Indian Journal of Chemistry
Vol. 64, February 2025, pp. 183-191
DOI: 10.56042/ijc.v64i2.15274

Synthesis of α-amino phosphonates catalyzed by bifunctional cyclohexane derived thiourea organocatalyst

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Received 24 November 2024; accepted(revised) 22 January 2025

Multicomponent phosphonylation is accomplished by convenient and efficient synthetic method using novel (S)-N-((cyclohexylmethyl) carbamothioyl) pyrrolidine-2-carboxamide (NCCPC) as bifunctional cyclohexane derived thiourea organocatalyst upon the reaction of an amine, substituted aldehyde with diethyl phosphite. This method not only provides novel and excellent complement for the synthesis but also gives green and transition-metal-free protocol, shows a broad substrate scope, providing a variety of α-amino phosphonates in moderate to good yields.

Keywords: Multicomponent phosphorylation, Thiourea organocatalyst, NCCPC, α-amino phosphonates

α-Aminophosphonates have significant importance in medicinal, pharmaceutical and agricultural chemistry[1-5] due to their potential biological activities such as antibiotics[6], herbicides, fungicides, insecticides[7], enzyme inhibitors[8], HIV protease[9], plant growth regulators[10], anti-thrombotic agents[11], peptidases and proteases[12], antibacterial[13], antibiotic[14], anti-oxidant[15], due the structural analogues of α-amino acids[16]. Besides these biological activities, α-hydroxy-phosphonates also acts as a starting material in organic transformations which gives its corresponding phosphonate derivatives[17]. The two major synthetic methods towards α-aminophosphonate derivatives embrace the Kabachnik–Fields (three-component one-pot condensation of an amine, an aldehyde or ketone and a >P(O)H reagent)[18], and the Pudovik (aza-Pudovik) reaction, (>P(O)H species is added on the double bond of imines)[19]. Among these two routes, Kabachnik-Fields reaction probed to be a convenient route for the synthesis of α-amino phosphonates[20]. Various synthetic methodologies have been reported by using different catalysts for the efficient and stipulated synthesis of α-aminophosphonates. Kabachnik-Fields reactions have been reported by using Lewis acid catalyst such as $InCl_3$[21], $LiClO_4$[22,23], $Mg(ClO_4)_2$[24], $ZrOCl_2 \cdot 5H_2O$[25], $Al(H_2PO_4)$[26], $BiCl_3$[27], $FeCl_3$[28], $YbCl_3$[29], $In(OTf)_3$[30], $Ce(OTf)_4$[31], $Al(OTf)_3$[32], CAN[33], $TaCl_5$–SiO_2[34], SmI_2[35], solid acids (montmorillonite KSF, silica sulfuric acid, Amberlyst-15, and Amberlite-IR 120)[36]. This reaction has been promoted by using the base catalysts and also other catalysts such as ZnO, TiO_2, and tosyl chloride and mesoporous aluminosilicate nanocage[37]. However, all of these methods require toxic metal reagents, which are expensive and requires harsh reaction conditions.

Organocatalyst received much attention in recent years to catalyze enantioselective reactions[38]. Now a days, for preparation of chiral building blocks, the design and synthesis of structural versatility of chiral organocatalysts has emerged as a viable strategy. L-proline and its derivatives have become a series of important molecules in asymmetric catalysis due to its rigid structure, easy availability and cheapness. L-proline and secondary amides[39], thiazides[40], sulfonamides[41], dipeptides[42] and tetrazole[43] containing analogues, have successfully used for asymmetric synthesis. L-proline and its analogues have shown influential values in conjugate reaction[44], like aldol reaction[45], Mannich reaction[46], aza-Diels–Alder reaction[47], Friedel–Crafts reaction[48], Strecker reaction[49], aza-Morita–Baylis–Hillman reaction[50], carbon–heteroatom bond formation[51] and others[52]. There are number of chemical reasons which prove the role of L-proline in catalysis. Bifunctional asymmetric catalysis has become a very successful strategy in the laboratory[53]. There are several ways that L-proline gives different asymmetric transformations, through iminium intermediate, hydrogen bonding formation etc[54].

