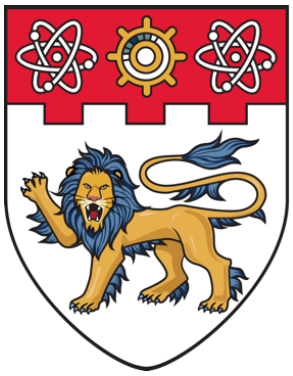

NANYANG TECHNOLOGICAL UNIVERSITY
SINGAPORE

REGIO- AND STEREOSELECIVE ALKYNE DIFUNCTIONALIZATION BY USING BENZIODOXOLE TRIFLATE AND PHOSPHATE ESTER

PLOYPAILIN TAN SIEW LING

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

2021

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

A thesis submitted to the Nanyang Technological University in partial fulfilment of the requirement for the degree of Master of Science

2021

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Table of Contents

Abstract

Stereoselective synthesis of tetrasubstituted alkenes has been one of the most challenging subjects in synthetic organic chemistry. Regio- and stereoselective difunctionalization of readily available alkynes represents a conceptually straightforward approach toward this goal. In this Masters study, I have developed such an alkyne difunctionalization reaction using a hypervalent iodine reagent as an electrophile and a phosphate ester as a nucleophile. Thus, a three-component reaction involving an internal alkyne, benziodoxole triflate (BXT), and triethyl phosphate or related phosphate ester proceeds smoothly at room temperature, resulting in *trans*-addition of the benziodoxole (BX) and phosphate groups. The reaction has proved applicable to a variety of symmetrical and unsymmetrical internal alkynes, thus affording the corresponding β-λ^3-iodanyl alkenyl phosphates in a regio- and stereoselective fashion. The BX and phosphate groups of the product can be utilized for sequential cross-coupling, thus allowing for the stereoselective synthesis of all-carbon tetrasubstituted alkenes.

List of abbreviations

δ	Chemical shift (ppm)
℃	Degree Celsius
µ	Micro
Ac	Acetyl
Ar	Aryl (substituted aromatic ring)
app.	Apparent
aq	Aqueous
br.	Broad
^{n}Bu	*n*-butyl
^{t}Bu	*t*-butyl
Bn	Benzyl
BX	Benziodoxole moiety
BXT	Benziodoxole triflate
C	Carbon
Cl	Chlorine
CN	Cyano

Cy	Cyclohexyl
d	Doublet
dd	Doublet of doublet
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DMF	*N*,*N*-dimethylacetamide
DMSO	*N*,*N*-dimethylformamide
MeCN	Acetonitrile
equiv	Equivalent
ESI	Electrospray ionization
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
F	Fluorine
h	Hour
H	Hydrogen
HRMS	High-resolution mass spectroscopy

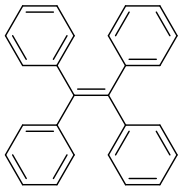
Hz	Hertz
J	Coupling
m	Multiplet
M	Molar (mol/L)
Me	Methyl
mg	Milligram
MHz	Megahertz
min	Minutes
mL	Millilitre
mmol	Millimole
mol%	Mole per cent
m.p.	Melting point
NMR	Nuclear magnetic resonance
OMe	Methoxy
P	Phosphorus
Ph	Phenyl
ppm	Parts per million

^{i}Pr	Iso-propyl
^{n}Pr	Linear propyl
q	Quartet
R_f	Retention factor
rfx	Reflux
rt	Room temperature
s	Singlet
S	Sulphur
sat.	Saturated
t	Triplet
TLC	Thin-layer chromatography
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
X	Halogen

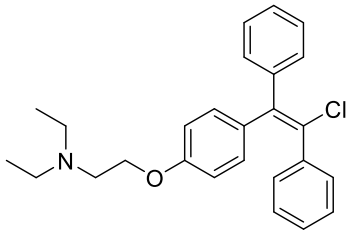
Introduction

Importance of Tetrasubstituted Alkenes

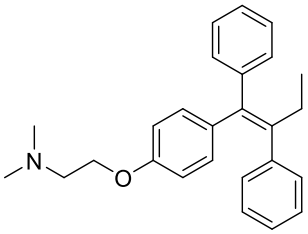
The synthesis of stereochemically well-defined tetrasubstituted alkenes represents one of the most challenging and important subjects in synthetic organic chemistry. Multisubstituted alkenes have found many biological and pharmaceutical applications, where the stereochemistry is vital for the proper function of such compounds (Figure 1). Representative examples of pharmaceutically relevant tetrasubstituted alkenes include Tamoxifen, which has been used as an estrogen antagonist in the treatment for breast cancer,[1–3] and Teriflunomide, used in the treatment for multiple sclerosis.[4] Apart from their use as the final products, stereochemically well-defined alkenes are also valuable starting materials for the stereocontrolled synthesis of saturated compounds through addition reactions, as the diastereo- and enantioselectivities of such reactions are often controlled or affected by the stereochemistry of the C=C bond.



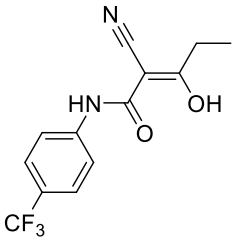
Tetraphenylethylene



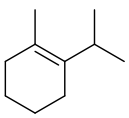
Clomifene



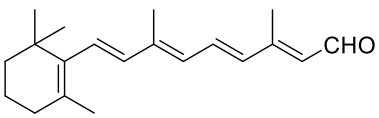
Tamoxifen



Teriflunomide



1-Menthene



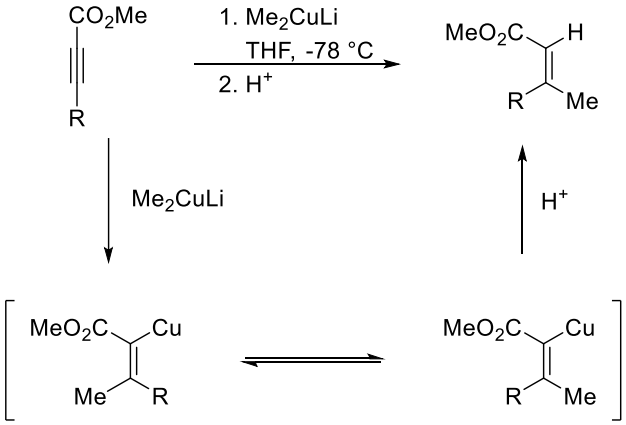
Retinal (Vitamin A)

Figure 1: Known compounds containing multisubstituted alkenes

Given the importance of multisubstituted alkenes, several different strategies for their stereocontolled synthesis have been explored, including carbonyl olefination,[5] elimination reactions,[6] cycloaddition and sigmatropic rearrangement[7] or radical cyclization reaction.[8] Conceptually, one of the most straightforward and atom-economical strategies in this respect is the regio- and stereoselective difunctionalization of alkynes, such as carbometallation.[9] Thus, the addition of two distinct functional groups across a C–C triple bond with control over the regiochemistry and the stereochemistry (i.e. *cis*- or *trans*-fashion) would allow for rapid access to a variety of tetrasubstituted alkenes bearing four different substituents in a pure form. If one or more of the substituents are electrofugal (e.g. boryl, silyl, stannyl) or nucleofugal (e.g. halide) leaving groups, the alkene products may further be utilized for cross-coupling. In the next section, representative examples of such alkyne difunctionalization are discussed.

Stereoselective Alkene Synthesis via Alkyne Difunctionalization

Carbometallation of alkyne has been one of the most well-versed methods for the formation of tetrasubstituted alkenes, with research dating as far back as the 1960s.[9] The earliest example of the carbometallation for the alkene formation is the one using an organocopper reagent reported by Corey's group.[10] Ever since the first discovery of the carbocupration method, there have been multiple breakthroughs in the stereoselective synthesis of alkenes via carbocupration. Besides carbocupration, many advancements have been made for transition metal-catalyzed alkyne carbometallation and related reactions using organoboron,[11–14] organomagnesium,[15–19] and other organometallic reagents.

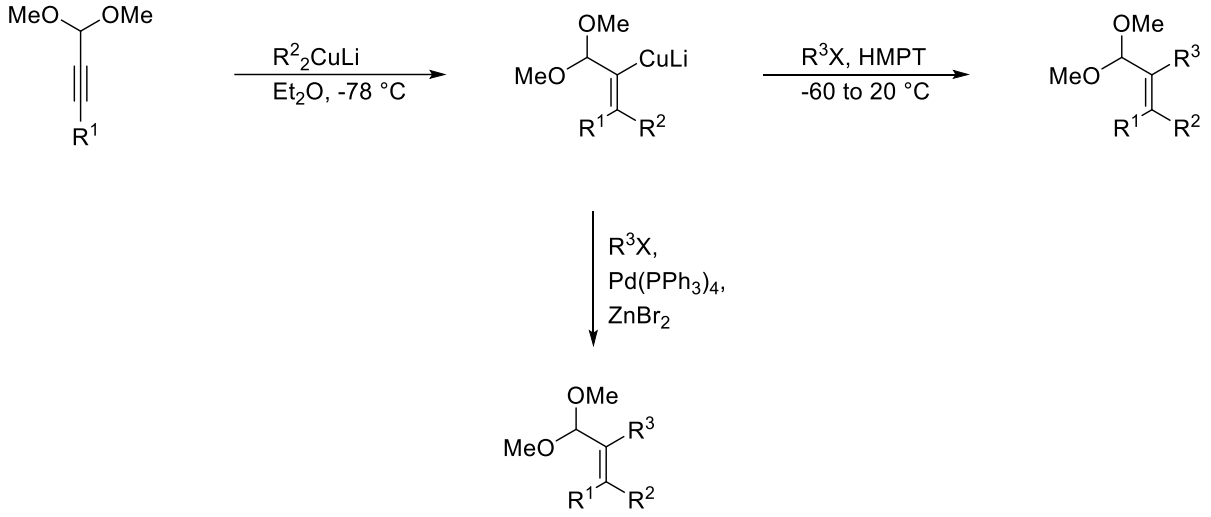


Scheme 1: Carbocupration of an alkynyl ester

Corey's group demonstrated an exclusively *syn*-addition reaction of a Gilman reagent (Me_2CuLi) onto an alkynyl ester, followed by protonation, to form a trisubstituted alkene as shown in Scheme 1.[10,20] To achieve high stereoselectivity, the reaction should be conducted at a low temperature as increasing the reaction temperature would lead to the formation of isomers. Building on the Corey's work, other groups such as Saegusa's group,[21] Deslongchamps's group[22] and Hall's group[23] attempted stereoselective synthesis of tetrasubstituted alkenes by electrophilic trapping of the alkenylcopper intermediate, with varying success.

Along this line of research, Alexakis's group was able to establish a carbocupration-based protocol for the stereoselective synthesis of tetrasubstituted alkenes (Scheme 2).[24] Using acetals as directing groups, the carbocupration was found to proceed with exclusive *syn*-selectivity. The resulting alkenylcopper intermediate can be intercepted by electrophiles with or without the presence of a palladium catalyst depending on the nature of the electrophile, thus affording various tetrasubstituted alkenes.[24] The major limitations and drawbacks of this

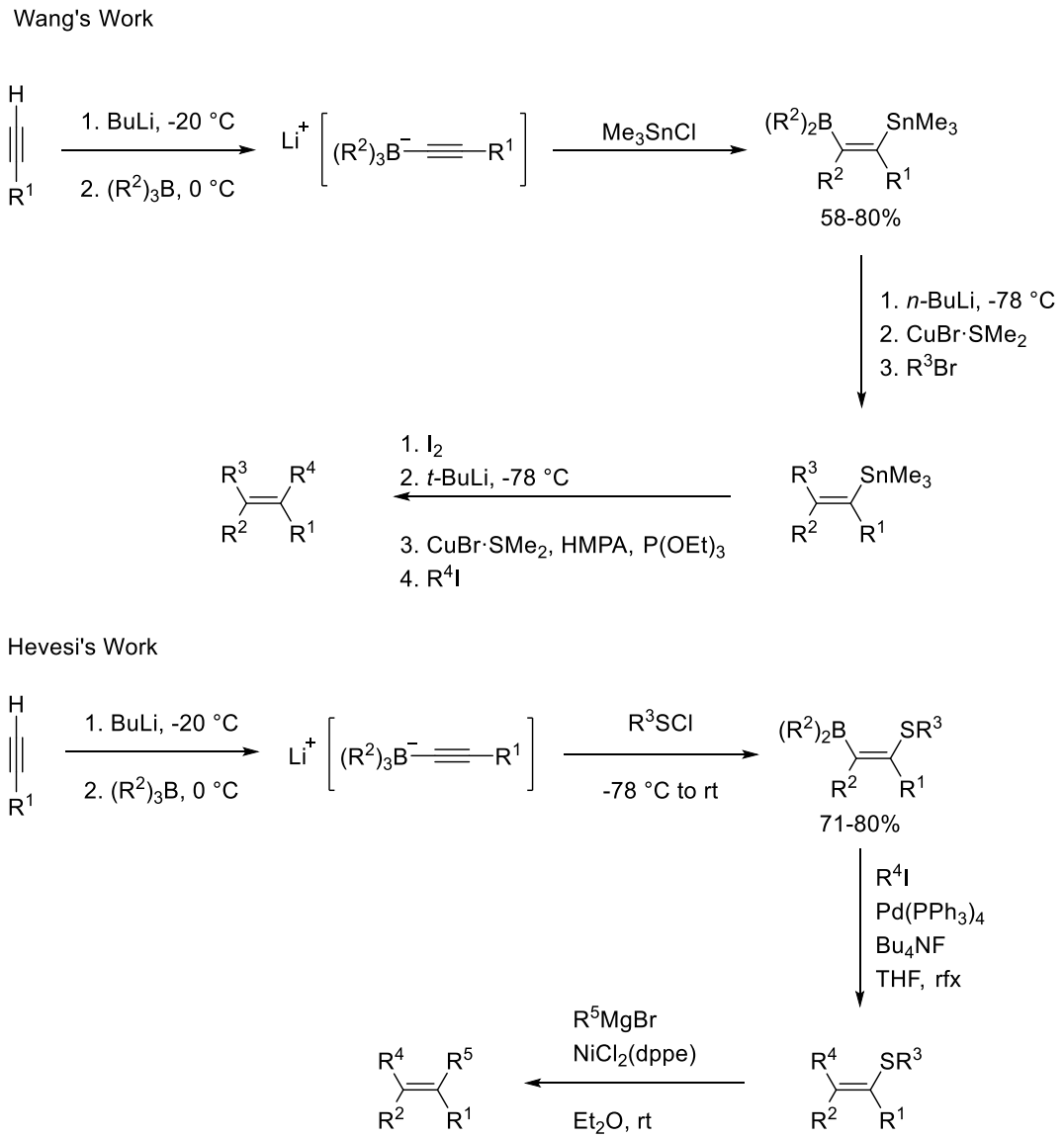
protocol include the requirement of the acetal directing group, the limitation in the variety of Gilman reagents, and the requirement for the low temperature to maintain the stereochemistry.



Scheme 2: Synthesis of tetrasubstituted alkenes via carbocupration–electrophilic trapping

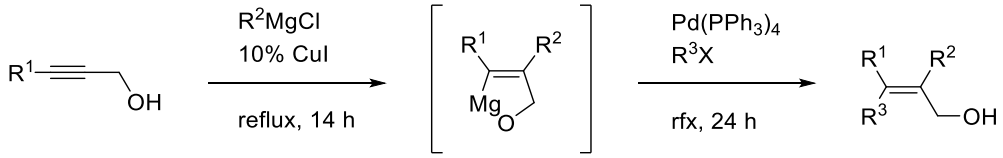
Apart from the conventional carbocupration, reactions of other organometallic reagents such as organoboron and organomagnesium reagents have also been explored to target the issue of the stereoselective alkene synthesis. One notable approach in this respect is the difunctionalization of an alkynylborate generated *in situ* from a terminal alkyne and a trialkylborane via deprotonation (Scheme 3). Wang's group[11] reported carbostannylation of an alkynylborate with trimethyltin chloride via electrophile-initiated 1,2-metallate shift. The reaction occurs in a stereoselective manner to afford *cis*-1-stannyl-2-borylalkenes, which can further be converted to tetrasubstituted alkenes via sequential transformation of the boryl and stannyl groups with the aid of organocopper chemistry. Hevesi's group[13,14] reported an analogous difunctionalization of an alkynylborate using a sulfenyl chloride as the electrophile.

The *cis*-1-alkylthio-2-borylalkene obtained by this stereoselective carbothiolation could be subjected to a sequence of Pd-catalyzed Suzuki–Miyaura coupling on the boryl group and Ni-catalyzed Kumada coupling on the alkylthio group, affording tetrasubstituted alkenes.



Scheme 3: Tetrasubstituted olefination using alkynylborate species

Another common form of carbometallation reaction onto the alkynes is the use of Grignard reagents. This was first exploited by Negishi's group[25] for the stereoselective synthesis of exocyclic alkenes. Thus far, a variety of transition metal catalysts and alkyne substrates have been explored for the carbomagnesiation reaction, where the stereochemistry can depend on the catalyst and the substrate. One example of *trans*-selective carbomagnesiation is shown in Scheme 4, where a copper salt and a propargylic alcohol are used as the catalyst and the substrate, respectively. The regio- and stereoselectivities of the reaction are attributed to the formation of a 5-membered ring organomagnesium intermediate. Pd-catalyzed cross-coupling of this intermediate allows for the stereoselective synthesis of tetrasubstituted allylic alcohols.



