JOC The Journal of Organic Chemistry

Article

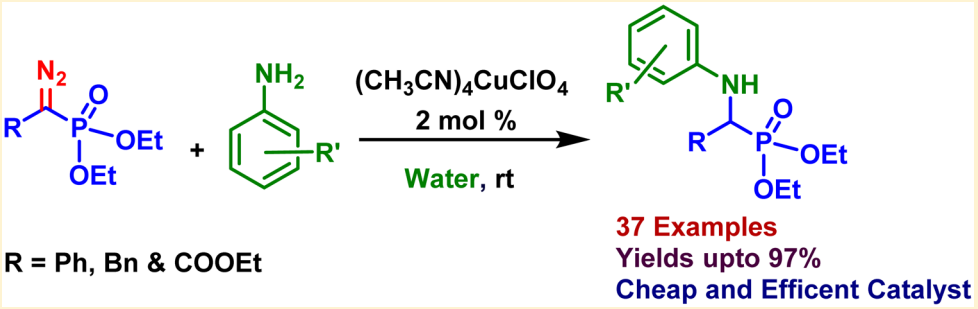
pubs.acs.org/joc

A Green Approach to the Synthesis of α-Amino Phosphonate in Water Medium: Carbene Insertion into the N−H Bond by Cu(I) Catalyst

Kankanala Ramakrishna, Jisha Mary Thomas, and Chinnappan Sivasankar*

Catalysis and Energy Laboratory (A Central University), Department of Chemistry Pondicherry University, Puducherry 605014, India

Supporting Information



ABSTRACT: Synthesis of amino phosphonates is more important owing to their significant applications in the biological systems. There are few methods already known in the literature to make these molecules; however, known methods have their own disadvantages. In this regard, synthesis of different kinds of amino phosphonates have been achieved via phosphonate substituted carbene insertion into the N−H bond of aniline catalyzed by readily available copper salt under mild reaction conditions in water. In order to find an efficient catalyst for carbene insertion reaction in neat water, a large number of transition metal catalysts were screened, and we found that the $[Cu(CH_3CN)_4]ClO_4$ was the best catalyst under employed reaction conditions. Using this environmentally benign methodology (copper catalyzed reaction in water), a large number of biologically important amino phosphonates have been synthesized, isolated (37 examples), and characterized using standard analytical and spectroscopic techniques.

INTRODUCTION

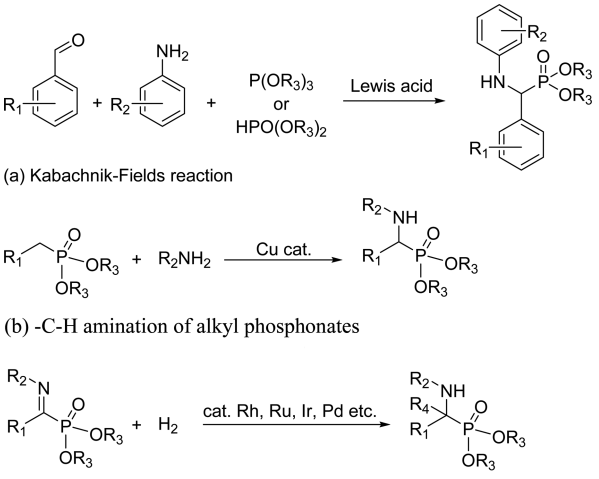
Among the mimics of natural bioactive molecules, α-amino phosphonates are important owing to their vast applications in biochemistry.[1,2] As a result of continuous efforts in this area, utilization of α-amino phosphonates are expanding into many new channels.[3,4] Among all the biological applications of α-amino phosphonates, more importantly it exhibits wide range of potential activities against cancer,[5−8] tuberculosis,[9,10] HIV[11,12] and bacterial agents, etc.[13−15] Amino phosphonates have been used as mimics of peptides, enzyme inhibitors and also as therapeutic agents for many diseases.[16−21] Apart from biological applications of amino phosphonates, α-amino phosphonates are serving as synthons for the construction of many new chemical entities.[22−24] Amino phosphonates facilitate simple methods for the synthesis of highly functionalized indoles, isocoumarins and many other heterocycles.[25−28]

Therefore, synthesis of amino phosphonates becomes more important. In this regard, nucleophilic addition of phosphonates to the imines using Lewis acid as a catalyst is being a current practice. This particular method is also called as Kabachnik−Fields reaction (Scheme 1a).[29,30] Most of the Lewis acids which are used as catalysts in the above method are sensitive toward water, which is generated as a byproduct of the imine formation. To overcome this problem, these reactions are need to be carried out in the presence of dehydrating agents or used water stable Lewis acids such as $InCl_3$, $Mg(ClO_4)_2$, etc.[31−33] For this methodology, researchers have developed different kinds of catalysts such as homogeneous, heterogeneous which includes magnetically separable and biphasic catalysts.[34−37] Owing to the harsh reaction conditions, low selectivity and incompatibility toward synthesis of low molecular weight amino phosphate, researchers have focused on other methods like C−H activation (Scheme 1b) and reduction of imino phosphonates (Scheme 1c), etc.[38−43] In the recent past, owing to the interesting applications of protein modification and protein labeling, more research work have been done on this area.[44−46] Labeling of proteins with phosphonate group may lead to interesting applications in biology; nevertheless, introduction of phosphonate group into the protein fold using the above-mentioned methods are very difficult owing to the harsh reaction conditions and low selectivity.[47] In order to extend the scope of amino phosphonates in biological applications, we need more efficient methods that work under mild reaction conditions possibly in aqueous medium with wide substrate scope and high selectivity.

Received: August 8, 2016
Published: September 29, 2016

DOI: 10.1021/acs.joc.6b01940
J. Org. Chem. 2016, 81, 9826−9835

Scheme 1. Different Approaches to α-Amino Phosphonate Synthesis



On the other hand, metal complexes catalyzed carbene insertion reactions is one of the fast growing methodologies in the present days.[48−50] Carbene insertion reactions provide several advantages such as mild reaction conditions, excellent yields with high enantiomeric excess,[51−54] chemoselective versions[55−57] and viability for protein labeling and modifications.[58−65] Among all the catalysts which are used for carbene insertion reaction, copper catalysts have its own benefits of cost economy, mild reaction conditions, biocompatibility,[63] chemoselectivity[55,56] and asymmetric versions.[51,66,67] In this regard few reports are available in the literature; nevertheless, these systems suffered owing to poor yields and harsh reaction conditions.[68,69] By considering the wide scope of carbene insertion reactions in water, few attempts were made to carry out the carbene insertion reaction in aqueous medium. To the best of our knowledge Che et al.[62] developed the first carbene insertion of diazo ester into aniline in neat water using ruthenium glycosylated porphyrin catalyst, later on Roelfes et al.,[70] Gillingham et al.,[63] Simonneaux et al.[65] and Rhee et al.[64] partially succeeded by developing methods for carbene insertion of diazo ester into aniline in aqueous media (mixture of solvents and buffer) using Cu and Fe based catalysts. However, the reported systems were failed either by complicated catalysts or by use of additives. As we stated earlier, by developing novel synthetic route to make amino phosphonates via carbene insertion reaction in aqueous medium or in neat water, one can make an easy way to labeling the protein and do further modification with enantiomerically pure phosphonates. By considering the importance of amino phosphonate synthesis with high selectivity in neat water and in continuation of our research on Cu(I) catalyzed N−H insertion reactions,[55,56,71] herewith we are reporting a viable method for amino phosphonate synthesis via carbene insertion of diazo phosphonates into aniline under mild reaction conditions with very good yields in neat water (Scheme 2).

RESULTS AND DISCUSSION

The reaction of simple aniline with α-phenyl diazo phosphonate using $Rh_2(OAc)_4$ produced very low yield <10% over 24 h (Table 1, entry 1) in water medium, though we observed 23% yield in DCM. Subsequently we screened

Scheme 2. N−H Insertion of α-Phenyl Diazo Phosphonate into Aniline

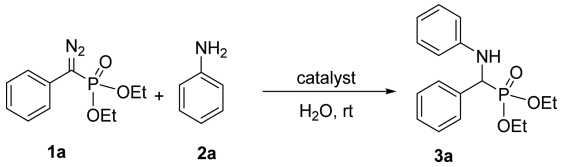


Table 1. Optimization of the Catalysts for N−H Insertion of α-Phenyl Diazo Phosphonate into Aniline in Water

entry[a]	catalyst	catalyst load (mol %)	time	yield (%)[b]
1	$Rh_2(OAc)_4$	1	24 h	<10 (23)
2	$[(COD)RhCl]_2$	1	16 h	81
3	$[Cp^*IrCl_2]_2$	1	24 h	ND (trace)
4	$[(COD)IrCl]_2$	1	24 h	ND
5	$[(p\text{-cymene})RuCl_2]_2$	1	24 h	ND (28)
6	$RuCl_3{\cdot}3H_2O$	2	24 h	trace
7	$RuCl_2(PPh_3)_3$	2	24 h	<10
8	$Pt(AcAc)_2$	2	24 h	trace
9	K_2PtCl_4	2	24 h	trace
10	$Pd_2(dba)_3$	2.5	24 h	34
11	$Pd(PPh_3)_4$	5	24 h	17
12	$PdCl_2$	5	24 h	12 (46)
13	$Pd(OOCH_3)_2$	5	24 h	<10
14	$Pd(OOCF_3)_2$	5	24 h	18
15	CuI	2	8 h	92
16	AgOTf	2	24 h	<10 (26)
17	AuCl	2	24 h	ND (ND)
18	$FeCl_2{\cdot}4H_2O$	5	24 h	<10
19	$Fe(BF_4)_2{\cdot}4H_2O$	5	24 h	11
20	$CoCl_2{\cdot}6H_2O$	5	24 h	<10
21	$Co(OAc)_2{\cdot}4H_2O$	5	24 h	<10
22	$Co(BF_4)_2{\cdot}4H_2O$	5	24 h	trace
23	$NiCl_2{\cdot}6H_2O$	5	24 h	trace
24	$Ni(OAc)_2{\cdot}4H_2O$	5	24 h	ND
25	$MnCl_2$	5	24 h	trace
26	$Mn(OAc)_2{\cdot}4H_2O$	5	24 h	ND
27	$CrCl_3$	5	24 h	trace
28	$InCl_3$	5	24 h	ND
29	$ZnCl_2$	5	24 h	ND
30	$Zn(OAc)_2{\cdot}2H_2O$	5	24 h	trace
31	$VO(SO_4)_2$	5	24 h	ND
32	VCl_3	5	24 h	trace
33	$DyCl_3{\cdot}6H_2O$	5	24 h	trace
34	$CuCl_2{\cdot}2H_2O$	2	15 min	66
35	$Cu(OTf)_2$	2	15 min	87 (81)[c]
36	$Cu(OAc)_2{\cdot}H_2O$	2	15 min	90
37	$Cu(SO_4){\cdot}5H_2O$	2	15 min	89
38	**$(CH_3CN)_4CuClO_4$**	**2**	**15 min**	**94 (87)**[c]
39[d]	$(CH_3CN)_4CuClO_4$	2	15 min	85

[a]All the reactions were carried out with 1 mmol of aniline and 1.1 mmol of diazo in 4 mL of water or DCM in a Schlenk tube under dinitrogen atmosphere. [b]Pure compound from column chromatography. [c]In DCM solvent reaction was completed over 2 h. [d]Reaction was carried out in open air atmosphere. Most of the cases we observed trace amount of water (O−H) inserted product. ND: not detected. Yield in DCM given in parentheses.

$[(COD)RhCl]_2$ as a catalyst (Table 1, entry 2), and it was observed to produce the expected product with 81% over 16 h. After conforming the product formation by standard

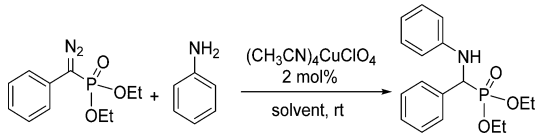
DOI: 10.1021/acs.joc.6b01940
J. Org. Chem. 2016, 81, 9826−9835

spectroscopic techniques, in order to enhance the yield and to reduce the reaction time, we continued our investigation with other possible catalysts for carbene insertion reactions (Table 1). We screened Cp^*IrCl_2 and $[(COD)IrCl]_2$ for carbene insertion; however, both the catalysts were failed to produce the expected product (Table 1, entry 3 and 4). Similarly, Ru based catalysts were also failed to offer the carbene inserted product (Table 1, entry 5−7). We have also tested Pt and Pd based catalysts for the carbene insertion reaction and we observed that Pt catalysts produced only trace amount of product in water (Table 1, entry 8 and 9) while Pd catalysts produced moderate yield in both water and DCM (Table 1, entry 10−14).