These catalysts effectively initiated asymmetric reactions; however, they also show some inherently intractable disadvantages. Enzymes are of high activity and enantioselectivity, but unstable and insoluble in organic solvents. For metal-based catalysts, the major disadvantage is the residual metal in the products. Small molecule organocatalysts exhibit difficulty in recovery and reuse, and immobilization of the catalysts on support can only partly solve this problem[55]. Accordingly, developing novel catalysts, which combine the respective advantages of the catalysts mentioned above and meanwhile circumvent the disadvantages aforementioned, is an excellent choice. However, designing and preparing such catalysts currently remains a big challenge.

Now a days thiourea based organocatalysts are mostly used for asymmetric aldol reaction, Mannich reaction and Micheal reaction. Chiral ureas and thioureas have recently arisen as highly enantioselective catalysts for the addition of carbon nucleophiles to activated π-systems[56]. Therefore, the thiourea based organocatalyst reported in this article provide a new opportunity. The novel micro spheres are prepared artificially from L-proline shows interesting asymmetric catalysis performance, and can be easily recycled. Thus, herein we discussed the synthesis of α-Amino phosphonates from amines, aldehydes or ketones and phosphonate ester using novel L-proline analogues as organocatalyst.

Results and Discussion

NCCPC simultaneously activate both acceptor and donor, due to this bifunctional activation, used as an important strategy in asymmetric small molecular catalysis. Here, NCCPC catalyst is used due to its strong activation of carbonyl groups through efficient double hydrogen-bonding interactions. NCCPC has two catalytic sites of thiourea and L-prolic amide skeleton, due to which it has drawn special attentions to catalyze the Kabachnik-Field reaction of substituted aromatic aldehydes and aniline with diethyl phosphite.We expected that this bifunctional catalyst could be used to catalyze Kabachnik-Field reaction.

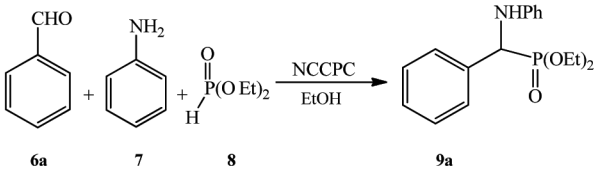
We started a research program, in order to develop general, practical and an environmentally benign method for the synthesis of α-amino phosphonates. During our probe, we viewed that it might be possible to prepare α-amino phosphonates through a one-pot three component reaction of substituted aldehyde, amine and diethyl phosphite using organocatalyst. Herein, we disclose the successful outcome of this attempt in which a new class of densely substituted α-amino phosphonates was prepared in good to excellent yields *via* a three-component reaction.

In the present work, NCCPC is the key catalyst for the interpretation of the three-component reactions. All the reactions were performed in ethanol under mild and metal-free conditions. In most cases, the products were obtained with exclusive selectivity, and the by-product generated in this system is only water. All these properties endowed our system toward green organic synthesis.

In order to describe the standard operating conditions, the reaction between benzaldehyde, aniline and diethyl phosphite was chosen as a model reaction. For optimization of the reaction, initially various catalysts were tested for the model reaction. A summary of the experiment optimization is provided in Table 1. Surprisingly, it was observed that, NCCPC was the most efficient catalyst compared with cyclodextrin, Me_3SiCl, $POCl_3$, Iodine, $PdCl_2$, $SnCl_2$ and $ZnCl_2$, which exhibited from moderate to poor catalytic properties (as shown in Table 1). Surprising result was obtained, when NCCPC used as catalyst (Table 1, entry 12, 10mol%, 92% yield). Effect of the amount of catalyst was also examined in this reaction. The results showed that low and larger amounts of the catalyst did not lead to any significant changes in the reaction yield. Only 10 mol% amount of the catalyst was sufficient to promote the reaction. Also we studied the model reaction catalyzed by NCCPC in different solvents. When reaction was carried out in EtOH at room temperature, the good yield could be obtained in a short time. The reaction was also carried out at above room temperature *i.e.* at 50 ^{o}C and 60 ^{o}C, the rate of formation of the expected product was improved but not the yield. Thus, based on overall circumstances, NCCPC catalyst in ethyl alcohol at room temperature should be a reasonable choice.