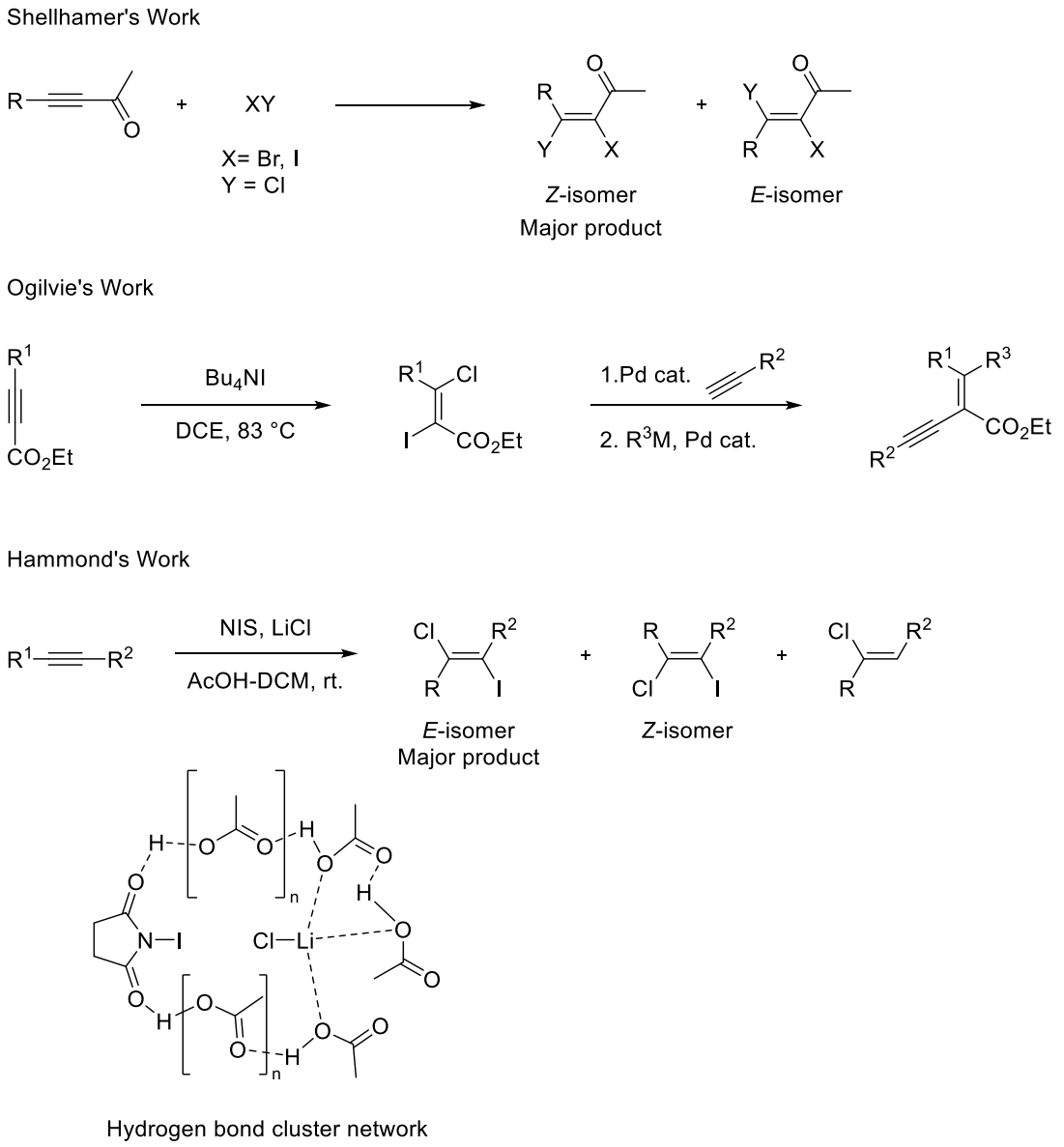
Scheme 4: Stereoselective synthesis of multisubstituted allylic alcohol via *trans*-selective carbomagnesiation of propargylic alcohol

Apart from using organometallic reagents for the difunctionalization of the alkyne, electrophilic halogen compounds, especially interhalogen compounds (XY), have been explored as reagents for the difunctionalization of alkynes. Shellhamer's group reported the addition of ICl and BrCl onto alkynyl ketones (Scheme 5).[26] The reaction mostly occurred regio- and stereoselectively to afford *cis*-dihalogenation product as the major product, while

the amount of the *trans*-dihalogenated isomer accompanied depends on the R group on the alkyne. The hazardous and toxic nature of the reagents also remained as a problem.

In 2006, Ogilvie's group reported the formation of a single-isomer tetrasubstituted alkene via asymmetric halogen incorporation onto the alkyne (Scheme 5).[27] They managed to achieve this by using Bu_4NI and dichloroethane as the halogen sources for the difunctionalization of alkynyl esters. Capitalizing on the distinct leaving group abilities of the iodo and chloro substituents, the product could be utilized for sequential, chemoselective cross-coupling reactions to afford tetrasubstituted alkenes.

Inspired by Shellhamer's work, Hammond and co-workers recently designed a protocol for stereoselective alkyne dihalogenation using interhalogen reagents generated *in situ*. Thus, the combination of N-iodosuccinimide (NIS) and LiCl in acetic acid/DCM mixed solvent allowed regioselective *trans*-dihalogenation of various terminal and internal alkynes to afford *trans*-1-iodo-2-chloroalkenes. NIS and LiCl are considered to form a hydrogen bond cluster network in acetic acid, from which the interhalogen reagent (ICl) is generated *in situ*. Hammond's group believed that acetic acid also plays a vital role in controlling the regio- and stereo-selectivity of the overall reaction. The combination of halogen sources has been extended to NIS-LiI, NIS-LiBr, NBS-LiBr and NBS-LiCl, with comparable success. The utility of the products obtained by this unsymmetrical dehalogenation in chemoselective cross-coupling has been extensively demonstrated. Hammond's protocol is also notable in reduction of the contact of the hazardous interhalogen compound with the user.



Scheme 5: Dihalogenation of alkynes using interhalogen reagents

Trivalent Iodine Electrophile for Alkyne Difunctionalization

In recent years, there have been increasing applications of hypervalent iodine compounds in synthetic organic chemistry. A unique chemical property of iodine is due to its ability to form a three-centre-four electron (3c-4e) bond to the overlapping 5p orbital with the

ligands,[28,29] resulting in the formation of hypervalent iodine species. Trivalent iodine compounds tend to form a T-shape geometry with the electron-withdrawing ligands taking the axial positions while the remaining substituent and lone pairs occupy the equatorial positions (Figure 2).[30,31] An additional benefit for the use of hypervalent iodine compounds is their environmental benignity and low toxicity.[28,29,32] Hypervalent iodine compounds have been known to undergo various reactions, such as halogenation,[33–37] oxidation,[38–43] radical reactions,[44,45] and C-C bond formation.[46]

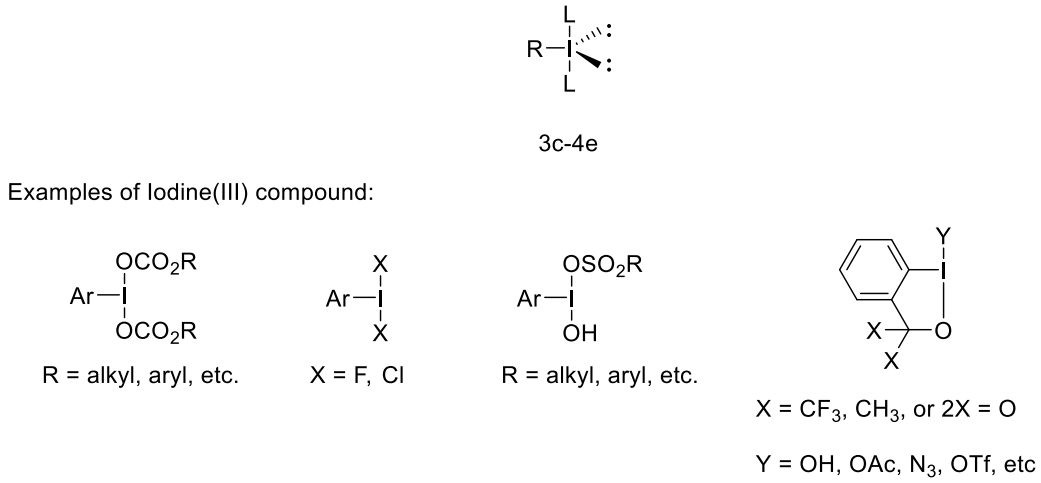
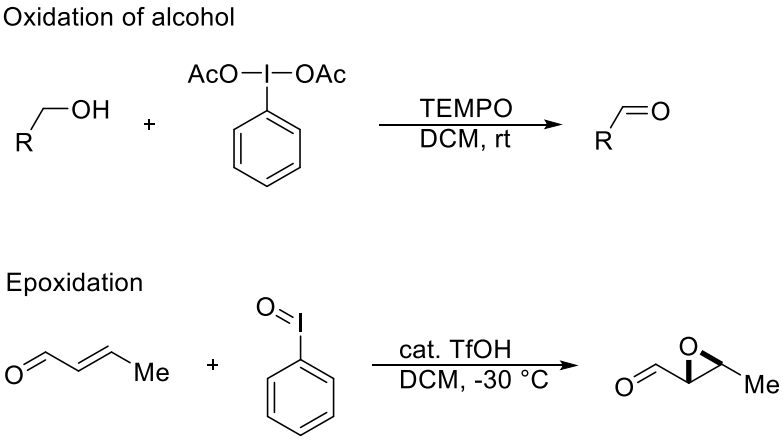


Figure 2: Types of trivalent iodine compounds

Hypervalent iodine compounds have been established as mild oxidants and often utilised in the oxidative transformation of organic substrates. The use of hypervalent iodine as an oxidising agent has been widely explored as a method to form epoxides or convert alcohol groups to their carbonyl counterparts.[28] As shown in Scheme 6, bis(acetoxy)iodobenzene can be used for the oxidation of an alcohol to an aldehyde,[40,47] while iodosylbenzene serves as an oxidant for the epoxidation of an α,β-unsaturated aldehyde.

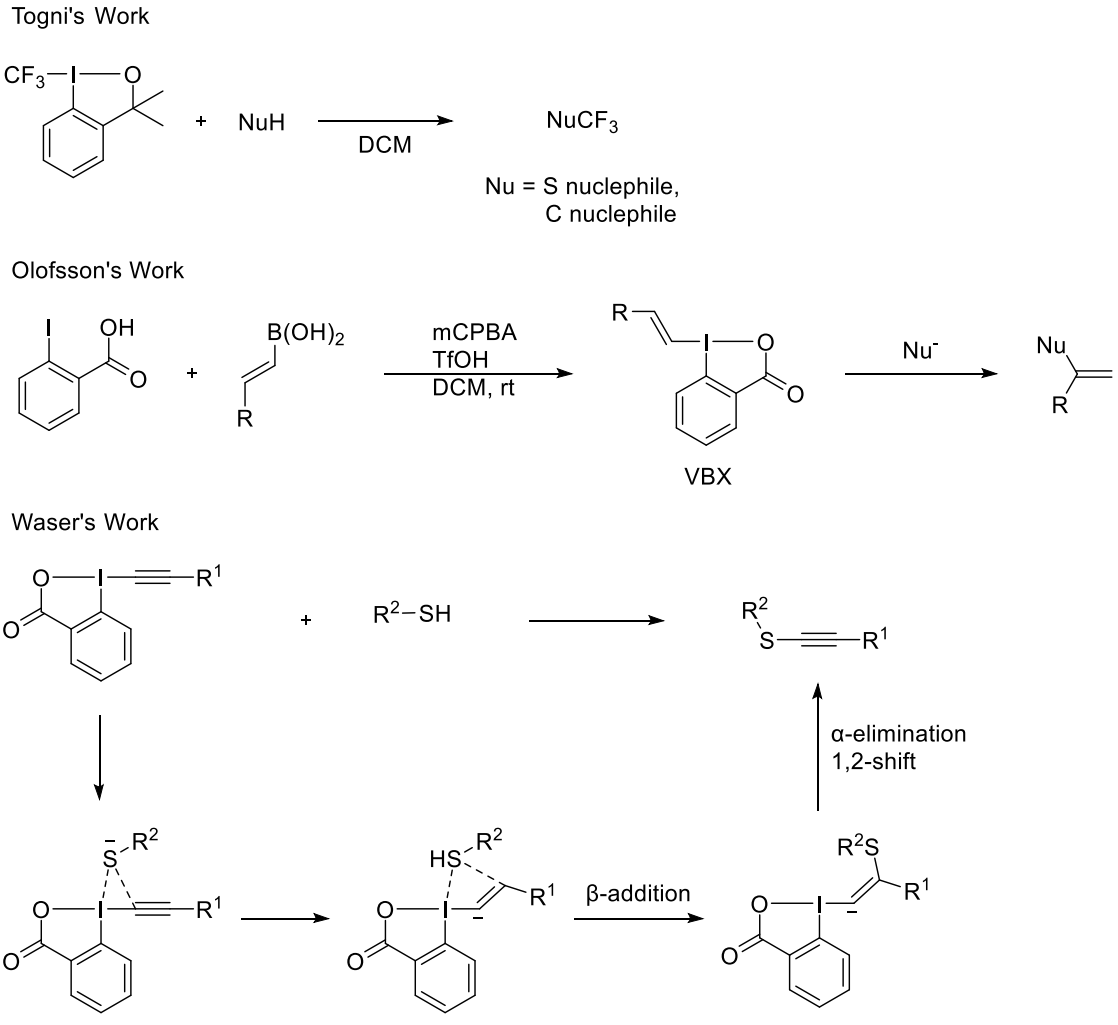


Scheme 6: Oxidative transformation using hypervalent iodine(III)

The other major use of hypervalent iodine compounds is as group transfer agents. Some of the most common functional group that undergoes the transfer are halogens (F^-, Cl^-, Br^- and I^-),[33–37] CF_3,[48] azides (N_3),[49,50] cyanation,[51] alkynyl,[52,53] and aryl[54] groups. Over the years, there has been an improvement in the design of the trivalent iodine reagents for the group transfer. One such design is represented by the Togni reagents, which are cyclic trivalent iodine compounds consisting of a benziodoxol(on)e backbone. The benziodoxol(on)e backbone allows for a better overlap between the π-orbitals of the benzene ring and the lone pair of the iodine.[48,55,56] Due to the overlap, the cyclic trivalent iodine compound exhibits more enhanced stability as compared to the acyclic trivalent iodine counterparts, allowing the ease in handling. Togni reagents were first used to explore the transfer of trifluoromethyl group onto the carbon- and sulphur-centred nucleophile (Scheme 7).[48]

