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Light-Driven Intermolecular Charge Transfer Induced Reactivity of Ethynylbenziodoxol(on)e (EBX) and Phenols

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ABSTRACT: Ethynylbenziodoxol(on)es (EBXs) have been widely used in organic synthesis as electrophilic alkyne-transfer reagents involving carbon- and heteroatom-based nucleophiles. However, potential reactions of EBXs with phenols remain uninvestigated. Here, we present the formation of (*Z*)-2-iodovinyl phenyl ethers with excellent regio- and stereoselectivity through the reactivity between EBXs and phenols driven by visible light. We propose that this light-activated transformation proceeds through electron donor-acceptor complexes to enable new reactivity beyond existing mechanisms for alkynylation of carbon- and heteroatom-based nucleophiles. This operationally robust process was employed for the synthesis of diverse (*Z*)-2-iodovinyl phenyl ethers through irradiating a solution containing a phenyl-EBX, a phenol, and the base Cs_2CO_3 with a commercially available blue LED at room temperature. The (*Z*)-2-iodovinyl phenyl ether products can be further stereospecifically functionalized to form tri-substituted alkenes, demonstrating the potential of these products *en route* to chemical complexity.

INTRODUCTION

Ethynylbenziodoxol(on)es (EBXs)[1-6] are electrophilic reagents which can be used for the alkynylation of carbon- and heteroatom-based nucleophiles.[7-19] Specifically, alkynylation of carbon,[7-11,14-17] sulfur,[12,13] nitrogen[18] and phosphorus[19] nucleophiles has been successfully developed (Figure 1a). In the process, an alkynyl group is transferred to the nucleophile and 2-iodobenzoic acid is commonly obtained as a stoichiometric byproduct. Other reactions involving EBX reagents such as copper-catalyzed oxyalkynylation of diazo compounds[20,21] (Figure 1d) and Pd(II)-catalyzed transformation of alkynylbenziodoxoles with *N*-aryl imines and carboxylic acids have also been reported (Figure 1b-c).[22-24] Although reactions of carbon- and heteroatom-based nucleophiles with EBX electrophiles have been extensively investigated, there remains unexplored chemistry using phenols as nucleophiles. From a synthetic standpoint, the development of strategies using EBXs and phenols is highly desirable.

Phenol-containing compounds are frequently found in plant secondary metabolites. Notable examples include vanillin, thymol and eugenol, which have been traditionally utilized as important food additives for color, flavor, and astringency.[25,26] Additionally, they are prevalent in a wide range of bioactive natural products such as, steroid hormones, thyroid hormones and monoamine neurotransmitters, such as estrone, estradiol, estriol,[27] triiodothyronine[28] and serotonin.[29] Phenol motifs are also important in medicines. Isoproterenol is used for the treatment of the heart block and levalbuterol is used for the treatment of asthma.[30] Industrially, phenol containing compounds are also one of the most versatile and important organic commodity chemicals.[25] Therefore, direct transformation involving conversion of phenols into a variety of products with a wide range of properties are highly desirable.

Recently, we reported a visible light promoted C-S cross-coupling reaction of thiophenols and aryl halides in the presence of a mild base, Cs_2CO_3.[31] The observed reactivity was enabled

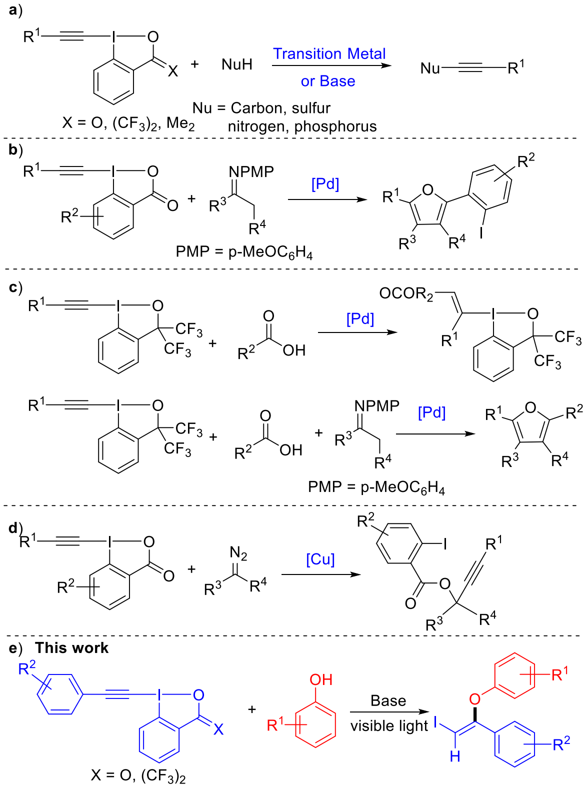


Figure 1. Development of reactions using ethynylbenziodoxol(on)e (EBX) reagents. a) Alkynylation of carbon- and heteroatom-based nucleophiles with EBX reagents. **b**) Palladium-catalyzed reaction of *N*-aryl Imines and EBX reagents to make multisubstituted furans. **c) upper**: Palladium-catalyzed reaction of EBX reagents and carboxylic acids; **lower**: Palladium-catalyzed three-component reaction of EBX reagents, carboxylic acids, and imines. **d**) Copper-catalyzed oxyalkynylation of diazo compounds using EBX reagents. **e**) This work: reactions of EBX reagents and phenols under visible light irradiation. Nu: nucleophile.

