ABSTRACT: Alkynes have found widespread applications in synthetic chemistry, biology and material 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. Alkynes are broadly applied as chemical building blocks for the synthesis of fine chemicals. In past years, they have also gained a lot of interest for applications in biochemistry or material sciences. 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. However, introducing triple bonds only to electrophilic positions strongly limits the flexibility and efficiency of alkyn synthesis. Major efforts have therefore been made to develop electrophilic alkynylation methods, relying on the umpoling of the innate reactivity of acetylenes (Scheme 1A).

Hypervalent iodine reagents such as alkynyliodonium salts have been particularly successful for the electrophilic alkynylation of nucleophiles. However, the use of alkynyliodonium salts is limited due to their low stability. Recently, EthynylBenziodoxol(on)e (EBX) have been introduced as excellent electrophilic reagents for the alkynylation of ketoesters, thiols, and aromatic C-H bonds using transition metal catalysis; among many other successful transformations. 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. Recently, Greaney and co-workers and Dauban and co-workers reported more atom economical transformations based on the use of the formed aryl iodosides in cross-coupling reactions with aryliodonium salts and Ph(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 alkynyliodonium salts to give furan derivatives.

Scheme 1. Alkynylation strategies and multi-component 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 complexes 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. 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. Recently, research in the area has focused on the development of multi-component reactions to afford products with high structural diversity, complexity, and atom economy (Scheme 1B). The only approach for the synthesis of alkynes from diazo compounds has been reported by Wang and co-workers for a reaction involving metal carbone migratory insertion with nucleophilic...
alcanes.\textsuperscript{12} 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 non-expensive copper catalyst (Scheme 1C). The reaction exhibits a broad scope towards 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-[[trisopropylsilyl]ethyl]-1,2-benzenodioxole-3(1H)-one (TIPS-EBX, 2a) using 5 mol% of Rh(OMAc)\textsubscript{3} in DCM at 40 °C, but did not obtain the desired product 3a (Table 1, entry 1). Replacing Rh(OMAc)\textsubscript{3} with Cu(OTf)\textsubscript{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\textsubscript{2}CN)\textsubscript{2}BF\textsubscript{4} was used (Table 1, entry 3), whereas the use of other metal catalysts such as CuCl, Cu(OAc)\textsubscript{2}, PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2}, and AuBr\textsubscript{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). Alkynyl 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: \textsuperscript{13} 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\textsubscript{2}CN)\textsubscript{2}BF\textsubscript{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-buty1 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,\textsuperscript{14} 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-diethy1acetamide, 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-3t). 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (x mol %)</th>
<th>Solvent (conc.) Time/T (°C)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh(OMAc)\textsubscript{3} (5.0)</td>
<td>DCM (0.1 M)</td>
<td>2 h/40</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OTf)\textsubscript{2} (5.0)</td>
<td>DCM (0.1 M)</td>
<td>20 h/40</td>
</tr>
<tr>
<td>3</td>
<td>Cu(CH\textsubscript{2}CN)\textsubscript{2}BF\textsubscript{4} (5.0)</td>
<td>DCM (0.1 M)</td>
<td>20 h/40</td>
</tr>
<tr>
<td>4</td>
<td>CuCl (5.0)</td>
<td>DCM (0.1 M)</td>
<td>20 h/40</td>
</tr>
<tr>
<td>5</td>
<td>Cu(OAc)\textsubscript{2} (5.0)</td>
<td>DCM (0.1 M)</td>
<td>20 h/40</td>
</tr>
<tr>
<td>6</td>
<td>PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2} (5.0)</td>
<td>DCM (0.1 M)</td>
<td>2 h/40</td>
</tr>
<tr>
<td>7</td>
<td>AuBr\textsubscript{3} (5.0)</td>
<td>DCM (0.1 M)</td>
<td>18 h/40</td>
</tr>
<tr>
<td>8</td>
<td>Cu(CH\textsubscript{2}CN)\textsubscript{2}BF\textsubscript{4} (5.0)</td>
<td>DCE (0.1 M)</td>
<td>2 h/65</td>
</tr>
<tr>
<td>9</td>
<td>Cu(CH\textsubscript{2}CN)\textsubscript{2}BF\textsubscript{4} (5.0)</td>
<td>DCE (0.1 M)</td>
<td>1 h/65</td>
</tr>
<tr>
<td>10</td>
<td>Cu(CH\textsubscript{2}CN)\textsubscript{2}BF\textsubscript{4} (2.0)</td>
<td>DCE (0.1 M)</td>
<td>1.5 h/65</td>
</tr>
<tr>
<td>11</td>
<td>Cu(CH\textsubscript{2}CN)\textsubscript{2}BF\textsubscript{4} (2.0)</td>
<td>DCE (0.05 M)</td>
<td>2.5 h/65</td>
</tr>
<tr>
<td>12</td>
<td>Cu(CH\textsubscript{2}CN)\textsubscript{2}BF\textsubscript{4} (2.0)</td>
<td>DCE (0.05 M)</td>
<td>1 h/RT</td>
</tr>
<tr>
<td>13</td>
<td>Cu(CH\textsubscript{2}CN)\textsubscript{2}BF\textsubscript{4} (2.0)</td>
<td>DCE (0.05 M)</td>
<td>20 h/RT</td>
</tr>
<tr>
<td>14</td>
<td>No catalyst</td>
<td>DCE (0.05 M)</td>
<td>20 h/65</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: 0.30 mmol ethyl diazoacetate (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. \textsuperscript{b}With 0.50 mmol 1a. \textsuperscript{c}With 2.5 mol % of 4a. \textsuperscript{d}With 2.5 mol % of 4b.

