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N-Phosphinyl Imine Chemistry (I): Design and Synthesis of Novel *N*-Phosphinyl Imines and their Application to Asymmetric aza-Henry Reaction

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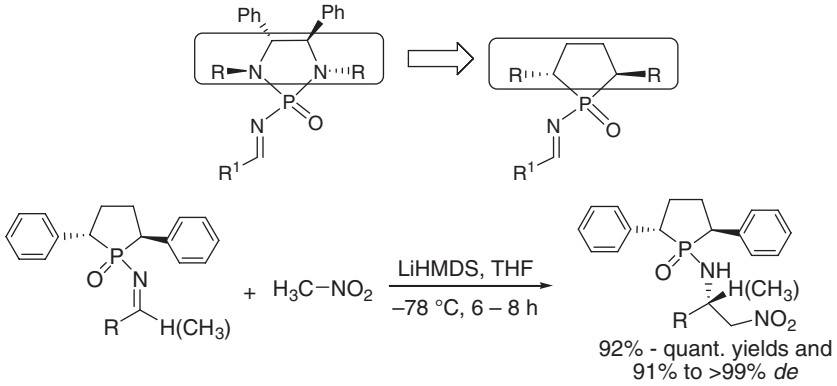
Novel chiral *N*-phosphinamide and *N*-phosphinyl imines have been designed, synthesized and applied to asymmetric aza-Henry reaction to give excellent chemical yields (92% – quant.) and diastereoselectivity (91% to >99%*de*). The reaction showed a great substrate scope in which aromatic/aliphatic aldehyde- and ketone-derived *N*-phosphinyl imines can be employed as electrophiles. The chiral *N*-phosphinamide can be stored at room temperature for more than 2 months without inert gas protection, and chiral *N*-phosphinyl imines were also proven to be highly stable at room temperature for a long period under inert gas protection. The *N*-phosphinyl group enabled the product purification to be performed simply by washing crude product with EtOAc and hexane. This reaction joined other eight GAP (Group-Assistant-Purification) chemistry processes that were developed in our laboratories. The absolute configuration has been unambiguously determined by converting a β-nitroamine product into a known *N*-Boc sample.

Imine chemistry has been playing a crucial role for drug development and discovery because most drugs and their precursors contain amino functionality; this places imine chemistry among the most important and active research areas in modern organic, bioorganic, and medicinal chemistry (1–12). β-Nitroamines are particularly important synthetic precursors because of their easy conversion into many other useful building blocks, such as vicinal diamines and α-amino acids (13–17). The vicinal diamine motif has been proven to play crucial roles in many biological systems. For example, the diamine functionality of some opioid ligands is responsible for their selective binding onto their receptors of μ, δ, and κ types for pharmacological studies in central and peripheral nervous systems (18–20). The diamine functionality was also found to exist in chemotherapeutical bleomycin A_2 and B_2 (21), glycopeptides (21) and edeine A_1 and B_1 of antibiotics (22). The evidence indicates that chirality of diamine ligands also plays critical roles in biological processes (20). In this work, we have shown a simple and facile methodology for the formation of the *S*-enantiomer of β-nitroamines in high enantioselectivity. There are many approaches to chiral diamine compounds (23,24), particularly those involving *N*-protected imine starting materials with various protecting groups, such as Ar_2CH-/Bn- (4,25–27), alkoxycarbonyl (7,28,29), Ar_2PO- (30,31), Aryl- (32–34), and $ArSO_2$, (35–38) can be employed as both electrophiles and dienophiles for asymmetric reactions (4–14). These protecting groups were often found to be crucial during



Key words: aza-Henry reaction, chiral *N*-phosphinamide, GAP (Group-Assistant-Purification) chemistry, *N*-phosphinyl imines

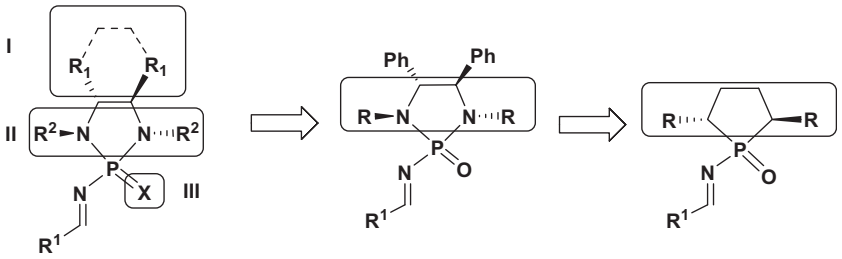
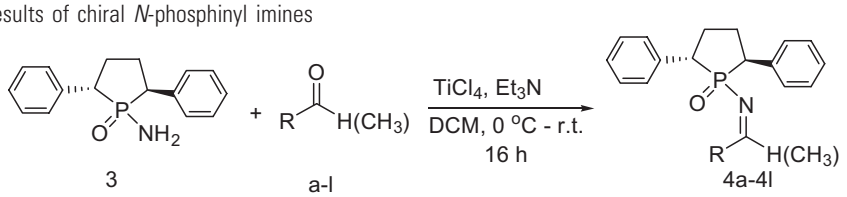


Figure 1: Design of novel chiral *N*-phosphinyl imines.