through visible light-induced electron transfer within the electron donor-acceptor (EDA) complex; e.g. an electron is transferred from the thiophenoxide (donor) to the aryl halide (acceptor). Inspired by this work, we hypothesized that in the presence of a suitable acceptor, phenol could also be employed as an electron donor in light-driven transformations utilizing EDA complexes.[32]

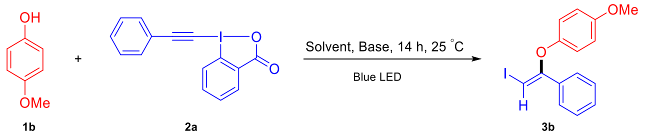
Herein, we report the formation of EDA complexes[33-35] between nucleophilic phenols and electrophilic EBX reagents. UtilizingCs_2CO_3 as a base and under blue LED irradiation, phenols and EBX reagents react to form (*Z*)-2-iodovinyl phenyl ethers with excellent regio- and stereoselectivity (Figure 1e). To the best of our knowledge, this represents the first example of reactivity between EBX reagents and phenols that exploits visible light irradiation at room temperature. Notably, in forming the (*Z*)-2-iodovinyl phenyl ether products, we discovered an unprecedented cleavage of the phenyl-I bond of EBX reagents to yield vinyl halide products. Vinyl halides are important intermediates in organic synthesis and we demonstrate these (*Z*)-2-iodovinyl phenyl ethers as versatile synthetic precursors to undergo a range of transition metal-catalyzed cross-coupling reactions, such as Buchwald–Hartwig,[36] Ullmann[37] and Suzuki[38] reactions, to generate functionally diverse tri-substituted alkenes.

RESULTS AND DISCUSSION

We commenced our studies by evaluating 4-methoxyphenol **1b** and phenyl-EBX **2a** in similar reaction conditions to those developed for our C-S cross-coupling reaction (Table 1).[31] Gratifyingly, reactivity between **1b** and **2a** was observed after 14 h of blue LED irradiation at room temperature (Table 1, entry 1) and the (*Z*)-2-iodovinyl phenyl ether product **3b** was isolated in 46% yield. Compared to the typical alkynylation products and 2-iodobenzoic acid byproduct (Figure 1a) obtained in previous EBX reactions,[7-19] we observed a unique phenyl-I bond cleavage to synthesize **3b** with benzoic acid or **14** as byproducts; this new reactivity is attributed to the photoinduced electron transfer in the EDA complex. Subsequent optimization experiments led to selection of acetonitrile as the solvent (Table 1, entry 1-4), a loading of **1b** is 1.5 equiv (entry 4-7), and a duration of 14 h irradiation to achieve good yield (entry 4, 8-9). Among multiple bases investigated (entry 4, 11-14), the use of 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) resulted in the highest yield (78%) while only trace product was detected in the absence of base (Table S2). Interestingly, **3b** was also formed in the absence of light when the strong organic base TBD was used, albeit at lower yield (58%, Table S2). Cs_2CO_3, which is less expensive than TBD, is also an excellent base for this transformation (74%, Table 1, entry 4) and was therefore used throughout the remainder of this study. Using the inorganic Cs_2CO_3 base, light irradiation is mandatory for reactivity (Table S2) while the presence of oxygen significantly reduces product formation (Table 1, entry 10).

Using the optimized reaction conditions, a variety of phenols were transformed into the corresponding 2-iodovinyl phenyl ethers in moderate to good yields with high regio- and stereoselectivities (Scheme 1). Overall, no significant electronic effects of the phenol on the reaction was observed. Explicitly, the reaction tolerated both electron-donating and electron-withdrawing substituents on the phenol, including amine (**3o**, **3p**, **3v**,), methoxy (**3b**, **3c**, **3x**, **3y**) and trimethylsilyl (**3d**) groups as well as halogens (**3e-l, 3w, 3x**), aldehyde (**3q**), ester (**3r, 3v**) and trifluoromethyl (**3s**) groups. A phenol bearing a boronic acid pinacol ester group also afforded the corresponding 2-iodovinyl phenyl ether derivative **3a**, albeit in modest yield (45%). When an allylic-containing substrate was employed, TBD was observed to be the best base for this transformation and provided the corresponding 2-iodovinyl phenyl ether derivative **3ag (**SI, page S8) in 52% yield. Notably, a protected amino acid could also be transformed to the desired product **3ah** (SI, page S8)in 40% yield using TBD as a base, demonstrating the high functional group tolerance of the transformation. Additionally, hydroxyl-heteroaryls, ubiquitous among biologically active molecules and pharmaceutical products, similarly reacted to provide the desired products **3ab**, **3ad**, **3ae** and **3af** in 61, 70, 52 and 40% yields, respectively. The 2-iodovinyl phenyl ether products obtained were assigned as (*Z*)-isomer, as supported from X-ray diffraction analysis of **3aa** (Scheme 1). Density functional theory (DFT) calculations corroborated that the (*Z*)-isomer of **3b** is 3.4 kcal/mol more stable than the corresponding (*E*)-isomer. Different alcohols were also explored. With CF_3CH_2OH, we were able to obtain the desired product at 31% yield, albeit with a mixture of *Z* and *E* isomers, while no desired products were isolated with other alcohols, such as 1,1,1,3,3,3-Hexafluoro-2-propanol, benzyl alcohol and ethanol (Table S3).