With this optimized procedure, a range of α-amino phosphonates were synthesized by the one-pot condensation of substituted benzaldehyde, aniline and diethyl phosphite under eco-friendly condition. The reaction preceded about 30-40 min in excellent yields at room temperature after the addition of the catalyst (see Table 2). The detailed mechanism of the above reaction remains to be fully clarified by the

Table 1 — Optimization of the reaction conditions for the synthesis of α-amino phosphonates

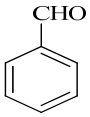
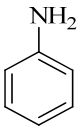
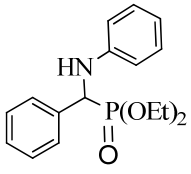
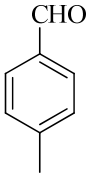
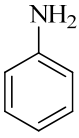
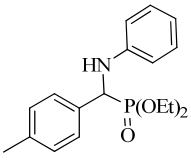
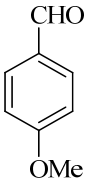
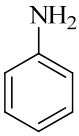
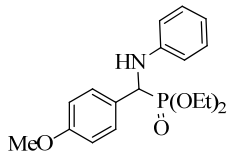


6a **7** **8** **9a**

Sr. No.	Catalyst	Solvent	Catalytic loading (mol%)	Temperature (°C)	Reaction Time (Min)	Yield (%)
1	β-cyclodextrin	DMF	10	RT*	70	80
2	Me_3SiCl	EtOH	10	RT	80	65
3	$POCl_3$	EtOH	10	RT	120	40
4	Iodine	Water	10	RT	75	85
5	$PdCl_2$	Water	10	RT	85	50
6	$Sncl_2$	EtOH	10	RT	150	35
7	$Zn(OTf)_2$	DMF	10	RT	100	82
8	$Zn(OTf)_2$	DCM	10	RT	80	75
9	NCCPC	Water	10	RT	65	78
10	NCCPC	DCM	10	RT	55	81
11	NCCPC	DMF	10	RT	72	90
12	NCCPC	EtOH	10	RT	30	92
13	NCCPC	EtOH	10	RT	30	92
14	NCCPC	EtOH	10	50	25	78
15	NCCPC	EtOH	10	60	21	75
16	NCCPC	EtOH	05	RT	60	80
17	NCCPC	EtOH	20	RT	55	72

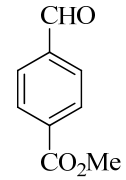
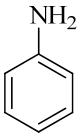
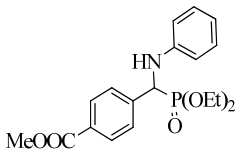
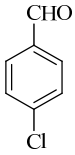
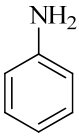
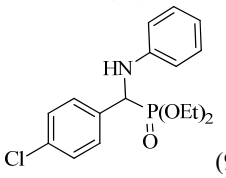
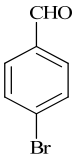
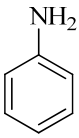
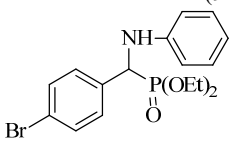
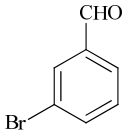
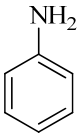
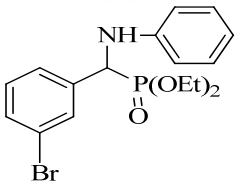
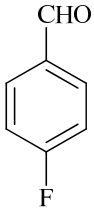
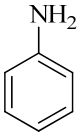
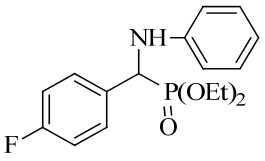
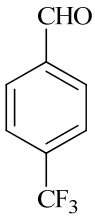
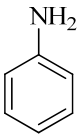
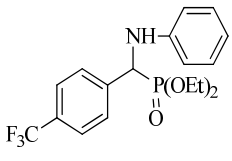
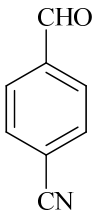
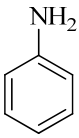
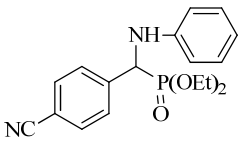
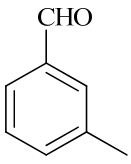
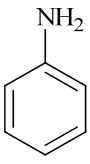
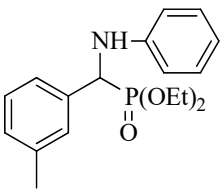
RT: Room Temperature

