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PAPER

Enantioselective Michael addition of 3-aryloxindoles to a vinyl bisphosphonate ester catalyzed by a cinchona alkaloid derived thiourea catalyst†

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A highly enantioselective Michael addition of 3-aryloxindole to vinyl bisphosphonate ester catalyzed by a cinchonidine derived thiourea catalyst has been investigated. The corresponding adducts, containing a chiral quaternary carbon center and geminal bisphosphonate ester fragment at the 3-position of the oxindole, were obtained in moderate to good yields (65–92%) and moderate to good enantioselectivities (up to 92% ee).

Introduction

Recently, the enantioselective synthesis of oxindoles bearing a quaternary chiral center at the 3-position has been of crucial importance and has attracted extensive attention as this structure motif is widely present in numerous biologically and pharmaceutically active natural products and molecules.[1] In this context, various excellent approaches for the asymmetric synthesis of 3,3-disubstituted oxindole derivatives have been reported to date.[2] The most common strategy is through enantioselective halogenation,[3] hydroxylation,[4] amination,[5] aldol and Mannich reactions,[6] allylic alkylation[7] and conjugate addition[8] by using 3-substituted oxindoles as nucleophiles. Moreover, synthesis of optically active 3-acylated oxindoles bearing a quaternary stereocenter can be achieved through a carboxyl migration of *O*-acylated oxindoles mediated by a chiral nucleophilic catalyst.[9]

Geminal bisphosphonates (gem-BPs) are structurally stable pyrophosphate analogues and constitute an important class of pharmacologically active compounds due to their high affinity for hydroxyapatite bone mineral surfaces.[10] Some of them have been used for the prevention and treatment of several bone diseases[11] and as carriers for bone-specific therapeutic agents.[10] Additionally, gem-BP compounds have also shown activity against the *in vitro* proliferation of several protozoan parasites that cause African sleeping sickness, malaria, and others.[12] These important biological activities and potential clinical utility of gem-BPs have stimulated intensive interest in their synthesis. A number of synthetic methods for gem-BPs have been developed in the past decades.[13] Among these, Michael addition of various nucleophiles to electron-deficient and highly reactive tetraalkyl ethylidene bisphosphonates has been proven as one of the most efficient approaches for accessing gem-BPs in good yields.[14] However, catalytic asymmetric approaches for the preparation of optically active gem-BPs are quite limited.[15] Organocatalyzed Michael addition of nucleophiles to vinylphosphonates has been underestimated as a valuable tool for the facile synthesis of optically active gem-BPs. Only four examples, including chiral secondary amine catalysis for unmodified aldehydes or ketones[15a–c] and chiral base-catalysis for β-ketoesters[15d] with vinyl bisphosphonates can be found in the literature.

As part of our ongoing interest in the enantioselective synthesis of chiral 3,3-disubstituted oxindoles, we have developed cinchona alkaloid catalyzed enantioselective chlorination of 3-aryl-*N*-Boc-oxindoles with *N*-chlorosuccinimide (NCS)[3h] and Michael addition of 3-aryl-*N*-Boc-oxindoles with phenyl vinyl sulfone.[8j] Considering that vinyl phosphonates as valuable and unique acceptors have been utilized in many asymmetric conjugate additions,[15,16] we envisioned that cinchona alkaloid catalysts could facilitate the Michael addition of 3-aryl-*N*-Boc-oxindoles to vinyl bisphosphonates to afford the desired adducts bearing a quaternary carbon stereocenter and gem-BP fragment at the 3-position of the oxindole, which have potential biological activity and synthetic potential in organic synthesis. To the best of our knowledge, there are no examples on the organocatalytic asymmetric Michael addition of simple vinyl bisphosphonates to 3-aryl-*N*-Boc-oxindoles. Herein, we wish to report our studies on this subject.

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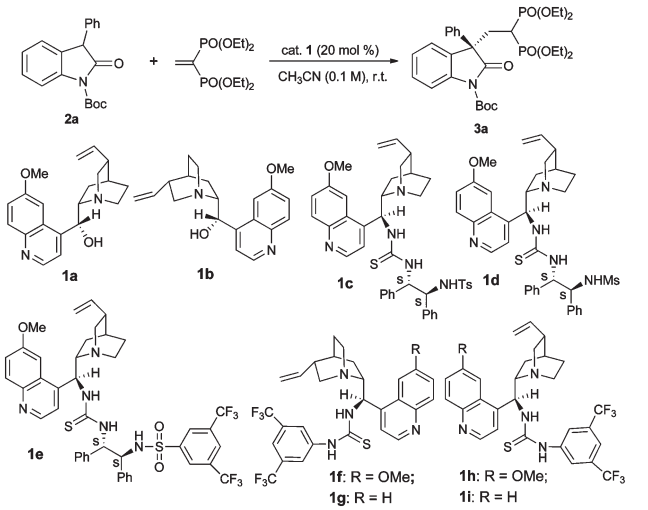
†Electronic supplementary information (ESI) available: NMR spectra of new compounds, HPLC traces for the determination of the enantiomeric excess for compounds **3**, **5**, **6**, **8** and X-ray crystal data of product **3u**. CCDC 867514. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25966d

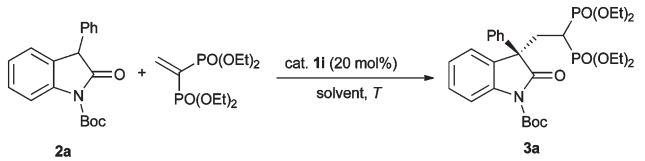
Table 1 Screening of catalysts for the enantioselective Michael addition of oxindoles **2a** to vinyl phosphate[a]



Entry	Cat. **1**	*t* [h]	Yield[b] [%]	ee[c] [%]
1	**1a**	3.5	80	13
2	**1b**	3.5	81	17[d]
3	**1c**	3.5	79	27
4	**1d**	3.5	88	50
5	**1e**	3.5	81	36
6	**1f**	3.5	80	69[d]
7	**1g**	3.5	73	68[d]
8	**1h**	3.5	81	68
9	**1i**	3.5	67	78

[a] All of reactions were carried out with oxindole **2a** (0.2 mmol), vinyl phosphate (0.1 mmol) and catalyst **1** (20 mol%) in CH_3CN (1.0 mL) at room temperature. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Opposite enantiomer was obtained.

Table 2 Optimization reaction conditions using cat. **1i** as the catalyst for enantioselective Michael addition of oxindole **2a** to vinyl phosphate[a]



Entry	Solvent	*T* (°C)	*t* [h]	Yield[b] [%]	ee[c] [%]
1	CH_3CN	r.t.	3.5	67	78
2	Acetone	r.t.	3.5	77	64
3	CH_3OH	r.t.	3.5	73	47
4	DMF	r.t.	3.5	81	20
5	DCM	r.t.	3.5	81	73
6	$CHCl_3$	r.t.	3.5	85	64
7	EtOAc	r.t.	3.5	85	44
8	Et_2O	r.t.	3.5	83	46
9	THF	r.t.	3.5	84	35
10[d]	CH_3CN	r.t	3.5	79	79
11[e]	CH_3CN	r.t	3.5	78	72
12[f]	CH_3CN	r.t	3.5	82	73
13[d,g]	CH_3CN	r.t	3.5	78	77
14[d]	CH_3CN	0	3.5	83	81
15[d]	CH_3CN	−10	3.5	75	87
16[d]	CH_3CN	−15	3.5	82	89
17[d]	CH_3CN	−20	3.5	84	88
18[d]	CH_3CN	−40	3.5	74	82
19[d,h]	CH_3CN	−15	3.5	80	85
20[d,i]	CH_3CN	−15	3.5	84	88
21[d,j]	CH_3CN	−15	3.5	78	80

[a] All of reactions were carried out with oxindole **2a** (0.2 mmol), vinyl phosphate (0.1 mmol) and catalyst **1i** (20 mol%) in solvent (1.0 mL). [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] 2.0 mL of CH_3CN was used. [e] 3.0 mL of CH_3CN was used. [f] 4.0 mL of CH_3CN was used. [g] The ratio of oxindole **2a** : vinyl phosphate is 1.2 : 1. [h] 30 mg of 4 Å molecular sieves were added. [i] 30 mg of 3 Å molecular sieves were added. [j] 10 mol% of catalyst **1i** was used.

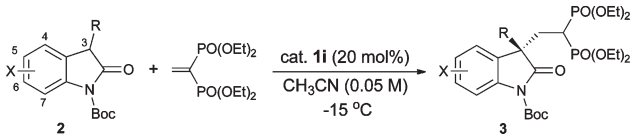
Results and discussion

Initial studies were carried out by using the reaction between 3-phenyl-*N*-Boc oxindole **2a** and tetraethyl vinylbisphosphonate in acetonitrile at room temperature as a model reaction in the presence of a variety of cinchona alkaloid derived organocatalysts to determine the optimal conditions and the results of these experiments are summarized in Table 1. Using naturally available quinine **1a** or quinidine **1b** as catalyst, the reactions took place smoothly and the desired product **3a** was obtained in good yields and low enantioselectivities (Table 1, entries 1 and 2). The cinchona alkaloid derived bifunctional amine-thiourea catalysts bearing sulfonamide with multiple hydrogen-bonding donors **1c–e**, which had shown good catalytic activity in the Michael addition of *N*-Boc-3-aryloxindole to phenyl vinyl sulfone,[8j] only showed moderate catalytic activity in this reaction, affording **3a** in good yields with moderate enantioselectivities (Table 1, entries 3–5). Further evaluation of cinchona alkaloid derived amine-thiourea catalysts **1f–i** (Table 1, entries 6–9) revealed that cinchonidine derived thiourea **1i** was the best catalyst for this reaction, furnishing **3a** in 67% yield and 78% ee (Table 1, entry 9).