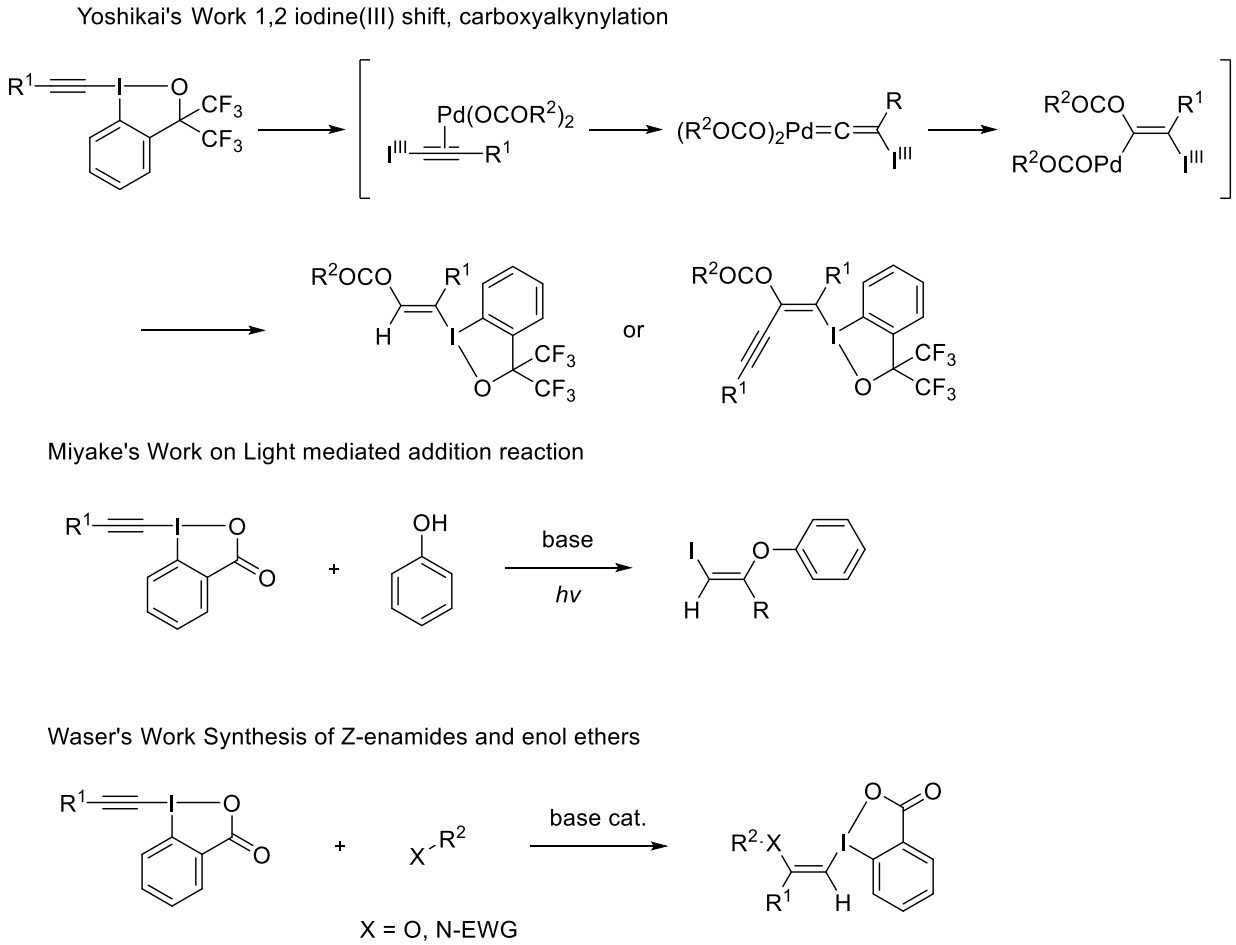
Other groups have also explored the use of the BX moiety as the structural element in new hypervalent iodine-based group transfer agents. One such group is the Olofsson's group,

who developed a method to synthesize *trans*-vinylbenziodoxolones (VBX) using 2-iodobenzoic acid *trans*-vinylboronic acid as the starting material (Scheme 7). They demonstrated the unique reactivity of VBX toward nitrocyclohexane as a nucleophile.[57] On the other hand, Waser's group identified the addition of a nucleophile to ethynylbenziodoxolone (EBX) as viable means to form VBX during their study on alkynylation of thiols using EBX. Thus, β-addition of a thiol to EBX was be followed by protonation of the α-position instead of α-elimination and 1,2-shift in some cases, thus affording β-alkylthio-VBX as a byproduct (Scheme 7).[58]



Scheme 7: Examples of reactions of benziodoxol(on)e-type compounds

The nucleophile addition to EBX has been explored by Waser's group, our group, and others as a synthetic approach to multisubstituted VBXs (Scheme 8).[56,59–68] Yoshikai's group reported a Pd-catalyzed addition of a carboxylic acid to EBX involving 1,2-iodine(III) shift, which stereoselectively afforded β-carboxy-substituted VBXs. As an extension, they also identified Pd-catalyzed conditions for carboxylative dimerization of EBX, affording enynyl-BX-type products.[59,68]



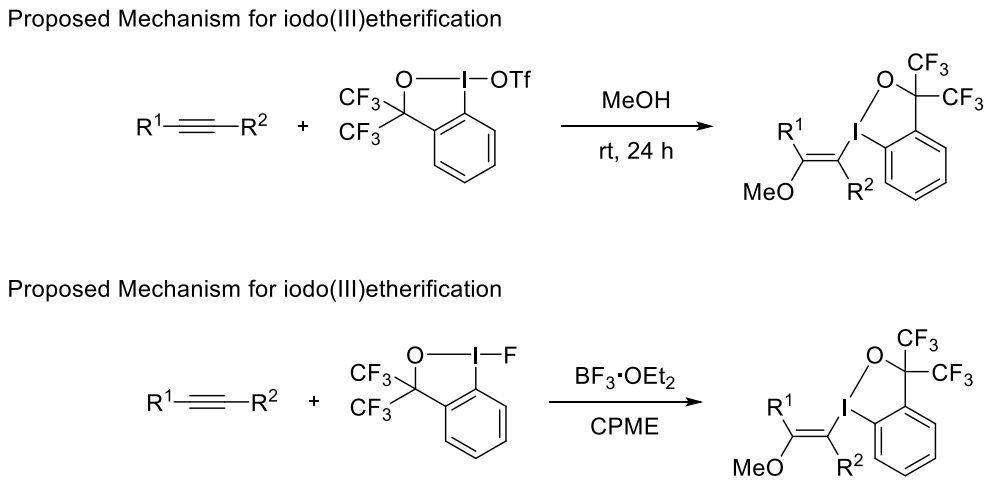
Scheme 8: Synthesis of VBXs via nucleophile addition to EBX

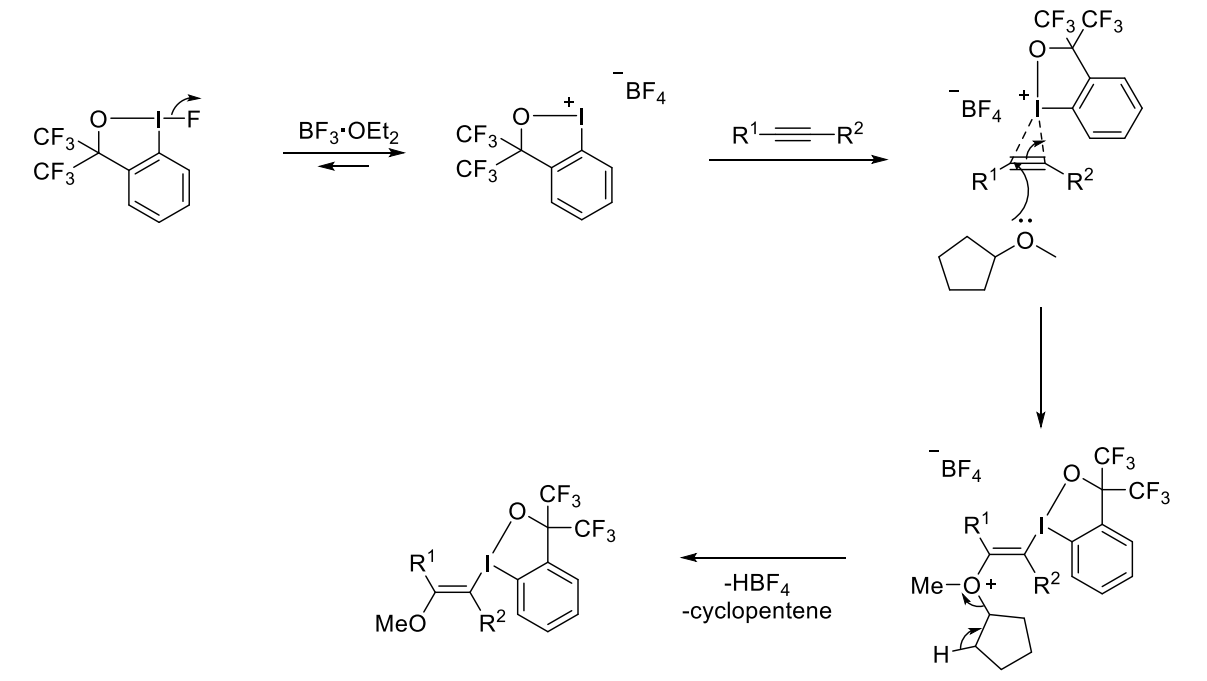
Miyake's group reported a light-promoted addition reaction of phenols to EBX in the presence of a base to form (*Z*)-β-iodovinyl ethers under transition metal-free conditions.[67] The reaction was found to initially afford VBX-type products, which decompose into the final products under the reaction conditions. Meanwhile, Waser's group was also able to develop a protocol for regio- and stereoselective addition of phenols and sulfonamides to EBX, affording the corresponding VBX products as only *Z*-isomers.[62]

The nucleophile addition to EBX is limited to the synthesis of trisubstituted VBXs. In addition, individual EBX reagents need to be prepared in order to access structurally diverse VBXs. In this respect, Yoshikai's group have explored difunctionalization of alkynes with benziodoxolone triflate (BXT) or related electrophile and a nucleophile as a means to access both tri- and tetrasubstituted VBXs (Scheme 9). Thus, *trans*-iodo(III)etherification of both internal and terminal alkynes with BXT and alcohol was found to proceed smoothly at room temperature, to produce the corresponding β-iodo(III)vinyl ethers in moderate to good yields.[60] The products proved amenable to various cross-coupling reactions with BX as the leaving group. Furthermore, Yoshikai *et al*. also demonstrated iodo(III)etherification using the combination of fluorobenziodoxole and BF_3•OEt_2 as an electrophilic BX source and an ethereal solvent such as cyclopentyl methyl ether as an alkoxy source.

A proposed mechanism of the latter iodo(III)etherification system is shown in Scheme 9. Activation of FBX with BF_3 would initially give rise to a BX cation paired with tetrafluoroborate. The BX cation would electrophilically activate the alkyne to trigger the

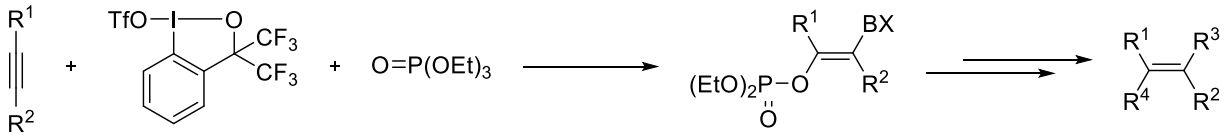
nucleophilic addition of CPME on the opposite side from the BX group to follow the Markovnikov selectivity. The resulting intermediate would undergo a β-elimination to eliminate the proton and cyclopentene leaving the desired product.[69]





Scheme 9: Proposed mechanism for iodo(III)etherification of alkynes using FBX/BF_3 and CPME

On the basis of the above previous studies on iodo(III)etherification, we wondered whether it is possible to engage other oxygen-based nucleophiles bearing proton and alkene as potential leaving groups in iodo(III)oxyfunctionalization of alkynes. In this respect, our attention was attracted to the potential reactivity of phosphate esters, such as triethyl phosphate. Triethyl phosphate is readily available and inexpensive, has Lewis basic and thus potentially nucleophilic P=O oxygen atom, and bears an ethyl group that can be viewed as leaving group consisting of proton and ethylene. Furthermore, alkenyl phosphates, usually prepared from carbonyl compounds via enolates, have been established as versatile alkenyl electrophiles in cross-coupling. Thus, the stereoselective addition of BX and phosphate groups onto alkynes is considered to give synthetically versatile difunctionalized alkenes. Here, we report on the development of such iodo(III)phosphatoxylation reaction.



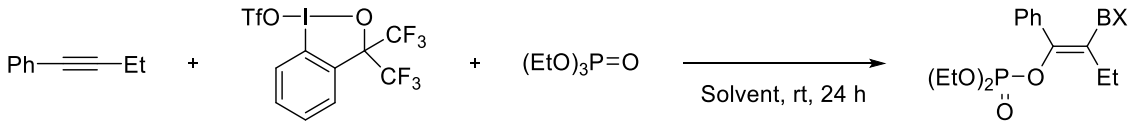
Scheme 10: This work

Results & Discussion

Optimization of Reaction Conditions

We chose 1-phenyl-1-butyne (**2a**) and triethyl phosphate (**3a**) as model reactants to explore the feasibility of iodo(III)functionalization using BXT (**1**). In light of the optimized conditions for the iodo(III)etherification, the reaction of **2a** (0.1 mmol), **1** (0.2 mmol, 2 equiv), and **3a** (0.3 mmol, 3 equiv) was initially performed in MeCN (0.5 mL) as the solvent at room temperature, which afforded the desired product **4aa** exclusively as the *trans* isomer in 23% yield (determined by ^{19}F NMR; Table 1, entry 1). Upon screening of solvents, less polar and noncoordinating solvents such as toluene, DCM, DCE, chlorobenzene, and 1,2-dichlorobenzene were found to significantly improve the yield of **4aa** (entries 2-6), where the highest yield of 67% was achieved in toluene (entry 2). The reaction in Et_2O afforded **4aa** in a modest yield of 26% (entry 7), while the desired reaction did not take place in more polar THF (entry 8). Likewise, polar and coordinating solvents such as DMF, DMSO, and acetone failed to give **4aa** (entries 9-11). Not unexpectedly, the reaction in MeOH resulted in the iodo(III)methoxylation of **1a** rather than the formation of **4aa** (entry 12).

Table 1: Reaction of 1-phenyl-1-butyne (**2a**), benziodoxole triflate (**1**), and triethyl phosphate (**3a**) in various solvents



2a 0.1 mmol | **1** 2.0 equiv | **3a** 3.0 equiv | **4aa**

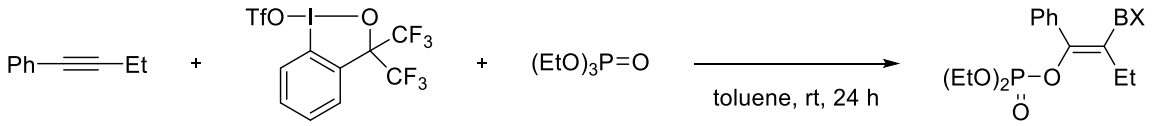
Entry	Solvent	Yield (%)[b]
1	MeCN	23
2	toluene	67
3	DCM	64
4	DCE	55
5	chlorobenzene	63
6	1,2-dichlorobenzene	48
7	Et_2O	26
8	THF	0
9	DMF	0
10	DMSO	0
11	acetone	0
12	MeOH	-[c]

[a] Reaction was performed on a 0.1 mmol scale in 0.5 mL solvent. [b] Yield of the compound **4aa** was determined by ^{19}F NMR using 1,4-bis(trifluoromethyl)benzene as an internal standard. [c] Iodo(III)vinyl ether product was obtained instead.

Based on the above results, we determined toluene as the optimal solvent for the present reaction. We next explored the influence of the ratio of the starting materials **2a**, **1**, and **3a** (Table 2). Starting from the originally adopted ratio of 1:2:3 (entry 1; 67% yield), changing the number of equivalents of the phosphate **3a** between 2 equiv to 10 equiv had little influence on

the yield of **4aa** (entries 2-4; 63-65%). In contrast, the increase of the number of equivalents of **1** to 3 equiv was found to significantly improve the yield of **4aa** to 89% (entry 5). Note that the reaction using **1** as the limiting reagent, with the **2a**/**1**/**3a** ratio of 2:1:3, afforded **4aa** in only 31% yield (entry 6). Not unexpectedly, the use of only a slight excess of **1** and **3a** with respect to **2a**, also resulted in unsatisfactory yield (entry 7).

Table 2: Effect of reactant stoichiometry



2a **1** **3a** **4aa**

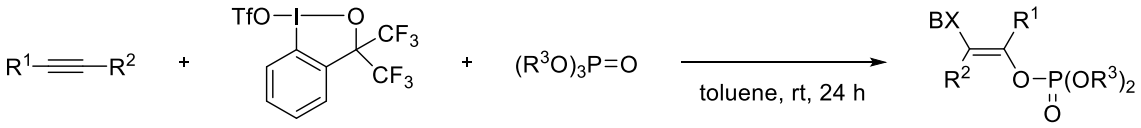
Entry	**2:1:3a**	Yield (%)[b]
1	1:2:3	67
2	1:2:2	65
3	1:2:5	63
4	1:2:10	63
5	1:3:3	89 (83)[c]
6	2:1:3	31
7	1:1.2:1.5	31

[a] Reaction was performed on a 0.1 mmol scale in 0.5 mL solvent. [b] Yield of the compound **4aa** was determined by ^{19}F NMR using 1,4-bis(trifluoromethyl)benzene as the internal standard. [c] Isolated yield was recorded in parentheses.

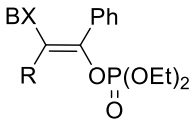
Substrate Scope

Using the optimized conditions (Table 2, entry 7) in hand, we explored the reaction of various internal alkynes together with BXT and triethyl phosphate (Table 3). A series of phenyl(alkyl)alkynes participated in the optimized reaction condition to obtain the corresponding products **4aa**–**4ga** in moderate to good yields with exclusive regio- and stereoselectivity. Besides unfunctionalized primary or secondary alkyl groups (see **4aa**–**4ea**), alkyl groups bearing methoxy (see **4fa**) or cyano (see **4ga**) group could be tolerated as the alkyne substituents. The present reaction also proved to tolerate aryl(alkyl)alkynes bearing various aryl groups, affording the products **4ha**–**4sa** in moderate to good yields. Thus, tolerable aryl groups include *para*-, *meta*-, or *ortho*-substituted phenyl groups bearing electron-withdrawing (i.e. halogen, CO_2Et, and CF_3) or electron-donating (i.e. Me and OMe) substituent (see **4ha**–**4qa**), thienyl group (see **4ra**), and 1-naphthyl group (see **4sa**). Notably, some of the aryl(alkyl)alkynes bearing electron-withdrawing substituent, i.e., **2j**, **2n**, and **2o**, afforded the products in a form of a mixture of two isomers in a ratio of 2.2:1 to 4.4:1. Judging from their NMR spectra, the minor isomer was assigned as the regioisomer (rather than the stereoisomer), where the BX group is bonded to the carbon proximal to the aryl group. These observed results may be attributed to the decreased propensity of the electron-deficient aryl group to facilitate the development of a positive charge on the proximal acetylenic carbon. Another notable observation was the NMR spectral behaviour of the 1-naphthyl-substituted product **4sa**. Its ^{1}H, ^{13}C, and ^{19}F NMR spectra indicated inequivalence of the two CF_3 groups on the BX ring as well as of the two ethyl groups on the phosphate moiety, which can be attributed to the restricted rotation of the bulky BX and naphthyl groups owing to the steric clash.

