N-Heterocyclic carbene-catalyzed domino hydroacylation/Stetter reactions of salicyl alkynylphosphonates and aromatic aldehydes

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Abstract

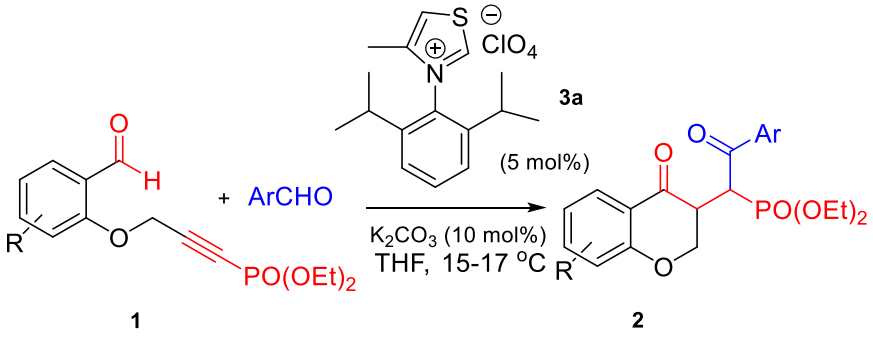
1,4-Dicarbonyl compounds **2** carrying a phosphonate group were obtained by utilizing a dually *N*-heterocyclic carbene (NHC) catalyzed domino reaction involving the intramolecular hydroacylation of salicyl alkynylphosphonates **1** and a subsequent intermolecular Stetter reaction with aromatic aldehyde at room temperature. In addition, **2** can also be applied for the synthesis of benzopyranopyrrole carrying a phosphonate group **4** in one pot and in moderate yield.

Keywords: *N*-Heterocyclic carbene; domino reaction; hydroacylation; Stetter reaction; 1,4-dicarbonyl compound; phosphonate

Introduction

During the past decades, domino reactions, which can rapidly form complicated molecule skeletons from readily available substrates in a single operation without isolation of intermediates, have received more and more attention of organic chemists. So, considerable efforts have been made to develop organocatalytic domino transformations.[1] 1,4-Dicarbonyl compounds are versatile intermediates in the synthesis of cyclopentenones[2] and a variety of heterocycles such as furan,[3] pyrrole,[4] thiophene,[5] and pyrrolidine.[6] Recently, *N*-heterocyclic carbenes (NHCs) have been widely used, not only as ligands in organometallic chemistry, but also as efficient nucleophilic organocatalysts in a variety of organic reactions, such as benzoin condensation, Stetter reaction, a^3 to d^3 umpolung, and so on, so the development of NHCs in organic synthesis has attracted more and more attention.[7] Glorius and coworkers have pioneered the development of a powerful NHC-catalyzed hydroacylation of unactivated alkynes leaded to the formation of α,β-unsaturated chromanones,[8] while intramolecular hydroacylation reactions of activated alkynes were reported recently.[9]

Recently, an effective *N*-heterocyclic carbene catalyzed intramolecular hydroacylation reaction of salicyl alkynylphosphonates was reported in our group, in which both exocyclic and endocyclic tautomers can be obtained at different temperatures.[9b] Because α,β-unsaturated ketones (exocyclic tautomers) are the major products at lower temperatures (15-17 ºC), this prompted us to investigate the possibility of developing a dually NHC-catalyzed domino reaction involving the intramolecular hydroacylation of salicyl alkynylphosphonates and a subsequent intermolecular Stetter reaction to prepare 1,4-dicarbonyl compounds **2** carrying a phosphonate group at room temperature (Scheme 2), which can be very important intermediates for the synthesis of biologically active phosphonyl heterocyclic compounds.[10] Although Glorius and coworkers reported the NHC-catalyzed cascade hydroacylation/Stetter reactions of salicyl alkynes,[8] the groups linking with alkynes are usually H or a Me group, other groups such as aromatic group, ester group linking with alkynes are not reported. As for activated alkynes, no domino hydroacylation/Stetter reaction is reported because in which endocyclic tautomers are the major product. In this paper, we report the first cascade hydroacylation/ Stetter reaction of activated alkynes **1** containing a phosphonyl group derived from substituted salicylaldehydes (Scheme 1).



