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N-Thiophosphoryl imines: convenient substrates in the aza-Henry reaction

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ABSTRACT

In the presence of 1,1,3,3-tetramethylguanidine (TMG), *N*-diethoxythiophosphorylimines **1** and *N*-diphenylthiophosphinoylimines **2** exhibited good reactivity in the aza-Henry reaction. The corresponding products were obtained in excellent chemical yields under mild conditions. Moreover, the asymmetric version of the *N*-thiophosphoryl imine **1**-based aza-Henry reaction was also realized with ee values up to 87% by employing Takemoto's thiourea as the catalyst.

1. Introduction

The nucleophilic addition of nitroalkanes to the C=N bond of imines, known as the aza-Henry (or nitro-Mannich) reaction, is a useful carbon–carbon bond-forming process in organic synthesis.[1] The resulting β-nitroamine derivatives can be readily transformed into valuable building blocks or biologically active compounds, such as vicinal diamines via reduction of the nitro group[2] and α-amino acids by means of the Nef reaction.[3] As a result, much attention has been paid to the aza-Henry reaction, especially for the catalytic asymmetric version of this reaction, over the past several years.[4,5] Most of the recent efforts on this reaction have been directed toward the search for efficient chiral catalysts to promote efficiency (yields) and selectivity (ee values), and have seldom dealt with the scope of the reaction. In the reported aza-Henry reactions, *N*-carbamate-activated imines, derived from aryl, heteroaryl, and aliphatic aldehydes, are the commonly used electrophiles. However, a common drawback associated with the use of this type of imines is certain precautions have to be taken in their preparation, handling, and storage because of their substantial hydrolytic liability. In contrast, *N*-phosphinoyl imine has rarely been used due to its troublesome preparation, poor stability, and relatively low reactivity, although phosphinoyl could be easily deprotected via acidic hydrolysis from the aza-Henry adduct. Shibasaki reported the first metal-catalyzed aza-Henry reaction of *N*-phosphinoyl imines, in which up to 91% ee was obtained.[4a,b] Ricci developed the TMG-catalyzed aza-Henry reaction of *N*-diphenylphosphinoyl imine.[2e] An alternative organocatalyzed aza-Henry reaction of *N*-diphenylphosphinoyl imine was later developed by Terada by employing TMG or phosphazene as the catalyst.[6] An asymmetric version of the organocatalyzed aza-Henry reaction of *N*-diphenylphosphinoyl imine was also realized with a highest enantioselectivity of 76% ee by Takemoto who employed a chiral bifunctional thiourea as the catalyst.[5a] Recently, we developed a convenient method for the preparation of *N*-thiophosphoryl imines,[7] which have been successfully employed as novel electrophiles in some organic transformations.[8] Compared to *N*-diphenylphosphinoyl imines, the thio analogue has the advantages of ease of preparation and its stability to water, heat as well as silica gel. For this reason, we thought that it would be of interest to employ *N*-thiophosphoryl protected imines in the aza-Henry reactions. Herein, we report our results on *N*-thiophosphorylimine-based aza-Henry reaction.

2. Results and discussion

According to the reported procedure, *N*-diethoxythiophosphoryl-protected imines **1** and *N*-diphenylthiophosphinoyl-blocked imines **2** were synthesized in good to excellent yield through thermal condensation of acetals and the corresponding thiophosphoramides.[7]

Firstly, different organic bases were screened as the catalyst using the coupling of *N*-diethoxythiophosphorylimines **1a** and nitromethane as the model (Table 1, entries 1–6). Except for 4-dimethylaminopyridine (DMAP), all the other bases evaluated exhibited good catalytic activities in this transformation. Among them, 1,1,3,3-tetramethylguanidine (TMG) was found to be particularly effective. The use of only 10 mol % of TMG afforded a clean and fast reaction in 3 h (Table 1, entry 1). Total conversion of the imine **1a** was also observed in less than 24 h even when the catalyst loading was reduced to 5 mol % (Table 1, entry 2).

On the basis of these results, *N*-thiophosphoryl imines **1**- and *N*-thiophosphoryl imines **2**-based aza-Henry reactions were thoroughly investigated employing TMG as the catalyst. The results are summarized in Tables 2 and 3, respectively.

As shown in Table 2, the aza-Henry reaction between *N*-thiophosphoryl imines **1** and nitromethane in the presence of 10 mol % of

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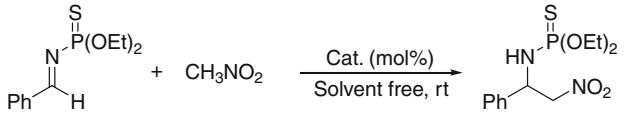
Table 1
Organic bases in the aza-Henry reaction of *N*-thiophosphorylimine[a]



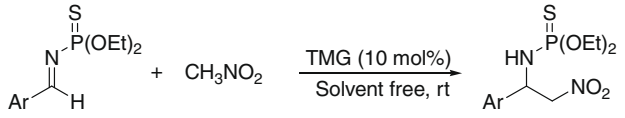
1a **3a**

Entry	Catalyst (mol %)	Time (h)	Conversion (%)
1	TMG (10)	3	>99
2	TMG (5)	24	>99
3	Et_3N (10)	12	>99
4	DMAP (10)	120	Trace
5	DABCO (10)	48	>99
6	$^iPr_2NEt$ (10)	48	>99

[a] All the reactions were carried out on a 0.5 mmol scale using 10 equiv of nitromethane.

TMG at room temperature led to promising results. The desired adducts were attained in excellent chemical yield in all the cases examined. Compared to electron-donating group-substituted imines, those imines bearing electron-withdrawing generally demonstrated higher reactivity, and required less reaction time for completion (Table 2, entries 6–8 vs entries 2–5).

