Chiral Squaramide Catalyzed Asymmetric Conjugate Additions of 3-Substituted Oxindoles to Vinylphosphonates

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Abstract: An efficient organocatalytic enantioselective conjugate addition of 3-substituted oxindoles to activated vinylphosphonates has been described. This reaction allows the facile synthesis of a new family of organophosphorus derivatives bearing an oxindole motif in high chemical yields with good to excellent stereoselectivities.

Key words: organophosphorus compounds, conjugate addition, oxindole, organocatalysis, squaramide catalyst

In the recent past, the construction of skeletally diverse chiral organophosphorus compounds has attracted considerable attention[1] because of their great prevalence in important natural products, pharmaceuticals, and agrochemicals.[2] Moreover, their unique reactivity in various chemical transformations, such as Horner–Wadsworth–Emmons olefination,[3] makes organophosphorus compounds a valuable class of building blocks in the construction of molecular complexity. In this context, conjugate addition[4] of carbo- and heteronucleophiles to vinylphosphonates has provided a practical and atom-economic route to these chiral compounds with highly functional group tolerance and stereoselective control.[5] Consequently, extensive research efforts have been directed toward the development of more efficient methods for the synthesis of organophosphorus compounds in an enantioselective manner. Pioneered by the first successful example of organocatalytic conjugate addition of bisphosphonates by the Alexakis group,[6] several elegant strategies have been reported for asymmetric addition with vinylphosphonates to afford chiral adducts in high yields and enantioselectivities.[7] Despite advances, the search for novel and more practical methods for the synthesis of enantioenriched phosphorus compounds with various functional groups for further manipulations is still highly desirable.

On the other hand, oxindole derivatives play a significant role in synthetic and medicinal chemistry,[8] and thus considerable efforts have been devoted in this topical area of research over the past few decades.[9] In this field, we have also developed a cinchona-derived, thiourea-catalyzed asymmetric conjugate addition/protonation cascade of ethyl 2-phthalimidoacrylate and 3-substituted oxindoles.[10] A new family of unnatural C^{γ}-tetrasubstituted α-amino acid derivatives were synthesized in excellent yields and stereoselectivities. As part of our ongoing research interest in oxindole chemistry[11] and inspired by the promising biological activity of organophosphorus compounds, we envisaged the possibility of organocatalytic stereoselective conjugate addition of 3-substituted oxindoles to activated vinylphosphonates to give a new class of oxindoles that have potential as candidates for drug discovery and biological investigations. Recently, Shi, Zhao, and co-workers reported a highly enantioselective cinchona alkaloid thiourea catalyzed conjugate addition of 3-aryloxindoles to a vinylbisphosphonate;[12] the corresponding geminal bisphosphonates were obtained in good yields and high enantioselectivities. Alternatively, we herein reported a chiral squaramide-catalyzed asymmetric conjugate addition reaction of 3-substituted oxindoles to α-phosphonoacrylates, affording phosphorus analogues of amino acids in excellent yields (90–97%) with good to excellent diastereo- (up to 94:6) and enantioselectivities (92% to >99% ee).

Initially, a model reaction between *tert*-butyl 2-oxo-3-phenylindoline-1-carboxylate (**1a**) and ethyl 2-(diethoxyphosphoryl)acrylate (**2**) was chosen to optimize the reaction conditions (Table 1). Catalyst screening first focused on commonly used bifunctional organocatalysts. It was found that amine-H bonding catalysts could promote this reaction using dichloromethane as the solvent at room temperature. For example, bifunctional amine-thiourea catalysts **I**–**III** (Figure 1) worked well for this reaction with catalyst **III** giving higher enantioselectivity (entry 3). Stimulated by our previous success in chiral squaramide catalysis,[11b] we extended our efforts to this promising catalyst category to improve further the diastereoselectivity. To our delight, the use of quinine-derived squaramide **IV** as catalyst does indeed increase the diastereoselectivity while maintained the excellent enantioselectivity (dr 72:28, 97% ee). Subsequently, evaluation of the reaction media revealed that chloroform was the best solvent in terms of yield and stereoselectivity (entry 5).

Inspired by the high efficiency and catalytic activity of the squaramide catalysts,[13] we hypothesize that finely tuning the electronic and steric properties of **IV** may increase diastereoselectivity. Remarkably, replacement of the 3,5-bis(trifluoromethyl)phenyl moiety in catalyst **IV** with the 3,5-dimethylphenyl group significantly improved the diastereoselectivity to 83:17 with great enantioselectivity

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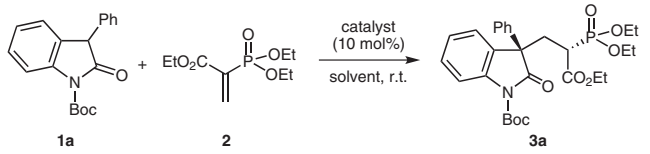
Table 1 Condition Optimization[a]



Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)	dr[c]	ee[c] (%)
1	**I**	CH_2Cl_2	1	88	66:34	35
2	**II**	CH_2Cl_2	1	93	51:49	75
3	**III**	CH_2Cl_2	1	92	68:32	95
4	**IV**	CH_2Cl_2	1	94	72:28	97
5	**IV**	$CHCl_3$	1	99	75:25	94
6	**IV**	toluene	1	93	69:31	95
7	**IV**	Et_2O	1	99	60:40	93
8	**IV**	THF	1	90	56:44	89
9	**IV**	MeCN	1	95	39:61	64
10	**IV**	DMF	0.5	99	72:28	2
11	**V**	$CHCl_3$	1	92	83:17	>99
12[d]	**V**	$CHCl_3$	8	89	83:17	>99
13[d,e]	**V**	$CHCl_3$	8	91	93:7	>99
14[e]	**VI**	$CHCl_3$	8	90	76:24	–95[f]

[a] Conditions **1a** (0.20 mmol), catalyst **I**–**VI** (0.02 mmol), **2** (0.24 mmol), solvent (1 mL), stirring, r.t.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] $CHCl_3$ (5 mL) was used.
[e] The reaction was conducted at –60 °C.
[f] Product was *ent*-**3a**.

