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Quinidine thiourea-catalyzed enantioselective synthesis of β-nitrophosphonates: beneficial effects of molecular sieves

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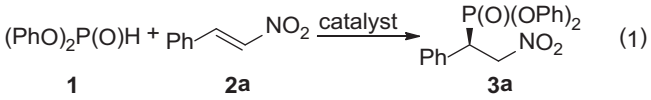
ABSTRACT

An efficient method for enantioselective synthesis of β-nitrophosphonates via the Michael addition of diphenyl phosphite to nitroalkenes using the readily available quinidine thiourea organocatalyst has been developed. The desired β-nitrophosphonates were obtained in good ee values. Molecular sieves were found to be crucial for achieving high reproducible yields in this reaction.

1. Introduction

In recent years β-nitrophosphonate derivatives have received considerable interest[1] because they are the direct precursors for the synthesis of β-aminophosphonic acids.[2] As non-proteinogenic analogues of β-amino acids, the latter compounds have been reported to possess many biological activities.[3,4] Interestingly, β-aminophosphonic acid was also found in the nature.[5] Several enantioselective methods have been reported for the synthesis of β-nitrophosphonate derivatives.[1a–h] Among these methods, enantioselective Michael addition of phosphites to nitroalkenes[1a–f] apparently is one of the most direct approaches.[6]

Our group is interested in developing novel methods for the enantioselective synthesis of phosphonate compounds.[1g,7] In this regard, we have reported a nitroaldol reaction of α-ketophosphonates for the highly enantioselective synthesis of α-hydroxy-β-nitrophosphonates.[1g] During the course of this study, we became interested in the organocatalyzed enantioselective synthesis of β-nitrophosphonates using the Michael addition of diphenyl phosphite (DPP) to nitroalkenes (Eq. 1). It should be pointed out that Wang's group[1c] has reported a cinchona alkaloid-catalyzed Michael addition of DPP to nitroalkenes, in which thioureas, such as quinine thiourea, were briefly evaluated as the catalyst. Nevertheless, poor results were obtained. For example, when quinine thiourea (**4**) was used as the catalyst, the Michael addition of DPP to *trans*-β-nitrostyrene gave only 38% yield and 11% ee for the *S*-enantiomer of the product.[1c,8] We recently reinvestigated this reaction, and found the reaction may be dramatically improved by using molecular sieves as the additives. Furthermore, we obtained much higher ee values in this reaction after the optimizations. Herein we wish to report our findings.



2. Results and discussion

Using quinidine thiourea (**5**), i.e., the pseudo-enantiomer of catalyst **4**, as the catalyst, the Michael addition reaction of DPP (**1**) to *trans*-β-nitrostyrene (**2a**) was conducted initially (Eq. 1). Although we also obtained a low yield of this product (42%), we did obtain a much higher ee value for product (72% ee for the *R*-enantiomer, Table 1, entry 1). Because a good ee value was obtained, we decided to carry out further study to improve the yield of this reaction. The results of this study are summarized in Table 1. As shown by the data in Table 1, although the ee value of the product remained constant during the study, to our surprise, we found the

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Table 1
Optimization of the reaction conditions for the Michael addition of DPP to *trans*-β-nitrostyrene[a]

Entry	Conditions	Time (h)	Yield[b] (%)	ee[c] (%)
1[d]	DPP-1 (upon opening)	24	42	72
2	DPP-1 (3 days after opening)	24	34	72
3	DPP-1 (7 days after opening)	24	25	72
4	DPP-1 (10 days after opening)	24	0	—
5[d]	DPP-2 (upon opening)	24	40	72
6[e]	DPP-3 (upon opening)	24	36	72
7	Distilled DPP	24	0	—
8	Distilled DPP+10% phenol	24	25	72
9	DPP (passed through Na_2HPO_4)	24	0	—
10	DPP (passed through MS 4 Å)	24	35	72
11[f]	DPP+MS 4 Å in the reaction	24	37	72
12[f]	DPP (passed through MS 4 Å)+MS 4 Å in the reaction	0.5	91	73
13[g]	DPP (passed through MS 4 Å)+MS 3 Å in the reaction	0.5	87	73
14[h]	DPP (passed through MS 4 Å)+MS 5 Å in the reaction	0.5	27	68
15[f,i]	DPP (passed through MS 4 Å)+MS 4 Å+H_2O in the reaction	0.5	55	68
16[j]	DPP (passed through Na_2SO_4)+Na_2SO_4 in the reaction	0.5	26	72
17[k]	DPP (passed through $MgSO_4$)+$MgSO_4$ in the reaction	0.5	26	72
18[l]	DPP (passed through MS 4 Å)+DOWEX® in the reaction	0.5	13	70
19[f,l]	DPP (passed through MS 4 Å)+DOWEX®+MS 4 Å in the reaction	0.5	83	72

[a] Unless otherwise indicated, all reactions were carried out with DPP (**1**, 0.10 mmol), *trans*-β-nitrostyrene (**2a**, 0.20 mmol), and quidine thiourea (**5**) as the catalyst (0.01 mmol, 10 mol %) in CH_2Cl_2 (0.5 mL) at rt.
[b] Yield of the isolated product.
[c] Determined by HPLC analysis on a ChiralPak AS column. The stereochemistry was assigned by comparison of the measured optical rotation with those reported data.
[d] The DPP samples DPP-1 and DPP-2 were purchased from Sigma–Aldrich.
[e] The DPP sample DPP-3 was purchased from Wako Chemicals.
[f] MS 4 Å (60.0 mg) was added to the reaction mixture.
[g] MS 3 Å (60.0 mg) was used to the reaction mixture.
[h] MS 5 Å (60.0 mg) was used to the reaction mixture.
[i] Water (0.10 mmol) was added to the reaction mixture.
[j] Na_2SO_4 (60.0 mg) was added to the reaction mixture.
[k] $MgSO_4$ (60.0 mg) was added to the reaction mixture.
[l] DOWEX® 50WX8, hydrogen form (100–200 mesh, 10 wt % of DPP) was added to the reaction mixture.

