

Copper-Catalyzed Oxyvinylation of Diazo Compounds

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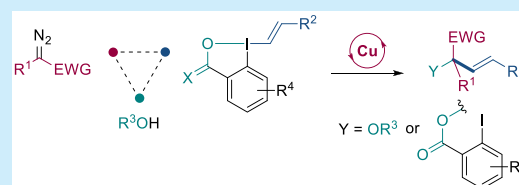
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ABSTRACT: A copper(I)-catalyzed vinylation of diazo compounds with vinylbenziodoxolone reagents (VBX) as partners is reported. The transformation tolerates diverse functionalities on both reagents delivering polyfunctionalized vinyated products. The strategy was successfully extended to a three-component/intermolecular version with alcohols. The obtained products contain synthetically versatile functional groups, such as an aryl iodide, an ester, and an allylic leaving group, enabling further modification.



Metal carbenes obtained from diazo compounds have been extensively used in synthetic chemistry,¹ and their *gem*-difunctionalization is a powerful method to access complex products (Scheme 1A).² The formation of at least one new C–C bond in this process has been realized for alkylation, arylation and alkynylation reactions using palladium,³ copper⁴ and rhodium⁵ catalysis. The most successful approaches involve cross-coupling through carbene migratory insertion (path a),^{2b} or trapping of transient ylides with carbon electrophiles (path b).^{2a}

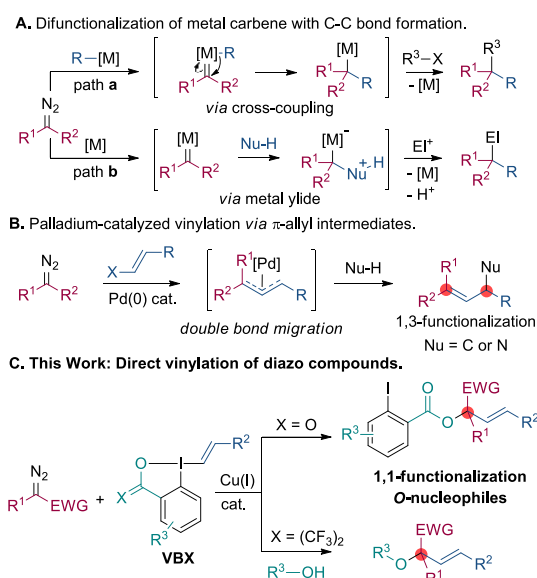
The introduction of an olefin in such processes has been limited to the formation of a C-alkenyl and a C–H bond,⁶ with the exception of a palladium-catalyzed cross-coupling combining vinylhalides and nucleophiles (Scheme 1B).⁷ The reaction proceeds via a π -allyl palladium species, resulting in a 1,3

relationship between the nucleophile and the vinyl group. We considered a reverse approach to develop an unprecedented 1,1-oxyvinylation: Addition of an oxygen nucleophile first, followed by reaction with an electrophilic hypervalent iodine vinylation reagent (Scheme 1C). Our group established an efficient copper-catalyzed 1,1-oxyalkynylation of diazo compounds based on the use of electrophilic ethynylbenziodoxolone (EBX) hypervalent iodine reagents.^{8,9} To develop the first direct vinylation of diazo compounds, we envisaged the use of the corresponding vinylbenziodoxolone (VBX) reagents recently reported by Olofsson and co-workers.¹⁰

In this work, we report a copper-catalyzed insertion of diazo compounds into VBX reagents proceeding with broad scope at room temperature. The transformation was successfully extended to the synthesis of allylic ethers using alcohols as external nucleophiles.