Table 2
TMG-catalyzed aza-Henry reaction of imine **1**[a]

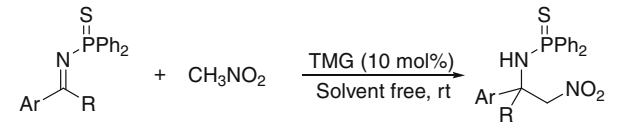


1a–i **3a–i**

Entry	Ar	Time (h)	Yield[b] (%)
1	Ph (**a**)	3	96
2	4-MeC_6H_4 (**b**)	3	92
3	2-$MeOC_6H_4$ (**c**)	3.5	94
4	3-$MeOC_6H_4$ (**d**)	3	90
5	4-$MeOC_6H_4$ (**e**)	3	93
6	2-ClC_6H_4 (**f**)	2	89
7	2-$F_3CC_6H_4$ (**g**)	1.5	87
8	3-FC_6H_4 (**h**)	1.5	97
9	2-Furyl (**i**)	3	91

[a] All the reactions were carried out on a 0.5 mmol scale using 10 equiv of nitromethane.
[b] Isolated yield after column chromatography on silica gel.

Table 3
TMG-catalyzed aza-Henry reaction of imine **2**[a]



2a–g **4a–g**

Entry	Ar	R	Time (min)	Yield[b] (%)
1	Ph (**a**)	H	10	98
2	4-$MeOC_6H_4$ (**b**)	H	10	98
3	3-FC_6H_4 (**c**)	H	10	92
4	4-BrC_6H_4 (**d**)	H	10	90
5	4-$NO_2C_6H_4$ (**e**)	H	2.4 h	95
6	3-$F_3CC_6H_4$ (**f**)	H	35	98
7	Ph (**g**)	Me	48 h	57

[a] All the reactions were carried out on a 0.5 mmol scale using 10 equiv of nitromethane.
[b] Isolated yield after column chromatography on silica gel.

Compared to imine **1**, imine **2** exhibited much higher reactivity (as shown in Table 3). In most cases, the reaction was completed in less than 35 min with excellent chemical yields. A somewhat longer reaction time was required for 4-nitro-substituted substrate **2e**, but it still gave excellent results (Table 3, entry 5, 95%, 2.4 h). It is worth noting that the inherently less reactive ketimine **2g** was also tolerated in this reaction, and the corresponding adduct **4g** was obtained in a fair yield after a prolonged reaction time (Table 3, entry 7, 57%, 48 h).

The asymmetric version of this reaction was also carried out using chiral tertiary amines as the catalyst. A brief survey of different amino alcohols **5**,[9] **6**,[10] and chiral thioureas **7**–**10**[11,5a,k,12] (Fig. 1) identified Takemoto's thiourea **8** to be an effective catalyst for the addition of nitromethane to *N*-diethoxythiophosphorylimine **1a**. The corresponding adduct was obtained in 89% yield with an enantioselectivity of 85% ee (Table 4, entry 4). With respect to imine **2a**, only the *N*-thiophosphorylated thiourea **9** could promote the reaction to afford the addition product **4a** in moderate yield, albeit with quite low stereoselectivity (Table 4, entry 8).

In further experiments, other factors, such as solvent, catalyst loading, and reaction temperature, which could influence the reaction, were thoroughly investigated by employing **8** as the catalyst and the reaction between *N*-diethoxythiophosphorylimine **1a** and nitromethane as the model. The results are listed in Table 5.

Solvent evaluation revealed that all of the solvents studied, except for methanol, afforded the desired product in good yield and ee values (Table 5, entries 1–6). Among the solvents tested, $CHCl_3$ was proven to be the best one in terms of both chemical yield and selectivity. The investigation of different catalyst loadings revealed that there was no significant influence on the stereoselectivity of the reaction. For example, the reaction proceeded in both high yield and ee value in the presence of 20 mol % **8** (Table 5, entry 6). The enantioselectivity was maintained when the catalyst loading was reduced to 15 mol % (Table 5, entry 7). Although almost the same selectivity was obtained at 10 mol % catalyst loading, the reaction became slightly sluggish, and only 80% conversion of the imine was observed after stirring for 144 h (Table 5, entry 8). In addition, performing the reaction at lower or higher temperature resulted in a little loss of stereocontrol (Table 5, entries 9 and 10, 81% and 80% ee, respectively).

Under the optimal reaction conditions (15 mol % of **8** as the catalyst, at 25 °C in $CHCl_3$), we next examined a variety of *N*-diethoxythiophosphorylimines with different structures in this asymmetric aza-Henry reaction. The results are summarized in Table 6.

As shown in Table 6, the reaction was general, and a number of diverse aryl-substituted aza-Henry adducts were obtained in good yields with high enantioselectivities (77–87% ee). The introduction of electron-donating or electron-withdrawing groups on the aromatic ring of imines did not affect the enantioselectivities (Table 6, entries 2–8). Moreover, the reaction also tolerated sterically hindered *ortho*-substituted imines **1c**, **1f**, and **1g**, giving the corresponding *o*-methoxy, *o*-chloro, and *o*-trifluoromethyl-substituted product with 84%, 82%, and 87% ee, respectively (Table 6, entries 3, 6, and 7). The electron-rich heteroaryl-substituted imine **2i** also appeared to be a good candidate, albeit with a slight decrease in stereoselectivity (Table 6, entry 9, 77% ee).