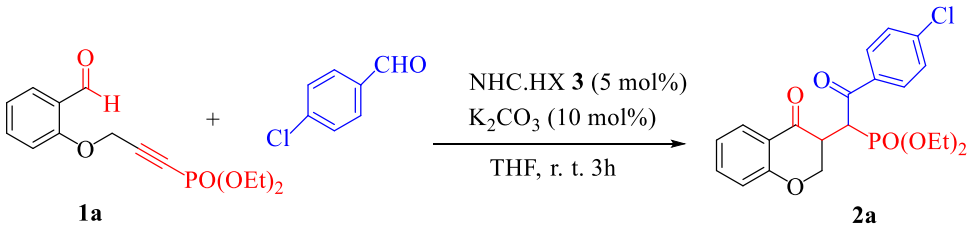
Scheme 1. Domino hydroacylation/Stetter reaction of activated alkynes containing a phosphonyl group.

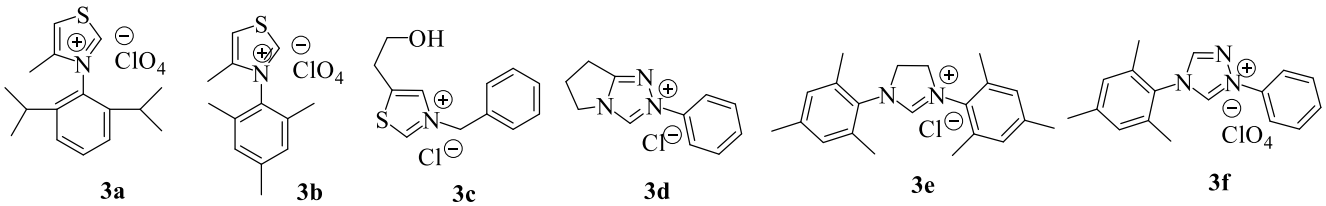
Results and Discussion

First of all, we used substrate **1a** and 4-chlorobenzaldehyde as a model in order to optimize the reaction condition. The initial screening was carried out at 15-17 °C with 5 mol% of catalyst and 10 mol% of K_2CO_3 in THF (Table 1, entries 1-6). When thiazolium salt **3a** was used as the catalyst and K_2CO_3 as the base, **2a** was obtained in 81% yield (Table1, entry 1), and **3a** is the most effective catalyst, however, the triazolium salt **3d** is not so effective (Table1, entry 4); Secondly, the effects of various bases (Table 1, entries 7-11) were explored using catalyst **3a** as a control, the moderate base (K_2CO_3) afforded the products in higher yields than other bases. Subsequently, we turned our attention to the influence of different solvents on the reaction

(Table 1, entries 12-17) and found THF to be the most effective, the more polar EtOH and DMF being less so. Different temperatures have some obvious effects on the reaction. The lower temperature (15-17 °C) is more beneficial to the reaction than the higher one (30-35 °C); when the reaction with **3a** and K_2CO_3 in THF was tested at 30-35 °C, the yield of **2a** is only 32%. Finally, the optimized conditions were established as following: thiazolium salt **3a** as the pre-catalyst (5 mol%), K_2CO_3 (10 mol%) as the base, THF as the solvent, and stirring at 15-17 °C for 3 h.

