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Copper-Catalyzed Oxy-Alkynylation of Diazo Compounds with Hypervalent Iodine Reagents

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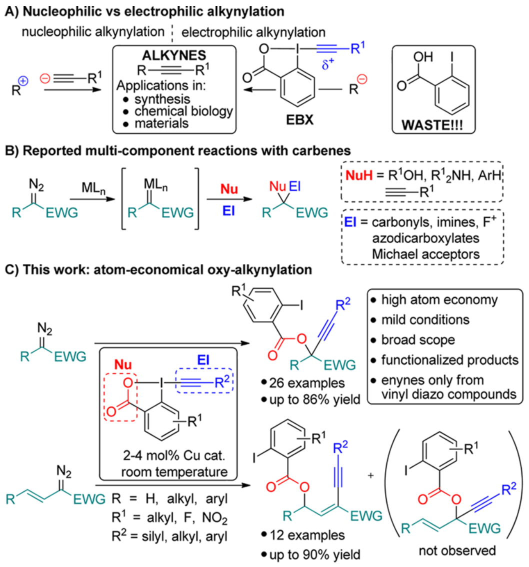
S Supporting Information

ABSTRACT: Alkynes have found widespread applications in synthetic chemistry, biology, and materials sciences. In recent years, methods based on electrophilic alkynylation with hypervalent iodine reagents have made acetylene synthesis more flexible and efficient, but they lead to the formation of one equivalent of an iodoarene as side-product. Herein, a more efficient strategy involving a copper-catalyzed oxy-alkynylation of diazo compounds with ethynylbenziodoxol(on)e (EBX) reagents is described, which proceeds with generation of nitrogen gas as the only waste. This reaction is remarkable for its broad scope in both EBX reagents and diazo compounds. In addition, vinyl diazo compounds gave enynes selectively as single geometric isomers. The functional groups introduced during the transformation served as easy handles to access useful building blocks for synthetic and medicinal chemistry.

The carbon−carbon triple bond is among the most valuable functional groups in organic chemistry because of its versatile reactivity.[1] Alkynes are broadly applied as chemical building blocks for the synthesis of fine chemicals.[2] In past years, they have also gained a lot of interest for applications in biochemistry or material sciences.[1,3] As a result of this growing importance of alkynes, developing more efficient and versatile methods for their synthesis is of fundamental importance. Alkynes are often accessed by the addition of acetylides on electrophilic positions of molecules.[4] However, introducing triple bonds only to electrophilic positions strongly limits the flexibility and efficiency of alkyne synthesis. Major efforts have therefore been made to develop electrophilic alkynylation methods, relying on the umpolung of the innate reactivity of acetylenes (Scheme 1A).[5]

Hypervalent iodine reagents such as alkynyliodonium salts have been particularly successful for the electrophilic alkynylation of nucleophiles.[6] However, the use of alkynyliodonium salts is limited due to their low stability. Recently, ethynylbenziodoxol(on)es (EBX)[7a,b] have been introduced as excellent electrophilic reagents for the alkynylation of ketoesters,[7c] thiols,[7d] and aromatic C−H bonds using transition metal catalysis,[7e−g] among many other successful transformations.[7h] Nevertheless, the developed methods are often restricted to the transfer of one type of acetylenes (either silyl-, aryl-, or alkyl- substituted). Furthermore, 2-iodobenzoic acid is usually obtained as a stoichiometric byproduct after alkynylation, resulting in low atom economy.[8] Recently, Greaney and co-workers[9a] and Dauban and co-workers[9b] reported more atom economical transformations based on the use of the formed aryl iodides in cross-coupling reactions with aryliodonium salts and $PhI(OPiv)_2$, respectively. With EBX reagents, progress in this area has been limited to a report of Yoshikai and co-workers on the palladium-catalyzed reaction of imines with alkynylbenziodoxolones to give furan derivatives.[10]

Scheme 1. Alkynylation Strategies and Multicomponent Reactions Using Diazo Compounds



To develop more efficient transformations with EBX reagents, we intended to make use of the nucleophilic properties of the formed iodobenzoate side products. In this context, metal carbene species are interesting reactive intermediates, as they display both nucleophilic and electrophilic reactivity on a single carbon atom and can be easily generated from α-diazo carbonyl compounds.[11] They have been used in a broad range of transformations such as X−H bond insertions, cyclopropanation, ylide formation, and 1,2- migration reactions and have been successfully applied in total synthesis.[12] Recently, research in the area has focused on the development of multicomponent reactions to afford products with high structural diversity, complexity, and atom economy (Scheme 1B).[13] The only