Table 1: Synthetic results of chiral *N*-phosphinyl imines



3 a-l 4a-4l

Entry	R	Product	Yield[a]
1	Phenyl	4a	94
2	*p*-nitrophenyl	4b	75
3	*o*-fluorophenyl	4c	86
4	*p*-fluorophenyl	4d	92
5	*o*-bromophenyl	4e	92
6	*p*-bromophenyl	4f	88
7	*o*-furanyl	4g	90
8	*o*-methylphenyl	4h	91
9	*p*-methylphenyl	4i	85
10	*p*-methoxyphenyl	4j	82
11	*t*-butyl	4k	Nd[b]
12	phenyl (methyl)	4l	Nd[b]

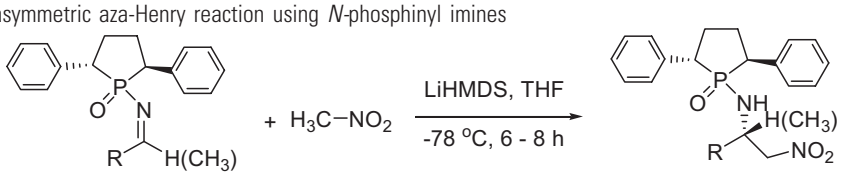
[a]Isolated yields after column chromatography.
[b]$Ti(iOPr)_4$ was used in place of $TiCl_4$ for the reaction; yields are not determined as they are unstable inside silica gel column; ^{1}H-NMR showed crude products are nearly pure.

the control of regio-, enantio-, and chemoselectivity for asymmetric reactions (4,7,25–38). Even though a great progress has been made in this field, the continuous search of new imines with superior properties for general use and for asymmetric synthesis still remains challenging (1–12).

In the past several years, we and others have established chiral *N*-phosphonyl and *N*-phosphoryl imine chemistry (39–50) and subsequently applied this chemistry to a series of asymmetric C-C bond formations *via* carbonyl-type additions including asymmetric catalytic Strecker reaction of achiral *N*-phosphonyl imines (39,40). These reactions have resulted in versatile chiral amino building blocks in good to excellent chemical yields and diastereo- and enantioselectivities. During continuing study of this chemistry, we encountered difficulty preparing aliphatic aldehyde- and ketone-derived *N*-phosphonyl imines; this prompted us to continue the search for new imines to overcome this problem. In this communication, we are pleased to present the design and synthesis of novel chiral *N*-phosphinyl imines of C_2 symmetry and their application to asymmetric aza-Henry reaction (Figure 1 and Tables 1 and 2). This special *N*-phosphinyl group showed efficient and easy deprotection and recovery of auxiliary for reuse; More importantly, it showed concise purification of crude product simply by washing with common organic solvents without the need for column chromatography or recrystallization, which has been defined as GAP (Group-Assistant-Purification) chemistry (40).

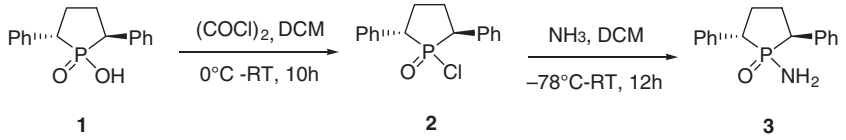
As shown in Figure 1, these novel imines are anticipated to serve as a new family of C=N electrophiles and dienophiles for advanced synthesis and asymmetric catalysis. The design of new imines is mainly divided into three regions: **I**, **II**, and **III**. Region **I** has been conducted by using 1,2-cyclohexyl and 1,2-diphenyl groups; X can be oxygen or sulfur atom. For region **II**, both primary and secondary alkyl groups have been employed for attaching onto nitrogens so far. The two amino centers become chiral after they are forced by their neighboring chiral carbon centers in region **I** (39–46). It is envisioned that directly introducing carbons to replace corresponding pro-chiral nitrogens would lead to efficient asymmetric induction for many reactions (51,52). At the same time, this design generates *N*-phosphinyl imines instead of *N*-posphonyl or *N*-posphoryl ones so as to lead to the successful preparation of aliphatic aldehyde- and ketone-derived imines.

Table 2: Results of asymmetric aza-Henry reaction using *N*-phosphinyl imines



Entry	Substrate	R	Product	Yield[a,b]	*de*[c]
1	4a	Phenyl	6a	96	94
2	4b	*p*-nitrophenyl	6b	Quant	>99
3	4c	*o*-fluorophenyl	6c	96	>99
4	4d	*p*-fluorophenyl	6d	92	98
5	4e	*o*-bromophenyl	6e	Quant	>99
6	4f	*p*-bromophenyl	6f	Quant	94
7	4g	*o*-furanyl	6g	Quant	91
8	4h	*o*-mehtylphenyl	6h	96	97
9	4i	*p*-mehtylphenyl	6i	98	>99
10	4j	*p*-mehtoxyphenyl	6j	94	94
11	4k	*t*-butyl	6k	96	96
12	4l	phenyl (methyl)	6l	94	>99

[a]Isolated yields after washing with ethylacetate.
[b]Combined yields of the two diastereomers.
[c]Greater than 99%*de* means only single isomer was observed based on ^{31}P-NMR analysis of crude samples.



Scheme 1: Synthesis of (*2S,5S*)-diphenyl *N*-phosphinamide.

Asymmetric aza-Henry reaction was chosen as the model reaction for this initial study because this reaction has become a highly active topic in asymmetric synthesis recently (53–56). The corresponding β-nitroamines can be converted into a series of amino compounds, such as vicinal diamines and α-amino acids, that are common structural motifs present in biologically active compounds and natural products (55,56). This reaction also serves as the model reaction for asymmetric catalytic systems using organometallic and organocatalysts (57–60).

Experimental Section

General remarks

All commercially available solvents, unless otherwise mentioned, were used without purification. THF was distilled from sodium/benzophenone ketyl. All the glasswares used were dried overnight at 100 °C. All melting points are uncorrected. The NMR spectra were recorded at 500, 125, and 202 MHz for ^{1}H, ^{13}C, and ^{31}P, respectively. Shifts are reported in ppm based on an internal TMS standard (for ^{1}H/CDCl3) or on residual solvent peaks (for ^{13}C/CDCl3). ^{31}P NMR spectra were referenced to external H_3PO_4 (0.00 ppm). LiHMDS, KHMDS, LDA, and *n*-BuLi were obtained from Acros. Nitromethane and titanium (IV) chloride (1.0 M solution in dichloromethane) were obtained from Aldrich and used as obtained from commercial sources without any further purification. Flash chromatographic columns were carried out on silica gel 60, (230–400 mesh).

