Stereoselective Photoredox-Catalyzed Vinylations to Functionalized Alkenes and *C*-Glycosides

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Abstract: We have disclosed two efficient radical-mediated C-C couplings through photoredox-catalyzed reactions of 4-alkyl-1,4-DHPs and vinylbenziodoxol(on)es (VBX, VBO). This transition-metal-free and mild photocatalytic method has excellent functional group tolerance and affords vinylated products in good yields, with excellent stereoselectivities where the alkene configuration is retained. The utility of the methodology is demonstrated by the diastereoselective synthesis of *C*-vinyl glycosides. Preliminary mechanistic studies signify that the C-C bond formation proceeds through a concerted radical coupling transition state.

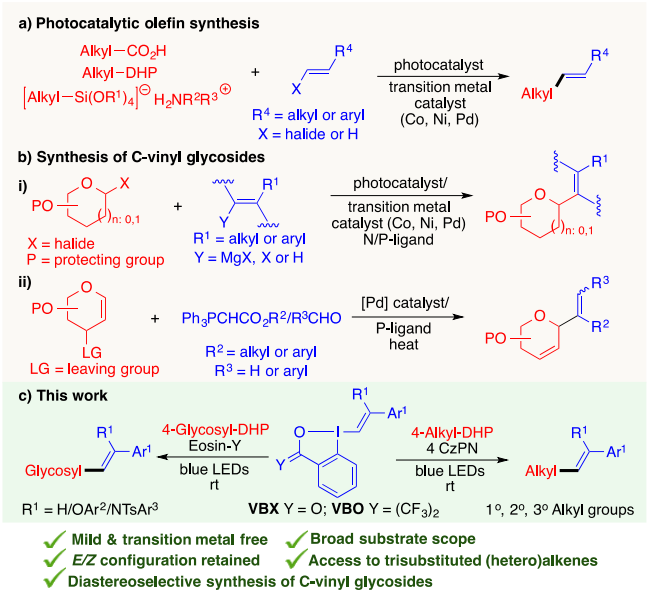
Introduction

Olefins are important substructures in synthetic organic chemistry, polymer chemistry and medicinal chemistry, and are omnipresent in natural products and pharmaceuticals.[1] Also *C*-vinyl glycosides, which are a central class of vinylated carbohydrates, are present in many natural products and pharmaceuticals.[2] While transition metal catalysis is ubiquitous in alkene synthesis,[3] the achievement of high regio- and stereoselectivity, as well as broad functional group tolerance, constitute some of the main synthetic challenges.[4]

Visible-light mediated photocatalysis has in recent years become an impressive strategy for the synthesis of complex organic molecules, enabling novel reaction pathways and mild reaction conditions.[5] Indeed, photocatalytic synthetic routes to olefins have been investigated extensively,[6] and commonly involve a transition metal-catalyzed cross-coupling between alkyl/aryl halides or styrenes and alkylation radical precursors such as carboxylic acids, 4-alkyl-dihydropyridines (4-alkyl-DHPs) or alkyl silicates (Scheme 1a). To achieve high yields, a dual catalytic system with ligands and external oxidants is generally required.[6a, 6d, 6e, 7]

The synthesis of *C*-vinyl glycosides has also been performed photocatalytically, but generally relies on a significant number of protection and deprotection steps, dual catalytic systems, elevated temperature, Grignard or dialkylzinc reagents and often employ ligands (Scheme 1b).[8]

In recent years, vinylbenziodoxolones (VBX) have received significant attention as potent vinylating reagents.[9] VBX reagents are easily synthesized in one-pot from 2-iodobenzoic acid,[9b] and



Scheme 1. Photocatalytic vinylations.

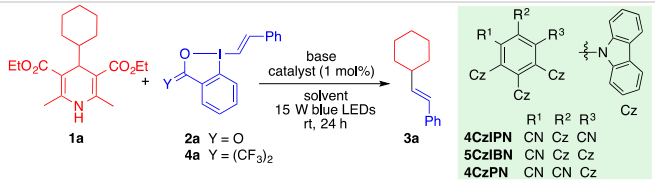
alternative routes leading to a wide scope of VBX reagents have been developed.[9e, 9j] Heteroatom-substituted VBX reagents (X-VBX) have been utilized in highly diastereoselective synthesis of complex heteroalkenes.[9a, 9i, 10] Yoshikai and coworkers introduced the corresponding vinylbenziodoxoles (VBO), which have found many applications especially in transition metal-catalyzed transformations.[9a, 11]