Having established a catalytic system, extensive screenings for the improvement of the reaction outcome were carried out and the results are shown in Table 2. In addition to acetonitrile, other solvents were also examined (Table 2, entries 1–9). To our disappointment, the results were unsatisfactory in all cases except for using dichloromethane which gave a higher yield, but with a slightly lower enantioselectivity (Table 2, entry 5). Changing the concentration from 0.1 to 0.05 M can improve the yield along with a similar enantioselectivity (Table 2, entries 10 *vs.* 1). Further lowering the concentration, the yields did not change but the ee's decreased significantly (Table 2, entries 11–12). Moreover, changing the ratio of oxindole **2a** : vinyl phosphonate from 2 : 1 to 1.2 : 1, the ee value decreased slightly. Further examination of the temperature effect revealed that lowering the reaction temperature could significantly improve the ee's of **3a** without sacrificing the yields (Table 2, entries 14–18). The best enantioselectivity for **3a** was obtained in acetonitrile at −15 °C. Further lowering the temperature, the ee decreased rather than increased. Studies on the effect of additives suggested that addition of 4 Å or 3 Å molecular sieves could not further improve the enantioselectivities of **3a** (Table 2, entries 19–20). However, reducing catalyst loading to 10 mol% led to a lower yield of **3a** along with lower enantioselectivity (Table 2, entry 21).

With the optimized reaction conditions in hand, the substrate scope of this reaction has been investigated by carrying out a

Table 3 Enantioselective Michael addition of various oxindoles **2** to vinyl phosphonate[a]



Entry	2	X	R	3	*t* [h]	Yield[b] [%]	ee[c] [%]
1	**2a**	H	Ph	**3a**	3.5	82	89
2	**2b**	5-F	Ph	**3b**	3.5	85	87
3	**2c**	5-Me	Ph	**3c**	3.5	88	89
4	**2d**	5-OMe	Ph	**3d**	3.5	88	89
5	**2e**	5-Br	Ph	**3e**	3.5	72	83
6	**2f**	6-MeO	Ph	**3f**	3.5	84	80
7	**2g**	6-Br	Ph	**3g**	3.5	75	84
8	**2h**	6-Cl	Ph	**3h**	3.5	84	81
9	**2i**	H	*p*-FC_6H_4	**3i**	3.5	84	86
10	**2j**	5-F	*p*-FC_6H_4	**3j**	3.5	76	85
11	**2k**	5-Me	*p*-FC_6H_4	**3k**	3.5	92	84
12	**2l**	5-OMe	*p*-FC_6H_4	**3l**	3.5	77	89
13	**2m**	H	*p*-MeC_6H_4	**3m**	3.5	76	83
14	**2n**	5-F	*p*-MeC_6H_4	**3n**	3.5	79	89
15	**2o**	5-Me	*p*-MeC_6H_4	**3o**	3.5	86	87
16	**2p**	5-OMe	*p*-MeC_6H_4	**3p**	3.5	65	90
17	**2q**	H	2-naphthyl	**3q**	3.5	75	83
18	**2r**	5-F	*m*-MeC_6H_4	**3r**	3.5	89	90
19	**2s**	H	3,5-$Me_2C_6H_3$	**3s**	3.5	66	92
20	**2t**	H	*m*-FC_6H_4	**3t**	3.5	82	85
21[d]	**2u**	H	*m*-$MeOC_6H_4$	**3u**	3.5	88(75)	88(99)
22	**2v**	5-F	*o*-MeC_6H_4	**3v**	48	trace	n.d.
23	**2w**	H	Me	**3w**	3.5	77	23
24	**2x**	H	Bn	**3x**	10	57	50

[a] All of the reactions were carried out with oxindole **2** (0.2 mmol), vinyl phosphate (0.1 mmol) and catalyst **1i** (20 mol%) in CH_3CN (2.0 mL) at −15 °C. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The data in parentheses were obtained after recrystallization.

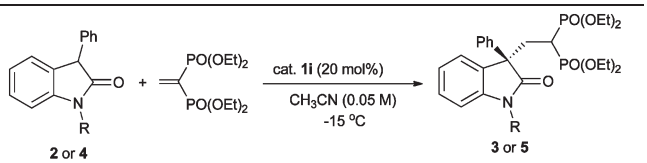
range of reactions, in which both the X and R in oxindole **2** were varied (Table 3). For *N*-Boc-3-phenyl substituted oxindole, substituents in both 5- and 6-positions were well tolerated and the corresponding adducts were obtained in good yields (72–88%) with good enantioselectivities (80–89% ee) (Table 3, entries 1–8). Substrates having substituents at the 6-position gave the products in slightly lower enantioselectivities than those of the corresponding substrates without substituent or having substituents at the 5-position (Table 3, entries 6–8 *vs.* 1–5). Further investigation of the substituent at the C-3 position revealed that the presence of a *para*-substituted aryl group led to a smooth reaction, giving adducts in good yields and ee's (Table 3, entries 8–16). Substrate **2q**, bearing a bulky 2-naphthyl group at the C-3 position of the oxindole, also gave the corresponding product **3q** in reasonable yield and good enantioselectivity (Table 3, entry 17). In the case of 3-(*meta*-substituted aryl group) substituted oxindoles **2r–2u**, the corresponding products were obtained in the best yields and enantioselectivities (Table 3, entries 18–21). The enantiopurity of the adduct **3u** could be enhanced to 99% ee by simple recrystallization with petroleum ether–ethyl acetate (Table 3, entry 21). However, as for 3-(*o*-tolyl)-substituted oxindole **2v**, the reaction was sluggish and only a trace of desired product **3v** was afforded even after prolonging the reaction time to 48 h, presumably due to steric hindrance (Table 3, entry 22). It should be noted that 3-alkyloxindoles **2w** and **2x** are not suitable substrates for this Michael addition, affording the corresponding adducts **3w** and **3x** in moderate yields along with lower enantioselectivities (Table 3, entries 23 and 24).

In order to investigate the effect of *N*-protecting group on this reaction, several 3-phenyl oxindoles with different *N*-protecting groups were subjected to this reaction under the standard conditions and the results are summarized in Table 4. Different from *N*-Boc oxindole **2a** (Table 4, entry 1), using *N*-unprotected oxindole **4a**, *N*-methyl substituted oxindole **4b** and *N*-benzyl substituted oxindole **4c** as the corresponding substrates, the reactions became sluggish (Table 4, entries 2–4). *N*-Acetyl protected oxindoles **4d** gave the corresponding product **5d** in moderate yield along with a lower ee value (Table 4, entry 5). However, *N*-ethoxycarbonyl and *N*-Cbz protected oxindoles **4e** and **4f** led to good yields with moderate enantioselectivities, thus indicating that the presence of a *N*-bulky carbonate-protecting group is crucial for a satisfactory yield and stereochemical outcome (Table 4, entries 6 and 7).

The absolute configuration was determined to be *R* by X-ray crystal structure analysis of the optically active adduct **3u** (Fig. 1, also see the ESI†).[17] The configurations of other adducts were deduced by analogy.

On the basis of the above results and commonly accepted mechanism, a plausible transition-state model is proposed as shown in Scheme 1. *N*-Boc-3-aryl substituted oxindole **2a** would

Table 4 Enantioselective Michael addition of various oxindoles **4** to vinyl phosphonate[a]



Entry	2, 4	R	3, 5	*t* [h]	Yield[b] [%]	ee[c] [%]
1	**2a**	Boc	**3a**	3.5	82	89
2	**4a**	H	**5a**	48	Trace	n.d.
3	**4b**	CH_3	**5b**	48	Trace	n.d.
4	**4c**	Bn	**5c**	48	36	33
5	**4d**	Ac	**5d**	3.5	70	13
6	**4e**	COOEt	**5e**	3.5	67	69
7	**4f**	Cbz	**5f**	3.5	83	57

[a] All of reactions were carried out with oxindole **2** or **4** (0.2 mmol), vinyl phosphate (0.1 mmol) and catalyst **1i** (20 mol%) in CH_3CN (2.0 mL) at −15 °C. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase.