Preparation of chiral phosphinamide

Chiral phosphinamide (**3**) was prepared starting from phosphinic chloride (**2**), which required the synthesis of phosphinic acid (**1**). Phosphinic acid was synthesized using the known procedure (61). Initially, phosphinic chloride was synthesized as shown in Scheme 1.

In a 100-mL oven-dried round-bottomed flask, phosphinic acid (**1**) (6.0 g, 22.08 mmol) was loaded. This was purged with nitrogen and then anhydrous dichloromethane (60 mL) was added. The suspension was brought to 0 °C, and oxalyl chloride (7.7 mL, 88.32 mmol) was added with syringe pump for 30 min. Then, reaction mixture was slowly brought to room temperature and stirred for 10 h. Solvent was evaporated, and trituration with hexane afforded phosphinic chloride (**2**) as a white solid.

A 250-mL round-bottomed flask was loaded with phosphinic chloride (**2**) (5.0 g, 18.4 mmol) and anhydrous dichloromethane (60 mL). Then, the flask was equipped with dewar condenser. The solution

was cooled to −78 °C, and ammonia gas was condensed using dewar and approximately 6 mL was added. Then, reaction mixture was stirred at −78 °C for 5 h and allowed to warm slowly to room temperature and stirred for another 7 h. The solution was diluted with dichloromethane and filtered through celite pad and solvent evaporated under vacuum. A pale yellow solid was obtained, and recrystallization with ethylacetate afforded phosphinamide (**3**) as white cottony crystals.

Compound 3 White crystals; yield (4.57 g, 98%); mp 190–192 °C,$[\alpha]^{D}_{24}$ = −101.00 (c 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.31 (m, 8H), 7.29-7.23 (m, 2H), 3.53-3.45 (m, 1H), 3.09-3.02 (m, 1H), 2.55-2.32 (m, 4H), 2.25-2.16 (m, 1H), 2.12-2.03 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8 (d, J = 5.0 Hz), 136.6 (d, J = 5.6 Hz), 128.8 (d, J = 2.5 Hz), 128.8 (d, J = 5.4 Hz), 128.5 (d, J = 1.5 Hz), 127.7 (d, J = 4.4 Hz), 126.9 (d, J = 3.0 Hz), 126.8 (d, J = 2.5), 47.9, 47.3, 46.5, 45.8, 31.1 (d, J = 10.4 Hz), 27.3 (d, J = 10.4 Hz). ^{31}P NMR (202 MHz, $CDCl_3$) δ 54.9.

HRMS (ESI): m/z calcd for $C_{16}H_{18}NNaOP$, 294.1018 $[M+Na]^+$, found: 294.1019.

General procedure for the synthesis of chiral N-*phosphinyl imine (4a-4j)*

In a dry vial, under inert gas protection, phosphinamide (**3**) (1.0 equiv.) was taken and dissolved in dry dichloromethane. To the solution, corresponding aldehyde (1.5equiv.) was added followed by the addition of triethylamine (3.0 equiv.). The reaction was cooled to 0 °C and titanium (IV) chloride (1.0 M solution in DCM, 0.5 equiv.) was added to the reaction (Scheme 2). The reaction was stirred at room temperature for 16–20 h and after that the mixture was loaded directly to silica gel. The reaction mixture was purified through column chromatography (ethyl acetate/hexane/1% Et_3N). Pure product was obtained by eluting the reaction mixture with ethyl acetate/hexane/triethylamine (60:40:1 mL) as white or pale yellow solid in all of the cases reported.

Preparation of aliphatic and ketimines 4k, 4l

In a round-bottomed flask, the chiral phosphinamide (1.0 equiv.) was taken and $Ti(OiPr)_4$ (1.5 equiv.) was then added to it. The flask was evacuated and protected with N_2 atmosphere. The dry toluene (6 mL) was added to the flask followed by the addition of triethylamine (3.0 equiv.). Finally, the corresponding aliphatic aldehyde or ketone (1.3 equiv.) was added to the mixture and the reaction mixture was refluxed overnight. The reaction completion was monitored by crude NMR. Upon completion of the reaction, the solvent was dried under vacuum and crude imine was used for the final aza-Henry reaction.

Compound 4a White solid; yield (0.186 g, 94%); mp 102–104 °C, $[\alpha]^{D}_{24}$ = −44.66 (c 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (d, J = 33.0 Hz, 1H), 7.71-7.69 (m, 2H), 7.52-7.49 (m, 1H), 7.43-7.38 (m, 2H), 7.38-7.29 (m, 6H), 7.29-7.23 (m, 1H), 7.23-7.19, (m, 2H), 7.11-7.07 (m, 1H), 3.66-3.53 (m, 2H), 2.76-2.66 (m, 1H), 2.58-2.34 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5 (d, J = 9.4 Hz), 136.7 (d, J = 4.4 Hz), 135.7 (d, J = 6.0 Hz), 135.6, 135.4, 133.3, 129.8, 128.9 (d, J = 5.4 Hz), 128.7, 128.6 (d, J = 2.0 Hz), 128.3, 126.7 (d, J = 2.4 Hz), 126.6 (d, J = 2.5 Hz), 49.3, 48.6, 45.3, 44.9, 32.4 (d, J = 9.4 Hz), 28.7 (d, J = 8.9 Hz). ^{31}P NMR (202 MHz, $CDCl_3$) δ 57.1.