Table 2 — Exploration of the substrate scope for the synthesis of α-amino phosphonates derivatives using NCCPC

Entry	Carbonyl compound 6(a-s)	Amine 7	Product 9(a-s)	Time in min	Yield[a] (%)
1			 (9a)	30	92
2			 (9b)	32	90
3			 (9c)	35	89

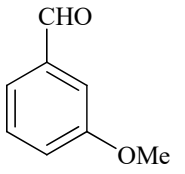
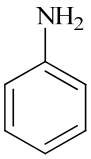
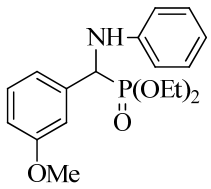
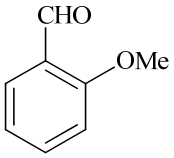
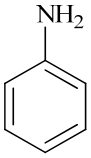
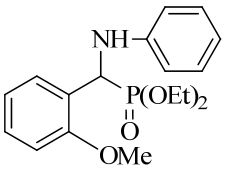
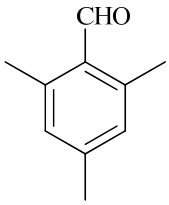
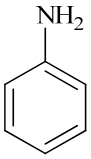
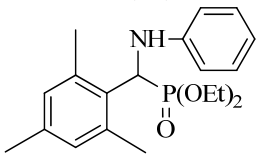
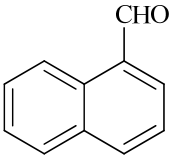
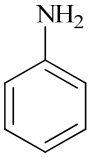
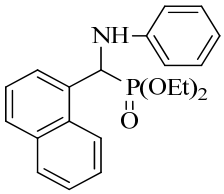
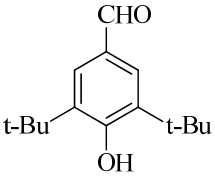
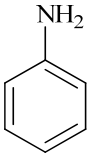
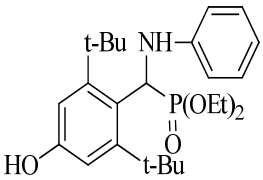
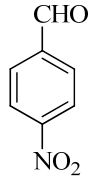
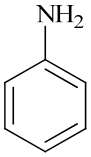
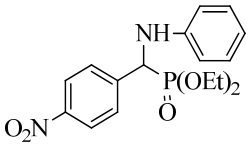
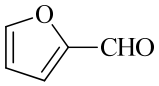
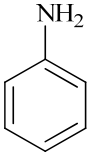
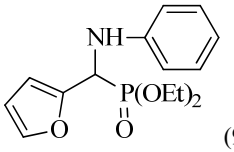
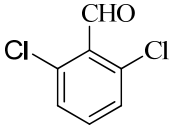
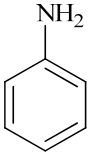
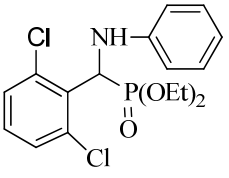
(*contd.*)