Further our screening process upon different types of catalysts was continued to test the coinage metals based catalysts such as CuI, AgOTf, and AuCl toward carbene insertion reaction. Among all the coinage metals catalysts used in the present study, CuI offered very good yield of 92% over 8 h (Table 1, entry 15). In the case of AgOTf we observed <10% and 26% in water and DCM respectively (Table 1, entry 16), whereas in the case of AuCl, we have not observed the expected product. During our investigation to search for good catalysts for carbene insertion reaction, we screened a large number of catalysts in water medium; however, none of the catalysts offered satisfactory yield (Table 1, entry 18−33). In order to reduce the reaction time we continued our screening with various Cu catalysts. Among the screened all possible Cu based catalysts, $(CH_3CN)_4CuClO_4$ offered excellent yields of 94% and 87% in water (15 min) and in DCM (2 h) respectively (Table 1, entry 38). The other Cu catalysts such as $Cu(OTf)_2$, $CuSO_4{\cdot}5H_2O$, and $Cu(OAc)_2{\cdot}H_2O$ were also offered reasonably good yields of 87%, 89%, and 90% respectively over 15 min (Table 1, entry 35−37); however, $CuCl_2{\cdot}2H_2O$ offered relatively low yield of 66% over 15 min (Table 1, entry 34). Though the $CuSO_4{\cdot}5H_2O$ and $Cu(OAc)_2{\cdot}H_2O$ are stable and of environmentally benign nature, to obtain the highest yields we have carried out reactions with $(CH_3CN)_4CuClO_4$ as a catalyst for further study. When we conducted the reaction with $(CH_3CN)_4CuClO_4$ as a catalyst in open atmosphere (Table 1, entry 39), the reaction was completed in 15 min and offered expected product with 85% yield (in closed vessel we obtained 94% (Table 1, entry 38)), and this experiment proved that the carbene intermediate is not sensitive toward open atmosphere like other carbene reactions.[49]

After finding a suitable catalyst for carbene insertion into the N−H bond, we screened various commonly used solvents for carbene insertion using $(CH_3CN)_4CuClO_4$ as a catalyst. In acetonitrile the reaction was not completed even after 24 h and offered maximum of 36% yield (Table 2, entry 2), this could be owing to the interception of carbene generation by acetonitrile binding to Cu(I) center. However, the carbene dimerized product was not observed and the unreacted diazo compounds were recovered. Similar to this observation, other coordinating solvents such as THF, DMSO and DMF were also offered low yields (Table 2, entry 3, 5, and 7). In case of DMSO, we did not observe the N−H inserted product, toluene offered good yield of 82% over 8 h (Table 2, entry 4). When we conducted the reaction in methanol, the reaction was completed within 1 h and offered 67% of N−H inserted product along with 26% of methanol O−H inserted product (Table 2, entry 6). The above screening processes suggested that the water and DCM would be the right solvents for carbene insertion reaction while using our choice of diazo compounds to make a large number of amino phosphonates. Therefore, all the reactions for the present study were carried out using $(CH_3CN)_4CuClO_4$ as a catalyst in water and also in DCM.

Table 2. Solvent Screening for N−H Insertion of α-Phenyl Diazo Phosphonate into Aniline

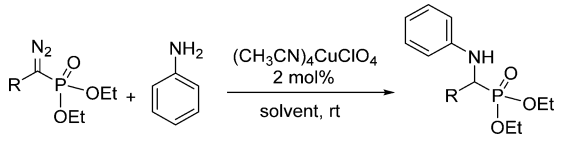


entry[a]	solvent	time	yield (%)[b]
1	DCM	2 h	87
2	CH_3CN	24 h	36
3	THF	6 h	74
4	Toluene	8 h	82
5	DMSO	12 h	trace
6[c]	CH_3OH	1 h	67
7	DMF	12 h	55
8	H_2O	15 min	94

[a]All the reactions were carried out with 1 mmol of aniline and 1.1 mmol of diazo in 4 mL of solvent in a Schlenk tube under dinitrogen atmosphere. [b]Pure compound from column chromatography. [c]We obsereved 26% of methanol O−H inserted product.

In order to show the substrate scope for making different kinds of amino phosphonates through carbene insertion into N−H bond under mild reaction conditions, we screened various diazo phosphonates. We used different kinds of α-aryl diazo phosphonates having electron withdrawing and electron donating substituents. In case of having electron withdrawing substituents, the carbene carbon becomes more electrophilic in nature and becomes susceptible to attack of nucleophiles, therefore reason the reaction was completed very fast, in particular the 2-Cl and 4-Cl substituents produced 93% and 94% yields respectively over 15 min in water medium. In DCM, we observed relatively low yields of 84% and 87% over 30 min and 1 h respectively (Table 3, entry 2 and 3). In case of electron donating 4-OMe substrate, the carbene carbon becomes less electrophilic in nature and stabilizes the carbene

Table 3. Scope of Diazo Phosphonates for N−H Insertion of α-Phenyl Diazo Phosphonates into Aniline



			water		DCM	
entry[a]	R	product	time	yield (%)[b]	time	yield (%)[b]
1	C_6H_5	**3a**	15 min	94	2 h	91
2	2-ClC_6H_4	**3b**	15 min	93	30 min	84
3	4-ClC_6H_4	**3c**	15 min	94	1 h	87
4	4-$MeOC_6H_4$	**3d**	30 min	95	2 h	81
5[c]	benzyl	**3e**	12 h	<10	2 h	∼70
6	$COOC_2H_5$	**3f**	12 h	28	6	43

[a]All the reactions were carried out with 1 mmol of aniline and 1.1 mmol of diazo in 4 mL of water or DCM with 2 mol % of the catalyst in a Schlenk tube under dinitrogen atmosphere. [b]Pure compound from column chromatography. [c]Yield from crude NMR and TLC experiment.

DOI: 10.1021/acs.joc.6b01940
J. Org. Chem. 2016, 81, 9826−9835

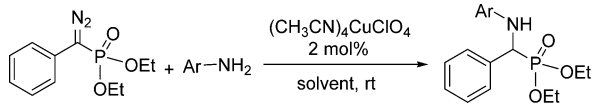
intermediate. Due to this reason the reaction occurred relatively at slow rate and offered excellent yield of 95% over 30 min in water, in DCM we observed 81% product over 2 h (Table 3, entry 4) and these observed trends are comparable with the reaction of rhodium and copper catalyzed α-aryl ester carbene insertion into N−H bond.[53,71] Furthermore, we also selected other substrates to synthesize some novel amino phosphonates (note that the corresponding products could not be synthesized by known conventional methods).[72] In this direction we studied benzyl, ester functionalized diazo phosphonates toward carbene insertion into N−H bond to produce novel amino phosphonates. These derivatives were produced relatively less yield in water when compared to DCM. Ester functionalized diazo phosphonate, which belongs to the acceptor/acceptor class of diazo compounds and relatively less reactive and offered the expected product with 28% yield over 12 h in water and 43% over 6 h in DCM. When the reaction was conducted with the benzyl diazo phosphonate in water, the reaction offered <10% over 12 h and the color of the reaction was turned to green indicating that the Cu(I) ion got oxidized to Cu(II) (Table 3, entry 5).

In order to show the substrate scope for various anilines, we screened a variety of electron donating and withdrawing group substituted anilines. First we have screened anilines having electron donating substituents, all these substrates smoothly underwent the reaction and offered very good yields (Table 4, entry 2−6). Among all the electron donating substituents, 3-methyl aniline offered highest yield (93% in 30 min) in water (Table 4, entry 2) and 4-methoxy aniline offered highest yield of 94% in 4 h in DCM (Table 4, entry 5). The 3,4-dimethoxy aniline offered lowest yield in water (79% in 4 h) (Table 4, entry 6). In case of DCM, 2,4,6-trimethyl aniline offered lowest yield over 4 h (Table 4, entry 4). The steric and electronic factors of different anilines did not show much effect on the yields of the carbene insertion into the N−H bond. We also have screened a large number of anilines having electron withdrawing groups. All the anilines underwent the insertion reaction smoothly and offered good to excellent yields (Table 4, entry 7−22). The anilines having halogens offered relatively very good yields when compared to other anilines having electron withdrawing functional groups.

Among all the screened anilines, 3-Cl aniline offered excellent yield of 97% over 15 min in water (Table 4, entry 10). The 3-nitro aniline offered the highest yield of 93% over 2 h in DCM (Table 4, entry 17) and the 2-aminobenzonitrile offered lowest yield of 44% and 47% in water and DCM over 12 and 8 h respectively (Table 4, entry 19). This might be owing to the formation of relatively stable complex of 2-aminobenzonitrile with Cu(I) salt. Similarly, the reaction was taken much longer time (8 and 5 h) for the completion of the reaction when 4-aminobenzonitrile was used in water and in DCM (Table 4, entry 20). When compared to the reaction in DCM, 2,6-difluoroaniline, 4-iodoaniline and 2-trifluoromethaneaniline offered very good yields in water (Table 4, entry 8, 16 and 21). Further when we used 2-aminopyridine (Table 3, entry 23), interestingly the reaction was completed over 12 h and offered 73% N−H inserted product. However, when we used benzyl amine, we observed only trace amount of the product even after 24 h.

In this line we screened different anilines having other functional groups such as trifluoro methane, acetyl and nitrile groups, and all these aniline derivatives underwent the reaction smoothly and offered very good yields (Table 4, entry 17−22).

Table 4. Scope of Anilines for N−H Insertion of α-Phenyl Diazo Phosphonates



			water		DCM	
entry[a]	Ar	product	time	yield (%)[b]	time	yield (%)[b]
1	4-MeC_6H_4	**4a**	30 min	91	4 h	83
2	3-MeC_6H_4	**4b**	30 min	93	3 h	84
3	2,4-$(Me)_2C_6H_3$	**4c**	2 h	92	4 h	91
4	2,4,6-$(Me)_3C_6H_2$	**4d**	2 h	90	4 h	81
5	4-$OMeC_6H_4$	**4e**	2 h	89	4 h	94
6	3,4-$(OMe)_2C_6H_3$	**4f**	4 h	79	4 h	85
7	4-FC_6H_4	**4g**	15 min	93	2 h	88
8	2,6-$(F)_2C_6H_3$	**4h**	15 min	81	2 h	57
9	4-ClC_6H_4	**4i**	15 min	96	2 h	93
10	3-ClC_6H_4	**4j**	15 min	97	2 h	90
11	2,4,5-$(Cl)_3C_6H_2$	**4k**	30 min	81	2 h	88
12	3-Cl,4-FC_6H_3	**4l**	30 min	92	2 h	90
13	2-BrC_6H_4	**4m**	15 min	92	1 h	83
14	4-BrC_6H_4	**4n**	15 min	93	2 h	87
15	2-Br,4-MeC_6H_3	**4o**	15 min	91	2 h	88
16	4-IC_6H_4	**4p**	15 min	92	3 h	74
17	3-$NO_2C_6H_4$	**4q**	15 min	88	2 h	93
18	4-$NO_2C_6H_4$	**4r**	15 min	85	6 h	81
19	2-CNC_6H_4	**4s**	12 h	44	8 h	47
20	4-CNC_6H_4	**4t**	8 h	78	5 h	85
21	2-$CF_3C_6H_4$	**4u**	30 min	94	2 h	79
22	4-$CH_3COC_6H_4$	**4v**	15 min	81	2 h	70
23[c]	2-Pyridine	**4w**	12 h	73	18 h	68

[a]All the reactions were carried out with 1 mmol of aniline and 1.1 mmol of diazo in 4 mL of water or DCM with 2 mol % of the catalyst in a Schlenk tube under dinitrogen atmosphere. [b]Pure compound from column chromatography. [c]Instead of aniline derivative reaction was carried out with 2-amino pyridine.

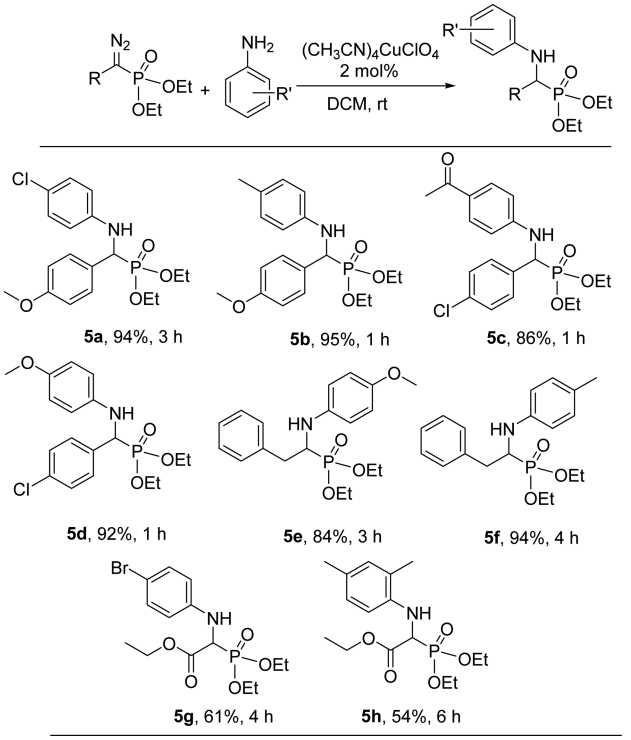
Among all the screened aniline derivatives, only few derivatives offered relatively good yield in DCM as compared in water (Table 4, entry 5, 6, 11 and 17).