HRMS (ESI): m/z calcd for $C_{23}H_{23}NOP$, 360.1512 $[M+Na]^+$, found: 360.1524.

Compound 4b sticky liquid; yield (0.167 g, 75%); $[\alpha]^{D}_{24}$ = −53.60 (c 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (d, J = 31.5 Hz, 1H), 8.24-8.22 (m, 2H), 7.82-7.80 (m, 2H), 7.35-7.33 (m, 4H), 7.32-7.30 (m, 2H), 7.27-7.19 (m, 3H), 7.11-7.08 (m, 1H), 3.71-3.58 (m, 2H), 2.79-2.69 (m, 1H), 2.61-2.38 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1 (d, J = 9.0 Hz), 150.2, 140.3 (d, J = 24.7Hz), 136.1 (d, J = 4.5Hz), 135.1 (d, J = 6.0), 130.2, 128.9 (d, J = 5.4 Hz), 128.6 (d, J = 1.5 Hz), 128.3 (d, J = 2.0 Hz), 127.9 (d, J = 4.5Hz), 127.0 (d, J = 2.5 Hz), 126.8 (d, J = 3.0 Hz), 123.8, 49.1, 48.5, 45.3, 44.6, 32.4 (d, J = 9.9 Hz), 28.1 (d, J = 9.4 Hz). ^{31}P NMR (202 MHz, $CDCl_3$) δ 58.0.

Compound 4c white solid; yield (0.179 g, 86%); mp 118–120 °C, $[\alpha]^{D}_{24}$ = −54.60 (c 0.6, $CHCl_3$); ^{1}H NMR: δ 9.07 (d, J = 32.5 Hz, 1H), 7.82 (t, J = 2.0 Hz, 1H), 7.49-7.02 (m, 13H), 3.82-3.55 (m, 2H), 2.78-2.37 (m, 4H). ^{13}C NMR: δ 168.2 (d, J = 11.8 Hz), 164.6, 162.5, 136.6 (d, J = 9.8 Hz), 135.6 (d, J = 10.0 Hz), 135.18, 135.11, 128.9, 128.6 (d, J = 8.0 Hz), 129.4 (d, J = 10.0 Hz), 128.25, 128.24, 128.14, 128.10, 126.9 (d, J = 8.4 Hz), 126.6 (d, J = 9.0 Hz), 124.2 (d, J = 7.5 Hz), 116.2, 116.1, 49.2 (d, J = 23.0 Hz), 45.5 (d, J = 21.8 Hz), 32.4 (d, J = 9.5 Hz), 28.5 (d, J = 6.0 Hz). ^{31}P NMR: δ 56.83.

Compound 4d sticky solid; yield (0.192 g, 94%); $[\alpha]^{D}_{24}$ = −48.20 (c 0.6, $CHCl_3$); **^{1}**H NMR: δ 8.71 (d, J = 33.0 Hz, 1H), 7.70 (t, J = 1.5 Hz, 1H), 7.34-7.07 (m, 13H), 3.61-3.55 (m, 2H), 2.74-2.32 (m, 4H). ^{13}C NMR: δ 165.2 (d, J = 11.8 Hz), 162.4, 136.8, 135.8 (d, J = 9.8 Hz), 135.6 (d, J = 10.0 Hz), 135.2, 135.0, 127.8, 127.4 (d, J = 8.0 Hz), 127.0 (d, J = 10.0 Hz), 126.5, 126.4, 126.1, 126.0, 125.8 (d, J = 8.0 Hz), 125.7 (d, J = 9.5 Hz), 125.2 (d, J = 6.5 Hz), 116.8, 116.3, 47.2 (d, J = 20.0 Hz), 43.5 (d, J = 21.0 Hz), 33.4 (d, J = 9.0 Hz), 28.1 (d, J = 6.0 Hz). ^{31}P NMR: δ 56.63.

Compound 4e pale yellow solid; yield (0.220 g, 92%); mp 105–107 °C, $[\alpha]^{D}_{24}$ = −36.00 (c 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.05 (d, J = 32.0 Hz, 1H), 7.82-7.79 (m, 1H), 7.56-7.52 (m, 1H), 7.37-7.35 (m, 4H), 7.34-7.31 (m, 4H), 7.28-7.21 (m, 3H), 7.13-7.09 (m, 1H), 3.70-3.55 (m, 2H), 2.76-2.65 (m, 1H), 2.59-2.35 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6 (d, J = 8.4 Hz), 136.6 (d, J = 4.0 Hz), 135.6 (d, J = 6.0 Hz), 134.1, 133.5, 129.4, 128.9 (d, J = 5.4 Hz), 128.7 (d, J = 2.0 Hz), 128.3 (d, J = 2.0 Hz), 128.0 (d, J = 5.0 Hz), 127.4, 127.0 (d, J = 2.5 Hz), 126.7 (d, J = 2.4 Hz), 49.1, 48.5, 45.5, 44.9, 32.4 (d, J = 9.9 Hz), 28.3 (d, J = 8.9 Hz). ^{31}P NMR (202 MHz, $CDCl_3$) δ 56.9.

HRMS (ESI): m/z calcd for $C_{23}H_{22}BrNOP$, 438.0617, found: 438.0625.