Table 2 — Exploration of the substrate scope for the synthesis of α-amino phosphonates derivatives using NCCPC (*contd.*)

Entry	Carbonyl compound 6(a-s)	Amine 7	Product 9(a-s)	Time in min	Yield[a] (%)
4			 (9d)	31	93
5			 (9e)	40	89
6			 (9f)	30	91
7			 (9g)	36	93
8			 (9h)	38	95
9			 (9i)	32	96
10			 (9j)	31	95
11			 (9k)	35	91

(*contd.*)

Table 2 — Exploration of the substrate scope for the synthesis of α-amino phosphonates derivatives using NCCPC (*contd.*)

Entry	Carbonyl compound 6(a-s)	Amine 7	Product 9(a-s)	Time in min	Yield[a] (%)
12			 (9l)	30	88
13			 (9m)	30	94
14			 (9n)	32	90
15			 (9o)	33	91
16			 (9p)	38	88
17			 (9q)	30	93
18			 (9r)	40	90
19			 (9s)	40	90

[a]Isolated Yield

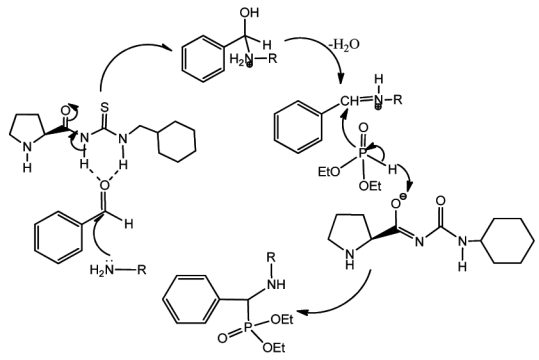


Fig. 1 — Plausible mechanism

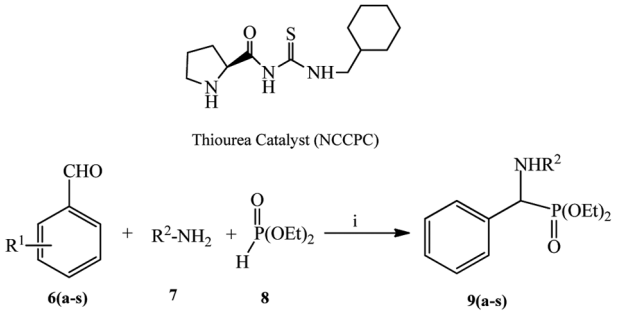


Fig. 2 — Reaction Conditions and Reagents: (i) NCCPC catalyst (10 mol%), Ethyl alcohol (10mL), Stir for 30-40 min at RT, 90-96%

Kabachnik–Fields reaction. A plausible mechanism is depicted in Fig. 1.

To establish the particularity, various aldehydes were subjected to a one-pot three-component reaction with aniline and triphenyl phosphites catalyzed by NCCPC (Table 2). It was observed that electronic and steric effects of the substituents on aromatic aldehydes, affect in the three-component couplings. Aromatic aldehydes with both electron-donating and withdrawing groups could be accomplished the one-pot reaction (Table 2, entries 2, 3, 4, 5, 6, 9 and 10) as well as that with electron-withdrawing group like *p*-nitro (Table 2, entry 17). Besides, the steric effect from the substituent positions looked to be another significant impact (Table 2, entry 16). For *p*-chloro and 2,6-dichlorobenzaldehyde (Table 2, entries 5–19 respectively), the reaction time was extended while the yields of products were moderately decreased. The reaction was compatible with various functional groups such as Cl, Br, F, OMe, NO_2, OH, t-Bu, CN, CH_3 and CO_2Me that do not interfere by competitive complex formation with the catalyst. Moreover, heteroaromatic aldehydes and napthaldehydes were all effective substrates to successfully execute the solvent-free Kabachnik-Field reactions by NCCPC.