We started our optimization by reacting Ph-VBX (1a) with ethyl diazoacetate (2a) (Table 1; see the Supporting Information for other tested conditions, Table S1). No desired product was isolated without copper catalyst or ligand (entries 1 and 2). Allylic ester 4a was formed in 90% yield when Cu(CH₃CN)₄BF₄ (4 mol %) was used in combination with diimine 3a (5 mol %) (entry 3).^{8a} A lower yield was obtained with more electron-rich VBX 1c (entry 4). No reaction occurred using the alkyl-substituted substrate 1j even at a higher temperature (entry 5). We therefore investigated bisoxazoline (BOX) ligands, which had also been successful in our previous work.^{8b} Using *t*Bu-BOX ligand 3b, the reaction could be performed in one hour at room temperature to give 4a in 95% yield as a racemate (entry 6). The nonchiral ligand 3c gave a similar result (entry 7). These conditions performed well with

Scheme 1. General Difunctionalization of Metal Carbenes (A) and Vinylation of Diazo Compounds (B and C)

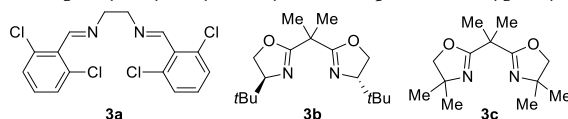
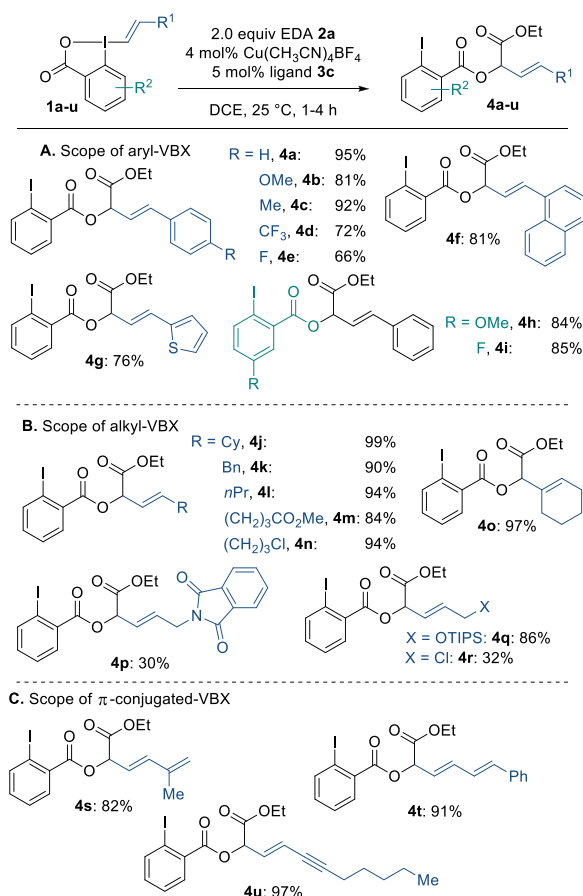


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Table 1. Optimization of the Insertion of Diazo Compounds 2a and 2b into VBX (1)^a

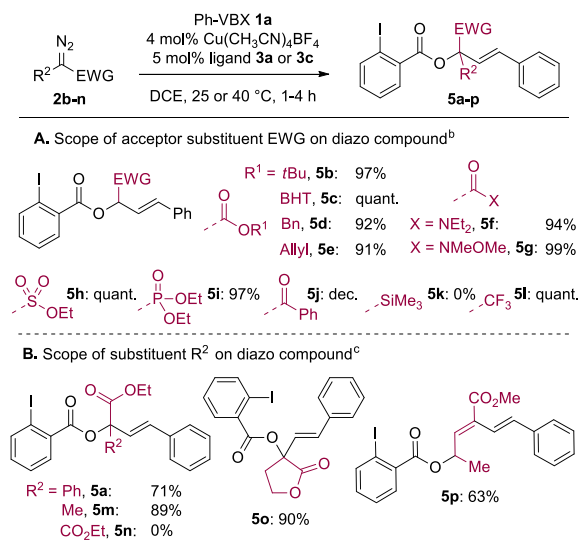
entry	ligand	diazo R ¹ =	VBX R ² =	product	temp	time	yield ^b
1 ^c	3a	H (2a)	Ph (1a)	4a	40 °C	4 h	0%
2	none	H (2a)	Ph (1a)	4a	40 °C	4 h	<5%
3	3a	H (2a)	Ph (1a)	4a	40 °C	4 h	90%
4	3a	H (2a)	PMP (1c)	4b	60 °C	24 h	50%
5	3a	H (2a)	Cy (1j)	4j	60 °C	24 h	<5%
6	3b	H (2a)	Ph (1a)	4a	25 °C	1 h	95%
7 ^d	3c	H (2a)	Ph (1a)	4a	25 °C	1 h	95%
8 ^d	3c	H (2a)	PMP (1c)	4b	25 °C	4 h	81%
9 ^d	3c	H (2a)	Cy (1j)	4j	25 °C	4 h	99%
10	3c	Ph (2b)	Ph (1a)	5a	40 °C	4 h	<5%
11	3a	Ph (2b)	Ph (1a)	5a	40 °C	4 h	80%

