Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2014, **12**, 5458

Synthesis of phosphaisocoumarin amidates *via* DIBAL-H-mediated selective amidation of phosphaisocoumarin esters†

Yu-Juan Guo, Pei-Jiang Chen, Bo Wang and Ai-Yun Peng*

Received 29th March 2014,
Accepted 29th May 2014

DOI: 10.1039/c4ob00663a

www.rsc.org/obc

A series of phosphaisocoumarin amidates were synthesized for the first time *via* DIBAL-H-mediated direct amidation of phosphaisocoumarin esters under mild conditions in good to excellent yields. The present reaction showed high selectivity. In each case, the phostone ring was intact and only the exocyclic ethoxy group was amidated. A plausible mechanism of the reaction was provided.

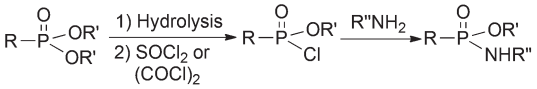
Introduction

Carboxamides are key structural units in many biologically active compounds (*i.e.* proteins) and modern pharmaceuticals, and the carboxamide-forming reactions have been extensively investigated.[1] Phosphonamidates, as important carboxamide analogues, have also gained considerable research interest in organic chemistry and biology, because they may mimic the tetrahedral transition states of carboxamide hydrolysis and may be used as potential probes and inhibitors of various enzymes.[2]

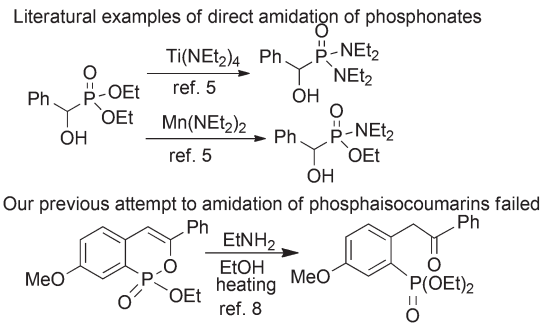
Despite the broad application prospects of phosphonamidates, only a few methods for their synthesis have been reported. The typical approach to obtain phosphonamidates is the coupling of amines with phosphonochloridates, which are usually formed by the hydrolysis of the corresponding phosphonic acid diesters to monoesters followed by treatment with thionyl chloride or oxalyl chloride (Scheme 1).[3] The limitations of this traditional route include lengthy steps, relatively low total yields, strict reaction conditions and tedious workup, which largely restrict the applications of phosphonamidates. Although some new methods starting from trivalent phosphorus species have been developed by several groups,[4] efficient, general and atom-economical methods for the synthesis of phosphonamidates under mild conditions are still in high demand.

Theoretically, direct amidation of phosphonic acid diesters is a more desirable protocol to synthesize phosphonamidates since the hydrolysis to the phosphonic acid monoesters and the subsequent synthesis of unstable phosphonochloridates are avoided. However, to date, little is known about such conversion. In 1987, Froneman *et al.* reported that $Ti(NEt_2)_4$ and $Mn(NEt_2)_2$ were unreactive with $PhCH_2P(O)(OEt)_2$,[5] but reacted smoothly with $(EtO)_2P(O)CH(OH)Ph$ to give the amidated products (Scheme 2). They thought that these processes might involve the anchimeric assistance of the hydroxy with the metal, which mediated the exchange of one or both EtO groups for the NEt_2 substituent. Unfortunately, the scope of this inspirational method is very limited, and no subsequent studies were reported thereafter.

In recent years, we synthesized a series of phosphaisocoumarin esters as isocoumarin analogues.[6] It has been reported that isocoumarins could be readily converted into the corresponding isoquinolones by treatment with primary amines in



Scheme 1 Typical procedure for the synthesis of phosphonamidates.



Scheme 2 Some attempts to direct amidation of phosphonates.

School of Chemistry & Chemical Engineering, Sun Yat-sen University, 135 Xingangxi Lu, Guangzhou, 510275, China. E-mail: cespay@mail.sysu.edu.cn; Fax: +86 020 84112245; Tel: +86 020 84110918

†Electronic supplementary information (ESI) available: NMR spectra for **2a–2k**. See DOI: 10.1039/c4ob00663a

alcohols or other solvents,[7] but we found that the reactions of phosphaisocoumarin esters with ethylamine in ethanol did not lead to any amidation products but the ring-opened alcoholysis products (Scheme 2).[8] This result indicated that the direct formation of phosphonamidates from phosphonates is very challenging, probably due to the steric encumbrance around the phosphonyl group and the stronger affinity of phosphorus to oxygen than to nitrogen.

