Explaining Regio-Divergent Vinylations with Vinylbenziodoxolones

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ABSTRACT: Vinylbenziodoxolones have recently been identified as efficient hypervalent iodine(III) reagents for electrophilic vinylations under transition metal-free conditions. The regiochemistry of the products have been found to vary with the nucleophile class, with thiols giving internal alkenes whereas phosphine oxides and similar P-nucleophiles give terminal alkenes. This paper constitutes the first mechanistic investigation of VBX vinylations, and makes use of NMR studies, deuterium labelling and computations to rationalize the observed regio- and stereochemical outcome. While the S-vinylation was found to proceed through the ligand coupling mechanism typical of diaryliodonium salts, the P-vinylations took place via a phosphinous acid-coordinated VBX complex, which underwent concerted deprotonation and Michael-type addition. Subsequent base-assisted protonation and E2 elimination delivered the terminal alkene. The findings can be used to predict the regioselectivity in vinylations of other nucleophile classes.

INTRODUCTION

Alkenes are important as biologically relevant functionalities and as lucrative and extremely versatile building blocks in drug discovery. Many regio- and stereoselective strategies to access alkenes have been developed over the past decades and generally involve transition metal-catalyzed cross coupling, C-H activation or metathesis.[1-5] With the increased focus on sustainable chemistry,[6] the development of transition metal-free, regio- and stereoselective alkenylations that proceed under mild conditions is highly important.[7]

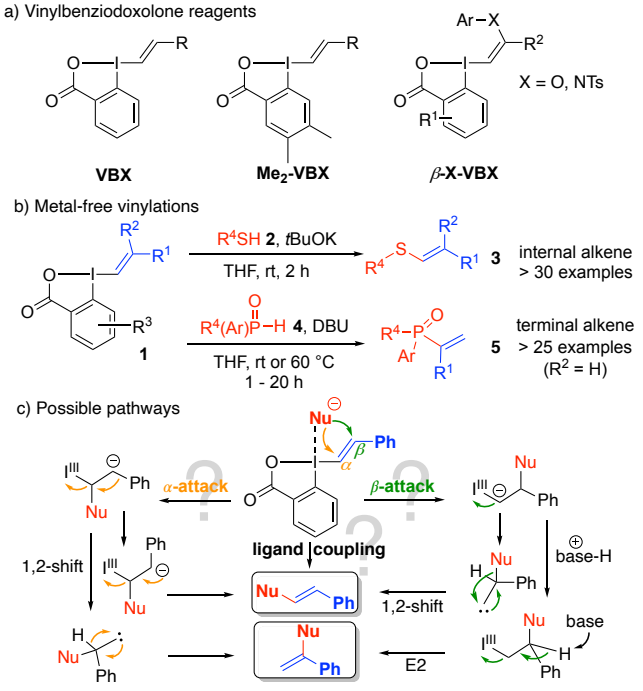
Vinylbenziodoxolones (VBX) have recently been reported as novel hypervalent iodine(III) reagents sharing the same benziodoxolone core as the popular ethynylbenziodoxolones (EBX) and Togni reagents.[8-9] VBX compounds have already been employed as electrophilic vinylation reagents under transition metal-catalyzed, photocatalytic and metal-free conditions with a variety of nucleophiles (Scheme 1a).[10-11] VBX shows interesting reactivity under mild conditions without need for excess reagents, and tolerates a variety of functional groups. Core-substituted Me_2-VBX was reported to give improved results in some cases.[12] In parallel, the chemistry of β-heteroatom-substituted VBX reagents and their benziodoxole counterparts has also been developed.[13-15]

Methodology for transition metal-free vinylations from our lab highlights the intriguing reactivity of VBX reagents **1**. The efficient, room temperature S-vinylation of thiols **2** resulted in formation of internal alkenes **3** with retention of the VBX alkene configuration (Scheme 1b).[12-13, 16-17] To the contrary, metal-free P-vinylation of phosphine oxides **4** or H-phosphinates delivered terminal alkenes **5** with complete regioselectivity (Scheme 1b).[18] The latter regiochemistry has only been observed under transition metal-free conditions with VBX.[8, 18]

Literature reports of reactions with vinyl(aryl)iodonium salts, which are related iodine(III) reagents, indicate that various mechanisms can be operative under metal-free conditions. Vinylic S_N1 or S_N2 or reactions via alkylidene carbene intermediates are common, whereas Michael additions are less likely.[19-22] Vinylidene carbene formation has also been proposed in reactions with alkynyliodonium salts[23-24] and EBX.[25-26] Mechanistic studies of the latter revealed that thiol alkynylation can proceed via ligand coupling or Michael-type addition depending on the electronics of the reagent.[25-26]

To increase the utility of VBX as an efficient vinylating agent, tools to understand and predict the principles for product regiochemistry are important. Based on literature precedent, several possible mechanisms could be proposed to explain the observed regiochemistry (Scheme 1c). In this work, we have used NMR studies, deuterium-labelling and extensive DFT calculations of the S- and P-vinylations to unravel the mechanisms of VBX vinylations under transition metal-free conditions. Two mechanistic pathways are presented together with tools to predict the regiochemistry with other nucleophile classes.