(>99% ee) (Table 1, entry 11 vs. entry 5). Finally, optimal results were obtained by treating **1a** and **2** at –60 °C in the presence of 10 mol% of **V**, resulting in the isolation of **3a** in 91% yield with dr 93:7 and >99% ee (entry 13). More importantly, the enantiomer of **3a** could also be obtained by simply changing the quinine-derived squaramide to its quinidine analogue, albeit with slightly decreased diastereoselectivity (entry 14).

With the optimal reaction conditions identified, we then examined the substrate scope of this asymmetric conjugate addition. As shown in Table 2, the reaction appeared to be general with various oxindole nucleophiles. In the case of either electron-rich (entries 4 and 5) or electron-deficient substrates (entries 1–3 and 6–16), the desired products was always obtained in excellent yields and good stereoselectivities. Importantly, variation of the substituent position (C4–C7) of the oxindole component does not affect the reaction efficiency.

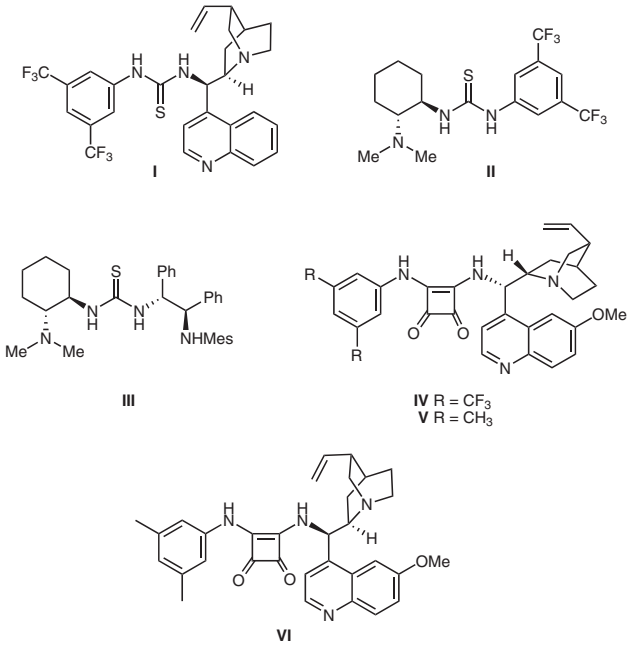


Figure 1 Organocatalysts used in the study

To further extend the substrate scope of this transformation, we synthesized a series of 3-aryl- and alkyl-substituted oxindoles and applied them to this asymmetric conjugate addition (Table 3). It was found that the corresponding adducts **3j**–**o** were afforded in good yields and stereoselectivities. Notably, a benzyl group can also be tolerated, giving the desired organophosphorus product in almost quantitative yield and excellent enantioselectivity.

In order to confirm the absolute configuration of the product, the Boc group in compound **3n** was removed to give **4**. The structural assignment of the resultant crystal compound **4** shows a (7*R*,18*S*) conformational outcome (Figure 2).[14]

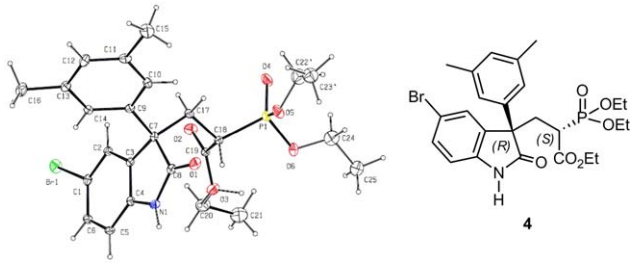
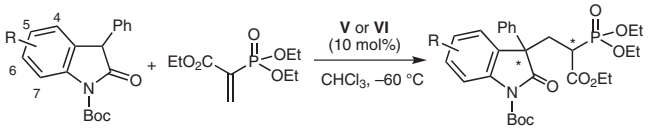


Figure 2 X-ray crystal structure of compound **4**

In order to demonstrate the synthetic utility of the current methodology, we applied the product **3a** to Horner–Wadsworth–Emmons olefination reaction (Scheme 1). Unfortunately, the expected alkene **5** was racemic but with good yield, probably because of the inevitable retro-Michael addition.

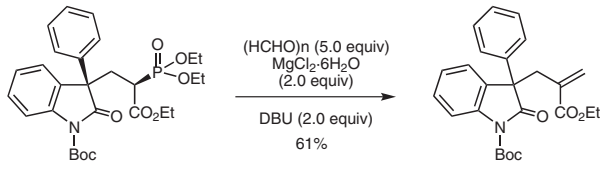
Table 2 Scope of the Asymmetric Conjugate Addition Reaction with 3-Phenyl-Substituted Oxindoles to Vinylphosphonates[a]



1 2 3

Entry	R	Catalyst	Time (h)	Yield[b] (%)		dr[c]	ee[c] (%)
1	H	**V**	8	**3a**	91	93:7	>99
2	H	**VI**	8	*ent*-**3a**	90	76:24	95
3	4-Cl	**V**	7	**3b**	92	84:16	92
4	5-Me	**V**	8	**3c**	90	94:6	>99
5	5-Me	**VI**	8	*ent*-**3c**	92	86:14	98
6	5-F	**V**	6	**3d**	94	93:7	>99
7	5-F	**VI**	6	*ent*-**3d**	90	81:19	97
8	5-Br	**V**	6	**3e**	97	89:11	99
9	5-Br	**VI**	6	*ent*-**3e**	99	75:25	97
10	5-OCF_3	**V**	6	**3f**	97	90:10	99
11	6-Cl	**V**	6	**3g**	92	91:9	>99
12	6-Cl	**VI**	6	*ent*-**3g**	90	70:30	98
13	6-Br	**V**	6	**3h**	94	90:10	99
14	6-Br	**VI**	6	*ent*-**3h**	95	71:29	97
15	7-F	**V**	6	**3i**	94	84:16	97
16	7-F	**VI**	6	*ent*-**3i**	90	82:18	95

[a] Conditions: **1** (0.20 mmol), **2** (0.24 mmol), catalyst **V** or **VI** (0.02 mmol), $CHCl_3$ (5 mL), stirring, –60 °C.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.