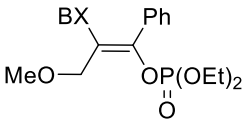
Table 3. Substrate scope [a]



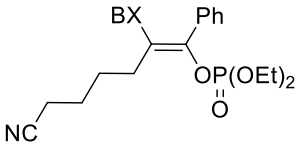
2 1.0 equiv | **1** 3.0 equiv | **3** 3.0 equiv | **4**



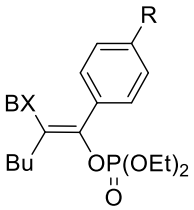
4aa (R = Et) 83%
4ba (R = Me) 77%
4ca (R = ^{n}Pr) 77%
4da (R = Bu) 66%
4ea (R = Cy) 78%



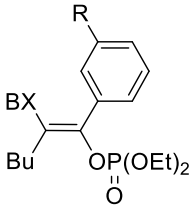
4fa, 77%



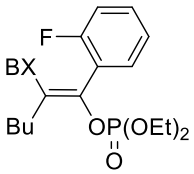
4ga, 65%



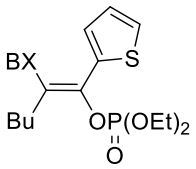
4ha (R = F) 72%
4ia (R = Cl) 66%
4ja (R = CO_2Et) 63% (2.2:1)[b]
4ka (R = Me) 63%
4aa (R = OMe) 54



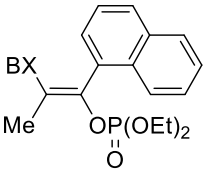
4ma (R = OMe) 76%
4na (R = Br) 76% (3.6:1)[b]
4oa (R = CF_3) 52% (4.4:1)[b]
4pa (R = Me) 46%



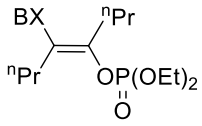
4qa 50%



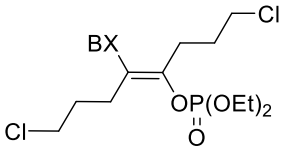
4ra, 65%



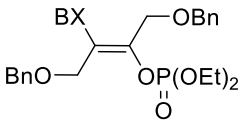
4sa, 65%



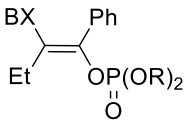
4ta, 81%



4ua, 46%



4va, 54%



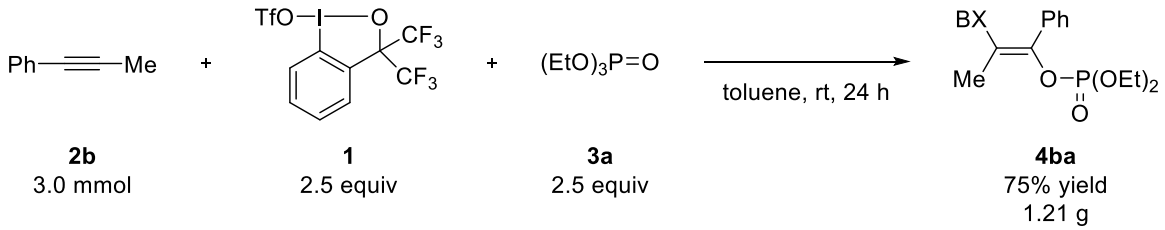
4ab (R = Me) 52%
4ac (R = ^{i}Pr) 46%
4ad (R = Ph) 68%[c]

[a] Reaction was performed on a 0.2 mmol scale using 1.0 mL toluene for 24 h at rt. The BX symbol symbolizes the benziodoxole moiety. [b] The regioisomer ratio is given in the parentheses.

The structure of the major regioisomer is shown. [c] Diphenyl phosphate was used as the phosphate reagent.

The present reaction also proved applicable to symmetrical dialkylalkynes, affording the products **4ta-4va** in moderate to good yields of 46%-81%, where chloro and benzyloxy groups were well tolerated. Besides triethyl phosphate, other phosphate esters such as trimethyl phosphate and triisopropyl phosphate also participated in the reaction with the alkyne **1a** and BXT, affording the corresponding products **4ab** and **4ac**, respectively, in moderate yields. While the latter phosphate ester would react in the same manner as triethylphosphate, with elimination of propene and HOTf as byproducts, the reaction of the former phosphate would involve the formation of MeOTf as byproduct. Not unexpectedly, triphenyl phosphate failed to participate in the present reaction (data not shown). On the other hand, the reaction using diphenyl phosphate afforded the desired product **4ad** in 68% yield.

To demonstrate the scalability of the present reaction, we proceeded to perform the reaction of alkyne **2b**, **1**, and **3a** on a 3 mmol scale. Using lower equivalents of **1** and **3a** (2.5 equiv each), the reaction proceeded smoothly to obtain the desired product **4ba** in 75% (Scheme 11).

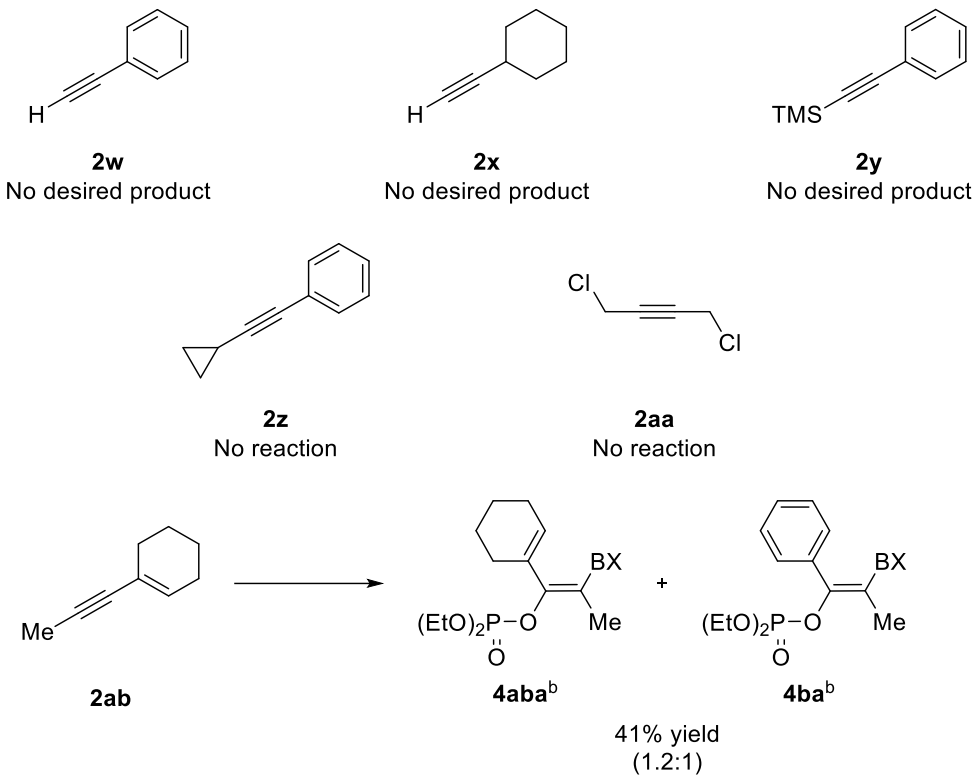


Scheme 11: Gram-scale reaction

Unsuccessful Substrates

Limitations of the present reaction with respect to alkyne substrates are summarized in Figure 3. One significant limitation is that we were unable to isolate the desired product when using terminal alkyne or silylated alkyne **2w-y**. During the initial TLC check, we observed possible product formation with an R_f value of 0.4 (Eluent: Et_2O), with accompanying spot for 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol as the decomposition product of **1**. However, over time the spot started to disappear, indicating that the final product was unstable. We first suspected that the compound was unstable on the slightly acidic silica gel, and hence attempted product isolation by column chromatography on triethylamine-treated silica gel, which was nevertheless unsuccessful. Preparative TLC was not effective either.

Among internal alkynes, (cyclopropylethynyl)benzene **2z** and the 1,4-dichlorobut-2-yne **2aa** failed to give the desired products for unknown reasons. Using 1-(prop-1-yn-1-yl)cyclohex-1-ene **2ab** as a substrate, we were able to get the desired product **4aba** along with an aromatized derivative **4ba** in a ratio of 1.2:1. The observed side product could be due to the oxidative dehydrogenation of the cyclohexene moiety to form the phenyl group[70] as a result of the BXT reagent undergoing oxidative reaction instead.



[a] Reaction was performed in 0.2 mmol scale using 1 mL toluene for 24 h at rt. [b] The BX symbol symbolizes the benziodoxole moiety

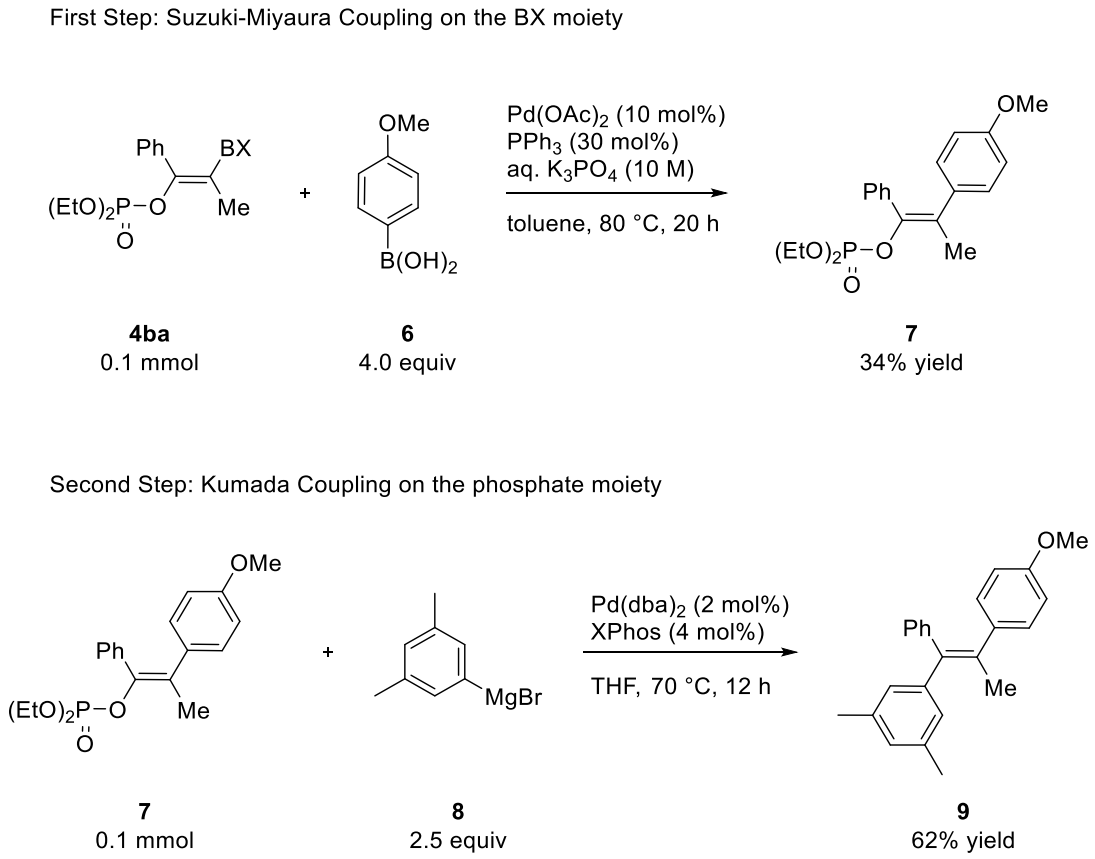
Figure 3: Unsuccessful alkyne substrates[a]

Product Transformations

Somewhat unexpectedly, the most challenging aspect of the project was transformation of the vinyl–BX products by cross-coupling. As illustrated in Scheme 12, we performed a two-step transformation of the product **4ba** to form a tetrasubstituted alkene. The first transformation was Suzuki–Miyaura cross-coupling on the BX moiety. This is followed by the second transformation step by Kumada cross-coupling on the phosphate group.

The first step was found to be unexpectedly challenging. Thus, the reaction of **4ba** with 4-methoxyphenylboronic acid (**6**, 2.0 equiv) under several typical Suzuki–Miyaura coupling

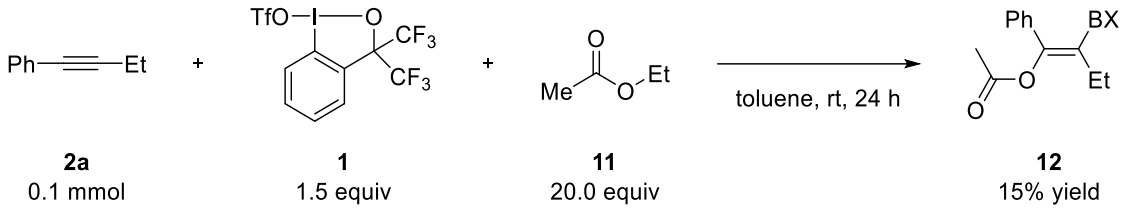
conditions resulted in recovery of a large amount of **4ba**, while the reagent **6** was completely consumed. Apart from this, only a small amount (< 10% yield) of the desired produce **7** was observed along with the homo-coupled product of **6**. After many attempts, using a large excess of **6** (4.0 equiv) under a catalytic system comprising of $Pd(OAc)_2$, PPh_3, and K_3PO_4, we managed to obtain **7** in a modest yield of 24%, where the majority of the starting material **4ba** still remained unreacted. Further improvement appears challenging if not impossible, and would require more extensive catalyst screening. The poor reactivity of **4ba** is in a sharp contrast to the smooth reaction of the analogous iodo(III)etherification product,[60] and is apparently attributed to the electronic and/or steric nature of the phosphate group. The second step, Kumada cross-coupling of the phosphate **7** with 3,5-dimethylphenylmagnesium bromide, was achieved using Brown's reaction conditions,[71] affording the desired tetrasubstituted product **9** in 62% yield with a trace amount of trisubstituted product.



Scheme 12: Product transformations

Ethyl Acetate as Nucleophile

Given the successful engagement of triethyl phosphate, we wondered if ethyl acetate could also serve as an oxygen nucleophile for the iodo(III)oxyfunctionalization (Scheme 13). Simple replacement of the phosphate ester with ethyl acetate in the above optimized reaction system led to only a trace amount of the desired iodo(III)acetoxylation product. Nonetheless, the use of a large excess (20.0 equiv) of ethyl acetate afforded the desired product **12**, albeit in a low yield of 15%. The reaction using ethyl acetate as the solvent improved the yield to 35%.



2a 0.1 mmol | **1** 1.5 equiv | **11** 20.0 equiv | **12** 15% yield

Scheme 13: Using ethyl acetate as a nucleophile

Conclusion

In conclusion, we have developed a regio- and stereoselective difunctionalization reaction of internal alkynes with benziodoxole triflate and phosphate esters. The reaction proceeds at room temperature to afford *trans*-iodo(III)alkenyl phosphates in moderate to good yields, which represent a new class of vinylbenziodoxoles. The reaction has proved to be applicable to a variety of aryl(alkyl)alkynes and dialkylalkynes. For the former type of alkynes, the phosphate group was introduced to the acetylenic carbon proximal to the aryl substituent, where a positive charge is better stabilized, often with exclusive regioselectivity. The BX and phosphate groups on the product can be utilized as leaving groups of distinct reactivities. Thus, sequential Pd-catalyzed cross-couplings on the BX and phosphate groups have been demonstrated to achieve the stereoselective synthesis of an all-carbon tetrasubstituted alkene, albeit with low efficiency of the first cross-coupling. Further improvement of the cross-coupling on the BX group would render the present difunctionalization reaction more attractive approach to the synthesis of various tetrasubstituted alkenes.

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Experimental Section

Materials and Methods: 1,1,1,3,3,3-hexafluoro-2-phenylisopropyl alcohol was purchased from TCI and consumed as received. Benziodoxole triflate (BXT) was synthesized according to the literature procedure.[63] Phosphates (**3a**-**3c**) and diphenyl phosphate (**3d**) were purchased from Sigma-Aldrich, Alfa Aesar, or other commercial suppliers and used as received. Alkynes were prepared according to the literature procedure except for **2a-c** and **2t** were purchased from Sigma-Aldrich, Alfa Asear, or other commercial suppliers and used as received.