Scheme 1. Metal-free vinylations with VBX



RESULTS AND DISCUSSION

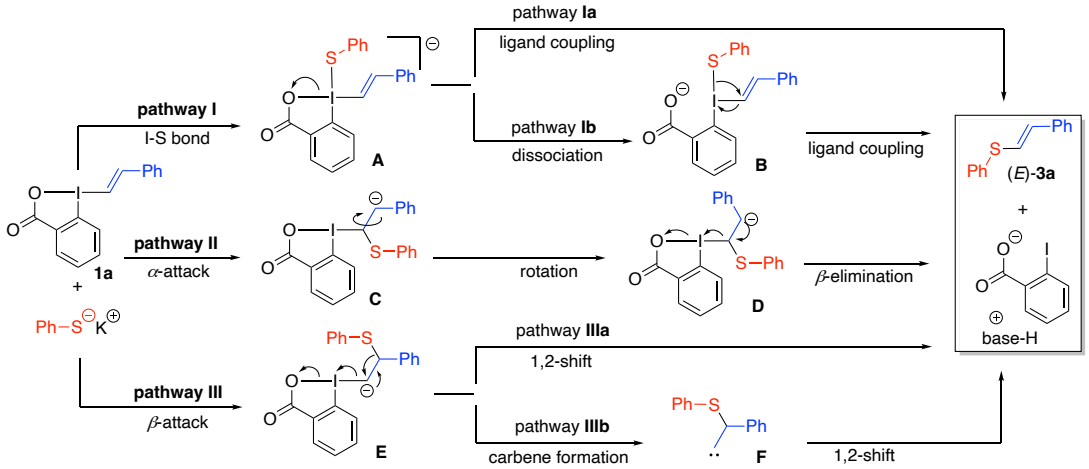
S-Vinylation of thiols

Earlier experimental observations were the starting point of this mechanistic study.[12] Vinylation of S-nucleophiles led exclusively to internal alkenes **3** (*E*:*Z* ratio generally >20:1), indicating that VBX does not react through a vinylic S_N2 mechanism[27] (Scheme 1b). Alkenes **3** were formed also in the presence of radical traps, and the reaction slowly proceeded also without base. Furthermore, core-substituted Me_2-VBX proved superior to the standard VBX as formation of disulfide $(ArS)_2$ byproduct was suppressed.[12]

On account of experimental observations, literature mechanisms with vinyliodonium salts[22] and the reported mechanistic investigations of S-alkynylations with EBX,[17, 25-26, 28] we proposed three possible pathways leading to (*E*)-**3a** and 2-iodobenzoate (Scheme 2). Thiophenol (**2a**) is first deprotonated by *t*BuOK, after which four-coordinated I–S intermediate **A** can form through ligand association (pathway **I**). This intermediate either undergoes direct ligand coupling to stereospecifically yield product (*E*)-**3a** (pathway **Ia**), or via release of the carboxylate ligand to intermediate **B** (pathway **Ib**).

A direct nucleophilic attack on the α- or β-carbon of the vinyl moiety could also lead to product **3a**, although the (*E*)-selectivity could be compromised through such routes. Pathway **II** depicts an α-attack of the thiolate to yield intermediate **C**, which could rotate to intermediate **D** followed by β-elimination to give (*E*)-**3a**. Finally, attack on the β-carbon would give intermediate **E** via pathway **III**. This could undergo a concerted elimination and 1,2-shift of either the phenyl or sulfide moiety to yield vinyl sulfide **3a** directly (pathway **IIIa**), or stepwise elimination of iodobenzoate to yield alkylcarbene **F**, followed by a 1,2-shift (pathway **IIIb**). A concerted asynchronous alternative in between these two extremes is also possible.