While the utility of VBX and VBO in photocatalytic reactions remains underexplored,[9g, 9h, 12] the corresponding alkynylations with ethynylbenziodoxolones (EBX) are well investigated.[9g, 9h, 12-13] Thus, we set out to develop a general, photocatalytic synthesis of functionalized alkenes and *C*-vinyl glycosides under mild and transition metal-free conditions, using VBX and VBO reagents (Scheme 1c). We selected DHPs as radical precursors, as they are easily synthesized from the corresponding aldehydes and widely utilized as versatile alkylation reagents in photoredox reactions.[14] Herein, we report the successful outcome of this study, giving access to functionalized *(E)*- and *(Z)*-alkenes with retention of the alkene configuration from VBX/VBO.

Results and Discussion

The optimization study commenced by choosing 4-cyclohexyl-1,4-dihydropyridine (**1a**) as the alkyl radical precursor and Ph-VBX reagent **2a** as the alkyl radical acceptor to give **3a** in the presence of blue LED (Table 1). Several common photocatalysts were screened in MeCN, such as carbazole dyes 4CzIPN, 5CzIBN and 4CzPN (entries 1-3),[15] and iridium-based photocatalysts (entries 4,5). Organocatalyst 4CzPN was found to give the best results in terms of yield and *(E)*-selectivity. A solvent screen revealed that the efficiency of the cross-coupling was enhanced by employing H_2O as a co-solvent (entries 6-8). Further improvements were achieved in presence of base (entries 9-11), and reactions with NaOAc provided **3a** in 74% isolated yield (entry 11). The related reagent VBO **4a** could also be employed, but was found to be less efficient (entry 12).

Table 1. Optimization of the reaction conditions.[a]

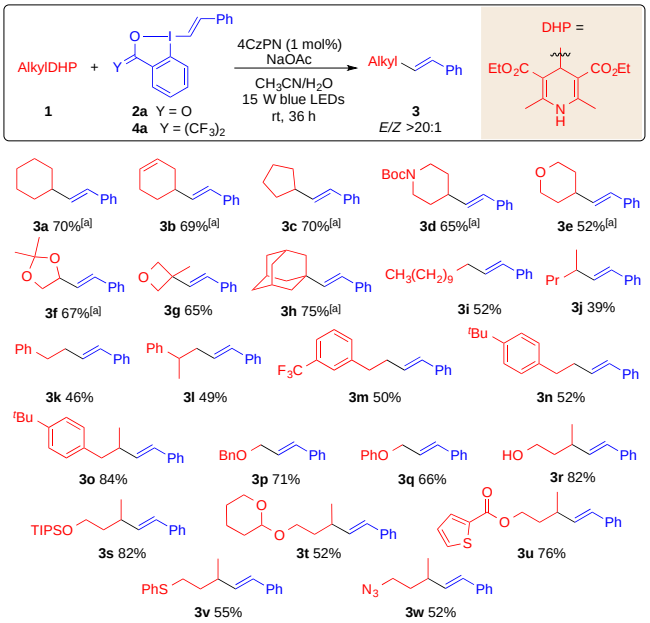


Entry	Solvent	Catalyst	Base	Yield (%)[b]	E/Z ratio[c]
1	MeCN	4CzIPN	-	42	2:1
2	MeCN	5CzIBN	-	49	9:1
3	MeCN	4CzPN	-	46	>20:1
4	MeCN	$Ir(dFppy)_3$	-	36	3:1
5	MeCN	$Ir(ppy)_3$	-	12	>20:1
6	CH_2Cl_2	4CzPN	-	72	9:1
7	Acetone	4CzPN	-	23	20:1
8	MeCN/H_2O (4:1)	4CzPN	-	69	>20:1
9	MeCN/H_2O (4:1)	4CzPN	K_2CO_3	74	>20:1
10	MeCN/H_2O (4:1)	4CzPN	CsOAc	78	>20:1
11	MeCN/H_2O (4:1)	4CzPN	NaOAc	83 (74[d])	>20:1
12[e]	MeCN/H_2O (4:1)	4CzPN	NaOAc	60	>20:1

[a] Reaction conditions: **1a** (0.05 mmol), **2a** (0.10 mmol), catalyst (1 mol%), base (0.05 mmol), solvent (0.1 M). [b] Crude ^1H NMR yields using 1,3,5-trimethoxybenzene as an internal standard. [c] *E*/*Z* ratios were determined by crude ^1H NMR. [d] Isolated yield. [e] Reaction with **4a** instead of **2a**. dFppy = 3,5-difluoro-2-(2-pyridinyl)phenyl; ppy = 2-(2-pyridinyl)phenyl.