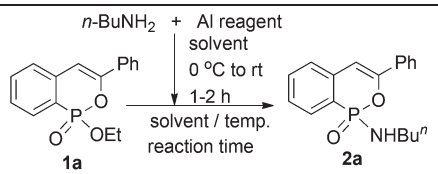
The aluminium amide intermediates, generated from amines or amine hydrochloride and aluminium reagents, such as $AlMe_3$,[9] Me_2AlCl[10] and DIBAL-H,[11] were reported to react with inactive lactones, esters, and acid chlorides,[12] leading to various carboxamides in moderate to excellent yields. We reasoned that such aluminium amide species may promote the direct amidation of phosphonates. However, to our surprise, this kind of aluminium-mediated amidation of phosphonates or phosphates has never been explored thus far. We herein present our findings about the DIBALH-mediated direct amidation of phosphaisocoumarin esters, affording a series of phosphaisocoumarin amidates in this study.[13]

Results and discussion

We first examined the amidation of **1a** (0.1 mmol) with *n*-butylamine under various conditions and the results are summarized in Table 1. A slight excess of amine (amine–Al = 1.2 : 1) was used in each case to exclude the effects of the free aluminium reagent on the subsequent amidation reaction. We found that the choice of the aluminium reagent was crucial for the success of this reaction. With no aluminium reagent or the use of $AlMe_3$, Et_2AlCl and $AlCl_3$, the reaction did not afford any amidation product (entries 1–6). Gratifyingly, the reaction of **1a** with the aluminium amide (i-$Bu_2AlNHBu^n$), generated from DIBAL-H (i-Bu_2AlH, 1.0 mmol) and *n*-butylamine (1.2 mmol) in THF accompanied by hydrogen evolution, proceeded smoothly at room temperature to give the corresponding phosphaisocoumarin amidate **2a** in high yield (entries 7 and 8). Screening the solvents showed that the reaction was sluggish in toluene (entry 9), but there were no apparent differences in THF, $CHCl_3$ and CH_2Cl_2 (entries 8, 10 and 11). Taking into account that the aluminium reagent has better solubility in THF, we selected THF as the solvent for the following reactions. Surprisingly, when the amount of i-$Bu_2AlNHBu^n$ was decreased to 0.15 mmol (1.5 equiv.), the yield of **2a** was significantly reduced even after doubling the reaction time (entry 12). Further studies indicated that excess i-$Bu_2AlNHBu^n$ was necessary and six equiv. of i-$Bu_2AlNHBu^n$ were sufficient to drive the reaction to completion (entries 13–16).

To explore the scope and limitations of this reaction, the reactions of a series of phosphaisocoumarin esters **1** and primary aliphatic amines were then investigated using DIBAL-H as an aluminium reagent and THF as a solvent and the results are shown in Table 2. Under the optimized reaction conditions, phosphaisocoumarin esters **1a–1h** could react smoothly with benzylamine and *n*-butyl amine, producing the desired products phosphaisocoumarin amidates **2a–2k** in good to excellent yields (entries 1–11). The reaction was not very sensitive to the electronic nature of the substrates. Various functionalities were all able to withstand the reaction con-

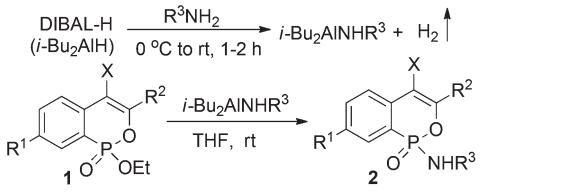
Table 1 Optimization of the amidation reaction of **1a**[a]



Entry	Aluminium reagent (equiv.)	Solvent	*T*/°C	Time/h	Yield[b] (%)
1	None	THF	0–rt	12	NR[c]
2	$AlCl_3$ (10)	THF	0–rt	12	NR
3	$AlCl_3$ (10)	$CHCl_3$	0–rt	12	NR
4	$AlCl_3$ (10)	THF	0–50	12	NR
5	$AlMe_3$ (10)	THF	0–rt	12	NR
6	Et_2AlCl (10)	THF	0–rt	12	NR
7	DIBAL-H (10)	THF	0–rt	3	91
8	DIBAL-H (10)	THF	rt	3	92
9	DIBAL-H (10)	Toluene	rt	3	53
10	DIBAL-H (10)	$CHCl_3$	rt	3	90
11	DIBAL-H (10)	CH_2Cl_2	rt	3	83
12	DIBAL-H (1.5)	THF	rt	6	35
13	DIBAL-H (2)	THF	rt	6	38
14	DIBAL-H (4)	THF	rt	6	70
15	DIBAL-H (5)	THF	rt	3	87
16	DIBAL-H (6)	THF	rt	3	92

[a] The reaction of the aluminium reagent, amine (1.2 equiv. of the aluminium reagent) was carried out under N_2 for 1–2 h followed by addition of **1a** (0.1 mmol). [b] Yield based on ^{31}P NMR. [c] No reaction.

Table 2 DIBAL-H-mediated amidation of phosphaisocoumarin esters with primary amines[a]



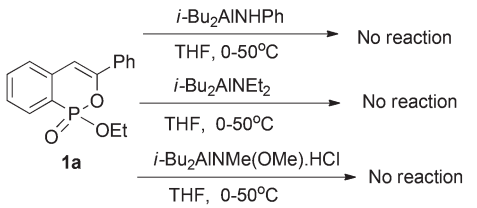
Entry	R^1	R^2	X	R^3	Time/h	Yield[b] (%)
1	H	Ph	H (**1a**)	*n*-Bu	3	77 (**2a**)
2	H	Ph	H (**1a**)	$PhCH_2$	1	91 (**2b**)
3	H	*n*-Bu	H (**1b**)	$PhCH_2$	3	64 (**2c**)
4	Cl	*n*-Bu	H (**1c**)	$PhCH_2$	4	83 (**2d**)
5	Cl	*n*-Bu	H (**1c**)	*n*-Bu	5	72 (**2e**)
6	Cl	Ph	H (**1d**)	*n*-Bu	4	81 (**2f**)
7	CH_3O	Ph	H (**1e**)	$PhCH_2$	6	81 (**2g**)
8	CH_3O	Ph	H (**1e**)	*n*-Bu	8	90 (**2h**)
9	H	Ph	Cl (**1f**)	$PhCH_2$	4	73 (**2i**)
10	H	Ph	Br (**1g**)	$PhCH_2$	4	76 (**2j**)
11	H	Ph	I (**1h**)	$PhCH_2$	4	84 (**2k**)