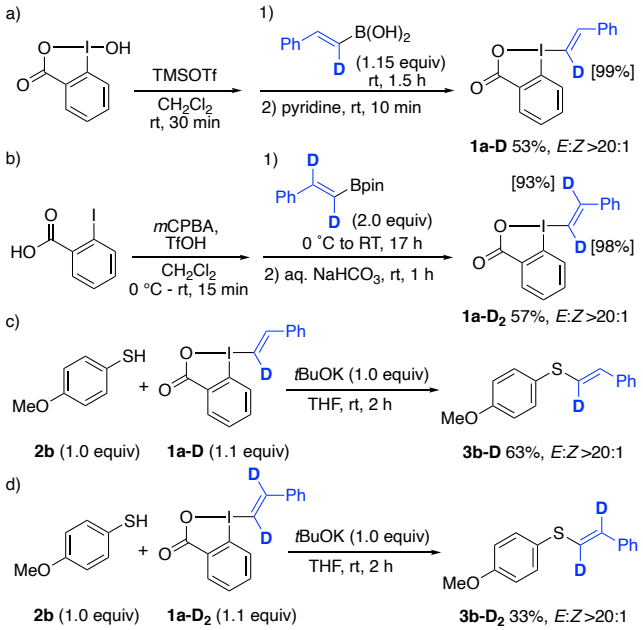
Scheme 2. Mechanistic pathways for S-vinylation with VBX



We followed the reaction of VBX **1a** with **2a** in THF-d_8 by ^{1}H NMR to investigate the formation of any intermediates and to rationalize the observed influence of the base addition order. When **2a** was mixed with *t*BuOK in an NMR tube, signals of the thiophenolate were immediately observed and the vinylation started instantly when **1a** was added. A similar NMR experiment with **1a** and **2a** in the absence of base showed no interaction between the two, and the reaction only started upon addition of the base. In both cases, no intermediates could be observed. Based on these results, we suggest that the experimental benefit of adding the base last is to suppress the formation of the disulfide byproduct, rather than a mechanistic pathway where initial S-I coordination is followed by deprotonation to give **A**.

To gain further understanding of the mechanism, deuterium-labelled VBX reagents **1a-D** and **1a-D$_2$** were synthesized (Scheme 3a,b).[8, 29-32] Thiophenol **2b** was employed as the model substrate to facilitate the NMR analysis of the reaction outcome. Reactions with **1a-D** under the standard conditions resulted in product **3b-D** as the only regioisomer, together with the corresponding disulfide byproduct in 11% yield (Scheme 3c). The reaction with **1b-D$_2$** delivered product **3b-D$_2$** in moderate yield together with the disulfide byproduct (Scheme 3d). To reach these products through pathway **II**, complete selectivity in β-elimination from intermediate **D** rather than **C** would be needed, otherwise an *E*:*Z* mixture would be obtained.

Scheme 3. Deuterium labelling study



Likewise, pathway **III** would require complete selectivity towards migration of the SPh moiety over the phenyl group to give **3b-D** as the only isomer.

DFT calculations were then performed at the B3LYP-D3 level of theory to investigate pathways **I** and **II**.[33] A low energy reaction profile was found for pathway **Ia**, starting with exothermic I-S bond formation to intermediate **A′** (Figure 1**)**. The long bond distances between the S-I and S-Cα atoms, (3.21 and 3.30 Å respectively) as well as the 166° S-I-C_{aryl} angle, are similar to the tilted intermediate found in S-alkynylation with EBX.[25] Ligand coupling through transition state $\mathbf{TS_1}$ leads stereospecifically to the vinylated product (*E*)-**3a** and iodobenzoate. The low energy of $\mathbf{TS_1}$ (14.1 kcal/mol) is in accordance with the experimentally observed high reaction rate at room temperature.