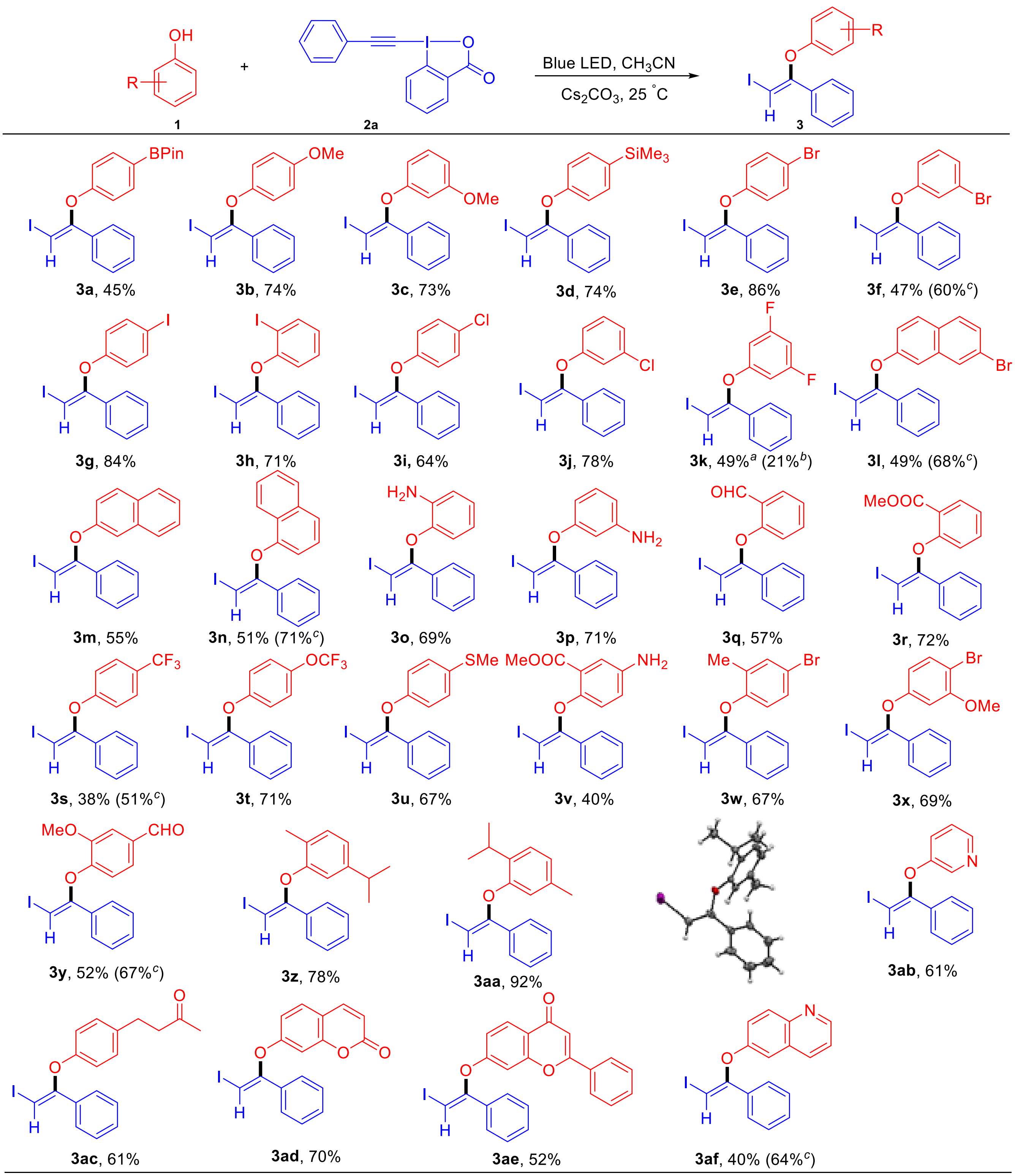
Table 1. Initial investigation of the synthesis of (Z)-2-iodovinyl phenyl ether.