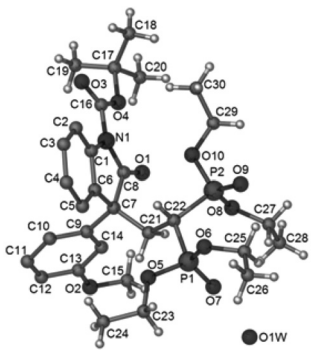
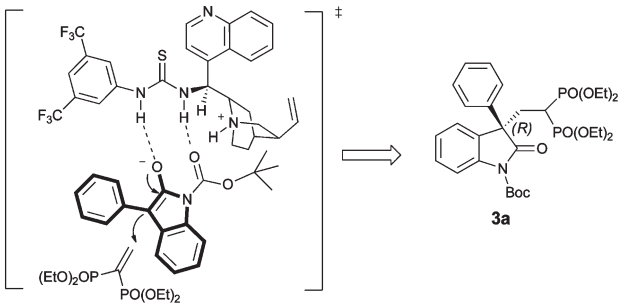


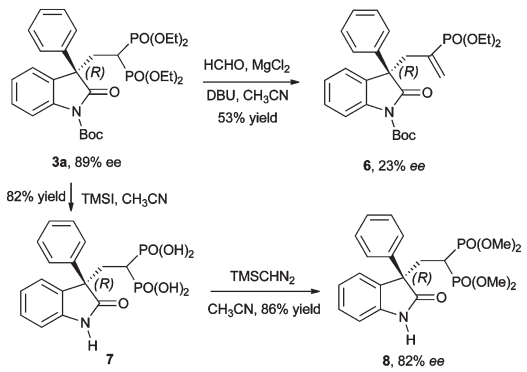
Fig. 1 X-ray crystal structure of compound **3u**.

be activated by tertiary amine-thiourea **1i** in a bifunctional mode and the enolized oxindole attacks the vinyl bisphosphonate ester from *Si*-face, affording the corresponding adduct with *R* configuration.

Our initial attempts to generate functionalized vinyl phosphonate **6** by Horner–Wadsworth–Emmons reaction of adduct **3a** with formaldehyde were unsuccessful because retro-Michael addition/aldol reaction occurred in the presence of various bases.[18] Although after several trials, vinyl phosphonate **6** can be obtained from adduct **3a** in moderate yield in the presence of DBU and magnesium chloride,[19] the ee decreased dramatically due to an inevitable partial retro-Michael reaction. Considering the wide applications of bisphosphonic acids in the therapy of most bone diseases, the tetraethyl ester **3a** was converted into the corresponding bisphosphonic acid **7** through cleavage of the *N*-Boc and the tetraethyl group of the BP moiety by treating with iodotrimethylsilane (TMSI) in good yield with comparable enantioselectivity. The ee value of bisphosphonic acid **7** was determined from tetramethyl bisphosphonate **8**, which was obtained by esterification of **7** with trimethylsilyl diazomethane ($TMSCHN_2$) in good yield (Scheme 2).



Scheme 1 Proposed transition-state model.



Scheme 2 Transformations of Michael adduct **3a**.

Conclusions

In conclusion, we have developed the first example of an asymmetric Michael addition of *N*-Boc-3-aryloxindole to tetraethyl vinylbisphosphonate catalyzed by a cinchonidine derived thiourea catalyst. High yields (up to 92%) and good enantioselectivities (80–92% ee's) were obtained under optimal conditions for a wide range of *N*-Boc-3-aryloxindole. Furthermore, the bisphosphonate adducts can be easily hydrolyzed to the corresponding acids, which provided a protocol to easily access a class of new optically active gem-BP derivatives containing a tetra-substituted oxindole fragment.

Experimental section

General remarks

NMR spectra were recorded with a Bruker AVANCE III 400 and 300 MHz spectrometer with solutions in $CDCl_3$ or d_6-DMSO and tetramethylsilane (TMS) as an internal standard; *J* values are reported in Hz. IR spectra were recorded with a Bio-Rad FTS-185 spectrometer. Chiral HPLC was performed with a SHIMADZU SPD-10A series instrument with chiral columns. Optical rotations were determined at 589 nm (sodium D line) using a Perkin-Elmer-341 MC digital polarimeter; $[a]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}. MS and HRMS (EI, ESI) were measured with a Finnigan MA^+ instrument. Flash column chromatography was performed using silica gel (300–400 mesh). Melting points are uncorrected. Unless otherwise noted, all commercially obtained reagents were used

without further purification. All reactions were carried out under air in a closed system. Catalysts **1c–e**,[8j] **1f–i**,[20] substrate **2**,[3d,h] **4**[8h] and tetraethyl vinylbisphosphonate[21] were prepared using literature method.

General procedure for the Michael addition of 3-aryloxindole to tetraethyl ethylidene bisphosphonate

To a solution of tetraethyl vinylbisphosphonate (0.1 mmol) in CH_3CN (2.0 mL) was added thiourea catalyst **1i** (11.3 mg, 0.02 mmol) with stirring. After the mixture was cooled to −15 °C (bath temperature) for 20 min, oxindole **2** (0.2 mmol) was added. The resulting mixture was stirred at −15 °C for 3.5–48 h (monitored by TLC until no vinyl bisphosphonate remained), concentrated, and purified by silica gel column chromatography to give compound **3**.

(*R*)-*tert*-Butyl 3-(2,2-bis(diethoxyphosphoryl)ethyl)-2-oxo-3-phenylindoline-1-carboxylate 3a. Yield: 49.8 mg (82%). Colorless oil. $[\alpha]_D^{20}$ = +57.7 (*c* = 1.24, CH_2Cl_2) (89% ee); Chiralpak AD-H, hexane–isopropanol = 90 : 10, 0.8 mL min^{-1}, 254 nm, t_{minor} = 8.07 min, t_{major} = 13.15 min; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.0 Hz, 1H), 7.42–7.37 (m, 2H), 7.31–7.23 (m, 6H), 4.20–3.95 (m, 8H), 3.40–3.30 (m, 1H), 3.00–2.85 (m, 1H), 2.30–2.18 (m, 1H), 1.59 (s, 9H), 1.34–1.23 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 149.3, 141.6, 140.6, 128.9, 128.5, 128.2, 127.6, 126.9, 126.4, 124.2, 115.4, 84.0, 62.9–62.5 (m), 56.2–56.1 (m), 33.8 (t, *J* = 134.4 Hz), 32.7 (t, *J* = 4.2 Hz), 28.0, 16.4–16.2 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.0, 22.7; IR (film) ν 1793, 1770, 1729, 1348, 1264, 1247, 1149, 1021 cm^{-1}; HRMS (ESI) Calcd for $C_{29}H_{41}NNaO_9P_2$ $[M + Na]^+$: 632.2154; found: 632.2155.

(*R*)-*tert*-Butyl 3-(2,2-bis(diethoxyphosphoryl)ethyl)-5-fluoro-2-oxo-3-phenylindoline-1-carboxylate 3b. Yield: 51.7 mg (85%). Colorless oil. $[\alpha]_D^{20}$ = +55.3 (*c* = 2.4, CH_2Cl_2) (87% ee); Chiralpak AD-H, hexane–isopropanol = 90 : 10, 0.8 mL min^{-1}, 254 nm, t_{minor} = 10.18 min, t_{major} = 14.20 min; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.8, 4.4 Hz, 1H), 7.32–7.24 (m, 5H), 7.14–7.08 (m, 2H), 4.21–4.00 (m, 8H), 3.39–3.29 (m, 1H), 2.97–2.82 (m, 1H), 2.26–2.12 (m, 1H), 1.59 (s, 9H), 1.34–1.26 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 159.6 (d, *J* = 242.7 Hz), 149.2, 140.9, 136.6 (d, *J* = 2.4 Hz), 130.2 (d, *J* = 8.0 Hz), 128.7, 127.9, 126.7, 116.7 (d, *J* = 8.6 Hz), 115.6 (d, *J* = 22.7 Hz), 113.7 (d, *J* = 23.6 Hz), 84.3, 63.0–62.6 (m), 56.5–56.4 (m), 33.7 (t, *J* = 134.5 Hz), 32.7 (t, *J* = 4.2 Hz), 28.0, 16.3–16.1 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.6, 22.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −117.4; IR (film) ν 1793, 1772, 1727, 1482, 1369, 1345, 1296, 1248, 1146, 1019 cm^{-1}; HRMS (ESI) Calcd for $C_{29}H_{41}FNO_9P_2$ $[M + H]^+$: 628.2241; found: 628.2237.

(*R*)-*tert*-Butyl 3-(2,2-bis(diethoxyphosphoryl)ethyl)-5-methyl-2-oxo-3-phenylindoline-1-carboxylate 3c. Yield: 50.1 mg (88%). Colorless oil. $[\alpha]_D^{20}$ = +56.5 (*c* = 2.73, CH_2Cl_2) (89% ee); Chiralpak AD-H, hexane–isopropanol = 90 : 10, 0.8 mL min^{-1}, 254 nm, t_{minor} = 8.80 min, t_{major} = 12.12 min; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.30–7.23 (m, 5H), 7.20–7.17 (m, 2H), 4.21–3.97 (m, 8H), 3.41–3.28 (m, 1H), 2.97–2.86 (m, 1H), 2.39 (s, 3H), 2.33–2.20 (m, 1H), 1.59 (s, 9H), 1.34–1.24 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 149.4, 141.8, 138.3, 133.8, 129.5, 128.5, 128.2, 127.6, 126.9, 126.8, 115.2, 83.9, 62.8–62.5 (m), 56.3–56.2 (m), 33.8 (t, *J* = 135.0 Hz), 32.7 (t, *J* = 4.4 Hz), 28.0, 21.1, 16.4–16.3 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.1, 22.8; IR (film) ν 1792, 1769, 1727, 1489, 1370, 1339, 1264, 1247, 1153, 1021 cm^{-1}; HRMS (ESI) Calcd for $C_{30}H_{43}NNaO_9P_2$ $[M + Na]^+$: 646.2311; found: 646.2315.