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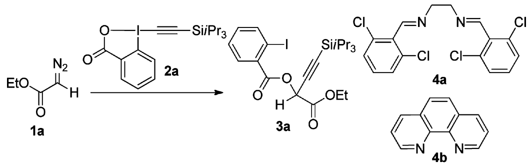
approach for the synthesis of alkynes from diazo compounds has been reported by Wang and co-workers for a reaction involving metal carbene migratory insertion with nucleophilic alkynes.[14] We envisioned a different strategy making use of the carboxylate of the EBX reagent as a nucleophile, and the alkyne as an electrophile.

Herein, we report the successful implementation of this strategy, resulting in a highly efficient and atom economical oxy-alkynylation of diazo compounds under mild conditions using a nonexpensive copper catalyst (Scheme 1C). The reaction exhibits a broad scope toward both diazo compounds and EBX-reagents and tolerates many functional groups. It provides access to both secondary and tertiary propargylic alcohol derivatives and can be used for the synthesis of silyl-, aryl-, and alkyl-substituted acetylenes. The iodine atom, the ester, and the triple bond of the product can serve as versatile handles for further transformations. Interestingly, when vinyl diazo compounds were used as starting materials, only 1,4-addition to give enynes was observed.

We first attempted the oxy-alkynylation of ethyl diazoacetate (**1a**) with 1-[(tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX, **2a**) using 5 mol % of $Rh_2(OAc)_4$ in DCM at 40 °C, but did not obtain the desired product **3a** (Table 1, entry 1).

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst (×mol %)	solvent (conc.)	time/*T* (°C)	yield
1	$Rh_2(OAc)_4$ (5.0)	DCM (0.1 M)	20 h/40	<5%
2	$Cu(OTf)_2$ (5.0)	DCM (0.1 M)	20 h/40	19%
3	$Cu(CH_3CN)_4BF_4$ (5.0)	DCM (0.1 M)	20 h/40	24%
4	CuCl (5.0)	DCM (0.1 M)	20 h/40	<5%
5	$Cu(OAc)_2$ (5.0)	DCM (0.1 M)	20 h/40	<5%
6	$PdCl_2(PPh_3)_2$ (5.0)	DCM (0.1 M)	2 h/40	<5%
7	$AuBr_3$ (5.0)	DCM (0.1 M)	18 h/40	<5%
8	$Cu(CH_3CN)_4BF_4$ (5.0)	DCE (0.1 M)	2 h/65	30%
9[b]	$Cu(CH_3CN)_4BF_4$ (5.0)	DCE (0.1 M)	1 h/65	46%
10[b]	$Cu(CH_3CN)_4BF_4$ (2.0)	DCE (0.1 M)	1.5 h/65	54%
11[b]	$Cu(CH_3CN)_4BF_4$ (2.0)	DCE (0.05 M)	2.5 h/65	60%
12[b,c]	$Cu(CH_3CN)_4BF_4$ (2.0)	DCE (0.05 M)	1 h/*RT*	86%
13[b,d]	$Cu(CH_3CN)_4BF_4$ (2.0)	DCE (0.05 M)	20 h/*RT*	<5%
14[b]	no catalyst	DCE (0.05 M)	20 h/65	<5%

[a] Reaction conditions: 0.30 mmol ethyldiazoacetate (**1a**), 0.25 mmol TIPS-EBX (**2a**). The reaction was run for 20 h or until full conversion of the EBX reagent. Yield after purification by column chromatography. [b] With 0.50 mmol **1a**. [c] With 2.5 mol % of **4a**. [d] With 2.5 mol % of **4b**.