Entry	t (h)	Eq (1b)	Solvent	Base	Yield (%)
1	14	1.5	DMSO	Cs_2CO_3	47 (46[†])
2	14	1.5	DMAc	Cs_2CO_3	44
3	14	1.5	DMF	Cs_2CO_3	47
4	**14**	**1.5**	**CH_3CN**	**Cs_2CO_3**	**75 (74[a])**
5	14	1.0	CH_3CN	Cs_2CO_3	46
6	14	2.0	CH_3CN	Cs_2CO_3	61
7	14	3.0	CH_3CN	Cs_2CO_3	51
8	2	1.5	CH_3CN	Cs_2CO_3	35
9	4	1.5	CH_3CN	Cs_2CO_3	48
10	14	1.5	CH_3CN	Cs_2CO_3	24[b]
11	14	1.5	CH_3CN	DBU	20
12	14	1.5	CH_3CN	MTBD	40
13	14	1.5	CH_3CN	TBD	79 (78[a])
14	14	1.5	CH_3CN	TMG	Trace
15	14	1.5	DMSO	TBD	53
16	14	1.5	THF	TBD	37
17	14	1.5	THF	TMG	20

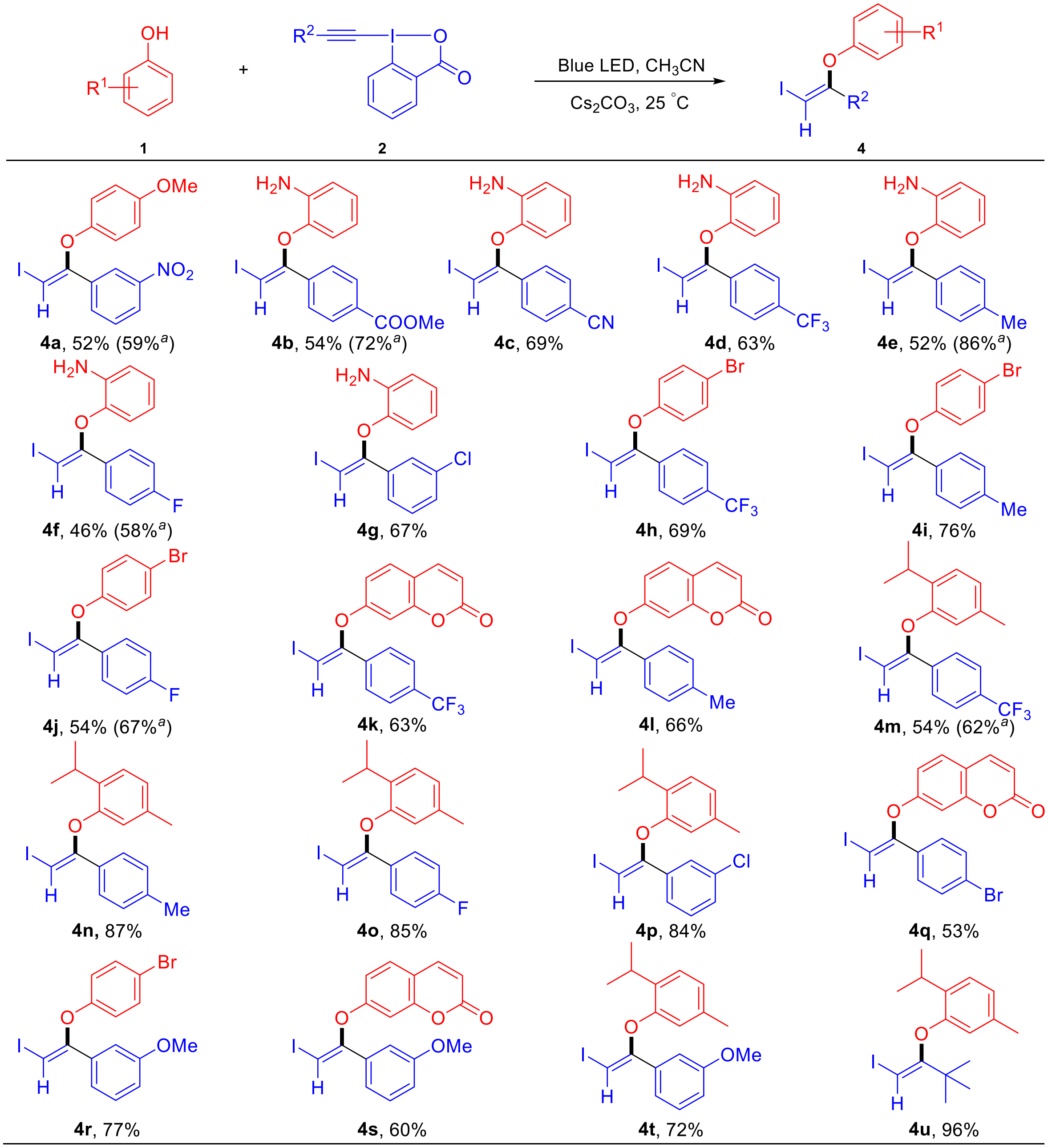
Reaction conditions: **1b** (0.30 mmol), **2a** (0.20 mmol), base (0.30 mmol), solvent (1.5 ml), room temperature, N_2. Yields are determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. [a]Isolated yield. [b]Reaction carried out under air. t: time; Eq: equivalent; DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene; MTBD: 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene; TBD: 1,5,7-triazabicyclo[4.4.0]dec-5-ene; TMG: 1,1,3,3-tetramethylguanidine; DMAc: *N,N'*-dimethylacetamide; DMF: *N,N'*-dimethylformamide; DMSO: dimethyl sulfoxide; THF: tetrahydrofuran.