With the optimized reaction conditions in hand, we evaluated the scope of alkyl DHPs that can participate in this new C-C cross coupling approach. A wide array of alkyl groups could be successfully vinylated, leading to the corresponding alkenes with excellent *(E)*-selectivity (Scheme 2).[16] Cyclic alkyl groups were easily vinylated with VBX **2a** (**3a**-**3c**), including alkenyl-substituted examples (**3b**). Heterocycles were well tolerated, as illustrated by piperidine **3d** and oxygen-containing products **3e**-**3g**. Steric hindrance was also accommodated well, as demonstrated by the synthesis of 3-methyl oxetane (**3g**) and adamantane (**3h**) products in good yields.

Vinylations with acyclic alkyl-DHPs gave more variable results, and VBO **4a** proved to give higher yields than **2a**.[15] Primary and secondary alkyl groups were transferred in moderate yields (**3i**, **3j**), and a series of homobenzylic substrates gave products **3k**-**3n** in similar yields irrespective of substitution pattern. Better results were observed in transfer of secondary benzylic radicals, cf **3n** with **3o**. Heteroatom-substituted alkyl groups were well tolerated, giving ethers **3p** and **3q** in 71 and 66% yield, respectively.



Scheme 2. Scope of alkyl-DHPs. Reaction conditions: **1a** (0.20 mmol), **4a** (0.40 mmol), 4CzPN (1 mol%), NaOAc (0.20 mmol), MeCN/H_2O (4:1, 0.1 M), 15 W blue LEDs with fan. Isolated yields, *E*/*Z*>20:1 in all cases. [a] With **2a** instead of **4a**.

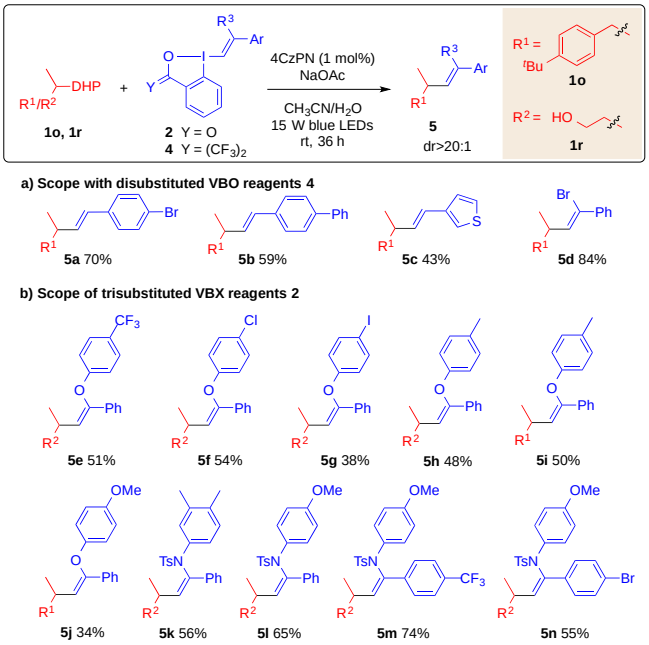
Interestingly, a free hydroxyl group resulted in superior yield compared to the unsubstituted alkyl chain (**3r** 82% vs **3j** 39%). Substrates with the hydroxyl group protected as the corresponding silyl ether (**3s**), acetal (**3t**) or functionalized ester (**3u**) reacted smoothly, and alkenes bearing thioether and azido functionalities (**3v**, **3w**) were well accommodated.

To extend the synthetic applicability of this method, we employed a set of substituted VBX and VBO reagents in vinylations of DHPs **1o** and **1r** (Scheme 3). As VBO reagents were superior coupling partners with acyclic alkyl-DHPs, we initiated the scope studies with disubstituted *(E)*-VBO **4**. The reactions provided the desired olefins **5a**-**5c** in moderate to good yields with complete *E*/*Z* stereoselectivity. X-ray diffraction analysis further confirmed the *E* geometry in **5a**.[15] Notably, also a trisubstituted *(Z)*-VBO underwent stereoselective C-C coupling to give *(Z)*-alkene **5d** in 84% yield.