^aReactions on 0.10 mmol scale with 2.0 equiv of 2, 4 mol % Cu(CH₃CN)₄BF₄, 5 mol % ligand in DCE (0.04 M). ^bIsolated yields. ^cWithout Cu(CH₃CN)₄BF₄. ^dOn 0.20 mmol scale. Ph = phenyl, Cy = cyclohexyl, PMP = *para*-methoxyphenyl.

Scheme 2. Scope of VBX Reagents^a

^aReactions using VBX 1 (0.2 mmol) and 2a (0.4 mmol) in DCE (0.04 M).

the more electron-rich and aliphatic substrates (entries 8 and 9), but were not successful for substituted diazo compound 2b

Scheme 3. Scope of Diazo Compounds 2^a

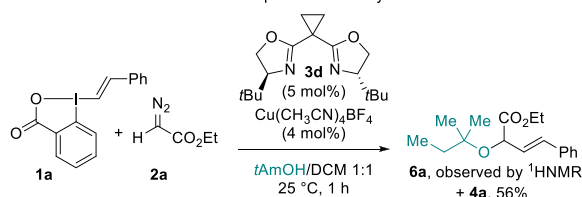
^aReactions using Ph-VBX (1a) (0.2 mmol) and 2 (0.4 mmol) in DCE (0.04 M). ^b3c as ligand at 25 °C. ^c3a as ligand at 40 °C.

(entry 10). Product 5a could be obtained in 80% yield using ligand 3a (entry 11). In all reactions, only the *E*-olefin was obtained.

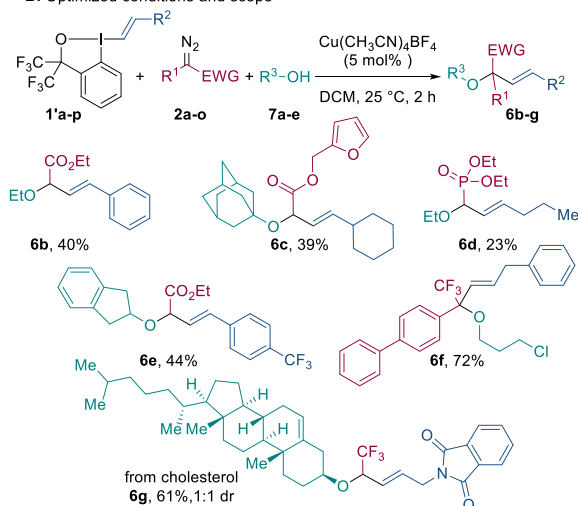
Diverse aryl-substituted VBXs were then explored with ethyl diazoacetate (2a) (Scheme 2A).¹¹ Electron donating ether and alkyl groups on the arene afforded products 4b,c in 81% and 92% yields, respectively. Fluorinated compounds 4d and 4e were obtained in 72% and 66% yields, respectively. A naphthyl-substituted VBX led to the formation of 4f in 81% yield. A slightly diminished yield was obtained for thiophene-substituted 4g (76% yield). Both electron-rich and -poor substituents on the benziodoxolone backbone were tolerated, affording 4h and 4i. Next, we turned our attention to alkyl-substituted VBX reagents (Scheme 2B). VBXs bearing aliphatic chains (Cy, Bn, and *n*Pr)