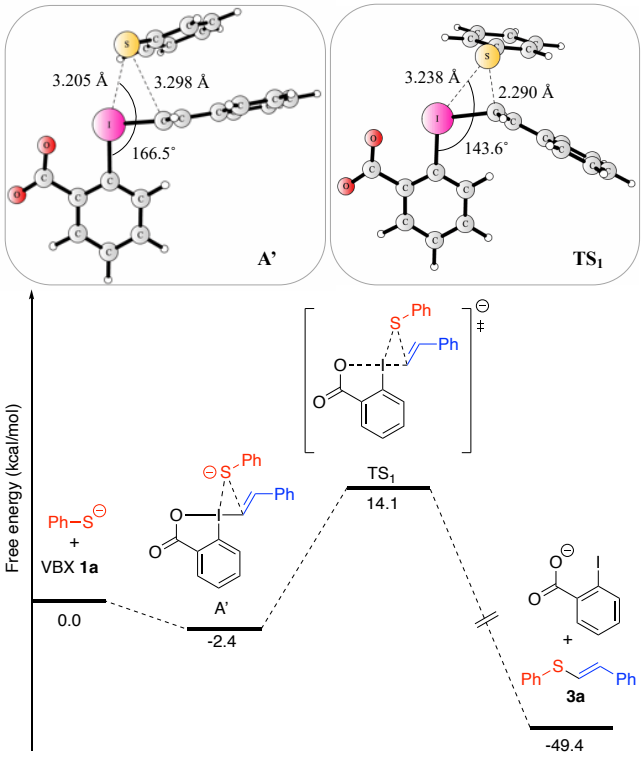


Figure 1. Reaction free energy profile for S-vinylation. Theory level B3LYP-D3 6-31g(d,p)/lanl2dz//(6-311+g(2d,2p)/lanl2dz.

Intermediates **B-F** were not possible to locate since the structures always converged to intermediate **A′**, indicating that the reaction proceeds through pathway **Ia**. We also computed the reaction profiles with Me_2-VBX **1b**, and *o*-Me-VBX **1c**, which resulted in very similar energies (Figures S12-S13). The benefit of reagent **1b** might be explained by the lower electrophilicity of the iodine compared to **1a**, thus resulting in cleaner reactions without formation of disulfide byproduct.

The energy profile for the reaction of **1a** and **2a** in the absence of base had a considerably higher TS energy (43 kcal/mol), which is in accordance with the observed low reactivity without base (Figure S11).

P-Vinylation of phosphine oxides

Contrary to the S-vinylation, the P-vinylation of diarylphosphine oxides **4** led exclusively to terminal alkenes **5** (Scheme 1b), and preliminary mechanistic studies revealed that a radical pathway was unlikely.[18] Hence a ligand coupling mechanism can be ruled out, as this would lead to the internal alkene product. With inspiration from previous P-functionalizations with vinyl-[34] and alkynyliodonium salts,[35] and recent mechanistic studies with EBX,[25-26, 36] we proposed five pathways leading to terminal alkene **5a** and 2-iodobenzoate (Scheme 4).

In the presence of base, diphenylphosphine oxide (**4a**) and VBX **1a** can react through an *α*-attack to give intermediate **G**, which could undergo double 1,2-shifts to reach the terminal alkene **5a** via carbene **H** (pathway **IV**). Alternatively, the regioselectivity can be rationalized through a phospha-Michael reaction, which is a versatile and powerful tool for phosphorus-carbon bond formation.[37-38] Pathway **V** depicts a direct *β*-attack, yielding anionic intermediate **I**, which can form **5a** through three alternative pathways. Due to the high leaving group ability of the iodine(III) moiety, **I** could decompose to carbene **J**, which would yield **5a** through a 1,2-hydride shift. Alternatively, anion **I** could undergo a concerted 1,2-hydride shift and elimination to **5a**. Finally, protonation of intermediate **I** would give intermediate **K** with subsequent base-mediated *β*-elimination to **5a**. In pathway **VI**, the I–P complex **L** forms prior to intramolecular Michael-type addition to yield intermediate **I**, with further subsequent steps to **5a** as described above.

Phosphine oxide **4a** exists in equilibrium with the more reactive and nucleophilic phosphinous acid **4a′**,[39-40] which can participate in Michael additions under basic conditions.[37, 41] This possibility is depicted in pathway **VII**, where isomer **4a′** and **1a** form the I–O bonded intermediate **M**, which is well aligned for a Michael-type addition to give intermediate **I**.