(*R*)-*tert*-Butyl 3-(2,2-bis(diethoxyphosphoryl)ethyl)-5-methoxy-2-oxo-3-phenylindoline-1-carboxylate 3d. Yield: 56.7 mg (88%). Colorless oil. $[\alpha]_D^{20}$ = +55.7 (*c* = 1.98, CH_2Cl_2) (89% ee); Chiralpak AD-H, hexane–isopropanol = 90 : 10, 1.0 mL min^{-1}, 254 nm, t_{minor} = 8.86 min, t_{major} = 12.61 min; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.8 Hz, 1H), 7.31–7.23 (m, 5H), 6.99 (d, *J* = 2.8 Hz, 1H), 6.92 (dd, *J* = 8.8, 2.8 Hz, 1H), 4.20–4.00 (m, 8H), 3.84 (s, 3H), 3.41–3.30 (m, 1H), 2.98–2.84 (m, 1H), 2.30–2.14 (m, 1H), 1.59 (s, 9H), 1.35–1.23 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 156.6, 149.4, 141.5, 133.9, 129.4, 128.6, 127.6, 126.9, 116.3, 114.4, 112.0, 83.8, 62.9–62.5 (m), 56.7–56.6 (m), 55.6, 33.6 (t, *J* = 134.9 Hz), 32.5 (t, *J* = 3.6 Hz), 28.0, 16.4–16.2 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.3, 22.9; IR (film) ν 1794, 1770, 1724, 1488, 1369, 1298, 1277, 1245, 1150, 1016 cm^{-1}; MS (EI): *m*/*z* 639 (M^+, 1%), 539 (11), 288 (43), 239 (100), 210 (33), 171 (27), 163 (33), 135 (16), 57 (16); HRMS (EI) Calcd for $C_{30}H_{43}NO_{10}P_2$ $[M]^+$: 639.2362; found: 639.2366.

(*R*)-*tert*-Butyl 3-(2,2-bis(diethoxyphosphoryl)ethyl)-5-bromo-2-oxo-3-phenylindoline-1-carboxylate 3e. Yield: 49.2 mg (72%). Colorless oil. $[\alpha]_D^{20}$ = +50.6 (*c* = 1.07, CH_2Cl_2) (83% ee); Chiralpak AD-H, hexane–isopropanol = 90 : 10, 0.8 mL min^{-1}, 254 nm, t_{minor} = 10.13 min, t_{major} = 12.69 min; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.8 Hz, 1H), 7.56–7.50 (m, 2H), 7.36–7.25 (m, 5H), 4.21–4.01 (m, 8H), 3.38–3.28 (m, 1H), 2.97–2.82 (m, 1H), 2.24–2.09 (m, 1H), 1.59 (s, 9H), 1.34–1.27 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 149.1, 140.8, 139.7, 132.0, 130.6, 129.3, 128.8, 127.9, 126.8, 117.3, 117.0, 84.5, 63.0–62.7 (m), 56.3–56.2 (m), 33.8 (t, *J* = 134.4 Hz), 32.7 (t, *J* = 3.5 Hz), 28.0, 16.4–16.3 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.6, 22.6; IR (film) ν 1775, 1731, 1473, 1369, 1336, 1294, 1270, 1245, 1152, 1021 cm^{-1}; HRMS (ESI) Calcd for $C_{29}H_{41}BrNO_9P_2$ $[M + H]^+$: 688.1440; found: 688.1441.

(*R*)-*tert*-Butyl 3-(2,2-bis(diethoxyphosphoryl)ethyl)-6-methoxy-2-oxo-3-phenylindoline-1-carboxylate 3f. Yield: 53.5 mg (84%). Colorless oil. $[\alpha]_D^{20}$ = +59.6 (*c* = 1.56, CH_2Cl_2) (80% ee); Chiralpak AD-H, hexane–isopropanol = 90 : 10, 0.8 mL min^{-1}, 254 nm, t_{minor} = 12.08 min, t_{major} = 20.12 min; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 2.4 Hz, 1H), 7.32–7.22 (m, 6H), 6.81 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.21–4.00 (m, 8H), 3.88 (s, 3H), 3.40–3.28 (m, 1H), 2.94–2.80 (m, 1H), 2.31–2.19 (m, 1H), 1.59 (s, 9H), 1.35–1.24 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 160.2, 149.3, 142.0, 141.6, 128.5, 127.6, 127.1, 126.9, 119.7, 110.0, 101.9, 84.0, 62.9–62.5 (m), 55.9–55.8 (m), 55.5, 33.8 (t, *J* = 134.8 Hz), 32.8 (t, *J* = 4.1 Hz), 28.0, 16.4–16.2 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.1, 22.8; IR (film) ν 1797, 1772, 1726, 1614, 1494, 1347, 1245, 1147, 1016 cm^{-1}; HRMS (ESI) Calcd for $C_{30}H_{44}NO_{10}P_2$ $[M + H]^+$: 640.2440; found: 640.2434.

(*R*)-*tert*-Butyl 3-(2,2-bis(diethoxyphosphoryl)ethyl)-6-bromo-2-oxo-3-phenylindoline-1-carboxylate 3g. Yield: 51.6 mg (75%). Colorless oil. $[\alpha]_D^{20}$ = +47.5 (*c* = 1.08, CH_2Cl_2) (84% ee); Chiralpak AD-H, hexane–isopropanol = 90 : 10, 0.8 mL min^{-1}, 254 nm, t_{minor} = 9.44 min, t_{major} = 12.58 min; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 1.6 Hz, 1H), 7.42 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.31–7.25 (m, 6H), 4.22–3.97 (m, 8H), 3.38–3.30 (m, 1H), 2.99–2.88 (m, 1H), 2.26–2.11 (m, 1H), 1.59 (s, 9H), 1.34–1.24 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 149.1, 141.7, 140.9, 128.7, 127.9, 127.7, 127.2, 126.7, 122.7, 118.8, 84.6, 63.0–62.5 (m), 56.1–56.0 (m), 33.7 (t, *J* = 133.4 Hz), 32.6 (t, *J* = 3.8 Hz), 27.9, 16.4–16.2 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.8, 22.6; IR (film) ν 1775, 1729, 1601, 1475, 1343, 1243, 1148, 1017 cm^{-1}; HRMS (ESI) Calcd for $C_{29}H_{41}BrNO_9P_2$ $[M + H]^+$: 688.1440; found: 688.1440.

(*R*)-*tert*-Butyl 3-(2,2-bis(diethoxyphosphoryl)ethyl)-6-chloro-2-oxo-3-phenylindoline-1-carboxylate 3h. Yield: 54.2 mg (84%). Colorless oil. $[\alpha]_D^{20}$ = +51.5 (*c* = 2.71, CH_2Cl_2) (81% ee); Chiralpak AD-H, hexane–isopropanol = 90 : 10, 0.8 mL min^{-1}, 254 nm, t_{minor} = 8.83 min, t_{major} = 12.11 min; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 1.6 Hz, 1H), 7.33–7.25 (m, 7H), 4.18–3.97 (m, 8H), 3.39–3.30 (m, 1H), 2.98–2.87 (m, 1H), 2.34–2.06 (m, 1H), 1.59 (s, 9H), 1.35–1.24 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 149.1, 141.5, 141.0, 134.7, 128.6, 127.8, 127.3, 126.7, 126.6, 124.3, 116.1, 84.6, 63.0–62.5 (m), 56.0–55.9 (m), 33.7 (t, *J* = 135.2 Hz), 32.7 (t, *J* = 3.9 Hz), 27.9, 16.4–16.2 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.8, 22.6; IR (film) ν 1776, 1729, 1605, 1476, 1344, 1246, 1147, 1016 cm^{-1}; HRMS (ESI) Calcd for $C_{29}H_{41}ClNO_9P_2$ $[M + H]^+$: 644.1945; found: 644.1949.