Replacing $Rh_2(OAc)_4$ with $Cu(OTf)_2$ gave the desired product **3a** in 19% yield after 20 h at 40 °C (Table 1, entry 2). Product **3a** was obtained in 24% yield when $Cu(CH_3CN)_4BF_4$ was used (Table 1, entry 3), whereas the use of other metal catalysts such as CuCl, $Cu(OAc)_2$, $PdCl_2(PPh_3)_2$, and $AuBr_3$ did not lead to the formation of the desired product **3a** (Table 1, entries 4−7). Use of DCE as a solvent at 65 °C gave **3a** in 30% yield (Table 1, entry 8). With two equivalents of **1a**, the yield could be raised to 46% (Table 1, entry 9). Decreasing the catalyst loading to 2 mol % gave **3a** in 54% yield (Table 1, entry 10). Alkyne **3a** was then obtained in 60% yield when the concentration of the reaction was decreased to 0.05 M (Table 1, entry 11). Finally, a major improvement was obtained when using 2.5 mol % of 1,2 diimine **4a** as ligand:[15] the yield increased to 86% and the reaction could be performed at room temperature (Table 1, entry 12). In contrast, the reaction did not take place when using 1,10-phenanthroline (**4b**) as ligand (Table 1, entry 13). In the absence of $Cu(CH_3CN)_4BF_4$, no product was obtained, demonstrating that the copper catalyst is necessary for the reaction (Table 1, entry 14).

The scope of the reaction was first examined using TIPS-EBX (**2a**) and a variety of α-diazo compounds (Figure 1A). *tert*-Butyl and benzyl diazoacetates provided the oxy-alkynylation products **3b** and **3c** in high yields. The transformation was also successful for disubstituted diazo compounds, leading to products **3d−f** with tertiary propargylic centers. Noteworthy, a cyclic diazo compound also afforded the desired product **3g** in 80% yield. Derivatives of α-hydroxy-alkynyl lactones are present in pharmaceutical molecules[16] but have never been synthesized directly from lactones to the best of our knowledge. In addition to α-diazo esters, several other diazo compounds including 2-diazo-*N*,*N*-diethylacetamide, ethyl diazomethanesulfonate, and diethyl (diazomethyl)phosphonate underwent the desired transformation in good to high yields (products **3h−j**). We then turned our attention to the scope of R-EBX reagents (Figure 1B). Electron-donating and -withdrawing groups were well tolerated on the aryl ring of TIPS-EBX (**2a**) (products **3k−m**). EBX reagents bearing aryl substituents on the alkyne worked efficiently in this transformation, giving products **3n−p** in 80−84% yield. Bromide-substituted product **3p**, which is useful for further chemical transformations, could be isolated in 83% yield. Several aliphatic EBX reagents bearing functional groups such as a chloro, an azido, and an ether also gave the desired products in moderate to high yields (products **3q−t**). A cyclopropyl derived EBX reagent can also be used in this reaction (product **3u**). A TMS-alkyne substituted EBX reagent gave product **3v** in 75% yield. In addition, ethyl 2-diazopropanoate can also be oxy-alkynylated successfully with aryl-substituted EBX reagents to furnish products **3w** and **3x** with tertiary propargylic centers in 78% and 72% yield, respectively.

Next, the developed method was applied to the oxy-alkynylation of vinyl diazo compounds (Figure 1C). Controlling the selectivity in the reaction of nucleophiles with vinyl diazo compounds is challenging, as they display electrophilic reactivity at both the carbenoid and the vinylogous center.[17] Gratifyingly, only vinylogous product **6a** was obtained as a single geometric isomer when using (*E*)-methyl 2-diazopent-3-enoate (**5a**) with TIPS-EBX (**2a**). We were pleased to see that (*E*)-methyl 2-diazohex-3-enoate (**5b**) and cyclic diazo compounds **5c** and **5d** could be used to give the desired vinylogous products **6b**, **6c**, and **6d** in good to high yields.[18] Various R-EBX reagents were then examined. TIPS-EBX reagents having substituents on the aromatic ring led to the desired products **6e** and **6f** in high yields. The reaction was also successful with aryl-substituted EBX reagents, and products **6g** and **6h** were obtained in 82% and 75% yield, respectively. Substituents containing a long alkyl chain, a chloro, and a cyclopropyl functional group were well tolerated in this reaction (products **6i−k**). A TMS-alkyne substituted EBX reagent gave the vinylogous product **6l** in 72% yield.

Modification of steroidal drugs provides an efficient route for the fine-tuning of their biological activity. Therefore, our method was applied to the late-stage oxy-alkynylation of diazo derivatives **7** and **8** of steroids,[19] which could be smoothly converted to the desired products **9** and **10** in 82% and 75% yield, respectively

