

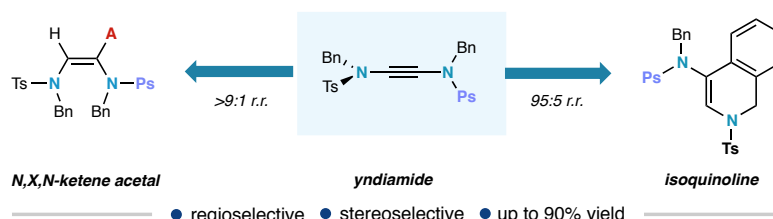
Regio- and stereoselective addition of Brønsted acids to yndiamides: Synthesis of *N,O,N*- and *N,S,N*-trisubstituted ketene acetals

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Abstract Yndiamides, *N,N*-disubstituted alkynes, are versatile building blocks for the synthesis of nitrogen-containing organic molecules. Unlike ynamides, relatives that are inherently polarized by a single nitrogen substituent, their *pseudo*-symmetric nature renders regioselective reactions challenging. Here we report investigations into the regioselective addition of Brønsted acids to non-symmetric yndiamides, a reaction that delivers *N,O,N*- and *N,S,N*-trisubstituted ketene acetals with excellent regio- and stereoselectivity.

Key words Yndiamide, keteniminium ion, hydroalkoxylation, regioselectivity

Yndiamides (**1**, Figure 1) are relatively new additions to the wider family of ynamides (**2**) and ynamines, featuring nitrogen (amide) substituents at both termini of an alkyne.¹ Ynamides display an inherent polarization of their triple bond due to the electron-donating nature of their single nitrogen atom, resulting in high regioselectivity in processes such as hydroalkoxylation and hydroaminations (Figure 1a).^{2,3} In contrast, yndiamides typically present an overall non-polar structure due to balanced and opposing electron-donation into orthogonal alkyne π -bonds by the two nitrogen substituents. Yndiamides nonetheless offer unique opportunities in synthesis: they can display heightened reactivity over ynamides, or distinct reaction outcomes in the formation of doubly-nitrogenated products.^{1,4}

Achieving control over the regioselectivity of functionalization of an yndiamide is a fundamental challenge, but also one that broadens the applicability of this motif in organic synthesis by enabling the site-selective installation of new substituents. In previous work, we developed a gold-catalyzed oxidative functionalization of yndiamides (Figure 1b),^{4a} which likely proceeds via initial formation of a keteniminium ion following activation of the yndiamide triple bond by the gold(I) catalyst. Subsequent regiocontrolled nucleophilic addition could be achieved through steric factors, where α -branching of one of

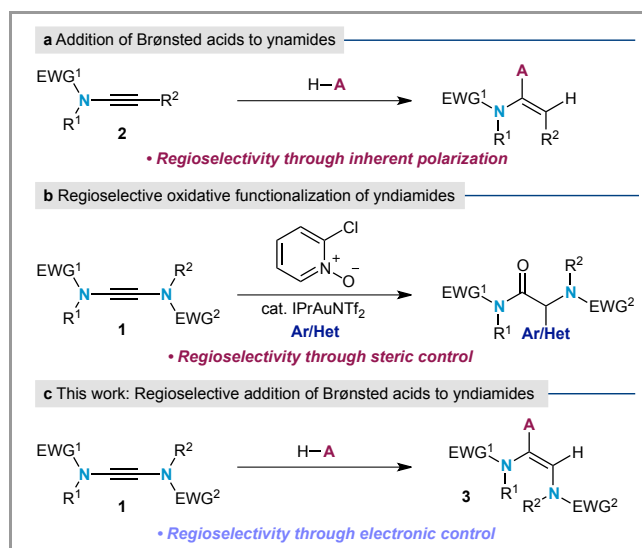
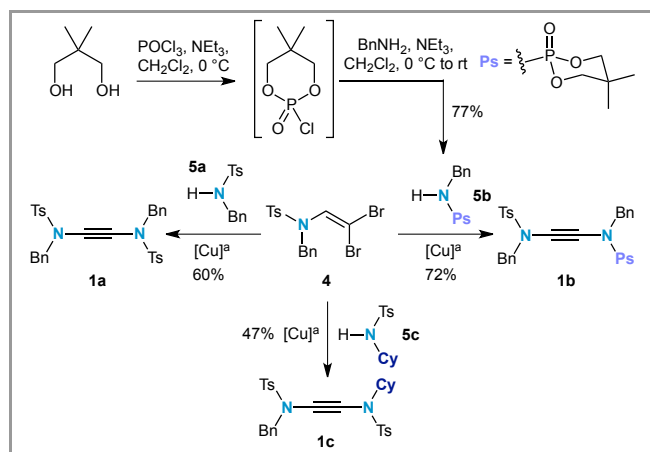


Figure 1 Previous regioselective yndiamide and ynamide functionalizations, and the regioselective addition of Brønsted acids described in this work.

the nitrogen alkyl substituents afforded regioselectivities (r.r.) of up to >20:1; differentiation through variation of the electron-withdrawing group proved less effective. We were keen to explore the addition of other functional groups to yndiamides, for example promoted by protonation of the triple bond^{3b} rather than association with a metal catalyst. Here we report the regioselective addition of Brønsted acids to yndiamides (Figure 1c), where optimum selectivity is found to arise from electronic, and not steric, effects. The chemistry operates displays broad substrate scope in the synthesis of *N,O,N*- and *N,S,N*-ketene acetals **3**, members of the wider family of ketene acetals that are finding increasing utility in synthesis.⁵

Symmetric yndiamide **1a** (Scheme 1) and unsymmetric yndiamides **1b** and **1c** were selected as representative



Scheme 1 Synthesis of symmetric yndiamide **1a** and non-symmetric yndiamides **1b** and **1c**. ^a[Cu] = CuI (20 mol%), 1,10-phen (40 mol%), Cs₂CO₃, THF, 60 °C

substrates to explore reactivity towards Brønsted acids, and the effect on regioselectivity of varying the electron withdrawing group (**1b**), or the yndiamide *N*-alkyl substituent (**1c**). *N*-Sulfonyl yndiamides **1a** and **1c** were prepared by copper-catalyzed coupling of dibromoamide **4** with benzyl (**5a**) or cyclohexylsulfonamide (**5c**) respectively.¹ Phosphoramidate yndiamide **1b** was synthesized by equivalent coupling with the benzyl phosphoramidate **5b**, itself prepared from 2,2-dimethylpropane-1,3-diol, POCl₃ and benzylamine in 77% yield. We note in passing that the synthesis of equivalent yndiamides in which the benzyl substituent on either partner was replaced with a methyl group was unsuccessful due to the instability of these yndiamide products towards chromatography.

With three yndiamides in hand, their reactivity towards Brønsted acids was evaluated using 2-iodobenzoic acid (Table 1). Pleasingly, addition to symmetric yndiamide **1a** proceeded smoothly in 2 h at room temperature in dichloromethane,^{5c} delivering the *syn* addition product **3a** in 81% yield. Addition of 2-iodobenzoic acid to yndiamides **1b** and **1c** also gave full conversion to the corresponding *N,O,N*-ketene acetals. While the regioselectivity with yndiamide **1c** (R = Cy, EWG = Ts) was moderate (75:25 *r.r.*, 38% isolated yield of major diastereomer **3c**), yndiamide **1b** (R = Bn, EWG = Ps) exhibited near complete selectivity for the formation of **3b** (>95:5 *r.r.*, 89% isolated yield); the structures of adducts **3a–3c** were confirmed using single-crystal X-ray diffraction.^{6,7} The outcome of these reactions is in marked contrast to gold-catalyzed yndiamide functionalization, where regioselectivity depended on steric and not electronic factors.

Given the striking regioselectivity observed upon variation of the electron-withdrawing groups, yndiamide **1b** was chosen as a substrate to explore the addition of other Brønsted acids (Scheme 2); by analogy with **3a–c**, all addition products are assumed to be of (*E*)-geometry. Pleasingly, a wide range of acids were found to be suitable for this regio- and stereoselective addition process. Carboxylic acids featuring aryl (**3a**, **3d**), alkyl (**3e**) and alkenyl (**3f**) substituents all added to yndiamide **3b** with excellent regioselectivity (>90:10 *r.r.*) and yield (77–90%). *N*-Boc protected phenylalanine also gave the corresponding *N,O*-ketene acetal **3g** with near perfect regioselectivity (>95:5 *r.r.*) and efficiency (90% isolated yield). The more acidic

Table 1 Addition of 2-iodobenzoic acid to ynamides **1a–c**.