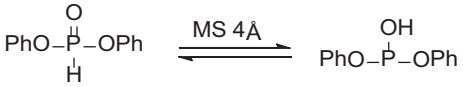
product yield could not be improved. Actually, the reaction has very poor reproducibility in terms of the product yield. For example, with the DPP sample we purchased from Sigma–Aldrich (DPP-1), a 42% yield of the desired product was obtained upon the opening of this sample for the first time (entry 1). Nonetheless, with the gradual aging of this sample, dwindling yields were obtained (entries 2–4), and no product could be isolated from the reaction mixture after the sample was only 10 days old after the opening (entry 4). To make sure this was not due to sample quality variations, we ordered another sample from Sigma–Aldrich (DPP-2), and a similar 40% yield of the desired product was obtained upon the first use (entry 5). Once again, this yield was not reproducible when this new sample was aged (data not shown). We then noticed that, in several reports where DPP was used, the samples were purchased from Wako Chemicals.[1a,b] Thus, we also ordered a sample from Wako Chemicals (DPP-3). However, as the results in Table 1 show, there was no improvement at all (entry 6). According to the product specification, the DPP sample from Sigma–Aldrich contains up to 15% phenol (according to the ^{1}H NMR of the sample, it contains about 15–16% phenol), we speculated whether phenol was the culprit that limited the conversion of the substrates. Thus, we distilled the DPP under nitrogen protection, and the freshly distilled DPP was then applied in this reaction (after repeated distillation the phenol concentration was negligible according to its ^{1}H NMR). Surprisingly, no formation of the desired product was observed (entry 7). Nevertheless, upon intentionally adding 10% of phenol to this distilled sample, the desired product was again obtained in 25% yield (entry 8). These results show that phenol does not do any harm to the reaction. On the contrary, it may have helped the reaction in some ways.

It is known that DPP is sensitive toward moisture,[9] and some acidic species generated during the hydrolysis may inhibit the catalysis. Pretreatment of DPP with a base[1a,8] to remove such acidic species is known. Thus, we passed the DPP sample through a pad of sodium hydrogen phosphate immediately before the reaction.[1a] Nonetheless, no product was obtained after such a treatment (entry 9). Molecular sieves 4 Å was also used as an acid scavenger for DPP.[1b] However, passing DPP through a pad of activated MS 4 Å and Celite immediately before use did not improve the conversion (entry 10), either, although ^{31}P NMR indicates that the sample has much less phosphorus-containing impurities as compared to the untreated sample. Similarly, adding freshly activated MS 4 Å (60 mg) directly to the reaction mixture containing untreated DPP was not helpful (entry 11). In contrast, when freshly activated MS 4 Å (60 mg) was added to the reaction mixture that contained the MS-treated DPP, a dramatic improvement was observed: The product yield was improved to 91% and the reaction time was shortened from 24 h to 0.5 h (entry 12). Also the ee value of the product was slightly improved to 73% (entry 12). Using MS 3 Å instead of MS 4 Å lead to a similar yield of the product with the same ee value (entry 13). However, the use of MS 5 Å showed no improvement as compared to those results without such an additive (entry 14). Since MS with smaller pore sizes work better, it seems reasonable to believe that the species that inhibits the reaction is pretty small. Since MS 3 Å and 4 Å are known to be a very good absorbent for water and MS 5 Å is not, we speculated that water might have played some role in inhibiting this reaction. Indeed, when 1 equiv of water was intentionally added to the aforementioned best reaction system, a much lower yield (55%) and a slightly lower ee value of the product was obtained (entry 15). Nonetheless, using neutral drying agents, such as Na_2SO_4 and $MgSO_4$, instead of MS 4 Å failed to improve the product yield (entries 16 and 17). These results clearly evince that water itself is only partially responsible for the low yield of this reaction.

Previously Terada and co-workers found MS 4 Å can improve the product yields in a chiral guanidine-catalyzed Michael addition, and its role was described as an acid scavenger, although no direct evidence was provided.[1b] In our hand, this is partially verified by comparing the ^{31}P NMR of the purchased DPP sample and that of the sample pretreated with MS 4 Å: The latter shows much less

unidentified peaks (both the number of peaks and their intensities reduced) around the main peak for DPP (0.9 ppm), which indicates that MS 4 Å helps remove some of the impurities in the commercial DPP sample. These impurities most likely are resulted from the decomposition of DPP and from the reaction of DPP with moisture. Conceivably, some acidic species formed in these reactions are able to neutralize the catalyst so that the reaction is inhibited. MS 4 Å added to the reaction mixture removes the acidic species and eliminates water simultaneously and thus prevents the hydrolysis of DPP from happening. To further clarify the role of MS 4 Å as an acid scavenger, we conducted the reaction with the MS-treated DPP in the presence of an acidic resin DOWEX® with and without MS 4 Å. As the data in Table 1 show, without MS 4 Å in the reaction mixture, DOWEX® almost totally inhibited the reaction (entry 18). However, if MS 4 Å was added, the reactivity was almost totally recovered (entry 19). These findings clearly indicate that MS 4 Å is functioning as an acid scavenger.[10]

On the other hand, the facts that DPP freshly treated with Na_2HPO_4 (Table 1, entry 9) and freshly distilled DPP (Table 1, entry 7) do not participate in the reaction and that MS 4 Å must be added to the reaction mixture to achieve the optimal results suggests molecular sieves have additional role in promoting the reaction than just a scavenger for water and acid. A tentative explanation is that, as a heterogeneous Lewis acid, MS is able to facilitate the equilibrium between the phosphonate and the phosphite forms of the DPP and favors the formation of the latter (Eq. 2). The phosphite form maybe is more reactive than the phosphonate form in the Michael addition. ^{31}P NMR spectra provide some evidence for this explanation. DPP sample from Sigma–Aldrich shows a major peak at 0.9 ppm and a minor peak appear at 128.5 ppm. The former corresponds to the phosphonate form of DPP, and the latter is most likely the phosphite form according to its chemical shift.[11] ^{31}P NMR of the untreated sample from Sigma–Aldrich shows the phosphite form is about 1.0% of the phosphonate form. After filtration through the MS 4 Å pad, this ratio increases to 1.1%. If the sample is filtered and treated with MS 4 Å for 30 min, then the ratio further increases to 1.4%. Although the phosphite form still remains as a minute component even after the treatment, the increase of its concentration is considerable (about 40% increases).