Scheme 1. Scope of phenols.



Reaction conditions: **1** (0.30 mmol), **2** (0.20 mmol), base (0.30 mmol), solvent (1.5 ml), room temperature, N_2. Isolated yield reported. TBD: 1,5,7-triazabicyclo[4.4.0]dec-5-ene; BPin: 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane. [a]TBD used as a base. [b]performed in the dark and obtained as ^{1}H NMR yield. [c]V_{CH3CN}:V_{Benzene} = 1:1, see Table S1.

Scheme 2. Scope of ethynylbenziodoxol(on)es.



Reaction conditions: **1** (0.30 mmol), **2** (0.20 mmol), base (0.30 mmol), solvent (1.5 ml), room temperature, N$_2$. Isolated yield reported. $^a V_{\mathrm{CH3CN}}:V_{\mathrm{Benzene}}$ = 1:1, see Table S1.

The substrate scope of EBXs was also explored (Scheme 2). A broad range of functional groups on EBXs, including nitro (**4a**), ester (**4b**), cyano (**4c**), trifluoromethyl (**4d**, **4h**, **4k**), methyl (**4e**, **4i**, **4n**), halogens (**4f**, **4g**, **4j**, **4o-q**) and methoxy (**4r-t**) groups, was well tolerated in this process, affording the corresponding (*Z*)-2-iodovinyl phenyl ether products in moderate to good yields. EBX reagents bearing an alkyl group could also be implemented (**4u**). No desired product, however, could be obtained with triisopropylsilyl-EBXs (see Supplementary Information (SI, page S7)). Markedly, phenyl-EBXs derived from other substituted 2-iodobenzoic acids (e.g. 2-Fluoro-6-iodo and 2-iodo-5-nitrobenzoic acid, see SI) similarly reacted with **1b** to produce the same product **3b** in 87% and 42% yields, respectively. This protocol was also applicable to bistrifluoromethyl-substituted benziodoxole (see SI, page S7), which reacted with **1b** to provide **3b** in 52% yield. We note that the use of mixed solvent ($V_{\mathrm{CH3CN}}:V_{\mathrm{Benzene}}$ = 1:1) in a number of cases has improved the product yield (see Scheme 1 and 2).

To demonstrate potential synthetic value of the (*Z*)-2-iodovinyl phenyl ether products, we investigated their chemistry for subsequent transformations (Figure 2). The vinyl ether **3r** efficiently engaged in a series of stereospecific palladium-catalyzed cross-coupling reactions, including Suzuki couplings (**5**, **7**), a Sonogashira reaction (**6**), an Ullmann reaction (**8**), and a