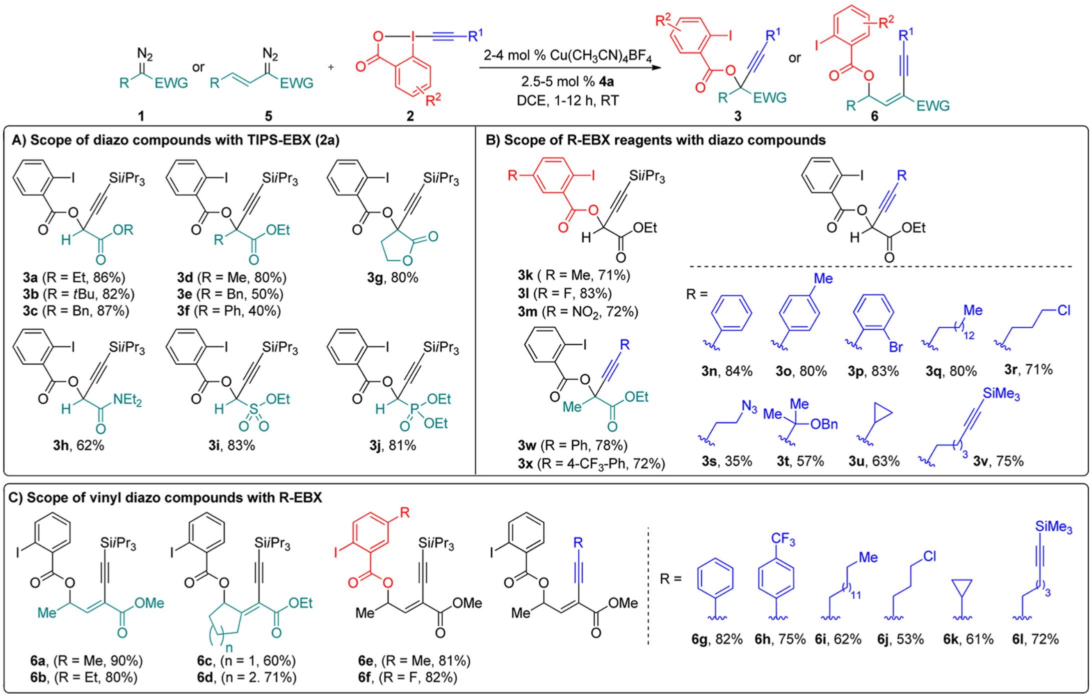
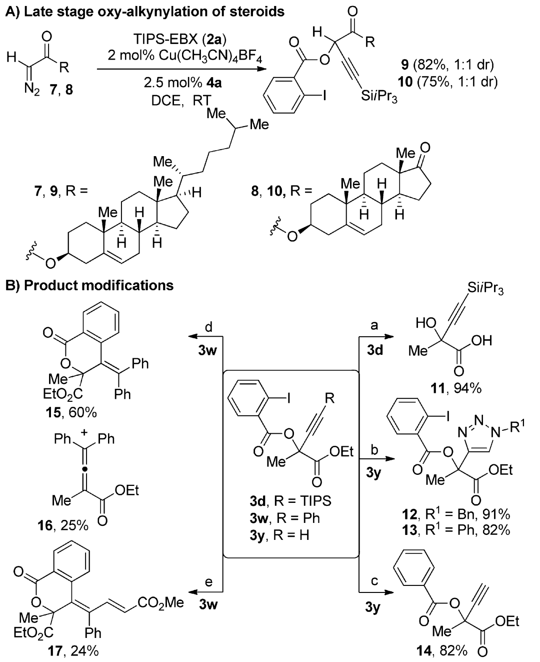


Figure 1. Scope of the copper-catalyzed oxy-alkynylation of diazo compounds with EBX reagents.

(Scheme 2A). This transformation highlights the chemoselectivity of the method in the presence of carbon−hydrogen bonds, olefins, and carbonyls, which can react with carbene intermediates.[20]

The obtained products contain three valuable functional groups: an alkyne, an iodide, and an ester. Oxy-alkynylated products **3a**, **3d**, and **3w** were synthesized on gram scale in 91%, 84%, and 79% yield, respectively. Ester **3d** could be readily hydrolyzed, affording the alkyne substituted *α*-hydroxy acid **11** in 94% yield (Scheme 2B). Copper-catalyzed cycloaddition of terminal alkyne **3y**, obtained by desilylation of **3d**, with benzyl and phenyl azides gave triazoles **12** and **13** in high yields. Deiodination of **3y** was achieved using visible light photoredox catalysis to give product **14** in 82% yield.[21] Isocoumarin derivative **15** could be synthesized using a domino carbopalladation/Suzuki cascade reaction[22] in 60% yield from **3w**. Tetra-substituted allene **16** was also obtained as a side product in the coupling reaction. Finally, a domino carbopalladation/Heck cascade reaction was also possible to furnish product **17** in 24% yield from **3w**.