Compound 4f pale yellow solid; yield (0.213 g, 88%); mp 138–140 °C, $[\alpha]^{D}_{24}$ = −46.00 (c 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (d, J = 32.0 Hz, 1H), 7.55 (s, 4H), 7.36-7.33 (m, 4H), 7.32-7.26

(m, 3H), 7.25-7.22 (m, 1H), 7.22-7.19 (m, 2H), 7.11-7.08 (m, 1H), 3.66-3.49 (m, 2H), 2.76-2.66 (m, 1H), 2.58-2.35 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2 (d, J = 9.4 Hz), 136.5 (d, J = 4.0 Hz), 135.6 (d, J = 6.0 Hz), 134.2 (2C), 132.1, 130.9, 128.9 (d, J = 5.4 Hz), 128.6 (d, J = 1.9 Hz), 128.3, 128.2 (d, J = 2.5 Hz), 128.1 (d, J = 4.5 Hz), 126.9 (d, J = 2.5 Hz), 126.7 (d, J = 2.5 Hz), 49.2, 48.6, 45.5, 44.8, 32.4 (d, J = 9.4 Hz), 28.5 (d, J = 9.4 Hz). ^{31}P NMR (202 MHz, $CDCl_3$) δ 57.3.

HRMS (ESI): m/z calcd for $C_{23}H_{22}BrNOP$, 438.0617, found: 438.0619.

Compound 4g sticky liquid; yield (0.174 g, 90%); $[\alpha]^D_{24}$ = −54.62 (c 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (d, J = 33.5 Hz, 1H), 7.61-7.60 (m, 1H), 7.36-7.30 (m, 7H), 7.29-7.21 (m, 3H), 7.14-7.10 (m, 1H), 6.91 (d, J = 3.5 Hz, 1H), 6.50 -6.49 (m, 1H), 3.68-3.56 (m, 2H), 2.73-2.63 (m, 1H), 2.53-2.31 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2 (d, J = 8.0 Hz), 151.9 (d, J = 28.6 Hz), 147.6, 136.7 (d, J = 3.9 Hz), 135.6 (d, J = 5.9 Hz), 128.9 (d, J = 5.5 Hz), 128.5, 128.2 (2C), 126.8 (d, J = 2.4 Hz), 126.6 (d, J = 2.5 Hz), 121.4, 112.6, 49.3, 48.7, 45.5, 44.8, 32.4 (d, J = 9.4 Hz), 28.3 (d, J = 9.4 Hz). ^{31}P NMR (202 MHz, $CDCl_3$) δ 58.3.

HRMS (ESI): m/z calcd for $C_{21}H_{20}NNaO_2P$, 372.1123 $[M+Na]^+$, found: 372.1128.

Compound 4h white solid; yield (0.187 g, 91%); mp 163–165 °C, $[\alpha]^D_{24}$ = −56.00 (c 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.54 (d, J = 33.3 Hz, 1H), 7.80-7.77 (m, 1H), 7.42-7.11 (m, 13H), 3.72-3.56 (m, 2H), 2.79-2.38 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9 (d, J = 9.4 Hz), 141.1, 137.2, 136.4 (d, J = 6.0 Hz), 133.1, 133.7, 133.3, 131.6, 129.7, 129.4 (d, J = 5.4 Hz), 129.1, 128.7 (d, J = 2.2 Hz), 128.6 (d, J = 4.5 Hz), 127.3, 127.0, 126.5, 49.8, 48.7, 46.4, 45.4, 32.9 (d, J = 9.1 Hz), 28.9 (d, J = 8.9 Hz), 19.9. ^{31}P NMR (202 MHz, $CDCl_3$) δ 57.2.

HRMS (ESI): m/z calcd for $C_{24}H_{24}NNaOP$, 396.1488 $[M+Na]^+$, found: 396.1490.

Compound 4i white solid; yield (0.175 g, 85%); mp 145–147 °C, $[\alpha]^D_{24}$ = −62.40 (c 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, J = 33.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.38-7.32 (m, 6H), 7.27-7.19 (m, 5H), 7.11-7.07 (m, 1H), 3.65-3.55 (m, 2H), 2.75-2.64 (m, 1H), 2.57-2.42 (m, 2H), 2.41-2.34 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1 (d, J = 9.4 Hz), 144.2, 136.8 (d, J = 4.0 Hz), 135.9 (d, J = 5.9 Hz), 133.2, 132.9, 129.9, 129.4, 128.9 (d, J = 5.4 Hz), 128.6 (d, J = 1.5 Hz), 128.3 (d, J = 5.0 Hz), 128.2 (d, J = 2.0 Hz), 126.8 (d, J = 2.4 Hz), 126.6 (d, J = 2.5 Hz), 49.3, 48.7, 45.6, 44.9, 32.3 (d, J = 9.4 Hz), 28.8 (d, J = 8.9 Hz), 21.8. ^{31}P NMR (202 MHz, $CDCl_3$) δ 56.9.

HRMS (ESI): m/z calcd for $C_{24}H_{25}NOP$, 374.1674 $[M+H]^+$, found: 374.1660.

Compound 4j pale yellow solid; yield (0.176 g, 82%); mp 136–138 °C, $[\alpha]^D_{24}$ = −106.00 (c 0.25 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, J = 33.0 Hz, 1H), 7.68-7.65 (m, 2H), 7.36-7.33 (m, 6H), 7.26-7.19 (m, 3H), 7.10-7.07 (m, 1H), 6.92-6.89 (m, 2H), 3.85 (s, 3H), 3.62-3.54 (m, 2H), 2.73-2.62 (m, 1H), 2.57-2.31 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2 (d, J = 8.9 Hz), 163.8, 136.9 (d, J = 3.4 Hz), 136.1 (d, J = 6.0 Hz), 131.9, 128.9 (d, J = 5.4 Hz), 128.6 (d, J = 2.0 Hz), 128.3 (d, J = 4.4 Hz), 128.1 (d, J = 2.0 Hz), 126.8 (d, J = 2.0 Hz), 126.5 (d, J = 2.5 Hz), 114.1, 55.5, 49.3, 48.7, 45.7, 45.0, 32.3 (d, J = 9.4 Hz), 28.9 (d, J = 8.9 Hz). ^{31}P NMR (202 MHz, $CDCl_3$) δ 56.8.