[a] The reaction was carried out in the presence of DIBAL-H (6 equiv.), primary amine (7.2 equiv.), N_2 at 0 °C in anhydrous THF for 1–2 h followed by phosphaisocoumarin ester **1** in anhydrous THF at room temperature. [b] Isolated yield.

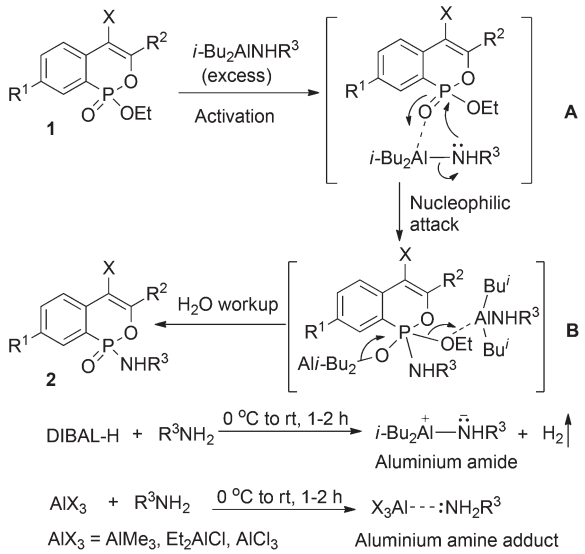
ditions, *e.g.* R^1 is electron-rich methoxy, electron-poor chlorine, neutral hydrogen, R^2 is aryl, alkyl, and X is chloro, bromo, iodo. The substrate **1e** with an electron-donating methoxy group could transform to the desired products smoothly, but needed a little longer reaction time (entries 7 and 8). Furthermore, the reactivity of benzylamine is relatively higher than that of *n*-butyl amine since the latter needed a longer time to complete the reactions (compare entries 1 and 2, 4 and 5, 7 and 8).

Next, we examined the amidation of **1a** with less reactive aromatic amines and secondary aliphatic amines. Unfortunately, when using phenylamine, *N*-methoxy-*N*-methyl (Weinreb) amine and diethyl amine as the amine source (Scheme 3), no desired amidation products but some decomposed unidentified compounds were observed. Extending the reaction time and increasing the reaction temperature did not make the reactions proceed. We speculated that it should be the steric hindrance of the secondary amines or aromatic amines that prevented them from approaching the phosphorus center.

Based on the above results, a plausible mechanism was proposed in Scheme 4. The formation of the aluminium amide is the key to the success of the reaction, probably because the aluminium might not only increase the nucleophilicity of amine, but also enhance the electrophilicity of the phosphorus by coordination with the phosphonyl oxygen (intermediate **A**). The attack of the activated amine on the phosphorus leads to intermediate **B**, which collapses to the desired product **2** upon hydrolytic workup. The reaction of DIBAL-H and amines could generate aluminium amides and hydrogen,[14] but $AlMe_3$, Et_2AlCl, $AlCl_3$ could not afford the aluminium amides but the 1 : 1 aluminium amine adducts (Scheme 4).[15] In the adducts, the nucleophilicity of the amine was greatly decreased by coordinating with the electron-weak aluminium, which might account for the results that only DIBAL-H could facilitate the present reaction (entries 2–7, Table 1). Besides, the fact that this reaction needed excess aluminium amide might be explained by the following two aspects. First, compared to the carboxylic esters, the more hindered phosphaisocoumarin esters are less reactive and need more nitrogen nucleophile to accelerate the reaction. Huang *et al.*[11] reported that the aminolysis of less reactive aromatic esters needed an excess of the DIBAL-H-amine reagents (up to 5 equiv.), which was consistent with our results. Second, the coordination of additional aluminium amide with the ethoxy might make it easier to leave (Scheme 4).



Scheme 3 DIBAL-H-mediated amidation of **1a** with phenylamine and secondary amines.



Scheme 4 Plausible mechanism of the aluminium amide-mediated amidation of **1**.

It is noteworthy that whereas the amidation of lactones often leads to lactams or ring opened amidated products, the present reaction showed high selectivity for phosphaisocoumarin amidates. In each case, only the exocyclic ethoxy group was amidated and no ring opened or other aminolysis products were detected by TLC and NMR monitoring of the crude reaction mixture.

The structures of **2** were determined by spectroscopic methods, especially by ^{1}H NMR spectral analysis and ESI-MS analysis. For example, the structure of **2a** was confirmed by the disappearance of ethyl protons of P–OEt and the appearance of *n*-butyl protons of P–NHBu^n, and the existence of the vinylic proton at the 4 position from its ^{1}H NMR spectrum, which is consistent with the proposed structure.