Scheme 2. Late Stage Reaction and Product Modifications[a]

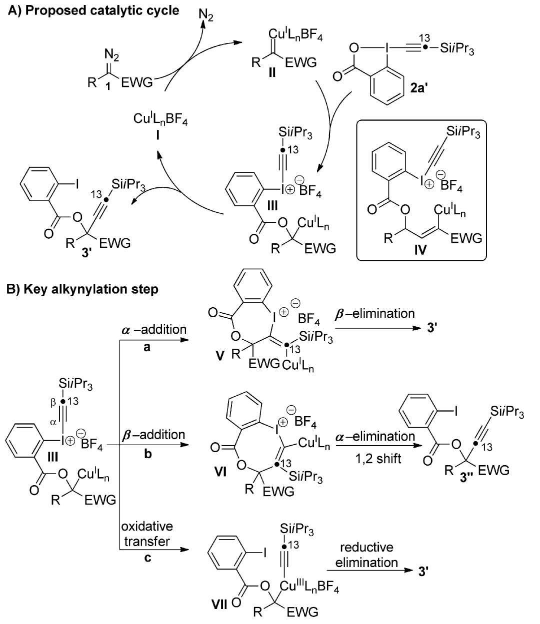


[a]Reaction conditions: (a) K_2CO_3, EtOH; (b) R^1N_3, 20 mol % $CuSO_4 \cdot 5H_2O$, sodium ascorbate, triazole ligand, *t*BuOH/H_2O; (c) 2.5 mol % *fac*-Ir(ppy)$_3$, NBu_3, HCO_2H, blue LED, MeCN; (d) 5 mol % Pd(PPh$_3$)$_4$, K_2CO_3, PhB(OH)$_2$, DMF; (e) ethyl acrylate, 5 mol % Pd(PPh$_3$)$_4$, NEt_3, DMF.

Based on literature reports[5,13,17] and our own results, we propose a tentative mechanism for the reaction (Scheme 3A). The Cu(I) catalyst **I** first reacts with diazo compound **1** to form copper-carbene intermediate **II**. Then the carboxylate group of EBX reagent **2** adds to carbene intermediate **II** to form organocopper species **III**. Finally, intramolecular alkyne transfer gives product **3**. For vinyl diazo compound **5**, conjugate addition on the formed carbene intermediate would give organocopper species **IV**, which affords enyne product **6** as a single geometric isomer after alkyne transfer. For the alkyne transfer step, several mechanisms could be envisaged (Scheme 3B): nucleophilic attack on either the *α* or *β* position of the alkynyliodonium salt (pathways **a** and **b**), or oxidative alkyne transfer to copper (pathway **c**). In the case of *α*-addition, *β*-elimination of the iodine would led directly to the product from the formed intermediate **V**. Alternatively, a concerted reaction could also be envisaged.[7d] However, *β*-addition would furnish first a vinylidene intermediate via *α*-elimination on addition product **VI**. A fast 1,2-silicon shift would then lead to product **3**.

When ^{13}C labeled TIPS-EBX reagent **2a′** was used in the reaction, product **3′** without 1,2-shift of the silyl group was obtained exclusively, which indicated that addition on the *β* position is less probable. However, oxidative alkyne transfer to

Scheme 3. Proposed Mechanism for Oxy-Alkynylation



give copper(III) intermediate **VII**, followed by reductive elimination (pathway **c**) would also lead to the observed product **3′**. Consequently, further investigations will be needed to elucidate the mechanism of the alkyne-transfer step.

In conclusion, we have developed an atom economical oxy-alkynylation of diazo compounds using EBX reagents. The reaction protocol is highly practical and characterized by mild reaction conditions, high yields, and the use of an inexpensive copper catalyst. A remarkably broad range of R-EBX reagents and diazo compounds were well tolerated in this transformation. In the case of vinyl diazo compounds, we obtained enyne products as single olefin isomers in high yields. The obtained products were efficiently transformed into useful building blocks such as α-hydroxy acids, triazoles, and isocoumarins. Further investigation using other hypervalent iodine reagents, studies to confirm the proposed mechanism of the reaction, and the development of an asymmetric version of the transformation are currently ongoing in our laboratories.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b00278.

Experimental procedures (PDF)
Analytical data (CIF)

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Notes

The authors declare no competing financial interest.

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