Experiment Section

Synthesis of α-amino phosphonates

General details

All solvents were used as commercial anhydrous grade without further purification. Aluminium sheets 20 x 20 cm, Silica gel 60 $F_{254,}$ Merck grade was used for thin layer chromatography to determine progress of reaction. Melting points were determined in open capillary tube and are uncorrected. ^{1}H and ^{13}C-NMR spectra were recorded on a Brucker AV-400 MHz and 126 MHZ spectrometer in $CDCl_3$ solvent.

General method for the Synthesis of Organocatalyst(S)-N-((cyclohexylmethyl) carbamo thioyl) pyrrolidine-2-carboxamide (NCCPC)

We used the general method for the synthesis of Organocatalyst(S)-N-((cyclohexylmethyl) carbamothioyl) pyrrolidine-2-carboxamide (NCCPC) from our previously published work[57] (Fig. 2).

General method for the synthesis of α-amino phosphonates

A mixture of aldehydes (1mmol, 1.0 equiv.), amine (1mmol, 1.0 equiv.) and Diethyl Phosphite (1.2 mmol, 1.2 equiv.) and NCCPC (10 mol%) in ethyl alcohol was stirred for a 30-40 min. After completion of reaction as monitored by TLC, EtOAc (2×10 ml) was added to the reaction mixture and catalyst was separated from reaction mixture by filtration. Organic layer was removed under reduced pressure. After purification by chromatography on silica gel (Ethyl acetate and n-Hexane 20:80) α-amino phosphonates were obtained. All products were characterized by IR, NMR, ^{13}C-NMR and Mass spectral and ^{31}P-NMR-spectral data, which for the known compounds were found to be identical with those described in literature.

Characterization of α-amino phosphate derivatives

Diethyl (phenyl (phenylamino)methyl)phos phonate, 9a: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, 2H), 7.42 – 7.10 (m, 5H), 6.77 (d, 2H), 6.65 (t,1H), 5.2 (s, 1H), 4.19 – 3.86 (m, 4H),3.42(s, NH), 1.32 (q, 6H). $^{13}C\{1H\}$ NMR (126 MHz, $CDCl_3$): δ 152.3 (d), 133.4 (d), 130.2, 129.2 (d), 127.6, 127.4, 119.1, 113.8, 63.6 (d), 62.4, 61.3 (d), 60.4(d), 16.5 (d), 16.2 (d). $^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 21.6. Elemental Analysis: Calculated: C, 63.94; H, 6.94; N,

4.39; O, 15.03; P, 9.70; Found: C, 63.91; H, 6.92; N, 4.37; O, 15.01; P, 8.98.

Diethyl((phenylamino)(*p*-tolyl)methyl) phosphor nate, 9b: ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.46 (d, 2H), 7.35 (t, 2H), 7.22 (d, 2H), 6.77 (d, 2H), 6.66 (t,1H), 5.2 (s, 1H), 4.26 – 4.01 (m, 4H), 3.91 (s, NH), 2.82 (s, 3H), 1.34 – 1.28 (m, 6H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 152.3 (d), 139.6, 133.2 (d), 129.1, 126.8 (d), 119.8, 113.8, 63.2 (d), 62.9 (d), 58.6 (d), 22.3, 16.5 (d), 16.2 (d). $^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 22.1. Elemental Analysis: Calculated: C, 64.85; H, 7.26; N, 4.20; O, 14.40; P, 9.29; Found: C, 64.82; H, 7.24; N, 4.19; O, 14.38; P, 9.27.

Diethyl ((4-methoxyphenyl) (phenylamino)methyl) phosphonate, 9c: **^{1}H-NMR (400 MHz, $CDCl_3$)**: δ 7.54 (d, 2H), 7.37 –7.34 (m, 2H), 6.79 (dd, 4H), 6.68 (t,1H), 5.34 (d, 1H), 4.26 – 4.0 (m, 4H), 3.89 (s, NH), 3.77 (s, 3H), 1.32 (q, 6H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 159.2, 152.3 (d), 133.2 (d), 129.1, 127.3 (d), 119.1, 115.2, 114.7, 64.1 (d), 63.1 (d), 61.5 (d), 56.1, 16.5, 16.3. $^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 22.2. Elemental Analysis: Calculated: C, 61.88; H, 6.92; N, 4.01; O, 18.32; P, 8.87; Found:C, 61.86; H, 6.90; N, 3.99; O, 18.30; P, 8.85.