Conclusion

In summary, we have developed a direct way to convert phosphaisocoumarin esters to phosphaisocoumarin amidates using aluminium amides (i-Bu_2AlNHR) as amidating reagents. The present amidation reaction showed high selectivity, in which the phostone ring of phosphaisocoumarin esters was not opened and only the exocyclic ester group was amidated under the reaction conditions. Further studies on the applications of this reaction and the amidation of other phostones and acyclic phosphonates are underway in our group.

Experimental

General

The ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Varian Mercury-Plus 300 or a Varian INOVA 400 NMR instrument. All

melting points are uncorrected. ^{31}P NMR spectra used 85% H_3PO_4 as the external reference. ESI-mass spectra were recorded on a LCMS-2010A liquid chromatography mass spectrometer. Elemental analysis was performed using a Vario EL elemental analyzer. HRMS was determined using a Thermo MAT95XP high resolution mass spectrometer. IR spectra were recorded as KBr pellets on a Bruker Equinox 55 FT/IR spectrometer. Solvents were purified and dried according to standard procedures. All commercially available reagents were used as received. Column chromatography was performed on 200–300 mesh silica gel. Thin-layer chromatography was conducted on a Kieselgel 60 F254. The starting materials **1** were prepared according to our previous procedures.[6]

Typical procedures for the preparation of phosphaisocoumarin amidates 2a–k. A solution of DIBAL-H (1.0 M in hexane, 1.8 mL, 1.8 mmol) was added to a cooled (0 °C) solution of *n*-butylamine (0.22 mL, 2.3 mmol) in anhydrous THF (1.0 mL) under nitrogen. The mixture was allowed to warm up and stirred at rt for 1–2 h. To this prepared i-$Bu_2AlNHBu^n$ solution was added a solution of **1** (0.3 mmol) in anhydrous THF (1.0 mL) under nitrogen at room temperature. After stirring at room temperature for an appropriate time (see Table 2), the reaction mixture was cooled to 0 °C, and then quenched with H_2O (3.5 mL) and saturated NH_4Cl (4 mL). The resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (EtOAc–PE: 1/6–1/4) to give the corresponding phosphaisocoumarin amides **2a–2k**. The isolated yield and the spectral data for **2a–2k** are as follows:

*1-Butylamino-3-phenylbenzo[c][1,2]oxaphosphinine 1-oxide (**2a**).* White solid, mp: 122–125 °C. Yield: 77%. IR (KBr): 3193, 3061, 2957, 1629, 1594, 1553, 1492, 1467, 1340, 1286, 1205, 1130, 1097, 1084, 1022, 982 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92–7.75 (m, 3H), 7.57 (td, J = 7.6, 1.1 Hz, 1H), 7.48–7.30 (m, 5H), 6.67 (s, 1H), 3.14 (s, 1H), 2.96–2.72 (m, 2H), 1.55–1.40 (m, 2H), 1.31 (dq, J = 13.8, 6.9 Hz, 2H), 0.84 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6 (d, J = 9.5 Hz), 138.4 (d, J = 7.2 Hz), 133.8 (d, J = 5.7 Hz), 132.8 (s), 129.9 (d, J = 9.3 Hz), 129.6 (s), 128.8 (s), 127.8 (d, J = 14.7 Hz), 127.1 (d, J = 11.1 Hz), 125.3 (s), 122.0 (d, J = 164.7 Hz), 103.7 (d, J = 11.8 Hz), 41.2 (s), 34.0 (d, J = 5.8 Hz), 20.0 (s), 14.0 (s); ^{31}P NMR (121 MHz, $CDCl_3$) δ 18.5 (s); MS (ESI): m/z: 314 $[M + H]^+$, 336 $[M + Na]^+$, 352 $[M + K]^+$; Anal. Calcd for $C_{18}H_{20}NO_2P$: C, 69.00; H, 6.43; N, 4.47. Found: C, 68.78; H, 6.56; N, 4.45.

*1-Benzylamino-3-phenylbenzo[c][1,2]oxaphosphinine 1-oxide (**2b**).* White solid, mp: 147–148 °C. Yield: 91%. IR (KBr): 3267, 3057, 3026, 2910, 1624, 1492, 1472, 1447, 1413, 1332, 1287, 1241, 1217, 1148, 1112, 1075, 1051, 1023, 914 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (ddd, J = 14.1, 7.6, 0.5 Hz, 1H), 7.76–7.69 (m, 2H), 7.53 (td, J = 7.6, 0.7 Hz, 1H), 7.44–7.06 (m, 10H), 6.64 (s, 1H), 4.13(s, 1H), 4.07–4.01 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7 (d, J = 9.7 Hz), 139.4 (d, J = 5.4 Hz), 138.4 (d, J = 7.1 Hz), 133.8 (d, J = 5.5 Hz), 132.9 (s), 130.0 (d, J = 9.3 Hz), 129.61(s), 128.7 (s), 127.9 (s), 127.7 (s), 127.5 (s), 127.5 (s), 127.2 (d, J = 11.4 Hz), 125.3 (s), 122.0 (d, J = 165.2 Hz), 103.7 (d, J = 12.0 Hz), 45.4 (s); ^{31}P NMR (121 MHz, $CDCl_3$) δ 17.9 (s); MS (ESI): m/z: 346 $[M - 1]^-$, 348 $[M + H]^+$, 370 $[M + Na]^+$, 386 $[M + K]^+$; Anal. Calcd for $C_{18}H_{20}NO_2P$: C, 72.61; H, 5.22; N, 4.03. Found: C, 72.89; H, 5.02; N, 4.08.