The reactivity of the more synthetically challenging *(Z)*-configured *N*- and *O*-VBX **2**, introduced by Waser and co-workers,[17] were explored next. C-C couplings with such reagents are attractive as they would allow direct access to trisubstituted enol ethers and enamides with high stereocontrol.

Indeed, a variety of *(Z)*-*O*-VBX could be utilized to provide the corresponding products **5e**-**5j** with complete *(Z)*-configuration retained (Scheme 3b).[18] Electron-deficient aryl groups on the

ether motif gave slightly better yields than electron rich rings (**5e** vs **5j**), whereas the alkyl-DHP had negligible effect on the outcome (**5h** vs **5i**). C(sp^2)-I bonds are prone to react under photocatalytic conditions,[19] and we were pleased that **5g** could be isolated in moderate yield. Complete *(Z)*-selectivity was retained in the furnished enol ethers. A range of *(Z)*-*N*-VBX reagents were then reacted with **1r** to give the corresponding trisubstituted enamides **5k**-**5n** with retained *(Z)*-configuration.

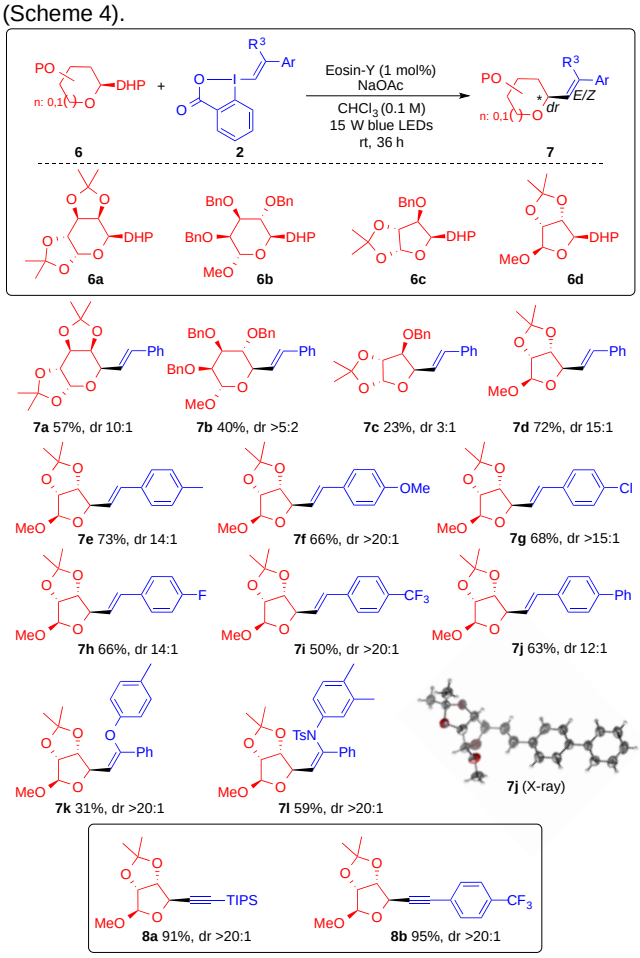


Scheme 3. Scope of VBX and VBO reagents. Reaction conditions: **1** (0.10-0.20 mmol), **2** or **4** (2 equiv), 4CzPN (1 mol%), NaOAc (1 equiv), MeCN/H_2O (4:1, 0.1 M), 15W blue LEDs with fan. Isolated yields, dr >20:1 in all cases.

To further evaluate the scope of the vinylation, we investigated whether a glycosyl radical could engage in a hitherto unknown radical vinylation process through the use of 4-glycosyl-DHP derivatives. This would lead to an efficient complementary method to stereoselectively synthesize vinyl-*C*-glycosides as classical methods require several steps or transition metal catalysis, and stereoselectivity remains a concern. To our satisfaction, initial reactions with the model galactosyl DHP **6a** and VBX **2a** were successful, and delivered product **7a** in 51% ^{1}H NMR yield and complete *(E)*-selectivity, with 5.5:1 *dr*. Upon reoptimization of the reaction conditions for this substrate class,[15] it was found that reactions in chloroform with Eosin-Y as the photocatalyst gave the best results. Under these new conditions, **7a** was isolated in 57% yield (66% ^{1}H NMR yield) with complete *(E)*-selectivity and 10:1 *dr* (Scheme 4).