In order to determine the absolute configuration of the newly generated stereogenic center, the aza-Henry adduct **3a** was transformed into compound **11** via successively dephosphorylation and *N*-Boc-protection (Scheme 1). By comparison of the sign of the specific rotation value, the absolute configuration of the major enantiomer of compound **11** could be assigned as (*R*).[5k] Since none of the bonds to the stereogenic carbon have been broken during the sequence of reactions, the original configuration of adduct **3a** is retained. Therefore, the aza-Henry adduct **3a** obtained by thiourea **8**-catalyzed aza-Henry reaction between *N*-thiophosphoryl imine **1a**

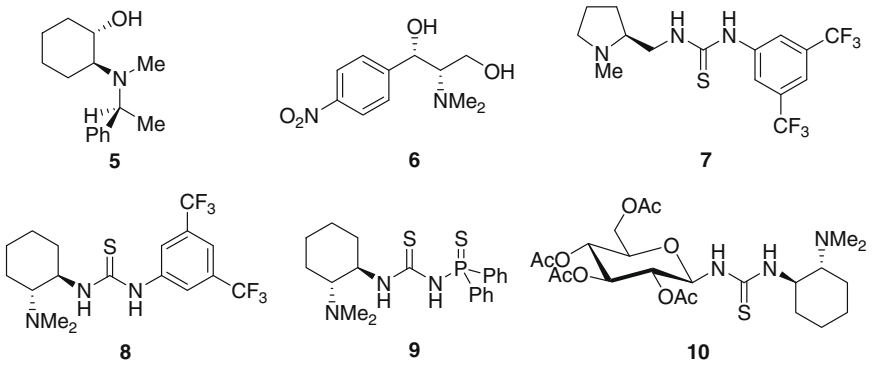
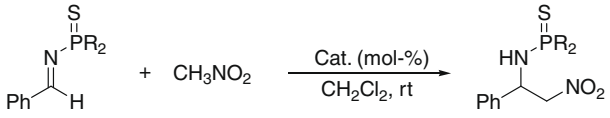


Figure 1. Screened catalysts for the addition of nitromethane to *N*-thiophosphorylimines **1a** and **2a**.

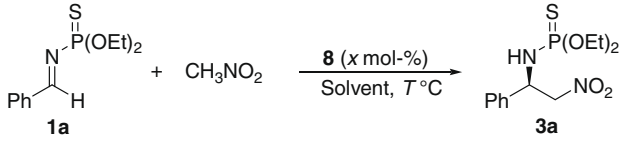
Table 4
Catalyst screening for the asymmetric aza-Henry reaction of *N*-thiophosphorylimine [a]



Entry	Imine	Catalyst (mol %)	Time (h)	Yield[b] (%)	ee[c] (%)
1	**1a**	**5** (20)	10 d	80	21
2	**1a**	**6** (20)	10 d	72	16
3	**1a**	**7** (20)	48	95	17
4	**1a**	**8** (20)	120	89	85
5	**1a**	**9** (20)	24	NR	
6	**1a**	**10** (15)	48	NR	
7	**2a**	**7** (20)	48	Trace	
8	**2a**	**8** (20)	72	Trace	
9	**2a**	**9** (20)	24	52	10
10	**2a**	**10** (15)	48	Trace	

[a] All the reactions were carried out on a 0.5 mmol scale using 10 equiv of nitromethane.
[b] Isolated yield after column chromatography on silica gel.
[c] Determined by chiral HPLC analysis.

Table 5
Optimization of the reaction conditions[a]

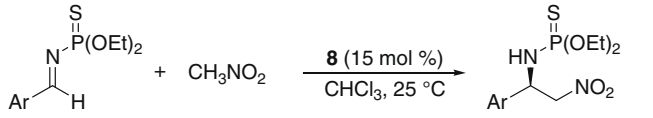


Entry	**8** (mol %)	Solvent	Temp (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	20	MeOH	25	120	66 (75)[d]	39
2	20	CH_3CN	25	120	84	70
3	20	EA	25	120	87	79
4	20	$PhCH_3$	25	120	85	81
5	20	CH_2Cl_2	25	120	89	85
6	20	$CHCl_3$	25	120	94	85
7	15	$CHCl_3$	25	123	94	85
8	10	$CHCl_3$	25	144	70 (80)[d]	84
9	15	$CHCl_3$	0	120	84	81
10	15	$CHCl_3$	40	120	88	80

[a] All the reactions were carried out on a 0.5 mmol scale using 10 equiv of nitromethane.
[b] Isolated yield after column chromatography on silica gel.
[c] Determined by chiral HPLC analysis.
[d] Data in the parentheses are the conversion of the imine **1a**.

and nitromethane was assigned as (*R*), and those of the other adducts **3b–i** were deduced on the basis of these results. It is worth noting that the aza-Henry reaction with *N*-benzylidenediphenylphosphinamide afforded the corresponding antipode adduct with much lower enantioselectivity under the same conditions (85% vs 67% ee).[5a] These results indicate that the protecting group on the nitrogen atom of imine has a determinant effect on the absolute configuration of the addition product and the enantiomeric excess.

Table 6
Chiral thiourea **8**-catalyzed asymmetric aza-Henry reaction of imine **1**[a]



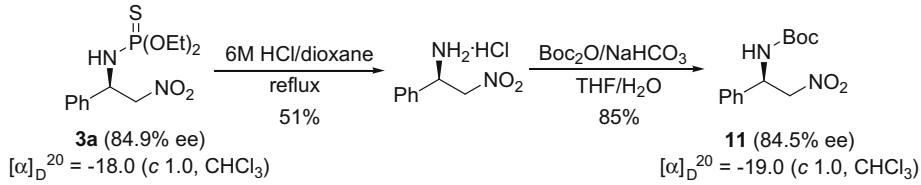
Entry	Ar	Time (d)	Yield[b] (%)	ee[c] (%)
1	Ph (**a**)	5	94	85
2	4-MeC_6H_4 (**b**)	6	84	86
3	2-$MeOC_6H_4$ (**c**)	6	87	84
4	3-$MeOC_6H_4$ (**d**)	6	83	87
5	4-$MeOC_6H_4$ (**e**)	6.5	78	87
6	2-ClC_6H_4 (**f**)	5	89	82
7	2-$CF_3C_6H_4$ (**g**)	5	93	87
8	3-FC_6H_4 (**h**)	5	88	83
9	2-Furyl (**i**)	8	80	77

[a] All the reactions were carried out on a 0.5 mmol scale using 10 equiv of nitromethane.
[b] Isolated yield after column chromatography on silica gel.
[c] Determined by chiral HPLC analysis.