With the optimized conditions at hand, we screened other cinchona alkaloid thioureas as the catalyst (Fig. 1) in the reaction of DPP and *trans*-β-nitrostyrene (Eq. 1), and the results are summarized in Table 2.

As is evident from Table 2, besides quinidine thiourea (**5**, entry 1), other cinchona thiourea catalysts also lead to good results under the optimized conditions. For example, with cinchonine thiourea (**6**), the product **3a** was obtained in 71% ee (entry 2). Similarly, the *S*-enantiomer was obtained in 84% yield and 70% ee within 6 h of reaction when quinine thiourea (**4**) was used (entry 3). These results are much better than those reported (24 h, 38% yield, and 11% ee).[1c] Cinchonidine thiourea (**7**) gave the expected *S*-enantiomer in 84% and 73% ee (entry 4). Modification of the aryl group attached to the thiourea moiety shows almost no effects on the reactivity as well as the enantioselectivity of this reaction, since quinidine derived thiourea catalysts **8** and **9** (entries 5 and 6) give similar results as those of catalyst **5**. Similarly, the increase of the steric hindrance at 6′-position by replacing the methyl with an isopropyl group (catalysts **10** and **11**) shows almost no effect (entries 7 and 8), either. Since catalyst **5** leads to the highest reactivity and stereoselectivity in this reaction, it was chosen for further optimization. As shown in Table 2, good ee values may be obtained in polar chlorinated solvents, such as CH_2Cl_2 (entry 1), $CHCl_3$ (entry 9), and

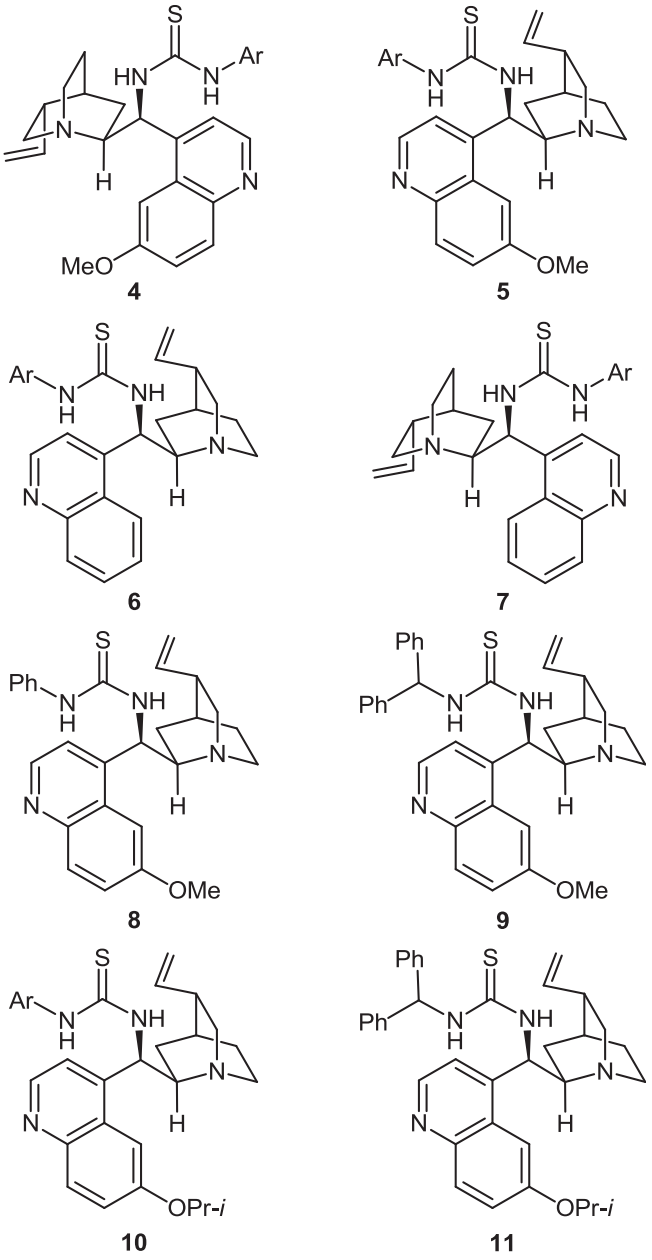


Fig. 1. Catalyst screened in the Michael addition reaction of DPP to *trans*-β-nitrostyrene (Ar=3,5-$(CF_3)_2C_6H_3$–).

$ClCH_2CH_2Cl$ (entry 10). Lower ee values were obtained in nonpolar solvents, such as CCl_4 (entry 11) and toluene (entry 12), in ethereal solvents, such as Et_2O (entry 13) and THF (entry 14), and in CH_3CN (entry 15). We found that, by lowering the reaction temperature to 5 °C, the ee value was increased to 79% (entry 16). However, further dropping the temperature to −15 °C showed no effects (entry 17). Furthermore, temperature has not much effect on the reactivity of this reaction (entries 16 and 17).