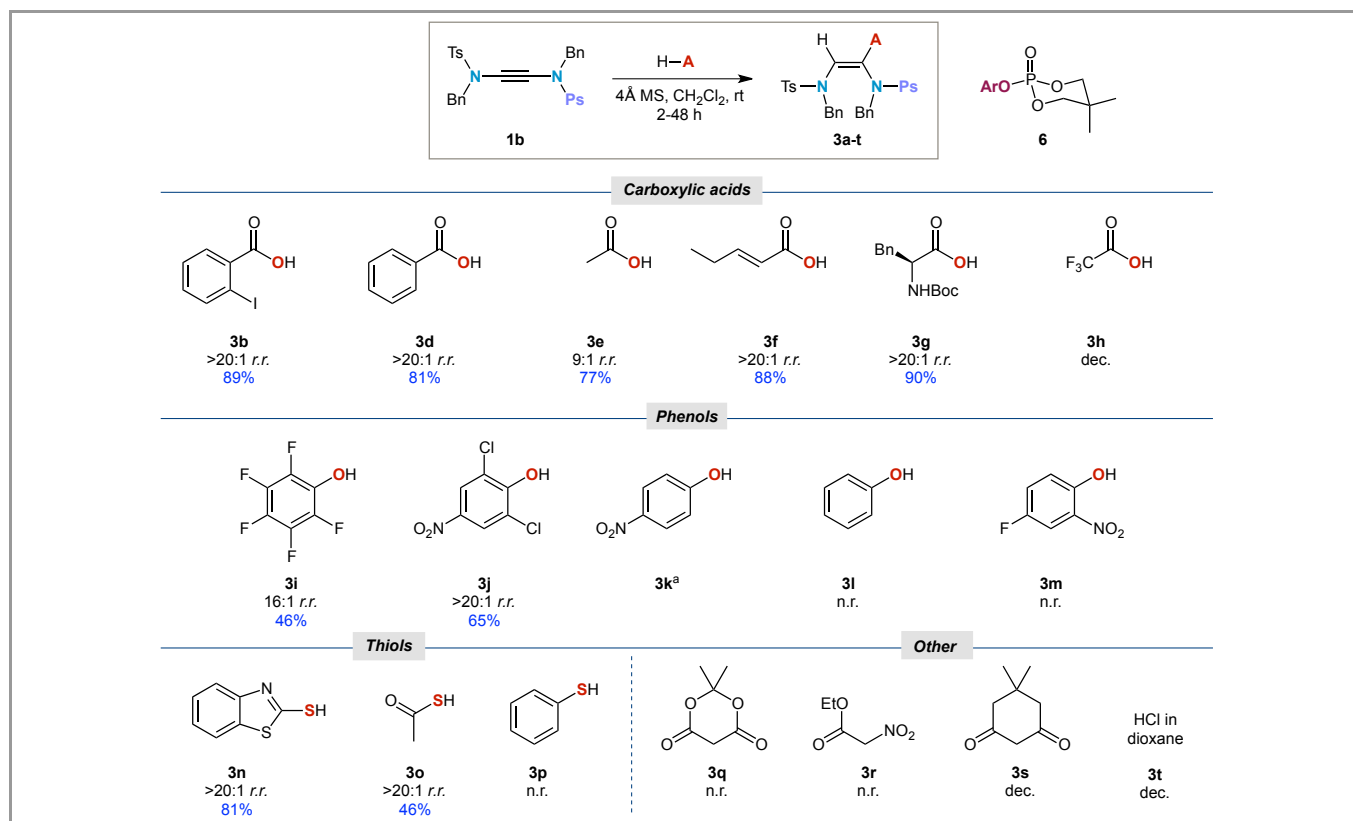
Yndiamide	R	EWG	Yield (%) ^a	<i>r.r.</i> ^b
1a	Bn	Ts	81	–
1b	Bn	Ps	89	>95:5
1c	Cy	Ts	38	75:25

^a Isolated yield of major regioisomer. ^b Regioisomer ratio (*r.r.*) of **3:3'** determined by integration of the ¹H NMR spectrum of the crude reaction mixture.

trifluoroacetic acid led only to decomposition (**3h**). We were excited to find that relatively acidic phenols (**3i**, **3j**) also reacted with very good regioselectivity (>16:1 *r.r.*); however a reduction in yield was observed due to the competing formation of aryl phosphate side products **6**, which presumably arise from competing nucleophilic attack by the phenol(ate) on the phosphoryl group. Indeed, the reaction with 4-nitrophenol (**3k**) predominantly gave this side-product instead of the desired *N,O*-acetal, while less acidic phenols did not react at all (**3l**, **3m**). Thiols also proved viable substrates, with benzothiazol-2-yl thiol and thioacetic acid affording addition products **3n** and **3o**, respectively, as single isomers. However, reaction with thioacetic acid afforded unidentified side-products in addition to the *N,S*-acetal, leading to a diminished yield (**3o**, 46%). No reaction was observed with thiophenol (**3p**), or with carbon-based acids such as Meldrum's acid and other 1,3-dicarbonyl equivalents (**3q–3s**). The use of HCl led only to complex mixtures under various conditions (**3t**).

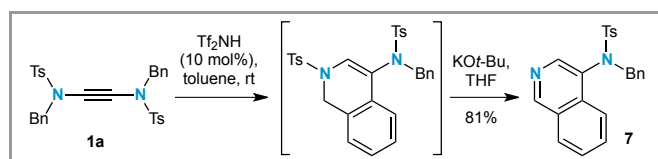
Although these reactions were conducted using dichloromethane as solvent, we note that *pK_a* in H₂O offers a reasonable guide as to whether or not an acid will react with an yndiamide, with productive reaction occurring up to a *pK_a* of ~6.5–7.5; acids with *pK_a* ≤ 3 typically gave multiple products. However, *pK_a* is clearly not the only factor to affect reactivity, given the unreactive nature of carbon-centered acids despite their similar acidity to alkyl/aryl carboxylic acids in water.⁸ It is worth noting that carbon-centred acids have not, to the best of our knowledge, been successfully added to ynamides at their acidic carbon atoms without the aid of transition metals.^{2b,9}

Given the high regioselectivity observed in these intermolecular addition processes, we next questioned whether equivalent regiocontrol could be induced in intramolecular cyclization reactions in which the benzyl substituent would act as a nucleophile, a process that we had observed for symmetric yndiamides on treatment with TfOH,¹ and which is also known for ynamides.¹⁰ We first explored the feasibility of this process



Scheme 2 Scope of the regioselective addition of Brønsted acids to yndiamide **1b**. Yields are isolated yields. Regioselectivities were determined by integration of ^1H NMR spectra of the crude reaction mixture.

using symmetric yndiamide **1a** with TsNH as catalyst (Scheme 3). To our delight, rapid and smooth cyclization occurred to the intermediate dihydroisoquinoline; direct treatment of the mixture with a solution of KOt-Bu in THF effected elimination of toluenesulfinic acid to give isoquinoline **7** in 81% yield.⁷



Scheme 3 Acid-promoted cyclization of yndiamide **1b**, and elimination to isoquinoline **7**.

Attempts to translate these cyclization conditions to non-symmetric yndiamide **1b** resulted in a clean but poorly regioselective reaction (Table 2, Entry 1, *r.r.* 61:39 **8b**:**8'b**). Use of triflic acid led to no improvement (Entry 2), but after a survey of a range of other acids we were pleased to find that cyclization with 2-bromothiophenol as promoter (Entry 3) gave mainly cyclization product **8b** (60% isolated yield) with excellent regioselectivity (95:5), albeit at a cost of some addition of this Brønsted acid to the yndiamide to form the corresponding *N,S,N*-ketene acetal **3u** (not shown). Attempts to accelerate the reaction by increasing the temperature from 21 °C to 75 °C (Entry 4) led to greater conversion after 24 hours; however, significantly more Brønsted acid adduct than cyclisation was observed. Addition of a co-catalytic amount of strong acid to promote keteniminium ion formation led only to non-regioselective cyclization (Entry 5).

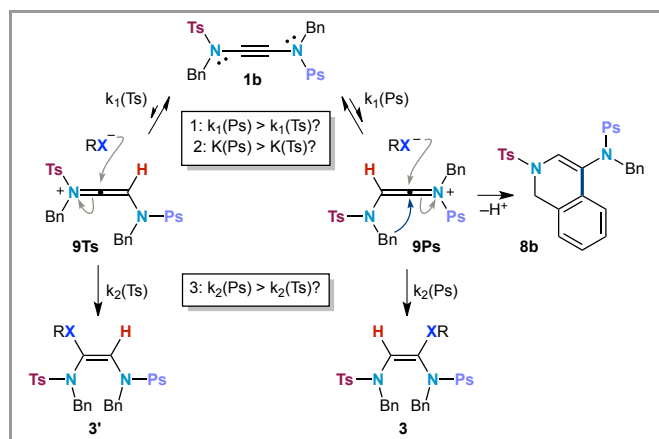
Interestingly, addition of an equimolar amount of a weak base (DTBMP) to buffer the reaction led to mostly Brønsted acid addition product **3u** and unreacted starting material, with only traces of cyclization product **8b** after 24 hours (Entry 6).

The reason why yndiamide **1b** gives such striking regioselectivity in both the addition of Brønsted acids and the thiophenol-promoted cyclization is unclear. Regioselectivity could arise from selective formation of keteniminium ion pair **9Ps** (scenario 1: $k_1(\text{Ps}) > k_1(\text{Ts})$); or a more favourable equilibrium constant increasing the concentration of the keteniminium ion

Table 2 Regioselective cyclization of yndiamide **1b**.^a

Entry	Acid	Temp (°C), Time	Additive	8b : 8'b : 3u ^b
1	Ts_2NH	21, 5 min	—	61:39:0
2	TfOH	-60, 5 min	—	66:34:0
3	2-bromothiophenol	21, 45 h	—	75(60):4:21
4	2-bromothiophenol	75, 24 h	—	12:1:87
5	2-bromothiophenol	21, 5 min	Ts_2NH	58:42:0
6	2-bromothiophenol	21, 24 h	DTBMP	2:0:98 ^c

^aAll reactions reached 100% conversion unless otherwise stated. ^bRatios determined from integration of ^1H NMR spectra of the crude reaction mixtures. Values in parentheses indicate isolated yield. **3u** = Brønsted acid adduct with 2-bromothiophenol. ^c40% conversion.