The high degree of selectivity observed in the current reaction indicates a catalyst-associated complex with a high degree of coordination.[13] To account for the observed enantioselectivity of the reaction, a ternary complex of catalyst **8**, imine **1**, and nitronate is proposed as a plausible transition state (Fig. 2). In the transition state, imine **1** and the nitronate anion coordinate to the thiourea moiety and tertiary amino group of catalyst **8** by hydrogen-bonding interaction, respectively.[5b] Then the *si*-facial attack of the nitronate anion leads to the formation of the (*R*)-enantiomer as the major product (except for **3i** in which the priority of the four groups is changed).

3. Conclusion

We have developed a readily available and stable *N*-thiophosphoryl imine-based aza-Henry reaction. The corresponding adducts were obtained in excellent yields in the presence of 10 mol % of TMG. Moreover, an asymmetric version of aza-Henry reaction of *N*-diethoxythiophosphorylimine was realized employing Takemoto's thiourea as the catalyst. Compared with reaction



Scheme 1. Transformation of β-nitroamine **3a** into **11**.

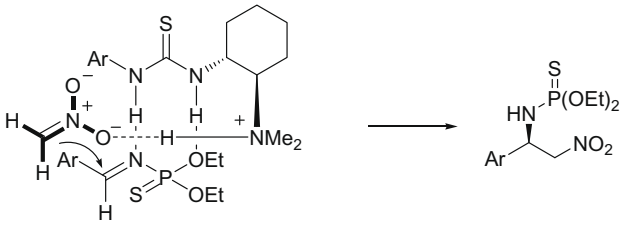


Figure 2. Proposed transition state of the thiourea-catalyzed aza-Henry reaction.

of *N*-diphenylphosphinoylimine, which gave moderate to good enantioselectivities (63–76% ee),[5a] this reaction provided better results (77–87% ee), which indicates that the protecting groups play an important role on the enantioselectivity of the reaction.

4. Experimental

4.1. Preparation of chiral *N*-thiophosphinoyl thiourea 9

To a solution of diphenylphosphinothioic acid isothiocyanate[14] (530 mg, 1.9 mmol) in dry THF (2 mL) was added dropwise a solution of (1*R*,2*R*)-*N*,*N*-dimethylcyclohexane-1,2-diamine (270 mg, 1.9 mmol) in anhydrous THF (4 mL) under a nitrogen atmosphere. The resulting mixture was stirred at room temperature for 5 h. After removal of the solvent, the residue was purified through column chromatography on silica gel (200–300 mesh, eluted with ethyl acetate/petroleum ether: 1/1) to give the thiourea catalyst as a white solid. 190 mg, 38% yield, mp 116–118 °C, $[\alpha]_D^{20} = -44.9$ (*c* 1.0, $CHCl_3$). ^{31}P NMR ($CDCl_3$, 161.7 MHz): δ = 51.50. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.10–1.22 (m, 4H), 1.58–1.74 (m, 4H), 1.99 (s, 6H), 2.24–2.26 (m, 1H), 2.49–2.52 (m, 1H), 3.81 (br s, 1H), 7.48–7.57 (m, 6Harom), 7.83–7.94 (m, 4Harom), 8.72 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 22.01, 24.35, 24.82, 39.75, 56.91, 57.93, 66.05, 128.71, 128.78, 128.85, 128.92, 131.15, 131.27, 131.48, 131.60, 132.56, 140.56, 189.81. Anal. Calcd for $C_{21}H_{28}N_3PS_2$: C, 60.40; H, 6.76; N, 10.06. Found: C, 60.20; H, 6.96; N, 10.07.

4.2. General procedure for TMG-catalyzed aza-Hentry reaction of nitromethane with *N*-thiophosphoryl imines 1 and 2

A mixture of TMG (11.5 mg, 0.1 mmol), *N*-thiophosphoryl imine (1 mmol), and nitromethane (1 mL) was stirred at room temperature until the imine substrate had disappeared. After removal of the excess nitromethane under reduced pressure, the crude product was purified via column chromatography on silica gel (200–300 mesh, gradient eluted with petroleum ether and ethyl acetate) to provide the desired adduct.

4.2.1. *N*-(2-Nitro-1-phenylethyl)-*N*,*N*-diphenylphosphinothioamide 4a

White solid, 98% yield, mp 110–112 °C. ^{31}P NMR ($CDCl_3$, 121.3 MHz): δ = 60.97. ^1H NMR ($CDCl_3$, 300 MHz): δ = 3.81 (s, 1H), 4.93 (s, 2H), 5.09 (s, 1H), 7.29–7.41 (m, 11Harom), 7.90 (s, 4Harom). ^{13}C NMR ($CDCl_3$, 75.0 MHz): 53.27, 79.78, 126.28, 128.06, 128.13, 128.22, 128.38, 128.64, 130.83, 130.98, 131.36, 131.51, 131.61, 131.76, 132.33, 132.91, 133.69, 134.27, 137.49, 137.55. Anal. Calcd for $C_{20}H_{19}N_2O_2PS$: C, 62.81; H, 5.01; N, 7.33. Found: C, 62.65; H, 4.95; N, 7.31.

4.2.2. *N*-(1-(4-Methoxyphenyl)-2-nitroethyl)-*N*,*N*-diphenylphosphino-thioamide 4b

White solid, 98% yield, mp 106–107 °C. ^{31}P NMR ($CDCl_3$, 121.3 MHz): δ = 60.76. ^1H NMR ($CDCl_3$, 400 MHz): δ = 3.59 (s, 1H), 3.78 (s, 3H), 4.94 (s, 2H), 4.97 (s, 1H), 6.85 (d, *J* = 8.0 Hz, 2Harom), 7.19 (d, *J* = 8.0 Hz, 2Harom), 7.37–7.51 (m, 6Harom), 7.86 (dd, *J* = 7.6 and 13.6 Hz, 2Harom), 7.92 (dd, *J* = 7.6 and 13.6 Hz, 2Harom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 53.04, 55.23, 80.21, 80.23, 114.31, 127.69, 128.40, 128.53, 128.66, 129.68, 129.74, 131.14, 131.25, 131.71, 131.82, 131.93, 132.07, 132.68, 133.29, 133.70, 134.30, 159.49. Anal. Calcd for $C_{21}H_{21}N_2O_3PS$: C, 61.15; H, 5.13; N, 6.79. Found: C, 60.91; H, 5.28; N, 6.74.