Table 1 Optimization of the reaction conditions[a]



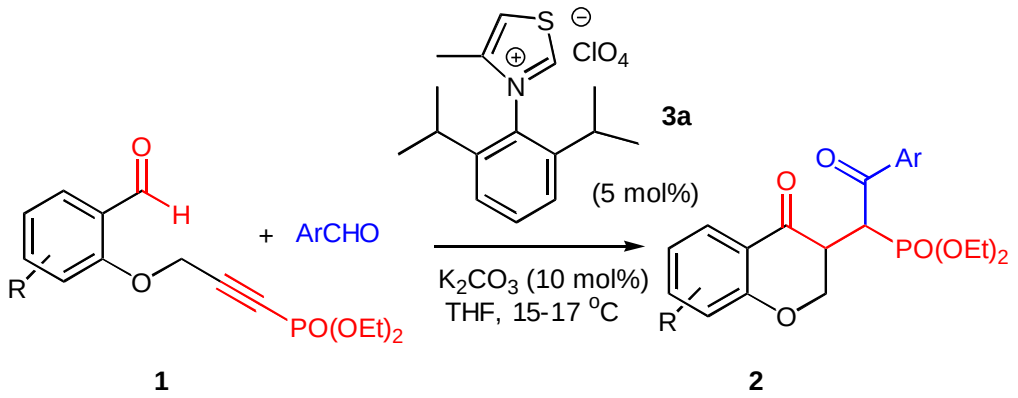


Entry	NHC-HX	Base	Solvent	Yield of **2a** [%] [b]
1	**3a**	K_2CO_3	THF	81
2	**3b**	K_2CO_3	THF	75
3	**3c**	K_2CO_3	THF	70
4	**3d**	K_2CO_3	THF	20
5	**3e**	K_2CO_3	THF	34
6	**3f**	K_2CO_3	THF	57
7	**3a**	Cs_2CO_3	THF	65
8	**3a**	DBU	THF	40
9	**3a**	DABCO	THF	38
10	**3a**	NaH	THF	71
11	**3a**	NaOH	THF	58
12	**3a**	K_2CO_3	Dioxane	72
13	**3a**	K_2CO_3	EtOH	40
14	**3a**	K_2CO_3	Toluene	65
15	**3a**	K_2CO_3	CH_3CN	68
16	**3a**	K_2CO_3	DMF	30
17	**3a**	K_2CO_3	DCM	76

[a] General conditions: **1a** (0.5 mmol), NHC-HX (5 mol%), base (10 mol%), solvent (2.0 ml), room temperature (15-17 °C), 3h; [b] Isolated yields.

With the optimised conditions thus established, we tested different substrates to give good results in the NHC catalyzed cascade reaction of hydroacylation and Stetter reaction. For salicyl alkynylphosphonates with both electron-donating groups and electron-withdrawing ones on the phenyl ring, the reactions proceeded smoothly and gave the corresponding **2** in good yields at room temperature. However, when benzaldehyde was used, the yield was very low (Table 2, entry 7); the reason for this is not clear.

Table 2 Scope of the domino hydroacylation/Stetter reactions. [a]