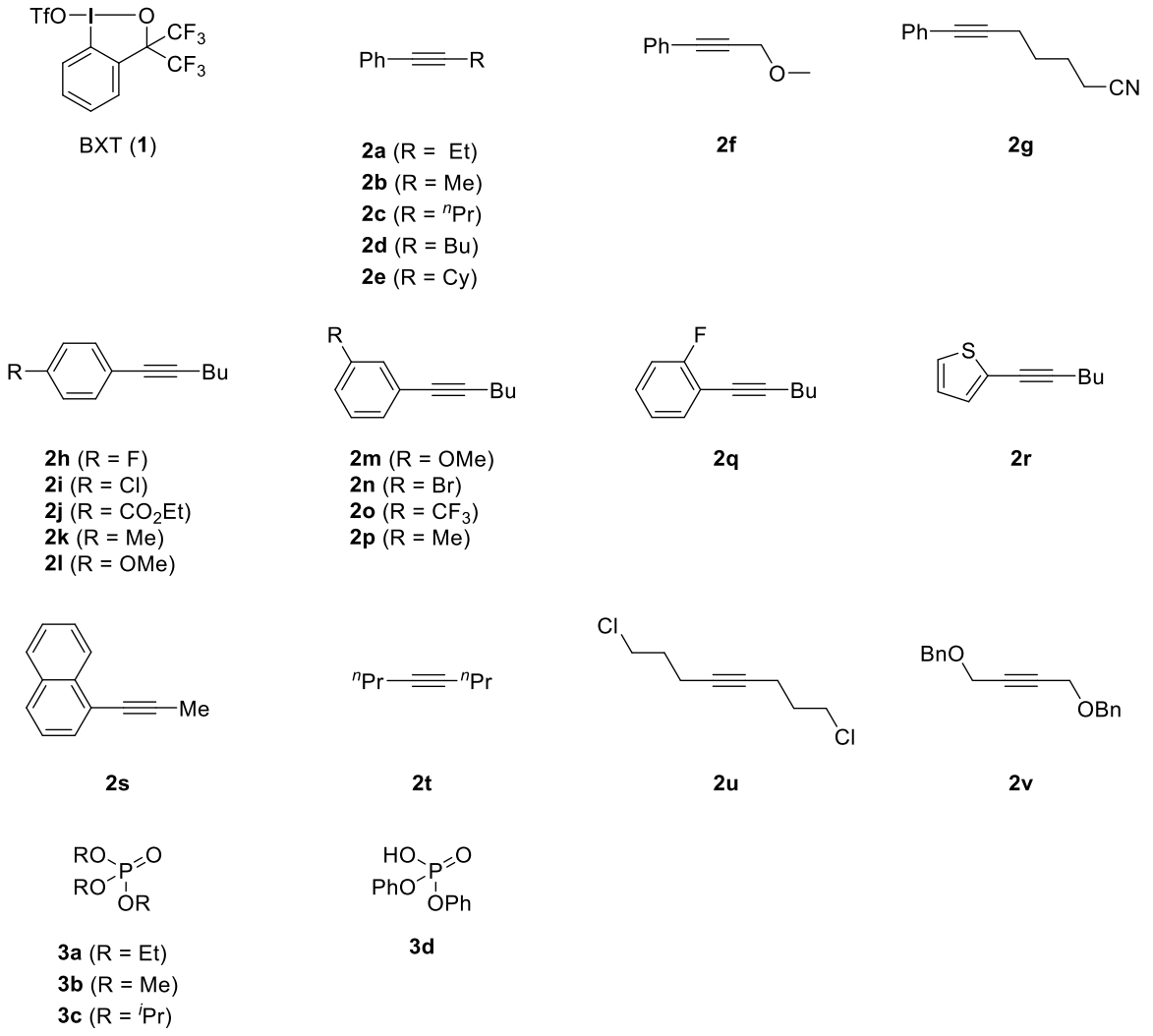
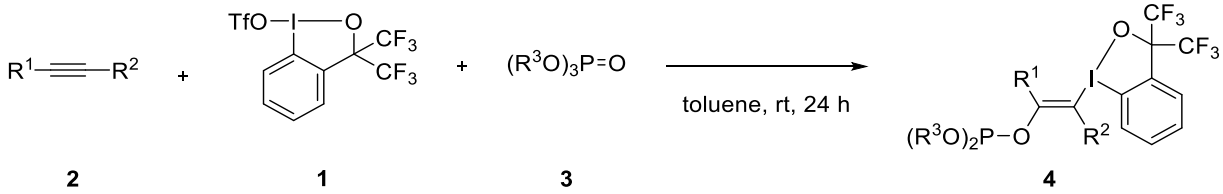
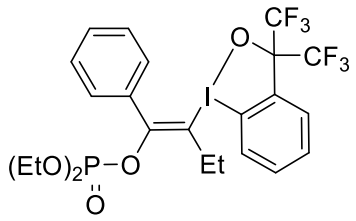


Figure 4: Starting materials used in this study.



General Procedure: To a 4 mL vial was equipped with a magnetic stir bar and charged with toluene (1 mL), alkyne **2** (0.2 mmol), and phosphate ester **3** (0.6 mmol), and followed by the

addition of BXT **1** (0.6 mmol). The resulting mixture was stirred at room temperature for 24 h. The reaction mixture was first quenched with saturated aq. Na_2CO_3 (4 mL) and then extracted with EA (5 mL x 3). Water (10 mL x 3) and brine (10 mL) was used to wash the organic layer and then Na_2SO_4 was used to dry the compound. The solvent was evaporated and the residue was further purified by flash chromatography on silica gel to afford the desired product.



(*E*)-2-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-phenylbut-1-en-1-yl diethyl phosphate (4aa): Using the general procedure, in toluene (1 mL), 1-phenyl-1-butyne (**2a**, 0.2 mmol), triethyl phosphate (**3a**, 3.0 equiv, 0.6 mmol) and BXT (**1**, 3.0 equiv, 0.6 mmol) . White solid (108.3 mg, 83% yield); R_f 0.33 (Et_2O); m.p. 148-151°C;

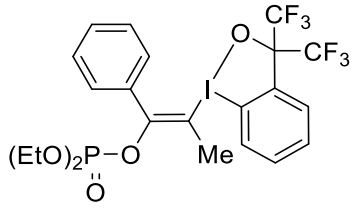
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (app. d, *J* = 7.4 Hz, 1H), 7.78 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.70-7.61 (m, 2H), 7.38-7.32 (m, 1H), 7.31-7.26 (m, 4H), 4.04-3.84 (m, 4H), 2.91 (brs, 2H), 1.23 (t, *J* = 7.4 Hz, 3H), 1.18 (t, *J* = 7.0 Hz, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4 (d, $^3J_{C\text{-}P}$ = 8.7 Hz), 134.9, 132.4, 131.4, 130.44, 130.37, 130.33, 128.9, 128.4, 127.6, 123.9 (q, $^1J_{C\text{-}F}$ = 289.5 Hz), 119.2 (d, $^2J_{C\text{-}P}$ = 7.8 Hz), 110.9, 81.7-80.5, 64.5 (d, $^3J_{C\text{-}P}$ = 6.2 Hz), 27.2, 15.8 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 13.8;

^{19}F NMR (282 MHz) δ -76.2;

^{31}P NMR (162 MHz) δ -6.7;

HRMS (ESI) Cal $C_{23}H_{25}O_5IF_6P$ $[M+H]^+$ 653.0388, found 653.0390



(*E*)-2-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-phenylprop-1-en-1-yl diethyl phosphate (4ba): Using the general procedure, in toluene (1 mL), 1-phenyl-1-

propyne (**2b**, 0.2 mmol), triethyl phosphate (**3a**, 3.0 equiv, 0.6 mmol) and BXT (**1**, 3.0 equiv, 0.6 mmol) . White solid (98.3 mg, 77% yield); R_f 0.38 (Et_2O); m.p. 109-111 °C;

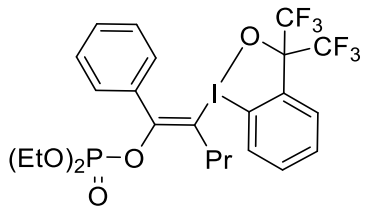
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.3 Hz, 1H), 7.76 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.71-7.63 (m, 2H), 7.39-7.34 (m, 1H), 7.30 (d, *J* = 4.4 Hz, 4H), 4.05-3.86 (m, 4H), 2.65 (d, *J* = 2.4 Hz, 3H), 1.18 (td, *J* = 7.1, 0.9 Hz, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8 (d, $^3J_{C\text{-}P}$ = 8.8 Hz), 134.8, 132.6, 131.2, 130.5, 130.4, 128.8, 128.4, 127.3, 123.9 (q, $^1J_{C\text{-}F}$ = 289.1 Hz), 110.5, 110.48 (d, $^2J_{C\text{-}P}$ =7.8 Hz), 81.6-80.5 (m), 64.5 (d, $^3J_{C\text{-}P}$ = 6.1 Hz), 27.2, 15.8 (d, $^2J_{C\text{-}P}$ =7.0 Hz);

^{19}F NMR (282 MHz) δ -76.1;

^{31}P NMR (162 MHz) δ -6.6;

HRMS (ESI) Cal $C_{22}H_{23}O_5F_6PI$ $[M+H]^+$ 639.0232, found 639.0232



(*E*)-2-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-phenylpent-1-en-1-yl diethyl phosphate (4ca): Using the general procedure, in toluene (1 mL), 1-phenyl-1-propyne (**2c**, 0.2 mmol), triethyl phosphate (**3a**, 3.0 equiv, 0.6 mmol) and BXT (**1**, 3.0 equiv, 0.6 mmol) . White solid (102.6 mg, 77% yield); R_f 0.62 (Et_2O); m.p. 165-167 °C;

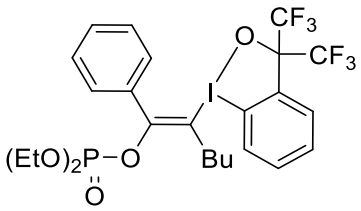
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.5 Hz, 1H), 7.79 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.70-7.62 (m, 2H), 7.38-7.33 (m, 1H), 7.28 (d, *J* = 4.4 Hz, 4H), 4.02-3.86 (m, 4H), 2.85 (brs, 2H), 1.72-1.62 (m, 2H), 1.18 (t, *J* = 7.0 Hz, 6H), 1.03 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8 (d, $^3J_{C\text{-}P}$ = 8.4 Hz), 134.9, 132.5, 131.4, 130.45, 130.40 (two peaks overlap), 130.35, 128.8, 128.4, 127.5, 123.9 (q, $^1J_{C\text{-}F}$ = 289.5 Hz), 117.4 (d, $^2J_{C\text{-}P}$ = 8.0 Hz), 110.9, 81.6-80.5 (m), 64.5 (d, $^3J_{C\text{-}P}$ = 6.1 Hz), 35.6, 22.5, 15.8 (d, $^2J_{C\text{-}P}$ =7.1 Hz), 13.7;

^{19}F NMR (282 MHz) δ -76.1;

^{31}P NMR (162 MHz) δ -6.6;

HRMS (ESI) Cal $C_{24}H_{27}O_5F_6PI$ $[M+H]^+$ 667.0545, found 667.0548



(*E*)-2-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-phenylhex-1-en-1-yl diethyl phosphate (4da): Using the general procedure, in toluene (1 mL), 1-phenyl-1-propyne (**2d**, 0.2 mmol), triethyl phosphate (**3a**, 3.0 equiv, 0.6 mmol) and BXT (**1**, 3.0 equiv, 0.6 mmol) . White solid (90.1 mg, 66% yield); R_f 0.46 (Et_2O); m.p. 109-111 °C;

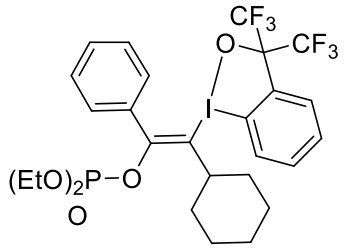
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (app. d, *J* = 7.3 Hz, 1H), 7.80 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.70-7.62 (m, 2H), 7.38-7.32 (m, 1H), 7.28 (d, *J* = 4.5 Hz, 4H), 4.01-3.86 (m, 4H), 2.87 (brs, 2H), 1.67-1.58 (m, 2H), 1.48-1.38 (m, 2H), 1.17 (t, *J* = 7.0 Hz, 6H), 0.96 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6 (d, $^3J_{C\text{-}P}$ = 8.5 Hz), 134.8, 132.5, 131.3, 130.45, 130.38, 130.34, 128.8, 128.4, 127.5, 123.87 (q, $^1J_{C\text{-}F}$ = 289.0 Hz), 117.6 (d, $^2J_{C\text{-}P}$ = 7.8 Hz), 110.9, 81.6-80.4 (m), 64.5 (d, $^3J_{C\text{-}P}$ = 6.2 Hz), 33.4, 31.2, 22.4, 15.8 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 13.8;

^{19}F NMR (282 MHz) δ -76.1;

^{31}P NMR (162 MHz) δ -6.6;

HRMS (ESI) Cal $C_{25}H_{29}O_5F_6PI$ $[M+H]^+$ 681.0701, found 681.074



(E)-2-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-2-cyclohexyl-1-phenylvinyl diethyl phosphate (4ea): Using the general procedure, in toluene (1 mL), (Cyclohexylethynyl)benzene (**2e**, 0.2 mmol), triethyl phosphate (**3a**, 3.0 equiv, 0.6 mmol) and BXT (**1**, 3.0 equiv, 0.6 mmol) . White solid (108.8 mg, 78% yield); R_f 0.58 (Et_2O); m.p. 154.3-155.4 °C;

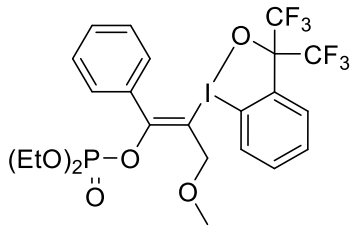
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.77 (app. d, *J* = 7.4 Hz, 1H), 7.66-7.58 (m, 2H), 7.32-7.20 (m, 5H), 4.11-3.74 (m, 4H), 3.05-2.98 (m, 1H), 1.89-1.68 (m, 5H), 1.44-1.07 (m, 11H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9 (d, $^3J_{C\text{-}P}$ = 8.5 Hz), 135.2, 132.0, 131.5, 130.3, 130.1, 130.0, 128.8, 128.3, 128.2, 125.3 (d, $^2J_{C\text{-}P}$ = 7.8 Hz), 124.0 (q, $^1J_{C\text{-}F}$ = 291.2 Hz), 112.1, 81.7-80.6 (m), 64.4, 40.8, 32.6 (d, $^3J_{C\text{-}P}$ =193.4 Hz), 25.9 (d, $^2J_{C\text{-}P}$ =29.1 Hz), 25.4, 15.9;

^{19}F NMR (282 MHz) δ -75.8, -76.5; (The ^{19}F NMR showed two signals, presumably due to the slow rotation of the vinyl-I bonds)

^{31}P NMR (162 MHz) δ -6.7;

HRMS (ESI) Cal $C_{27}H_{31}O_5F_6PI$ $[M+H]^+$ 707.0858, found 707.0859



(*E*)-2-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-3-methoxy-1-phenylprop-1-en-1-yl diethyl phosphate (4fa): Using the general procedure, in toluene (1 mL), 2-methoxyethynylbenzene (**2f**, 0.2 mmol), triethyl phosphate (**3a**, 3.0 equiv, 0.6 mmol) and BXT (**1**, 3.0 equiv, 0.6 mmol) . White solid (106.5 mg, 77% yield); R_f 0.27 (Et_2O); m.p. 130.0-132.0 °C;

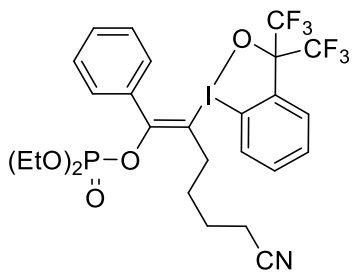
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.78 (m, 2H), 7.67-7.60 (m, 2H), 7.38 -7.34 (m, 1H), 7.30-7.27 (m, 4H), 4.50 (d, J = 1.9 Hz, 2H), 4.05-3.86 (m, 4H), 3.41 (s, 3H), 1.19 (t, J = 7.2 Hz, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4 (d, $^3J_{C\text{-}P}$ = 8.7 Hz), 134.3, 132.4, 131.3, 130.6, 130.3, 130.1, 128.7, 128.3, 128.0, 123.9 (q, $^1J_{C\text{-}F}$ = 289.7 Hz), 115.6 (d, $^2J_{C\text{-}P}$ = 7.7 Hz), 112.2, 81.8-80.6 (m), 70.0, 64.7 (d, $^3J_{C\text{-}P}$ = 6.1 Hz), 58.9, 15.8 (d, $^2J_{C\text{-}P}$ = 7.1 Hz);

^{19}F NMR (282 MHz) δ -76.1;

^{31}P NMR (162 MHz) δ -6.8;

HRMS (ESI) Cal $C_{23}H_{25}O_6F_6PI$ [M+H$^+$] 669.0338, found 669.0339



(*E*)-2-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-6-cyano-1-phenylhex-1-en-1-yl diethyl phosphate (4ga): Using the general procedure, in toluene (1 mL), 7-phenyl-6-heptynenitrile (**2g**, 0.2 mmol), triethyl phosphate (**3a**, 3.0 equiv, 0.6 mmol) and BXT (**1**, 3.0 equiv, 0.6 mmol) . Colourless oil (91.7 mg, 65% yield); R_f 0.22 (Et_2O);