4.2.3. *N*-(1-(3-Fluorophenyl)-2-nitroethyl)-*N*,*N*-diphenylphosphino-thioamide 4c

White solid, 92% yield, mp 99–100 °C. ^{31}P NMR ($CDCl_3$, 121.3 MHz): δ = 61.29. ^1H NMR ($CDCl_3$, 300 MHz): δ = 3.68–3.73 (m, 1H), 4.81–5.04 (m, 3H), 6.90–7.00 (m, 3Harom), 7.19–7.48 (m, 7Harom), 7.79 (dd, *J* = 7.2 and 13.5 Hz, 2Harom), 7.86 (dd, *J* = 7.2 and 13.5 Hz, 2Harom). ^{13}C NMR ($CDCl_3$, 75.0 MHz): 52.97, 79.86, 79.90, 113.58, 113.88, 115.25, 115.33, 122.11, 122.15, 128.38, 128.56, 128.73, 130.52, 130.63, 131.08, 131.23, 131.61, 131.76, 131.99, 132.03, 132.12, 132.16, 132.35, 132.96, 133.12, 132.16, 132.35, 132.96, 133.72, 134.32, 140.20, 140.28, 140.37, 161.18, 164.46. Anal. Calcd for $C_{20}H_{18}FN_2O_2PS$: C, 59.99; H, 4.53; N, 7.00. Found: C, 60.09; H, 4.57; N, 7.06.

4.2.4. *N*-(1-(4-Bromophenyl)-2-nitroethyl)-*N*,*N*-diphenylphosphino-thioamide 4d

White solid, 90% yield, mp 120–1121 °C. ^{31}P NMR ($CDCl_3$, 121.3 MHz): δ = 61.24. ^1H NMR ($CDCl_3$, 300 MHz): δ = 3.74 (dd, *J* = 5.7, 13.2 Hz, 1H) 4.85–5.05 (m, 3H), 7.14 (d, *J* = 8.4 Hz, 2Harom), 7.37–7.52 (m, 8Harom), 7.83 (dd, *J* = 7.2 and 13.5 Hz, 2Harom), 7.91 (dd, *J* = 7.2 and 13.5 Hz, 2Harom). ^{13}C NMR ($CDCl_3$, 75.0 MHz): 52.92, 79.83, 79.87, 122.44, 128.23, 128.39, 128.55, 128.71, 131.07, 131.22, 131.57, 131.72, 131.97, 132.02, 132.11, 132.15, 132.35, 132.92, 133.72, 134.27, 136.73, 136.81. Anal. Calcd for $C_{20}H_{18}BrN_2O_2PS$: C, 52.07; H, 3.93; N, 6.07. Found: C, 51.75; H, 4.35; N, 5.57.

4.2.5. *N*-(2-Nitro-1-(4-nitrophenyl)ethyl)-*N*,*N*-diphenylphosphinothioamide 4f

Pale yellow solid, 95% yield, mp 164–165 °C. ^{31}P NMR ($CDCl_3$, 121.3 MHz): δ = 60.21. ^1H NMR ($CDCl_3$, 300 MHz): δ = 3.94 (s, 1H), 4.94 (dd, *J* = 4.8 and 12.9 Hz, 1H), 5.07 (dd, *J* = 4.8 and 12.9 Hz, 1H), 5.17 (s, 1H), 7.38–7.50 (m, 8Harom), 7.83 (dd, *J* = 7.5 and 13.5 Hz, 2Harom), 7.92 (dd, *J* = 7.5 and 13.5 Hz, 2Harom), 8.16 (d, *J* = 8.1 Hz, 2Harom). ^{13}C NMR ($CDCl_3$, 75.0 MHz): 53.01, 79.74, 79.77, 123.44, 123.47, 123.51, 123.55, 125.25, 125.28, 125.32, 125.36, 128.44,

128.57, 128.65, 128.78, 129.51, 130.00, 131.10, 131.21, 132.08, 132.11, 132.23, 132.26, 132.34, 133.00, 133.37, 134.02, 138.77, 138.82. Anal. Calcd for $C_{20}H_{18}N_3O_4PS$: C, 56.20; H, 4.24; N, 9.83. Found: C, 55.91; H, 4.25; N, 10.03.

4.2.6. *N*-(2-Nitro-1-(3-(trifluoromethyl)phenyl)ethyl)-*N*,*N*-diphenyl-phosphinothioamide 4e

White solid, 98% yield, mp 84–85 °C. ^{31}P NMR ($CDCl_3$, 161.7 MHz): δ = 60.21. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.80 (dd, J = 6.0 and 10.4 Hz, 1H), 4.94 (dd, J = 4.5 and 13.2 Hz, 1H), 5.01 (dd, J = 5.6 and 13.2 Hz, 1H), 5.12–5.21 (m, 1H), 7.34–7.39 (m, 2Harom), 7.43–7.56 (m, 8Harom), 7.82 (ddd, J = 1.2, 8.4 and 13.6 Hz, 2Harom), 7.90 (ddd, J = 1.2, 8.4 and 13.6 Hz, 2Harom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 53.01, 79.74, 79.77, 123.44, 123.47, 123.51, 123.55, 125.25, 125.28, 125.32, 125.36, 128.44, 128.57, 128.65, 128.78, 129.51, 130.00, 131.10, 131.21, 132.08, 132.11, 132.23, 132.26, 132.34, 133.00, 133.37, 134.02, 138.77, 138.82. Anal. Calcd for $C_{21}H_{18}F_3N_2O_2PS$: C, 56.00; H, 4.03; N, 6.22. Found: C, 55.85; H, 4.27; N, 6.26.