Scheme 3 Possible mechanistic scenarios.

intermediate (scenario 2: $K(\text{Ps}) > K(\text{Ts})$); or from selective attack on keteniminium ion pair **9Ps** in a Curtin-Hammett situation (scenario 3: $k_2(\text{Ps}) > k_2(\text{Ts})$). Reversibility of product formation also cannot be ruled out; nonetheless, the nature of the acid is clearly influential on regioselectivity. Computational studies on the formation of keteniminium ions from related ynamides suggest that the acid plays an important role in the reaction pathway: for example, with TfOH, formation of the keteniminium ion and Brønsted acid adduct is predicted to be reversible,¹¹ but with carboxylic acids, formation of the Brønsted acid adduct is predicted to be irreversible.¹² Notably, both studies emphasize that the keteniminium ion pair $[\text{YndH}]^+[\text{X}]^-$ is transient and is rapidly converted to the product enamide. The major product **8b** from 2-bromothiophenol-promoted cyclization is also consistent with cyclisation via keteniminium **9Ps**; interestingly, exclusive 6-membered ring formation is observed, in agreement with the revised Baldwin's rules for cationic digonal cyclisations of alkynes which suggest 5-*endo*-dig cyclisations to be 'borderline / problematic' and 6-*exo*-dig cyclisations to be 'favoured'.¹³

In conclusion, we have established the first examples of regioselective additions of Brønsted acids to yndiamides. In contrast to gold-catalyzed functionalizations, variation of the nitrogen alkyl group R group (Bn vs Cy) proved less effective than variation of the electron-withdrawing group (Ts vs Ps) in controlling regiochemistry of addition. This work underlines the potential for the regiocontrolled introduction of two nitrogen atoms into organic molecules using yndiamides as dinitrogenated two-carbon building blocks.

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Proton (¹H), carbon (¹³C), phosphorous (³¹P) and fluorine (¹⁹F) NMR spectra were recorded on Bruker AVN400 (400/101 MHz) or Bruker AVB400 (400/101 MHz) spectrometers. Chemical shifts (δ) are quoted in ppm. ¹H NMR spectra were recorded using an internal deuterium lock for the residual protons in CDCl₃ (δ 7.26). ¹³C NMR spectra were recorded using an internal deuterium lock in CDCl₃ (δ 77.0). Assignments were determined either on the basis of unambiguous chemical shift or coupling patterns, COSY, HMBC and/or HSQC experiments. Coupling constants (J) are reported to the nearest 0.1 Hz. Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer with the sample being prepared as a thin film on a diamond ATR module. Low resolution mass spectra were recorded on a Micromass LCT Premier Open Access using electrospray ionisation (ESI). Accurate mass (HRMS) data was determined under conditions of ESI on a Bruker MicroTOF. Melting points were obtained using a Griffin melting point apparatus and are uncorrected. Optical

rotations were recorded on a Perkin-Elmer 241 or 341 polarimeter with a 1 dm path length cell (using the sodium D line, 589 nm). All reagents were used directly as supplied from commercial sources. Anhydrous THF, NEt₃ and CH₂Cl₂ were obtained from solvent dispenser units having been passed through an activated alumina column under argon. Unless otherwise stated, non-aqueous reactions were performed in flame-dried apparatus under a nitrogen atmosphere at room temperature.

Procedures

General procedure 1 for the synthesis of yndiamides.¹ To a nitrogen flushed flask containing a stirrer bar was added the amide (1.0 eq.), dibromoenamide (1.1 eq.), CuI (20 mol%), 1,10-phenanthroline (40 mol%) and powdered, anhydrous caesium carbonate (2.5–3.0 eq., see experimental details). The flask was purged under high vacuum for 10 minutes, followed by addition of nitrogen; this flush cycle was repeated twice more. Anhydrous THF (3 mL mmol⁻¹ of amide substrate) was added. The resulting suspension (dark blue, green or brown depending on amide substrate) was stirred under a nitrogen atmosphere at 60 °C until reaction completion, as analysed by TLC (~18–36 h). During this time, the reaction mixture changes colour to give a beige/brown mixture, before turning dark blue/black when nearing completion. Upon completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a celite pad (eluting with ethyl acetate). The filtrate was concentrated *in vacuo*, and purification was performed as described for each compound.

General procedure 2 for addition of Brønsted acids. To a vial containing 4 Å molecular sieves (~10 mg) and a stirrer bar was added yndiamide (1.0 eq.) and Brønsted acid (equivalents noted per compound). The vial was evacuated and backfilled with nitrogen (\times 3), and then anhydrous CH₂Cl₂ (0.1 M) was added. The reaction was stirred at room temperature until the yndiamide was completely consumed (as determined by TLC analysis). The reaction mixture was either worked up by i) dilution with CH₂Cl₂, then addition of saturated aqueous NaHCO₃ followed by extraction with CH₂Cl₂ (\times 3); the combined organic layers were then washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*; or ii) concentrated *in vacuo*; and then purified as described.

N-Benzyl-N-(2,2-dibromovinyl)tosylamide 4.¹ To a nitrogen flushed flask containing a stirrer bar was added N-benzyltosylamide (5.00 g, 19.1 mmol, 1.0 eq.) and anhydrous THF (115 mL). The stirred solution was cooled to 0 °C, then a solution of *n*-butyllithium (8.42 mL, 19.1 mmol, 1.0 eq., 2.3 M solution in hexanes) was added dropwise over 5 minutes, and left to stir at 0 °C for 10 minutes. A solution of 1*H*-benzotriazole-1-carbaldehyde (BtCHO) (3.38 g, 21.1 mmol, 1.1 eq.) in anhydrous THF (69 mL) was added at 0 °C. The reaction was then warmed to room temperature and stirred until completion, as analysed by TLC (~20 min). The reaction was quenched by addition of H₂O and Et₂O (1:1) and the organic layer was separated. The remaining BtCHO was removed from the organic layer by extraction with 2 M aqueous K₂CO₃ (2–4 washes, as determined by TLC analysis). The organic layer was dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude formamide was used in the next step without purification.

To a nitrogen flushed flask containing a stirrer bar was added triphenylphosphine (20.1 g, 76.5 mmol, 4.0 eq.) and anhydrous CH₂Cl₂ (184 mL), and the solution was cooled to -10 °C whilst stirring. Tetrabromomethane (12.7 g, 38.3 mmol, 2.0 eq.) was added and the mixture stirred at -10 °C for 30 min. The resulting yellow/orange solution was cooled to -30 °C and a solution of crude formamide in anhydrous CH₂Cl₂ (66 mL) was added dropwise over 15–20 minutes. The stirred reaction mixture was allowed to warm gradually to room temperature and stirred until completion (~4 h). The resulting dark red mixture was concentrated *in vacuo* to roughly 50% volume and then filtered through a silica gel column (eluting with 10–30% EtOAc/petrol) to afford the crude dibromoenamide. The resulting solid was then recrystallized from hot EtOH to give the title compound (7.28 g, 16.2 mmol, 85%, m.p. 110–111 °C) as a white powder.

¹H NMR (CDCl₃, 400 MHz): δ = 7.72 (2H, d, J = 8.3 Hz, H3), 7.36–7.24 (7H, m, H2, H5, H6, H7), 6.62 (1H, s, H8), 4.54 (2H, s, H4), 2.45 (3H, s, H1).

^{13}C NMR (CDCl_3 , 101 MHz): δ = 144.2, 135.7, 135.0, 131.3, 129.9, 128.6, 128.5, 128.1, 127.4, 97.2, 52.7, 21.6.

Data consistent with literature values.¹

2-(Benzylamino)-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide **5b**.

To a flame-dried round bottomed flask containing a stirrer bar was added POCl_3 (1.47 g, 9.60 mmol, 1.0 eq.), NEt_3 (2.7 mL, 19.2 mmol, 2.0 eq.) and anhydrous CH_2Cl_2 (20 mL). 2,2-Dimethylpropane-1,3-diol (1.00 g, 9.60 mmol, 1.0 eq.) was added at 0 °C and the resultant mixture stirred for 30 minutes at 0 °C. Benzylamine (1.26 mL, 11.5 mmol, 1.2 eq.) and NEt_3 (1.6 mL, 11.5 mmol, 1.2 eq.) were added at 0 °C, and the resulting mixture was allowed to warm to room temperature (21 °C) and stirred overnight. The reaction mixture was washed once with H_2O and once with 5 M HCl . The separated organic phase was then dried with Na_2SO_4 and concentrated *in vacuo*. The resulting crude product was purified by column chromatography (EtOAc) followed by recrystallisation from CH_2Cl_2 /pentane to afford the title compound (1.70 g, 7.39 mmol, 77%, m.p. 120–121 °C) as colourless crystals.

^1H NMR (CDCl_3 , 400 MHz): δ = 7.62–7.02 (5H, m, *H1*, *H2*, *H3*), 4.33 (2H, dd, J = 10.8, 4.1, *H6*), 4.22 (2H, dd, J = 10.4, 7.0 Hz, *H4*), 3.83 (2H, dd, J = 20.2, 10.8 Hz, *H6*), 3.52–3.39 (1H, m, *H5*), 1.23 (3H, s, *H7*), 0.93 (3H, s, *H7*).

^{13}C NMR (CDCl_3 , 101 MHz): δ = 139.2 (1C, d, J = 6.3 Hz), 128.4, 127.3, 127.2, 76.1 (2C, d, J = 5.4 Hz), 46.2, 31.7 (1C, d, J = 5.0 Hz), 21.9, 20.7.

^{31}P NMR (CDCl_3 , 162 MHz): δ = 4.99. Data consistent with literature values.¹⁴

***N,N'*-(Ethyne-1,2-diyl)bis(*N*-benzyltosylamide) **1a**.** Synthesized from *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide **4** (800 mg, 1.80 mmol, 1.1 eq.), *N*-benzyltosylamide **5a** (427 mg, 1.63 mmol, 1.0 eq.), CuI (62 mg, 0.33 mmol, 0.2 eq.), 1,10-phenanthroline (118 mg, 0.65 mmol, 0.4 eq.) and powdered anhydrous Cs_2CO_3 (1.33 g, 4.09 mmol, 2.5 eq.) in anhydrous THF (4.9 mL) following General Procedure 1. Recrystallization from CH_2CH_2 /pentane/diethyl ether gave the title compound (534 mg, 0.98 mmol, 60%, m.p. 142–144 °C) as yellow crystals.