*1-Benzylamino-3-butylbenzo[c][1,2]oxaphosphinine 1-oxide (**2c**).* Oil. Yield: 64%. IR (film): 3183, 3065, 2959, 2930, 2872, 1725, 1656, 1596, 1468, 1428, 1379, 1343, 1227, 1148, 1106, 1045, 964, 912 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (dd, J = 14.0, 7.6 Hz, 1H), 7.54–7.43 (m, 1H), 7.37–7.07 (m, 7H), 5.86 (s, 1H), 3.96 (dd, J = 11.5, 6.7 Hz, 2H), 3.91–3.77 (m, 1H), 2.44–2.24 (m, 2H), 1.67–1.52 (m, 2H), 1.37 (dq, J = 14.1, 7.1 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2 (d, J = 10.5 Hz), 139.3 (d, J = 5.7 Hz), 138.6 (d, J = 7.2 Hz), 132.8 (s), 129.9 (d, J = 9.2 Hz), 128.7 (s), 127.5 (s), 127.3 (s), 127.1 (s), 126.1 (d, J = 11.2 Hz), 121.2 (d, J = 164.3 Hz), 104.2 (d, J = 11.9 Hz), 45.2 (s), 34.9 (d, J = 4.5 Hz), 28.9 (s), 22.5 (s), 14.2 (s); ^{31}P NMR (121 MHz, $CDCl_3$) δ 17.9 (s); MS (ESI): m/z: 328 $[M + H]^+$; HRMS (EI): calcd for $C_{19}H_{22}NO_2P$ (M^+): 327.1383; found: 327.1384.

*1-Benzylamino-7-chloro-3-butylbenzo[c][1,2]oxaphosphinine 1-oxide (**2d**).* White solid, mp: 74–77 °C. Yield: 83%. IR (KBr): 3155, 2956, 2927, 1722, 1661, 1528, 1459, 1385, 1344, 1218, 1160, 1099, 1004, 973 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (dd, J = 14.6, 2.0 Hz, 1H), 7.44 (dd, J = 8.4, 2.2 Hz, 1H), 7.36–7.21 (m, 5H), 7.12 (dd, J = 8.4, 5.9 Hz, 1H), 5.86 (s, 1H), 4.00 (d, J = 11.6 Hz, 2H), 3.63 (s, 1H), 2.35 (td, J = 7.4, 3.5 Hz, 2H), 1.68–1.53 (m, 2H), 1.37 (ddt, J = 8.6, 7.2, 4.1 Hz, 2H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6 (d, J = 10.5 Hz), 138.9 (d, J = 5.1 Hz), 136.8 (d, J = 6.7 Hz), 133.0 (d, J = 1.5 Hz), 132.9 (s), 132.6 (s), 129.6 (d, J = 10.5 Hz), 128.7 (s), 127.7 (s), 127.5 (s), 123.0 (d, J = 163.4 Hz), 103.5 (d, J = 11.7 Hz), 45.3 (s), 34.9 (d, J = 4.9 Hz), 28.8 (s), 22.5 (s), 14.2 (s); ^{31}P NMR (121 MHz, $CDCl_3$) δ 15.9 (s); MS (ESI): m/z: 362 $[M + H]^+$, 384 $[M + Na]^+$; Anal. Calcd for $C_{19}H_{21}ClNO_2P$: C, 63.07; H, 5.85; N, 3.87. Found: C, 63.21; H, 5.58; N, 3.79.

*1-Butylamino-7-chloro-3-butylbenzo[c][1,2]oxaphosphinine 1-oxide (**2e**).* Oil. Yield: 72%. IR (film): 3208, 2957, 2869, 1721, 1656, 1471, 1384, 1343, 1285, 1230, 1103, 1047, 962 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 14.3 Hz, 1H), 7.41 (d, J = 8.3 Hz, 1H), 7.09 (dd, J = 8.1, 6.0 Hz, 1H), 5.84 (s, 1H), 3.74 (s, 1H), 2.83–2.64 (m, 2H), 2.50–2.28 (m, 2H), 1.63 (dt, J = 15.4, 7.6 Hz, 2H), 1.51–1.22 (m, 6H), 0.88 (dt, J = 26.2, 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6 (d, J = 10.7 Hz), 136.8 (d, J = 6.7 Hz), 132.7 (s), 132.5 (s), 129.4 (d, J = 10.4 Hz), 127.6 (d, J = 12.2 Hz), 123.4 (d, J = 163.3 Hz), 103.5 (d, J = 11.7 Hz), 41.1 (s), 35.0 (d, J = 4.8 Hz), 33.9 (d, J = 5.7 Hz), 28.9 (s), 22.4 (s), 20.0 (s), 14.2 (s), 14.0 (s); ^{31}P NMR (121 MHz, $CDCl_3$) δ 16.2 (s); MS (ESI): m/z: 328 $[M + H]^+$, 350 $[M + Na]^+$; Anal. Calcd for $C_{16}H_{23}ClNO_2P$: C, 58.63; H, 7.07; N, 4.27. Found: C, 58.65; H, 7.08; N, 3.98.