The vinylation of glycosyl-DHPs **6b-d** was then examined, and low diastereoselectivity was observed with mannosyl DHP **6b** and xylosyl DHP **6c**. Ribosyl DHP **6d** proved to be a better substrate, delivering product **7d** in good yield and 15:1 *dr*. The high stereoselectivities observed with substrates **6a** and **6d** are likely due to the steric interactions induced by the adjacent acetonide, and the results are consistent with Nakamura's and Molander's transition metal-catalyzed radical C-arylations of glycosyl donors.[20]

Substrate **6d** was employed in the VBX scope, and the desired products **7e-7j** were obtained in 50-73% yield with good to excellent diastereoselectivities and complete *(E)*-selectivity using both electron rich and electron poor *(E)*-VBXs. The structure of **7j** (major diastereomer) was confirmed by X-ray crystallographic analysis.[21] Trisubstituted heteroatom-VBX were next explored, and the desired *C*-vinyl glycosides **7k** and **7l** could indeed be synthesized with excellent diastereoselectivity and complete *(Z)*-selectivity. The applicability of the methodology was briefly explored with EBX reagents[12, 22] and gratifyingly, the reaction conditions worked equally well for alkynylations to afford **8a** and **8b** in 91% and 95% yield, respectively with excellent *dr* (Scheme 4).

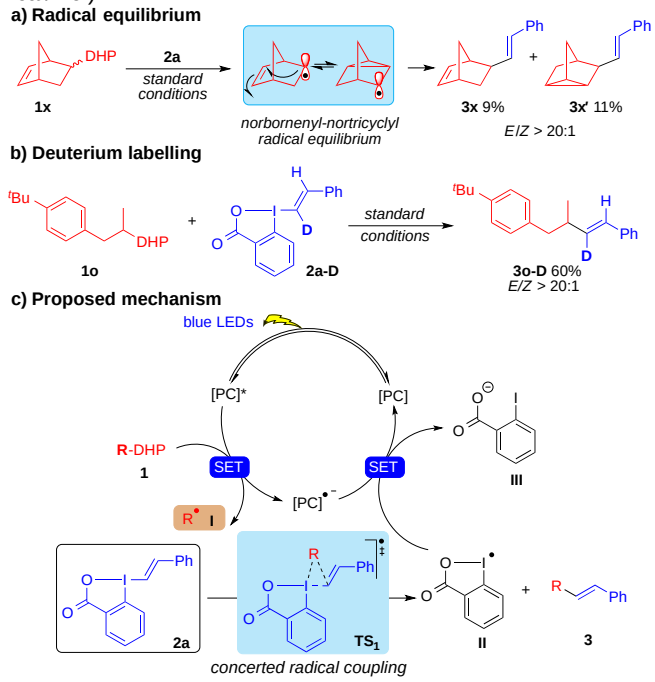


Scheme 4. Scope with glycosyl DHPs. Reaction conditions: **6** (0.10-0.20 mmol), **2** (2 equiv), Eosin-Y (1 mol%), NaOAc (1 equiv), $CHCl_3$ (0.1 M), 15W blue LEDs with fan. Isolated yields, complete retention of alkene configuration in all cases.

Subsequent mechanistic studies with substrate **1i** and VBX **2a** supported our hypothesis of a photocatalytic radical coupling. Control experiments in the absence of 4CzPN or LED light resulted in no product formation. Furthermore, reactions in the presence of TEMPO were inhibited, and the alkyl-TEMPO adduct was detected by HRMS.[15] Furthermore, vinylation of bridgehead-DHP **1x** delivered a 1:1 mixture of norbornenyl and nortricyclyl products **3x** and **3x'**, indicating a radical equilibrium during the coupling process (Scheme 5a).[23] A reaction of **1i** with the deuterated VBX **2a-D** delivered product **3o-D** in 60% isolated yield as the only regio- and stereoisomer, indicating that no rearrangement takes place during the vinylation (Scheme 5b).

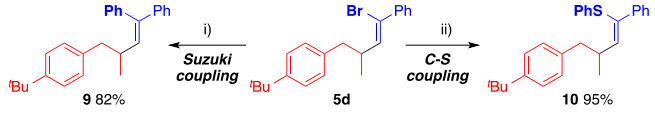
Based on the experimental results and well-established pathways for photoredox reactions with alkyl-DHPs,[24] we propose that the vinylation takes place through the mechanism depicted in Scheme 5c. The catalytic cycle begins by excitation of photocatalyst [PC] to [PC]*, followed by SET oxidation of alkyl-DHP **1** by [PC]* to generate the PC radical anion and radical intermediate **I**.[14a, 14d, 24] This intermediate reacts with VBX **2a** to form product **3** and benziodoxolone radical **II**,[9h] which is reduced by $[PC]^{\bullet-}$ to regenerate PC and give iodobenzoate **III**.