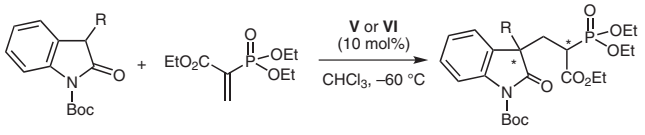


3a >99% ee **5** 2% ee

Scheme 1 Horner–Wadsworth–Emmons olefination of **3a**

In conclusion, an efficient and practical asymmetric conjugate addition of 3-substituted oxindoles to vinylphosphonate catalyzed by easily accessible squaramide catalysts has been disclosed. This transformation provides a highly efficient method for incorporating the phosphonate unit into oxindole skeletons, affording a new class of oxindole derivatives. Further expansion of the reaction scope and biological evaluation of these products are currently underway in our laboratories.

Table 3 Scope of the Asymmetric Conjugate Addition Reaction with 3-Substituted Oxindoles to Vinylphosphonates[a]



1 2 3

Entry	R	Catalyst	Time (h)	Yield[b] (%)		dr[c]	ee[c] (%)
1	4-FC_6H_4	**V**	6	**3j**	91	91:9	98
2	4-FC_6H_4	**VI**	6	*ent*-**3j**	94	81:19	97
3	4-MeC_6H_4	**V**	8	**3k**	92	85:15	98
4	4-$MeOC_6H_4$	**V**	8	**3l**	97	88:12	99
5	2-naphthyl	**V**	8	**3m**	96	85:15	>99
6[d]	3,5-$Me_2C_6H_3$	**V**	8	**3n**	97	86:14	99
7	Bn	**V**	10	**3o**	96	84:16	95

[a] Conditions **1** (0.20 mmol), **2** (0.24 mmol), catalyst **V** or **VI** (0.02 mmol), $CHCl_3$ (5 mL), stirring at –60 °C.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] One Br atom is introduced into 5-position of the benzene ring.

^{1}H NMR spectra were recorded on Varian Mercury 400/600 (400/600 MHz) spectrometers; solvent resonance as the internal standard ($CDCl_3$: δ = 7.26 ppm). ^{13}C NMR spectra were recorded on Varian Mercury 400/600 (100/150 MHz) with complete proton decoupling spectrometers ($CDCl_3$: δ = 77.0 ppm). Mass spectra were measured on API 2000 LC/MS/MS (ESI-MS). Enantiomeric ratios were determined by chiral HPLC on Agilent 1100 series with chiral columns with hexane and *i*-PrOH as the solvents. Optical rotations were measured with Jasco P-1020 polarimeter.

tert-Butyl (_R_)-3-[(_S_)-2-(Diethoxyphosphoryl)-3-ethoxy-3-oxopropyl]-2-oxo-3-phenylindoline-1-carboxylate (3a); Typical Procedure

To a soln of ethyl 2-(diethoxyphosphoryl)acrylate (**2**, 56.7 mg, 0.24 mmol) in $CHCl_3$ (5 mL) at –60 °C, a mixture of *tert*-butyl 2-oxo-3-phenylindoline-1-carboxylate (**1a**, 61.9 mg, 0.20 mmol) and squaramide **V** (10.5 mg, 0.02 mmol) was added. The resulting soln was stirred at a constant temperature until completion (TLC monitoring). The crude product was purified by chromatography (silica gel, PE–EtOAc, 2:1) to give the corresponding conjugate adduct **3a** as a light yellow oil; yield: 98.1 mg (91%); dr 93:7; >99% ee; $[\alpha]_D^{18}$ +23.30 (*c* 1.00, CH_2Cl_2). The diastereoisomers cannot be separated by chromatography, so some NMR data contain both isomers.

HPLC (Chiralpak AD-H column; detected at 254 nm; hexane–*i*-PrOH, 90:10; flow: 1 mL/min): t_R: t_1 = 8.84, t_2 = 9.86, t_3 = 10.94, t_4 = 14.38 min.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.1 Hz, 1 H), 7.36–7.26 (m, 6 H, major + minor), 7.20–7.17 (m, 2 H), 4.19–4.13 (m, 4 H, major + minor), 3.88–3.76 (m, 1 H), 3.59–3.55 (m, 1 H), 3.09–2.96 (m, 2 H), 2.84–2.76 (m, 1 H), 1.63 (s, 9 H), 1.33 (t, *J* = 7.0 Hz, 6 H), 1.05 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.71, 175.02, 168.43, 168.38, 148.78, 140.08, 139.71, 138.75, 128.98, 128.76, 128.55, 128.51, 127.68, 127.09, 126.76, 126.10, 124.89, 124.36, 124.04, 115.38, 114.96, 84.44, 84.17, 63.25, 63.20, 63.04, 62.79, 62.63, 62.57, 61.53, 61.40, 56.39, 56.24, 42.64, 41.37, 34.94, 34.42, 27.87, 16.15, 13.72, 13.53.

^{31}P NMR (162 MHz, $CDCl_3$): δ = 20.44.

MS: *m*/*z* = 545.24 ($[M]^+$).

HRMS (EI^+): *m*/*z* [M + NH_4^+] calcd for $C_{28}H_{40}N_2O_8P$: 563.2522; found: 563.2511.

***tert*-Butyl (*R*)-4-Chloro-3-[(*S*)-2-(diethoxyphosphoryl)-3-ethoxy-3-oxopropyl]-2-oxo-3-phenylindoline-1-carboxylate (3b)**

Light yellow oil; yield: 106.7 mg (92%); dr 84:16; 92% ee; $[\alpha]_D^{17}$ +41.14 (*c* 1.00, CH_2Cl_2); HPLC (Chiralpak IC column; detected at 254 nm; hexane–*i*-PrOH, 70:30; flow: 1 mL/min): t_R: t_1 = 10.62, t_2 = 11.71, t_3 = 18.86, t_4 = 63.48 min.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.2 Hz, 1 H), 7.36–7.26 (m, 4 H, major + minor), 7.22 (d, *J* = 7.8 Hz, 2 H), 7.11 (d, *J* = 8.1 Hz, 1 H), 4.21–4.12 (m, 4 H), 3.85–3.79 (m, 1 H), 3.65–3.59 (m, 1 H), 3.39–3.31 (m, 1 H), 3.18 (t, *J* = 14.4 Hz, 1 H), 2.81 (dd, *J* = 23.9, 10.7 Hz, 1 H), 1.61 (s, 9 H), 1.36 (t, *J* = 6.9 Hz, 6 H), 1.09 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): 174.59, 167.66, 167.61, 148.56, 141.88, 136.81, 132.15, 130.15, 128.57, 127.80, 126.69, 126.55, 125.67, 113.41, 84.90, 63.46, 63.39, 62.83, 62.76, 61.51, 57.14, 56.99, 42.69, 41.42, 30.51, 27.85, 16.22, 13.57.