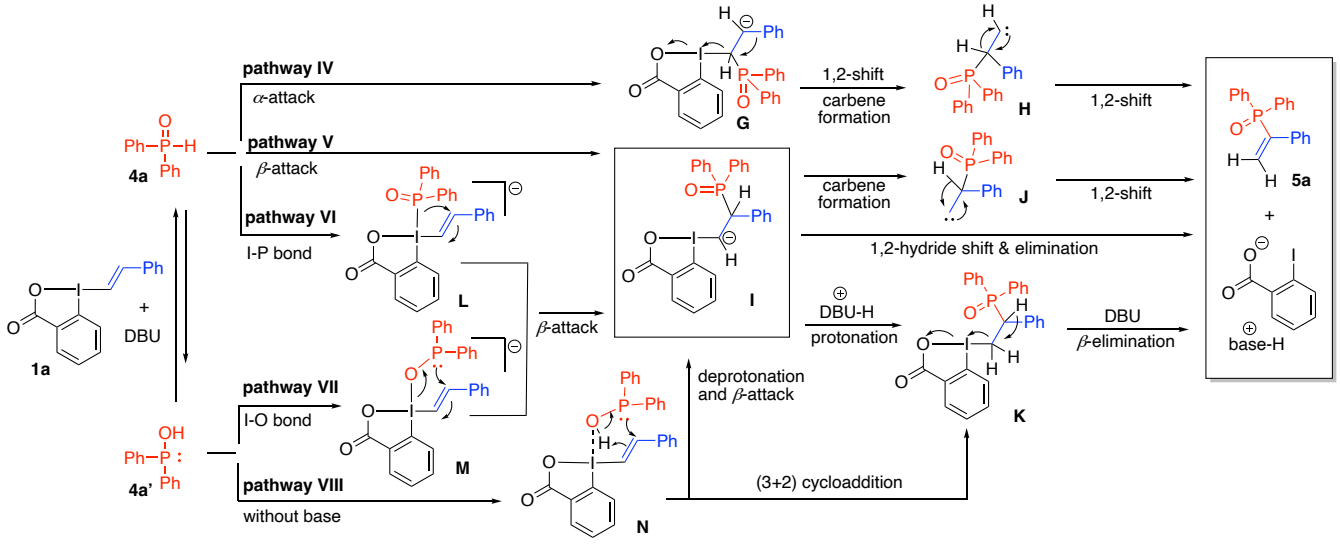
Finally, we also considered pathway **VIII**, where **4a′** and **1a** form the weakly I–O coordinated intermediate **N** prior to deprotonation. This species could either undergo concerted deprotonation and *β*-attack to **I**, or undergo a (3+2) cycloaddition to intermediate **K**, followed by base-mediated *β*-elimination to **5a**.

NMR experiments in THF-d_8 were carried out to observe any reaction intermediates. In the absence of VBX **1a**, no reaction was observed between DBU and **4a**. When **1a** was added, product **5a** started forming immediately. Likewise, no adduct could be observed upon mixing **1a** and **4a** in the absence of DBU. These results indicate a concerted reaction between all three reaction components rather than initial deprotonation or formation of **K** through a (3+2) cycloaddition in pathway **VIII**.

Deuterium-labelled VBX reagents **1a-D** and **1a-D_2** were utilized in a series of experiments to study whether any rearrangement or protonation took place (Scheme 5). The reaction of **4a** with **1a-D** delivered monodeuterated products **5a-D** in a 7:1 *Z*:*E* mixture as the only vinylation products observed (Scheme 5a). To verify these results, the reaction was repeated *p*-methoxy-substituted phosphine oxide **4b** and **1a-D**, which simplified the NMR analysis (Figure S15-S17).

The vinylation of **4a** with **1a-D_2** resulted in a 1:1 mixture of **5a-D** isomers and no di-deuterated products were observed (Scheme 5b). A crossover experiment was performed with **1a-D_2** and **1d**, in which the expected products **5a-D** and **5c** were formed together with a trace amount of **5c-D** (Scheme 5c). Finally, deuterated phosphine oxide **4a-D** was employed with VBX **1a**, which resulted in the expected product **5a** as major product, with some deuterium incorporation to **5a-D**, now with the (*E*)-isomer as major isomer (Scheme 5d).