(*R*)-*tert*-Butyl 3-(2,2-bis(diethoxyphosphoryl)ethyl)-3-(4-fluorophenyl)-2-oxoindoline-1-carboxylate 3i. Yield: 52.4 mg (84%). Colorless oil. $[\alpha]_D^{20}$ = +56.8 (*c* = 2.63, CH_2Cl_2) (86% ee); Chiralpak AD-H, hexane–isopropanol = 90 : 10, 1.0 mL min^{-1}, 254 nm, t_{minor} = 7.72 min, t_{major} = 18.17 min; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.8 Hz, 1H), 7.43–7.36 (m, 2H), 7.29–7.24 (m, 3H), 6.96 (t, *J* = 8.8 Hz, 2H), 4.20–4.08 (m, 8H), 3.36–3.28 (m, 1H), 2.95–2.81 (m, 1H), 2.27–2.14 (m, 1H), 1.60 (s, 9H), 1.37–1.23 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 162.2 (d, *J* = 245.4 Hz), 149.2, 140.6, 137.3 (d, *J* = 3.1 Hz), 129.1, 128.7 (d, *J* = 8.0 Hz), 128.0, 126.3, 124.3, 115.5, 115.3 (d, *J* = 20.9 Hz), 84.2, 62.9–62.5 (m), 55.7–55.6 (m), 33.8 (t, *J* = 134.4 Hz), 33.0 (t, *J* = 3.6 Hz), 28.0, 16.4–16.2 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.9, 22.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.8; IR (film) ν 1795, 1771, 1728, 1506, 1480, 1347, 1244, 1148, 1018 cm^{-1}; HRMS (ESI) Calcd for $C_{29}H_{40}FNNaO_9P_2$ $[M + Na]^+$: 650.2060; found: 650.2061.

(*R*)-*tert*-Butyl 3-(2,2-bis(diethoxyphosphoryl)ethyl)-5-fluoro-3-(4-fluorophenyl)-2-oxoindoline-1-carboxylate 3j. Yield: 49.0 mg (76%). Colorless oil. $[\alpha]_D^{20}$ = +60.2 (*c* = 2.45, CH_2Cl_2) (85% ee); Chiralpak AD-H, hexane–isopropanol = 90 : 10, 0.8 mL min^{-1}, 254 nm, t_{minor} = 9.73 min, t_{major} = 21.90 min; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (q, *J* = 4.8 Hz, 1H), 7.29–7.24 (m, 2H), 7.15–7.09 (m, 2H), 6.99 (t, *J* = 8.8 Hz, 2H), 4.21–4.01 (m, 8H), 3.37–3.25 (m, 1H), 2.93–2.78 (m, 1H), 2.22–2.09 (m, 1H), 1.59 (s, 9H), 1.34–1.26 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 162.3 (d, *J* = 246.8 Hz), 159.6 (d, *J* = 242.6 Hz), 149.2, 136.60 (d, *J* = 3.6 Hz), 136.56 (d, *J* = 4.4 Hz), 129.9 (d, *J* = 7.9 Hz), 128.6 (d, *J* = 8.9 Hz), 116.8 (d, *J* = 7.8 Hz), 115.8 (d, *J* = 22.5 Hz), 115.5 (d, *J* = 21.0 Hz), 113.7 (d, *J* = 23.9 Hz), 84.4, 63.0–62.6 (m), 55.9–55.8 (m), 33.7 (t, *J* = 135.1 Hz), 33.0 (t, *J* = 3.5 Hz), 27.9, 16.3–16.1 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.6, 22.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.3, −117.2; IR (film) ν 1794, 1772, 1729, 1507, 1484, 1344, 1297, 1246, 1146, 1015 cm^{-1}; MS (EI): *m/z* 639 (M^+, 1%), 288 (12), 245 (100), 216 (39), 171 (20), 163 (23), 135 (10), 57 (12); HRMS (EI) Calcd for $C_{29}H_{39}F_2NO_9P_2$ $[M]^+$: 645.2068; found: 645.2069.

(*R*)-*tert*-Butyl 3-(2,2-bis(diethoxyphosphoryl)ethyl)-3-(4-fluorophenyl)-5-methyl-2-oxoindoline-1-carboxylate 3k. Yield: 58.8 mg (92%). Colorless oil. $[\alpha]_D^{20}$ = +66.8 (*c* = 3.05, CH_2Cl_2) (84% ee); Chiralpak AD-H, hexane–isopropanol = 90 : 10, 0.8 mL min^{-1}, 254 nm, t_{minor} = 8.95 min, t_{major} = 17.46 min; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.4 Hz, 1H), 7.29–7.25 (m, 2H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.16 (s, 1H), 6.96 (t, *J* = 8.8 Hz, 2 H), 4.20–3.97 (m, 8H), 3.37–3.25 (m, 1H), 2.93–2.78 (m, 1H), 2.40 (s, 3H), 2.28–2.15 (m, 1H), 1.59 (s, 9H), 1.34–1.24 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 162.2 (d, *J* = 245.7 Hz), 149.3, 138.2, 137.4 (d, *J* = 2.7 Hz), 134.0, 129.7, 128.7 (d, *J* = 7.9 Hz), 127.9, 126.8, 115.32 (d, *J* = 21.1 Hz), 115.28, 84.1, 62.9–62.5 (m), 55.8–55.6 (m), 33.8 (t, *J* = 134.9 Hz), 32.9 (t, *J* = 4.0 Hz), 28.0, 21.1, 16.4–16.2 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.1, 22.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.9; IR (film) ν 1793, 1770, 1728, 1506, 1490, 1338, 1245, 1152, 1017 cm^{-1}; HRMS (ESI) Calcd for $C_{30}H_{42}FNNaO_9P_2$ $[M + Na]^+$: 664.2217; found: 664.2220.

(*R*)-*tert*-Butyl 3-(2,2-bis(diethoxyphosphoryl)ethyl)-3-(4-fluorophenyl)-5-methoxy-2-oxoindoline-1-carboxylate 3l. Yield: 50.2 mg (77%). Colorless oil. $[\alpha]_D^{20}$ = +45.5 (*c* = 1.83, CH_2Cl_2) (89% ee); Chiralpak AD-H, hexane–isopropanol = 85 : 15, 1.0 mL min^{-1}, 254 nm, t_{minor} = 7.02 min, t_{major} = 12.72 min; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.8 Hz, 1H), 7.29–7.26 (m, 2H), 6.99–6.91 (m, 4H), 4.19–3.99 (m, 8H), 3.84 (s, 3H), 3.38–3.25 (m, 1H), 2.93–2.79 (m, 1H), 2.27–2.12 (m, 1H), 1.59 (s, 9H), 1.35–1.25 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 162.2 (d, *J* = 245.6 Hz), 156.7, 149.3, 137.2 (d, *J* = 2.9 Hz), 133.8, 129.1, 128.7 (d, *J* = 7.9 Hz), 116.4, 115.3 (d, *J* = 20.9 Hz), 114.5, 112.0, 84.0, 62.9–62.5 (m), 56.1–56.0 (m), 55.6, 33.6 (t, *J* = 134.8 Hz), 32.7 (t, *J* = 3.8 Hz), 28.0, 16.4–16.1 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.2, 22.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.7; IR (film) ν 1791, 1769, 1726, 1507, 1490, 1265, 1247, 1151, 1021 cm^{-1}; HRMS (ESI) Calcd for $C_{30}H_{42}FNNaO_{10}P_2$ $[M + Na]^+$: 680.2166; found: 680.2169.

(*R*)-*tert*-Butyl 3-(2,2-bis(diethoxyphosphoryl)ethyl)-2-oxo-3-(*p*-tolyl)indoline-1-carboxylate 3m. Yield: 47.1 mg (76%). Colorless oil. $[\alpha]_D^{20}$ = +51.8 (*c* = 2.56, CH_2Cl_2) (83% ee); Chiralpak AD-H, hexane–isopropanol = 90 : 10, 0.8 mL min^{-1}, 254 nm, t_{minor} = 8.05 min, t_{major} = 17.60 min; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.4 Hz, 1H), 7.40–7.35 (m, 2H), 7.27–7.23 (m, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 4.20–3.95 (m, 8H), 3.38–3.29 (m, 1H), 2.97–2.83 (m, 1H), 2.29–2.18 (m, 1H), 1.59 (s, 9H), 1.32–1.23 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 149.4, 140.6, 138.7,

137.4, 129.2, 128.9, 128.5, 126.7, 126.3, 124.2, 115.3, 84.0, 62.9–62.4 (m), 56.0–55.8 (m), 33.8 (t, J = 135.1 Hz), 32.7 (t, J = 3.9 Hz), 28.0, 20.8, 16.4–16.2 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.9, 22.7; IR (film) ν 1796, 1772, 1726, 1509, 1480, 1464, 1347, 1299, 1245, 1148, 1018 cm^{-1}; HRMS (ESI) Calcd for $C_{30}H_{44}FNO_9P_2$ $[M + H]^+$: 624.2491; found: 624.2493.

(*R*)-*tert*-Butyl 3-(2,2-bis(diethoxyphosphoryl)ethyl)-5-fluoro-2-oxo-3-(*p*-tolyl)indoline-1-carboxylate 3n. Yield: 50.3 mg (79%). Colorless oil. $[\alpha]_D^{20}$ = +57.2 (c = 2.25, CH_2Cl_2) (89% ee); Chiralpak AD-H, hexane–isopropanol = 90 : 10, 1.0 mL min^{-1}, 254 nm, t_{minor} = 7.24 min, t_{major} = 17.94 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, J = 8.8, 4.4 Hz, 1H), 7.14–7.04 (m, 6H), 4.18–3.98 (m, 8H), 3.37–3.25 (m, 1H), 2.92–2.77 (m, 1H), 2.28 (s, 3H), 2.24–2.08 (m, 1H), 1.56 (s, 9H), 1.32–1.23 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 159.5 (d, J = 242.5 Hz), 149.3, 138.0, 137.6, 136.5 (d, J = 2.2 Hz), 130.4 (d, J = 8.2 Hz), 129.3, 126.6, 116.6 (d, J = 7.6 Hz), 115.4 (d, J = 22.6 Hz), 113.7 (d, J = 24.5 Hz), 84.2, 62.9–62.5 (m), 56.2–56.1 (m), 33.7 (t, J = 134.5 Hz), 32.6 (t, J = 3.7 Hz), 27.9, 20.8, 16.3–16.1 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.6, 22.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −117.5; IR (film) ν 1772, 1728, 1484, 1345, 1297, 1247, 1146, 1019 cm^{-1}; HRMS (ESI) Calcd for $C_{30}H_{42}FNNaO_9P_2$ $[M + Na]^+$: 664.2217; found: 664.2215.