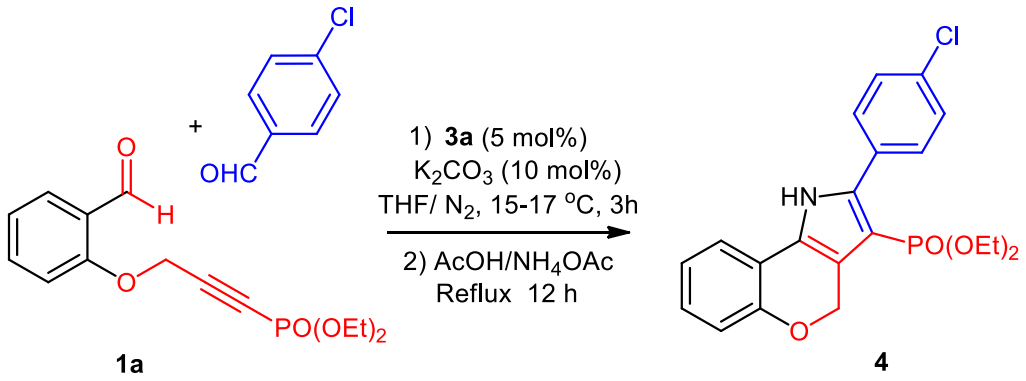


1 **2**

Entry	R	Ar	Yield of **2** [%] [b]
1	H (**1a**)	4-ClC$_6$H$_4$	81 (**2a**)
2	4-MeO (**1b**)	4-BrC$_6$H$_4$	84 (**2b**)
3	4-F (**1c**)	4-BrC$_6$H$_4$	83 (**2c**)
4	4-*t*-Bu **(1d)**	4-BrC$_6$H$_4$	71 (**2d**)
5	6-Me (**1e**)	4-BrC$_6$H$_4$	77 (**2e**)
6	4,6-di-*t*-Bu **(1f)**	4-BrC$_6$H$_4$	69 (**2f**)
7	H (**1a**)	C$_6$H$_5$	<5

[a] General conditions: **1** (0.5 mmol, 1.0 equiv), **3a** (0.025 mmol, 5 mol%), K_2CO_3 (0.05 mmol, 10 mol%), ArCHO (0.5 mmol, 1.0 equiv), THF (2.0 ml), 15-17 ºC, 3h; [b] Isolated yields

In order to prepare novel heterocycles containing a phosphonyl group with potent biological activities, **2** can be applied to the synthesis of benzopyranopyrrolephosphonate **4** successfully *via* a one-pot reaction in 50% yield (Scheme 2).



Scheme 2 Preparation of the benzopyranopyrrolephosphonate **4** by a one-pot reaction.

Conclusions

In conclusion, 1,4-dicarbonyl compounds **2** carrying a phosphonate group were obtained by utilizing a dually NHC-catalyzed domino reaction involving the intramolecular hydroacylation of salicyl alkynylphosphonates **1** and a subsequent intermolecular Stetter reaction with aromatic aldehyde in good yields at room temperature. In addition, **2** can be also applied successfully for the synthesis of benzopyranopyrrole containing a phosphonyl group **4** in one-pot reaction in moderate yield.

Experimental Section

General. All reagents and solvents for reactions were used as received with the following exceptions. THF, toluene and dioxane were distilled from Na/benzophenone. Dichloromethane, acetonitrile and *N*,*N*-dimethylformamide (DMF) were distilled from calcium hydride. Ethanol and *n*-butyl alcohol were distilled form Mg turnings. K_2CO_3 was dried by heating at 110 °C for 12 h and left to cool under Ar. *N*-Heterocyclic carbene (NHC) precursors **3** were prepared according to the literature.[11] The substituted salicyl alkynylphosphonates **1** were synthesized according to the the reported method.[9b] All other commercially available solvents and reagents were used without further purification. All reactions were performed in oven-dried apparatus under N_2 or Ar atmosphere. Reactions were monitored by thin layer chromatography (TLC) and visualized by UV light or $KMnO_4$ staining solution followed by heating.

Melting points were determined with a WRS-1B digital melting point apparatus. ^{1}H NMR, ^{13}C NMR spectra and ^{31}P NMR spectra were obtained with a Varian Mercury PLUS 600 spectrometer. Chemical shift in ppm, internal standard TMS or $CHCl_3$, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constants Hz. ^{13}C NMR chemical shifts are reported in ppm from $CDCl_3$ (taken as 77.0 ppm). ^{31}P NMR spectra were recorded with

85% H_3PO_4 as external standard. The mass spectra (ESI) were obtained using an Applied Biosystems API 2000 LC/MS/MS (ESI-MS) spectrometer. Elemental analyses were performed with an Elementar Vario ELIII CHNSO elemental analyzer.

Synthesis of 2-phosphonyl 1,4-diketones 2: general procedure. To an oven-dried round-bottomed flask equipped with a magnetic stirring bar was added diethyl 3-(2-formylphenoxy)prop-1-ynylphosphonate **1** (0.5 mmol, 1.0 equiv), pre-catalyst **3a** (9 mg, 0.025 mmol, 0.05 equiv), substituted benzaldehyde (0.5 mmol, 1.0 equiv), dry THF (2 ml) and dry K_2CO_3 (6.9 mg, 0.05 mmol, 0.10 equiv) under a N_2 or Ar atmosphere at 15-17 °C. The resulting mixture was then stirred for 3h at the same temperature. The progress of the reaction was monitored by TLC. Upon completion, the mixture was pre-absorbed on silica gel and purified by flash column chromatography on silica gel (eluent: hexane/ AcOEt 1:1) to afford **2** as a white solid.