Scheme 4. Possible mechanistic pathways for P-vinylation with VBX

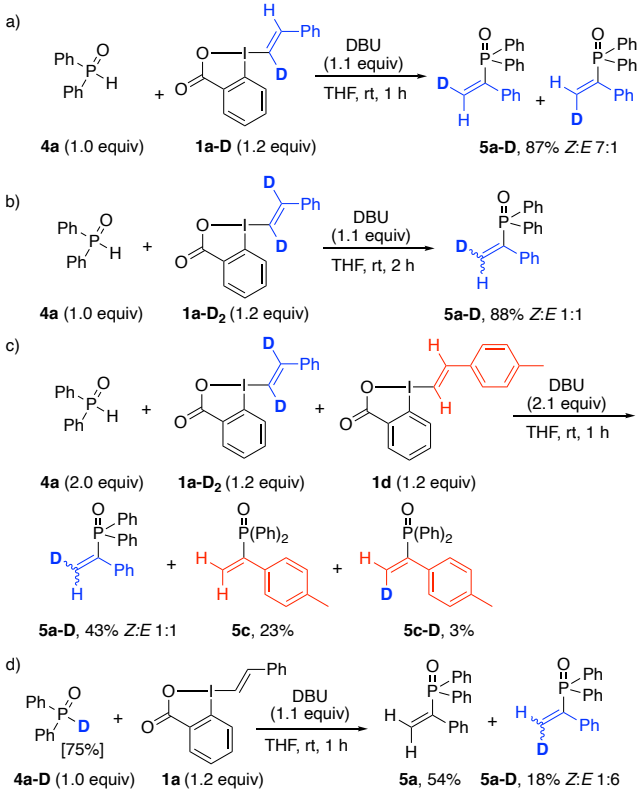


Based on these results, we propose that the reaction does not proceed through carbenes **H** or **J**, as these intermediates would give **5a-D₂** with reagent **1a-D₂**. Likewise, a concerted hydride shift and elimination from **I** is ruled out. The results from Schemes 5c-d indicate that the base is involved in protonation, which aligns well with pathways **V-VIII** proceeding through intermediates **I** and **K**.

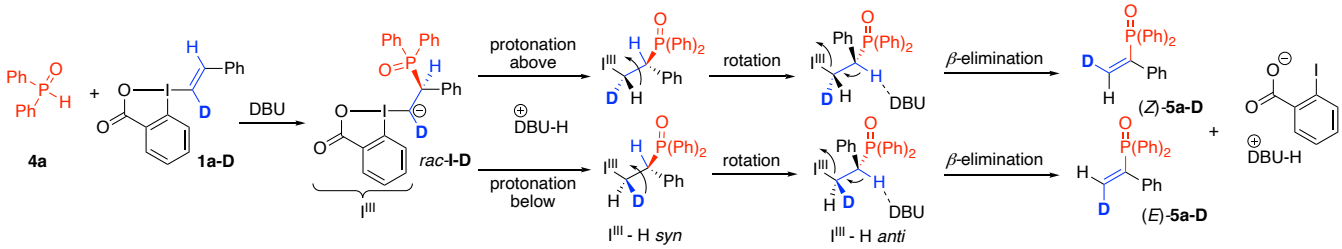
These pathways were analyzed in more detail to rationalize the observed stereoselectivity in formation of **5a-D** (Scheme 6). The reaction of phosphine oxide **4a** with **1a-D** would generate anionic intermediate **I-D**, which could either be protonated from above or below by $^{+}$DBU-H to reach two diastereomeric intermediates. Rotation around the single bond to obtain *anti*-periplanar alignment followed by *β*-elimination yields (*Z*)-**5a-D** and (*E*)-**5a-D**, respectively. With the assumption that *anti*-elimination (E2) is favored over *syn*-elimination in this system, the observed high (*Z*)-selectivity in Scheme 5a indicates that protonation of **I-D** preferentially takes place from the same face as the phosphorous addition.

This is also in agreement with the opposite stereoselectivity observed in Scheme 5d, where $^{+}$DBU-D is used in the protonation step. The formation of **5a** as the major product in that reaction indicates that protonation with $^{+}$DBU-H, which forms in the E2-elimination, is much faster than with $^{+}$DBU-D. This is expected as a competitive proton/deuterium transfer should display a significant primary kinetic isotope effect.

Scheme 5 Deuterium labelling study



Scheme 6. Stereochemistry analysis with 1a-D



DFT calculations were then performed to investigate the most plausible mechanisms in Scheme 4 based on the experimental observations.[33] Phosphine oxide **4a** could be deprotonated by DBU, followed by a Michael-type addition on VBX **1a** to give intermediate **I** either directly or via I-P coordinated intermediate **L**. Alternatively, deprotonation of **4a** could be concerted with P-C bond formation. Likewise, base-catalyzed isomerization to phosphinous acid **4a′** followed by deprotonation would yield intermediate **M** upon reaction with VBX, whereas concerted deprotonation and P-C bond formation would yield intermediate **I** either directly or via I–O coordinated complex **N**.

Computations starting from **4a** and **1a** revealed a low-energy pathway where intermediate **M′** is formed via $\mathbf{TS_1}$ (Figure 2, black pathway). Coordination to the protonated base $^{+}$DBU-H stabilizes the partial negative charge on the oxygen. The mechanism proceeds by Michael-type addition via transition state $\mathbf{TS_2}$ (18.8 kcal/mol) to anionic intermediate **I′**. A 1,2-hydride shift (Figure S25) was found to be higher in energy than base-assisted conversion of **I′** to **5a**. Protonation by $^{+}$DBU-H preferentially takes place from above, to yield *syn*-**K′** (Figure S23), which rotates to *anti*-**K′**. As expected, subsequent E2-elimination is favored over the corresponding *β*-elimination from *syn*-**K'**, (Figure S24) and provides **5a** and 2-iodobenzoate.