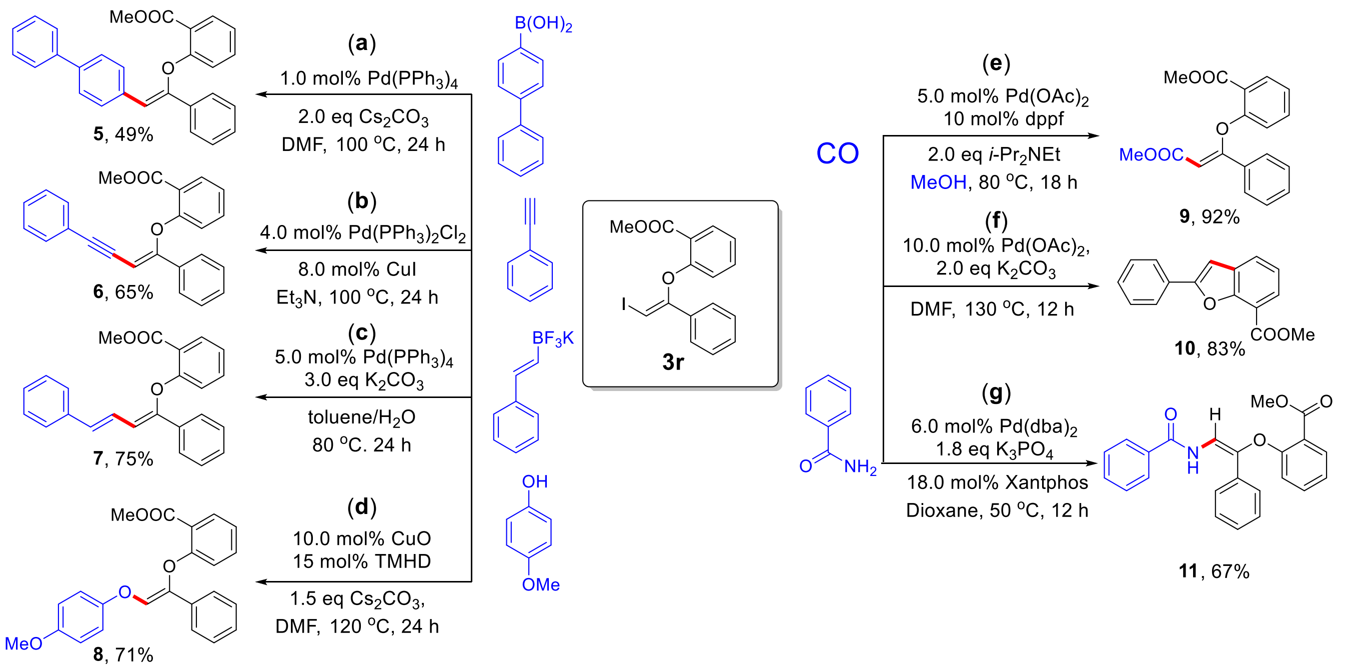


Figure 2. Transition metal-catalyzed transformations of (*Z*)-2-iodovinyl phenyl ethers. **a**) Suzuki coupling; **b**) Sogonashira coupling; **c**) Suzuki coupling; **d**) Ullmann coupling; **e**) Carbonylation; **f**) C-H activation; **g**) Buchwald-Hartwig coupling. PPh$_3$: Triphenylphosphine; TMHD: 2,2,6,6-Tetramethyl-3,5-heptanedione; dppf: 1,1′-Ferrocenediyl-bis(diphenylphosphine); Xantphos: 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

Buchwald−Hartwig amidation (**11**). Furthermore, Pd-catalyzed methoxycarbonylation of **3r** generated **9** in 92% yield. Notably, Pd-catalyzed intramolecular C-H activation furnished benzo[*b*]furan **10** in 83% yield. Using nuclear Overhauser effect spectroscopy (NOESY), we found that compounds **3r**, **5**, **6**, **8**, and **9** are *(Z)*-isomers and that **5**, **6**, **8**, and **9** retained their *(Z)*-conformations after metal-catalyzed transformations. On the contrary, the amidation product of **11** was determined to be an *(E)*-isomer (see SI, page S163). Overall, these results demonstrate the potential of this reaction to provide a unified approach for the preparation of tri-substituted alkenes from readily available phenols and EBX reagents.

A series of experiments and computations were performed to gain insight into this reactivity between EBXs and phenols (Figure 3). In the absence of light, we observed that phenol nucleophilically adds across the triple bond of EBX **2a** to form a vinylbenziodoxolone intermediate (**12**), which is isolatable (Figure 3a). This nucleophilic addition step was computed to be exergonic by 28.3 kcal/mol. We then subjected **12** to our standard reaction condition. Upon combining vinylbenziodoxolone (**12**), **1b** and Cs$_2$CO$_3$ in MeCN, the solution gradually turned yellow, distinctly different from the colorless parent compounds (Figure S7). In accord to the C-S coupling we examined previously,[31] this significant red-shift in the UV-vis absorption suggests the formation of an EDA charge transfer complex. TD-DFT calculations are consistent with the EDA hypothesis as the lowest excitation of the vinylbenziodoxolone **12**-phenoxide complex has extensive charge transfer character (Figure 3a, inset). Specifically, 75% and 14% of the lowest energy excitation is composed of π_{HOMO}-π_{LUMO} and π_{HOMO}- $\pi_{\mathrm{LUMO+1}}$ transitions, respectively, where the π_{HOMO} stems from phenoxide (donor) while the π_{LUMO} and $\pi_{\mathrm{LUMO+1}}$ are derived from vinylbenziodoxolone **12** (acceptor).

To further investigate the EDA complex, we analyzed a Job plot to characterize the complexion between **12b** and sodium phenoxide (Figures S8 and S9). Sodium phenoxide was used as the donor instead of (phenol + Cs$_2$CO$_3$) because the phenol is not completely deprotonated by Cs$_2$CO$_3$ and thus the concentration of the donor is unknown. Using UV-vis spectroscopy, we monitored the absorbance values at 400 nm (corresponding to the $\lambda_{\max}$ of the absorption of the EDA complex) and plotted them as a function of molar fraction of sodium phenoxide. We obtained a parabolic curve with a maximum absorbance value at 50% mole fraction of sodium phenoxide, indicating a 1:1 EDA complex between **12b** and sodium phenoxide. Furthermore, setting [**12b**] at a constant value of 0.005M, we measured the absorbance values at 400 nm as we varied [sodium phenoxide] from 0.005 to 0.045M. Using the Benesi–Hildebrand method,[39-40] we plotted 1/absorbance versus 1/[sodium phenoxide] and obtained a liner relationship (Figures S10 and S11). Through linear regression, the y-intercept and slope values allowed for estimation of the association constant of the EDA complex (K_{EDA}) as 38.9 in DMSO.