After demonstrating the wide range of substrate scope for different anilines in water and in DCM, we checked the substrate scope of various combinations of diazo phosphonates and anilines in DCM. Among the screened substrates 4-methoxyphenyl diazo phosphonate offered excellent yield of 94% and 95% with 4-OMe and 4-Me anilines respectively (Scheme 3, **5a** and **5b**) whereas ethyl acetate phosphonate diazo offered relatively lower yield among all the screened substrates (Scheme 3, **5g** and **5h**).

In conclusion, we have developed a methodology to prepare various amino phosphonates via carbene insertion into the N−H bond using Cu(I) complexes as catalysts in neat water. In the screening processes of finding an efficient catalyst for carbene insertion reaction in neat water, we screened a large number of transition metal sources as catalysts toward carbene insertion reaction. By considering the wide range of applications of α-amino phosphonates, we successfully utilized the developed methodology for making a large number of amino phosphates with good yields via carbene insertion in neat water and also in DCM, and characterized all the new and known amino phosphonates using standard analytical and spectroscopic

DOI: 10.1021/acs.joc.6b01940
J. Org. Chem. 2016, 81, 9826−9835

Scheme 3. Scope of Various Anilines and Diazo Phosphonates for Cu(I) Catalyzed N−H Insertion Reaction



techniques. We hope in the near future this methodology would be much useful for protein labeling with various phosphonates. Further studies on carbene insertion reactions in neat water are under progress in our laboratory.

EXPERIMENTAL SECTION

General Information. Unless otherwise specified all the reactions were carried out with oven-dried glassware under dry nitrogen atmosphere. All the solvents were distilled prior to use using standard procedures. Distilled water was purged for 5 min with dinitrogen gas and used, dichloromethane was distilled from the CaH_2 and used. Anilines were procured from commercial sources and used as received. Cu(I) salts of organic ligands are explosive in nature therefore should be used with adequate care. All the diazo compounds were prepared by following the standard literature procedures.[73] TLC was performed on precoated silica gel 60 F_{254} on aluminum plates and UV light (254 nm). Column chromatography was performed on silica gel 100−200 mesh size. ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz (^{1}H) and 100 MHz (^{13}C), Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references for ^{1}H NMR and ^{13}C NMR. HR-MS was recorded on UHD Q-TOF mass spectrometer.

General Procedure for Cu(I) Catalyzed Carbene Insertion into N−H Bond in Neat Water (A). A 20 mL Schlenk flask was charged with aniline (1 mmol) and catalyst (2 mol %), then 4 mL of water was added to the reaction mixture. Then diazo compound (1.1 mmol) was added dropwise to the reaction mixture, then the reaction mixture was stirred at room temperature for reported time. The progress of the reaction was monitored by TLC experiment for every 15 min using appropriate mixture of hexane and ethyl acetate (~1:1) as eluent. After completion of reaction, the reaction mixture was extracted with 15 mL (5 mL × 3) of EtOAc. Then EtOAc was evaporated under reduced pressure and the crude residue was purified using column chromatography on silica gel using (3:1) hexane/ethyl acetate.

General Procedures for Cu(I) Catalyzed Carbene Insertion into N−H Bond in DCM (B). A 20 mL Schlenk flask was charged with aniline (1 mmol) and catalyst (2 mol %), then 3 mL of DCM was added to the reaction mixture. The diazo compound (1.1 mmol) was dissolved in 1 mL of DCM and dropwise added to the reaction mixture at room temperature. Then the reaction mixture was stirred for reported time. The progress of the reaction was monitored by TLC experiment for every 30 min using appropriate mixture of hexane and ethyl acetate (~1:1) as eluent. After completion of reaction, the solvent was evaporated under reduced pressure and the crude residue was purified using column chromatography on silica gel using (3:1) hexane/ethyl acetate.

Diethyl (phenyl(phenylamino)methyl)phosphonate (***3a***).[31] Prepared according to the general procedure **A**: Off-White solid (301 mg, 94% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.44 (m, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.26 (dt, J = 7.5, 3.4 Hz, 1H), 7.09 (t, J = 7.9 Hz, 2H), 6.68 (t, J = 7.3 Hz, 1H), 6.59 (d, J = 7.8 Hz, 2H), 4.79 (s, 1H), 4.73 (s, 1H), 4.18−4.03 (m, 2H), 3.93 (m, 1H), 3.74−3.60 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H), 1.11 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 146.45 (d, J_{C-P} = 14.6 Hz), 136.05 (d, J_{C-P} = 2.8 Hz), 129.3, 128.7, 128.7, 128.0, 118.5, 114.0, 63.40 (d, J_{C-P} = 2.9 Hz), 63.33 (d, J_{C-P} = 3.0 Hz), 56.23 (d, J_{C-P} = 150.4 Hz), 16.54 (d, J_{C-P} = 5.8 Hz), 16.29 (d, J_{C-P} = 5.8 Hz); IR (Film) 3295, 3029, 2982, 2908, 1604, 1525, 1497, 1453, 1316, 1273, 1236, 1162, 1058, 1018, 966, 798, 768, 751, 696 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calculated (for $C_{17}H_{23}NO_3P$) 320.1416, found 320.1421.

Diethyl ((2-chlorophenyl)(phenylamino)methyl)phosphonate (***3b***).[74] Prepared according to the general procedure **A**: Off-White solid (329 mg, 93% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dt, J = 7.3, 2.3 Hz, 1H), 7.38 (d, J = 7.2 Hz, 1H), 7.22 (ddd, J = 8.9, 7.6, 3.9 Hz, 2H), 7.11 (t, J = 7.9 Hz, 2H), 6.69 (t, J = 7.3 Hz, 1H), 6.59 (d, J = 8.0 Hz, 2H), 5.38 (m, 1H), 4.97 (t, J = 9.1 Hz, 1H), 4.21 (m, 2H), 3.95−3.84 (m, 1H), 3.69−3.57 (m, 1H), 1.33 (t, J = 7.1 Hz, 3H), 1.06 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 145.83 (d, J_{C-P} = 14.7 Hz), 134.27 (d, J_{C-P} = 7.4 Hz), 129.54 (d, J_{C-P} = 2.4 Hz), 129.4, 129.19 (d, J_{C-P} = 3.2 Hz), 129.02 (d, J_{C-P} = 4.2 Hz), 127.47 (d, J_{C-P} = 3.0 Hz), 63.58 (d, J_{C-P} = 4.1 Hz), 63.51 (d, J_{C-P} = 3.9 Hz), 51.66 (d, J_{C-P} = 152.9 Hz), 16.55 (d, J_{C-P} = 5.9 Hz), 16.19 (d, J_{C-P} = 5.8 Hz); IR (Film) 3299, 3107, 3058, 3028, 2984, 2932, 2910, 1602, 1521, 1497, 1477, 1443, 1389, 1269, 1235, 1059, 1014, 981, 802, 786, 752, 722, 693 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calculated (for $C_{17}H_{22}ClNO_3P$) 354.1026, found 354.1021.

Diethyl ((4-chlorophenyl)(phenylamino)methyl)phosphonate (***3c***).[74] Prepared according to the general procedure **A**: Off-White solid (333 mg, 94% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, J = 8.5, 2.1 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.10 (t, J = 7.9 Hz, 2H), 6.71 (t, J = 7.3 Hz, 1H), 6.56 (d, J = 8.4 Hz, 2H), 4.87−4.63 (m, 2H), 4.20−4.05 (m, 2H), 4.02−3.91 (m, 1H), 3.83−3.72 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 146.12 (d, J_{C-P} = 14.6 Hz), 134.70 (d, J_{C-P} = 3.1 Hz), 133.79 (d, J_{C-P} = 3.9 Hz), 129.3, 129.24 (d, J_{C-P} = 5.4 Hz), 128.88 (d, J_{C-P} = 2.7 Hz), 118.7, 113.9, 63.51 (d, J_{C-P} = 7.1 Hz), 63.42 (d, J_{C-P} = 7.0 Hz), 55.62 (d, J_{C-P} = 150.5 Hz), 16.52 (d, J_{C-P} = 5.8 Hz), 16.34 (d, J_{C-P} = 5.7 Hz); IR (Film) 3414, 3305, 3050, 3026, 2978, 2905, 1603, 1522, 1499, 1485, 1311, 1288, 1268, 1243, 1230, 1054, 1025, 938, 753, 692 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calculated (for $C_{17}H_{22}ClNO_3P$) 354.1026, found 354.1035.

Diethyl ((4-methoxyphenyl)(phenylamino)methyl)phosphonate (***3d***).[37] Prepared according to the general procedure **A**: Off-White solid (332 mg, 95% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, J = 8.7, 2.2 Hz, 2H), 7.10 (t, J = 7.8 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 6.68 (t, J = 7.3 Hz, 1H), 6.59 (d, J = 8.1 Hz, 2H), 4.74 (s, 1H), 4.68 (s, 1H), 4.16−4.05 (m, 2H), 3.99−3.89 (m, 1H), 3.77 (s, 3H), 3.73−3.65 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H), 1.13 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.29 (d, J_{C-P} = 3.1 Hz), 146.35 (d, J_{C-P} = 14.9 Hz), 129.1, 128.95 (d, J_{C-P} = 5.6 Hz), 127.66 (d, J_{C-P} = 2.9 Hz), 118.3, 114.05 (d, J_{C-P} = 2.5 Hz), 113.9, 63.26 (d, J_{C-P} = 4.0 Hz), 63.19 (d, J_{C-P} = 4.0 Hz), 55.34 (d, J_{C-P} = 151.2 Hz), 55.2, 16.45 (d, J_{C-P} = 5.8 Hz), 16.27 (d, J_{C-P} = 5.8 Hz); IR (Film) 3463, 3294, 3030, 2984, 2932, 2909, 2838, 1600, 1511, 1492, 1442, 1309, 1262, 1232, 1182, 1159, 1061, 1020, 973, 836, 757, 694 cm^{-1}. HRMS-ESI (m/z) [M + H]$^+$ calculated (for $C_{18}H_{25}NO_4P$) 350.1521, found 350.1539.

DOI: 10.1021/acs.joc.6b01940
J. Org. Chem. 2016, 81, 9826−9835

*Ethyl 2-(diethoxyphosphoryl)-2-(phenylamino)acetate (**3f**).*[75] Prepared according to the general procedure **A**: Off-White solid (89 mg, 28% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (dd, J = 11.0, 4.4 Hz, 2H), 6.79 (td, J = 7.4, 0.7 Hz, 1H), 6.67 (d, J = 8.2 Hz, 2H), 4.63–4.43 (m, 2H), 4.29–4.13 (m, 6H), 1.30 (m, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.5, 146.28 (d, J_{C-P} = 11.3 Hz), 129.4, 119.5, 114.1, 64.11 (d, J_{C-P} = 6.7 Hz), 63.63 (d, J_{C-P} = 7.1 Hz), 62.3, 56.54 (d, J_{C-P} = 148.6 Hz), 16.47 (t, J_{C-P} = 5.5 Hz), 14.2; IR (Film) 3292, 3114, 2987, 2934, 2908, 1750, 1604, 1527, 1502, 1394, 1301, 1274, 1256, 1214, 1187, 1169, 1144, 1028, 985, 967, 838, 755, 695 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calculated (for $C_{14}H_{23}NO_5P$) 316.1314, found 316.1323.

*Diethyl (phenyl(p-tolylamino)methyl)phosphonate (**4a**).*[74] Prepared according to the general procedure **A**: Off-White solid (304 mg, 91% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, J = 7.3, 1.3 Hz, 2H), 7.31 (t, J = 7.4 Hz, 2H), 7.27–7.22 (m, 1H), 6.90 (d, J = 8.2 Hz, 2H), 6.51 (d, J = 8.4 Hz, 2H), 4.73 (d, J = 24.2 Hz, 1H), 4.16–4.02 (m, 2H), 3.98–3.88 (m, 1H), 3.73–3.63 (m, 1H), 2.17 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.11 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 144.09 (d, J_{C-P} = 15.1 Hz), 136.15 (d, J_{C-P} = 2.7 Hz), 129.7, 128.64 (d, J_{C-P} = 2.7 Hz), 128.0, 127.9, 127.9, 127.7, 114.1, 63.35 (d, J_{C-P} = 6.0 Hz), 63.29 (d, J_{C-P} = 5.9 Hz), 56.46 (d, J_{C-P} = 150.5 Hz), 20.4, 16.52 (d, J_{C-P} = 5.8 Hz), 16.28 (d, J_{C-P} = 5.8 Hz); IR (Film) 3297, 3029, 2982, 2908, 1616, 1522, 1238, 1056, 1024, 978,821, 803, 773, 699 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calculated (for $C_{18}H_{25}NO_3P$) 334.1572, found 334.1575.