4.2.7. *N*-(1-Nitro-2-phenylpropan-2-yl)-*N*,*N*-diphenylphosphinothioamide 4g

White solid, 57% yield, mp 143–144 °C. ^{31}P NMR ($CDCl_3$, 161.7 MHz): δ = 53.61. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.62 (s, 3H), 4.25 (s, 1H), 5.01 (d, J = 13.6 Hz, 1H), 6.20 (d, J = 13.6 Hz, 1H), 7.30 (t, J = 7.6 Hz, 1Harom), 7.39 (t, J = 7.6 Hz, 2Harom), 7.46–7.54 (m, 8Harom), 7.98 (dd, J = 7.2 and 13.2 Hz, 2Harom), 8.26 (dd, J = 7.2 and 14.0 Hz, 2Harom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 26.53, 26.57, 60.67, 60.69, 82.09, 124.35, 127.77, 128.38, 128.51, 128.65, 128.77, 128.88, 130.41, 130.53, 131.73, 131.76, 131.86, 131.89, 132.17, 132.28, 134.30, 135.08, 135.35, 136.10, 143.44, 143.52. Anal. Calcd for $C_{21}H_{21}N_2O_2PS$: C, 63.62; H, 5.34; N, 7.07. Found: C, 63.65; H, 5.12; N, 7.03.

4.3. General procedure for the enantioselective aza-Henry reaction of nitromethane with *N*-thiophosphoryl imine 1

Nitromethane (10 equiv, 305 mg) was added to a stirred solution of imine **1** (0.5 mmol) and thiourea **8** (0.15 equiv, 31 mg) in chloroform, and the resulting mixture was stirred at room temperature for the total consumption of the imine **1** (monitored by TLC). Then the reaction mixture was concentrated in vacuo, and the obtained residue was purified by column chromatography on silica gel (200–300 mesh, gradient eluted with petroleum ether and ethyl acetate) to afford the desired adduct **3**.

4.3.1. Diethyl-(*R*)-*O*,*O*-2-nitro-1-phenylethylphosphorothioamidate 3a

Pale yellow liquid, n_D^{10} 1.5207, $[\alpha]_D^{20} = -18.0$ (c 1.0, $CHCl_3$), 85% ee. ^{31}P NMR ($CDCl_3$, 161.7 MHz): δ = 69.12. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.08 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 3.65–3.75 (m, 1H), 3.90–4.10 (m, 4H), 4.62 (ddd, J = 1.2, 5.2, 12.4 Hz, 1H), 4.71 (dd, J = 8.0, 12.4 Hz, 1H), 5.03–5.12 (m, 1H), 7.28–7.37 (m, 5Harom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 15.42 (d, J = 8.7 Hz), 15.66 (d, J = 8.6 Hz), 54.22, 63.08 (d, J = 4.7 Hz), 63.31 (d, J = 5.0 Hz), 80.18 (d, J = 6.7 Hz), 126.19, 128.49, 128.93, 137.77 (d, J = 3.3 Hz). Anal. Calcd for $C_{12}H_{19}N_2O_4PS$: C, 45.28; H, 6.02; N, 8.80. Found: C, 45.02; H, 5.95; N, 8.63. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 98:2, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 28.17 (minor), 31.83 min (major).

4.3.2. Diethyl-(*R*)-*O*,*O*-1-(4-methylphenyl)-2-nitroethylphosphorothioamidate 3b

Pale yellow liquid, n_D^{10} 1.5379, $[\alpha]_D^{20} = -5.6$ (c 1.0, $CHCl_3$), 86% ee. ^{31}P NMR ($CDCl_3$, 161.7 MHz): δ = 69.28. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.12 (t, J = 7.2 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H), 2.31 (s, 3H), 3.68–3.78 (m, 1H), 3.91–4.07 (m, 4H), 4.61 (dd, J = 5.6, 12.4 Hz, 1H), 4.69 (dd, J = 7.6, 12.4 Hz, 1H), 4.99–5.08 (m, 1H), 7.15 (d, J = 8.0 Hz, 2Harom), 7.20 (d, J = 8.0 Hz, 2Harom). ^{13}C NMR ($CDCl_3$, 75.0 MHz): 15.33 (d, J = 8.3 Hz), 15.54 (d, J = 8.2 Hz), 20.79, 53.96, 62.94 (d, J = 4.5 Hz), 63.14 (d, J = 4.7 Hz), 80.18 (d, J = 6.8 Hz), 126.03, 129.43, 134.84 (d, J = 3.8 Hz), 138.12. Anal. Calcd for $C_{13}H_{21}N_2O_4PS$: C, 46.98; H, 6.37; N, 8.43. Found: C, 46.77; H, 6.14; N, 8.28. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 98:2, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 25.58 (minor), 29.55 min (major).