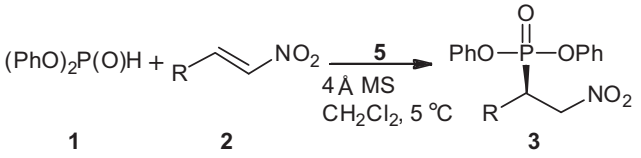
Next the scope of this reaction was evaluated with different nitroalkenes and the results are summarized in Table 3. As the results in Table 3 show, the reaction works very well with aryl-substituted nitroalkenes (entries 1–13). The reaction generally is not sensitive toward the electronic nature of the substituents on the phenyl ring: Nitroalkenes with both an electron-donating and an electron-withdrawing group on the phenyl ring give almost the same yields and ee values (ca. 80%, entries 1–6). Similarly, the

Table 2
Catalyst screening and further optimizations[a]

Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	**5**	CH_2Cl_2	0.5	91	73
2	**6**	CH_2Cl_2	2.0	58	71
3[d]	**4**	CH_2Cl_2	6.0	84	70
4[d]	**7**	CH_2Cl_2	2.5	84	73
5	**8**	CH_2Cl_2	3.0	80	72
6	**9**	CH_2Cl_2	3.5	84	67
7	**10**	CH_2Cl_2	3.0	90	73
8	**11**	CH_2Cl_2	2.0	82	73
9	**5**	CH_2Cl_2	2.0	85	71
10	**5**	$ClCH_2CH_2Cl$	2.0	70	73
11	**5**	CCl_4	2.0	65	57
12	**5**	Toluene	1.0	94	60
13	**5**	Et_2O	1.0	90	60
14	**5**	THF	3.0	48	55
15	**5**	CH_3CN	4.0	40	60
16[e]	**5**	CH_2Cl_2	0.5	91	79
17[f]	**5**	CH_2Cl_2	0.5	90	79

[a] Unless otherwise indicated, all reactions were carried out with DPP (**1**, 0.10 mmol, pretreated with MS 4 Å immediately before reaction), *trans*-β-nitrostyrene (0.20 mmol), the catalyst (0.01 mmol, 10 mol %), and MS 4 Å (60.0 mg) in the specified solvent (0.5 mL) at rt.
[b] Yield of the isolated product.
[c] Determined by HPLC analysis on a ChiralPak AS column.
[d] The *S*-enantiomer was obtained as the major product.
[e] Carried out at 5 °C.
[f] Carried out at −15 °C.

Table 3
Scope of the quinidine thiourea-catalyzed Michael addition reaction[a]



1 2 3

Entry	R	Time (h)	Yield[b] (%)	ee[c] (%)
1	Ph (**3a**)	0.5	91	79
2	4-MeC_6H_4 (**3b**)	0.5	92	80
3	4-$MeOC_6H_4$ (**3c**)	0.5	89	80
4	4-ClC_6H_4 (**3d**)	0.5	90	80
5	4-BrC_6H_4 (**3e**)	0.5	90	80
6	4-CNC_6H_4 (**3f**)	1.0	75	70
7	2-$MeOC_6H_4$ (**3g**)	0.5	88	80
8	2-BrC_6H_4 (**3h**)	0.5	92	80
9	2-$NO_2C_6H_4$ (**3i**)	1.0	91	80
10	3-BrC_6H_4 (**3j**)	1.0	90	77
11	1-Naphthyl (**3k**)	0.5	90	84
12	Thiophen-2-yl (**3l**)	1.0	70	77
13	*c*-C_6H_{11} (**3m**)	2.0	79	68
14	Me_2CH (**3n**)	2.0	60	64

[a] Unless otherwise indicated, all reactions were carried out with DPP (**1**, 0.10 mmol, pretreated with MS 4 Å immediately before reaction), nitroalkenes (0.20 mmol), catalyst **5** (0.01 mmol, 10 mol %), and MS 4 Å (60.0 mg) in CH_2Cl_2 (0.5 mL) at 5 °C.
[b] Yield of the isolated product.
[c] Determined by HPLC analysis on a ChiralPak AS column.

position of the substituent on the phenyl has almost no influence on the enantioselectivity and reactivity, either (entries 7–10). Good results were also obtained for 1-naphthyl-substituted nitroalkene (entry 11) and a nitroalkene with a thiophene substituent (entry 12). Besides nitroalkenes with an aryl substituent, the reaction also works with nitroalkenes with an aliphatic substituent: nitroalkenes with a cyclohexyl and an isopropyl substituent give the desired product in slight lower ee values in 68% and 64%, respectively (entries 13–14). The product yields are also lower as compared to their aromatic counterparts.

3. Conclusion

In summary, we reinvestigated the Michael addition reaction of diphenyl phosphite and nitroalkenes catalyzed by cinchona alkaloid thioureas, and discovered that a dramatic improvement of the efficiency of this reaction may be achieved by simply filtering the diphenyl phosphite sample through MS 4 Å and by adding MS (4 Å or 3 Å) to the reaction mixture. The MS was found to act as a scavenger of water and acid to remove the impurities in DPP samples and may facilitate the equilibrium between the phosphonate and phosphite forms of the DPP. The synergistic effects of these functions promote the reaction dramatically. After such a modification of the reaction procedure, high and reproducible yields of the desired β-nitrophosphonates may be obtained in very good ee values (up to 84% ee).