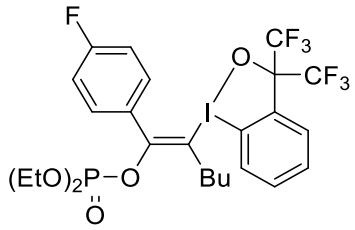
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (app. d, J = 7.2 Hz, 1H), 7.76 (dd, J = 7.7, 1.7 Hz, 1H), 7.71-7.64 (m, 2H), 7.40-7.36 (m, 1H), 7.32-7.29 (m, 4H), 4.00-3.86 (m, 4H), 2.93 (brs, 2H), 2.44-2.41(m, 2H), 1.82-1.78 (m, 4H), 1.19 (t, J = 6.4 Hz, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4 (d, $^3J_{C\text{-}P}$ = 8.5 Hz), 134.7, 132.7, 131.4, 130.64, 130.58, 128.8, 128.5, 127.3, 123.9 (q, $^1J_{C\text{-}F}$ = 289.7 Hz), 119.1, 116.2 (d, $^2J_{C\text{-}P}$ = 7.7 Hz), 110.8, 81.7-80.4 (m), 77.2, 64.7 (d, $^3J_{C\text{-}P}$ = 6.2 Hz), 31.9, 28.1, 25.0, 16.9, 15.9 (d, $^2J_{C\text{-}P}$ = 6.0 Hz);

^{19}F NMR (282 MHz) δ -76.1;

^{31}P NMR (162 MHz) δ -6.6;

HRMS (ESI) Cal $C_{26}H_{28}NO_5F_6PI$ $[M+H]^+$ 706.0654, found 706.0656



(*E*)-2-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-(4-fluorophenyl)hex-1-en-1-yl diethyl phosphate (4ha): Using the general procedure, in toluene (1 mL), 1-fluoro-4-(hex-1-yn-1-yl)benzene (**2h**, 0.2 mmol), triethyl phosphate (**3a**, 3.0 equiv, 0.6 mmol) and (**1**, 3.0 equiv, 0.6 mmol) . Colourless oil (100.3 mg, 72% yield); R_f 0.51 (Et_2O);

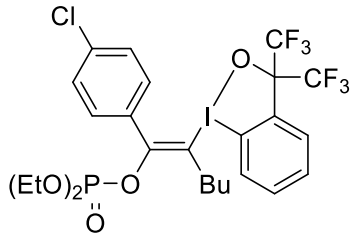
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (app. d, *J* = 7.0 Hz, 1H), 7.78-7.74 (m, 1H), 7.70-7.63 (m, 2H), 7.30-7.26 (m, 2H), 7.01-6.95 (m, 2H), 4.04-3.90 (m, 4H), 2.86 (brs, 2H), 1.66-1.58 (m, 2H), 1.47-1.38 (m, 2H), 1.21 (t, *J* = 7.1 Hz, 6H), 0.96 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6 (d, $^{1}J_{C\text{-}F}$ = 250.2 Hz), 153.6 (d, $^{3}J_{C\text{-}P}$ = 8.4 Hz), 132.6, 131.4, 131.1, 131.0, 130.55, 130.50, 127.4, 123.9 (q, $^{1}J_{C\text{-}F}$ = 289.8 Hz), 118.3 (d, $^{2}J_{C\text{-}P}$ = 7.9 Hz), 115.6 (d, $^{2}J_{C\text{-}F}$ = 21.8 Hz), 110.9, 81.6-80.5 (m), 64.5 (d, $^{3}J_{C\text{-}P}$ = 6.2 Hz), 33.5, 31.2, 22.4, 15.9 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz), 13.7;

^{19}F NMR (282 MHz) δ -76.2, -108.8;

^{31}P NMR (162 MHz) δ -6.5;

HRMS (ESI) Cal $C_{25}H_{28}O_5F_7PI$ $[M+H]^+$ 699.0607, found 699.0609



(*E*)-2-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-(4-chlorophenyl)hex-1-en-1-yl diethyl phosphate (4ia): Using the general procedure, in toluene (1 mL), 1-chloro-4-(hex-1-yn-1-yl)benzene (**2i**, 0.2 mmol), triethyl phosphate (**3a**, 3.0 equiv, 0.6 mmol) and BXT (**1**, 3.0 equiv, 0.6 mmol) . Colourless oil (97.3 mg, 68% yield); R_f 0.62 (Et_2O);

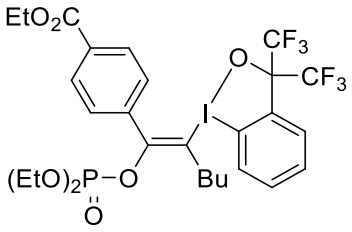
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (app. d, *J* = 7.0 Hz, 1H), 7.78-7.74 (m, 1H), 7.70-7.63 (m, 2H), 7.29-7.21 (m, 4H), 4.05-3.91 (m, 4H), 2.86 (brs, 2H), 1.65-1.57 (m, 2H), 1.47-1.38 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 6H), 0.95 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4 (d, $^3J_{C\text{-}P}$ = 8.6 Hz), 136.6, 133.3, 132.6, 131.4, 130.6, 130.5, 130.2, 128.7, 127.4, 123.9 (q, $^1J_{C\text{-}F}$ = 289.5 Hz), 118.5 (d, $^2J_{C\text{-}P}$ = 7.9 Hz), 110.9, 81.6-80.8 (m), 64.6 (d, $^3J_{C\text{-}P}$ = 6.1 Hz), 33.5, 31.1, 22.4, 15.9 (d, $^2J_{C\text{-}P}$ = 6.9 Hz), 13.7;

^{19}F NMR (282 MHz) δ -76.1;

^{31}P NMR (162 MHz) δ -6.5;

HRMS (ESI) Cal $C_{25}H_{28}O_5F_6P^{35}ClI$ $[M+H]^+$ 715.0312, found 715.0315



Ethyl (*E*)-4-(2-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-((diethoxyphosphoryl)oxy)hex-1-en-1-yl)benzoate (4ja): Using the general procedure, in toluene (1 mL), ethyl 4-(hex-1-yn-1-yl)benzoate (**2j**, 0.2 mmol), triethyl phosphate (**3a**, 3.0 equiv, 0.6 mmol) and BXT (**1**, 3.0 equiv, 0.6 mmol) . White solid (94.7 mg, 63% yield, regioisomer ratio = 2.2:1); R_f 0.55 (Et_2O); m.p. 113.2-115.8 °C;

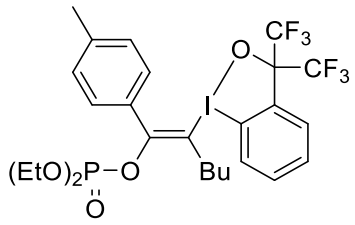
^{1}H NMR (400 MHz, $CDCl_3$, two isomers) δ 8.06-7.96 (m, 2H+1.35H, Major+Minor), 7.86-7.84 (m, 1H+0.45H, Major+Minor), 7.78 (dd, *J* = 7.7, 1.5 Hz, 1H, Major), 7.72-7.64 (m, 2H+0.90H, Major+Minor), 7.44-7.42 (m, 0.90H, Minor), 7.38-7.36 (m, 2H, Major), 4.36 (q, *J* = 7.1 Hz, 2H+0.90H, Major+Minor), 4.04-3.77 (m, 4H+1.80H, Major+Minor), 2.86-2.82 (m, 2H+0.9H, Major+Minor), 1.73-1.59 (m, 2H+0.90H, Major+Minor), 1.48-1.35 (m, 5H+2.25H, Major+Minor), 1.26-1.17 (m, 6H+2.70H, Major+Minor), 0.98-0.90 (m, 3H+1.35H, Major+Minor);

^{13}C NMR (100 MHz, $CDCl_3$, two isomers) δ 165.7, 165.4, 158.4 (d, $^3J_{C\text{-}P}$ = 8.1 Hz), 153.3 (d, $^3J_{C\text{-}P}$ = 8.6 Hz), 141.4, 138.9, 132.8, 132.6, 132.1, 131.4, 130.8, 130.6, 130.55, 130.2, 129.7, 129.5, 129.4, 128.9, 127.45, 127.42, 123.9 (q, $^1J_{C\text{-}F}$ = 289.6 Hz), 123.8 (q, $^1J_{C\text{-}F}$ = 288.5 Hz), 118.9 (d, $^2J_{C\text{-}P}$ = 7.8 Hz), 111.9 (d, $^2J_{C\text{-}P}$ = 7.8 Hz), 111.2, 110.8, 81.6-80.4 (m) (two peaks overlap), 64.6 (d, $^3J_{C\text{-}P}$ = 6.1 Hz), 64.5 (d, $^3J_{C\text{-}P}$ = 6.2 Hz), 61.3, 61.1, 36.2, 33.5, 31.1, 29.7, 29.6, 22.4, 22.2, 15.9 (d, $^2J_{C\text{-}P}$ = 6.8 Hz), 14.20, 14.15, 13.7, 13.6;

^{19}F NMR (376 MHz) δ -76.0 (Minor), -76.1 (Major);

^{31}P NMR (162 MHz) δ -6.5 (Major), -7.3 (Minor);

HRMS (ESI) Cal $C_{28}H_{33}O_7F_6PI$ $[M+H]^+$ 753.0913, found 753.0909



(*E*)-2-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-(*p*-tolyl)hex-1-en-1-yl diethyl phosphate (4ka): Using the general procedure, in toluene (1 mL), 1-(1-hexyn-1-yl)-4-methylbenzene (**2k**, 0.2 mmol), triethyl phosphate (**3a**, 3.0 equiv, 0.6 mmol) and (**1**, 3.0 equiv, 0.6 mmol) . Yellow oil (87.6 mg, 63% yield); R_f 0.41 (Et_2O);

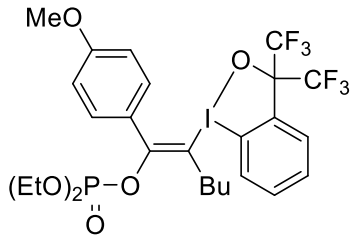
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (app. d, *J* = 7.1 Hz, 1H), 7.78 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.69-7.61 (m, 2H), 7.17 (d, *J* = 8.2 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 4.03-3.87 (m, 4H), 2.84 (brs, 2H), 2.32 (s, 3H), 1.64-1.57 (m, 2H), 1.46-1.37 (m, 2H), 1.19 (t, *J* = 7.2 Hz, 6H), 0.95 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0 (d, $^3J_{C\text{-}P}$ = 8.5 Hz), 140.7, 132.4, 132.0, 131.5, 130.4, 129.0, 128.8, 127.5, 123.9 (q, $^1J_{C\text{-}F}$ = 289.7 Hz), 117.3 (d, $^2J_{C\text{-}P}$ = 7.8 Hz), 110.9, 81.7-80.5 (m), 77.2, 64.4 (d, $^3J_{C\text{-}P}$ = 6.2 Hz), 33.4, 31.2, 22.4, 21.2, 15.8 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 13.7;

^{19}F NMR (282 MHz) δ -76.1;

^{31}P NMR (162 MHz) δ -6.6;

HRMS (ESI) Cal $C_{26}H_{31}O_5F_6PI$ $[M+H]^+$ 695.0858, found 695.0860



(*E*)-2-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-(4-methoxyphenyl)hex-1-en-1-yl diethyl phosphate (4la): Using the general procedure, in toluene (1 mL), 1-(1-hexyn-1-yl)-4-methoxylbenzene (**2l**, 0.2 mmol), triethyl phosphate (**3a**, 3.0 equiv, 0.6 mmol) and BXT (**1**, 3.0 equiv, 0.6 mmol) . Colourless oil (76.2 mg, 54% yield); R_f 0.42 (Et_2O);

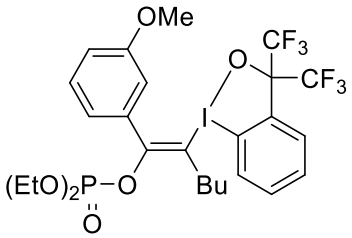
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (app. d, *J* = 7.2 Hz, 1H), 7.77 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.69-7.62 (m, 2H), 7.23-7.20 (m, 2H), 6.80-6.76 (m, 2H), 4.04-3.88 (m, 4H), 3.77 (s, 3H), 2.84 (brs, 2H), 1.64-1.57 (m, 2H), 1.46-1.37 (m, 2H), 1.21 (t, *J* = 7.0 Hz, 6H), 0.95 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 154.8 (d, $^3J_{C\text{-}P}$ = 8.5 Hz), 132.5, 131.5, 130.5 (two peaks overlap), 127.5, 127.1, 124.0 (q, $^1J_{C\text{-}F}$ = 293.5 Hz), 117.0 (d, $^2J_{C\text{-}P}$ = 8.0 Hz), 113.8, 110.9, 81.7-80.6 (m), 64.4 (d, $^3J_{C\text{-}P}$ = 6.1 Hz), 55.3, 33.5, 31.3, 22.4, 15.9 (d, $^2J_{C\text{-}P}$ = 6.9 Hz), 13.7;

^{19}F NMR (282 MHz) δ -76.0;

^{31}P NMR (162 MHz) δ -6.5;

HRMS (ESI) Cal $C_{26}H_{31}O_6F_6PI$ $[M+H]^+$ 711.0807, found 711.0809



(*E*)-2-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-(3-methoxyphenyl)hex-1-en-1-yl diethyl phosphate (4ma): Using the general procedure, in toluene (1 mL), 1-(1-hexyn-1-yl)-3-methoxylbenzene (**2m**, 0.2 mmol), triethyl phosphate (**3a**, 3.0 equiv, 0.6 mmol) and BXT (**1**, 3.0 equiv, 0.6 mmol) . Yellow oil (108.6 mg, 76% yield); R_f 0.50 (Et_2O);

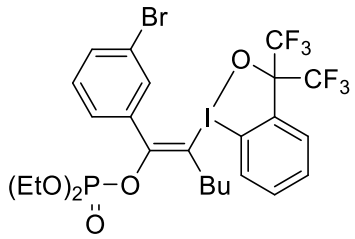
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.81 (m, 2H), 7.71-7.62 (m, 2H), 7.19 (t, *J* = 8.0 Hz, 1H), 6.90-6.85 (m, 2H), 6.77 (s, 1H), 4.01-3.90 (m, 4H), 3.33 (s, 3H), 2.86 (brs, 2H), 1.67-1.58 (m, 2H), 1.47-1.38 (m, 2H), 1.20 (t, *J* = 6.9 Hz, 6H), 0.96 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 154.5 (d, $^3J_{C\text{-}P}$ = 8.6 Hz), 136.1, 132.5, 131.4, 130.4, 129.6, 127.6, 123.9 (q, $^1J_{C\text{-}F}$ = 289.8 Hz), 121.1, 117.7 (d, $^2J_{C\text{-}P}$ = 7.8 Hz), 116.6, 113.9, 111.2, 81.7-80.2 (m), 64.5 (d, $^3J_{C\text{-}P}$ = 6.1 Hz), 55.0, 33.4, 31.2, 22.4, 15.8 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 13.7;

^{19}F NMR (282 MHz) δ -76.1;

^{31}P NMR (162 MHz) δ -6.6;

HRMS (ESI) Cal $C_{26}H_{31}O_6F_6PI$ $[M+H]^+$ 711.0807, found 711.0809



(*E*)-2-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-(3-bromophenyl)hex-1-en-1-yl diethyl phosphate (4na): Using the general procedure, in toluene (1 mL), 1-bromo-3-(hex-1-yn-1-yl)benzene (**2n**, 0.2 mmol), triethyl phosphate (**3a**, 3.0 equiv, 0.6 mmol) and BXT (**1**, 3.0 equiv, 0.6 mmol) . White solid (116.0 mg, 76% yield, regioisomer = 3.6:1); R_f 0.21 (Hex:EA = 3:1); m.p. 91.3-95.3°C;

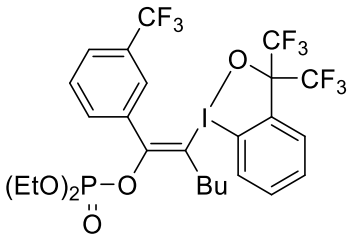
^{1}H NMR (400 MHz, $CDCl_3$, two isomers) δ 8.05 (dd, *J* = 7.9 1.65Hz, 0.28H, Minor), 7.88-7.84 (m, 1H+0.28H, Major+Minor), 7.75 (dd, *J* = 7.9, 1.5 Hz, 1H, Major), 7.72-7.64 (m, 2H+0.56H, Major+Minor), 7.54-7.53 (m, 0.28H, Minor), 7.50 (dt, *J* = 7.8, 1.7 Hz, 1H, Major), 7.45 (t, *J* = 1.8 Hz, 1H), 7.42-7.39 (m, 0.28H, Minor), 7.25-7.11 (m, 2H+0.56H, Major+Minor), 4.03-3.82 (m, 4H+1.12H, Major+Minor), 2.82-2.78 (m, 2H+0.28H, Major+Minor), 1.71-1.57 (m, 2H+0.56H, Major+Minor), 1.46-1.34 (m, 2H+0.56H, Major+Minor), 1.26-1.20 (m, 6H+1.68H, Major+Minor), 0.96 (t, *J* = 7.3 Hz, 3H, Major), 0.91 (t, *J* = 7.3 Hz, 0.84H, Minor);