(*R*)-*tert*-Butyl 3-(2,2-bis(diethoxyphosphoryl)ethyl)-5-methyl-2-oxo-3-(*p*-tolyl)indoline-1-carboxylate 3o. Yield: 54.4 mg (86%). Colorless oil. $[\alpha]_D^{20}$ = +55.4 (c = 2.51, CH_2Cl_2) (87% ee); Chiralpak AD-H, hexane–isopropanol = 90 : 10, 0.8 mL min^{-1}, 254 nm, t_{minor} = 8.45 min, t_{major} = 16.33 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.4 Hz, 1H), 7.17–7.14 (m, 4H), 7.07 (d, J = 8.4 Hz, 2H), 4.19–3.95 (m, 8H), 3.36–3.27 (m, 1H), 2.91–2.79 (m, 1H), 2.37 (s, 3H), 2.28 (s, 3H), 2.30–2.16 (m, 1H), 1.57 (s, 9H), 1.32–1.22 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 149.4, 138.9, 138.2, 137.3, 133.7, 129.3, 129.2, 128.4, 126.7, 115.1, 83.8, 62.8–62.4 (m), 56.0–55.9 (m), 33.7 (t, J = 135.1 Hz), 32.5 (t, J = 4.1 Hz), 28.0, 21.0, 20.8, 16.3–16.2 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.1, 22.9; IR (film) ν 1792, 1770, 1727, 1489, 1338, 1264, 1246, 1153, 1021 cm^{-1}; HRMS (ESI) Calcd for $C_{31}H_{45}FNNaO_9P_2$ $[M + Na]^+$: 660.2467; found: 660.2463.

(*R*)-*tert*-Butyl 3-(2,2-bis(diethoxyphosphoryl)ethyl)-5-methoxy-2-oxo-3-(*p*-tolyl)indoline-1-carboxylate 3p. Yield: 42.3 mg (65%). Colorless oil. $[\alpha]_D^{20}$ = +42.1 (c = 2.04, CH_2Cl_2) (90% ee); Chiralpak AD-H, hexane–isopropanol = 85 : 15, 1.0 mL min^{-1}, 254 nm, t_{minor} = 6.25 min, t_{major} = 12.57 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.8 Hz, 1H), 7.15 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 2.0 Hz, 1H), 6.89 (dd, J = 8.8, 2.4 Hz, 1H), 4.19–3.93 (m, 8H), 3.81 (s, 3H), 3.38–3.26 (m, 1H), 2.94–2.79 (m, 1H), 2.27 (s, 3H), 2.28–2.18 (m, 1H), 1.56 (s, 9H), 1.32–1.22 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 156.6, 149.4, 138.6, 137.4, 133.9, 129.6, 129.2, 126.7, 116.2, 114.2, 111.9, 83.7, 62.9–62.4 (m), 56.4–56.2 (m), 55.5, 33.6 (t, J = 134.8 Hz), 32.5 (t, J = 4.2 Hz), 28.0, 20.8, 16.4–16.1 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.3, 22.9; IR (film) ν 1794, 1771, 1723, 1489, 1369, 1275, 1245, 1151, 1064 cm^{-1}; HRMS (ESI) Calcd for $C_{31}H_{46}NO_{10}P_2$ $[M + H]^+$: 654.2597; found: 654.2599.

(*R*)-*tert*-Butyl 3-(2,2-bis(diethoxyphosphoryl)ethyl)-3-(naphthalen-2-yl)-2-oxoindoline-1-carboxylate 3q. Yield: 49.3 mg (75%). Colorless oil. $[\alpha]_D^{20}$ = +55.7 (c = 2.18, CH_2Cl_2) (83% ee); Chiralpak AD-H, hexane–isopropanol = 85 : 15, 1.0 mL min^{-1}, 254 nm, t_{minor} = 6.16 min, t_{major} = 11.14 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.8 Hz, 1H), 7.80–7.71 (m, 3H), 7.59 (s, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.46–7.42 (m, 4H), 7.32–7.27 (m, 1H), 4.21–3.97 (m, 8H), 3.55–3.42 (m, 1H), 3.09–2.94 (m, 1H), 2.38–2.24 (m, 1H), 1.59 (s, 9H), 1.33–1.25 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 149.3, 140.7, 138.9, 132.9, 132.5, 129.0, 128.5, 128.30, 128.25, 127.3, 126.4, 126.3, 126.1, 125.8, 124.8, 124.3, 115.4, 84.1, 62.9–62.5 (m), 56.4–56.2 (m), 33.8 (t, J = 134.8 Hz), 32.6 (t, J = 4.2 Hz), 28.0, 16.3–16.2 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.9, 22.7; IR (film) ν 1794, 1771, 1728, 1480, 1464, 1343, 1299, 1287, 1245, 1148, 1018 cm^{-1}; HRMS (ESI) Calcd for $C_{33}H_{43}NNaO_9P_2$ $[M + Na]^+$: 682.2311; found: 682.2313.

(*R*)-*tert*-Butyl 3-(2,2-bis(diethoxyphosphoryl)ethyl)-5-fluoro-2-oxo-3-(*m*-tolyl)indoline-1-carboxylate 3r. Yield: 56.8 mg (89%). Colorless oil. $[\alpha]_D^{20}$ = +45.1 (c = 2.73, CH_2Cl_2) (90% ee); Chiralpak AD-H, hexane–isopropanol = 90 : 10, 0.8 mL min^{-1}, 254 nm, t_{minor} = 7.22 min, t_{major} = 9.98 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94–7.90 (m, 1H), 7.17–7.04 (m, 5H), 6.98 (d, J = 7.6 Hz, 1H), 4.20–3.99 (m, 8H), 3.36–3.26 (m, 1H), 2.94–2.79 (m, 1H), 2.29 (s, 3H), 2.21–2.08 (m, 1H), 1.57 (s, 9H), 1.33–1.24 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 159.5 (d, J = 242.8 Hz), 149.3, 140.9, 138.4, 136.6 (d, J = 3.0 Hz), 130.3 (d, J = 8.0 Hz), 128.7, 128.4, 127.4, 123.7, 116.6 (d, J = 7.5 Hz), 115.5 (d, J = 22.5 Hz), 113.8 (d, J = 24.5 Hz), 84.3, 63.0–62.5 (m), 56.4–56.3 (m), 33.7 (t, J = 135.1 Hz), 32.6 (t, J = 3.8 Hz), 28.0, 21.5, 16.4–16.2 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.7, 22.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −117.5; IR (film) ν 1777, 1718, 1483, 1347, 1299, 1246, 1146, 1013 cm^{-1}; HRMS (ESI) Calcd for $C_{30}H_{43}FNO_9P_2$ $[M + H]^+$: 642.2397; found: 642.2396.

(*R*)-*tert*-Butyl 3-(2,2-bis(diethoxyphosphoryl)ethyl)-3-(3,5-dimethylphenyl)-2-oxoindoline-1-carboxylate 3s. Yield: 42.1 mg (66%). White solid. Mp: 56.8–59.1 °C; $[\alpha]_D^{20}$ = +60.2 (c = 1.87, CH_2Cl_2) (92% ee); Chiralpak AD-H, hexane–isopropanol = 90 : 10, 0.8 mL min^{-1}, 254 nm, t_{minor} = 5.95 min, t_{major} = 8.41 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.0 Hz, 1H), 7.41–7.35 (m, 2H), 7.29–7.24 (m, 1H), 6.88 (s, 3H), 4.22–3.95 (m, 8H), 3.38–3.27 (m, 1H), 2.99–2.83 (m, 1H), 2.26–2.12 (m, 1H), 1.60 (s, 9H), 1.35–1.24 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 149.3, 141.5, 140.5, 137.9, 129.3, 128.8, 128.4, 126.4, 124.5, 124.1, 115.2, 83.9, 62.9–62.3 (m), 56.1–56.0 (m), 33.7 (t, J = 134.3 Hz), 32.6 (t, J = 3.9 Hz), 28.0, 21.4, 16.4–16.2 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.1, 22.8; IR (film) ν 1796, 1771, 1727, 1480, 1346, 1244, 1148, 1020 cm^{-1}; HRMS (ESI) Calcd for $C_{31}H_{46}NO_9P_2$ $[M + H]^+$: 638.2648; found: 638.2648.