4. Experimental section

4.1. General information

Unless otherwise mentioned all the *trans*-β-nitrostyrenes were purchased from Sigma–Aldrich. 4-CN-*trans*-β-nitrostyrene (**2f**) was purchased from TCI America. These compounds were used as received. *trans*-β-Nitrostyrenes (**2k**, **2l**, **2m**, **2n**) were prepared according to the literature procedures.[12,13] Celite was purchased from Fluka. Diphenyl phosphite was purchased from Sigma–Aldrich (contains 15–16% of phenol according to its ^1H NMR) and Wako (contains 5–6% of phenol according to its ^1H NMR). Unless otherwise noted, this compound was passed through a pad of Celite (lower layer) and molecular sieves (4 Å, top layer) right before the reaction. Molecular sieves were purchased from Sigma–Aldrich and were activated and powdered before use (MS was activated at an oven temperature of 110 °C overnight). All the solvents used for purification were purchased from Fischer Scientific. Dichloromethane (GC grade) that was used in the reaction as the solvent was purchased Fischer Scientific. All the thiourea catalysts were prepared according to the literature procedure.[14]

4.2. General procedure for the enantioselective synthesis of Michael addition of diphenyl phosphite to nitroalkenes

A mixture of *trans*-β-nitrostyrene (29.8 mg, 0.20 mmol), catalyst **5** (5.9 mg, 0.010 mmol, 10 mol %), and freshly activated MS 4 Å (60.0 mg) in dichloromethane (0.5 mL) was cooled to 5 °C and stirred for 20 min at this temperature. Right before addition, diphenyl phosphite was passed through a bed of powdered activated MS 4 Å and Celite. A portion of the filtered diphenyl phosphite (23.5 mg, 0.10 mmol) was added to the reaction mixture immediately. The reaction mixture was further stirred for 30 min (monitored by TLC). After the reaction was completed, the mixture was directly transferred to a silica gel column. The product was purified by flash column chromatography (hexane/AcOEt=9.6/0.4 to 8/2) to give (*R*)-diphenyl 2-nitro-1-phenylethylphosphonate (**1a**, 35.0 mg, 91% yield).

*4.2.1. (R)-Diphenyl 2-nitro-1-phenylethylphosphonate (**3a**)*[1a–c]. White solid, yield 91%, 79% ee, ^1H NMR (300 MHz, $CDCl_3$) δ 7.46–7.09 (m, 13H; Ar), 6.74 (d, J=8.0 Hz, 2H; Ar), 5.26–5.07 (m, 2H; CH_2), 4.44 (ddd, J_{HP}=24.5 Hz, J_1=11.5, J_2=5.1 Hz, 1H; CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0 (d, J_{CP}=9.3 Hz), 149.9 (d, J_{CP}=9.8 Hz), 130.7 (d, J_{CP}=7.6 Hz), 130.1, 129.8, 129.4, 129.1, 125.9, 125.6, 120.5 (d, J_{CP}=4.4 Hz), 120.3 (d, J_{CP}=4.3 Hz), 75.2 (d, J_{CP}=4.8 Hz), 43.7 (d, J_{CP}=140.3 Hz). HPLC conditions: Chiralpak AS

column, *i*-PrOH/hexane 20:80, flow rate 0.5 mL/min at 25 °C, UV detection at 254 nm, t_R (major)=14.8 min, t_R (minor)=22.5 min.

*4.2.2. (R)-Diphenyl 1-(4-methylphenyl)-2-nitroethylphosphonate (**3b**)*[1b,c]. White solid, yield 92%, 80% ee, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.29 (m, 4H; Ar), 7.19–7.16 (m, 5H; Ar), 7.12–7.08 (m, 3H; Ar), 6.78 (d, J=8.0 Hz, 2H; Ar), 5.18 (ddd, J_{HP}=13.5 Hz, J_1=8.0, J_2=5 Hz, 1H; CH_2), 5.09 (ddd, J_{HP}=17.0 Hz, J_1=11.5, J_2=7.5 Hz, 1H), 4.39 (ddd, J_{HP}=24.6 Hz, J_1=11.0, J_2=4.5 Hz, 1H; CH), 2.33 (s, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.0 (d, J_{CP}=9.6 Hz), 149.9 (d, J_{CP}=10.1 Hz), 138.7, 129.9, 129.6, 129.0, 129.02 (d, J_{CP}=6.7 Hz), 127.4 (d, J_{CP}=7.7 Hz), 125.6, 125.4, 120.3 (d, J_{CP}=3.8 Hz), 120.1 (d, J_{CP}=3.8 Hz), 75.0 (d, J_{CP}=5.5 Hz), 43.0 (d, J_{CP}=140.6 Hz), 21.0. HPLC conditions: Chiralpak AS column, *i*-PrOH/hexane 10:90, flow rate 0.5 mL/min at 25 °C, UV detection at 254 nm, t_R (major)=14.1 min, t_R (minor)=21.6 min.

*4.2.3. (R)-Diphenyl 1-(4-methoxyphenyl)-2-nitroethylphosphonate (**3c**)*[1a–c]. White solid, yield 89%, 80% ee, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.29 (m, 5H; Ar), 7.21–7.17 (m, 3H; Ar), 7.12–7.09 (m, 2H; Ar), 6.89 (d, J=8.5 Hz, 2H; Ar), 6.78 (d, J=7.6 Hz, 2H; Ar), 5.18 (ddd, J_{HP}=13.5 Hz, J_1=6.9, J_2=4.7 Hz, 1H; CH_2), 5.07 (ddd, J_{HP}=18.2 Hz, J_1=10.8, J_2=7.5 Hz, 1H; CH_2), 4.39 (ddd, J_{HP}=24.5 Hz, J_1=10.8, J_2=4.6 Hz, 1H; CH), 3.8 (s, 3H; OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6 (d, J_{CP}=6.7 Hz), 150.4 (d, J_{CP}=9.6 Hz), 150.3 (d, J_{CP}=9.7 Hz), 130.2 (d, J_{CP}=3.2 Hz), 130.0, 129.8, 129.4 (d, J_{CP}=5.5 Hz), 125.6, 125.4, 121.3 (d, J_{CP}=2.9 Hz), 120.5 (d, J_{CP}=4.5 Hz), 120.2 (d, J_{CP}=4.4 Hz), 119.4 (d, J_{CP}=7.6 Hz), 111.6, 74.8 (d, J_{CP}=4.6 Hz), 56.1, 36.5 (d, J_{CP}=142.8 Hz). HPLC conditions: Chiralpak AS column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min at 25 °C, UV detection at 254 nm, t_R (major)=10.5 min, t_R (minor)=16.0 min.