*1-Butylamino-7-chloro-3-phenylbenzo[c][1,2]oxaphosphinine 1-oxide (**2f**).* White solid, mp: 110–112 °C. Yield: 81%. IR (KBr): 3232, 3061, 2967, 2929, 2869, 1629, 1580, 1492, 1467, 1446, 1427, 1385, 1336, 1281, 1235, 1195, 1149, 1124, 1043, 1022, 979 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88–7.72 (m, 3H), 7.50 (dd, J = 8.4, 1.7 Hz, 1H), 7.46–7.35 (m, 3H), 7.29 (dd,

J = 8.4, 5.8 Hz, 1H), 6.63 (d, J = 1.7 Hz, 1H), 3.53 (s, 1H), 2.84 (m, 2H), 1.54–1.40 (m, 2H), 1.40–1.25 (m, 2H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8 (d, J = 9.3 Hz), 136.7 (d, J = 6.4 Hz), 133.4 (d, J = 15.4 Hz), 133.1 (s), 132.9 (s), 129.8 (s), 129.4 (d, J = 10.4 Hz), 128.8 (s), 128.6 (s), 125.3 (s), 124.2 (d, J = 160.8 Hz), 102.9 (d, J = 11.6 Hz), 41.2 (s), 33.9 (d, J = 5.5 Hz), 20.0 (s), 14.0 (s); ^{31}P NMR (121 MHz, $CDCl_3$) δ 16.1 (s); MS (ESI): m/z: 348 $[M + H]^+$, 370 $[M + Na]^+$, 386 $[M + K]^+$; Anal. Calcd for $C_{18}H_{19}ClNO_2P$: C, 62.16; H, 5.51; N, 4.03. Found: C, 61.97; H, 5.556; N, 3.94.

*1-Benzylamino-7-methoxy-3-phenylbenzo[c][1,2]oxaphosphinine 1-oxide (**2g**).* White solid, mp: 172–176 °C. Yield: 81%. IR (KBr): 3161, 3026, 3004, 2916, 1955, 1893, 1736, 1631, 1598, 1552, 1489, 1452, 1415, 1330, 1313, 1287, 1265, 1215, 1180, 1122, 1077, 1038, 1022, 920 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78–7.72 (m, 2H), 7.45–7.21 (m, 10H), 7.14 (ddd, J = 8.4, 2.8, 0.4, 1H), 6.64 (d, J = 1.9 Hz, 1H), 4.18–4.00 (m, 2H), 3.83 (s, 3H), 3.69–3.60 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0 (d, J = 18.1 Hz), 148.6 (d, J = 9.7 Hz), 139.1 (d, J = 5.9 Hz), 133.6 (d, J = 6.1 Hz), 131.3 (d, J = 6.9 Hz), 129.1 (s), 128.9 (s), 128.7 (s), 128.6 (d, J = 6.0 Hz), 127.4 (s), 127.3 (s), 124.8 (s), 122.8 (d, J = 164.7 Hz), 120.8 (d, J = 2.8 Hz), 112.5 (d, J = 10.7 Hz), 103.1 (d, J = 11.7 Hz), 55.6 (s), 45.0 (s); ^{31}P NMR (121 MHz, $CDCl_3$) δ 22.6 (s); MS (ESI): m/z: 378 $[M + H]^+$; Anal. Calcd for $C_{22}H_{20}NO_3P$: C, 70.02; H, 5.34; N, 3.71. Found: C, 70.06; H, 5.39; N, 3.58.

*1-Butylamino-7-methoxy-3-phenylbenzo[c][1,2]oxaphosphinine 1-oxide (**2h**).* White solid, mp: 158–161 °C. Yield: 90%. IR (KBr): 3235, 3071, 3009, 2960, 2932, 2870, 1886, 1756, 1632, 1596, 1552, 1485, 1335, 1284, 1268, 1212, 1178, 1128, 1105, 1079, 1037, 1021, 977 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.79 (m, 2H), 7.46–7.28 (m, 5H), 7.14 (dd, J = 8.6, 2.4 Hz, 1H), 6.64 (d, J = 1.4 Hz, 1H), 3.89 (s, 3H), 3.33 (s, 1H), 2.96–2.75 (m, 2H), 1.53–1.41 (m, 2H), 1.38–1.25 (m, 2H), 0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0 (d, J = 18.0 Hz), 148.6 (d, J = 9.6 Hz), 133.8 (d, J = 5.9 Hz), 131.3 (d, J = 6.8 Hz), 129.0 (s), 128.7 (d, J = 13.4 Hz), 128.5 (s), 124.8 (s), 123.2 (d, J = 164.4 Hz), 120.4 (d, J = 1.9 Hz), 112.7 (d, J = 10.5 Hz), 103.1 (d, J = 11.6 Hz), 55.6 (s), 40.8 (s), 33.7 (d, J = 5.8 Hz), 19.6 (s), 13.6 (s); ^{31}P NMR (121 MHz, $CDCl_3$) δ 18.0 (s); MS (ESI): m/z: 344 $[M + H]^+$; Anal. Calcd for $C_{19}H_{22}NO_3P$: C, 66.46; H, 6.46; N, 4.08. Found: C, 66.37; H, 6.50; N, 4.00.