Computations with phosphinous acid **4a′** disclosed O-I intermediate **N′** with a hydrogen-bonded DBU molecule (Figure 2, red pathway). Deprotonation proceeds simultaneously with the Michael addition via 5-membered $\mathbf{TS_2}$' (12.5 kcal/mol) to give anionic intermediate **I′**, after which the reaction proceeds as above. We also investigated carbene formation (*cf* **J** in Scheme 4), and indeed found a high-energy carbene intermediate from $\mathbf{TS_2}$' (Figure S26). Based on these calculations, the reaction proceeds via phosphinous acid **4a′**, with formation of **I′** through $\mathbf{TS_2}$' as the rate determining step

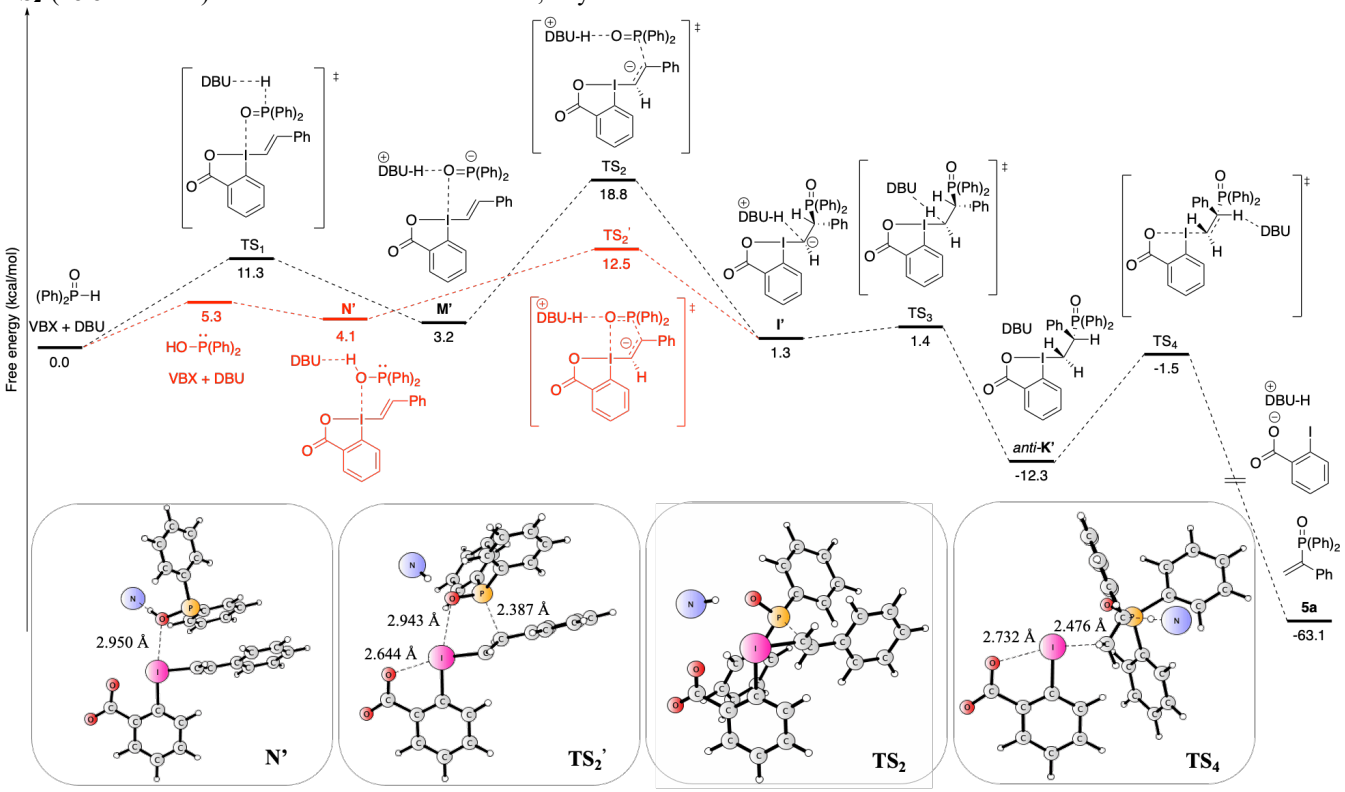
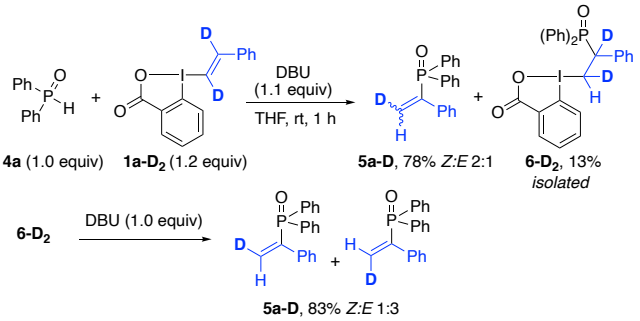