(*R*)-*tert*-Butyl 3-(2,2-bis(diethoxyphosphoryl)ethyl)-3-(3-fluorophenyl)-2-oxoindoline-1-carboxylate 3t. Yield: 51.6 mg (82%). Colorless oil. $[\alpha]_D^{20}$ = +52.7 (c = 2.13, CH_2Cl_2) (85% ee); Chiralpak AD-H, hexane–isopropanol = 90 : 10, 0.8 mL min^{-1}, 254 nm, t_{minor} = 8.50 min, t_{major} = 12.96 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.4 Hz, 1H), 7.44–7.36

(m, 2H), 7.30–7.22 (m, 2H), 7.09 (d, J = 7.6 Hz, 1H), 7.03–6.93 (m, 2H), 4.18–3.97 (m, 8H), 3.37–3.25 (m, 1H), 2.97–2.82 (m, 1H), 2.29–2.14 (m, 1H), 1.60 (s, 9H), 1.34–1.24 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 162.6 (d, J = 245.1 Hz), 149.2, 143.9 (d, J = 7.8 Hz), 140.6, 129.9 (d, J = 8.2 Hz), 129.2, 127.6, 126.3, 124.4, 122.6 (d, J = 3.3 Hz), 115.5, 114.6 (d, J = 20.6 Hz), 114.3 (d, J = 23.3 Hz), 84.3, 62.9–62.5 (m), 56.0–55.9 (m), 33.7 (t, J = 135.0 Hz), 32.8 (t, J = 3.7 Hz), 28.0, 16.4–16.2 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.8, 22.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −112.0; IR (film) ν 1795, 1771, 1728, 1480, 1346, 1299, 1244, 1145, 1018 cm^{-1}; HRMS (ESI) Calcd for $C_{29}H_{41}FNO_9P_2$ $[M + H]^+$: 628.2241; found: 628.2244.

(*R*)-*tert*-Butyl 3-(2,2-bis(diethoxyphosphoryl)ethyl)-3-(3-methoxyphenyl)-2-oxoindoline-1-carboxylate 3u. Yield: 56 mg (88%). White solid. Mp: 55.6–57.9 °C; $[\alpha]_D^{20}$ = +61.3 (c = 2.65, CH_2Cl_2) (88% ee); Chiralpak AD-H, hexane–isopropanol = 90 : 10, 0.8 mL min^{-1}, 254 nm, t_{minor} = 9.13 min, t_{major} = 14.32 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.0 Hz, 1H), 7.41–7.36 (m, 2H), 7.29–7.17 (m, 2H), 6.88 (d, J = 8.0 Hz, 1H), 6.84 (d, J = 1.6 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 4.20–3.97 (m, 8H), 3.75 (s, 3H), 3.40–3.28 (m, 1H), 2.98–2.84 (m, 1H), 2.30–2.21 (m, 1H), 1.59 (s, 9H), 1.34–1.24 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 159.5, 149.2, 143.1, 140.5, 129.4, 128.9, 128.1, 126.3, 124.2, 119.2, 115.3, 113.3, 112.5, 84.0, 62.8–62.4 (m), 56.2–56.0 (m), 55.1, 33.7 (t, J = 135.4 Hz), 32.5 (t, J = 3.8 Hz), 28.0, 16.3–16.2 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.9, 22.7; IR (film) ν 1795, 1772, 1727, 1480, 1346, 1244, 1148, 1018 cm^{-1}; HRMS (ESI) Calcd for $C_{30}H_{44}NO_{10}P_2$ $[M + H]^+$: 640.2440; found: 640.2438.

(*S*)-*tert*-Butyl 3-(2,2-bis(diethoxyphosphoryl)ethyl)-3-methyl-2-oxoindoline-1-carboxylate 3w. Yield: 41.9 mg (77%). Colorless oil. $[\alpha]_D^{20}$ = +5.8 (c = 2.07, CH_2Cl_2) (23% ee); Chiralpak AD-H, hexane–isopropanol = 90 : 10, 0.8 mL min^{-1}, 254 nm, t_{minor} = 10.02 min, t_{major} = 10.84 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.0 Hz, 1H), 7.36–7.26 (m, 2H), 7.17 (t, J = 7.6 Hz, 1H), 4.19–4.01 (m, 8H), 2.71–2.35 (m, 3H), 1.64 (s, 9H), 1.45 (s, 3H), 1.34–1.27 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 149.3, 138.9, 131.7, 128.2, 124.3, 123.4, 115.0, 84.0, 62.8–62.4 (m), 47.4–47.2 (m), 32.6 (t, J = 4.3 Hz), 32.2 (t, J = 134.2 Hz), 28.0, 25.8, 16.3–16.2 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.0, 23.3; IR (film) ν 1792, 1771, 1727, 1480, 1351, 1292, 1248, 1151, 1022 cm^{-1}; HRMS (ESI) Calcd for $C_{24}H_{39}NNaO_9P_2$ $[M + Na]^+$: 570.1998; found: 570.2001.

(*S*)-*tert*-Butyl 3-benzyl-3-(2,2-bis(diethoxyphosphoryl)ethyl)-2-oxoindoline-1-carboxylate 3x. Yield: 35.2 mg (57%). Colorless oil. $[\alpha]_D^{20}$ = +6.2 (c = 1.06, CH_2Cl_2) (50% ee); Chiralpak AD-H, hexane–isopropanol = 90 : 10, 0.8 mL min^{-1}, 254 nm, t_{minor} = 10.33 min, t_{major} = 23.34 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.0 Hz, 1H), 7.28–7.14 (m, 3H), 7.06–6.97 (m, 3H), 6.69 (d, J = 6.8 Hz, 2H), 4.18–3.98 (m, 8H), 3.19 (d, J = 12.4 Hz, 1H), 2.96 (d, J = 12.4 Hz, 1H), 2.91–2.82 (m, 1H), 2.72–2.56 (m, 1H), 2.51–2.38 (m, 1H), 1.50 (s, 9H), 1.32–1.22 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 148.6, 140.1, 134.4, 129.9, 128.43, 128.39, 127.5, 126.7, 124.2, 123.9, 114.8, 83.5, 62.9–62.5 (m), 54.1–54.0 (m), 47.2, 32.8 (t, J = 132.4 Hz), 31.5 (t, J = 3.5 Hz), 27.9, 16.4–16.2 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.0, 22.9; IR (film) ν 1794, 1771, 1727, 1480, 1368, 1357, 1247, 1150, 1020 cm^{-1}; HRMS (ESI) Calcd for $C_{30}H_{43}NNaO_9P_2$ $[M + Na]^+$: 646.2311; found: 646.2314.

(*R*)-Tetraethyl (2-(1-benzyl-2-oxo-3-phenylindolin-3-yl)ethane-1,1-diyl)bis(phosphonate) 5c. Yield: 21.8 mg (36%). White solid; Mp: 76.3–78.1 °C. $[\alpha]_D^{20}$ = +21.0 (c = 1.17, CH_2Cl_2) (33% ee); Chiralpak AD-H, hexane–isopropanol = 80 : 20, 1.0 mL min^{-1}, 254 nm, t_{minor} = 9.74 min, t_{major} = 19.32 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.41 (m, 3H), 7.32–7.17 (m, 9H), 7.07 (t, J = 7.6 Hz, 1H), 6.71 (d, J = 7.6 Hz, 1H), 5.17 (d, J = 15.6 Hz, 1H), 4.67 (d, J = 16.0 Hz, 1H), 4.17–3.89 (m, 8H), 3.33–3.20 (m, 1H), 3.09–2.94 (m, 1H), 2.39–2.25 (m, 1H), 1.33–1.28 (m, 9H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 143.5, 141.1, 135.9, 130.0, 128.6, 128.5, 127.35, 127.32, 127.0, 126.9, 126.6, 122.2, 109.2, 62.8–62.3 (m), 56.0–55.9 (m), 44,0, 33.4 (t, J = 133.2 Hz), 32.2 (t, J = 4.0 Hz), 16.3–16.1 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.2, 23.2; IR (film) ν 1718, 1612, 1489, 1366, 1264, 1163, 1067, 1023 cm^{-1}; HRMS (ESI) Calcd for $C_{31}H_{39}NNaO_7P_2$ $[M + Na]^+$: 622.2099; found: 622.2095.

(*R*)-Tetraethyl (2-(1-acetyl-2-oxo-3-phenylindolin-3-yl)ethane-1,1-diyl)bis(phosphonate) 5d. Yield: 38.5 mg (70%). Colorless oil. $[\alpha]_D^{20}$ = +4.1 (c = 2.37, CH_2Cl_2) (13% ee); Chiralpak AD-H, hexane–isopropanol = 90 : 10, 0.9 mL min^{-1}, 254 nm, t_{minor} = 18.78 min, t_{major} = 21.69 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 8.4 Hz, 1H), 7.45–7.39 (m, 1H), 7.33–7.23 (m, 7H), 4.16–3.93 (m, 8H), 3.42–3.31 (m, 1H), 3.01–2.85 (m, 1H), 2.63 (s, 3H), 2.31–2.16 (m, 1H), 1.32–1.24 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 171.2, 141.4, 141.1, 129.1, 128.65, 128.61, 127.8, 126.7, 125.7, 124.9, 116.9, 62.8–62.4 (m), 56.2–56.1 (m), 53.4, 33.7 (t, J = 133.9 Hz), 32.7 (t, J = 3.8 Hz), 26.5, 16.3–16.1 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.6, 22.3; IR (film) ν 1762, 1708, 1604, 1464, 1370, 1340, 1246, 1161, 1017 cm^{-1}; HRMS (ESI) Calcd for $C_{26}H_{36}NO_8P_2$ $[M + H]^+$: 552.1916; found: 552.1919.