Typical procedure for aza-Henry reaction with chiral N*-phosphinyl imines*

A oven-dried reaction vial was purged with nitrogen and loaded with nitromethane (0.03 mL, 0.556 mmol) and 3 mL of dry THF. The reaction vial was cooled to −78 °C, and 1 M solution of LiHMDS (0.278 mL, 0.278 mmol) was added slowly. The reaction mixture was stirred at the same temperature for 45 min. Then, predissolved solution of imine in dry THF (3 mL) was added slowly. Stirring was continued at −78 °C for 8 h. At this temperature, reaction was quenched with 2 mL of NH_4Cl followed by 10 mL of water. Then the aqueous layer was extracted with 2 × 10 mL of ethylacetate. After extraction, the organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated to obtain pale yellow solid, which was washed with minimum amount of ethylacetate followed by hexanes to afford the pure product as a white solid without any further purification.

Compound 6a White solid; yield (0.056 g, 96%); mp 195–197 °C,$[\alpha]^D_{24}$ = −77.00 (c 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.31 (m, 2H), 7.29-7.14 (m, 11H), 6.79-6.78 (m, 2H), 4.50-4.44 (m, 1H), 4.35-4.28 (m, 2H), 3.61-3.53 (m, 1H), 3.32 (t, J = 10.0 Hz, 1H) 3.01-2.95 (m, 1H), 2.53-2.39 (m, 2H), 2.26-2.17 (m, 1H), 2.12-2.03 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7 (d, J = 4.0 Hz), 136.1 (d, J = 5.9 Hz), 135.9 (d, J = 5.0 Hz), 129.0 (d, J = 2.4 Hz), 128.8 (d, J = 5.4 Hz), 128.7, 128.6 (d, J = 1.5 Hz), 128.1, 127.5 (d, J = 5.0 Hz), 127.1 (d, J = 3.0 Hz), 127.0 (d, J = 2.5 Hz), 126.1, 80.8 (d, J = 3.4 Hz), 52.4 (d, J = 1.0 Hz), 47.9, 47.3, 47.0, 46.4, 30.6 (d, J = 11.4 Hz), 27.2 (d, J = 9.9 Hz),. ^{31}P NMR (202 MHz, $CDCl_3$) δ 56.3.

HRMS (ESI): m/z calcd for $C_{24}H_{25}N_2NaO_3P$, 443.1490 $[M+Na]^+$, found: 443.1492.

Compound 6b White solid; yield (0.057 g, quantitative); mp 208–210 °C,$[\alpha]^D_{24}$ = −57.8 (c 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97-7.96 (m, 2H), 7.38-7.21 (m, 10H), 6.89 (d, J = 9.0 Hz, 2H), 4.74-4.68 (m, 1H), 4.52-4.42 (m, 2H), 3.62-3.53 (m, 1H), 3.36 (t, J = 11.0 Hz, 1H) 3.04-2.97 (m, 1H), 2.58-2.43 (m, 2H), 2.29-2.20 (m, 1H), 2.14-2.05 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.4, 144.7 (d, J = 3.9 Hz), 136.2 (d, J = 5.9 Hz), 135.4 (d, J = 5.4 Hz), 129.2 (d, J = 2.5 Hz), 128.8 (d, J = 1.5 Hz), 128.7 (d, J = 5.4 Hz), 127.5 (d, J = 4.5 Hz), 127.3 (d, J = 2.4 Hz), 127.3 (d, J = 3.0 Hz), 127.1, 123.7, 80.5 (d, J = 2.9 Hz), 51.5, 48.0 (d, J = 7.4 Hz), 47.4 (d, J = 7.9 Hz), 30.5 (d, J = 11.9 Hz), 27.3 (d, J = 10.4 Hz),. ^{31}P NMR (202 MHz, $CDCl_3$) δ 56.9.

HRMS (ESI): m/z calcd for $C_{24}H_{24}N_3NaO_5P$, 488.1351 $[M+Na]^+$, found: 488.1344.

Compound 6c White solid; yield (0.056 g, 96%); mp 178–180 °C; $[\alpha]^D_{24}$ = −60.52 (c 0.6, CHCl3) ^{1}H NMR: δ 7.37-7.17 (m, 12H), 6.946-6.944 (m, 2H), 6.75 (t, J = 4.5 Hz, 1H), 4.74-4.68 (m,

1H), 4.43-4.34 (m, 2H), 3.59-3.50 (m, 1H), 3.34 (t, J = 11.0 Hz, 1H), 3.05-2.98 (m, 1H), 2.56-2.38 (m, 2H), 2.38-2.18 (m, 1H), 2.12-2.03 (m, 1H). ^{13}C NMR: δ 160.9, 158.9, 135.8, 129.9 (d, J = 10.8 Hz), 128.9 (d, J = 9.8 Hz), 128.86 (d, J = 7.8 Hz), 128.80 (d, J = 6.5 Hz), 128.7 (d, J = 10.5 Hz), 127.3 (d, J = 10.3 Hz, 2C), 127.1 (d, J = 8.0 Hz), 127.0 (d, J = 7.0 Hz), 124.5 (d, J = 11.0 Hz), 115.6, 115.5, 79.8, 48.7, 47.2, 46.6, 30.7 (d, J = 8.0 Hz), 27.2 (d, J = 6.0 Hz), 27.6 (d, J = 9.8 Hz), 27.3, 27.2. ^{31}P NMR: δ 55.70.HRMS (ESI): m/z calcd for $C_{24}H_{25}FN_2O_3P$ 439.1587 $[M+H]^+$, found: 439.1563.