Methyl 4-((diethoxyphosphoryl) (phenylamino) methyl) benzoate, 9d: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, 2H), 7.67 (d, 2H), 7.37 (t,2H), 6.96 (d, 2H), 6.82 (t,1H), 5.21 (s, 1H), 4.32 – 3.98 (m, 4H), 3.62(s, NH), 2.86 (s, 3H), 1.35 – 1.26 (m, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 167.6, 151 (d), 138.7 (d),128.8 (d), 128.3, 127.7 (d), 119.4, 115.9, 64.2 (d), 63.4 (d), 61.8 (d), 53.2 (d), 18.9 (d), 16.4 (d). $^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 21.3.Elemental Analysis: Calculated: C, 61.88; H, 6.92; N, 4.01; O, 18.32; P, 8.87; Found:C, 61.86; H, 6.90; N, 3.99; O, 18.30; P, 8.85.

Diethyl((4-chlorophenyl)(phenylamino)methyl) phosphonate, 9e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d,2H), 7.39 – 7.32 (m,4H), 6.76 (d,2H), 6.68 (t,1H), 5.31 (s,1H), 4.27– 4.2(m, 4H), 3.96 (s, NH), 1.34 – 1.24 (m, 6H).$^{13}C\{^{1}H\}$ NMR(126 MHz, $CDCl_3$): δ 152.2 (d), 135.1, 134.4 (d), 131.4 (d), 128.5, 127.7, 117.4, 115.4, 63.2 (d), 62.2 (dd), 60.5 (d), 16.4 (d), 16.3 (d). $^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$) δ 21.3. Elemental Analysis: Calculated: C, 57.71; H, 5.98; Cl, 10.02; N, 3.96; O, 13.57; P, 8.76; Found: C, 57.69; H, 5.96; Cl, 10.00; N, 3.94; O, 13.55; P, 8.74.

Diethyl((4-bromophenyl)(phenylamino)methyl) phosphonate, 9f: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, 2H), 7.47 (d, 2H), 7.34 (t,2H), 6.77 (d,2H), 6.72 (t, 1H), 5.28 (d,1H), 4.28 – 4.02 (m, 4H), 3.80 (s, NH) 1.36 – 1.30 (m, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 151.2 (d), 134.6 (d), 132.6, 131.5 (d), 128.2, 121.3, 119.4, 115.3, 64.2 (d), 63.3 (d), 61.5 (d), 16.6 (d), 16.4 (d). $^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 21.4. Elemental Analysis: C, 51.25; H, 5.30; Br, 20.04;N, 3.50; O, 12.03; P, 7.76; Found: C, 51.25; H, 5.30; Br, 20.03;N, 3.51; O, 12.03; P, 7.76.

Diethyl (mesityl(phenylamino) methyl) phosphor nate, 9n: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (t, 2H), 6.73 (s, 2H), 6.62 (t,1H), 6.53 (d,2H), 5.31 (d,1H), 4.23 – 4.16 (m, 4H), 3.91 (s, NH), 2.61 (s, 6H), 2.33 (s, 3H), 1.32 (t,3H), 1.20 – 1.17 (m, 3H). $^{13}C\{^{1}H\}$NMR (101 MHz, $CDCl_3$): δ 151.4 (d), 138.1 (d), 128.6, 127.1, 116.6, 114.8, 64.3 (d), 62.8 (d), 62.1, 58.6, 37.3 (d), 20.8, 16.4 (t). $^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 22.5. Elemental Analysis: Calculated: C, 66.46; H, 7.81; N, 3.88; O, 13.28; P, 8.57; Found: C, 66.44; H, 7.79; N, 3.86; O, 13.26; P, 8.55.