Upon blue LED irradiation of the yellow solution (containing vinylbenziodoxolone (**12**), phenol **1b** and Cs$_2$CO$_3$), we obtained the desired product **3b**, whereas only trace amount of product was obtained in the absence of light (Scheme S3). Thus, this observation supports the role of light in phenyl-I bond cleavage to yield product **3b**. We suggest that in the EDA complex, photoinduced electron transfer occurs from the phenoxide (donor) to the vinylbenziodoxolone **12** (acceptor). DFT calculations support that the 1 electron reduction of vinylbenziodoxolone **12** leads to spontaneous phenyl-I bond cleavage to generate **3b** and radical intermediates **13** (Figure 3a); in support of the formation of **13a**, a small amount of benzoic acid could be isolated (see SI). The radical intermediate **13** can then quench to form a C-C

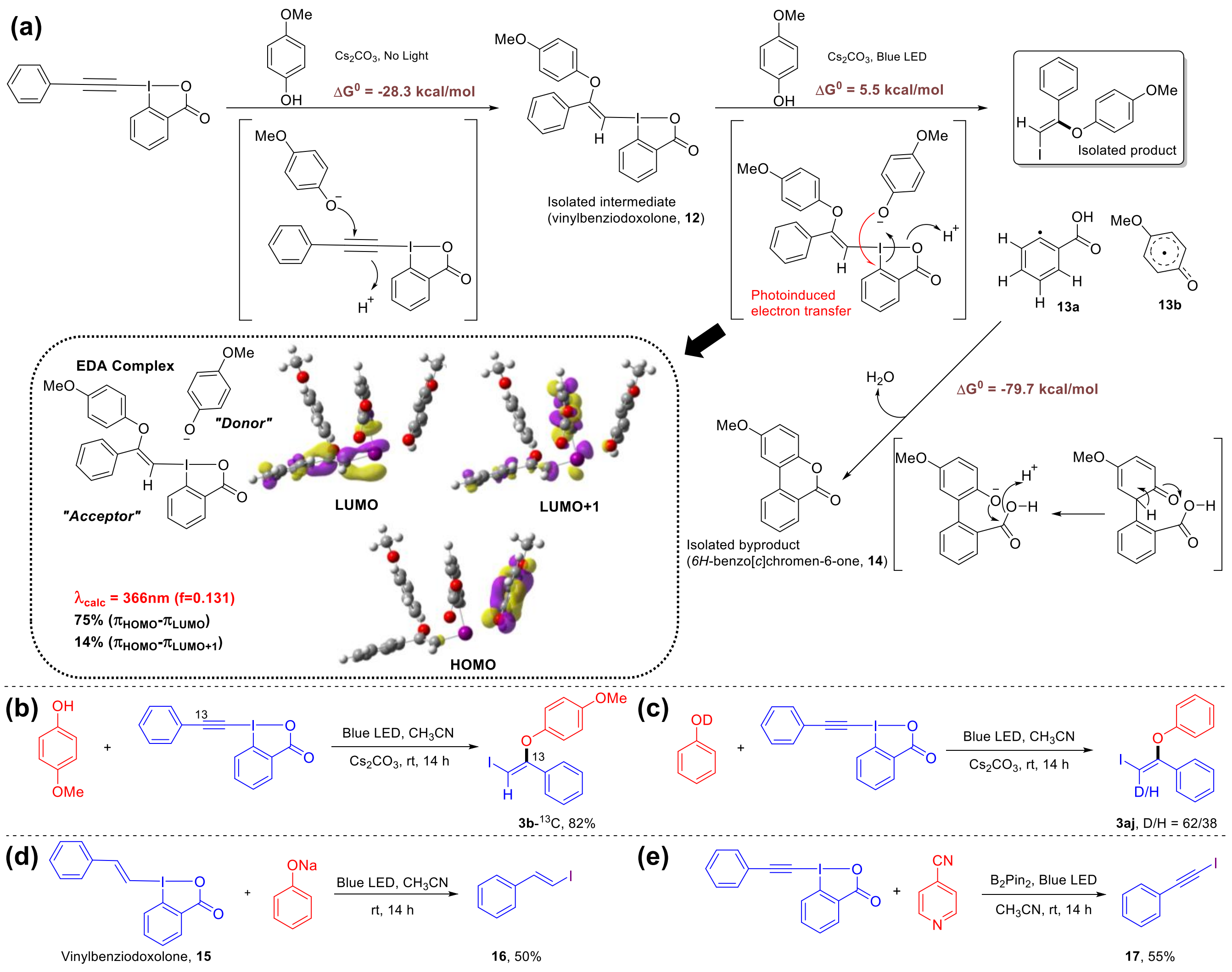


Figure 3. Mechanistic studies. a) Proposed mechanism for the reactivity between EBXs and phenols under the influence of visible light. Thermochemistry evaluation was conducted at the M06/Lanl2dz level of theory with CPCM-described solvation in acetonitrile; CPCM: conductor-like polarizable continuum model. Time-dependent density functional theory (TD-DFT) calculations to model the lowest excited states of the EDA complex were conducted at the CAM-B3LYP/Lanl2dz/CPCM-MeCN level of theory. HOMO: highest occupied molecular orbital; LUMO: lowest unoccupied molecular orbital; f: predicted oscillator strength. λ_{calc}: predicted maximum wavelength of absorption of the lowest excited state. **b)** ^{13}C-labelling experiment. **c)** Experiment involving deuterated phenol. **d)** Experiment involving vinylbenziodoxoione and sodium phenoxide. **e)** Light-driven reaction between EBX **2a**, diboronate ester and pyridine to yield (iodoethynyl)benzene.