*4.2.4. (R)-Diphenyl 1-(4-chlorophenyl)-2-nitroethylphosphonate (**3d**)*[1c]. White solid, yield 90%, 80% ee, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.32 (m, 6H; Ar), 7.27–7.20 (m, 3H; Ar), 7.16–7.10 (m, 3H; Ar), 6.81 (d, J=9.8 Hz, 2H; Ar), 5.20 (ddd, J_{HP}=13.9 Hz, J_1=6.9, J_2=4.3 Hz, 1H; CH_2), 5.09 (ddd, J_{HP}=18.2 Hz, J_1=11.2, J_2=7.0 Hz, 1H; CH_2), 4.42 (ddd, J_{HP}=24.7 Hz, J_1=11.2, J_2=4.2 Hz, 1H; CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.1 (d, J_{CP}=9.6 Hz), 150.0 (d, J_{CP}=9.7 Hz), 135.3, 130.7 (d, J_{CP}=6.6 Hz), 130.1 (d, J_{CP}=27.7 Hz), 129.7, 129.5 (d, J_{CP}=7.6 Hz), 125.9 (d, J_{CP}=25.7 Hz), 120.5 (d, J_{CP}=3.8 Hz), 120.3 (d, J_{CP}=4.8 Hz), 75.0, 43.1 (d, J_{CP}=140.8 Hz). HPLC conditions: Chiralpak AS column, *i*-PrOH/hexane 10:90, flow rate 0.5 mL/min at 25 °C, UV detection at 254 nm, t_R (major)=21.4 min, t_R (minor)=28.0 min.

*4.2.5. (R)-Diphenyl 1-(4-bromophenyl)-2-nitroethylphosphonate (**3e**)*[1a–c]. White solid, yield 90%, 80% ee, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, J=8.2 Hz, 2H; Ar), 7.35–7.30 (m, 4H; Ar), 7.22–7.20 (m, 3H; Ar), 7.11–7.08 (m, 3H; Ar), 6.81 (d, J=8.2 Hz, 2H; Ar), 5.20 (ddd, J_{HP}=13.9 Hz, J_1=6.9, J_2=4.5 Hz, 1H; CH_2), 5.08 (ddd, J_{HP}=18.0 Hz, J_1=11.0, J_2=7.0 Hz, 1H; CH_2), 4.41 (ddd, J_{HP}=24.6 Hz, J_1=10.8, J_2=4.4 Hz, 1H; CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1 (d, J_{CP}=7.2 Hz), 149.9 (d, J_{CP}=9.7 Hz), 132.6, 131.0 (d, J_{CP}=6.5 Hz), 130.2, 130.0, 126.0, 125.8, 123.4, 120.5 (d, J_{CP}=4.4 Hz), 120.2 (d, J_{CP}=4.4 Hz), 74.5 (d, J_{CP}=4.9 Hz), 43.2 (d, J_{CP}=141.1 Hz). HPLC conditions: Chiralpak AS column, *i*-PrOH/hexane 10:90, flow rate 0.5 mL/min at 25 °C, UV detection at 254 nm, t_R (major)=23.5 min, t_R (minor)=31.1 min.

*4.2.6. (R)-Diphenyl 1-(4-cyanophenyl)-2-nitroethylphosphonate (**3f**)*. White solid, yield 75%, 70% ee, $[\alpha]_D^{25}$ −6.7 (*c* 1.5 in CH_2Cl_2), mp: 90–92 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69–7.57 (m, 4H; Ar), 7.35–7.06 (m, 9H; Ar), 6.79 (d, J=8.4 Hz, 1H; Ar), 5.23 (ddd, J_{HP}=14.1 Hz, J_1=6.9, J_2=4.4 Hz, 1H; CH_2), 5.12 (ddd, J_{HP}=17.5 Hz, J_1=11.0, J_2=6.5 Hz, 1H; CH_2), 4.49 (ddd, J_{HP}=24.8 Hz, J_1=11.0, J_2=4.4 Hz, 1H; CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 149.9 (d, J_{CP}=10.7 Hz), 149.7 (d, J_{CP}=9.6 Hz), 136.5, 133.0, 132.6, 130.3 (d, J_{CP}=2.8 Hz), 130.2, 130.0 (d, J_{CP}=4.2 Hz), 128.6 (d, J_{CP}=5.8 Hz), 126.2, 126.0, 125.6, 120.6 (d, J_{CP}=4.6 Hz), 120.4 (d, J_{CP}=4.5 Hz), 120.1 (d, J_{CP}=4.4 Hz), 118.2, 113.2, 74.6 (d, J_{CP}=4.1 Hz), 43.8 (d, J_{CP}=140.0 Hz), 30.1; ν_{max} (neat, cm^{-1}): 3070, 3021, 2922, 2226, 1589, 1563, 1374, 1269, 1214; HRMS calcd for $C_{21}H_{18}N_2O_5P$ $(M+H)^+$ 409.0953; found 409.0921. HPLC conditions: Chiralpak AS column, *i*-PrOH/hexane 10:90, flow rate 1.0 mL/min at 25 °C, UV detection at 226 nm, t_R (major)=24.2 min, t_R (minor)=33.1 min.