*1-Benzylamino-3-phenyl-4-chlorobenzo[c][1,2]oxaphosphinine 1-oxide (**2i**).* White solid, mp: 158–159 °C. Yield: 73%. IR (KBr): 3162, 2898, 1592, 1491, 1445, 1224, 1151, 1117, 1072, 1004, 963 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97–7.90 (m, 1H), 7.83 (dd, J = 14.6, 7.5 Hz, 1H), 7.76–7.63 (m, 3H), 7.48–7.41 (m, 4H), 7.25–7.23 (m, 5H), 4.45 (s, 1H), 4.07 (dd, J = 11.8, 7.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.3 (d, J = 10.4 Hz), 139.1 (d, J = 5.6 Hz), 137.1 (d, J = 6.5 Hz), 133.6 (d, J = 4.6 Hz), 133.1 (s), 129.9 (s), 129.7 (s), 129.6 (s), 128.8 (s), 128.6 (s), 128.1 (s), 127.6 (s), 125.8, 125.7, 122.7 (d, J = 165.3 Hz), 113.4 (d, J = 12.4 Hz), 45.5 (s); ^{31}P NMR (121 MHz, $CDCl_3$) δ 16.4 (s); MS (ESI): m/z: 380 $[M - H]^-$, 382 $[M + H]^+$, 404 $[M + Na]^+$, 420 $[M + K]^+$; Anal. Calcd for $C_{21}H_{17}ClNO_2P$: C, 66.06; H, 4.49; N, 3.67. Found: C, 66.144; H, 4.606; N, 3.60.

*1-Benzylamino-3-phenyl-4-bromobenzo[c][1,2]oxaphosphinine 1-oxide (**2j**).* White solid, mp: 149–151 °C. Yield: 76%. IR (KBr): 3179, 2895, 1587, 1490, 1454, 1282, 1248, 1222, 1151, 1118, 1068, 1002, 938 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98–7.92 (m, 1H), 7.80 (dd, J = 14.6, 7.5 Hz, 1H), 7.67–7.63 (m, 3H), 7.42 (t, J = 7.0 Hz, 4H), 7.23 (s, 5H), 4.48 (s, 1H), 4.06 (dd, J = 11.4, 1.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5 (d, J = 10.0 Hz), 139.0 (d, J = 5.6 Hz), 137.7 (d, J = 6.6 Hz), 135.1 (d, J = 4.7 Hz), 133.2 (s), 129.9 (s), 129.8 (s), 129.6 (s), 128.8 (s), 128.7 (d, J = 14.1 Hz), 128.5, 128.3, 128.0 (s), 127.6 (s), 122.8 (d, J = 165.6 Hz), 104.2 (d, J = 12.2 Hz), 45.5 (s); ^{31}P NMR (121 MHz, $CDCl_3$) δ 16.5 (s); MS (ESI): m/z: 424 $[M - H]^-$, 428 $[M + H]^+$, 450 $[M + Na]^+$; Anal. Calcd for $C_{21}H_{17}BrNO_2P$: C, 59.17; H, 4.02; N, 3.29. Found: C, 59.21; H, 4.141; N, 3.24.

*1-Benzylamino-3-phenyl-4-iodobenzo[c][1,2]oxaphosphinine 1-oxide (**2k**).* White solid, mp: 127–128 °C. Yield: 84%. IR (KBr): 3179, 2894, 1574, 1547, 1488, 1453, 1280, 1252, 1217, 1151, 1118, 1062, 1025, 1000, 925 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98–7.89 (m, 1H), 7.78 (dd, J = 14.6, 7.5 Hz, 1H), 7.68–7.56 (m, 3H), 7.48–7.39 (m, 4H), 7.32–7.20 (m, 5H), 4.22–3.99 (m, 2H), 3.73 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1 (d, J = 10.0 Hz), 139.3 (d, J = 6.8 Hz), 138.9 (d, J = 6.5 Hz), 137.7 (d, J = 4.4 Hz), 133.4 (s), 133.3 (d, J = 10.6 Hz), 130.2 (s), 129.9 (s), 129.6 (d, J = 9.3 Hz), 128.9 (s), 128.7 (s), 128.1 (s), 127.6 (s), 127.5 (s), 122.5 (d, J = 165.6 Hz), 80.3 (d, J = 11.7 Hz), 45.5 (s); ^{31}P NMR (121 MHz, $CDCl_3$) δ 16.2 (s); MS (ESI): m/z: 474 $[M + H]^+$, 496 $[M + Na]^+$, 512 $[M + K]^+$; Anal. Calcd for $C_{21}H_{17}INO_2P$: C, 53.30; H, 3.52; N, 2.96. Found: C, 52.95; H, 3.629; N, 2.85.

Acknowledgements

This work was supported by research grants from the National Natural Science Foundation of China (grant no. 20602043).