bond, which upon rearrangement and elimination of water, finally yields the 6*H*-benzo[*c*]chromen-6-one byproduct **14**. The free energy change for this step was computed to be -79.7 kcal/mol and the byproduct **14** was successfully isolated (20% yield, see SI). To further investigate the observed phenyl-I bond cleavage, we utilized an organic phenoxazine-based photoredox catalyst,[41-44] developed by our group as a strong excited state reductant, to directly reduce vinylbenziodoxolone **12** under blue LED irradiation. Consistent with our proposed mechanism, **3b** was isolated in 47% yield (Scheme S3), which supports our proposition that the phenyl-I bond can be reductively cleaved.

The formation of byproduct **14** may suggest that at least 2.0 equiv of **1b** are needed for reaction completion; however, we empirically determined that 1.5 equiv loading of **1b** was optimum, as higher or lower loadings led to decreased yields (Table 1, entries 5, 6 and 7). Also, at 1.5 equiv. loading, in many cases we obtained yield greater than the theoretical limit of 75% (Scheme 1 and 2). Thus, we hypothesize that the formation of byproduct **14** only contributes in part to **3b**'s formation, as evident from isolation of **14** in 20% yield. It is also interesting to note that when TBD was added to a solution containing vinylbenziodoxolone and phenol **1b**, a more intense yellow solution was observed (as compared to the addition of Cs$_2$CO$_3$). However, in this instance, no light was needed to promote the formation of **3b** (Scheme S3) in good yield. Thus, with TBD, we propose that thermally activated electron transfer results in the phenyl-I bond cleavage.[45]

In addition, we examined reactions using ^{13}C-labeled EBX **2a*** and phenol-OD. As shown in Figure 3b, the reaction of phenol **1b** and ^{13}C-labeled EBX **2a*** afforded **3b-**^{13}C, where ^{1}H and ^{13}C NMR spectrums confirmed the bonding of the phenoxy group to the ^{13}C atom and showed a vinylic hydrogen signal with a J_{C-H} coupling constant of 10 Hz (see SI). Furthermore, the reaction of deuterated phenol(-OD) with EBX **2a** afforded **3aj**

(Figure 3c) where the vinylic hydrogen contains about 62% deuterium (Figure 3c). Using the structurally related di-substituted vinylbenziodoxolone (**15**)[46] and sodium phenoxide, we demonstrated conceptually similar phenyl-I bond cleavage to generate (2-iodovinyl)benzene **16** in 50% yield under blue LED irradiation; while no reactivity was observed in the dark (Figure 3d). This experiment established that phenoxide (deprotonated phenol) is the electron donor and that photoinduced electron transfer can also promote phenyl-I cleavage in structurally related di-substituted vinylbenziodoxolone **15**. Lastly, by applying mechanistic concepts elucidated above, we utilized a diboronate ester and pyridine as electron donor species[47], resulting in reductive phenyl-I cleavage of EBX **2a** upon visible light irradiation to produce (iodoethynyl)benzene (**17**) in 55% yield (Figure 3e).

CONCLUSIONS

We report new reactivity between ethynylbenziodoxol(on)es and phenols to afford a diverse collection of (*Z*)-2-iodovinyl phenyl ether derivatives under irradiation with visible light. To generate the (*Z*)-2-iodovinyl phenyl ether products, we propose a photoinduced electron transfer step involving an intermediary vinylbenziodoxolone-phenoxide EDA complex that subsequently leads to the unprecedented phenyl-I bond cleavage. Using the (*Z*)-2-iodovinyl phenyl ethers as precursors, a series of transition metal-catalyzed chemistries were performed to access unique tri-substituted alkene derivatives with significant control of stereo and regiochemistry, underscoring the potential of this transformation in the pharmaceutical and agrochemical industries.

ASSOCIATED CONTENT

Supporting Information. General Information; Reaction Development and Optimization; X-ray crystallographic coordinates for structures of 3ab; UV-Visible Spectroscopy; Computational Details; Characterizations; NMR Spectrums.

The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interests.

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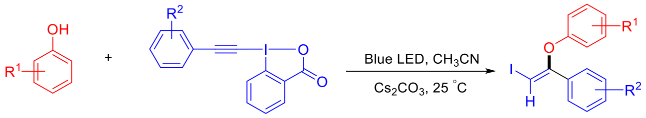

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