^1H NMR (CDCl_3 , 400 MHz): δ = 7.54 (4H, d, J = 8.0 Hz, *H3*), 7.30–7.15 (10H, m, *H2*, *H6*, *H7*), 7.07–6.98 (4H, m, *H5*), 4.39 (4H, s, *H4*), 2.43 (6H, s, *H1*).

^{13}C NMR (CDCl_3 , 101 MHz): δ = 144.4, 134.8, 134.5, 129.5, 128.6, 128.4, 128.0, 127.6, 69.9, 55.9, 21.6. Data consistent with literature values.¹

***N*-Benzyl-*N*-((benzyl[5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl]amino)ethynyl)tosylamide **1b**.** Synthesized from *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide **4** (1.00 g, 2.25 mmol, 1.1 eq.), 2-(benzylamino)-5,5-dimethyl-1,3,2-dioxaphosphinan 2-oxide **5b** (521 mg, 2.04 mmol, 1.0 eq.), CuI (77.8 mg, 0.41 mmol, 0.2 eq.), 1,10-phenanthroline (147 mg, 0.82 mmol, 0.4 eq.) and powdered anhydrous Cs_2CO_3 (1.66 g, 5.11 mmol, 2.5 eq.) in anhydrous THF (6.75 mL) following General Procedure 1. Flash chromatography (50% EtOAc /pentane) afforded the title compound (789 mg, 1.47 mmol, 72%, m.p. 112–115 °C) as a tan solid.

^1H NMR (CDCl_3 , 400 MHz): δ = 7.57 (2H, d, J = 8.1 Hz, *H2*), 7.35–7.29 (3H, m, *H10*, *H11*), 7.29–7.18 (8H, m, *H2*, *H6*, *H7*, *H9*), 7.15–7.10 (2H, m, *H5*), 4.36 (2H, s, *H4*), 4.36 (2H, d, J = 4.9 Hz, *H8*), 3.96–3.80 (4H, m, *H12*), 2.44 (3H, s, *H1*), 1.10 (3H, s, *H13*), 0.69 (3H, s, *H13*).

^{13}C NMR (CDCl_3 , 101 MHz): δ = 44.3, 136.6 (1C, d, J = 1.5 Hz), 134.9, 134.7, 129.6, 129.2, 128.4 (2C), 128.3, 128.2, 127.7, 127.6, 79.2 (2C, d, J = 7.3 Hz), 72.8 (1C, d, J = 5.1 Hz), 64.6 (1C, d, J = 5.1 Hz), 55.7* (1C, d, J = 7.3 Hz), 31.7 (1C, d, J = 7.3 Hz), 21.7, 21.6, 20.4.

^{31}P NMR (CDCl_3 , 162 MHz): δ = -4.95. Data consistent with literature values.¹

***N*-Benzyl-*N*-((*N*-cyclohexyltosylamido)ethynyl)tosylamide **1c**.**

Synthesized from *N*-benzyl-*N*-(2,2-dibromovinyl)tosylamide **4** (200 mg, 449 μmol , 1.1 eq.), *N*-cyclohexyltosylamide **4c** (103.4 mg, 408 μmol , 1.0 eq.), CuI (15.6 mg, 81.7 μmol , 0.2 eq.), 1,10-phenanthroline (29.4 mg, 163 μmol , 0.4 eq.) and powdered anhydrous Cs_2CO_3 (399 mg, 1.23 mmol, 3.0 eq.) in anhydrous THF (6.75 mL) following General Procedure 1. Flash chromatography (15% Et_2O /pentane) followed by recrystallization from TBME, then recrystallization from CH_2Cl_2 /pentane, afforded the title compound as colorless crystals (103 mg, 192 μmol , 47%, m.p. 113 °C).

^1H NMR (CDCl_3 , 400 MHz): δ = 7.69 (2H, d, J = 8.2 Hz, *H3*), 7.62 (2H, d, J = 8.2 Hz, *H12*), 7.31–7.22 (7H, m, *H2*, *H6*, *H7*, *H13*), 7.22–7.17 (2H, m, *H5*), 4.53 (2H, s, *H4*), 3.64 (1H, tt, J = 11.7, 4.1 Hz, *H8*), 2.42 (6H, s, *H14*, *H1*), 1.58 (2H, dt, J = 13.8, 3.4 Hz, *H10*), 1.53–1.45 (1H, m, *H11*), 1.38 (2H, dd, J = 12.9, 3.8 Hz, *H9*), 1.17 (2H, qt, J = 13.2, 3.5 Hz, *H10*), 0.96 (2H, qd, J = 12.5, 3.7 Hz, *H9*), 0.81 (1H, qt, J = 13.0, 3.7 Hz, *H11*).

^{13}C NMR (CDCl_3 , 101 MHz): δ = 144.4, 144.1, 136.2, 134.8, 134.7, 129.6, 129.5, 128.9, 128.3, 128.0, 127.7, 127.3, 70.4, 67.5, 59.1, 55.8, 30.6, 25.1, 24.6, 21.6. Data consistent with literature values.¹

(*E*)-1,2-Bis((*N*-benzyl-tosyl)vinyl 2-iodobenzoate **3a.** Synthesized from *N,N'*-(ethyne-1,2-diyl)bis(*N*-butyl-tosylamide) **1a** (100 mg, 184 μmol , 1.0 eq.), 2-iodobenzoic acid (50.1 mg, 202 μmol , 1.1 eq.) and 4Å molecular sieves (20 mg) in anhydrous CH_2Cl_2 (1.84 mL) according to General Procedure 2 (3 h reaction time). The solvent was removed *in vacuo* and the resulting residue triturated with toluene to give the title compound (118 mg, 184 μmol , 81%, m.p. 139–141 °C; R_f 0.20 in 20% EtOAc /pentane) as a white powder. Crystals suitable for X-ray diffraction were grown by vapour diffusion of pentane into a concentrated solution of the title compound in chloroform.

IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 3064, 3029, 2952, 1749, 1692, 1597, 1581, 1495, 1450, 1436, 1401, 1384, 1350, 1311, 1289, 1253, 1227, 1163, 1114, 1069, 1042, 1011, 975, 957, 903, 881, 861, 839, 820, 807, 776, 737, 715 704, 692, 670, 657, 641, 627, 616.

^1H NMR (CDCl_3 , 400 MHz): δ = 7.97 (1H, d, J = 7.8 Hz, *H4*), 7.67 (2H, d, J = 7.9 Hz, *H3*), 7.44 (2H, d, J = 7.9 Hz, *H17*), 7.28–6.95 (18H, m, *H2*, *H5*–7, *H10*–16, *H18*), 6.79 (1H, s, *H8*), 4.67 (2H, s, *H9*), 4.24 (2H, s, *H13*), 2.37 (3H, s, *H1*), 2.27 (3H, s, *H19*).

^{13}C NMR (CDCl_3 , 101 MHz): δ = 163.8, 143.9, 143.8, 141.5, 136.5, 136.0, 135.5, 134.4, 133.2, 132.8, 131.2, 129.8, 129.6, 129.5, 129.3, 129.0, 128.2, 127.9, 127.6, 127.5, 127.2, 125.3, 121.6, 95.0, 53.3, 50.5, 21.5 (2C).

HRMS (ES^+): calc. for $\text{C}_{37}\text{H}_{33}\text{O}_6\text{N}_2\text{INaS}_2$ [$\text{M}+\text{Na}$] $^+$ 815.0717, found 815.0713.

(*E*)-1-(Benzyl[5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl]amino)-2-((*N*-benzyl-tosyl)vinyl 2-iodobenzoate, **3b.** Synthesized from *N*-benzyl-*N*-((benzyl[5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl]amino)ethynyl)tosylamide **1b** (50.0 mg, 92.8 μmol , 1.0 eq.), 2-iodobenzoic acid (25.3 mg, 102 μmol , 1.1 eq.) in anhydrous CH_2Cl_2 (0.93 mL) following General Procedure 2. Flash chromatography (50% EtOAc /pentane) afforded the title compound (64.7 mg, 82.6 μmol , 89%, >95:5 *r.r.*, m.p. 110–111 °C, R_f 0.28 in 50% EtOAc /pentane) as a white foam. Crystals suitable for X-ray diffraction were grown by slow evaporation of a CH_2Cl_2 /benzene/hexane solution of the title compound.

IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 3059, 2974, 2918, 1765, 1665, 1595, 1583, 1496, 1476, 1454, 1433, 1397, 1362, 1346, 1291, 1267, 1246, 1212, 1181, 1168, 1146, 1122, 1082, 1057, 1045, 996, 981, 955, 922, 895, 849, 832, 820, 796 776, 757, 735, 714 697, 661, 638, 624, 607.

^1H NMR (CDCl_3 , 400 MHz): δ = 7.93 (1H, d, J = 7.9 Hz, *H7*), 7.78 (2H, d, J = 7.9 Hz, *H16*), 7.48 (1H, dd, J = 7.8, 1.8 Hz, *H9*), 7.29 (1H, d, J = 7.8 Hz, *H10*), 7.26–7.20 (4H, m, *H17*, *H4*), 7.17–7.00 (9H, m, *H5*, *H6*, *H8*, *H13*, *H14*, *H15*), 5.85 (1H, s, *H11*), 4.62 (2H, s, *H12*), 4.38 (2H, d, J = 11.7 Hz, *H3*), 4.20–3.90 (4H, m, *H2*), 2.39 (3H, s, *H18*), 1.06–0.95 (6H, m, *H1*).