Diethyl 2-(4-chlorophenyl)-1-(4-oxochroman-3-yl)-2-oxoethylphosphonate (2a). Prepared according to the general procedure. The product was obtained as a white solid (81% yield), mp 102-104 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.01 (d, *J* 8.4 Hz, 2H), δ 7.75 (d, *J* 7.8 Hz, 1H), δ 7.49 (d, *J* 7.8 Hz, 3H), δ 6.98 (d, *J* 8.4 Hz, 2H), δ 5.17 (dd, *J* 15.0 Hz, *J* 5.4 Hz, 1H), δ 4.38-4.43 (m, 2H), δ 4.01-4.16 (m, 5H), δ 1.28 (t, *J* 7.2 Hz, 3H), δ 1.17 (t, *J* 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 193.3, 192.2, 161.5, 139.4, 136.3, 135.6, 130.2, 128.8, 127.3, 121.5, 119.8, 117.6, 69.6, 63.2, 46.9, 44.3 (d, *J* 128.4 Hz), 16.1. ^{31}P NMR (243 MHz, $CDCl_3$): δ 18.8. ESI-MS: *m/z* 437 $[M+H]^+$, 459 $[M+Na]^+$, 475 [M+K]. Anal. calcd for $C_{21}H_{22}ClO_6P$: C, 57.74; H, 5.08. Found: C, 56.83; H, 5.01 %.

Diethyl 2-(4-bromophenyl)-1-(6-methoxy-4-oxochroman-3-yl)-2-oxoethylphosphonate (**2b**). Prepared according to the general procedure. The product was obtained as white solid (84%), m p 126-127 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.93 (d, *J* 8.4 Hz, 2H), δ 7.64 (d, *J* 8.4 Hz, 2H), δ 7.16 (s, 1H), δ 7.08 (d, *J* 9.6 Hz, 1H), δ 6.93 (d, *J* 9.6 Hz, 1H), δ 5.13 (dd, *J* 11.4 Hz, *J* 4.8 Hz, 1H), δ 4.34-4.39 (m, 2H), δ 4.03-4.16 (m, 5H), δ 3.71 (s, 3H), δ 1.28 (t, *J* 6.6 Hz, 3H), δ 1.18 (t, *J* 6.6 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 193.4, 192.3, 156.3, 154.0, 136.1, 131.8, 130.5, 130.2, 128.2, 125.6, 119.1, 107.3 (d, *J* 101.4 Hz), 69.7, 63.1, 55.6, 46.9, 43.9 (d, *J* 130.4 Hz), 16.1. ^{31}P NMR (243 MHz, $CDCl_3$): δ 16.4. ESI-MS: *m/z* 512 $[M+H]^+$, 434 $[M+Na]^+$, 550 [M+K]. Anal. calcd for $C_{22}H_{24}BrO_7P$: C, 51.68; H, 4.73. Found: C, 51.86; H, 4.84 %.

Diethyl 2-(4-bromophenyl)-1-(6-fluoro-4-oxochroman-3-yl)-2-oxoethylphosphonate (**2c**). Prepared according to the general procedure. The product was obtained as white solid (83%), mp 97-99 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.92 (d, *J* 8.4 Hz, 2H), δ 7.64 (d, *J* 8.4 Hz, 2H), δ 7.39 (dd, *J* 8.4 Hz, *J* 3.0 Hz, 1H), δ 7.20 (t, *J* 3.0 Hz, 1H), δ 6.98 (dd, *J* 4.2 Hz, *J* 9.0 Hz, 1H), δ 5.17 (dd, *J* 11.4 Hz, *J* 5.4 Hz, 1H), δ 4.40 (m, 2H), δ 4.03-4.14 (m, 5H), δ 1.27 (t, *J* 7.2 Hz, 3H), δ 1.18 (t, *J* 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 193.3, 191.3, 161.4, 157.8, 135.9, 131.9, 131.6 (d, *J* 32 Hz), 130.3 (d, *J* 30 Hz), 128.4, 123.9 (d, *J* 25 Hz), 119.4, 112.2 (d, *J* 23 Hz), 69.8, 63.3 (t, *J* 41.2 Hz), 46.8, 43.8 (d, *J* 129 Hz), 16.2 (d, *J* 16 Hz). ^{31}P NMR (243 MHz,