^{13}C NMR (100 MHz, $CDCl_3$, two isomers) δ 158.4 (d, $^3J_{C\text{-}P}$ = 8.1 Hz), 152.8 (d, $^3J_{C\text{-}P}$ = 8.6 Hz), 138.9, 136.8, 133.4, 132.9, 132.6, 132.3, 131.8, 131.4, 131.3, 130.8, 130.6, 130.50, 130.2, 129.9, 127.9, 127.5, 127.4, 123.9 (q, $^1J_{C\text{-}F}$ = 289.2 Hz) (two peaks overlap), 122.35, 122.31, 118.9 (d, $^2J_{C\text{-}P}$ = 8.0 Hz), 111.1 (d, $^2J_{C\text{-}P}$ = 5.1 Hz), 111.02, 110.98, 81.64-80.5 (m) (two peaks overlap), 64.63 (d, $^3J_{C\text{-}P}$ = 6.2 Hz), 64.55 (d, $^3J_{C\text{-}P}$ = 6.1 Hz), 36.1, 33.5, 31.1, 29.6, 22.4, 22.2, 16.0, 15.9 (d, $^2J_{C\text{-}P}$ =6.7.Hz), 15.8 (d, $^2J_{C\text{-}P}$ =7.0 Hz), 13.7, 13.6;

^{19}F NMR (282 MHz) δ -76.0 (Minor), -76.1 (Major);

^{31}P NMR (162 MHz) δ -6.6 (Major), -7.2 (Minor);

HRMS (ESI) Cal $C_{25}H_{28}O_5F_6P^{78}BrI$ $[M+H]^+$ 758.9807, found 758.9811



(*E*)-2-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-(3-(trifluoromethyl)phenyl)hex-1-en-1-yl diethyl phosphate (4oa): Using the general procedure, in toluene (1 mL), 1-(hex-1-yn-1-yl)-3-(trifluoromethyl)benzene (**2o**, 0.2 mmol), triethyl phosphate (**3a**, 3.0 equiv, 0.6 mmol) and BXT (**1**, 3.0 equiv, 0.6 mmol) . Yellow solid (77.8 mg, 52% yield, regioisomer = 4.4:1); R_f 0.54 (Et_2O); m.p. 78.7-80.5 °C;

^{1}H NMR (400 MHz, $CDCl_3$, two isomers) δ 8.08-8.04 (m, 0.22H, Minor), 7.89-7.83 (m, 1H+0.22H, Major+Minor), 7.78 (dd, *J* = 8.0, 1.4 Hz, 1H, Major), 7.73-7.64 (m, 2H+0.44H, Major+Minor), 7.63-7.61 (m, 1H+0.22H, Major+Minor), 7.53 (s, 1H+0.22H, Major+Minor), 7.49-7.40 (m, 2H+0.44H, Major+Minor), 4.00-3.77 (m, 4H+0.88H, Major+Minor), 2.85-2.81 (m, 2H+0.44H, Major+Minor), 1.74-1.60 (m, 2H+0.44H, Major+Minor), 1.47-1.38 (m, 2H+0.44H, Major+Minor), 1.21-1.17 (m, 6H+1.32H, Major+Minor), 0.97 (t, *J* = 7.3 Hz, 3H, Major), 0.92 (t, *J* = 7.3 Hz, 0.66H, Minor);

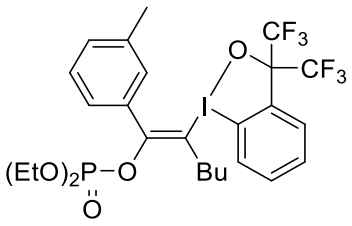
^{13}C NMR (100 MHz, $CDCl_3$, two isomers) δ 158.7 (d, $^3J_{C\text{-}P}$ = 8.0 Hz), 152.7 (d, $^3J_{C\text{-}P}$ = 8.0 Hz), 137.8, 135.8, 132.9, 132.7, 132.5, 132.2, 131.3, 131.2, 130.9, 130.7, 130.6, 129.4, 129.1, 127.4, 127.3, 127.0, 126.4, 125.8, 125.3, 124.9, 123.81 (q, $^1J_{C\text{-}F}$ = 289.3 Hz), 123.84 (q, $^1J_{C\text{-}F}$ = 303.0 Hz), 123.33 (q, $^1J_{C\text{-}F}$ = 270.5 Hz), 119.4 (d, $^2J_{C\text{-}P}$ = 7.9 Hz), 111.2 (d, $^2J_{C\text{-}P}$ = 5.0 Hz), 111.0,

81.6-80.7 (m) (two peaks overlap), 64.7 (d, $^{3}J_{C\text{-}P}$ = 7.0 Hz), 64.5 (d, $^{3}J_{C\text{-}P}$ = 7.0 Hz), 36.2, 33.6, 31.1, 29.7, 22.5, 22.2, 15.8 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz) (two peaks overlap), 13.7, 13.6;

^{19}F NMR (377 MHz) δ -62.8 (Minor), -63.2 (Major), -76.0 (Minor), -76.2 (Major);

^{31}P NMR (162 MHz) δ -6.4 (Major), -7.2 (Minor);

HRMS (ESI) Cal $C_{26}H_{28}O_5F_9PI$ $[M+H]^+$ 749.0575, found 749.0577



(*E*)-2-(3,3-Bis(trifluoromethyl)-1λ^{3}-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-(*m*-tolyl)hex-1-en-1-yl diethyl phosphate (4pa): Using the general procedure, in toluene (1 mL), 1-(1-hexyn-1-yl)-3-methylbenzene (**2p**, 0.2 mmol), triethyl phosphate (**3a**, 3.0 equiv, 0.6 mmol) and BXT (**1**, 3.0 equiv, 0.6 mmol) . Colourless oil (63.0 mg, 46% yield); R_f 0.60 (Et_2O);

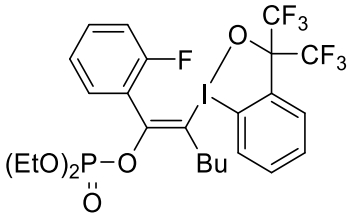
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (app. d, *J* = 7.3 Hz, 1H), 7.79 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.70-7.62 (m, 2H), 7.18- 7.14 (m, 2H), 7.09-7.06 (m, 2H), 4.02-3.86 (m, 4H), 2.86 (brs, 2H), 2.20 (s, 3H), 1.65-1.58 (m, 2H), 1.47-1.38 (m, 2H), 1.18 (t, *J* = 7.1 Hz, 6H), 0.96 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9 (d, $^{3}J_{C\text{-}P}$ = 8.6 Hz), 138.2, 134.8, 132.5, 131.4, 131.1, 130.40, 130.35, 129.4, 128.3, 127.6, 125.9, 124.0 (q, $^{1}J_{C\text{-}F}$ = 289.8 Hz), 117.5 (d, $^{2}J_{C\text{-}P}$ = 8.0 Hz), 111.1, 81.78-80.5 (m), 64.4 (d, $^{3}J_{C\text{-}P}$ = 6.1 Hz), 33.4, 31.3, 22.4, 21.1, 15.8 (d, $^{2}J_{C\text{-}P}$ = 7.1 Hz), 13.7;

^{19}F NMR (282 MHz) δ -76.1;

^{31}P NMR (162 MHz) δ -6.6;

HRMS (ESI) Cal $C_{26}H_{31}O_6F_6PI$ $[M+H]^+$ 695.0858 found 695.0859;



(*E*)-2-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-(2-fluorophenyl)hex-1-en-1-yl diethyl phosphate (4qa): Using the general procedure, in toluene (1 mL), 1-fluoro-2-(hex-1-yn-1-yl)benzene (**2q**, 0.2 mmol), triethyl phosphate (**3a**, 3.0 equiv, 0.6 mmol) and BXT (**1**, 3.0 equiv, 0.6 mmol) . White solid (69.8 mg, 50% yield); R_f 0.51 (Et_2O); m.p. 85.8-89.8 °C;

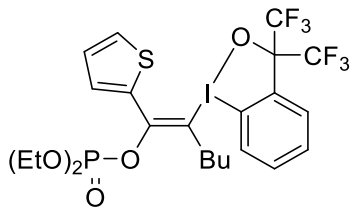
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (app. d, *J* = 7.0 Hz, 1H), 7.72-7.68 (m, 1H), 7.64-7.59 (m, 2H), 7.40-7.34 (m, 1H), 7.24 (app. d, *J* = 7.6, 1.9 Hz, 1H), 7.06 (t, *J* = 8.5 Hz, 2H), 4.00 (brs, 4H), 2.86 (brs, 2H), 1.63 (m, 2H), 1.44 (m, 2H), 1.21 (s, 6H), 0.96 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9 (d, $^1J_{C\text{-}F}$ = 248.4 Hz), 148.9 (d, $^3J_{C\text{-}P}$ = 8.6 Hz), 132.5 (d, $^3J_{C\text{-}F}$ = 8.2 Hz), 132.3, 131.4, 131.0, 130.42, 130.35, 127.8, 124.2 (d, $^4J_{C\text{-}F}$ = 3.7 Hz), 123.9 (q, $^1J_{C\text{-}F}$ = 289.5 Hz), 123.0 (d, $^2J_{C\text{-}F}$ = 15.4 Hz), 120.8 (d, $^2J_{C\text{-}P}$ = 8.0 Hz), 116.0 (d, $^2J_{C\text{-}F}$ =21.2 Hz), 110.2, 81.6-80.5 (m), 64.6 (d, $^3J_{C\text{-}P}$ = 6.3 Hz), 33.0, 31.2, 22.3, 15.8 (d, $^2J_{C\text{-}P}$ = 7.0 Hz), 13.7;

^{19}F NMR (282 MHz) δ -76.1, -121.0;

^{31}P NMR (162 MHz) δ -7.0;

HRMS (ESI) Cal $C_{25}H_{28}O_5F_7PI$ $[M+H]^+$ 699.0607, found 699.0605



(*E*)-2-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-(thiophen-2-yl)hex-1-en-1-yl diethyl phosphate (4ra): Using the general procedure, in toluene (1 mL), 2-(hex-1-yn-1-yl)thiophene (**2r**, 0.2 mmol), triethyl phosphate (**3a**, 3.0 equiv, 0.6 mmol) and BXT (**1**, 3.0 equiv, 0.6 mmol) . Yellow solid (89.3 mg, 65% yield); R_f 0.15 (Hex:EA = 2:1); m.p. 123.2-124.7 °C;

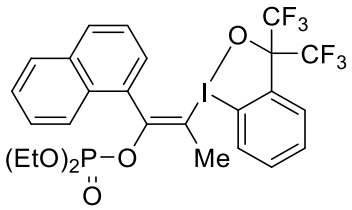
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.84 (m, 1H), 7.79-7.74 (m, 1H), 7.68-7.62 (m, 2H), 7.35 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.08 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.92 (dd, *J* = 5.1, 3.6 Hz, 1H), 4.13-3.95 (m, 4H), 2.88 (brs, 2H), 1.65-1.57 (m, 2H), 1.42 (m, 2H), 1.25 (t, *J* = 7.0 Hz, 6H), 0.95 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1 (d, $^3J_{C\text{-}P}$ = 8.9 Hz), 135.7, 132.6, 131.2, 130.51, 130.46, 130.4, 128.7, 127.6, 126.8, 123.9 (q, $^1J_{C\text{-}F}$ = 289.9 Hz), 120.1 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 111.3, 81.7-80.6 (m), 64.7 (d, $^3J_{C\text{-}P}$ = 6.1 Hz), 34.2, 31.1, 22.4, 15.9 (d, $^2J_{C\text{-}P}$ = 7.0 Hz), 13.7;

^{19}F NMR (282 MHz) δ -76.0;

^{31}P NMR (162 MHz) δ -6.3;

HRMS (ESI) Cal $C_{23}H_{27}O_5F_6PSI$ $[M+H]^+$ 687.0266, found 687.0264



(*E*)-2-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-(naphthalen-1-yl)prop-1-en-1-yl diethyl phosphate (4sa): Using the general procedure, in toluene (1 mL), 1-(prop-1-yn-1-yl)naphthalene (**2s**, 0.2 mmol), triethyl phosphate (**3a**, 3.0 equiv, 0.6 mmol) and (**1**, 3.0 equiv, 0.6 mmol) . White solid (89.5 mg, 65% yield); R_f 0.33 (Et_2O); m.p. 65.8-69.8 °C;

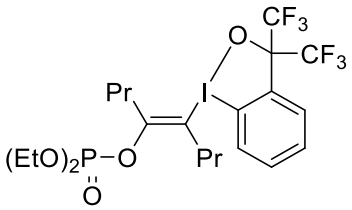
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94-7.91(m, 1H), 7.89-7.86 (m, 2H), 7.84-7.78 (m, 2H), 7.73-7.69 (m, 1H), 7.65-7.61 (m, 2H), 7.56-7.50 (m, 2H), 7.41-7.39 (m, 1H), 7.34-7.30 (m, 1H), 4.13-3.93 (m, 2H), 3.61-3.45 (m, 2H), 2.76-2.75 (m, 3H), 1.19 (td, *J* = 7.0, 1.2 Hz, 3H), 0.78 (td, *J* = 7.2, 1.2 Hz, 3H); (splitting pattern was observed due to restrict rotation of naphthalene group and BX moiety)

^{13}C NMR (100 MHz, $CDCl_3$,) δ 153.7 (d, $^3J_{C\text{-}P}$ = 8.6 Hz), 133.5, 132.5, 132.1, 131.4, 131.3, 131.0, 130.4, 128.8, 127.8, 127.5, 127.4, 126.6, 123.9 (q, $^1J_{C\text{-}F}$ = 289.3 Hz), 124.8, 124.4, 113.2 (d, $^2J_{C\text{-}P}$ = 7.8 Hz), 110.5, 81.3-80.7 (m) (two peaks overlap), 64.5 (d, $^3J_{C\text{-}P}$ = 6.1 Hz), 64.3 (d, $^3J_{C\text{-}P}$ = 6.4 Hz), 20.6, 15.8 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 15.3 (d, $^2J_{C\text{-}P}$ = 7.3 Hz);

^{19}F NMR (376 MHz,) δ -76.0 (q, *J* = 8.7 Hz), -76.2 (q, *J* = 8.6 Hz); (two signal was observed due to the restricted rotation between naphthalene group and BX moiety)

^{31}P NMR (162 MHz) δ -7.0;

HRMS (ESI) $C_{26}H_{25}O_5F_6PI$ $[M+H]^+$ 689.0388, found 689.0386



(*E*)-5-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)oct-4-en-4-yl diethyl phosphate (4ta): Using the general procedure, in toluene (1 mL), 4-octyne (**2t**, 0.2 mmol), triethyl phosphate (**3a**, 3.0 equiv, 0.6 mmol) and BXT (**1**, 3.0 equiv, 0.6 mmol) . White solid (102.5 mg, 81% yield); R_f 0.71 (Et_2O); m.p. 165.3-167.7 °C;

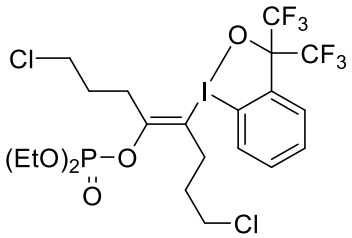
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (app. d, *J* = 7.1 Hz, 1H), 7.68-7.55 (m, 3H), 4.25 (p, *J* = 7.4 Hz, 4H), 2.72-2.69 (m, 4H), 1.66-1.52 (m, 4H), 1.42 (td, *J* = 7.1, 1.1 Hz, 6H), 0.94 (dt, *J* = 13.0, 7.4 Hz ,6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1 (d, $^3J_{C\text{-}P}$ = 8.6 Hz), 132.3, 131.4, 130.5, 130.4, 127.3, 124.1 (q, $^1J_{C\text{-}F}$ = 289.3 Hz), 114.7 (d, $^2J_{C\text{-}P}$ = 7.7 Hz), 109.6, 81.8-80.6 (m), 64.7 (d, $^3J_{C\text{-}P}$ = 6.1 Hz), 37.5, 35.5, 22.5, 20.9, 16.1 (d, $^2J_{C\text{-}P}$ = 6.8 Hz), 13.6, 13.3;

^{19}F NMR (282 MHz) δ -76.0;

^{31}P NMR (162 MHz) δ -6.8;

HRMS (ESI) Cal $C_{21}H_{29}O_5F_6PI$ $[M+H]^+$ 633.0701, found 633.0697



(*E*)-5-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1,8-dichlorooct-4-en-4-yl diethyl phosphate (4ua): Using the general procedure, in toluene (1 mL), 1,8-

dichlorooct-4-yne (**2u**, 0.2 mmol), triethyl phosphate (**3a**, 3.0 equiv, 0.6 mmol) and BXT (**1**, 3.0 equiv, 0.6 mmol) . Clear oil (122.2 mg, 87% yield); R_f 0.13 (Et_2O);