Compound 6d White solid; yield (0.053 g, 92%); mp 198–200 °C, $[\alpha]^D_{24}$ = −68.40 (c 0.6, CHCl3); ^{1}H NMR: δ 7.34-7.26 (m, 10H), 6.83-6.78 (m, 2H), 6.68-6.59 (m, 2H), 4.78-464 (m, 1H), 4.39-4.26 (m, 2H), 3.63-3.52 (m, 1H), 3.36 (t, J = 10.0 Hz, 1H), 3.29-3.12 (m, 1H), 2.62-2.14 (m, 4H). ^{13}C NMR: δ 163.2, 161.3, 136.1, 135.7 (d, J = 4.8 Hz), 133.4, 129.0 (d, J = 9.8 Hz, 2C), 128.7 (d, J = 10.5 Hz), 128.6 (d, J = 11.5 Hz, 2C), 127.9 (d, J = 12.3 Hz, 2C), 127.5 (d, J = 10.0 Hz, 2C), 127.1 (d, J = 12.0 Hz), 80.8, 51.7, 47.9, 47.3, 46.7, 30.5 (d, J = 11.0 Hz), 29.6 (2C), 27.3 (d, J = 9.8 Hz). ^{31}P NMR: δ 56.43. HRMS (ESI): m/z calcd for $C_{24}H_{24}FN_2NaO_3P$ 461.1406 $[M+Na]^+$, found: 461.1402.

Compound 6e White solid; yield (0.057 g, quantitative); mp 210–212 °C,$[\alpha]^D_{24}$ = −83.00 (c 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.43 (m, 1H), 7.35-7.15 (m, 12H), 6.99-6.94 (m, 1H), 4.92-4.81 (m, 1H), 4.38 (dd, J_1 = 6.0 Hz, J_2 = 12.9 Hz 1H), 4.32 (dd, J_1 = 4.5 Hz, J_2 = 12.6 Hz 1H), 3.96-3.89 (m, 1H), 3.69-3.55 (m, 1H), 3.05-2.94 (m, 1H), 2.61-2.40 (m, 2H), 2.32-2.13 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.4 (d, J = 2.4 Hz), 135.8, 135.7, 133.0, 129.8, 128.9 (d, J = 2.4 Hz), 128.8 (d, J = 3.4 Hz), 128.6 (d, J = 1.9 Hz), 127.9, 127.3 (d, J = 4.4 Hz), 127.1 (d, J = 3.0 Hz), 126.9 (d, J = 2.0 Hz), 121.9, 79.2 (d, J = 5.0 Hz), 52.0, 47.7, 47.1, 46.5, 45.9, 30.7 (d, J = 11.4 Hz), 27.1 (d, J = 9.9 Hz). ^{31}P NMR (202 MHz, $CDCl_3$) δ 56.4.

HRMS (ESI): m/z calcd for $C_{24}H_{25}BrN_2O_3P$, 499.0786 $[M+H]^+$, found: 499.0778.

Compound 6f White solid; yield (0.057 g, quantitative); mp 194–196 °C,$[\alpha]^D_{24}$ = −79.00 (c 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.27 (m, 12H), 6.67 (d, J = 8.1, 2H), 4.53-4.45 (m, 1H), 4.34 (d, J = 5.7Hz, 2H), 3.66-3.45 (m, 2H), 3.06-2.95 (m, 1H), 2.58-2.41 (m, 2H), 2.31-2.06 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8 (d, J = 3.9 Hz) 136.1 (d, J = 5.5 Hz), 136.7 (d, J = 4.9 Hz), 131.8, 129.1 (d, J = 2.5 Hz), 128.7 (d, J = 5.4 Hz), 128.6 (d, J = 2.0 Hz), 127.9, 127.5 (d, J = 4.4 Hz), 127.1 (d, J = 2.0 Hz), 122.1, 80.5 (d, J = 4.0 Hz), 51.8, 47.9, 47.3 (d, J = 10.4 Hz), 46.6, 30.4 (d, J = 11.4 Hz), 27.2 (d, J = 10.4 Hz). ^{31}P NMR (202 MHz, $CDCl_3$) δ 56.7.

Compound 6g White solid; yield (0.070 g, 96%); mp 192–194 °C,$[\alpha]^D_{24}$ = −87.00 (c 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.24 (m, 10H), 7.19-7.18 (m, 1H), 6.16-6.15 (m, 1H), 5.71 (d, J = 3.5 Hz, 1H), 4.61-4.55 (m, 1H), 4.45-4.35 (m, 2H), 3.62-3.53 (m, 1H), 3.11-3.01 (m, 2H), 2.56-2.39 (m, 2H), 2.28-2.18 (m, 1H), 2.13-2.03 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.3 (d, J = 5.4 Hz), 142, 136.0 (d, J = 3.4 Hz), 134.6 (d, J = 5.4 Hz), 129.4 (d, J = 2.4 Hz), 128.8 (d, J = 5.4 Hz), 128.7 (d, J = 1.5 Hz), 127.5 (d, J = 4.9 Hz), 127.1 (d, J = 1.9 Hz), 110.5, 107.6, 78.6 (d, J = 3.5 Hz), 77.2, 77.0, 76.7, 47.9, 47.3, 47.1, 46.9, 30.6 (d, J = 11.9 Hz), 27.2. ^{31}P NMR (202 MHz, $CDCl_3$) δ 56.0.

HRMS (ESI): m/z calcd for $C_{22}H_{24}N_2O_4P$, 411.1474 $[M+H]^+$, found: 411.1490.