$CDCl_3$): δ 19.5. ESI-MS: *m/z* 499 $[M+H]^+$, 521 $[M+Na]^+$, 537 [M+K]. Anal. calcd for $C_{21}H_{21}BrFO_6P$: C, 50.52; H, 4.24. Found: C, 50.41; H, 4.35 %.

Diethyl 2-(4-bromophenyl)-1-(6-tert-butyl-4-oxochroman-3-yl)-2-oxoethylphosphonate (**2d**). Prepared according to the general procedure. The product was obtained as white solid (71%), m p 99-101 °C. ^1H NMR (600 MHz, $CDCl_3$): δ 7.95 (d, *J* 7.8 Hz, 2H), 7.74 (s, 1H), δ 7.65 (d, *J* 7.8 Hz, 2H), δ 7.54 (d, *J* 7.2 Hz, 1H), δ 6.93 (d, *J* 9.0 Hz, 1H), δ 5.13 (dd, *J* 12.0 Hz, *J* 6.0 Hz, 1H), δ 4.32-4.38 (m, 2H), δ 4.03-4.15 (m, 5H), δ 1.29 (t, *J* 7.2 Hz, 3H), δ 1.25 (t, *J* 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 193.5, 192.7, 159.5, 144.5, 136.1, 134.2, 130.5, 128.8, 128.2, 123.4, 119.0, 117.3, 69.6, 63.2, 47.2, 43.5, 34.3, 31.2 (d, *J* 142.6 Hz), 16.3. ^{31}P NMR (243 MHz, $CDCl_3$): δ 13.2. ESI-MS: *m/z* 537 $[M+H]^+$, 559 $[M+Na]^+$, 575 [M+K]. Anal. calcd for $C_{25}H_{30}BrO_6P$: C, 55.88; H, 5.63. Found: C, 55.71; H, 5.57 %.

Diethyl 2-(4-bromophenyl)-1-(8-methyl-4-oxochroman-3-yl)-2-oxoethylphosphonate (**2e**). Prepared according to the general procedure. The product was obtained as white solid (77%), m p 109-110 °C. ^1H NMR (600 MHz, $CDCl_3$): δ 7.93 (d, *J* 8.4 Hz, 2H), δ 7.65 (d, *J* 8.4 Hz, 2H), δ 7.59 (d, *J* 8.4 Hz, 1H), δ 7.34 (d, *J* 7.2 Hz, 1H), δ 6.88 (t, *J* 7.8 Hz, 1H), δ 5.20 (dd, *J* 11.4 Hz, *J* 5.4 Hz, 1H), δ 4.36-4.41 (m, 2H), δ 4.04-4.17 (m, 5H), δ 1.29 (t, *J* 7.2 Hz, 3H), δ 1.19 (t, *J* 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 193.5, 192.4, 159.8, 137.2, 136.1, 131.8, 130.3, 128.2, 127.0, 124.9, 120.9, 119.4, 63.2, 46.9, 44.3, 43.5, 16.2, 15.5. ^{31}P NMR (243 MHz, $CDCl_3$): δ 15.1. ESI-MS: *m/z* 495 $[M+H]^+$, 517 $[M+Na]^+$, 533 [M+K]. Anal. calcd for $C_{22}H_{24}BrO_6P$: C, 53.35; H, 4.88. Found: C, 53.19; H, 4.64 %.