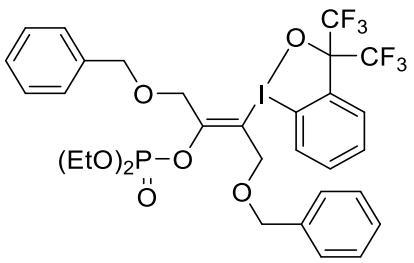
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (app. d, *J* = 7.2 Hz, 1H), 7.67-7.60 (m, 3H), 4.31-4.24 (m, 4H), 3.58-3.51 (m, 4H), 2.94 (t, *J* = 7.3 Hz, 2H), 2.54 (brs, 2H), 2.09-2.00 (m, 4H), 1.43 (td, *J* = 7.0, 1.2 Hz, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9 (d, $^3J_{C\text{-}P}$ = 8.6 Hz), 132.5, 131.4, 130.6, 127.3, 123.9 (q, $^1J_{C\text{-}F}$ = 289.5 Hz), 114.4 (d, $^2J_{C\text{-}P}$ = 7.7 Hz), 109.8, 81.7-80.6 (m), 65.0 (d, $^3J_{C\text{-}P}$ = 6.2 Hz), 43.9, 43.4, 33.1, 31.4, 31.3, 29.5, 16.1 (d, $^2J_{C\text{-}P}$ = 7.0 Hz);

^{19}F NMR (282 MHz) δ -75.9;

^{31}P NMR (162 MHz) δ -6.5;

HRMS (ESI) Cal $C_{21}H_{27}O_5F_6PI^{35}Cl_2$ 700.9922, found 700.9924



(*E*)-1,4-Bis(benzyloxy)-3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)but-2-en-2-yl diethyl phosphate (4va): Using the general procedure, in toluene (1 mL), 1,4-bis(benzyloxy)but-2-yne (**2v**, 0.2 mmol), triethyl phosphate (**3a**, 3.0 equiv, 0.6 mmol) and BXT (**1**, 3.0 equiv, 0.6 mmol) . Clear oil (85.6 mg, 54% yield); R_f 0.35 (EtO_2);

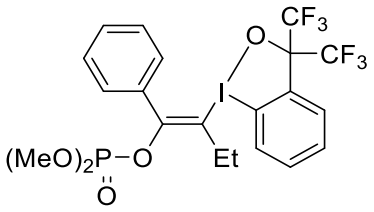
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.7 Hz, 1H), 7.62 (d, *J* = 8.3 Hz, 1H), 7.56 (t., *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.2 Hz, 1H), 7.26-7.23 (m, 6H), 7.17-7.12 (m, 4H), 4.52 (s, 2H), 4.44 (d, J = 5.0 Hz, 4H), 4.42 (s, 2H), 4.20-4.09 (m, 4H), 1.77 (s, 1H), 1.31 (t, *J* = 7.1 Hz, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5 (d, $^3J_{C\text{-}P}$ = 8.9 Hz), 137.0, 136.6, 132.1, 131.2, 130.2, 130.0, 128.44, 128.42, 128.39, 128.1, 127.87, 127.85, 127.6, 122.6 (q, $^1J_{C\text{-}F}$ = 289.2 Hz), 117.1 (d, $^2J_{C\text{-}P}$ = 7.5 Hz), 111.4, 82.0-80.8 (m), 73.24, 73.20, 70.2, 67.2, 65.0 (d, $^3J_{C\text{-}P}$ = 6.2 Hz), 16.0 (d, $^2J_{C\text{-}P}$ = 6.9 Hz);

^{19}F NMR (282 MHz) δ -75.9;

^{31}P NMR (162 MHz) δ -6.9;

HRMS (ESI) Cal $C_{31}H_{33}O_7F_6PI$ $[M+H]^+$ 789.0913, found 789.0911



(*E*)-2-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-phenylbut-1-en-1-yl dimethyl phosphate (4ab): Using the general procedure, in toluene (1 mL), 1-phenyl-1-butyne (**2a**, 0.2 mmol), trimethyl phosphate (**3b**, 3.0 equiv, 0.6 mmol) and BXT (**1**, 3.0 equiv, 0.6 mmol) . White solid (65.0 mg, 52% yield); R_f 0.2 (Et_2O); m.p. 169.0-171.4 °C;

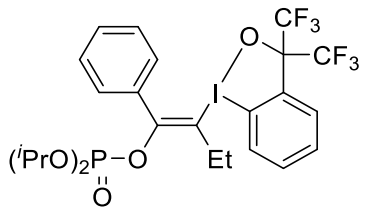
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (app. d, *J* = 7.3 Hz, 1H), 7.77 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.71-7.62 (m, 2H), 7.39-7.34 (m, 1H), 7.31-7.28 (m, 4H), 3.59 (d, *J* = 11.5 Hz, 6H), 2.90 (s, 2H), 1.23 (t, *J* = 7.5 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1 (d, $^3J_{C\text{-}P}$ = 8.3 Hz), 134.7, 132.5, 131.3, 130.45, 130.43, 130.4, 128.8, 128.4, 127.5, 123.9 (q, $^1J_{C\text{-}F}$ = 289.5 Hz), 119.3 (d, $^2J_{C\text{-}P}$ = 7.8 Hz), 110.8, 81.6-80.4 (m), 54.6 (d, $^2J_{C\text{-}P}$ = 6.1 Hz), 27.1, 13.7;

^{19}F NMR (282 MHz) δ -76.1;

^{31}P NMR (162 MHz) δ -4.2;

HRMS (ESI) Cal $C_{21}H_{21}O_5F_6PI$ $[M+H]^+$ 625.0075, found 625.0072



(*E*)-2-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-phenylbut-1-en-1-yl diisopropyl phosphate (4ac): Using the general procedure, in toluene (1 mL), 1-phenyl-1-butyne (**2a**, 0.2 mmol), triisopropyl phosphate (**3c**, 3.0 equiv, 0.6 mmol) and BXT (**1**, 3.0 equiv, 0.6 mmol) . White solid (62.6 mg, 46% yield); R_f 0.58 (Et_2O); m.p. 128.9-131.3 °C;

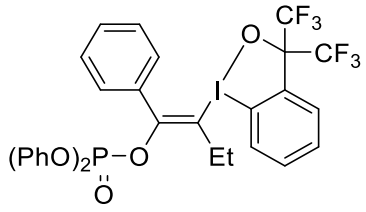
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (app. d, J = 7.1 Hz, 1H), 7.78 (dd, J = 7.8, 1.5 Hz, 1H), 7.69-7.61 (m, 2H), 7.37-7.32 (m, 1H), 7.30-7.26 (m, 4H), 4.56-4.48 (m, 2H), 2.90 (s, 2H), 1.26-1.20 (m, 9H), 1.13 (d, J = 6.2 Hz, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9 (d, $^3J_{C\text{-}P}$ = 8.8 Hz), 135.0, 132.4, 131.5, 130.43, 130.39, 130.2, 129.0, 128.3, 127.6, 124.0 (q, $^1J_{C\text{-}F}$ = 291.6 Hz), 118.9 (d, $J_{C\text{-}P}$ = 8.0 Hz), 110.9, 81.7-80.5 (m), 73.6 (d, $^2J_{C\text{-}P}$ = 6.2 Hz), 27.3, 23.5 (d, $^3J_{C\text{-}P}$ = 4.6 Hz), 23.3 (d, $^2J_{C\text{-}P}$ = 5.6 Hz), 13.8;

^{19}F NMR (282 MHz) δ -76.1;

^{31}P NMR (162 MHz) δ -8.3;

HRMS (ESI) Cal $C_{25}H_{29}O_5F_6PI$ $[M+H]^+$ 681.0701, found 681.0699



(*E*)-2-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-phenylbut-1-en-1-yl diphenyl phosphate (4ad): Using the general procedure, in toluene (1 mL), 1-phenyl-1-butyne (**2a**, 0.2 mmol), diphenyl hydrogen phosphate (**3d**, 3.0 equiv, 0.6 mmol) and BXT (**1**, 3.0 equiv, 0.6 mmol)) . White solid (101.3 mg, 68% yield); R_f 0.2 (Hex:EA = 3:1); m.p. 140.2-142.2 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.80 (m, 1H), 7.72-7.68 (m, 1H), 7.63-7.58 (m, 2H), 7.36-7.23 (m, 9H), 7.22-7.16 (m, 2H), 7.01 (d, *J* = 8.0 Hz, 4H), 2.71 (brs, 2H), 1.08 (d, *J* = 7.4 Hz, 3H);

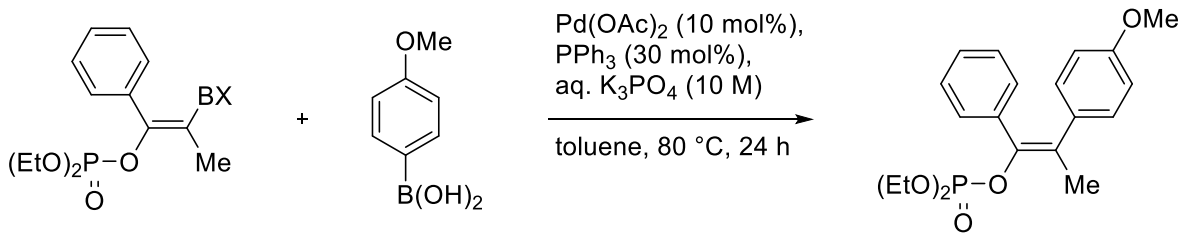
^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7 (d, $^2J_{C\text{-}P}$ = 9.1 Hz), 150.2 (d, $^3J_{C\text{-}P}$ = 7.4 Hz), 134.1, 132.5, 131.4, 130.6, 130.5, 130.4, 129.8, 129.0, 128.5, 127.5, 125.7, 123.9 (q, $^1J_{C\text{-}F}$ = 290.0 Hz), 119.9 (d, $^2J_{C\text{-}P}$ = 8.2 Hz), 119.9 (d, $^3J_{C\text{-}P}$ = 4.9 Hz), 110.9, 81.7-80.5 (m), 27.2, 13.7 (d, $^4J_{C\text{-}P}$ = 1.9 Hz)

^{19}F NMR (282 MHz) δ -76.1;

^{31}P NMR (162 MHz) δ -17.6;

HRMS (ESI) Cal $C_{31}H_{25}O_5F_6PI$ $[M+H]^+$ 749.0388, found 749.0386

Suzuki–Miyaura coupling on the BX moiety



4ba
0.1 mmol

4.0 equiv

5
34% yield

(*E*)-Diethyl-(2-(4-methoxyphenyl)-1-phenylprop-1-en-1-yl) phosphate (5): A 10 mL Schlenk tube loaded with a magnetic stir bar was added with $Pd(OAc)_2$ (2.25 mg, 10.0 μmol,

10 mol%), triphenylphosphine (7.89 mg, 30.0 μmol, 30 mol%) and (4-methoxyphenyl)boronic acid (60.8 mg, 0.40 mmol, 4.0 equiv). **4ba** (63.8 mg, 0.10 mmol), toluene (0.4 mL) and aq. K_3PO_4 (10 M, 0.14 mL) was then added into the mixture. The resulting mixture was left to stir at 80 °C for 24 h under nitrogen atmosphere. The reaction was first quenched with 1 M KOH (1 mL), water (1 mL), and followed by an extracted using Et_2O (3 x 3 mL). Water and brine was used to wash the organic layer. The compound was left to dry over Na_2SO_4, and the solvent was evaporated. The residue was further purified using flash chromatography on silica gel. Yellow oil (9.0 mg, 24% yield); R_f 0.29 (Hex:EA = 2:1);

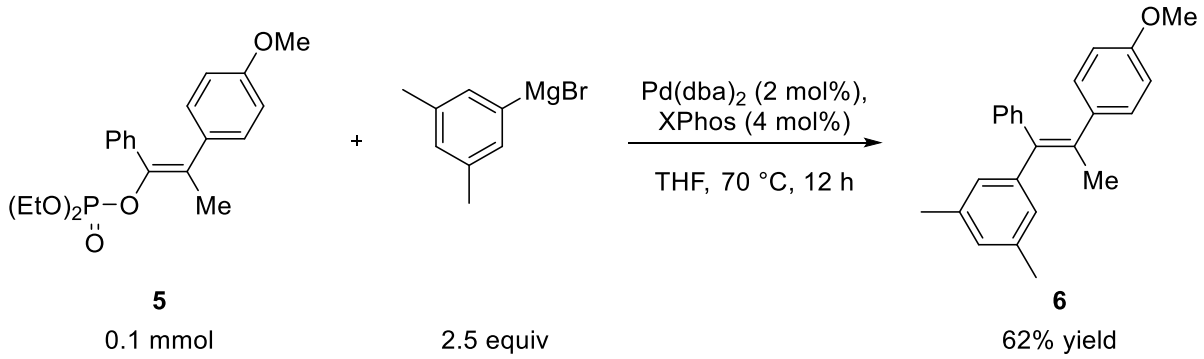
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.84 (m, 2H), 7.74 (s, 2H), 7.34-7.26 (m, 4H), 2.65 (brs., 2H), 2.43 (s, 3H), 1.19 (d, J = 6.2 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 142.5 (d, $^3J_{C\text{-}P}$ = 10.0 Hz), 135.7, 132.9, 130.2, 129.8, 127.7, 127.6, 125.4 (d, $^2J_{C\text{-}P}$ = 8.0 Hz), 113.4, 64.0 (d, $^3J_{C\text{-}P}$ = 6.0 Hz), 55.1, 19.4, 15.9 (d, $^2J_{C\text{-}P}$ = 8.0 Hz);

^{31}P NMR (162 MHz) δ -5.6;

HRMS (ESI) Cal $C_{20}H_{26}O_5P$ $[M+H]^+$ 377.1518, found 377.1515

Kumada coupling on the phosphate moiety

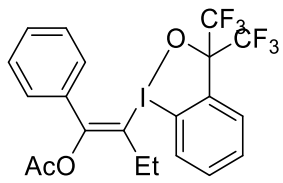


(*E*)-1-(2-(4-Methoxyphenyl)-1-phenylprop-1-en-1-yl)-3,5-dimethylbenzene (6): To a 10 mL Schlenk tube was loaded with a magnetic stir bar and then added $Pd(dba)_2$ (1.2 mg, 2.0 μmol, 2 mol%), XPhos (1.9 mg, 4.0 μmol, 4 mol%), **5** (37.6 mg, 0.10 mmol) and THF (0.7 mL). To the stirred mixture was added 3,5-dimethylphenylmagnesium bromide (prepared from the corresponding bromide and Mg; (ca. 0.63 M, 0.4 mL, 0.25 mmol) dropwise over 5 min. The mixture was then stirred at 70 °C for 12 h. The reaction was quenched with 1M HCl (1 mL), water (1 mL) and extracted using Et_2O (3 x 3 mL). The compound was dried over Na_2SO_4 and then evaporated. The residue was further purified by flash chromatography on silica gel.[71] Colourless oil (20.2 mg, 62% yield); R_f 0.25 (Hex);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06-6.99 (m, 5H), 6.92-6.88 (m, 3H), 6.85 (s, 2H), 6.71-6.67 (m, 2H), 2.30 (s, 6H), 2.09 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 143.6, 143.4, 139.0, 137.4, 136.4, 134.7, 130.85, 130.75, 128.1, 127.6, 127.4, 125.5, 113.2, 55.1, 23.3, 21.3;

HRMS (ESI) Cal $C_{24}H_{25}O$ $[M+H]^+$ 329.1905, found 329.1901



(*E*)-2-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)-1-phenylbut-1-en-1-yl acetate (12a):

To a 4 mL vial was equipped with a magnetic stir bar then added but-1-yn-1-ylbenzene (**2a**, 0.1 mmol), toluene (0.5 mL), ethyl acetate (2.0 mmol, 20.0 equiv) and BXT (**1**, 0.15 mmol, 1.5 equiv). The resulting mixture was stirred at room temperature for 24 h. The mixture was diluted

with ethyl acetate and saturated aq. Na_2CO_3, and extracted with ethyl acetate (3 x 3 mL). Water and brine was used to wash the organic layer, dried over Na_2SO_4, and the solvent was evaporated. The residue was further purified by flash chromatography on silica gel. Pale yellow solid (8.1 mg, 15% yield), R_f 0.22 (Hex:EtOAc = 3:1); m.p. 132-135°C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.87 (m, 1H), 7.84 (app. d, *J* = 6.9 Hz, 1H), 7.69-7.62 (m, 2H), 7.37-7.31 (m, 1H), 7.27 (d, *J* = 4.3 Hz, 4H), 2.65 (brs, 2H), 2.24 (s, 3H), 1.19 (t, *J* = 7.5 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 155.2, 135.2, 132.5, 131.4, 130.5, 130.4, 128.6, 128.5, 127.8, 123.9 (q, $^1J_{C\text{-}F}$ = 288.7), 120.3, 110.7, 82.7-80.4 (m), 27.6, 20.6, 13.8;

^{19}F NMR (282 MHz) δ -76.1;

HRMS (ESI) Cal $C_{21}H_{18}O_3F_6I$ $[M+H]^+$ 559.0205, found 559.0206