*Diethyl (phenyl(m-tolylamino)methyl)phosphonate (**4b**).*[37] Prepared according to the general procedure **A**: White solid (310 mg, 93% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.43 (m, 2H), 7.31 (t, J = 7.4 Hz, 2H), 7.23 (t, J = 7.2 Hz, 1H), 6.96 (t, J = 7.8 Hz, 1H), 6.52–6.35 (m, 3H), 4.78 (s, 1H), 4.72 (d, J = 7.3 Hz, 1H), 4.17–4.04 (m, 2H), 3.97–3.87 (m, 1H), 3.72–3.61 (m, 1H), 2.19 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.10 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 146.42 (d, J_{C-P} = 14.3 Hz), 138.9, 136.1, 129.1, 128.58 (d, J_{C-P} = 2.6 Hz), 127.90 (d, J_{C-P} = 1.5 Hz), 127.8, 119.4, 114.8, 110.8, 63.3, 63.2, 56.09 (d, J_{C-P} = 150.4 Hz), 21.6, 16.46 (d, J_{C-P} = 5.7 Hz), 16.21 (d, J_{C-P} = 5.8 Hz); IR (Film) 3298, 3040, 2985, 2909, 2867, 1607, 1532, 1490, 1453, 1321, 1275, 1236, 1172, 1059, 1018, 969, 771, 697 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calculated (for $C_{18}H_{25}NO_3P$) 334.1572, found 334.1567.

*Diethyl (((2,4-dimethylphenyl)amino)(phenyl)methyl)-phosphonate (**4c**).* Prepared according to the general procedure **A**: Light brown thick liquid (320 mg, 92% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.43 (m, 2H), 7.32 (t, J = 7.5 Hz, 2H), 7.27–7.23 (m, 1H), 6.88 (s, 1H), 6.75 (d, J = 8.1 Hz, 1H), 6.30 (d, J = 8.1 Hz, 1H), 4.77 (d, J_{H-P} = 24.1 Hz, 1H), 4.54 (s, 1H), 4.20–4.04 (m, 2H), 4.00–3.89 (m, 1H), 3.76–3.65 (m, 1H), 2.25 (s, 3H), 2.16 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 142.07 (d, J_{C-P} = 14.6 Hz), 136.14 (d, J_{C-P} = 3.0 Hz), 131.2, 128.66 (d, J_{C-P} = 2.7 Hz), 127.93 (d, J_{C-P} = 3.3 Hz), 127.80 (d, J_{C-P} = 5.4 Hz), 127.33, 127.27, 123.1, 111.6, 63.41 (d, J_{C-P} = 7.0 Hz), 63.29 (d, J_{C-P} = 6.9 Hz), 56.43 (d, J_{C-P} = 150.0 Hz), 20.4, 17.6, 16.53 (d, J_{C-P} = 5.8 Hz), 16.30 (d, J_{C-P} = 5.8 Hz); IR (Film) 3425, 2982, 2910, 1619, 1514, 1451, 1390, 1308, 1243, 1162, 1095, 1053, 1023, 969, 801, 699 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calculated (for $C_{19}H_{27}NO_3P$) 348.1729, found 348.1720.

*Diethyl ((mesitylamino)(phenyl)methyl)phosphonate (**4d**).* Prepared according to the general procedure **A**: Light yellow solid (326 mg, 80% yield); mp 85–88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.39 (m, 2H), 7.32–7.25 (m, 3H), 6.72 (s, 2H), 4.43 (d, J = 22.4 Hz, 1H), 4.18–4.10 (m, 2H), 4.06 (s, 1H), 3.94–3.85 (m, 1H), 3.61 (m, 1H), 2.17 (s, 9H), 1.28 (t, J = 7.1 Hz, 3H), 1.03 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 141.64 (d, J_{C-P} = 10.2 Hz), 137.3, 131.1, 129.6, 128.9, 128.5, 128.46–128.39 (m), 127.90 (d, J_{C-P} = 2.3 Hz), 62.93 (t, J_{C-P} = 7.2 Hz), 59.40 (d, J_{C-P} = 148.3 Hz), 20.9, 18.9, 16.50 (d, J_{C-P} = 6.0 Hz), 16.21 (d, J_{C-P} = 5.7 Hz); IR (Film) 3355, 3060, 3032, 2977, 2938, 2859, 2731, 1482, 1452, 1390, 1310, 1228, 1161, 1095, 1028, 954, 859, 795, 723, 702 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calculated (for $C_{20}H_{29}NO_3P$) 362.1885, found 362.1874.

*Diethyl (((4-methoxyphenyl)amino)(phenyl)methyl)phosphonate (**4e**).*[31] Prepared according to the general procedure **A**: White solid (311 mg, 89% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.43 (m, 2H), 7.32 (t, J = 7.5 Hz, 2H), 7.27–7.22 (m, 1H), 6.68 (t, J = 6.1 Hz, 2H), 6.55 (t, J = 6.1 Hz, 2H), 4.69 (d, J_{H-P} = 24.0 Hz, 1H), 4.15–4.03 (m, 2H), 3.97–3.88 (m, 1H), 3.67 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.11 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.7, 140.5, 140.3, 136.1, 128.63 (d, J_{C-P} = 2.6 Hz), 127.95 (d, J_{C-P} = 5.7 Hz), 115.3, 114.8, 63.29 (t, J_{C-P} = 6.7 Hz), 57.06 (d, J_{C-P} = 150.5 Hz), 55.70, 16.50 (d, J_{C-P} = 5.8 Hz), 16.26 (d, J_{C-P} = 5.8 Hz); IR (Film) 3333, 3037, 2988, 2933, 2907, 2832, 1513, 1456, 1316, 1265, 1233, 1177, 1089, 1052, 1014, 965, 819, 792, 758, 726, 697 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calculated (for $C_{18}H_{25}NO_4P$) 350.1521, found 350.1516.

*Diethyl (((3,4-dimethoxyphenyl)amino)(phenyl)methyl)-phosphonate (**4f**).*[76] Prepared according to the general procedure **A**: Light brown solid (301 mg, 79% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.44 (m, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.26 (t, J = 6.8 Hz, 1H), 6.62 (d, J = 8.6 Hz, 1H), 6.26 (d, J = 2.5 Hz, 1H), 6.06 (dd, J = 8.6, 2.6 Hz, 1H), 4.70 (d, J_{H-P} = 23.9 Hz, 1H), 4.19–4.08 (m, 2H), 3.97–3.91 (m, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.71–3.65 (m, 1H), 1.30 (t, J = 7.1 Hz, 3H), 1.11 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 149.9, 142.2, 141.06 (d, J_{C-P} = 15.8 Hz), 136.19 (d, J_{C-P} = 3.0 Hz), 128.71 (d, J_{C-P} = 2.7 Hz), 128.03 (d, J_{C-P} = 3.3 Hz), 127.93 (d, J_{C-P} = 5.5 Hz), 112.9, 104.8, 100.1, 63.40 (d, J_{C-P} = 3.5 Hz), 63.33 (d, J_{C-P} = 3.6 Hz), 57.02 (d, J_{C-P} = 149.6 Hz), 56.58, 55.74, 16.56 (d, J_{C-P} = 5.8 Hz), 16.31 (d, J_{C-P} = 5.8 Hz); IR (Film) 3312, 2984, 2832, 1615, 1515, 1452, 1235, 1166, 1140, 1052, 1025, 968, 767, 700 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calculated (for $C_{19}H_{27}NO_5P$) 380.1627, found 380.1634.

*Diethyl (((4-fluorophenyl)amino)(phenyl)methyl)phosphonate (**4g**).*[76] Prepared according to the general procedure A: Off-White solid (315 mg, 93% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.41 (m, 2H), 7.33 (t, J = 7.3 Hz, 2H), 7.26 (dd, J = 8.4, 5.9 Hz, 1H), 6.80 (dd, J = 12.2, 5.1 Hz, 2H), 6.52 (dt, J = 6.8, 4.0 Hz, 2H), 4.69 (m, 2H), 4.18–4.05 (m, 2H), 3.97–3.87 (m, 1H), 3.72–3.61 (m, 1H), 1.29 (t, J = 7.1 Hz, 3H), 1.11 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.38 (d, J_{C-F} = 236.3 Hz), 142.71 (d, J_{C-F} = 15.3 Hz), 135.8, 128.75 (d, J_{C-P} = 2.7 Hz), 128.12 (d, J_{C-P} = 3.2 Hz), 127.95 (d, J_{C-P} = 5.5 Hz), 115.74 (d, J_{C-F} = 22.4 Hz), 114.94 (d, J_{C-F} = 7.5 Hz), 63.39 (t, J_{C-P} = 7.5 Hz), 56.85 (d, J_{C-P} = 150.6 Hz), 16.53 (d, J_{C-P} = 5.8 Hz), 16.29 (d, J_{C-P} = 5.8 Hz); IR (Film) 3296, 3064, 2985, 2930, 2908, 2885, 1508, 1448, 1390, 1367, 1305, 1269, 1238, 1183, 1157, 1123, 1076, 1029, 978, 825, 793, 777, 701 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calculated (for $C_{17}H_{22}FNO_3P$) 338.1321, found 338.1318.

*Diethyl (((2,6-difluorophenyl)amino)(phenyl)methyl)-phosphonate (**4h**).* Prepared according to the general procedure A: White solid (289 mg, 81% yield); mp 60–62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 7.7 Hz, 2H), 7.30 (t, J = 7.3 Hz, 2H), 7.26–7.22 (m, 1H), 6.74 (dd, J = 17.4, 8.8 Hz, 2H), 6.64 (dt, J = 9.3, 6.4 Hz, 1H), 5.04 (dd, J_{H-F} = 23.2 Hz, J_{H-P} = 11.3 Hz, 1H), 4.70 (dd, J_{H-P} = 10.7 Hz, J_{H-H} = 8.1 Hz, 1H), 4.23–4.15 (m, 2H), 3.98–3.89 (m, 1H), 3.71–3.62 (m, 1H), 1.33 (t, J = 7.1 Hz, 3H), 1.08 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.11 (dd, J_{C-F} = 242.1 Hz, J_{C-P} = 7.0 Hz), 136.2, 128.63 (d, J_{C-P} = 2.2 Hz), 128.4, 128.20 (d, J_{C-P} = 2.9 Hz), 127.97 (d, J_{C-P} = 5.9 Hz), 127.2, 123.92 (q, J_{C-F} = 13.9 Hz), 119.46 (t, J_{C-F} = 9.6 Hz), 111.62 (dd, J_{C-F} = 16.7 Hz, J_{C-P} = 7.1 Hz), 63.41 (d, J_{C-P} = 3.9 Hz), 63.35 (d, J_{C-P} = 3.8 Hz), 57.56 (dt, J_{C-P} = 151.4, J_{C-F} = 4.1 Hz), 16.55 (d, J_{C-P} = 5.8 Hz), 16.25 (d, J_{C-P} = 5.8 Hz); IR (Film) 3285, 3068, 2980, 2911, 1598, 1489, 1462, 1390, 1279, 1251, 1227, 1209, 1098, 1051, 1027, 998, 967, 943, 812, 788, 753, 738, 694 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calculated (for $C_{17}H_{21}F_2NO_3P$) 356.1227, found 356.1205.

*Diethyl (((4-chlorophenyl)amino)(phenyl)methyl)phosphonate (**4i**).*[37] Prepared according to the general procedure **A**: Off-White solid (341 mg, 96% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.39 (m, 2H), 7.33 (t, J = 7.4 Hz, 2H), 7.29–7.25 (m, 1H), 7.03 (d, J = 8.7 Hz, 2H), 6.51 (d, J = 8.8 Hz, 2H), 4.86 (d, J = 5.9 Hz, 1H), 4.69 (dd, J_{H-P} = 24.0 Hz, J_{H-H} = 7.4 Hz, 1H), 4.21–4.03 (m, 2H), 3.97–3.87 (m, 1H), 3.72–3.60 (m, 1H), 1.29 (t, J = 7.1 Hz, 3H), 1.10 (t, J = 7.1

DOI: 10.1021/acs.joc.6b01940
J. Org. Chem. 2016, 81, 9826–9835

Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 145.03 (d, J_{C-P} = 15.0 Hz), 135.6, 129.1, 128.8, 128.8, 127.9, 127.9, 115.1, 63.52 (d, J_{C-P} = 7.0 Hz), 63.37 (d, J_{C-P} = 7.0 Hz), 56.33 (d, J_{C-P} = 150.7 Hz), 16.54 (d, J_{C-P} = 5.7 Hz), 16.30 (d, J_{C-P} = 5.8 Hz); IR (Film) 3293, 2982, 2905, 1599, 1516, 1492, 1312, 1235, 1094, 1058, 1026, 979, 820, 700 cm^{-1}; HRMS-ESI (m/z) $[M + H]^+$ calculated (for $C_{17}H_{22}ClNO_3P$) 354.1026, found 354.1033.