^{31}P NMR (162 MHz, $CDCl_3$): δ = 20.18.

MS: *m*/*z* = 579.03 ($[M]^+$).

HRMS (EI^+): *m*/*z* [M + NH_4^+] calcd for $C_{28}H_{39}ClN_2O_8P$: 597.2133; found: 597.2125.

***tert*-Butyl (*R*)-3-[(*S*)-2-(Diethoxyphosphoryl)-3-ethoxy-3-oxopropyl]-5-methyl-2-oxo-3-phenylindoline-1-carboxylate (3c)**

Light yellow oil; yield: 100.7 mg (90%); dr 94:6; >99% ee; $[\alpha]_D^{17}$ +24.51 (*c* 1.01, CH_2Cl_2); HPLC (Chiralpak OD-H column; detected at 254 nm; hexane–*i*-PrOH, 90:10; flow: 1 mL/min): t_R: t_1 = 5.91, t_2 = 6.77, t_3 = 8.56, t_4 = 13.74 min.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.3 Hz, 1 H), 7.35–7.30 (m, 4 H), 7.28–7.25 (m, 1 H), 7.13 (d, *J* = 8.3 Hz, 1 H), 6.97 (s, 1 H), 4.18–4.10 (m, 4 H), 3.87–3.81 (m, 1 H), 3.63–3.58 (m, 1 H), 3.07–2.95 (m, 2 H), 2.79 (dd, *J* = 24.0, 10.5 Hz, 1 H), 2.33 (s, 3 H), 1.62 (s, 9 H), 1.33 (t, *J* = 6.8 Hz, 6 H), 1.06 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.96, 168.56, 148.91, 139.00, 137.37, 133.72, 129.32, 128.60, 127.66, 126.85, 126.54, 114.82, 84.31, 63.21, 62.81, 61.35, 56.51, 56.37, 42.70, 41.42, 34.38, 27.95, 20.95, 16.22, 13.61.

^{31}P NMR (162 MHz, $CDCl_3$): δ = 20.53.

MS: *m*/*z* = 559.16 ($[M]^+$).

HRMS (EI^+): *m*/*z* [M + NH_4^+] calcd for $C_{29}H_{42}N_2O_8P$: 577.2679; found: 577.2672.

***tert*-Butyl (*R*)-3-[(*S*)-2-(Diethoxyphosphoryl)-3-ethoxy-3-oxopropyl]-5-fluoro-2-oxo-3-phenylindoline-1-carboxylate (3d)**

Light yellow oil; yield: 99.5 mg (94%); dr 93:7; >99% ee; $[\alpha]_D^{18}$ +21.15 (*c* 1.01, CH_2Cl_2); HPLC (Chiralpak IC column; detected at 254 nm; hexane–*i*-PrOH, 70:30; flow: 1 mL/min): t_R: t_1 = 6.95, t_2 = 10.07, t_3 = 12.57, t_4 = 20.12 min.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.90 (dd, *J* = 8.9, 4.4 Hz, 1 H), 7.33 (s, 4 H), 7.29 (d, *J* = 4.2 Hz, 1 H), 7.05 (t, *J* = 8.8 Hz, 1 H), 6.91 (d, *J* = 7.7 Hz, 1 H), 4.18–4.10 (m, 4 H), 3.93–3.87 (m, 1 H), 3.76–3.71 (m, 1 H), 3.08–2.95 (m, 2 H), 2.79 (dd, *J* = 24.1, 10.5 Hz, 1 H), 1.62 (s, 9 H), 1.34 (t, *J* = 7.0 Hz, 6 H), 1.10 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.35, 168.43, 168.37, 160.73, 158.30, 148.80, 138.23, 135.68, 130.82, 130.74, 127.97, 126.71, 116.43, 115.58, 115.36, 113.43, 113.19, 84.72, 63.34, 63.28, 62.95, 61.58, 56.65, 56.51, 42.66, 41.39, 34.27, 27.92, 16.20, 13.66.

^{31}P NMR (162 MHz, $CDCl_3$): δ = 20.17.

MS: *m*/*z* = 563.23 ($[M]^+$).

HRMS (EI^+): *m*/*z* [M + NH_4^+] calcd for $C_{28}H_{39}FN_2O_8P$: 581.2428; found: 581.2417.

***tert*-Butyl (*R*)-5-Bromo-3-[(*S*)-2-(diethoxyphosphoryl)-3-ethoxy-3-oxopropyl]-2-oxo-3-phenylindoline-1-carboxylate (3e)**

Light yellow oil; yield: 120.9 mg (97%); dr 89:11; 99% ee; $[\alpha]_D^{19}$ +29.60 (*c* 1.00, CH_2Cl_2); HPLC (Chiralpak IC column; detected at 254 nm; hexane–*i*-PrOH, 70:30; flow: 1 mL/min): t_R: t_1 = 7.32, t_2 = 10.78, t_3 = 12.99, t_4 = 19.48 min.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.7 Hz, 1 H), 7.47 (d, *J* = 8.7 Hz, 1 H), 7.33–7.28 (m, 6 H), 4.16–4.10 (m, 4 H, major + minor), 3.96–3.91 (m, 1 H), 3.81–3.76 (m, 1 H), 3.06 (t, *J* = 14.7 Hz, 1 H), 2.97 (t, *J* = 12.5 Hz, 1 H), 2.75 (dd, *J* = 24.2, 10.4 Hz, 1 H), 1.62 (s, 9 H), 1.33 (t, *J* = 7.0 Hz, 6 H), 1.12 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.86, 168.29, 148.58, 138.74, 138.09, 131.73, 130.97, 128.75, 127.94, 126.61, 117.12, 116.71, 84.81, 63.21, 62.80, 61.67, 56.42, 56.27, 42.67, 41.40, 34.23, 27.83, 16.15, 13.64.