Notes and references

1 For recent representative examples and reviews, see: (*a*) J. D. Goodreid, P. A. Duspara, C. Bosch and R. A. Batey, *J. Org. Chem.*, 2014, **79**, 943–954; (*b*) T. L. Ohshima, Y. Hayashi, K. Agura, Y. Fuji, A. Yoshiyama and K. Mashima, *Chem. Commun.*, 2012, **48**, 5434–5436; (*c*) B. Gnanaprakasam and D. Milstein, *J. Am. Chem. Soc.*, 2011, **133**, 1682–1685; (*d*) A. El-Faham and F. Albericio, *Chem. Rev.*, 2011, **111**, 6557–6602; (*e*) C. L. Allen and J. M. J. Williams, *Chem. Soc. Rev.*, 2011, **40**, 3405–3415; (*f*) V. R. Pattabiraman1 and J. W. Bode1, *Nature*, 2011, **480**, 471–479; (*g*) H. Charville, D. Jackson, G. Hodges and A. Whiting, *Chem. Commun.*, 2010, **46**, 1813–1823.

2 (*a*) M. Quintiliani, J. Balzarini and C. McGuigan, *Tetrahedron*, 2013, **69**, 9111–9119; (*b*) K.-W. Yang, X. Cheng, C. Zhao, C.-C. Liu, C. Jia, L. Feng, J.-M. Xiao, L.-S. Zhou, H.-Z. Gao, X. Yang and L. Zhai, *Bioorg. Med. Chem. Lett.*,

2011, **21**, 7224–7227; (*c*) C. Xu, R. Hall, J. Cummings and F. M. Raushel, *J. Am. Chem. Soc.*, 2006, **128**, 4244–4245.

3 (*a*) W. P. Malachowski and J. K. Coward, *J. Org. Chem.*, 1994, **59**, 7616–7624; (*b*) W. P. Malachowski and J. K. Coward, *J. Org. Chem.*, 1994, **59**, 7625–7634.

4 (*a*) I. Wilkening, G. Signore and C. P. R. Hackenberger, *Chem. Commun.*, 2011, **47**, 349–351; (*b*) N. Fu, Q. Zhang, L. Duan and J. Xu, *J. Pept. Sci.*, 2006, **12**, 303–309; (*c*) H. Ai, H. Fu and Y. Zhao, *Chem. Commun.*, 2003, 2724–2725.

5 M. Froneman, T. A. Modro, L. Qaba and S. M. Vather, *Tetrahedron Lett.*, 1987, **28**, 2979–2980.

6 (*a*) A.-Y. Peng, F. Hao, B. Li, Z. Wang and Y. Du, *J. Org. Chem.*, 2008, **73**, 9012–9015; (*b*) A.-Y. Peng and Y.-X. Ding, *Tetrahedron*, 2005, **61**, 10303–10308; (*c*) A.-Y. Peng and Y.-X. Ding, *Org. Lett.*, 2004, **6**, 1119–1121; (*d*) A.-Y. Peng and Y.-X. Ding, *J. Am. Chem. Soc.*, 2003, **125**, 15006–15007.

7 (*a*) A. Morrell, M. S. Placzek, J. D. Steffen, S. Antony, K. Agama, Y. Pommier and M. Cushman, *J. Med. Chem.*, 2007, **50**, 2040–2048; (*b*) I. Parveen, D. P. Naughton, W. J. D. Whish and M. D. Threadgill, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2031–2036; (*c*) T. Minami, A. Nishimoto, Y. Nakamura and M. Hanaka, *Chem. Pharm. Bull.*, 1994, **42**, 1700–1702.

8 A.-Y. Peng, Y.-J. Guo, Z.-H. Ke and S. Zhu, *Eur. J. Org. Chem.*, 2008, 5277–5282.

9 (*a*) D. Glynn, D. Bernier and S. Woodward, *Tetrahedron Lett.*, 2008, **49**, 5687–5688; (*b*) A. Novak, L. D. Humphreys, M. D. Walkerb and S. Woodwarda, *Tetrahedron Lett.*, 2006, **47**, 5767–5769; (*c*) D. R. Sidler, T. C. Lovelace, J. M. McNamara and P. J. Reider, *J. Org. Chem.*, 1994, **59**, 1231–1233; (*d*) J. I. Levin, E. Turns and S. M. Weinreb, *Synth. Commun.*, 1982, **12**, 989–993.

10 T. Shimizu, K. Osako and T. Nakata, *Tetrahedron Lett.*, 1997, **38**, 2685–2688.

11 P.-Q. Huang, X. Zheng and X.-M. Deng, *Tetrahedron Lett.*, 2001, **42**, 9039–9041.

12 D. K. An, J. K. Park and W. K. Shin, *Bull. Korean Chem. Soc.*, 2013, **34**, 1592–1594.

13 A.-Y. Peng, Y.-J. Guo, Z. Wang, B. Li and Y. Du, *CN Pat*, 101367840, 2009.

14 N. M. Yoon and Y. S. Gyoung, *J. Org. Chem.*, 1985, **50**, 2443–2450.

15 (*a*) D. C. Bradley, *Adv. Inorg. Chem. Radiochem.*, 1972, **15**, 259–322; (*b*) P. B. Hitchcock, H. A. Jasim, M. F. Lappert and H. D. Williams, *Polyhedron*, 1990, **9**, 245–251; (*c*) V. Passarelli, G. Carta, G. Rossetto and P. Zanella, *Dalton Trans.*, 2003, 1284–1291.