Diethyl (((3-chlorophenyl)amino)(phenyl)methyl)phosphonate (**4j**).[77] Prepared according to the general procedure A: White solid (343 mg, 97% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.48−7.40 (m, 2H), 7.34 (t, J = 7.3 Hz, 2H), 7.30−7.24 (m, 1H), 6.99 (t, J = 8.0 Hz, 1H), 6.64 (d, J = 7.8 Hz, 1H), 6.59 (s, 1H), 6.45 (dd, J = 8.2, 1.6 Hz, 1H), 4.97 (bs, 1H), 4.71 (dd, J_{H-P} = 24.1 Hz, J_{H-H} = 7.7 Hz, 1H), 4.18−4.05 (m, 2H), 3.92 (m, 1H), 3.70−3.59 (m, 1H), 1.28 (d, J = 7.0 Hz, 3H), 1.10 (t, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 147.69 (d, J_{C-P} = 14.7 Hz), 135.6, 135.0, 130.3, 128.82 (d, J_{C-P} = 2.5 Hz), 128.24 (d, J_{C-P} = 3.2 Hz), 127.92 (d, J_{C-P} = 5.4 Hz), 118.4, 113.8, 112.1, 63.55 (d, J_{C-P} = 7.0 Hz), 63.38 (d, J_{C-P} = 7.0 Hz), 56.03 (d, J_{C-P} = 150.9 Hz), 16.55 (d, J_{C-P} = 5.8 Hz), 16.30 (d, J_{C-P} = 5.8 Hz); IR (Film) 3292, 3067, 2981, 2908, 1598, 1523, 1480, 1453, 1321, 1282, 1235, 1163, 1092, 1056, 1017, 970, 768, 699, 683 cm^{-1}; HRMS-ESI (m/z) $[M + Na]^+$ calculated (for $C_{17}H_{21}ClNNaO_3P$) 376.0845, found 376.0849.

Diethyl (phenyl((2,4,5-trichlorophenyl)amino)methyl)-phosphonate (**4k**). Prepared according to the general procedure **A**: White solid (343 mg, 81% yield); mp 90−93 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46−7.41 (m, 2H), 7.37 (t, J = 7.4 Hz, 2H), 7.34−7.27 (m, 2H), 6.52 (s, 1H), 5.45 (dd, J = 9.8, 7.9 Hz, 1H), 4.69 (dd, J_{H-P} = 23.9 Hz, J_{H-H} = 7.5 Hz, 1H), 4.16−4.04 (m, 2H), 4.00−3.92 (m, 1H), 3.78−3.68 (m, 1H), 1.29 (t, J = 7.0 Hz, 3H), 1.14 (t, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 142.02 (d, J_{C-P} = 14.2 Hz), 134.48 (d, J_{C-P} = 3.3 Hz), 131.6, 130.1, 129.00 (d, J = 2.7 Hz), 128.57 (d, J_{C-P} = 3.2 Hz), 127.70 (d, J_{C-P} = 5.3 Hz), 120.7, 118.8, 113.5, 63.58 (d, J_{C-P} = 7.2 Hz), 63.50 (d, J_{C-P} = 7.2 Hz), 55.92 (d, J_{C-P} = 151.4 Hz), 16.42 (d, J_{C-P} = 5.7 Hz), 16.20 (d, J_{C-P} = 5.8 Hz); IR (Film) 3390, 2982, 2932, 1591, 1498, 1442, 1377, 1294, 1225, 1099, 1053, 1023, 964, 939, 878, 759, 697, 674 cm^{-1}; HRMS-ESI (m/z) $[M + Na]^+$ calculated (for $C_{17}H_{19}Cl_3NNaO_3P$) 444.0066, found 444.0067.

Diethyl (((3-chloro-4-fluorophenyl)amino)(phenyl)methyl)-phosphonate (**4l**).[78] Prepared according to the general procedure **A**: Off-White solid (343 mg, 92% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.46−7.41 (m, 2H), 7.35 (t, J = 7.5 Hz, 2H), 7.30 (dd, J = 7.1, 1.6 Hz, 1H), 6.86 (t, J = 8.8 Hz, 1H), 6.61 (dd, J = 6.0, 2.9 Hz, 1H), 6.41 (dt, J = 8.9, 3.3 Hz, 1H), 4.85 (t, J = 8.4 Hz, 1H), 4.65 (dd, J_{H-P} = 24.0 Hz, J_{H-H} = 7.5 Hz, 1H), 4.18−4.05 (m, 2H), 3.97−3.86 (m, 1H), 3.70−3.59 (m, 1H), 1.30 (t, J = 7.1 Hz, 3H), 1.10 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.36 (d, J_{C-F} = 238.7 Hz), 143.34 (dd, J_{C-F} = 15.3 Hz, J_{C-P} = 2.2 Hz), 135.28 (d, J_{C-P} = 2.7 Hz), 128.71 (d, J_{C-P} = 2.6 Hz), 128.17 (d, J_{C-P} = 3.2 Hz), 127.83 (d, J_{C-P} = 5.5 Hz), 121.00 (d, J_{C-F} = 18.6 Hz), 116.68 (d, J_{C-F} = 22.0 Hz), 115.2, 112.90 (d, J_{C-P} = 6.3 Hz), 63.47 (d, J_{C-P} = 7.0 Hz), 63.27 (d, J_{C-P} = 7.0 Hz), 56.38 (d, J_{C-P} = 151.4 Hz), 16.42 (d, J_{C-P} = 5.8 Hz), 16.17 (d, J_{C-P} = 5.7 Hz); IR (Film) 3301, 3117, 3061, 2980, 2906, 2850, 1610, 1532, 1502, 1452, 1392, 1331, 1235, 1051, 1024, 977, 864, 810, 790, 774, 698 cm^{-1}; HRMS-ESI (m/z) $[M + H]^+$ calculated (for $C_{17}H_{21}ClFNO_3P$) 372.0932, found 372.0933.

Diethyl (((2-bromophenyl)amino)(phenyl)methyl)phosphonate (**4m**).[79] Prepared according to the general procedure A: Colorless thick liquid (367 mg, 92% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.47−7.41 (m, 3H), 7.34 (t, J = 7.5 Hz, 2H), 7.29−7.25 (m, 1H), 7.03−6.97 (m, 1H), 6.56 (td, J = 7.8, 1.3 Hz, 1H), 6.45−6.40 (m, 1H), 5.51−5.37 (m, 1H), 4.79 (dd, J_{H-P} = 24.3 Hz, J_{H-H} = 7.2 Hz, 1H), 4.16−3.98 (m, 3H), 3.86−3.77 (m, 1H), 1.27 (t, J = 7.0 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.45 (d, J_{C-P} = 14.4 Hz), 135.32 (d, J_{C-P} = 3.3 Hz), 132.6, 128.77 (d, J_{C-P} = 2.8 Hz), 128.41 (d, J_{C-P} = 2.8 Hz), 128.17 (d, J_{C-P} = 3.3 Hz), 127.79 (d, J_{C-P} = 5.3 Hz), 119.1, 112.8, 110.6, 63.70 (d, J_{C-P} = 7.0 Hz), 63.50 (d, J_{C-P} = 6.9 Hz), 56.28 (d, J_{C-P} = 150.5 Hz), 16.53 (d, J_{C-P} = 5.7 Hz), 16.35 (d, J_{C-P} = 5.8 Hz); IR (Film) 3396, 2983, 1714, 1593, 1508, 1455, 1433, 1317, 1249, 1096, 1051, 1021, 969, 743, 699 cm^{-1}; HRMS-ESI (m/z) $[M + H]^+$ calculated (for $C_{17}H_{22}BrNO_3P$) 398.0521, found 398.0508.

Diethyl (((4-bromophenyl)amino)(phenyl)methyl)phosphonate (**4n**).[74] Prepared according to the general procedure A: Off-White solid (371 mg, 93% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.46−7.40 (m, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.30−7.25 (m, 1H), 7.17 (d, J = 8.8 Hz, 2H), 6.47 (d, J = 8.8 Hz, 2H), 4.90 (t, J = 8.6 Hz, 1H), 4.69 (dd, J_{H-P} = 24.1 Hz, J_{H-H} = 7.6 Hz, 1H), 4.18−4.04 (m, 2H), 3.92 (m, 1H), 3.65 (m, 1H), 1.29 (t, J = 7.1 Hz, 3H), 1.10 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 145.44 (d, J_{C-P} = 14.9 Hz), 135.49 (d, J_{C-P} = 2.9 Hz), 132.0, 128.79 (d, J_{C-P} = 2.7 Hz), 128.20 (d, J_{C-P} = 3.2 Hz), 127.89 (d, J_{C-P} = 5.5 Hz), 115.6, 110.3, 63.53 (d, J_{C-P} = 7.0 Hz), 63.37 (d, J_{C-P} = 7.0 Hz), 56.16 (d, J_{C-P} = 150.7 Hz), 16.54 (d, J_{C-P} = 5.8 Hz), 16.29 (d, J_{C-P} = 5.8 Hz); IR (Film) 3292, 2981, 2905, 1593, 1515, 1489, 1450, 1391, 1313, 1273, 1236, 1098, 1025, 978, 817, 798, 763, 733, 699, 628, 607 cm^{-1}; HRMS-ESI (m/z) [M + H]+ calculated (for $C_{17}H_{22}BrNO_3P$) 398.0521, found 398.0508.

Diethyl (((2-bromo-4-methylphenyl)amino)(phenyl)methyl)-phosphonate (**4o**).[80] Prepared according to the general procedure A: Light orange solid (376 mg, 91% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 7.4 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.28−7.24 (m, 2H), 6.81 (d, J = 8.2 Hz, 1H), 6.34 (d, J = 8.3 Hz, 1H), 5.36−5.22 (m, 1H), 4.76 (dd, J_{H-P} = 24.3 Hz, J_{H-H} = 7.4 Hz, 1H), 4.16−3.97 (m, 3H), 3.81 (m, 1H), 2.16 (s, 3H), 1.27 (t, J = 7.0 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 141.18 (d, J_{C-P} = 14.8 Hz), 135.56 (d, J_{C-P} = 3.3 Hz), 133.0, 129.0, 128.75 (d, J = 2.8 Hz), 128.7, 128.11 (d, J_{C-P} = 3.3 Hz), 127.84 (d, J_{C-P} = 5.3 Hz), 112.8, 110.5, 63.68 (d, J_{C-P} = 7.0 Hz), 63.43 (d, J_{C-P} = 6.9 Hz), 56.54 (d, J_{C-P} = 150.4 Hz), 20.1, 16.57 (d, J_{C-P} = 5.7 Hz), 16.39 (d, J_{C-P} = 5.9 Hz); IR (Film) 3399, 3060, 3029, 2974, 2922, 1716, 1610, 1514, 1452, 1396, 1369, 1314, 1253, 1224, 1158, 1098, 1057, 1019, 972, 808, 782, 757, 692 cm^{-1}; HRMS-ESI (m/z) $[M + H]^+$ calculated (for $C_{18}H_{24}BrNO_3P$) 412.0677, found 412.0680.

Diethyl (((4-iodophenyl)amino)(phenyl)methyl)phosphonate (**4p**).[81] Prepared according to the general procedure **A**: Off-White solid (410 mg, 92% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.46−7.40 (m, 2H), 7.33 (t, J = 8.0 Hz, 4H), 7.29−7.25 (m, 1H), 6.37 (d, J = 8.7 Hz, 2H), 4.96−4.85 (m, 1H), 4.69 (dd, J_{H-P} = 24.1 Hz, J_{H-H} = 7.6 Hz, 1H), 4.16−4.05 (m, 2H), 3.96−3.85 (m, 1H), 3.70−3.59 (m, 1H), 1.28 (t, J = 7.1 Hz, 1H), 1.10 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 146.06 (d, J_{C-P} = 14.9 Hz), 137.9, 135.46 (d, J_{C-P} = 3.0 Hz), 128.80 (d, J_{C-P} = 2.6 Hz), 128.21 (d, J_{C-P} = 3.2 Hz), 127.88 (d, J_{C-P} = 5.4 Hz), 116.2, 79.5, 63.54 (d, J_{C-P} = 7.0 Hz), 63.37 (d, J_{C-P} = 7.0 Hz), 55.99 (d, J_{C-P} = 150.7 Hz), 16.54 (d, J_{C-P} = 5.8 Hz), 16.29 (d, J_{C-P} = 5.8 Hz); IR (Film) 3287, 3063, 3027, 2981, 2927, 2906, 1591, 1508, 1486, 1452, 1392, 1313, 1294, 1271, 1233, 1064, 1028, 978, 797, 766, 698, 602 cm^{-1}; HRMS-ESI (m/z) $[M + H]^+$ calculated (for $C_{17}H_{22}INO_3P$) 446.0382, found 446.0376.

Diethyl (((3-nitrophenyl)amino)(phenyl)methyl)phosphonate (**4q**).[81] Prepared according to the general procedure **A**: Yellow solid (322 mg, 88% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (t, J = 6.2 Hz, 4H), 7.35 (t, J = 7.3 Hz, 2H), 7.31−7.26 (m, 1H), 7.19 (t, J = 8.0 Hz, 1H), 6.88 (dd, J = 8.1, 1.6 Hz, 1H), 5.80 (s, 1H), 4.81 (dd, J_{H-P} = 24.2 Hz, J_{H-H} = 8.1 Hz, 1H), 4.23−4.12 (m, 2H), 3.96 (m, 1H), 3.72−3.61 (m, 1H), 1.31 (t, J = 7.1 Hz, 3H), 1.11 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.3, 147.7, 135.1, 129.7, 128.9, 128.4, 128.10 (d, J_{C-P} = 5.5 Hz)., 119.2, 112.6, 108.4, 63.82 (d, J_{C-P} = 7.0 Hz), 63.39 (d, J_{C-P} = 7.1 Hz), 55.85 (d, J_{C-P} = 152.5 Hz).16.56 (d, J_{C-P} = 5.8 Hz), 16.27 (d, J_{C-P} = 5.8 Hz); IR (Film) 3287, 3082, 2979, 1622, 1585, 1533, 1480, 1351, 1283, 1233, 1055, 1016, 976, 802, 770, 737, 699, 677 cm^{-1}; HRMS-ESI (m/z) $[M + H]^+$ calculated (for $C_{17}H_{22}N_2O_5P$) 365.1266, found 365.1269.