^{13}C NMR (CDCl_3 , 101 MHz): δ = 163.6, 143.8, 141.1, 138.1, 138.0, 137.0, 135.6, 134.7, 133.1, 133.0, 131.8, 129.6, 128.5, 128.3, 128.2, 128.0, 127.7, 127.5, 127.2, 113.4 (1C, d, J = 6.2 Hz), 94.8, 77.2 (2C, d, J = 6.2 Hz), 52.7, 51.9 (1C, d, J = 4.4 Hz), 32.1 (1C, d, J = 6.0 Hz), 21.6, 21.5, 21.3.

^{31}P NMR (CDCl_3 , 162 MHz): δ = -1.85.

HRMS (ES^+): calc. for $\text{C}_{35}\text{H}_{37}\text{O}_7\text{N}_2\text{IPS}$ [$\text{M}+\text{H}$] $^+$ 787.1098, found 787.1097.

(*E*)-2-((*N*-benzyl-4-methylphenyl)sulfonamido)-1-(*N*-cyclohexyl-tosyl)vinyl 2-iodobenzoate **3c.** Synthesized from *N*-benzyl-*N*-((*N*-cyclohexyltosylamido)ethynyl)tosylamide **1c** (50.0 mg, 92.8 μmol , 1.0 eq.), 2-iodobenzoic acid (25.4 mg, 103 μmol , 1.1 eq.) in anhydrous CH_2Cl_2 (0.93 mL) following General Procedure 2. Column chromatography (5→10% acetone/pentane) afford the title compound (28.4 mg, 39%, >95:5 *r.r.*) as a viscous yellow oil. Crystals suitable for X-ray crystallography were grown by vapour diffusion of pentane into a

concentrated solution of the title compound in chloroform (m.p. 157–160 °C; R_f 0.17 in 10% acetone/pentane).

IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 2936, 2857, 1750, 1598, 1496, 1454, 1354, 1284, 1240, 1167, 1120, 1089, 1071, 1039, 1013, 966, 910, 814, 788, 734, 705, 667, 615.

¹H NMR (CDCl₃, 400 MHz): δ = 7.98 (1H, d, J = 7.6 Hz, *H*₉), 7.64 (4H, t, J = 8.1 Hz, *H*₃, *H*₁₇), 7.39 (2H, d, J = 7.3 Hz, *H*₁₄), 7.31–7.11 (8H, m, *H*₁₀, *H*₁₁, *H*₁₂, *H*₁₅, *H*₁₆, *H*₁₈), 7.05 (1H, s, *H*₈), 7.02 (2H, d, J = 8.1 Hz, *H*₂), 5.04 (2H, s, *H*₁₃), 3.66–3.49 (1H, m, *H*₄), 2.35 (3H, s, *H*₁₉), 2.28 (3H, s, *H*₁), 1.52–1.36 (5H, m, *H*₅, *H*₇), 1.07 (4H, p, J = 11.8, *H*₆), 0.91–0.70 (1H, m, *H*₇)

¹³C NMR (CDCl₃, 101 MHz): δ = 163.7, 143.8*, 141.4, 137.4, 136.7, 135.8, 134.1, 133.0, 130.7, 129.6, 129.4, 128.3, 128.2, 128.1, 127.8, 127.7*, 127.2, 124.5, 94.6, 61.9, 51.3, 31.4, 26.1, 24.6, 21.5 (2C).

HRMS (ES⁺): calc. for C₃₆H₃₇O₆N₂INaS₂ [M+Na]⁺ 807.1030, found 807.1029.

(E)-1-(Benzyl(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino)-2-((N-benzyl-tosyl)vinyl benzoate 3d. Synthesized from *N*-benzyl-*N*-((benzyl(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino)ethynyl) tosylamide **1b** (50.0 mg, 92.8 μ mol, 1.0 eq.), benzoic acid (12.5 mg, 102 μ mol, 1.1 eq.) in anhydrous CH₂Cl₂ (0.93 mL) following General Procedure 2. Flash chromatography (10→25% acetone/hexane) afforded the title compound (47.4 mg, 75.2 μ mol, 81%, >95:5 *r.r.*, m.p. 67–69 °C; R_f 0.17 in 25% acetone/hexane) as a white foam.

IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 3063, 2965, 2917, 1746, 1674, 1599, 1496, 1472, 1453, 1391, 1349, 1261, 1210, 1163, 1085, 1049, 1026, 1003, 947, 895, 813, 803, 765, 733, 700, 661, 642.

¹H NMR (CDCl₃, 400 MHz): δ = 7.77 (2H, d, J = 7.7 Hz, *H*₇), 7.72 (2H, d, J = 8.1 Hz, *H*₁₅), 7.52 (1H, t, J = 7.7 Hz, *H*₉), 7.35 (2H, t, J = 7.7 Hz, *H*₈), 7.28 (2H, d, J = 6.9 Hz, *H*₄), 7.23 (2H, d, J = 8.1 Hz, *H*₁₆), 7.18–7.02 (8H, m, *H*₅, *H*₆, *H*₁₂, *H*₁₃, *H*₁₄), 5.98 (1H, s, *H*₁₀), 4.74 (2H, s, *H*₁₁), 4.38 (2H, d, J = 11.5 Hz, *H*₃), 4.15–3.98 (4H, m, *H*₂), 2.39 (3H, s, *H*₁₇), 1.03 (3H, s, *H*₁), 0.99 (3H, s, *H*₁).

¹³C NMR (CDCl₃, 101 MHz): δ = 164.1, 143.7, 137.6 (1C, d, J = 2.5 Hz), 137.1, 135.9, 135.0, 133.4, 130.1, 129.6, 128.8, 128.4 (2C), 128.2, 128.1, 127.7, 127.4, 127.2, 114.7 (1C, d, J = 4.9 Hz), 77.1, 52.5, 52.2 (1C, d, J = 4.1 Hz), 32.1 (1C, d, J = 5.9 Hz), 21.5 (3C).

³¹P NMR (CDCl₃, 162 MHz): δ = -0.93.

HRMS (ES⁺): calc. for C₃₅H₃₈O₇N₂PS [M+H]⁺ 661.2132, found 661.2125.

(E)-1-(Benzyl(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino)-2-((N-benzyl-tosyl)vinyl acetate 3e. Synthesized from *N*-benzyl-*N*-((benzyl(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino)ethynyl) tosylamide **1b** (50.0 mg, 92.8 μ mol, 1.0 eq.) in acetic acid (0.93 mL) following General Procedure 2. Flash chromatography (60% EtOAc/pentane) afforded the title compound (42.9 mg, 71.5 μ mol, 77%, 90:10 *r.r.*, R_f 0.28 in 50% EtOAc/pentane) as a viscous yellow oil.

IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 2966, 1768, 1720, 1674, 1598, 1497, 1455, 1349, 1210, 1162, 1091, 1052, 1002, 815, 725, 699, 659.

¹H NMR (CDCl₃, 400 MHz): δ = 7.68 (2H, d, J = 8.3 Hz, *H*₁₃), 7.41–6.99 (14H, m, *H*₅–7, *H*₁₀–12, *H*₁₄), 5.60 (1H, s, *H*₈), 4.65 (2H, s, *H*₉), 4.32 (2H, d, J = 11.7 Hz, *H*₄), 4.16–4.04 (4H, m, *H*₂), 2.37 (3H, s, *H*₁₅), 1.78 (3H, s, *H*₃), 1.06 (3H, s, *H*₁), 1.02 (3H, s, *H*₁).

¹³C NMR (CDCl₃, 101 MHz): δ = 168.6, 143.7, 138.5 (2C, d, J = 3.5 Hz), 137.1, 135.9, 134.8, 129.5, 128.7, 128.3 (2C), 128.2, 127.7, 127.6, 127.3, 113.3 (1C, d, J = 5.9 Hz), 77.1 (2C, d, J = 4.3 Hz), 52.8, 51.7 (1C, d, J = 4.1 Hz), 32.2, 21.5 (3C), 20.6.

³¹P NMR (CDCl₃, 162 MHz): δ = -1.09.

HRMS (ES⁺): calc. for C₃₀H₃₅O₇N₂NaPS [M+Na]⁺ 621.1795, found 621.1784.

(E)-1-(Benzyl(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino)-2-((N-benzyl-4-methylphenyl)sulfonamido)vinyl (E)-pent-2-enoate 3f. Synthesized from *N*-benzyl-*N*-((benzyl(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino)ethynyl) tosylamide **1b** (50.0 mg, 92.8 μ mol, 1.0 eq.) and 2-pentenoic acid (10.3 μ L, 102 μ mol, 1.1 eq.)

in anhydrous CH₂Cl₂ (0.93 mL) following General Procedure 2. Column chromatography (20→30% EtOAc/toluene) afford the title compound (52.1 mg, 81.7 μ mol, 88%, >95:5 *r.r.*, R_f 0.32 in 40% EtOAc/toluene) as a viscous yellow oil.

IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 3064, 3032, 2967, 2935, 2886, 1744, 1672, 1650, 1597, 1496, 1455, 1349, 1283, 1211, 1164, 1106, 1091, 1054, 1028, 1002, 948, 923, 885, 817, 734, 702, 661, 625; ¹H NMR (CDCl₃, 400 MHz): δ = 7.67 (2H, d, J = 8.3 Hz, *H*₁₆), 7.28–7.08 (10H, m, *H*₄, *H*₅, *H*₁₃, *H*₁₄, *H*₁₇), 7.08–7.00 (2H, m, *H*₆, *H*₁₅), 6.85 (1H, dt, J = 15.7, 6.1 Hz, *H*₈), 5.74 (1H, s, *H*₁₁), 5.58 (1H, d, J = 15.7 Hz, *H*₇), 4.66 (2H, s, *H*₁₂), 4.34 (2H, d, J = 11.5 Hz, *H*₃), 4.15–4.01 (4H, m, *H*₂), 2.36 (3H, s, *H*₁₈), 2.14 (2H, dt, J = 7.5, 6.1 Hz, *H*₉), 1.06–0.98 (9H, m, *H*₁, *H*₁₀).