The key C-C bond formation between radical **I** and **2a** could take place in several ways. Based on previous mechanistic studies with VBX[25] and EBX[10a, 10b, 26], the radical coupling could proceed via α-addition, β-addition or a concerted radical coupling pathway to deliver product **3**. The high stereoselectivity observed in the reaction, as well as formation of **3o-D** as the only isomer indicates a concerted process. Density functional theory (DFT) studies of the three pathways using DHP **1a** and VBX **2a** showed that the lowest energy profile was found for the concerted radical pathway, proceeding *via* the depicted transition state $\mathbf{TS_1}$ (12.7 kcal/mol).[15]



Scheme 5. Mechanistic studies.

Finally, post-synthetic derivatization of alkenyl bromide **5d** was performed to demonstrate the product utility (Scheme 6). A Pd-catalyzed Suzuki coupling with phenylboronic acid pinacol ester[27] afforded trisubstituted alkene **9**. Likewise, thioenol ether **10** was easily obtained through a Pd-catalyzed C-S cross-coupling[28] with thiophenol.



Scheme 6. Product transformations. i) $Pd(PPh_3)_4$ (5 mol%), 3M NaOH, THF, 60 °C, 36 h; ii) PhSH, $Pd_2(dba)_3$ (1 mol%), dppf (5 mol%), LiHMDS, toluene, 110 C, 24 h, isolated yields.

Conclusion

In conclusion, we have reported a transition metal-free photoredox-catalyzed cross-coupling reaction of VBX with alkyl-DHPs. The reaction conditions are mild and the method tolerates common functional groups, producing straightforward access to corresponding alkenes in good to high yields with retention of the alkene configuration. The method was also applied to 4-glycosyl-DHPs, resulting in a diastereoselective synthesis of vinyl *C*-glycosides with excellent *E/Z* ratios in good yields. The method opens up a novel synthetic strategy to synthesize trisubstituted enamides and enol ethers with excellent stereoselectivity. Preliminary mechanistic studies support the involvement of a concerted radical coupling as the key step. Given the uncomplicated synthesis of the starting materials and simple reaction setup, we anticipate that the protocol will find broad applications in the synthesis of di- and trisubstituted alkenes and a variety of pharmaceutically important *C*-vinyl/alkynyl glycosides.

Experimental Section

General Procedure for the Photocatalytic Vinylation: A 8 mL screw cap vial was charged with DHP **1** (0.2 mmol, 1.0 equiv), VBX **2** (2.0 equiv), 4CzPN (1 mol %) and NaOAc (1.0 equiv). The vial was sealed with a teflon cap, put under vacuum for 15 minutes and then purged with argon. Degassed MeCN/H_2O (4:1, 0.1 M) was then added. The solution was degassed by freeze-pump-thaw (3 cycles), then the vial was filled with argon. The vial was irradiated with blue LEDs and stirred for 36 h with a cooling fan placed on top of the setup. After completion of the reaction, the mixture was concentrated *in vacuo* and purified by column chromatography to obtain product **3**.

Acknowledgements

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Keywords: alkenes • *C*-vinyl glycosides • photo-redox catalysis • stereoselectivity • vinylbenziodoxolones

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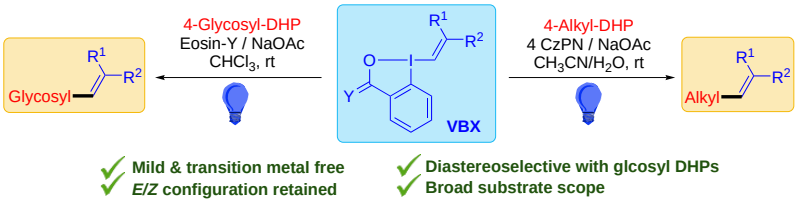

A convenient photo-catalyzed, transition-metal-free C-C cross-coupling reaction has been developed with DHPs and VBXs to synthesize di- and trisubstituted alkenes with complete *E:Z* selectivity. A diastereoselective *C*-vinylation of glycosides was also developed. Preliminary mechanistic studies indicate a concerted radical coupling pathway.

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