Diethyl (((4-nitrophenyl)amino)(phenyl)methyl)phosphonate (**4r**).[81] Prepared according to the general procedure **A**: Yellow solid (310 mg, 85% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, J = 8.1, 3.4 Hz, 2H), 7.48 (d, J = 6.4 Hz, 2H), 7.39−7.28 (m, 3H), 6.62 (dd, J = 9.2, 2.4 Hz, 2H), 6.24 (d, J = 8.5 Hz, 1H), 4.89−4.79 (m, 1H), 4.22−4.10 (m, 2H), 3.93 (m, 1H), 3.69−3.55 (m, 1H), 1.31 (t, J = 7.1 Hz, 3H), 1.11 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.40 (d, J_{C-P} = 13.5 Hz), 138.6, 134.79 (d, J_{C-P} = 2.6 Hz), 128.80

DOI: 10.1021/acs.joc.6b01940
J. Org. Chem. 2016, 81, 9826−9835

(d, J_{C-P} = 2.5 Hz), 128.42 (d, J_{C-P} = 3.1 Hz), 127.91 (d, J_{C-P} = 5.4 Hz), 126.0, 112.3, 63.83 (d, J_{C-P} = 7.1 Hz), 63.36 (d, J_{C-P} = 7.2 Hz), 55.39 (d, J_{C-P} = 152.4 Hz), 16.43 (d, J_{C-P} = 5.7 Hz), 16.17 (d, J_{C-P} = 5.6 Hz); IR (Film) 3273, 3193, 3068, 2981, 1597, 1547, 1500, 1480, 1313, 1285, 1239, 1111, 1046, 1022, 973, 844, 798, 753, 699 cm^{-1}; HRMS-ESI (m/z) $[M + H]^+$ calculated (for $C_{17}H_{22}N_2O_5P$) 365.1266, found 365.1271.

Diethyl (((2-cyanophenyl)amino)(phenyl)methyl)phosphonate (**4s**). Prepared according to the general procedure **A**: Light orange solid (152 mg, 44% yield); mp 78−80 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 6.9 Hz, 2H), 7.42−7.24 (m, 5H), 6.70 (dd, J = 9.5, 5.2 Hz, 1H), 6.49 (d, J = 8.5 Hz, 1H), 5.67−5.42 (m, 1H), 4.82 (dd, J_{H-P} = 24.1 Hz, J_{H-H} = 7.0 Hz, 1H), 4.12−3.97 (m, 3H), 3.94−3.85 (m, 1H), 1.29−1.19 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 148.80 (d, J_{C-P} = 13.3 Hz), 134.76 (d, J_{C-P} = 3.5 Hz), 134.1, 132.9, 128.87 (d, J_{C-P} = 2.7 Hz), 128.66−128.11 (m), 127.64 (d, J_{C-P} = 5.3 Hz), 118.1, 117.3, 112.3, 97.5, 63.66 (d, J_{C-P} = 7.1 Hz), 63.44 (d, J_{C-P} = 7.1 Hz), 55.86 (d, J_{C-P} = 150.3 Hz), 16.36 (d, J_{C-P} = 5.5 Hz), 16.25 (d, J_{C-P} = 5.8 Hz); IR (Film) 3402, 2981, 2911, 2208, 1605, 1579, 1510, 1459, 1326, 1275, 1253, 1230, 1055, 1014, 976, 748, 700 cm^{-1}; HRMS-ESI (m/z) $[M + H]^+$ calculated (for $C_{18}H_{22}N_2O_3P$) 345.1368, found 345.1360.

Diethyl (((4-cyanophenyl)amino)(phenyl)methyl)phosphonate (**4t**).[31] Prepared according to the general procedure A: White solid (267 mg, 78% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 6.9 Hz, 2H), 7.38−7.27 (m, 5H), 6.59 (d, J = 8.3 Hz, 2H), 5.64−5.49 (m, 1H), 4.76 (dd, J_{H-P} = 24.1 Hz, J_{H-P} = 7.6 Hz, 1H), 4.20−4.06 (m, 2H), 3.96−3.86 (m, 1H), 3.68−3.57 (m, 1H), 1.30 (t, J = 7.1 Hz, 3H), 1.10 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 150.0 (t, J_{C-P} = 15.1 Hz), 134.9, 133.65 (d, J_{C-P} = 3.3 Hz), 128.9, 128.5, 127.84 (d, J_{C-P} = 4.8 Hz), 120.1, 113.6, 100.2, 63.80 (d, J_{C-P} = 6.7 Hz), 63.38 (d, J_{C-P} = 7.1 Hz), 55.55 (d, J_{C-P} = 151.3 Hz), 16.52 (d, J_{C-P} = 5.7 Hz), 16.26 (d, J_{C-P} = 5.7 Hz); IR (Film) 3305, 3160, 3086, 3034, 2986, 2931, 2920, 2211, 1604, 1527, 1506, 1341, 1285, 1232, 1174, 1097, 1060, 1026, 975, 833, 807, 701 cm^{-1}; HRMS-ESI (m/z) $[M + H]^+$ calculated (for $C_{18}H_{22}N_2O_3P$) 345.1368, found 345.1362.

Diethyl (phenyl((2-(trifluoromethyl)phenyl)amino)methyl)-phosphonate (**4u**).[82] Prepared according to the general procedure **A**: Off-White solid (365 mg, 94% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 7.5 Hz, 3H), 7.35 (t, J = 7.5 Hz, 2H), 7.31−7.27 (m, 1H), 7.20 (t, J = 7.8 Hz, 1H), 6.72 (t, J = 7.5 Hz, 1H), 6.50 (d, J = 8.4 Hz, 1H), 5.55−5.42 (m, 1H), 4.81 (dd, J = 24.6, 6.9 Hz, 1H), 4.13−3.97 (m, 3H), 3.88−3.79 (m, 1H), 1.25 (t, J = 7.1 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.95 (d, J_{C-F} = 14.7 Hz), 135.20 (d, J_{C-P} = 3.6 Hz), 133.0, 128.80 (d, J_{C-P} = 2.8 Hz), 128.19 (d, J_{C-P} = 3.3 Hz), 127.66 (d, J_{C-P} = 5.2 Hz), 126.71 (q, J_{C-F} = 5.5 Hz), 126.5, 117.3, 114.76 (q, J_{C-F} = 29.5 Hz), 113.1, 63.64 (d, J_{C-P} = 7.0 Hz), 63.45 (d, J_{C-P} = 7.0 Hz), 55.75 (d, J_{C-P} = 149.7 Hz), 16.38 (d, J_{C-P} = 5.6 Hz), 16.22 (d, J_{C-P} = 5.9 Hz); IR (Film) 3465, 3030, 2987, 2910, 1612, 1588, 1523, 1478, 1456, 1328, 1286, 1255, 1162, 1127, 1106, 1066, 1020, 969, 786, 751, 695, 653 cm^{-1}; HRMS-ESI (m/z) $[M + H]^+$ calculated (for $C_{18}H_{22}F_3NO_3P$) 388.1289, found 388.1281.

Diethyl (((4-acetylphenyl)amino)(phenyl)methyl)phosphonate (**4v**).[81] Prepared according to the general procedure A: White solid (293 mg, 81% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.7 Hz, 2H), 7.47−7.44 (m, 2H), 7.35 (t, J = 7.4 Hz, 2H), 7.31−7.27 (m, 1H), 6.59 (d, J = 8.8 Hz, 2H), 5.42 (t, J = 8.8 Hz, 1H), 4.82 (dd, J_{H-P} = 24.1 Hz, J_{H-H} = 7.7 Hz, 1H), 4.12 (m, 2H), 3.96−3.88 (m, 1H), 3.69−3.61 (m, 1H), 2.45 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.11 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.4, 150.6, 150.5, 135.25 (d, J_{C-P} = 2.9 Hz), 130.7, 128.88 (d, J_{C-P} = 2.7 Hz), 128.36 (d, J_{C-P} = 3.2 Hz), 128.05−127.74 (m), 112.81, 63.72 (d, J_{C-P} = 7.0 Hz), 63.39 (d, J_{C-P} = 7.1 Hz), 55.62 (d, J_{C-P} = 150.9 Hz), 26.1, 16.41 (d, J_{C-P} = 5.8 Hz), 16.16 (d, J_{C-P} = 5.8 Hz); IR (Film) 3269, 3166, 3080, 3052, 2987, 1661, 1600, 1532, 1362, 1278, 1236, 1177, 1026, 959, 839, 797, 703 cm^{-1}; HRMS-ESI (m/z) $[M + H]^+$ calculated (for $C_{19}H_{25}NO_4P$) 362.1521, found 362.1514.

Diethyl (phenyl(pyridin-2-ylamino)methyl)phosphonate (**4w**).[81] Prepared according to the general procedure A: White solid (235 mg, 73% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 8.11−8.03 (m, 1H), 7.54−7.49 (m, 2H), 7.37−7.30 (m, 3H), 7.29−7.25 (m, 1H), 6.60−6.54 (m, 1H), 6.42 (d, J = 8.4 Hz, 1H), 5.57−5.45 (m, 2H), 4.18−4.03 (m, 2H), 3.96 (m, 1H), 3.74 (m, 1H), 1.24 (td, J = 7.1, 1.7 Hz, 3H), 1.11 (td, J = 7.1, 0.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.11 (d, J_{C-P} = 11.5 Hz), 148.1, 137.4, 136.3, 128.60 (d, J_{C-P} = 1.7 Hz), 128.13 (d, J_{C-P} = 5.8 Hz), 127.9, 114.0, 108.52 (d, J_{C-P} = 3.9 Hz), 63.3, 63.2, 52.81 (d, J_{C-P} = 148.9 Hz), 16.49 (d, J_{C-P} = 5.8 Hz), 16.29 (d, J_{C-P} = 5.8 Hz); IR (Film) 3307, 2979, 2936, 2831, 1602, 1515, 1483, 1421, 1364, 1291, 1227, 1065, 1020, 973, 954, 777, 742 cm^{-1}; HRMS-ESI (m/z) $[M + H]^+$ calculated (for $C_{16}H_{22}N_2O_3P$) 321.1368, found 321.1376.

Diethyl (((4-chlorophenyl)amino)(4-methoxyphenyl)methyl)-phosphonate (**5a**).[83] Prepared according to the general procedure **B**: White solid (362 mg, 94% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.30 (m, 2H), 7.09−6.99 (m, 2H), 6.90−6.80 (m, 2H), 6.55−6.45 (m, 2H), 4.64 (d, J_{H-P} = 23.7 Hz, 1H), 4.15−4.03 (m, 2H), 3.97−3.89 (m, 1H), 3.77 (d, J = 6.1 Hz, 3H), 3.72−3.63 (m, 1H), 1.32−1.25 (m, 3H), 1.13 (td, J = 7.1, 0.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.56 (d, J_{C-P} = 3.0 Hz), 145.07 (d, J_{C-P} = 15.0 Hz), 129.1, 129.05 (d, J = 5.6 Hz), 127.3, 123.2, 115.2, 114.28 (d, J_{C-P} = 2.5 Hz), 63.50 (d, J_{C-P} = 6.9 Hz), 63.34 (d, J_{C-P} = 7.1 Hz), 55.64 (d, J_{C-P} = 151.5 Hz), 55.4, 16.58 (d, J_{C-P} = 5.8 Hz), 16.39 (d, J_{C-P} = 5.7 Hz); IR (Film) 3459, 3294, 2981, 2908, 2838, 1610, 1596, 1510, 1491, 1461, 1442, 1307, 1268, 1238, 1180, 1075, 1020, 979, 836, 805, 766, 657 cm^{-1}; HRMS-ESI (m/z) $[M + H]+$ calculated (for $C_{18}H_{24}ClNO_4P$) 384.1131, found 384.1127.