^{31}P NMR (162 MHz, $CDCl_3$): δ = 20.09.

MS: *m*/*z* = 623.13 ($[M]^+$).

HRMS (EI^+): *m*/*z* [M + NH_4^+] calcd for $C_{28}H_{39}BrN_2O_8P$: 641.1627; found: 641.1618.

***tert*-Butyl (*R*)-3-[(*S*)-2-(Diethoxyphosphoryl)-3-ethoxy-3-oxopropyl]-2-oxo-3-phenyl-5-(trifluoromethoxy)indoline-1-carboxylate (3f)**

Light yellow oil; yield: 121.6 mg (97%); dr 90:10; 99% ee; $[\alpha]_D^{19}$ +29.07 (*c* 1.00, CH_2Cl_2); HPLC (Chiralpak IC column; detected at 254 nm; hexane–*i*-PrOH, 70:30; flow: 1 mL/min): t_R: t_1 = 5.20, t_2 = 7.58, t_3 = 8.41, t_4 = 13.29 min.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.9 Hz, 1 H), 7.37–7.28 (m, 5 H, major + minor), 7.22 (d, *J* = 8.6 Hz, 1 H), 7.08 (s, 1 H), 4.18–4.10 (m, 4 H, major + minor), 3.93–3.87 (m, 1 H), 3.71–3.66 (m, 1 H), 3.07–2.96 (m, 2 H), 2.83 (dd, *J* = 24.3, 10.1 Hz, 1 H), 1.63 (s, 9 H), 1.35–1.32 (m, 6 H), 1.09 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.17, 168.34, 168.28, 148.71, 145.57, 138.20, 137.98, 130.78, 128.86, 128.07, 126.71, 121.52, 119.22, 116.21, 84.98, 63.30, 62.97, 62.90, 61.75, 61.48, 56.57, 56.43, 42.62, 41.35, 34.30, 27.92, 16.22, 13.65, 0.94.

^{31}P NMR (162 MHz, $CDCl_3$): δ = 20.06.

MS: *m*/*z* = 629.16 ($[M]^+$).

HRMS (EI^+): *m*/*z* [M + NH_4^+] calcd for $C_{29}H_{39}F_3N_2O_9P$: 647.2345; found: 647.2334.

***tert*-Butyl (*R*)-6-Chloro-3-[(*S*)-2-(diethoxyphosphoryl)-3-ethoxy-3-oxopropyl]-2-oxo-3-phenylindoline-1-carboxylate (3g)**

Light yellow oil; yield: 106.6 mg (92%); dr 91:9; >99% ee; $[\alpha]_D^{19}$ +32.98 (*c* 1.00, CH_2Cl_2); HPLC (Chiralpak IC column; detected at 254 nm; hexane–*i*-PrOH, 70:30; flow: 1 mL/min): t_R: t_1 = 7.45, t_2 = 9.74, t_3 = 11.25, t_4 = 20.12 min.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.99 (s, 1 H), 7.32 (s, 4 H, major + minor), 7.30–7.28 (m, 1 H), 7.16 (d, *J* = 8.1 Hz, 1 H), 7.11 (d, *J* = 8.1 Hz, 1 H), 4.16–4.09 (m, 4 H, major + minor), 3.89–3.84 (m, 1 H), 3.67–3.62 (m, 1 H), 3.04 (t, *J* = 14.5 Hz, 1 H), 2.96 (t, *J* = 12.5 Hz, 1 H), 2.77 (dd, *J* = 24.0, 10.5 Hz, 1 H), 1.63 (s, 9 H), 1.35–1.32 (m, 6 H), 1.09 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.23, 168.48, 148.60, 140.68, 138.25, 134.59, 128.73, 127.94, 127.04, 126.70, 124.18, 115.68, 85.04, 63.28, 62.85, 61.66, 56.22, 56.08, 42.64, 41.37, 34.46, 27.88, 16.21, 13.57.

^{31}P NMR (162 MHz, $CDCl_3$): δ = 20.08.

MS: *m*/*z* = 579.15 ($[M]^+$).

HRMS (EI^+): *m*/*z* [M + NH_4^+] calcd for $C_{28}H_{39}ClN_2O_8P$: 597.2133; found: 597.2118.

***tert*-Butyl (*R*)-6-Bromo-3-[(*S*)-2-(diethoxyphosphoryl)-3-ethoxy-3-oxopropyl]-2-oxo-3-phenylindoline-1-carboxylate (3h)**

Light yellow oil; yield: 117.4 mg (94%); dr 90:10; 99% ee; $[\alpha]_D^{19}$ +23.24 (*c* 1.00, CH_2Cl_2); HPLC (Chiralpak IC column; detected at 254 nm; hexane–*i*-PrOH, 70:30; flow: 1 mL/min): t_R: t_1 = 8.03, t_2 = 10.52, t_3 = 12.17, t_4 = 21.87 min.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 1.5 Hz, 1 H), 7.37–7.23 (m, 6 H, major + minor), 7.05 (d, *J* = 8.1 Hz, 1 H), 4.17–4.09 (m, 4 H), 3.89–3.84 (m, 1 H), 3.67–3.62 (m, 1 H), 3.06–2.93 (m, 2 H), 2.77 (m, 1 H), 1.63 (s, 9 H), 1.33 (t, *J* = 7.0 Hz, 6 H), 1.09 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.10, 168.52, 168.47, 148.58, 140.81, 138.15, 128.72, 127.93, 127.57, 127.42, 127.09, 126.68, 122.50, 118.44, 85.02, 63.25, 62.82, 61.67, 56.26, 56.12, 42.62, 41.34, 34.37, 27.86, 16.19, 13.59.

