deprotonation pathway resulting in C–H activation. Regioselective insertion of the alkyne moiety of EBX into the Rh–C bond, followed by α-elimination of 2-iodobenzoic acid and subsequent rearrangement furnishes the new C_{sp}–C_{sp^2} bond.

The reversed polarity of the alkyne unit in EBX reagents paved the way to an electrophilic alkynylation of thiols **19**, enabling the synthesis of very electron-rich carbon–carbon triple-bond systems (Scheme 5).[6] Such compounds have commonly been generated by the reaction of lithiated alkynes and organic thiocyanates.[7] The very mild reaction conditions of this novel reaction easily allow for the preparation of fluorophore-tagged biomolecules as the products are ideally suited for click chemistry.[6]

Very recently, the Waser group demonstrated that modified EBX reagents can even be used for domino cyclizations, delivering C5-alkynylated indoles **22** from readily available pyrroles of type **21** (Scheme 6). A platinum salt catalyzes this highly complex transformation, presumably by activating the triple bond of the substrate, which leads to the formation of the indole ring.[8] Subsequently, the electrophilic triple bond is delivered from EBX to the heteroarene intermediate. The indoles thus accessible are useful synthetic building blocks, which are otherwise not so easily obtained. Classical C–H functionalization strategies would always favor the formation of the respective C2- or C3-substituted products. Furthermore, with the method of Waser et al., the corresponding C6-



Scheme 6. Indole synthesis using an EBX derivative. Reaction conditions: **4*** (2.0 equiv), $PtBr_2$ (10 mol%), $NaHCO_3$ (2.0 equiv), 72–120 h.

alkynylated indoles are available starting from C3-substituted pyrroles.

Over the last few years, EBX reagents have moved into the focus of the organic chemistry community. Compared to electrophilic alkynylation reactions, which often utilize unstable and highly toxic halogen-substituted acetylenes, transformations with EBX are conducted under much milder reaction conditions. The reagents are readily available from inexpensive 2-iodobenzoic acid, stable, and easy to handle. TIPS-EBX (**4**) is even commercially available. We are curious which novel applications of EBX derivatives will emerge in the future. The electrophilic delivery of alkynyl moieties to sp^3-hybridized carbon atoms in a diastereo- and enantioselective fashion would be particularly desirable.

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 8876–8878
Angew. Chem. **2015**, *127*, 9002–9004

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Received: April 15, 2015
Published online: July 14, 2015