Diethyl (naphthalen-1-yl(phenylamino)methyl) phosphonate, 9o: **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 8.36 (d,1H), 7.81 (d, 2H), 7.52 (d, 2H), 7.38 (t,1H), 7.34 – 7.27 (m, 2H), 7.23 (t, H), 7.01 (d, 2H), 6.81 (t,1H), 5.83 (d, 1H), 4.15 – 4.06 (m, 4H), 3.79(s, NH), 1.35 – 1.24 (m, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 148.9 (d), 135.2 (d),133.5 (d), 131.9 (d), 128.6, 128.2, 128.1, 127.7 (d), 125.6, 124.9, 124.2, 124.7, 118.8,114.5 (d), 62.3 (dd), 61.1, 57.5, 16.6 (d), 16.4 (d). $^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 22.5. Elemental Analysis: Calculated: C, 68.28; H, 6.55; N, 3.79; O, 12.99; P, 8.39; Found: C, 68.26; H, 6.53; N, 3.77; O, 12.97; P, 8.36.

Diethyl ((2,6-di-tert-butyl-4-hydroxyphenyl) (phenylamino) methyl) phosphonate, 9p: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 2H), 7.35 – 7.31 (m, 2H), 6.78 (d, 2H), 6.66 (t, 1H), 5.36 (d,1H), 5.28 (s, 1H), 4.22 – 3.82 (m, 4H), 3.78 (s, NH), 1.28 (s, 18H), 1.08 (q, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 152.4 (d), 151.8 (d),136.4 (d), 134.9, 128.3, 124.8 (d), 123.8 (d), 116.8, 115.7 (d), 113.3, 63.8 (d), 63.6, 63.1 (d), 62.0, 35.4, 31.5, 16.8 (d), 16.4 (d). $^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 23.1. Elemental Analysis: Calculated: Elemental Analysis: C, 67.09;

H, 8.56; N, 3.13; O, 14.30; P, 6.92; Found: Elemental Analysis: C, 67.07; H, 8.55; N, 3.11; O, 14.29; P, 6.90.

Diethyl(furan-2-yl(phenylamino)methyl) phosph onate, 9r: **^{1}HNMR(400MHz,$CDCl_3$)**: δ7.47(d,1H), 7.38 – 7.33 (m, 2H), 6.84 (d, 2H), 6.72 (t,1H), 6.54-6.51(m, 1H), 6.26-6.23(m,1H), 5.21 (d, 1H), 4.27 – 4.06 (m, 4H), 3.83 (s, NH), 1.16-1.10 (m, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ151.3 (d), 147.1 (d),141.6 (d), 128.2,114.5,113.4,111.9, 111.8,111.4, 62.5 (d), 56.04, 55.5 (d), 16.6 (d), 16.5 (d). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 20.41. Elemental Analysis: Calculated: C, 58.25; H, 6.52; N, 4.53; O, 20.69; P, 10.01; Found: C, 58.23; H, 6.50; N, 4.51; O, 20.68; P, 10.00.

Conclusion

In summary, this novel work reports efficient and green methodology for the synthesis of phosphonates using novel NCCPC ((S)-N-((cyclohexylmethyl) carbamothioyl) pyrrolidine-2-carboxamide) as bifunctional cyclohexane derived thiourea organocatalyst. NCCPC is the assembly of structurally well-defined cyclohexane scaffold with thiourea moieties and amine functionalities constituted the new class of organocatalyst. The novel NCCPC catalyst is first time used for the synthesis of phosphonates. This catalytic system could be reused with negligible loss in catalytic activity. The advantages of this method include good substrate generality, mild reaction conditions, experimental operation simplicity, high atom economy, environmental impact and high yields.

Acknowledgement

The authors acknowledge SAIF/CIL, Punjab University, Chandigarh and CSIR-IICT, Hyderabad for providing spectral data.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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