^{31}P NMR (162 MHz, $CDCl_3$): δ = 20.05.

MS: *m*/*z* = 623.13 ($[M]^+$).

HRMS (EI^+): *m*/*z* [M + NH_4^+] calcd for $C_{28}H_{39}BrN_2O_8P$: 641.1627; found: 641.1618.

***tert*-Butyl (*R*)-3-[(*S*)-2-(Diethoxyphosphoryl)-3-ethoxy-3-oxopropyl]-7-fluoro-2-oxo-3-phenylindoline-1-carboxylate (3i)**

Light yellow oil; yield: 105.9 mg (94%); dr 84:16; 97% ee; $[\alpha]_D^{18}$ +19.71 (*c* 1.00, CH_2Cl_2); HPLC (Chiralpak IC column; detected at 254 nm; hexane–*i*-PrOH, 70:30; flow: 1 mL/min): t_R: t_1 = 16.64, t_2 = 19.06, t_3 = 25.84, t_4 = 40.38 min.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 5 H), 7.12 (m, 2 H), 6.99 (d, *J* = 7.2 Hz, 1 H), 4.20–4.06 (m, 4 H, major + minor), 3.89–3.84 (m, 1 H), 3.66–3.61 (m, 1 H), 3.07–2.98 (m, 2 H), 2.85–2.79 (m, 1 H), 1.61 (s, 9 H), 1.35–1.32 (m, 6 H), 1.07 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.29, 168.43, 149.65, 147.10, 138.08, 132.23, 128.72, 127.92, 126.95, 126.68, 125.06, 124.99, 121.88, 116.91, 116.71, 85.10, 63.29, 63.22, 62.90, 62.84, 61.47, 57.06, 56.92, 42.43, 41.16, 34.40, 27.49, 16.17, 13.59.

^{31}P NMR (162 MHz, $CDCl_3$): δ = 20.14.

MS: *m*/*z* = 563.20 ($[M]^+$).

HRMS (EI^+): *m*/*z* [M + NH_4^+] calcd for $C_{28}H_{39}FN_2O_8P$: 581.2428; found: 581.2415.

***tert*-Butyl (*R*)-3-[(*S*)-2-(Diethoxyphosphoryl)-3-ethoxy-3-oxopropyl]-3-(4-fluorophenyl)-2-oxoindoline-1-carboxylate (3j)**

Light yellow oil; yield: 102.5 mg (91%); dr 91:9; 98% ee; $[\alpha]_D^{17}$ +47.42 (*c* 0.99, CH_2Cl_2); HPLC (Chiralpak AD-H column; detected at 254 nm; hexane–*i*-PrOH, 90:10; flow: 1 mL/min): t_R: t_1 = 8.62, t_2 = 10.32, t_3 = 11.33, t_4 = 16.33 min.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.3 Hz, 1 H), 7.38–7.30 (m, 3 H), 7.18 (d, *J* = 3.5 Hz, 2 H), 7.00 (t, *J* = 8.6 Hz, 2 H), 4.20–4.07 (m, 4 H, major + minor), 3.86–3.80 (m, 1 H), 3.61–3.55 (m, 1 H), 3.03–2.93 (m, 2 H), 2.81–2.75 (m, 1 H), 1.63 (s, 9 H), 1.33 (t, *J* = 7.1 Hz, 6 H), 1.05 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.63, 168.40, 168.35, 163.31, 160.85, 148.75, 139.73, 134.47, 128.97, 128.77, 128.69, 128.25, 126.08, 124.17, 115.50, 115.29, 115.12, 84.61, 63.30, 63.24, 62.89, 62.83, 61.48, 55.83, 55.68, 42.65, 41.37, 34.74, 27.90, 16.18, 13.57.

^{31}P NMR (162 MHz, $CDCl_3$): δ = 20.27.

MS: *m*/*z* = 563.11 ($[M]^+$).

HRMS (EI^+): *m*/*z* [M + NH_4^+] calcd for $C_{28}H_{39}FN_2O_8P$: 581.2428; found: 581.2420.

***tert*-Butyl (*R*)-3-[(*S*)-2-(Diethoxyphosphoryl)-3-ethoxy-3-oxopropyl]-2-oxo-3-(4-tolyl)indoline-1-carboxylate (3k)**

Light yellow oil; yield: 103.5 mg (92%); dr 85:15; 98% ee; $[\alpha]_D^{18}$ +28.07 (*c* 1.00, CH_2Cl_2); HPLC (Chiralpak IC column; detected at 254 nm; hexane–*i*-PrOH, 80:20; flow: 0.7 mL/min): t_R: t_1 = 21.87, t_2 = 24.04, t_3 = 44.51, t_4 = 64.68 min.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.2 Hz, 1 H), 7.33 (t, *J* = 7.5 Hz, 1 H), 7.22 (d, *J* = 7.6 Hz, 2 H, major + minor), 7.19–7.16 (m, 2 H), 7.11 (d, *J* = 7.7 Hz, 2 H), 4.17–4.08 (m, 4 H), 3.85–3.79 (m, 1 H), 3.59–3.54 (m, 1 H), 3.05–2.94 (m, 2 H), 2.80 (dd, *J* = 23.8, 10.4 Hz, 1 H), 2.30 (s, 3 H), 1.62 (s, 9 H), 1.33 (t, *J* = 7.0 Hz, 6 H, major + minor), 1.04 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.83, 168.48, 168.43, 148.85, 139.72, 137.46, 135.87, 129.23, 128.71, 126.64, 126.06, 124.01, 114.93, 84.35, 63.25, 63.18, 62.82, 62.76, 61.39, 56.12, 55.97, 42.68, 41.40, 34.46, 27.89, 20.78, 16.17, 13.54.

^{31}P NMR (162 MHz, $CDCl_3$): δ = 20.44.

MS: *m*/*z* = 559.07 ($[M]^+$).

HRMS (EI^+): *m*/*z* [M + NH_4^+] calcd for $C_{29}H_{42}N_2O_8P$: 577.2679; found: 577.2663.