4.3.3. Diethyl-(*R*)-*O*,*O*-1-(2-methoxyphenyl)-2-nitroethylphosphorothioamidate 3c

White solid, mp 56–57 °C, $[\alpha]_D^{20} = -23.0$ (c 1.0, $CHCl_3$), 84% ee. ^{31}P NMR ($CDCl_3$, 161.7 MHz): δ = 69.71. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.13 (t, J = 7.2 Hz, 3H), 1.28 (t, J = 7.2 Hz), 3.66–3.72 (m, 1H), 3.90 (s, 3H), 3.92–4.05 (m, 3H), 4.38 (dd, J = 12.0, 14.4 Hz, 1H), 4.67 (ddd, J = 1.2, 6.0, 12.0 Hz, 1H), 4.81 (dd, J = 8.0, 12.0 Hz, 1H), 5.04–5.13 (m, 1H), 6.90–6.96 (m, 2Harom), 7.23 (dd, J = 1.6, 7.6 Hz, 1Harom), 7.31 (dt, J = 1.6, 8.0 Hz, 1Harom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 15.37 (d, J = 8.6 Hz), 15.58 (d, J = 8.5 Hz), 53.25, 55.30, 62.76 (d, J = 4.7 Hz), 63.02 (d, J = 4.8 Hz), 78.80 (d, J = 6.9 Hz), 110.91, 120.83, 125.10 (d, J = 2.9 Hz), 129.04, 129.80, 156.56. Anal. Calcd for $C_{13}H_{21}N_2O_5PS$: C, 44.82; H, 6.08; N, 8.04. Found: C, 44.68; H, 5.95; N, 7.96. HPLC analysis (Chiralpak AS-H column, hexane/2-propanol = 98:2, flow rate = 1.2 mL/min, wavelength = 254 nm): t_R = 91.21 (major), 109.38 min (minor).

4.3.4. Diethyl-(*R*)-*O*,*O*–1-(3-methoxyphenyl)-2-nitroethylphosphorothioamidate 3d

White solid, mp 55–56 °C, $[\alpha]_D^{20} = -10.0$ (c 1.0, $CHCl_3$), 87% ee. ^{31}P NMR ($CDCl_3$, 161.7 MHz): δ = 69.51. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.14 (t, J = 7.2 Hz, 3H), 1.29 (t, J = 7.2 Hz), 3.73–3.78 (m, 1H), 3.79 (s, 3H), 3.89–4.09 (m, 4H), 4.63 (ddd, J = 1.2, 5.6, 12.4 Hz, 1H), 4.70 (dd, J = 8.0, 12.4 Hz, 1H), 5.01–5.10 (m, 1H), 6.83–6.84 (m, 3Harom), 7.26–7.30 (m, 1Harom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 15.52 (d, J = 8.5 Hz), 15.71 (d, J = 8.3 Hz), 54.22, 55.24, 63.19 (d, J = 4.3 Hz), 63.39 (d, J = 4.6 Hz), 80.21 (d, J = 6.6 Hz), 112.22, 113.76, 118.27, 130.11, 139.41 (d, J = 3.7 Hz), 159.96. Anal. Calcd for $C_{13}H_{21}N_2O_5PS$: C, 44.82; H, 6.08; N, 8.04. Found: C, 44.79; H, 5.93; N, 7.94. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 98:2, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 45.57 (minor), 48.53 min (major).

4.3.5. Diethyl-(*R*)-*O*,*O*-1-(4-methoxyphenyl)-2-nitroethylphosphorothioamidate 3e

White solid, mp 59–60 °C, $[\alpha]_D^{20} = -4.7$ (c 1.0, $CHCl_3$), 87% ee. ^{31}P NMR ($CDCl_3$, 161.7 MHz): δ = 69.28. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.12 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz), 3.68–3.75 (m, 1H), 3.77 (s, 3H), 3.90–4.06 (m, 4H), 4.59 (ddd, J = 1.2, 5.6, 12.4 Hz, 1H), 4.69 (dd, J = 7.6, 12.4 Hz, 1H), 4.98–5.06 (m, 1H), 6.86 (d, J = 8.4 Hz, 2Harom), 7.22 (d, J = 8.4 Hz, 2Harom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 15.50 (d, J = 8.6 Hz), 15.68 (d, J = 8.5 Hz), 53.70, 55.19, 63.08 (d, J = 4.7 Hz), 63.30 (d, J = 4.9 Hz), 80.29 (d, J = 6.5 Hz), 114.26, 127, 44, 129.85 (d, J = 5.7 Hz), 159.53. Anal. Calcd for $C_{13}H_{21}N_2O_5PS$: C, 44.82; H, 6.08; N, 8.04. Found: C, 44.73; H, 6.01; N, 7.96. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 98:2, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 43.67 (minor), 50.95 min (major).

4.3.6. Diethyl-(*R*)-*O*,*O*-1-(2-chlorophenyl)-2-nitroethylphosphorothioamidate 3f

White solid, mp 90–91 °C, $[\alpha]_D^{20} = -5.0$ (c 1.0, $CHCl_3$), 82% ee. ^{31}P NMR ($CDCl_3$, 161.7 MHz): δ = 69.02. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.09 (t, J = 7.2 Hz, 3H), 1.28 (t, J = 7.2 Hz), 3.69–3.79 (m, 1H), 3.91–4.12 (m, 3H), 4.26 (t, J = 11.6 Hz), 4.73 (d, J = 6.4 Hz, 2H), 5.41–5.49 (m, 1H), 7.28–7.31 (m, 2Harom), 7.38–7.42 (m, 2Harom).

^{13}C NMR ($CDCl_3$, 75.0 MHz): 15.48 (d, J = 8.3 Hz), 15.73 (d, J = 8.1 Hz), 52.26, 63.27 (d, J = 4.6 Hz), 63.50 (d, J = 4.7 Hz), 78.76 (d, J = 6.2 Hz), 127.46, 128.65, 129.84, 130.19, 132.18, 135.11. Anal. Calcd for $C_{12}H_{18}ClN_2O_4PS$: C, 40.86; H, 5.14; N, 7.94. Found: C, 40.67; H, 5.01; N, 7.74. HPLC analysis (Chiralpak AS-H column, hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 43.25 (minor), 56.02 min (major).