¹³C NMR (CDCl₃, 101 MHz): δ = 163.9, 153.3, 143.5, 138.1 (1C, d, J = 2.7 Hz), 137.1, 135.9, 134.9, 129.4, 128.5, 128.3, 128.1, 128.0, 127.6, 127.4, 127.1, 119.0, 113.6 (1C, d, J = 4.0 Hz), 77.0, 52.6, 51.8 (1C, d, J = 4.0 Hz), 32.1 (1C, d, J = 6.1 Hz), 25.4, 21.5, 21.4 (2C), 11.8.

³¹P NMR (CDCl₃, 162 MHz): δ = -1.18.

HRMS (ES⁺): calc. for C₃₃H₄₀O₇N₂PS [M+H]⁺ 639.2288, found 639.2283.

(E)-1-(Benzyl(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino)-2-((N-benzyl-tosyl)vinyl (t-butoxycarbonyl)-(R)-phenylalaninate 3g. Synthesized from *N*-benzyl-*N*-((benzyl(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino)ethynyl) tosylamide **1b** (50.0 mg, 92.8 μ mol, 1.0 eq.), *N*-(t-butoxycarbonyl)-l-phenylalanine (27.2 mg, 102 μ mol, 1.1 eq.) in anhydrous CH₂Cl₂ (0.93 mL) following General Procedure 2. Column chromatography (50% EtOAc/pentane) afforded the title compound (66.1 mg, 83.5 μ mol, 90%, >95:5 *r.r.*, R_f 0.22 in 50% EtOAc/pentane) as a white foam.

IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 3435, 3290, 3064, 3031, 2975, 2932, 1768, 1710, 1598, 1496, 1455, 1392, 1350, 1253, 1211, 1163, 1112, 1090, 1051, 1029, 998, 947, 910, 814, 730, 670, 661, 646.

¹H NMR (CDCl₃, 400 MHz): δ = 7.53 (2H, d, J = 7.7 Hz, *H*₁₉), 7.21–6.94 (17H, m, *H*₄–6, *H*₁₁–13, *H*₁₆–18, *H*₂₀), 5.81 (1H, s, *H*₁₄), 4.78–4.59 (3H, m, *H*₈, *H*₁₅), 4.23–4.09 (3H, m, *H*₃, *H*₇), 4.10–3.81 (4H, m, *H*₂), 2.87 (1H, dd, J = 13.9, 4.6 Hz, *H*₁₀), 2.59 (1H, dd, J = 13.9, 7.5 Hz, *H*₁₀), 2.30 (3H, s, *H*₂₁), 1.49–1.21 (9H, m, *H*₉) 0.94 (3H, s, *H*₁), 0.89 (3H, s, *H*₁).

¹³C NMR (CDCl₃, 101 MHz): δ = 69.3, 154.9, 143.8, 137.2, 136.3, 136.1, 135.8, 135.2, 129.6, 129.3, 128.7, 128.5, 128.3 (2C), 128.2 (2C), 127.6, 127.5, 126.9, 115.6, 79.8, 77.0 (2C, d, J = 6.6 Hz), 54.5, 52.4, 52.1, 37.5, 32.1 (1C, J = 6.0 Hz), 28.3, 21.6, 21.5, 21.4.

³¹P NMR (toluene-*d*₈, 90 °C, 162 MHz): δ = -1.01.

HRMS (ES⁺): calc. for C₄₂H₅₁N₅O₉PS [M+H]⁺ 804.3078, found 804.3075

$[\alpha]_{\text{D}}^{25}$ = +12.7 (c 0.1, CHCl₃)

(E)-N-Benzyl-N-(2-(benzyl(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino)-2-(perfluorophenoxy)vinyl)-tosylamide 3i. Synthesized from *N*-benzyl-*N*-((benzyl(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino)ethynyl) tosylamide (50.0 mg, 92.8 μ mol, 1.0 eq.), 2,3,4,5,6-pentafluorophenol (18.8 mg, 102 μ mol, 1.1 eq.) in anhydrous CH₂Cl₂ (0.93 mL) following General Procedure 2. Flash chromatography (30→60% EtOAc/pentane) afforded the title compound (31.1 mg, 42.7 μ mol, 46%, 94:6 *r.r.*, R_f 0.49 in 50% EtOAc/pentane) as a viscous yellow oil.

IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 3034, 2965, 1674, 1598, 1517, 1456, 1348, 1282, 1262, 1212, 1163, 1091, 1053, 998, 947, 924, 804, 733, 701, 644.

¹H NMR (CDCl₃, 400 MHz): δ = 7.54 (2H, d, J = 8.3 Hz, *H*₁₂), 7.29 – 7.07 (11H, m, *H*₃ – 6, *H*₇, *H*₁₀, *H*₁₁, *H*₁₃), 7.05 (2H, d, J = 7.4 Hz, *H*₉), 4.96 (2H, s, *H*₈), 4.51 (2H, J = 10.7 Hz, *H*₃), 4.25 (2H, dd, J = 11.0, 7.7 Hz, *H*₂), 4.01 (2H, dd, J = 16.7, 10.9 Hz), 2.37 (3H, s, *H*₁₄), 1.13 (3H, s, *H*₁), 0.99 (3H, s, *H*₁).

¹³C NMR (CDCl₃, 101 MHz): δ = 149.8, 144.0, 136.8, 135.3, 134.6, 129.5, 129.3, 128.3, 128.1 (2C), 127.7, 127.6, 127.5, 104.6 (1C, d, J = 6.3 Hz), 77.0 (2C, d, J =), 53.6, 52.2 (2C, d, J = 3.3 Hz), 32.1 (1C, d, J = 5.6 Hz), 21.7, 21.5, 21.2;

^{19}F NMR (CDCl_3 , 376 MHz): δ = -150.6 – -152.8 (2F, m), -158.7 (1F, t, J = 22.4 Hz), -161.9 (2F, td, J = 22.4, 5.5 Hz).

^{31}P NMR (CDCl_3 , 162 MHz): δ = -0.93.

HRMS (ES⁺): calc. for $\text{C}_{34}\text{H}_{33}\text{O}_6\text{N}_2\text{F}_5\text{P}^{32}\text{S}$ $[\text{M}+\text{H}]^+$ 723.1712, found 723.1707.

Only the peaks for the major diastereomer are reported. Peaks for carbons adjacent to ^{19}F were not resolved due to large C-F coupling constants.

(*E*)-*N*-Benzyl-*N*-(2-(benzyl(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino)-2-(2,6-dichloro-4-nitrophenoxy)vinyl)-tosylamide 3j. Synthesized from *N*-benzyl-*N*-((benzyl(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino)ethynyl) tosylamide **1b** (50.0 mg, 92.8 μmol , 1.0 eq.), 2,5-dichloro-4-nitrophenol (16.0 mg, 102 μmol , 1.1 eq.) in anhydrous CH_2Cl_2 (0.93 mL) following General Procedure 2. Column chromatography (30 \rightarrow 50% EtOAc) afforded the title compound (44.8 mg, 66.4 μmol , 65%, >95:5 *r.r.*, R_f 0.38 in 50% EtOAc/pentane) as a viscous yellow oil.

IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 3090, 2968, 1669, 1597, 1537, 1497, 1454, 1393, 1344, 1252, 1211, 1162, 1054, 1001, 947, 916, 817, 736, 660.

^1H NMR (CDCl_3 , 400 MHz): δ = 8.09 (2H, s, *H3*), 7.53 (2H, d, J = 8.3 Hz, *H13*), 7.44 (2H, d, J = 6.7 Hz, *H5*), 7.30–7.08 (10H, m, *H6*, *H7*, *H10*, *H11*, *H12*, *H14*), 4.73 (2H, s, *H9*), 4.61 (2H, d, J = 11.4 Hz, *H4*), 4.36–4.25 (3H, m, *H2*, *H8*), 3.94 (2H, dd, J = 18.1, 11.4 Hz, *H2*), 2.34 (3H, s, *H15*), 1.09 (3H, s, *H1*), 0.95 (3H, s, *H1*).

^{13}C NMR (CDCl_3 , 101 MHz): δ = 151.1 (1C, d, J = 5.9 Hz), 150.3, 144.8, 143.8, 137.3, 135.9, 134.6, 130.6, 129.8, 129.4, 128.3, 128.1, 128.0, 127.8, 127.7, 127.3, 124.4, 101.9 (1C, d, J = 5.7 Hz), 76.9 (2C, d, J = 5.6 Hz), 53.9, 53.3 (1C, d, J = 2.4 Hz), 32.1 (1C, d, J = 5.6 Hz), 22.1, 21.5, 21.2

^{31}P NMR (CDCl_3 , 162 MHz): δ = -1.0.

HRMS (ES⁺): calc. for $\text{C}_{34}\text{H}_{35}\text{O}_8\text{N}_3^{35}\text{Cl}_2\text{P}^{32}\text{S}$ $[\text{M}+\text{H}]^+$ 746.1254, found 746.1252.

2-(2,6-Dichloro-4-nitrophenoxy)-5,5-dimethyl-1,3,2-dioxaphosphinane-2-oxide 6j. Synthesized from *N*-benzyl-*N*-((benzyl(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino)ethynyl) tosylamide **1b** (50.0 mg, 92.8 μmol , 1.0 eq.), 2,5-dichloro-4-nitrophenol (16.0 mg, 102 μmol , 1.1 eq.) in anhydrous CH_2Cl_2 (0.93 mL) following General Procedure 2. Flash chromatography (30 \rightarrow 50% EtOAc) afforded the title compound and a small amount of impurity with the same R_f (11.6 mg, 35.7 μmol , ~35%, R_f 0.56 in 50% EtOAc/pentane) as a viscous yellow oil.

IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 3092, 2972, 1537, 1456, 1395, 1347, 1318, 1265, 1212, 1150, 1056, 1009, 990, 927, 896, 858, 803, 762, 736, 659, 617.

^1H NMR (CDCl_3 , 400 MHz): δ = 8.27 (2H, s, *H3*), 4.51 (2H, dd, J = 11.0, 1.9 Hz, *H2*), 4.14 (dd, J = 23.1, 11.0 Hz, *H2*), 1.39 (3H, s, *H1*), 0.99 (3H, s, *H1*).

^{13}C NMR (CDCl_3 , 101 MHz): δ = 149.5 (1C, d, J = 8.4 Hz), 144.5, 129.5 (2C, d, J = 3.8 Hz), 124.3 (2C, d, J = 1.8 Hz), 79.0 (2C, d, J = 7.5 Hz), 32.2 (d, J = 6.0 Hz), 21.8, 20.2.

^{31}P NMR (CDCl_3 , 162 MHz): δ = -15.6

HRMS (ES⁺): calc. for $\text{C}_{11}\text{H}_{13}\text{O}_6\text{N}^{35}\text{Cl}_2\text{P}$ $[\text{M}+\text{H}]^+$ 355.9852, found 355.9853.

5,5-Dimethyl-2-(4-nitrophenoxy)-1,3,2-dioxaphosphinane 2-oxide 3k and (*E*)-*N*-benzyl-*N*-(2-(benzyl(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino)-1-(4-nitrophenoxy)vinyl)-tosylamide 6k. Synthesized from *N*-benzyl-*N*-((benzyl(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino)ethynyl) tosylamide **3.09** (50.0 mg, 92.8 μmol , 1.0 eq.), 4-nitrophenol (14.2 mg, 102.1 μmol , 1.1 eq.) in anhydrous CH_2Cl_2 (0.93 mL) following General Procedure 2. Flash chromatography (30 \rightarrow 50% EtOAc) afforded an inseparable mixture of the phosphoramidate (**3k**) and Brønsted acid adduct (**6k**) in a 86:14 ratio (21.3 mg, R_f 0.36, 50% EtOAc/pentane) as a viscous yellow oil

IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 2972, 1613, 1592, 1522, 1482, 1374, 1346, 1308, 1228, 1163, 1111, 1057, 1008, 928, 863, 802, 753, 699, 642

Brønsted acid adduct **3k**: ^1H NMR (CDCl_3 , 400 MHz): δ = 7.91 (2H, d, J = 9.3 Hz, *H9*), 7.61 (2H, d, J = 8.3 Hz, *H14*), 7.35–7.10 (12H, *H3*, *H4*, *H5*, *H11*, *H12*,

H13, *H15*), 6.75 (2H, d, J = 9.3 Hz, *H10*), 5.27 (1H, d, *H7*), 4.81 (2H, s, *H10*), 4.49 (2H, d, J = 10.4 Hz, *H6*), 4.38 (2H, d, J = 11.6 Hz, *H2*), 3.81 (2H, dd, J = 20.5, 11.6 Hz, *H2*), 2.38 (3H, s, *H16*), 1.19 (3H, s, *H1*), 0.92 (3H, s, *H1*)

^{13}C NMR (CDCl_3 , 101 MHz): δ = 160.6, 148.7 (1C, d, J = 6.0 Hz), 143.9, 143.1, 136.9 (2C, d, J = 1.4 Hz), 134.9, 129.7, 129.3, 128.7, 128.3 (2C, d, J = 5.1 Hz), 128.1, 127.8, 127.5*, 125.2, 118.3, 110.1 (1C, d, J = 5.5 Hz), 76.8 (2C, d, J = 5.5 Hz), 53.0, 52.2 (1C, d, J = 2.9 Hz), 32.1 (1C, d, J = 5.3 Hz), 22.4, 21.5, 20.9.

^{31}P NMR (CDCl_3 , 162 MHz): δ = 1.1.

HRMS (ES⁺): calc. for $\text{C}_{34}\text{H}_{37}\text{O}_8\text{N}_3\text{P}^{32}\text{S}$ 678.2034, found 678.2030.

Phosphoramidate **6k**: ^1H NMR (CDCl_3 , 400 MHz): δ = 8.25 (2H, d, J = 9.1 Hz, *H4*), 7.41 (2H, dd, J = 9.1, 0.9 Hz, *H3*), 4.25 (2H, d, J = 9.8 Hz, *H2*), 4.04 (2H, dd, J = 22.5, 9.8 Hz, *H2*), 1.35 (3H, d, *H1*), 0.93 (3H, s, *H1*).

^{13}C NMR (CDCl_3 , 101 MHz): δ = 155.1 (1C, d, J = 6.0 Hz), 144.7, 125.8, 120.2 (2C, d, J = 5.6 Hz), 78.8 (2C, d, J = 7.2 Hz), 32.3 (1C, d, J = 6.1 Hz), 21.6, 20.1 (1C, d, J = 1.3 Hz)

^{31}P NMR (CDCl_3 , 162 MHz): δ = -15.0.

HRMS (ES⁺): calc. for $\text{C}_{11}\text{H}_{15}\text{O}_6\text{NP}$ $[\text{M}+\text{H}]^+$ 288.0632, found 288.0631.

(*E*)-*N*-(2-(Benzo[d]thiazol-2-ylthio)-2-(benzyl(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino)vinyl)-*N*-benzyl-tosylamide 3n. Synthesized from *N*-benzyl-*N*-((benzyl(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino)ethynyl) tosylamide **1b** (50.0 mg, 92.8 μmol , 1.0 eq.), 2-mercaptobenzothiazole (17.1 mg, 102 μmol , 1.1 eq.) in anhydrous CH_2Cl_2 (0.93 mL) following General Procedure 2. Flash chromatography (30–60% EtOAc/pentane) afford the title compound (52.8 mg, 75.2 μmol , 81%, >95:5 *r.r.*, R_f 0.19 in 50% EtOAc/pentane) as a white foam.

IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 3064, 3031, 2964, 2931, 2887, 1617, 1496, 1456, 1427, 1401, 1356, 1310, 1261, 1211, 1186, 1165, 1089, 1052, 1005, 985, 946, 932, 912, 887, 916, 729, 706, 656, 636.

^1H NMR (CDCl_3 , 400 MHz): δ = 7.79 (1H, dt, J = 8.2, 0.9 Hz, *H1*), 7.74 (1H, dt, J = 8.1, 0.9 Hz, *H4*), 7.47–7.40 (4H, m, *H11*, *H2*, *H16*), 7.33 (1H, ddd, J = 8.1, 7.2, 1.2 Hz, *H15*), 7.17–7.05 (9H, m, *H13*, *H8-10*, *17*), 6.94 (1H, t, J = 6.5 Hz, *H15*), 6.91–6.84 (2H, m, *H14*), 4.99 (2H, s, *H12*), 4.33–4.19 (4H, m, *H5*, *H7*), 3.75 (2H, dd, J = 20.4, 11.2 Hz, *H5*), 2.35 (3H, s, *H18*), 1.16 (3H, s, *H6*), 0.87 (3H, s, *H6*).

^{13}C NMR (CDCl_3 , 101 MHz): δ = 168.5, 153.4, 144.0, 137.2 (2C, d, J = 6.1 Hz), 136.2 (3C), 136.1, 135.6, 129.5, 129.1, 128.0, 127.9, 127.6, 127.5, 127.0, 126.0, 124.4, 121.9, 121.0, 112.2, 76.8 (2C, d, J = 5.5 Hz), 53.0 (2C, d, J = 5.3 Hz), 49.5, 32.1 (1C, d, J = 5.6 Hz), 22.0, 21.5 (1C, d, J = 2.5 Hz), 21.0.

^{31}P NMR (CDCl_3 , 162 MHz): δ = 2.51.

HRMS (ES⁺): calc. for $\text{C}_{35}\text{H}_{37}\text{O}_5\text{N}_3\text{P}^{32}\text{S}_3$ $[\text{M}+\text{H}]^+$ 706.1628, found 706.1624;

(*E*)-*S*-(1-(benzyl(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino)-2-(*N*-benzyl-4-methylphenylsulfonamido)vinyl)ethanethioate 3o. Synthesized from *N*-Benzyl-*N*-((benzyl(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino)ethynyl) tosylamide **1b** (50.0 mg, 92.8 μmol , 1.0 eq.), thioacetic acid (12.7 μL , 102 μmol , 1.1 eq.) in anhydrous CH_2Cl_2 (0.93 mL) following General Procedure 2. Column chromatography (15 \rightarrow 30% EtOAc followed by 5% \rightarrow 10% acetone in pentane) afford the title compound (26.4 mg, 43.0 μmol , 46%, >95:5 *r.r.*, R_f 0.21 in 10% acetone/pentane) as a viscous yellow oil. The regioselectivity of addition was assigned by the observation of an IR carbonyl stretch at 1705 cm^{-1} which is consistent with that expected for a thioester.

IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 3032, 2970, 1705, 1623, 1496, 1455, 1354, 1258, 1211, 1186, 1165, 1090, 1054, 1008, 945, 912, 887, 816, 731, 707, 657, 638, 615

^1H NMR (CDCl_3 , 400 MHz): δ = 7.50 (2H, d, J = 8.4 Hz, *H13*), 7.20–7.10 (9H, m, *H5*, *H10*, *H11*, *H12*, *H14*), 7.08–7.00 (3H, m, *H6*, *H7*), 6.98 (1H, d, J = 2.0 Hz, *H8*), 4.89 (2H, s, *H9*), 4.22 (2H, dd, J = 11.1, 3.2 Hz, *H2*), 3.99 (2H, d, J = 11.8 Hz, *H4*), 3.71 (2H, dd, J = 20.7, 11.1 Hz, *H2*), 2.38 (3H, s, *H15*), 2.13 (3H, s, *H3*), 1.13 (3H, s, *H1*), 0.85 (3H, s, *H1*)

^{13}C NMR (CDCl_3 , 101 MHz): δ = 195.0, 144.0, 137.3 (2C, d, J = 6.0 Hz), 136.8, 136.0, 135.7, 129.6, 129.1, 128.1, 127.4, 127.1, 126.8, 108.1, 76.7 (2C, d, J = 8.6 Hz), 52.8, 52.7, 49.1, 32.0 (1C, d, J = 5.8 Hz), 29.5, 21.9, 21.5, 20.8

^{31}P NMR (CDCl_3 , 162 MHz): δ = 2.61.