***tert*-Butyl (*R*)-3-[(*S*)-2-(Diethoxyphosphoryl)-3-ethoxy-3-oxopropyl]-3-(4-methoxyphenyl)-2-oxoindoline-1-carboxylate (3l)**

Light yellow oil; yield: 111.6 mg (97%); dr 88:12; 99% ee; $[\alpha]_D^{18}$ +31.53 (*c* 1.00, CH_2Cl_2); HPLC (Chiralpak IC column; detected at 254 nm; hexane–*i*-PrOH, 80:20; flow: 1 mL/min): t_R: t_1 = 20.59, t_2 = 23.71, t_3 = 35.89, t_4 = 62.22 min.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.2 Hz, 1 H), 7.33 (t, *J* = 7.7 Hz, 1 H), 7.25 (d, *J* = 8.6 Hz, 2 H), 7.19–7.15 (m, 2 H), 6.83 (d, *J* = 8.6 Hz, 2 H), 4.17–4.08 (m, 4 H, major + minor), 3.84–3.80 (m, 1 H), 3.76 (s, 3 H), 3.60–3.56 (m, 1 H), 3.03–2.92 (m, 2 H), 2.82–2.77 (m, 1 H), 1.62 (s, 9 H), 1.33 (t, *J* = 7.0 Hz, 6 H, major + minor), 1.04 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.92, 168.46, 168.41, 158.89, 148.84, 139.70, 130.71, 128.65, 127.99, 126.07, 124.00, 114.96, 113.80, 84.35, 63.23, 63.18, 62.82, 62.76, 61.38, 55.74, 55.59, 55.06, 42.67, 41.40, 34.58, 27.87, 16.15, 13.53.

^{31}P NMR (162 MHz, $CDCl_3$): δ = 20.45.

MS: *m*/*z* = 575.29 ($[M]^+$).

HRMS (EI^+): *m*/*z* [M + NH_4^+] calcd for $C_{29}H_{42}N_2O_9P$: 593.2628; found: 593.2608.

***tert*-Butyl (*R*)-3-[(*S*)-2-(Diethoxyphosphoryl)-3-ethoxy-3-oxopropyl]-3-(naphthalen-2-yl)-2-oxoindoline-1-carboxylate (3m)**

Light yellow oil; yield: 124.1 mg (96%); dr 85:15; >99% ee; $[\alpha]_D^{18}$ +1.76 (*c* 0.99, CH_2Cl_2); HPLC (Chiralpak IC column; detected at 254 nm; hexane–*i*-PrOH, 80:20; flow: 0.7 mL/min): t_R: t_1 = 21.97, t_2 = 24.30, t_3 = 42.79, t_4 = 51.05 min.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.2 Hz, 1 H), 7.79 (m, 4 H), 7.45–7.43 (m, 3 H), 7.37 (t, *J* = 7.8 Hz, 1 H), 7.23 (d, *J* = 7.4 Hz, 1 H), 7.19 (t, *J* = 7.5 Hz, 1 H), 4.20–4.13 (m, 4 H), 3.86–3.81 (m, 1 H), 3.61–3.56 (m, 1 H), 3.21–3.17 (m, 1 H), 3.12–3.08 (m, 1 H), 2.92–2.87 (m, 1 H), 1.63 (s, 9 H), 1.35 (t, *J* = 7.0 Hz, 6 H), 1.04 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.72, 168.46, 168.41, 148.84, 139.73, 136.09, 132.83, 132.40, 128.83, 128.46, 128.06, 127.21, 126.28, 126.16, 126.06, 125.88, 124.57, 124.17, 115.03, 84.46,

63.26, 63.20, 62.84, 62.78, 61.41, 56.55, 56.40, 42.64, 41.36, 34.20, 27.89, 16.19, 13.55.

^{31}P NMR (162 MHz, $CDCl_3$): δ = 20.45.

MS: *m*/*z* = 595.18 ($[M]^+$).

HRMS (EI^+): *m*/*z* [M + NH_4^+] calcd for $C_{32}H_{42}N_2O_8P$: 613.2679; found: 613.2659.

***tert*-Butyl (*R*)-5-Bromo-3-[(*S*)-2-(diethoxyphosphoryl)-3-ethoxy-3-oxopropyl]-3-(3,5-dimethylphenyl)-2-oxoindoline-1-carboxylate (3n)**

Light yellow oil; yield: 126.6 mg (97%); dr 84:16; 99% ee; $[\alpha]_D^{17}$ +20.13 (*c* 1.01, CH_2Cl_2); HPLC (Chiralpak IC column; detected at 254 nm; hexane–*i*-PrOH, 90:10; flow: 1 mL/min): t_R: t_1 = 13.83, t_2 = 21.08, t_3 = 36.29, t_4 = 41.08 min.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 8.7 Hz, 1 H), 7.46 (d, *J* = 8.7 Hz, 1 H), 7.24 (s, 1 H), 6.92 (s, 1 H), 6.87 (s, 2 H), 4.17–4.11 (m, 4 H), 3.96–3.92 (m, 1 H), 3.82–3.77 (m, 1 H), 3.07–3.02 (m, 1 H), 2.97–2.93 (m, 1 H), 2.77–2.72 (m, 1 H), 2.28 (s, 6 H), 1.63 (s, 9 H), 1.34 (t, *J* = 7.1 Hz, 6 H), 1.13 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.13, 168.39, 148.69, 138.66, 138.32, 138.13, 131.64, 129.66, 128.62, 124.71, 124.28, 117.16, 116.65, 84.77, 63.29, 63.23, 62.81, 61.68, 56.36, 56.22, 42.62, 41.35, 33.92, 27.89, 21.32, 16.19, 13.69.

^{31}P NMR (162 MHz, $CDCl_3$): δ = 20.25.

MS: *m*/*z* = 651.30 ($[M]^+$).

HRMS (EI^+): *m*/*z* [M + NH_4^+] calcd for $C_{30}H_{43}BrN_2O_8P$: 669.1940; found: 669.1923.