4.3.7. Diethyl-(*R*)-*O*,*O*-2-nitro-1-(2-(trifluoromethyl)phenyl)-ethyl-phosphorothioamidate 3g

White solid, mp 106–108 °C, $[\alpha]_D^{20} = -10.4$ (c 1.0, $CHCl_3$), 87% ee. ^{31}P NMR ($CDCl_3$, 161.7 MHz): δ = 67.84. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.96 (t, J = 6.8 Hz, 3H), 1.30 (t, J = 6.8 Hz), 3.59–3.69 (m, 1H), 3.86–4.11 (m, 3H), 4.22–4.30 (m, 1H), 4.55 (dd, J = 8.4, 12.4 Hz, 1H), 4.63 (ddd, J = 2.0, 4.0, 12.4 Hz, 1H), 5.49 (dq, J = 4.0, 9.2 Hz, 1H), 7.46 (t, J = 7.2 Hz, 1Harom), 7.57 (d, J = 6.8 Hz, 1Harom), 7.61 (t, J = 7.2 Hz, 1Harom), 7.70 (d, J = 8.0 Hz, 1Harom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 15.10 (d, J = 8.8 Hz), 15.56 (d, J = 8.5 Hz), 50.33, 63.03 (d, J = 4.7 Hz), 63.47 (d, J = 4.7 Hz), 80.10 (d, J = 7.6 Hz), 122.58, 125.30, 126.16 (d, J = 5.4 Hz), 127.6 (q, J = 30.2 Hz), 128.04, 128.58, 132.63, 137.03. Anal. Calcd for $C_{13}H_{18}F_3N_2O_4PS$: C, 40.42; H, 4.70; N, 7.25. Found: C, 40.17; H, 4.52; N, 7.01. HPLC analysis (Chiralpak AS-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 11.72 (minor), 17.99 min (major).

4.3.8. Diethyl-(*R*)-*O*,*O*-1-(3-fluorophenyl)-2-nitroethylphosphorothioamidate 3h

Pale yellow liquid, n_D^{10} 1.5293, $[\alpha]_D^{20} = -5.6$ (c 1.0, $CHCl_3$), 83% ee. ^{31}P NMR ($CDCl_3$, 161.7 MHz): δ = 69.33. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.14 (t, J = 7.2 Hz, 3H), 1.28 (t, J = 7.2 Hz), 3.75–3.85 (m, 1H), 3.93–4.09 (m, 4H), 4.65 (ddd, J = 1.2, 5.2, 12.8 Hz, 1H), 4.72 (dd, J = 7.2, 12.8 Hz, 1H), 5.05–5.14 (m, 1H), 6.99–7.12 (m, 3Harom), 7.31–7.37 (m, 1Harom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 15.50 (d, J = 8.5 Hz), 15.68 (d, J = 8.3 Hz), 53.74, 63.30 (d, J = 4.9 Hz), 63.51 (d, J = 5.0 Hz), 79.93 (d, J = 6.6 Hz), 113.54 (d, J = 22.7 Hz), 115.49 (d, J = 21.0 Hz), 121.87 (d, J = 3.0 Hz), 130.66 (d, J = 8.1 Hz), 140.39 (dd, J = 3.3, 6.7 Hz), 162.79 (d, J = 247.8 Hz). Anal. Calcd for $C_{12}H_{18}FN_2O_4PS$: C, 42.85; H, 5.39; N, 8.33. Found: C, 42.69; H, 5.06; N, 8.12. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 98:2, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 23.73 (minor), 27.72 min (major).

4.3.9. Diethyl-(*S*)-*O*,*O*-1-(furan-2-yl)-2-nitroethylphosphorothioamidate 3i

Brown liquid, n_D^{10} 1.5130, $[\alpha]_D^{20} = -18.6$ (c 1.0, $CHCl_3$), 77% ee. ^{31}P NMR ($CDCl_3$, 161.7 MHz): δ = 69.70. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.26 (t, J = 7.2 Hz, 3H), 1.30 (t, J = 7.2 Hz), 3.77 (t, J = 11.2 Hz, 1H), 3.92–4.09 (m, 4H), 4.70 (dd, J = 6.0, 12.8 Hz, 1H), 4.78 (dd, J = 6.8, 12.8 Hz, 1H), 5.13–5.22 (m, 1H), 6.32–6.35 (m, 2Harom), 7.37 (s, 1Harom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 15.74 (d, J = 8.3 Hz), 15.82 (d, J = 8.3 Hz), 48.53, 63.42 (d, J = 5.0 Hz), 63.57 (d, J = 5.1 Hz), 78.01 (d, J = 5.3 Hz), 107.77, 110.67, 142.87, 450.38 (d, J = 5.6 Hz). Anal. Calcd for $C_{10}H_{17}N_2O_5PS$: C, 38.96; H, 5.56; N, 9.09. Found: C, 38.78; H, 5.23; N, 8.85. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 94:6, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 11.02 (minor), 13.11 min (major).

4.4. Procedure for the transformation of β-nitroamine 3a into 11

A mixture of aza-Henry adduct **3a** (95.5 mg, 0.3 mmol, 84.9% ee) in 5 mL of 6.0 M HCl/1,4-dioxane (v/v 1:1) was refluxed until the total consumption of the starting material. After removal of solvent under reduced pressure, 2 mL of ether was added and the resulting mixture was stirred for 5 min. The precipitate was collected by suction and dried in vacuo to provide the corresponding 2-nitro-1-phenylethylamine hydrochloride as a white solid (31.0 mg, 51% yield).

To a stirred mixture of the aforementioned β-nitroamine hydrochloride (30.0 mg, 0.15 mmol), sodium hydrogencarbonate (39 mg, 0.45 mmol), water (1 mL), and THF (1 mL) was added a solution of Boc_2O (39 mg, 0.18 mmol) in THF (1 mL) at 0 °C. After stirring at the same temperature for 30 min, the reaction mixture was warmed to room temperature for an additional 5 h. The solvent was removed under reduced pressure, and the residue was purified through column chromatography on silica gel (200–300 mesh, gradient eluted with petroleum ether and ethyl acetate) to afford compound **11** as a white solid (33.5 mg, 85%). $[\alpha]_D^{20} = -19.0$ (*c* 0.3, $CHCl_3$), 84.5% ee.

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