*4.2.7. (R)-Diphenyl 1-(2-methoxyphenyl)-2-nitroethylphosphonate (**3g**)*[1a–c]. White solid, yield 88%, 80% ee, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.48 (td, J_1=7.6, J_2=1.8 Hz, 1H; Ar), 7.34–7.31 (m, 3H; Ar), 7.23–7.17 (m, 3H; Ar), 7.14–7.09 (m, 3H; Ar), 7.01–6.98 (m, 1H; Ar), 6.90 (d, J=8.5 Hz, 1H; Ar), 6.85 (d, J=8 Hz, 2H; Ar), 5.26–5.07 (m, 3H; CH, CH_2), 3.78 (s, 3H; OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6 (d, J_{CP}=6.7 Hz), 150.3 (d, J_{CP}=9.5 Hz), 150.2 (d, J_{CP}=9.4 Hz), 130.2 (d, J_{CP}=3.2 Hz), 130.0, 129.8, 129.4 (d, J_{CP}=5.5 Hz), 125.5 (d, J_{CP}=14.4 Hz), 120.5 (d, J_{CP}=4.5 Hz), 120.3 (d, J_{CP}=4.5 Hz), 119.4 (d, J_{CP}=7.6 Hz), 111.6, 74.9 (d, J_{CP}=4.7 Hz), 56.1, 36.5 (d, J_{CP}=142.8 Hz). HPLC conditions: Chiralpak AS column, *i*-PrOH/hexane 10:90, flow rate 0.5 mL/min at 25 °C, UV detection at 254 nm, t_R (major)=21.5 min, t_R (minor)=28.8 min.

*4.2.8. (R)-Diphenyl 1-(2-bromophenyl)-2-nitroethylphosphonate (**3h**)*[1a,b]. White solid, yield 92%, 80% ee, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, 2H; Ar), 7.35–7.30 (m, 3H; Ar), 7.19–7.07 (m, 7H; Ar), 6.78 (d, J=8.1 Hz, 2H; Ar), 5.29–5.08 (m, 3H; CH, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1 (d, J_{CP}=9.5 Hz), 149.9 (d, J_{CP}=10 Hz), 134.0 (d, J_{CP}=2.4 Hz), 130.9 (d, J_{CP}=7 Hz), 130.4 (d, J_{CP}=3.2 Hz), 130.1, 129.9, 129.3 (d, J_{CP}=4.5 Hz), 128.4 (d, J_{CP}=3.1 Hz), 126.6 (d, J_{CP}=9.3 Hz), 125.9, 125.6, 120.6 (d, J_{CP}=4.4 Hz), 120.1 (d, J_{CP}=4.5 Hz), 74.9 (d, J_{CP}=4.9 Hz), 43.0 (d, J_{CP}=142.0 Hz). HPLC conditions: Chiralpak AS column, *i*-PrOH/hexane 10:90, flow rate 0.5 mL/min at 25 °C, UV detection at 254 nm, t_R (major)=20.1 min, t_R (minor)=34.9 min.

*4.2.9. (R)-Diphenyl 1-(2-nitrophenyl)-2-nitroethylphosphonate (**3i**)*[1a,b]. White solid, yield 91%, 80% ee, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J=8 Hz, 1H; Ar), 7.81 (d, J=9.9 Hz, 1H; Ar), 7.63 (t, J=7.4 Hz, 1H; Ar), 7.49 (t, J=9.3 Hz, 1H; Ar), 7.33 (t, J=7.5 Hz, 2H; Ar), 7.22–7.05 (m, 6H; Ar), 6.83 (d, J=8.2 Hz, 2H; Ar), 5.74 (ddd, J_{HP}=26 Hz, J_1=10.4, J_2=4.8 Hz, 1H; CH_2), 5.26 (ddd, J_{HP}=14.5 Hz, J_1=6.9, J_2=4.9 Hz, 1H; CH_2), 5.17 (ddd, J_{HP}=17.5 Hz, J_1=10.4, J_2=7.2 Hz, 1H; CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 150.0 (d, J_{CP}=9.5 Hz), 149.9 (d, J_{CP}=9.9 Hz), 133.7, 130.2, 129.9, 129.8, 129.7, 126.6 (d, J_{CP}=6.7 Hz), 126.4, 125.8, 120.5 (d, J_{CP}=4.4 Hz), 120.04 (d, J_{CP}=4.5 Hz) 74.7 (d, J_{CP}=4.4 Hz), 37.2 (d, J_{CP}=140.9 Hz). HPLC conditions: Chiralpak AS column, *i*-PrOH/hexane 20:80, flow rate 0.5 mL/min at 25 °C, UV detection at 254 nm, t_R (major)=12.3 min, t_R (minor)=19.1 min.

*4.2.10. (R)-Diphenyl 1-(3-bromophenyl)-2-nitroethylphosphonate (**3j**)*[1a]. White solid, yield 90%, 77% ee, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J=1.7 Hz, 1H; Ar), 7.48 (d, J=7.7 Hz, 1H; Ar), 7.39 (d, J=7.6 Hz, 1H; Ar), 7.33 (t, J=7.6 Hz, 2H; Ar), 7.26–7.09 (m, 7H; Ar), 6.8 (d, J=7.9 Hz, 2H; Ar), 5.19 (ddd, J_{HP}=13.9 Hz, J_1=7.1, J_2=4.5 Hz, 1H; CH_2), 5.08 (ddd, J_{HP}=18 Hz, J_1=10.8, J_2=7.1 Hz, 1H; CH_2), 4.4 (ddd, J_{HP}=24.5 Hz, J_1=10.7, J_2=4.4 Hz, 1H; CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1 (d, J_{CP}=9.5 Hz), 149.9 (d, J_{CP}=9.9 Hz), 134.0 (d, J_{CP}=2.3 Hz), 130.9 (d, J_{CP}=6.9 Hz), 130.4 (d, J_{CP}=3.1 Hz), 130.2, 129.9, 129.3 (d, J_{CP}=4.5 Hz), 128.4 (d, J_{CP}=3.1 Hz), 126.6 (d, J_{CP}=9.3 Hz), 125.9, 125.6, 120.6 (d, J_{CP}=4.4 Hz), 120.1 (d, J_{CP}=4.5 Hz), 74.9 (d, J_{CP}=4.8 Hz), 42.0 (d, J_{CP}=142.0 Hz). HPLC conditions: Chiralpak AS column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min at 25 °C, UV detection at 254 nm, t_R (major)=8.3 min, t_R (minor)=16.7 min.