***tert*-Butyl (*S*)-3-Benzyl-3-[(*S*)-2-(diethoxyphosphoryl)-3-ethoxy-3-oxopropyl]-2-oxoindoline-1-carboxylate (3o)**

Light yellow oil; yield: 107.4 mg (96%); dr 84:16; 95% ee; $[\alpha]_D^{19}$ +5.29 (*c* 1.00, CH_2Cl_2); HPLC (Chiralpak AD-H column; detected at 254 nm; hexane–*i*-PrOH, 90:10; flow: 1 mL/min): t_R: t_1 = 8.31, t_2 = 9.09, t_3 = 11.86, t_4 = 24.06 min.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.55–7.45 (m, 1 H), 7.19–7.14 (m, 2 H), 7.10–7.09 (m, 1 H), 7.07–7.03 (m, 1 H), 7.02–6.99 (m, 2 H), 6.76–6.72 (m, 2 H), 4.17–4.14 (m, 2 H), 4.13–4.03 (m, 2 H, major + minor), 3.75–3.72 (m, 1 H), 3.46–3.43 (m, 1 H), 3.18 (d, *J* = 12.9 Hz, 1 H), 3.01 (d, *J* = 13.0 Hz, 1 H), 2.80–2.60 (m, 3 H), 1.55 (s, 9 H), 1.37–1.32 (m, 6 H), 0.96 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.67, 168.51, 148.24, 139.82, 134.14, 129.51, 128.37, 127.44, 127.02, 126.62, 124.80, 123.49, 114.35, 83.84, 63.16, 63.10, 62.76, 61.24, 54.89, 54.74, 45.55, 42.66, 41.38, 33.46, 27.78, 16.15, 13.42.

^{31}P NMR (162 MHz, $CDCl_3$): δ = 20.34.

MS: *m*/*z* = 559.02 ($[M]^+$).

HRMS (EI^+): *m*/*z* [M + NH_4^+] calcd for $C_{29}H_{42}N_2O_8P$: 577.2679; found: 577.2662.

***tert*-Butyl 3-[2-(Ethoxycarbonyl)allyl]-2-oxo-3-phenylindoline-1-carboxylate (5)**

To a stirred soln of **3a** (109.1 mg, 0.2 mmol) in MeCN (4 mL) were added $MgCl_2 \cdot 6\ H_2O$ (81.3 mg, 0.4 mmol), DBU (60 μL, 0.4 mmol), and paraformaldehyde (30.3 mg, 1.0 mmol). The mixture was stirred at r.t. When the reaction was complete (TLC monitoring), the solvent was removed. The product was purified by flash chromatography directly to give a white solid; yield: 51.8 mg (61%); dr 2% ee; HPLC (Chiralpak AD-H column; detected at 254 nm; hexane–*i*-PrOH, 90:10; flow: 1 mL/min): t_R: t_1 = 6.51, t_2 = 7.23 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 8.2 Hz, 1 H), 7.36–7.22 (m, 7 H), 7.08 (t, *J* = 7.5 Hz, 1 H), 5.92 (s, 1 H), 5.44 (s, 1 H), 3.83 (dd, *J* = 14.1, 7.0 Hz, 2 H), 3.41 (s, 2 H), 1.53 (s, 9 H), 1.03 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.28, 166.76, 149.02, 139.89, 139.47, 135.95, 128.67, 128.54, 127.96, 127.64, 127.06, 126.40, 123.84, 114.90, 84.24, 60.66, 57.37, 38.40, 27.97, 13.99.

MS: *m*/*z* = 421.08 ($[M]^+$).

Organocatalysts V and VI

Prepared according to the literature procedure.[13e]

Catalyst V

^{1}H NMR (600 MHz, DMSO-d_6): δ = 9.58 (s, 1 H), 8.83 (d, *J* = 18 Hz, 1 H), 8.01 (s, 1 H), 7.99 (d, *J* = 4.5 Hz, 1 H), 7.80 (s, 1 H), 7.67 (s, 1 H), 7.45–7.45 (m, 1 H), 6.96 (s, 2 H), 6.65 (s, 1 H), 6.01–5.96 (m, 2 H), 5.01–4.98 (m, 2 H), 3.96 (s, 3 H), 3.49–3.45 (m, 1 H), 3.22–3.18 (m, 1 H), 2.72–2.62 (m, 2 H), 2.23 (m, 1 H), 2.21 (s, 6 H), 1.52 (s, 3 H), 0.65 (s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 183.89, 179.89, 167.79, 163.66, 157.83, 147.76, 144.28, 143.25, 142.18, 138.42, 131.49, 127.47, 124.45, 121.87, 115.92, 114.26, 101.47, 58.76, 55.64, 27.30, 26.13, 21.00.

MS: *m*/*z* = 522.46 ($[M]^+$).

Catalyst VI

^{1}H NMR (600 MHz, DMSO-d_6): δ = 9.55 (s, 1 H), 8.82 (d, *J* = 3.4 Hz, 1 H), 8.05 (s, 1 H), 7.97 (d, *J* = 9.1 Hz, 1 H), 7.78 (s, 1 H), 7.67 (d, *J* = 3.4 Hz, 1 H), 7.43 (d, *J* = 8.8 Hz, 1 H), 6.95 (s, 2 H), 6.61 (s, 1 H), 6.13 (s, 1 H), 5.91–5.76 (m, 1 H), 5.20 (d, *J* = 17.4 Hz, 1 H), 5.07 (d, *J* = 10.5 Hz, 1 H), 3.95 (s, 3 H), 3.48–3.39 (m, 1 H), 3.18 (s, 1 H), 2.94 (d, *J* = 10.2 Hz, 1 H), 2.89–2.71 (m, 2 H), 2.18 (s, 6 H), 1.53 (s, 2 H), 1.48 (s, 1 H), 1.07 (s, 1 H), 0.89 (s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 184.03, 179.84, 167.94, 163.53, 157.86, 147.73, 144.28, 143.46, 140.75, 138.42, 131.48, 127.48, 124.41, 122.07, 115.89, 114.36, 101.14, 59.71, 58.66, 55.58, 52.44, 48.95, 45.56, 38.49, 27.20, 26.15, 25.22, 21.00, 20.70.

MS: *m*/*z* = 522.29 ($[M]^+$).

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(14) Please see Supporting Information for X-ray crystal structure for compound **4** (CCDC 921101).