Diethyl 2-(4-bromophenyl)-1-(6,8-di-tert-butyl-4-oxochroman-3-yl)-2-oxoethylphosphonate (**2f**). Prepared according to the general procedure. The product was obtained as white solid (69%), mp 114-116 °C. ^1H NMR (600 MHz, $CDCl_3$): δ 7.93 (d, *J* 8.4 Hz, 2H), δ 7.65 (d, *J* 8.4 Hz, 2H), δ 7.63 (s, 1H), δ 7.53 (s, 1H), δ 5.19 (dd, *J* 11.4 Hz, *J* 5.4 Hz, 1H), δ 4.31-4.35 (m, 2H), δ 4.04-4.16 (m, 5H), δ 1.40 (s, 9H), δ 1.26 (t, *J* 7.2 Hz, 3H), δ 1.23 (s, 9H), δ 1.17 (t, *J* 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 193.5, 183.8, 158.7, 143.4, 138.2, 136.2, 131.8, 131.1, 130.3, 128.1, 121.4, 119.7, 63.2 (d, *J* 30 Hz), 47.0, 44.4, 43.5, 35.0, 34.4, 31.2, 29.6, 16.2. ^{31}P NMR (243 MHz, $CDCl_3$): δ 12.6. ESI-MS: *m/z* 593 $[M+H]^+$, 615 $[M+Na]^+$, 631 [M+K]. Anal. calcd for $C_{29}H_{38}BrO_6P$: C, 58.69; H, 6.45. Found: C, 58.82; H, 6.51 %.

Synthesis of diethyl [2-(4-chlorophenyl)-1,4-dihydro-chromeno[4,3-*b*]pyrrole-3- phosphonate (4): To an oven-dried round-bottom flask equipped with a magnetic bar was added **1a** (296 mg, 1.0 mmol, 1.0 equiv), pre-catalyst **3a** (18 mg, 0.05 mmol, 0.05 equiv), 4-chlorobenzaldehyde (140 mg, 1.0 mmol, 1.0 equiv), anhydrous THF (2 ml), and dry K_2CO_3 (14 mg, 0.1 mmol, 0.10 equiv.) under a N_2 or Ar atmosphere at r.t. The resulting mixture was then stirred for 3 h at 15-17 °C. The progress of the reaction was monitored by TLC. NH_4OAc (231 mg, 3 mmol) and gacial AcOH (3 ml) were added under N_2 atmosphere, the mixture was allowed to be stirred under reflux for 12 h. Upon completion, the mixture was cooled to r.t. The workup involved addition of ice water (20 ml) and extraction of the product mixture into $CHCl_3$ (3 × 20 ml), washing with sat. aq. $NaHCO_3$ and sat. brine. After phase separation, drying over Na_2SO_4, filtration and evaporation, the crude product was purified by chromatography on silica using a

mixture of petroleum ether and AcOEt (2:1) as an eluent to give **4** as white solid (208.5 mg, 50%). Mp 106-107 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 10.33 (s, 1H), δ 7.50 (d, *J* 7.8 Hz, 2H), δ 7.39 (d, *J* 7.2 Hz, 1H), δ 7.18 (d, *J* 7.2 Hz, 2H), δ 7.07 (t, *J* 7.8 Hz, 1H), δ 6.85-6.89 (m, 2H), δ 5.43 (s, 2H), δ 3.85-3.92 (m, 4H), δ 1.13 (t, *J* 7.2 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 158.4, 156.5, 149.3, 138.4, 136.5, 135.7, 134.1, 131.7, 129.8, 128.5, 126.2, 122.7, 122.2, 116.7, 66.5, 62.6, 16.4. ^{31}P NMR (243 MHz, $CDCl_3$): δ 15.57. ESI-MS: *m/z* 418 $[M+H]^+$, 440 $[M+Na]^+$, 456 [M+K]. Anal. calcd for $C_{21}H_{21}ClNO_4P$: C, 60.37; H, 5.07; N, 3.35. Found: C, 60.24; H, 5.15; N 3.21 %.

Acknowledgements

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