HRMS (ES⁺): calc. for $[\text{M}+\text{H}]^+$ 615.1752, found 615.1747.

***N*-Benzyl-*N*-(isoquinolin-4-yl)-tosylamide 7.** To a flame dried vial containing a stirrer bar was added *N,N'*-(ethyne-1,2-diyl)bis(*N*-benzyltosylamide) **1a** (50 mg, 91.8 μmol , 1.0 eq.) followed by a solution of TF_2NH in toluene (0.37 mL, 0.25 M). Immediately, the vial was cooled to 0 °C and a solution of KOT-Bu in THF (184 μL , 2.0 eq., 1.0 M, 2.0 eq.) was added dropwise. The reaction was stirred until completion as determined by TLC analysis (~20 min). Once complete, the solution was quenched by addition of saturated aqueous NH_4Cl (1 mL) and diluted with EtOAc (1 mL). The layers were separated, and the aqueous layer extracted with EtOAc (3 x 1 mL), dried with Na_2SO_4 then filtered and concentrated *in vacuo*. Column chromatography (50% EtOAc/pentane) afforded the title compound as a pale yellow solid (28.8 mg, 81%, m.p. 160 °C, R_f 0.20 in 30% EtOAc/pentane). Crystals suitable for X-ray crystallography were grown by slow evaporation of a solution of the title compound in benzene.

IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$) 3032, 2920, 1625, 1597, 1579, 1496, 1455, 1391, 1348, 1305, 1163, 1092, 1045, 980, 905, 815, 782, 754, 704, 691, 661, 616

^1H NMR (CDCl_3 , 400 MHz): δ = 9.10 (1H, s, *H2*), 8.00 (1H, d, J = 7.4 Hz, *H6*), 7.89 (1H, d, J = 8.2 Hz, *H3*), 7.83 (1H, s, *H1*), 7.66–7.58 (3H, m, *H7*, *H5*), 7.55 (1H, ddd, J = 8.1, 6.9, 1.2 Hz, *H4*), 7.33 (2H, d, J = 7.6 Hz, *H8*), 7.16–7.06 (5H, m, *H12*, *H13*, *H14*), 5.13 (1H, d, J = 13.7 Hz, *H11*), 4.54 (1H, d, J = 13.7 Hz, *H11*), 2.46 (3H, s, *H10*)

^{13}C NMR (CDCl_3 , 101 MHz): δ = 152.7, 144.0, 143.1, 135.9, 135.2, 135.1, 131.4, 130.9, 129.8, 129.2, 129.1, 128.3, 127.9 (2C), 127.7, 127.2, 123.3, 56.5, 21.6

HRMS (ES⁺): calc. for $\text{C}_{23}\text{H}_{21}\text{O}_2\text{N}_2\text{S}$ $[\text{M}+\text{H}]^+$ 389.1318, found 389.1319.

2-(Benzyl(2-tosyl-1,2-dihydroisoquinolin-4-yl)amino)-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide 8b and **(*E*)-*N*-Benzyl-*N*-(2-benzyl(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino)-2-((2-bromophenyl)thio)vinyl)-tosylamide 3u.** Synthesized from *N*-benzyl-*N*-((benzyl(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino)ethynyl) tosylamide **1b** (50.0 mg, 92.8 μmol , 1.0 eq.), 2-bromothiophenol (12.7 μL , 102 μmol , 1.1 eq.) in anhydrous CH_2Cl_2 (0.93 mL) following General Procedure 2. Column chromatography (50→70% EtOAc/pentane) afforded **8b** (60%, 55.4 μmol , >95:5 *r.r.*, R_f 0.12 in 50% EtOAc/pentane) as a viscous yellow oil, along with **3u** (10 mg, ~15%, 13.7 μmol , >95:5 *r.r.*, R_f 0.19 in 50% EtOAc/pentane) as a viscous yellow oil.

8b: IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 3031, 2966, 2930, 2886, 1636, 1597, 1494, 1455, 1401, 1354, 1306, 1276, 1247, 1211, 1186, 1169, 1141, 1090, 1056, 1007, 970, 913, 828, 768, 729, 720, 701, 665, 641, 629.

^1H NMR (CDCl_3 , 400 MHz): δ = 7.38–7.31 (3H, m, *H8*, *H15*), 7.30–7.14 (9H, m, *H4*–6, *H9*, *H12*, *H13*), 6.99 (1H, d, J = 7.4 Hz, *H12*), 6.58 (1H, d, J = 2.4 Hz, *H7*), 5.08 (1H, dd, J = 14.7, 8.0 Hz, *H3*), 4.64 (1H, d, J = 13.4 Hz, *H11*), 4.34 (2H, dd, J = 21.5, 11.4 Hz, *H2*), 3.97–3.82 (3H, m, *H2*, *H3*, *H11*), 3.69 (1H, dd, J = 21.5, 11.4 Hz, *H2*), 2.42 (3H, s, *H10*), 1.06 (3H, s, *H1*), 0.84 (3H, s, *H1*).

^{13}C NMR (CDCl_3 , 101 MHz): δ = 144.0, 137.9, 133.8, 129.9, 129.1 (2C, J = 2.5 Hz), 129.0 (2C), 128.3, 128.2, 128.1, 127.8, 127.4, 127.2, 125.7, 121.8, 120.2 (1C, d, J = 2.5 Hz), 76.9 (1C, d, J = 5.5 Hz), 76.6 (1C, d, J = 5.5 Hz), 55.3, 52.3 (1C, d, J = 8.5 Hz), 47.1, 31.9 (1C, d, J = 5.6 Hz), 22.0, 21.6, 20.8.

^{31}P NMR (CDCl_3 , 162 MHz): δ = 3.33.

HRMS (ES⁺): calc. for $\text{C}_{28}\text{H}_{31}\text{O}_5\text{N}_2\text{NaPS}$ $[\text{M}+\text{Na}]^+$ 561.1584, found 561.1581.

3u: IR (thin film, $\nu_{\text{max}}/\text{cm}^{-1}$): 3062, 2969, 1600, 1496, 1447, 1352, 1260, 1211, 1164, 1090, 1053, 1003, 974, 913, 887, 818, 750, 706, 657, 639.

^1H NMR (CDCl_3 , 400 MHz): δ = 7.49–7.32 (4H, m, *H1*, *H4*, *H16*), 7.19–6.98 (12H, m, *H2*, *H3*, *H8*, *H9*, *H10*, *H13*, *H15*, *H17*), 6.92 (2H, d, J = 6.6 Hz, *H13*), 6.77 (1H, d, J = 1.3 Hz, *H11*), 4.88 (2H, s, *H12*), 4.32 (2H, d, J = 9.8 Hz, *H7*), 4.23 (2H, dd, J = 11.1, 3.9 Hz, *H6*), 3.72 (2H, dd, J = 20.0, 11.1, *H6*), 2.35 (3H, s, *H18*), 1.14 (3H, s, *H5*), 0.87 (3H, s, *H5*).

^{13}C NMR (CDCl_3 , 101 MHz): δ = 143.7, 136.3 (1C, d, J = 4.8 Hz), 135.7, 132.8, 131.9, 131.4 (1C, d, J = 5.6 Hz), 129.5, 129.1, 128.1, 128.0 (2C), 127.9, 127.6 (2C), 127.5, 127.4, 127.0, 124.3, 119.3 (1C, d, J = 3.1 Hz), 77.3 (2C, d, J = 5.5 Hz), 52.3 (1C, d, J = 5.4 Hz), 50.3, 32.1 (1C, d, J = 5.6 Hz), 32.0, 21.4, 21.1.

^{31}P NMR (CDCl_3 , 162 MHz): δ = 2.16.

HRMS (ES⁺): calc. for $\text{C}_{34}\text{H}_{37}\text{O}_5\text{N}_2\text{BrP}^{32}\text{S}_2$ $[\text{M}+\text{H}]^+$ 727.1059, found 727.1057.

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Supporting Information

YES

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

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- (6) The major regioisomer **3b** could also be assigned via ^1H NMR spectroscopy in which the enamide proton appeared as a singlet, rather than a doublet due to coupling with the phosphorous

atom; in other Brønsted acid adducts, this proton appeared as a doublet in the minor regioisomer (e.g. **3'e**) in the ¹H NMR spectrum of the crude reaction mixture.

- (7) Low temperature single crystal X-ray diffraction data for **3a**, **3b**, **3c** and **7** were collected using a Rigaku Oxford SuperNova diffractometer at 150 K. Raw frame data were reduced using CrysAlisPro and the structures were solved using 'Superflip' [Palatinus, L.; Chapuis, G., *J. Appl. Cryst.* **2007**, *40*, 786] before refinement with CRYSTALS [(a) Parois, P.; Cooper, R. I.; Thompson, A. L., *Chem. Cent. J.* **2015**, 9:30. (b) Cooper, R. I.; Thompson, A. L.; Watkin, D. J., *J. Appl. Cryst.* **2010**, *43*, 1100]. Further details about the refinements, including disorder modelling and restraints, are documented in the CIF; Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 2103193–2103196) and can be obtained via www.ccdc.cam.ac.uk/data_request/cif.
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