Figure 2. Simplified reaction free energy profile for P-vinylation. Theory level B3LYP-D3 6-31g(d,p)/lanl2dz//(6-311+g(2d,2p)/lanl2dz. For clarity, 1,8-diazabiciclo[5.4.0]undec-7-en (DBU) is shown as a circled N and all atoms are omitted.

The reaction through pathway **VIII**, with cycloaddition from **N** to **K**, was computed with a TS energy of >33 kcal/mol (Figure S29). The proposed *α*-attack in pathway **IV** to give anion **G** could not be found, instead the internal alkene product was formed through a 4-membered ligand coupling TS (Figure S21). Likewise, pathway **VI** via intermediate **L** resulted in a three-membered ligand coupling TS at 16 kcal/mol (Figure S28) which is 3.5 kcal/mol higher than $\mathbf{TS_2}$' (Figure 2). These results are in agreement with the observed complete regioselectivity for terminal over internal alkene formation.

Further investigations were performed to support the formation of intermediate **K**. Upon shorter reaction time, the synthesis of **5a-D** from **4a** and **1a-D$_2$** was accompanied by isolation of another product, which was identified as compound **6-D$_2$** (Scheme 7). This finding was highly unexpected, as iodine(III) compounds with alkyl ligands are generally unstable.[42]

Scheme 7. Support for iodine(III) intermediate K



Compound **6-D$_2$** could be converted to product **5a-D** upon treatment with DBU, which supports that **K** is an intermediate in the reaction. Upon kinetic NMR studies of reactions of **4a** with **1a**, the corresponding intermediate **6-H$_2$** could be detected in minor amounts (Figure S20). The varying *Z*:*E* ratios obtained for **5a-D** can be explained by different selectivity in protonation of **I-D** vs **I-D$_2$** from above or below, as the energy difference for *syn*- vs *anti*-elimination is much higher.

The mechanistic differences between VBX vinylations of thiols and phosphorus nucleophiles can be rationalized by invoking the preferential formation of a 5-membered TS over a 3-membered TS, which is generally required in ligand coupling mechanisms. This is in line with our previous findings in arylation of enolates with diaryliodonium salts, where a 5-membered pathway via an I–O intermediate was preferred over a 3-membered ligand coupling TS from the corresponding I–C intermediate.[43] Based on this conclusion, other ambident nucleophiles would also be expected to coordinate to the iodine with subsequent Michael-type attack to yield terminal alkenes, whereas mononucleophilic species should give internal vinylation products. This is in line with the C-vinylation of nitrocyclohexanone, which gave the terminal product as the major regioisomer.[8] Strong nucleophiles could prefer I–Nu coordination followed by ligand coupling or α-attack to give the internal product, as observed in vinylation of in situ-generated sulfenate anions.[16] The possibility to control the regioselectivity by modulating the nucleophile structure should be of great interest in organic synthesis, and our continued studies of controlling VBX reactivity will be reported in due time.

CONCLUSIONS

A combined experimental and theoretical study of transition metal-free vinylations with the recently discovered hypervalent iodine(III) reagent VBX has revealed two different pathways leading either to the internal or the terminal alkene. Deuterium-labelling studies and computations support that the S-vinylation of thiols proceeds through deprotonation followed by a ligand coupling to provide the experimentally observed internal alkenes with retained *E*-configuration. The P-vinylation of diarylphosphine oxides instead begins with I–O coordination of the corresponding phosphinous acid to VBX. A simultaneous deprotonation and Michael-type addition then gives an anionic intermediate, which is transformed to the terminal alkene through a base-assisted protonation and E2 elimination. A general regioselectivity trend for VBX vinylations under metal-free conditions is predicted, where ambident nucleophiles will deliver terminal alkenes whereas monodent or strong nucleophiles will provide internal alkenes.

ASSOCIATED CONTENT

Supporting Information

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

Experimental details, analytical data and NMRs (PDF)
DFT calculations (PDF)

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Notes

The authors declare no competing financial interest.

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