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 carbeneid and the vinylogous center.\textsuperscript{15} 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-diazo-hex-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.\textsuperscript{16} 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-6k). 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,\textsuperscript{19} which could be smoothly converted to the desired products 9 and 10 in 82% and 75% yield, respectively (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.\textsuperscript{20}
Figure 1. Scope of the copper-catalyzed oxy-alkynylation of diazo compounds with EBX reagents.

The obtained products contain three valuable functional groups: an alkyne, an iodide, and an ester. Oxy-alkynylation 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. Isocoumarins derivative 15 could be synthesized using a domino carbopalladation/Suzuki cascade reaction 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.

Based on literature reports 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 compounds 5, conjugate addition on the formed carbene intermediate would give organocopper species IV, which affords to 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 alkynylidonium salt (pathways a and b), or oxidative alkyne transfer to copper (pathway c). In case of α-addition, β-elimination of the iodine would lead directly to the product from the formed intermediate V. Alternatively, a concerted reaction could also be envisaged. On the other hand, β-addition would furnish first to a vinylidene intermediate via α-elimination on addition product VI. A fast, 1,2-silicon shift would then lead to product 3.

Scheme 2. Late stage Reaction and Product Modifications.

A) Late stage oxy-alkynylation of steroids

B) Product modifications

Reaction conditions: a) K₂CO₃, EtOH. b) RʼNₛ, 20 mol % CuSO₄•5H₂O, sodium ascorbate, triazole ligand, RBuOH/H₂O. c) 2.5 mol % fac-Ir(ppy)₃, NBu₃, HCO₂H, blue LED, MeCN. d) 5 mol % Pd(PPh₃)₄, K₂CO₃, PhB(OH)₂, DMF. e) Ethyl acrylate, 5 mol % Pd(PPh₃)₄, NEt₃, DMF.
The authors declare no competing financial interests.

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**REFERENCES**


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

Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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**Notes**

The authors declare no competing financial interests.
The diagram illustrates a chemical reaction process involving the conversion of two different molecular structures. The process is catalyzed by 2-4 mol% Cu(I) and proceeds at room temperature (RT).

Key features of the process include:
- 12 examples with up to 90% yield
- 26 examples with up to 86% yield
- High atom economy
- Mild conditions
- Broad scope

The chemical structures depicted suggest a transformation that involves nucleophilic addition or substitution reactions, potentially involving electrophilic substitution or other organic chemistry reactions.