Diethyl ((4-methoxyphenyl)(p-tolylamino)methyl)phosphonate (**5b**).[83] Prepared according to the general procedure **B**: Off-White solid (347 mg, 95% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, J = 8.8, 2.3 Hz, 2H), 6.90 (d, J = 8.2 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 6.51 (d, J = 8.4 Hz, 2H), 4.68 (d, J_{H-P} = 23.9 Hz, 1H), 4.15−4.05 (m, 2H), 3.98−3.91 (m, 1H), 3.76 (s, 3H), 3.73−3.62 (m, 1H), 2.17 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.13 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.35 (d, J_{C-P} = 3.0 Hz), 144.2, 144.0, 129.7, 129.0 (d, J_{C-P} = 5.6 Hz), 127.92 (d, J_{C-P} = 2.8 Hz), 127.6, 114.1, 63.32 (d, J_{C-P} = 6.1 Hz), 63.25 (d, J_{C-P} = 6.0 Hz), 55.73 (d, J_{C-P} = 151.3 Hz), 55.3, 20.4, 16.53 (d, J_{C-P} = 5.8 Hz), 16.35 (d, J_{C-P} = 5.8 Hz); IR (Film) 3313, 3296, 2983, 2907, 1611, 1303, 1511, 1275, 1255, 1237, 1176, 1050, 1023, 969, 826, 817, 801 cm^{-1}; HRMS-ESI (m/z) $[M + H]^+$ calculated (for $C_{19}H_{27}NO_4P$) 364.1678, found 364.1677.

Diethyl (((4-acetylphenyl)amino)(4-chlorophenyl)methyl)-phosphonate (**5c**). Prepared according to the general procedure **B**: White solid (341 mg, 86% yield); mp 170−172 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.6 Hz, 2H), 7.41 (dd, J = 8.3, 1.6 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 6.62−6.52 (m, 2H), 5.49 (s, 1H), 4.80 (dd, J_{H-P} = 24.3, J_{H-H} = 7.5 Hz, 1H), 4.19−4.08 (m, 2H), 4.02−3.94 (m, 1H), 3.82−3.69 (m, 1H), 2.46 (s, 3H), 1.30 (t, J = 7.0 Hz, 3H), 1.16 (t, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.4, 150.28 (d, J_{C-P} = 13.9 Hz), 134.1, 134.0, 130.6, 129.16 (d, J_{C-P} = 5.3 Hz), 129.0, 128.1, 112.8, 63.72 (d, J_{C-P} = 6.9 Hz), 63.56 (d, J_{C-P} = 7.0 Hz), 55.02 (d, J_{C-P} = 151.4 Hz), 26.1, 16.52 (d, J_{C-P} = 5.7 Hz), 16.34 (d, J_{C-P} = 5.6 Hz); IR (Film) 3284, 3162, 3088, 2987, 2904, 2865, 1665, 1598, 1531, 1486, 1358, 1333, 1274, 1234, 1180, 1054, 1019, 978, 952, 844, 827, 815, 753 cm^{-1}; HRMS-ESI (m/z) $[M + H]^+$ calculated (for $C_{19}H_{24}ClNO_4P$) 396.1131, found 396.1143.

Diethyl ((4-chlorophenyl)((4-methoxyphenyl)amino)methyl)-phosphonate (**5d**).[34] Prepared according to the general procedure **B**: Off-White solid (354 mg, 92% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J = 8.4, 1.9 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 6.71−6.66 (m, 2H), 6.51 (d, J = 8.7 Hz, 2H), 4.66 (d, J_{H-P} = 24.1 Hz, 1H), 4.16−4.06 (m, 2H), 4.02−3.95 (m, 1H), 3.84−3.76 (m, 1H), 3.68 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.9, 140.09 (d, J_{C-P} = 15.4 Hz), 134.86 (d, J_{C-P} = 3.1 Hz), 133.70 (d, J_{C-P} = 4.0 Hz), 129.26 (d, J_{C-P} = 5.5 Hz), 128.82 (d, J_{C-P} = 2.7 Hz), 115.3, 114.8, 63.48 (d, J_{C-P} = 7.0 Hz), 63.30 (d, J_{C-P} = 6.9 Hz), 56.51 (d, J_{C-P} = 150.6 Hz), 55.7, 16.50 (d, J_{C-P} = 5.8 Hz), 16.32 (d, J_{C-P} = 5.7 Hz); IR (Film) 3299, 3100, 3055, 2992, 2961, 2929, 2906, 2832, 1508, 1491, 1263, 1231, 1175, 1021, 977, 949,

DOI: 10.1021/acs.joc.6b01940
J. Org. Chem. 2016, 81, 9826−9835

835, 802, 768, 713, 676 cm^{-1}; HRMS-ESI (m/z) $[M + H]^+$ calculated (for $C_{18}H_{24}ClNO_4P$) 384.1131, found 384.1142.

*Diethyl (1-((4-methoxyphenyl)amino)-2-phenylethyl)-phosphonate (**5e**).* Prepared according to the general procedure **B**: Off-White solid (306 mg, 84% yield); mp 84−86 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28−7.16 (m, 5H), 6.69 (d, J = 8.9 Hz, 2H), 6.50 (d, J = 8.7 Hz, 2H), 4.14−4.03 (m, 3H), 3.99−3.84 (m, 2H), 3.70 (s, 3H), 3.28−3.20 (m, 1H), 3.00−2.91 (m, 1H), 1.24 (t, J = 7.1 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.6, 141.05 (d, J_{C-P} = 6.0 Hz), 137.61 (d, J_{C-P} = 11.7 Hz), 129.4, 128.4, 126.6, 115.3, 114.7, 62.87 (d, J_{C-P} = 7.0 Hz), 62.09 (d, J_{C-P} = 7.4 Hz), 55.7, 53.96 (d, J_{C-P} = 155.8 Hz), 36.51 (d, J_{C-P} = 4.5 Hz), 16.46 (t, J_{C-P} = 6.0 Hz); IR (Film) 3306, 3189, 3126, 3064, 3028, 2979, 2930, 2906, 2837, 1619, 1540, 1506, 1478, 1453, 1442, 1264, 1238, 1213, 1183, 1170, 1044, 1010, 967, 949, 817, 799, 783, 756, 740, 696 cm^{-1}; HRMS-ESI (m/z) $[M + H]^+$ calculated (for $C_{19}H_{27}NO_4P$) 364.1678, found 364.1688.

*Diethyl (2-phenyl-1-(p-tolylamino)ethyl)phosphonate (**5f**).* Prepared according to the general procedure **B**: Off-White solid (327 mg, 94% yield); mp 106−108 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26−7.16 (m, 5H), 6.91 (d, J = 8.2 Hz, 2H), 6.47 (d, J = 8.3 Hz, 2H), 4.11−4.02 (m, 3H), 4.00−3.91 (m, 2H), 3.24 (td, J = 13.7, 4.8 Hz, 1H), 3.01−2.95 (m, 1H), 2.20 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.15 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.6, 137.54 (d, J_{C-P} = 11.3 Hz), 129.7, 129.5, 128.4, 127.5, 126.7, 113.9, 62.96 (d, J_{C-P} = 7.0 Hz), 62.12 (d, J_{C-P} = 7.3 Hz), 52.98 (d, J_{C-P} = 156.0 Hz), 36.5, 20.5, 16.47 (t, J_{C-P} = 6.0 Hz); IR (Film) 3726, 3702, 3626, 3448, 3312, 3027, 2991, 2913, 2858, 1738, 1617, 1529, 1509, 1228, 1213, 1052, 1011, 968, 820, 804, 735, 701, 668 cm^{-1}; HRMS-ESI (m/z) $[M + H]^+$ calculated (for $C_{19}H_{27}NO_3P$) 348.1729, found 348.1736.

*Ethyl 2-((4-bromophenyl)amino)-2-(diethoxyphosphoryl)acetate (**5g**).* Prepared according to the general procedure **B**: White solid (241 mg, 61% yield); mp 79−81 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29−7.26 (m, 2H), 6.62−6.49 (m, 2H), 4.59 (d, J = 6.5 Hz, 1H), 4.44 (dd, J_{H-P} = 22.5 Hz, J_{H-H} = 8.6 Hz, 1H), 4.35−4.04 (m, 6H), 1.36−1.26(m, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.1, 145.28 (d, J_{C-P} = 11.5 Hz), 132.1, 115.6, 111.2, 64.09 (d, J_{C-P} = 6.4 Hz), 63.69 (d, J_{C-P} = 6.5 Hz), 62.4, 56.35 (d, J_{C-P} = 148.1 Hz), 16.4, 14.1; IR (Film) 3726, 3308, 3171, 3111, 3049, 2979, 2931, 1750, 1597, 1536, 1491, 1316, 1296, 1240, 1210, 1174, 1155, 1044, 1010, 972, 954, 824, 805, 621 cm^{-1}; HRMS-ESI (m/z) $[M + H]^+$ calculated (for $C_{14}H_{22}BrNO_5P$) 394.0419, found 394.0408.

*Ethyl 2-(diethoxyphosphoryl)-2-((2,4-dimethylphenyl)amino)-acetate (**5h**).* Prepared according to the general procedure **B**: Light Brown Liquid (187 mg, 54% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.89 (s, 1H), 6.48 (d, J = 8.8 Hz, 1H), 4.51 (dd, J_{H-P} = 22.9 Hz, J_{H-H} = 9.4 Hz, 1H), 4.35 (dd, J = 9.2, 6.0 Hz, 1H), 4.27−4.18 (m, 6H), 2.23 (s, 3H), 2.22 (s, 3H), 1.36−1.27 (m, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.80 (d, J_{C-P} = 2.3 Hz), 142.18 (d, J_{C-P} = 11.6 Hz), 131.4, 128.5, 127.4, 124.0, 111.5, 64.13 (d, J_{C-P} = 6.7 Hz), 63.59 (d, J_{C-P} = 7.0 Hz), 62.2, 57.00 (d, J_{C-P} = 149.1 Hz), 20.4, 17.4, 16.48 (t, J_{C-P} = 5.5 Hz), 14.2; IR (Film) 3403, 2983, 2931, 2128, 1740, 1620, 1515, 1257, 1179, 1160, 1097, 1024, 974, 803 cm^{-1}; HRMS-ESI (m/z) $[M + H]^+$ calculated (for $C_{16}H_{27}NO_5P$) 344.1627, found 344.1635.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01940.

^1H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: siva.che@pondiuni.edu.in. Tel.: +91 413 2654709. Fax: +91 413 2655987.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

C. S gratefully acknowledges the Council of Scientific and Industrial Research (CSIR), New Delhi, India for the financial support (No. 01(2535)/11/EMR-II). K.R. gratefully acknowledges the UGC for a Senior Research Fellowship. We thank Dr. N. Dastagiri Reddy and his group, who allowed us to conduct few reactions in their laboratory. We also thank the Central Instrumentation Facility, Pondicherry University, for NMR spectra and DST-FIST for the ESI-MS facility.

■ REFERENCES

(1) Moonen, K.; Laureyn, I.; Stevens, C. V. *Chem. Rev.* **2004**, *104* (12), 6177.

(2) Demmer, C. S.; Krogsgaard-Larsen, N.; Bunch, L. *Chem. Rev.* **2011**, *111* (12), 7981.

(3) Popa, A.; Ene, R.; Visinescu, D.; Dragan, E. S.; Ilia, G.; Iliescu, S.; Parvulescu, V. *J. Mol. Catal. A: Chem.* **2015**, *408*, 262.

(4) Ménard, L.; Fontaine, L.; Brosse, J.-C. *React. Polym.* **1994**, *23* (2), 201.

(5) Ye, M.-Y.; Yao, G.-Y.; Pan, Y.-M.; Liao, Z.-X.; Zhang, Y.; Wang, H.-S. *Eur. J. Med. Chem.* **2014**, *83*, 116.

(6) Huang, X.-C.; Wang, M.; Pan, Y.-M.; Yao, G.-Y.; Wang, H.-S.; Tian, X.-Y.; Qin, J.-K.; Zhang, Y. *Eur. J. Med. Chem.* **2013**, *69*, 508.

(7) Huang, K.-B.; Chen, Z.-F.; Liu, Y.-C.; Li, Z.-Q.; Wei, J.-H.; Wang, M.; Zhang, G.-H.; Liang, H. *Eur. J. Med. Chem.* **2013**, *63*, 76.

(8) Ali, N.; ali, S.; Zakir, S.; Patel, M.; Farooqui, M.; Bhattacharya, A. K.; Raut, D. S.; Rana, K. C.; Polanki, I. K.; Khan, M. S.; Iram, S.; Huang, K.-B.; Chen, Z.-F.; Liu, Y.-C.; Li, Z.-Q.; Wei, J.-H.; Wang, M.; Zhang, G.-H.; Liang, H.; Huang, X.-C.; Wang, M.; Pan, Y.-M.; Yao, G.-Y.; Wang, H.-S.; Tian, X.-Y.; Qin, J.-K.; Zhang, Y.; Ye, M.-Y.; Yao, G.-Y.; Pan, Y.-M.; Liao, Z.-X.; Zhang, Y.; Wang, H.-S. *Eur. J. Med. Chem.* **2013**, *66*, 116.

(9) Mulla, S. A. R.; Pathan, M. Y.; Chavan, S. S.; Gample, S. P.; Sarkar, D. *RSC Adv.* **2014**, *4* (15), 7666.

(10) Subhedar, D. D.; Shaikh, M. H.; Nawale, L.; Yeware, A.; Sarkar, D.; Shingate, B. B. *Res. Chem. Intermed.* **2016**, *42* (8), 6607.