Scheme 4. Extension to Three-Component Reaction^a

A. Initial observation of a three-component diazovinylation reaction



B. Optimized conditions and scope



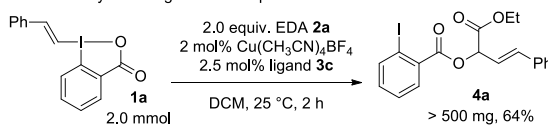
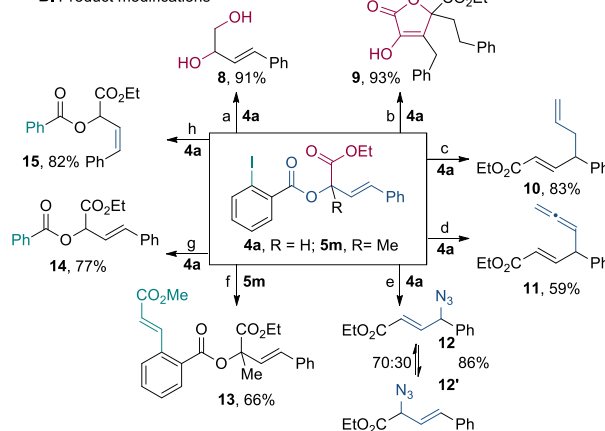
^aReactions using VBX (1v–z) (0.3 mmol) and R³OH (0.9 mmol) in DCM (0.075 M). Diazo 2 (0.6 mmol, 0.6 M in DCM) added via syringe pump over 1 h.

provided allylic esters 4j–l in 90–99% yield. The incorporation of an ester (4m) or a chloride (4n) group could also be achieved. Trisubstituted alkene 4o was accessed in 97% yield. VBXs with amines, silyl ethers, and chlorides in the allylic position delivered the corresponding products 4p–r. A lower yield was obtained for 4p and 4r, maybe due to the low solubility of the corresponding VBX reagents in DCE. π -Conjugated systems were readily incorporated (Scheme 2C). An isoprene skeleton was introduced to give 4s in 82% yield. Conjugated diene 4t and enyne 4u were also successfully synthesized.

We next investigated the scope of the acceptor substituent on the diazo compounds (Scheme 3A). Various esters such as *t*Bu or BHT were tolerated giving 5b and 5c in quantitative yield.¹² Product 5d bearing a benzyl group was obtained in 92% yield and 5e with an allyl group in 91%. 2-Diazo-*N,N*-diethylacetamide provided 5f in 94% yield. Weinreb amide derivative 5g was isolated in 99% yield. Sulfonate- and phosphonate-diazo compounds were efficient coupling partners, generating products 5h and 5i in quantitative yields.¹³ Unfortunately, diazoketones underwent degradation through Wolff rearrangement (5j) and no conversion was obtained using trimethylsilyldiazomethane (5k, 0% yield). However, compound 5l incorporating a trifluoromethyl group was isolated in quantitative yield. Organofluorine compounds are important for the pharmaceutical, agrochemical, and materials industries.¹⁴ Other less stable diazo compounds lacking an electron-withdrawing group were not yet investigated. Finally, the reaction of disubstituted diazo compounds was investigated using diimine ligand 3a (Scheme 3B). Products 5a and 5m with tertiary allylic centers were formed in 71 and 89% yield. A second electron-withdrawing group suppressed the reactivity

Scheme 5. Scale-up Synthesis and Product Modifications

A. Low catalyst loading and scale-up

B. Product modifications^a

^aReaction conditions: (a) LiAlH₄ (3.00 equiv), THF, 0 °C to rt, 1 h, 91%; (b) DBU (10 equiv), MeOH, 50 °C, 6 h, 93%; (c) allyl-TMS (1.5 equiv), TiCl₄ (1.05 equiv), DCM, 0 °C, 15 min, 83%; (d) propargyl-TMS (2.0 equiv), TiCl₄ (1.05 equiv), DCM, −78 to 0 °C, 59%; (e) TMSN₃ (1.5 equiv), TiCl₄ (1.05 equiv), DCM, −20 to 0 °C, 12/12' 70:30, 86%; (f) methyl acrylate (5.0 equiv), PdCl₂(PPh₃)₃ (5 mol %), PPh₃ (5 mol %), Et₃N, 80 °C, 24 h, 66%; (g) H₂, Pd/C (10 mol %), 10% w/w, DABCO (10 equiv), MeOH, rt, 10 min, 77%; (h) *fac*-Ir(ppy)₃ (2.5 mol %), NBu₃ (10 equiv), HCO₂H (10 equiv), blue LED, MeCN, 40 °C, 18 h, 82%.