*4.2.11. (R)-Diphenyl 1-(1-naphthyl)-2-nitroethylphosphonate (**3k**)*[1a,b]. White solid, yield 90% 84% ee, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, J=8.5 Hz, 1H; Ar), 7.90–7.82 (m, 3H; Ar), 7.62–7.43 (m, 3H;

Ar), 7.33–6.98 (m, 8H; Ar), 6.59 (d, J=7.9 Hz, 2H; Ar), 5.50–5.28 (m, 3H; CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2 (d, J_{CP}=9.6 Hz), 150.1 (d, J_{CP}=10.0 Hz), 134.4, 132.1 (d, J_{CP}=6.6 Hz), 130.2, 129.7, 129.3, 127.4, 127.2 (d, J_{CP}=7.5 Hz), 126.5, 125.9, 125.5, 122.9, 120.6 (d, J_{CP}=4.4 Hz), 120.1 (d, J_{CP}=4.4 Hz), 75.7 (d, J_{CP}=4.2 Hz), 37.4 (d, J_{CP}=140.0 Hz). HPLC conditions: Chiralpak AS column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min at 25 °C, UV detection at 254 nm, t_R (major)=8.5 min, t_R (minor)=14.7 min.

*4.2.12. (R)-Diphenyl 1-(thiophen-2-yl)-2-nitroethylphosphonate (**3l**)*[1a–c]. ^1H NMR (300 MHz, $CDCl_3$) δ 7.31–7.23 (m, 3H; Ar), 7.25–7.14 (m, 5H; Ar), 7.11–7.07 (m, 2H; Ar), 7.00–6.97 (m, 1H; Ar), 6.87 (d, J=8.5 Hz, 2H; Ar), 5.24–5.14 (m, 1H; CH_2), 5.07–4.96 (m, 1H; CH_2), 4.73 (ddd, J_{HP}=24.4 Hz, J_1=10.7, J_2=4.2 Hz, 1H; CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1 (d, J_{CP}=9.7 Hz), 149.9 (d, J_{CP}=9.7 Hz), 131.9 (d, J_{CP}=8.9 Hz), 130.1, 129.9, 128.8 (d, J_{CP}=8.0 Hz), 127.6, 126.9, 125.9 (d, J_{CP}=12.9 Hz), 120.5 (d, J_{CP}=4.3 Hz), 120.3 (d, J_{CP}=4.4 Hz), 76.1 (d, J_{CP}=5.5 Hz), 39.2 (d, J_{CP}=146.0 Hz). HPLC conditions: Chiralpak AS column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min at 25 °C, UV detection at 254 nm, t_R (major)=8.2 min, t_R (minor)=16.7 min.

*4.2.13. (R)-Diphenyl 1-cyclohexyl-2-nitroethylphosphonate (**3m**)*[1a,b]. White solid, yield 79%, 68% ee, ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.25 (m, 4H; Ar), 7.20–7.08 (m, 6H; Ar), 4.93 (td, J_{HP}=14.0 Hz, J=5.3 Hz, 1H; CH_2), 4.75 (td, J_{HP}=14.0 Hz, J=7.3 Hz, 1H; CH_2), 3.14 (dddd, J_{HP}=23.3 Hz, J_1=7.4, J_2=5.3, J_3=3.5 Hz, 1H; CH), 2.15–1.63 (m, 6H; C_6H_{11}), 1.43–1.14 (m, 5H; CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1 (d, J_{CP}=9.0 Hz), 149.9 (d, J_{CP}=10.2 Hz), 130.0, 125.7, 120.6, 72.8 (d, J_{CP}=3.9 Hz), 41.9 (d, J_{CP}=139.5 Hz), 37.5 (d, J_{CP}=2.8 Hz), 31.6 (d, J_{CP}=11.0 Hz), 30.2 (d, J_{CP}=3.1 Hz), 26.9, 26.7, 26.1. HPLC conditions: Chiralpak AS column, *i*-PrOH/hexane 5:95, flow rate 0.5 mL/min at 25 °C, UV detection at 254 nm, t_R (major)=18.8 min, t_R (minor)=22.4 min.

*4.2.14. (R)-Diphenyl 3-methyl-1-nitrobutan-2-ylphosphonate (**3n**)*[1a]. White solid, yield 60%, 64% ee, ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.27 (m, 4H; Ar), 7.19–7.06 (m, 6H; Ar), 4.93 (td, J_{HP}=14.0 Hz, J=5.6 Hz, 1H; CH_2), 4.72 (td, J_{HP}=14.1 Hz, J=7.3 Hz, 1H; CH_2), 3.19 (dddd, J_1=3.5, J_2=5.3, J_3=7.1, J_4=23.3 Hz, 1H; CH), 2.45 (d septet d, J_{HP}=20.5 Hz, J_1=7.2, J_2=3.8 Hz, 1H; CH), 1.16 (d, J=6.7 Hz, 3H; CH_3), 1.15 (d, J=6.8 Hz, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.1 (d, J_{CP}=9.0 Hz), 149.9 (d, J_{CP}=10.0 Hz), 130.0, 125.7, 125.6, 120.6 (d, J_{CP}=4.5 Hz), 120.5 (d, J_{CP}=4.7 Hz), 72.5, 42.0 (d, J_{CP}=140.5 Hz), 27.6 (d, J_{CP}=2.8 Hz), 21.2 (d, J_{CP}=12.0 Hz), 19.5 (d, J_{CP}=3.3 Hz). HPLC conditions: Chiralpak AS column, *i*-PrOH/hexane 10:90, flow rate 0.5 mL/min at 25 °C, UV detection at 254 nm, t_R (major)=13.2 min, t_R (minor)=16.1 min.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.07.059.

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