(11) Stowasser, B.; Budt, K.-H.; Jian-Qi, L.; Peyman, A.; Ruppert, D. *Tetrahedron Lett.* **1992**, *33* (44), 6625.

(12) Lacbay, C. M.; Mancuso, J.; Lin, Y.-S.; Bennett, N.; Götte, M.; Tsantrizos, Y. S. *J. Med. Chem.* **2014**, *57* (17), 7435.

(13) Ali, N.; ali, S.; Zakir, S.; Patel, M.; Farooqui, M. *Eur. J. Med. Chem.* **2012**, *50*, 39.

(14) Sampath, C.; Harika, P.; Revaprasadu, N. *Phosphorus, Sulfur Silicon Relat. Elem.* **2016**, *191* (8), 1081.

(15) SIVALA, M. R.; DEVINENI, S. R. A. O.; GOLLA, M.; MEDARAMETLA, V.; POTHURU, G. K.; CHAMARTHI, N. R. *J. Chem. Sci.* **2016**, *128*, 1303.

(16) De Schutter, J. W.; Park, J.; Leung, C. Y.; Gormley, P.; Lin, Y.-S.; Hu, Z.; Berghuis, A. M.; Poirier, J.; Tsantrizos, Y. S. *J. Med. Chem.* **2014**, *57* (13), 5764.

(17) Ewa, B.; Maciej, W.; Marcin, S.; Grzegorz, D.; Michał, Z.; Jan, P.; Józef, O. *Bioorg. Med. Chem. Lett.* **2012**, *22* (17), 5574.

(18) Leon, A.; Liu, L.; Yang, Y.; Hudock, M. P.; Hall, P.; Yin, F.; Studer, D.; Puan, K.-J.; Morita, C. T.; Oldfield, E. *J. Med. Chem.* **2006**, *49* (25), 7331.

(19) Leung, C. Y.; Park, J.; De Schutter, J. W.; Sebag, M.; Berghuis, A. M.; Tsantrizos, Y. S. *J. Med. Chem.* **2013**, *56* (20), 7939.

(20) Leung, C.-Y.; Langille, A. M.; Mancuso, J.; Tsantrizos, Y. S. *Bioorg. Med. Chem.* **2013**, *21* (8), 2229.

(21) Wang, Q.; Zhu, M.; Zhu, R.; Lu, L.; Yuan, C.; Xing, S.; Fu, X.; Mei, Y.; Hang, Q. *Eur. J. Med. Chem.* **2012**, *49*, 354.

(22) Tora, G.; Degnan, A. P.; Conway, C. M.; Kostich, W. A.; Davis, C. D.; Pin, S. S.; Schartman, R.; Xu, C.; Widmann, K. A.; Macor, J. E.; Dubowchik, G. M. *Bioorg. Med. Chem. Lett.* **2013**, *23* (20), 5684.

(23) Jin, C. H.; Sreenu, D.; Krishnaiah, M.; Subrahmanyam, V. B.; Rao, K. S.; Nagendra Mohan, A. V.; Park, C.-Y.; Son, J.-Y.; Son, D.-H.;

DOI: 10.1021/acs.joc.6b01940
J. Org. Chem. 2016, 81, 9826−9835

Park, H.-J.; Sheen, Y. Y.; Kim, D.-K. *Eur. J. Med. Chem.* **2011**, *46* (9), 3917.
(24) Krishnaiah, M.; Jin, C. H.; Sreenu, D.; Subrahmanyam, V. B.; Rao, K. S.; Son, D.-H.; Park, H.-J.; Kim, S. W.; Sheen, Y. Y.; Kim, D.-K. *Eur. J. Med. Chem.* **2012**, *57*, 74.
(25) Ding, Q.; Ye, Y.; Fan, R.; Wu, J. *J. Org. Chem.* **2007**, *72* (14), 5439.
(26) Bukšnaitienė, R.; Urbanaitė, A.; Čikotienė, I. *J. Org. Chem.* **2014**, *79* (14), 6532.
(27) Nakamura, Y.; Ukita, T. *Org. Lett.* **2002**, *4* (14), 2317.
(28) Debrouwer, W.; Heugebaert, T. S. A.; Stevens, C. V. *J. Org. Chem.* **2014**, *79* (10), 4322.
(29) Abdel-Rahman, R. M.; Ali, T. E.; Abdel-Kariem, S. M. *ARKIVOC* **2015**, *2016* (1), 183.
(30) Ordóñez, M.; Viveros-Ceballos, J. L.; Cativiela, C.; Sayago, F. J. *Tetrahedron* **2015**, *71* (12), 1745.
(31) Li, X.-C.; Gong, S.-S.; Zeng, D.-Y.; You, Y.-H.; Sun, Q. *Tetrahedron Lett.* **2016**, *57* (16), 1782.
(32) Bhagat, S.; Chakraborti, A. K. *J. Org. Chem.* **2008**, *73* (15), 6029.
(33) Bhagat, S.; Chakraborti, A. K. *J. Org. Chem.* **2007**, *72* (4), 1263.
(34) Das, B.; Satyalakshmi, G.; Suneel, K.; Damodar, K. *J. Org. Chem.* **2009**, *74* (21), 8400.
(35) Gao, Y.; Huang, Z.; Zhuang, R.; Xu, J.; Zhang, P.; Tang, G.; Zhao, Y. *Org. Lett.* **2013**, *15* (16), 4214.
(36) Ghafuri, H.; Rashidizadeh, A.; Esmaili Zand, H. R. *RSC Adv.* **2016**, *6* (19), 16046.
(37) Ying, A.; Liu, S.; Yang, J.; Hu, H. *Ind. Eng. Chem. Res.* **2014**, *53* (42), 16143.
(38) Hu, G.; Chen, W.; Ma, D.; Zhang, Y.; Xu, P.; Gao, Y.; Zhao, Y. *J. Org. Chem.* **2016**, *81* (4), 1704.
(39) Wang, A.-E.; Chang, Z.; Sun, W.-T.; Huang, P.-Q. *Org. Lett.* **2015**, *17* (3), 732.
(40) Yan, Z.; Wu, B.; Gao, X.; Chen, M.-W.; Zhou, Y.-G. *Org. Lett.* **2016**, *18* (4), 692.
(41) McDonald, S. L.; Wang, Q. *Angew. Chem., Int. Ed.* **2014**, *53* (7), 1867.
(42) Vicario, J.; Ortiz, P.; Ezpeleta, J. M.; Palacios, F. *J. Org. Chem.* **2015**, *80* (1), 156.
(43) Kowalczyk, D.; Albrecht, L. *Chem. Commun.* **2015**, *51* (19), 3981.
(44) Tian, H.; Fürstenberg, A.; Huber, T. *Chem. Rev.* **2016**, DOI: 10.1021/acs.chemrev.6b00084.
(45) Rashidian, M.; Dozier, J. K.; Distefano, M. D. *Bioconjugate Chem.* **2013**, *24* (8), 1277.
(46) ElSohly, A. M.; Francis, M. B. *Acc. Chem. Res.* **2015**, *48* (7), 1971.
(47) Rashidian, M.; Dozier, J. K.; Distefano, M. D. *Bioconjugate Chem.* **2013**, *24* (8), 1277.
(48) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. *Chem. Rev.* **2015**, *115* (18), 9981.
(49) Gillingham, D.; Fei, N. *Chem. Soc. Rev.* **2013**, *42* (12), 4918.
(50) Zhu, S.-F.; Zhou, Q.-L. *Acc. Chem. Res.* **2012**, *45* (8), 1365.
(51) Zhu, Y.; Liu, X.; Dong, S.; Zhou, Y.; Li, W.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2014**, *53* (6), 1636.
(52) Xu, B.; Zhu, S.-F.; Zuo, X.-D.; Zhang, Z.-C.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2014**, *53* (15), 3913.
(53) Xu, B.; Zhu, S.-F.; Xie, X.-L.; Shen, J.-J.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2011**, *50* (48), 11483.
(54) Xie, X.-L.; Zhu, S.-F.; Guo, J.-X.; Cai, Y.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2014**, *53* (11), 2978.
(55) Ramakrishna, K.; Murali, M.; Sivasankar, C. *Org. Lett.* **2015**, *17* (15), 3814.
(56) Ramakrishna, K.; Sivasankar, C. *J. Org. Chem.* **2016**, *81* (15), 6609.
(57) Yu, Z.; Ma, B.; Chen, M.; Wu, H.-H.; Liu, L.; Zhang, J. *J. Am. Chem. Soc.* **2014**, *136* (19), 6904.
(58) Mix, K. A.; Raines, R. T. *Org. Lett.* **2015**, *17* (10), 2358.
(59) Chen, Z.; Vohidov, F.; Coughlin, J. M.; Stagg, L. J.; Arold, S. T.; Ladbury, J. E.; Ball, Z. T. *J. Am. Chem. Soc.* **2012**, *134* (24), 10138.
(60) Antos, J. M.; McFarland, J. M.; Iavarone, A. T.; Francis, M. B. *J. Am. Chem. Soc.* **2009**, *131* (17), 6301.
(61) Chen, Z.; Popp, B. V.; Bovet, C. L.; Ball, Z. T. *ACS Chem. Biol.* **2011**, *6* (9), 920.
(62) Ho, C.-M.; Zhang, J.-L.; Zhou, C.-Y.; Chan, O.-Y.; Yan, J. J.; Zhang, F.-Y.; Huang, J.-S.; Che, C.-M. *J. Am. Chem. Soc.* **2010**, *132* (6), 1886.
(63) Tishinov, K.; Fei, N.; Gillingham, D. *Chem. Sci.* **2013**, *4* (12), 4401.
(64) Saha, P.; Jeon, H.; Mishra, P. K.; Rhee, H.-W.; Kwak, J. H. *J. Mol. Catal. A: Chem.* **2016**, *417*, 10.
(65) Srour, H. F.; Maux, P. Le; Chevance, S.; Carrié, D.; Yondre, N. Le; Simonneaux, G. *J. Mol. Catal. A: Chem.* **2015**, *407*, 194.
(66) Zhu, S.-F.; Xu, B.; Wang, G.-P.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2012**, *134* (1), 436.
(67) Zhu, S.-F.; Song, X.-G.; Li, Y.; Cai, Y.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2010**, *132* (46), 16374.
(68) Lecerclé, D.; Gabillet, S.; Gomis, J.-M.; Taran, F. *Tetrahedron Lett.* **2008**, *49* (13), 2083.
(69) Jugelt, W.; Schmidt, D. *Tetrahedron* **1969**, *25* (23), 5569.
(70) Oelerich, J.; Roelfes, G. *Chem. Sci.* **2013**, *4* (5), 2013.
(71) Ramakrishna, K.; Sivasankar, C. *J. Organomet. Chem.* **2016**, *805*, 122.
(72) Zhao, Y.; Chen, X.; Chen, T.; Zhou, Y.; Yin, S.-F.; Han, L.-B. *J. Org. Chem.* **2015**, *80* (1), 62.
(73) Romanova, I. P.; Musina, E. I.; Nafikova, A. A.; Zverev, V. V.; Yakhvarov, D. G.; Sinyash, O. G. *Russ. Chem. Bull.* **2003**, *52* (8), 1750.
(74) Hou, J.-T.; Gao, J.-W.; Zhang, Z.-H. *Appl. Organomet. Chem.* **2011**, *25* (1), 47.
(75) Haigh, D. *Tetrahedron* **1994**, *50* (10), 3177.
(76) Milen, M.; Ábrányi-Balogh, P.; Dancsó, A.; Frigyes, D.; Pongó, L.; Keglevich, G. *Tetrahedron Lett.* **2013**, *54* (40), 5430.
(77) NASSERI, M. A. L. I.; SADEGHZADEH, M. *J. Chem. Sci.* **2013**, *125* (3), 537.
(78) Reddy, B. V. S.; Krishna, A. S.; Ganesh, A. V.; Kumar, G. G. K. S. N. *Tetrahedron Lett.* **2011**, *52* (12), 1359.
(79) Hamadi, H.; Kooti, M.; Afshari, M.; Ghiasifar, Z.; Adibpour, N. *J. Mol. Catal. A: Chem.* **2013**, *373*, 25.
(80) Yadav, J. S.; Reddy, B. V. S.; Raj, K. S.; Reddy, K. B.; Prasad, A. R. *Synthesis* **2001**, *2001* (15), 2277.
(81) Bhattacharya, T.; Majumdar, B.; Dey, D.; Sarma, T. K. *RSC Adv.* **2014**, *4* (86), 45831.
(82) Gruss, U.; Hägele, G. *Phosphorus, Sulfur Silicon Relat. Elem.* **1994**, *97* (1–4), 209.
(83) Sharghi, H.; Ebrahimpourmoghaddam, S.; Doroodmand, M. M. *Tetrahedron* **2013**, *69* (23), 4708.

NOTE ADDED AFTER ASAP PUBLICATION

Throughout the paper, α-amino phosphonate was incorrectly named α-amino phosphate. The corrected version reposted on October 21, 2016.

DOI: 10.1021/acs.joc.6b01940
J. Org. Chem. 2016, 81, 9826–9835