(*R*)-Ethyl 3-(2,2-bis(diethoxyphosphoryl)ethyl)-2-oxo-3-phenylindoline-1-carboxylate 5e. Yield: 38.8 mg (67%). Colorless oil. $[\alpha]_D^{20}$ = +20.3 (c = 2.13, CH_2Cl_2) (69% ee); Chiralpak AD-H, hexane–isopropanol = 85 : 15, 1.0 mL min^{-1}, 254 nm, t_{minor} = 8.65 min, t_{major} = 13.07 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.6 Hz, 1H), 7.44–7.23 (m, 8H), 4.45–4.36 (m, 2H), 4.17–3.96 (m, 8H), 3.42–3.32 (m, 1H), 3.01–2.87 (m, 1H), 2.31–2.16 (m, 1H), 1.40 (t, J = 7.2 Hz, 3H), 1.32–1.24 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 151.0, 141.4, 140.4, 129.1, 128.6, 128.3, 127.7, 126.8, 126.3, 124.5, 115.5, 63.1, 62.9–62.5 (m), 56.3–56.2 (m), 33.7 (t, J = 135.2 Hz), 32.7 (t, J = 3.7 Hz), 16.3–16.2 (m), 14.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.8, 22.6; IR (film) ν 1799, 1774, 1730, 1480, 1465, 1370, 1345, 1234, 1157, 1016 cm^{-1}; HRMS (ESI) Calcd for $C_{27}H_{38}NO_9P_2$ $[M + H]^+$: 582.2022; found: 582.2026.

(*R*)-Benzyl 3-(2,2-bis(diethoxyphosphoryl)ethyl)-2-oxo-3-phenylindoline-1-carboxylate 5f. Yield: 53.4 mg (83%). Colorless oil. $[\alpha]_D^{20}$ = +10.5 (c = 2.56, CH_2Cl_2) (57% ee); Chiralpak AD-H, hexane–isopropanol = 80 : 20, 1.0 mL min^{-1}, 254 nm, t_{minor} = 9.32 min, t_{major} = 14.14 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 6.8 Hz, 2H), 7.43–7.23 (m, 11H), 5.45 (d, J = 12.4 Hz, 1H), 5.31 (d, J = 12.4 Hz, 1H),

4.15–3.90 (m, 8H), 3.44–3.32 (m, 1H), 3.01–2.87 (m, 1H), 2.30–2.15 (m, 1H), 1.31–1.12 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 150.9, 141.4, 140.2, 134.8, 129.1, 128.6, 128.5, 128.35, 128.30, 128.2, 127.7, 126.7, 126.2, 124.5, 115.5, 68.4, 62.8–62.5 (m), 56.2–56.1 (m), 33.7 (t, J = 134.3 Hz), 32.6 (t, J = 3.9 Hz), 16.3–16.0 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.8, 22.4; IR (film) ν 1800, 1773, 1729, 1606, 1480, 1382, 1347, 1244, 1225, 1156, 1016 cm^{-1}; HRMS (ESI) Calcd for $C_{32}H_{40}NO_9P_2$ $[M + H]^+$: 644.2178; found: 644.2180.

HWE reaction for the synthesis of vinyl phosphonate 6

To a solution of adduct **3a** (50 mg, 0.082 mmol) in CH_3CN (2 mL) was added $MgCl_2$ (15.6 mg, 0.164 mmol), DBU (24 μL, 0.164 mmol) and $(CH_2O)_n$ (12.3 mg, 0.411 mmol). The resulting mixture was refluxed at 70 °C overnight and monitored by TLC. After consumption of adduct **3a**, the reaction mixture was concentrated, and purified by flash chromatography (acetone–petroleum ether = 1 : 10) to give the product **6** as colorless oil (21.1 mg, 53% yield). $[\alpha]_D^{20}$ = +8.5 (c = 0.5, CH_2Cl_2) (23% ee); Chiralpak AD-H, hexane–isopropanol = 90 : 10, 0.5 mL min^{-1}, 254 nm, t_{minor} = 14.21 min, t_{major} = 15.97 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.4 Hz, 1H), 7.31–7.13 (m, 8H), 5.90 (d, J = 23.6 Hz, 1H), 5.44 (d, J = 49.2 Hz, 1H), 3.93–3.72 (m, 4H), 3.42–3.35 (m, 1H), 3.17 (dd, J = 14.8, 12.0 Hz, 1H), 1.54 (s, 9H), 1.20–1.18 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 149.1, 139.8 (d, J = 4.2 Hz), 135.4, 133.7, 132.6 (d, J = 7.5 Hz), 129.2, 128.7 (d, J = 5.2 Hz), 127.8, 126.9, 126.0, 124.2, 115.1, 84.4, 61.9–61.7 (m), 56.3 (d, J = 6.1 Hz), 38.1 (d, J = 11.3 Hz), 29.6, 28.0, 16.3–16.1 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 18.3; IR (film) ν 1766, 1729, 1479, 1465, 1347, 1022, 963 cm^{-1}; MS (EI): m/z 485 (M^+, 1%), 385 (21), 208 (100); HRMS (EI) Calcd for $C_{26}H_{32}NO_6P$ $[M]^+$: 485.1967; found: 485.1966.

Hydrolysis of the tetraethyl ester 3a to bisphosphonic acid 7 and subsequent esterification to 8

To a stirred solution of tetraethylbisphosphonate **3a** (100 mg, 0.16 mmol) in 1.5 mL of CH_3CN was added freshly distilled TMSI (0.4 mL, 2.81 mmol) dropwise under argon. After being stirred at room temperature for 24 h, the reaction mixture was evaporated under reduced pressure. The residue was treated with 4.0 mL MeOH and the resulting mixture stirred overnight. After evaporation of the solvent, an insoluble brown precipitate was formed immediately and was washed consecutively with $CHCl_3$ and Et_2O, and then dried under vacuum at 65 °C for 8 h affording bisphosphonic acid **7** as a brown–yellow solid (53.4 mg, 82% yield). ^{1}H NMR (d_6-DMSO, 400 MHz) δ 10.31 (s, 1H), 8.24 (s, br., 4H), 7.34–7.22 (m, 7H), 7.03 (t, J = 7.5 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 3.08–2.96 (m, 1H), 2.64–2.49 (m, 1H), 1.78 (td, J = 31.6, 8.8 Hz, 1H); ^{31}P NMR (162 MHz, d_6-DMSO) δ 26.0 (d, J = 4.9 Hz), 25.1 (d, J = 5.3 Hz); MS(EI): m/z 209 {100%, $M^+ - CH_2CH[(PO(OEt)_2)]_2$}, 180 (81), 165 (5), 152 (6); HRMS (ESI) Calcd For $C_{16}H_{17}NO_7P_2$ $[M]^+$: 397.0480, found 397.0471.

To a stirred solution of bisphosphonic acid **7** (40 mg, 0.1 mmol) in 2.0 mL of CH_3CN was added dropwise a solution of 2.0 M $TMSCHN_2$ in hexane (0.75 mL, 15 equiv.). After stirring overnight at room temperature, the reaction mixture was concentrated and purified by column chromatography [acetone–petroleum ether = 2 : 1 to ethyl acetate–methanol = 10 : 1 (1% of Et_3N) as eluent] to afford the corresponding tetramethyl ester **8** as colorless oil (39 mg, 86% yield). $[\alpha]_D^{20}$ = −3.1 (c = 0.5, CH_2Cl_2) (82% ee); Chiralpak AD-H, hexane–isopropanol = 85 : 15, 1.0 mL min^{-1}, 254 nm, t_{minor} = 35.34 min, t_{major} = 46.36 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92 (s, 1H), 7.30 (d, J = 5.7 Hz, 2H), 7.23–7.16 (m, 5H), 7.02 (t, J = 5.7 Hz, 2H), 6.85 (d, J = 5.7 Hz, 1H), 3.66–3.56 (m, 12H), 3.21–3.14 (m, 1H), 2.89–2.77 (m, 1H), 2.40–2.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2, 142.2, 141.0, 130.0, 128.5, 128.2, 127.2, 126.6, 126.0, 121.8, 110.3, 56.1–55.9 (m), 53.33–53.27 (m), 53.0–52.9 (m), 32.3–31.5 (m); ^{31}P NMR (121 MHz, $CDCl_3$) δ 26.9, 25.5; IR (film) ν 1760, 1713, 1464, 1377, 1263, 1081, 1025 cm^{-1}; MS (EI): m/z 453 (M^+, 13%), 232 (100), 209 (9), 180 (9), 124 (18); HRMS (EI) Calcd for $C_{20}H_{25}NO_7P_2$ $[M]^+$: 453.1106; found: 453.1107.

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