(5n, 0% yield). A cyclic diazo compound afforded the desired product 5o in 90% yield. Diene product 5p could be obtained in good yield when starting from a vinyl diazo precursor. Attack of the nucleophile at the vinylogous center was favored.¹⁵

We then investigated an enantioselective version of the reaction. Testing various substrates, chiral ligands, and reaction conditions, we achieved a maximum of 75:25 er with ligand 3d for the formation of 5c (see Table S3 for details).¹⁶ Interestingly, with *tert*-amyl alcohol as the cosolvent, we observed ¹H NMR signals tentatively assigned to allylic ether product 6a in the crude reaction mixture, in addition to expected 4a for the reaction of VBX 1a and 2a (Scheme 4A).

To favor the three-component reaction, we used less nucleophilic bis-trifluoromethyl benziodoxole VBX 1' and removed the ligand (see Table S2 for details).¹⁷ With 3 equiv of alcohol, the three-component products were obtained in 23–72% yield (Scheme 4B). Primary, secondary, and tertiary alcohols were combined with different VBXs and diazo compounds leading to functionalized allylic ethers bearing esters (6b, 6c, and 6e), phosphonate (6d), chloride (6f), furan (6c), indanyl (6e), adamantyl (6c), or trifluoromethyl (6e and 6f) groups. The vinylation of cholesterol was achieved in 61% yield affording 6g with a trifluoromethyl and a phthalimide group.

Product 4a was synthesized on the 2.0 mmol scale using a lower catalyst loading at higher concentration (Scheme 5A). The ester groups in 4a were readily reduced with LiAlH₄ to produce diol 8 (Scheme 5B). Butenolide 9 resulting from the formation of an α -keto ester followed by dimerization was formed under basic conditions. Treatment of 4a with TiCl₄ and

allyl-TMS led to the formation of conjugated ester **10**. Propargyl-TMS could also be used as nucleophile giving allene-containing product **11**. The introduction of an azide was accomplished using TMSN₃ to form **12**, which isomerizes spontaneously.¹⁸ A Heck reaction between **5m** and methyl acrylate afforded **13** in 66% yield. Hydrogenolysis of the iodoarene was achieved with hydrogen and poisoned Pd/C to give product **14** in 77% yield. Visible light photoredox catalysis gave access to the deiodinated product **15** in 82% yield with *E* to *Z* isomerization of the olefin.

Based on literature precedence and our work on the copper-catalyzed oxy-alkynylation reaction,^{8a-c} a tentative reaction mechanism would involve an electrophilic copper-carbene generated from the diazo compound (see Scheme S1 in the Supporting Information). Nucleophilic attack of the carboxylate part of the VBX reagent or the alcohol nucleophile would generate an ylide intermediate, which is then vinylated.

In summary, we have developed a copper-catalyzed insertion of diazo compounds into vinylbenziodoxolone (VBX) reagents. The transformation provides access to a broad scope of functionalized allylic esters.¹⁹ Extension of the strategy to a three-component reaction with alcohol nucleophiles allowed the synthesis of structurally diverse allylic ethers. The obtained products can be further modified to give important building blocks. Ongoing research is focused on the elucidation of the reaction mechanism and the development of the asymmetric version of the transformation based on our preliminary results.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.0c01150>.

Supplementary tables (Tables S1 and S2: details for optimization of the reactions, Table S3: attempts towards an enantioselective reaction), and scheme (Scheme S1: proposal for the reaction mechanism), experimental procedures, and characterization data (NMR, IR, MS, X-ray) (PDF)

Accession Codes

CCDC 1993681 and 1897009 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

Raw NMR, IR, and MS data is available at zenodo.org, DOI: 10.5281/zenodo.3764827.

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their reactivity, are very different, leading to different interactions with the ligands in the transition state. Obviously, another type of ligand will be needed to achieve high enantioinduction in this case.

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