Compound 6h White solid; yield (0.055 g, 96%); mp 174–176 °C,$[\alpha]^D_{24}$ = −83.01 (c 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.01 (m, 13H), 6.82-6.79 (m, 1H), 4.89-4.78 (m, 1H), 4.37-4.25 (m, 2H), 3.60-3.38 (m, 2H), 3.10-2.99 (m, 1H), 2.58-2.35 (m, 2H), 2.29-2.05 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1 (d, J = 5.4 Hz), 135.9 (2C), 134.6, 130.7, 128.8 (d, J = 2.5 Hz), 128.8 (d, J = 5.5 Hz), 128.5 (d, J = 2.0 Hz), 127.9, 127.4 (d, J = 5.0 Hz), 127.0 (d, J = 2.5 Hz), 126.9 (d, J = 2.5 Hz), 126.5, 125.2, 80.3 (d, J = 5.0 Hz), 48.9, 47.9, 47.3, 46.9, 46.2, 30.7 (d, J = 11.4 Hz), 27.4 (d, J = 9.9 Hz), 18.9. ^{31}P NMR (202 MHz, $CDCl_3$) δ 55.7.

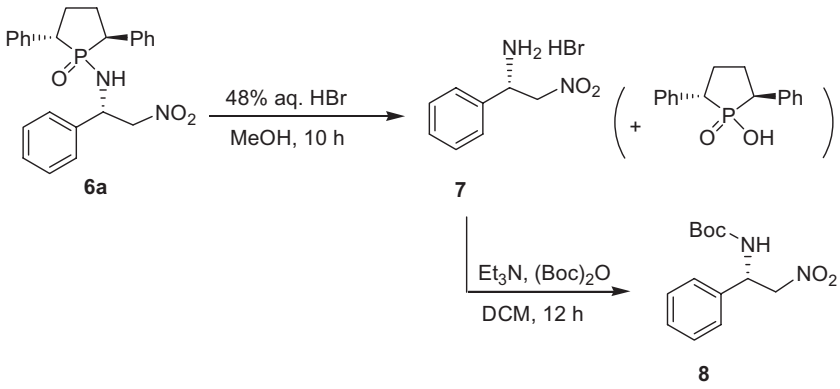
Compound 6i White solid; yield (0.057 g, 98%); mp 188–190 °C,$[\alpha]^D_{24}$ = −79.00 (c 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.25 (m, 10H), 6.97 (d, J = 8.0 Hz, 2H), 6.68 (d, J = 8.0 Hz, 2H), 4.48-4.37 (m, 2H), 4.34-4.29 (m, 1H), 3.61-3.53 (m, 1H), 3.08 (t, J = 10.0 Hz, 1H), 3.01-2.94 (m, 1H), 2.53-2.38 (m, 2H), 2.27 (s, 3H), 2.25-2.18 (m, 1H), 2.11-2.02 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 136.2 (d, J = 5.9 Hz), 136.0 (d, J = 5.5 Hz), 134.6 (d, J = 3.4 Hz), 129.4, 129.1 (d, J = 2.5 Hz), 128.8 (d, J = 5.4 Hz), 128.6 (d, J = 2.0 Hz), 127.5 (d, J = 4.5 Hz), 127.1 (d, J = 3.0 Hz), 127.0 (d, J = 2.4 Hz), 125.9, 80.8 (d, J = 4.0 Hz), 55.2 (d, J = 1.5 Hz), 48.0, 47.4, 47.1, 46.5, 30.7 (d, J = 11.4 Hz), 27.3 (d, J = 10.4 Hz), 21.0. ^{31}P NMR (202 MHz, $CDCl_3$) δ 55.7.

HRMS (ESI): m/z calcd for $C_{25}H_{27}N_2NaO_3P$, 457.1657 $[M+Na]^+$, found: 457.1667.

Compound 6j White solid; yield (0.054 g, 94%); mp 210–212 °C,$[\alpha]^D_{24}$ = −82.00 (c 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.26 (m, 10H), 6.74-6.89 (m, 4H), 4.48-4.43 (m, 2H), 4.35-4.31 (m, 1H), 3.76 (s, 3H), 3.63-3.54 (m, 1H), 3.02-2.95 (m, 2H), 2.55-2.39 (m, 2H), 2.27-2.19 (m, 1H), 2.12-2.03 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 136.2 (d, J = 6.0 Hz), 136.0 (d, J = 4.9 Hz), 129.6 (d, J = 4.0 Hz), 129.1 (d, J = 2.5 Hz), 128.8 (d, J = 5.5 Hz), 128.6 (d, J = 2.0 Hz), 127.6 (d, J = 5.0 Hz), 127.3, 127.1 (d, J = 3.0 Hz), 127.0 (d, J = 2.5 Hz), 114.1, 80.8 (d, J = 3.4 Hz), 55.2, 52.1, 48.1, 47.5, 47.2, 46.6, 30.8 (d, J = 11.3 Hz), 27.3 (d, J = 10.4 Hz). ^{31}P NMR (202 MHz, $CDCl_3$) δ 55.8.

HRMS (ESI): m/z calcd for $C_{25}H_{27}N_2NaO_4P$, 473.1606 $[M+Na]^+$, found: 473.1624.

Compound 6k Sticky off white solid; yield (0.072 g, 96%); $[\alpha]^D_{24}$ = −64.52 (c 0.6, CHCl3); ^{1}H NMR: δ 7.33-7.26 (m, 10H), 4.14-4.06 (m, 2H), 3.54-3.45 (m, 2H), 2.62-2.56 (m, 1H), 2.52-2.48 (m, 1H), 2.45-2.31 (m, 4H), 2.54 (t, J = 8.5 Hz, 1H), 1.18 (s, 9H). ^{13}C NMR: δ 136.7 (d, J = 10,0 Hz), 135.8 (d, J = 9.0 Hz, 2C), 128.9 (d, J = 10.0 Hz), 128.5, 128.4, 128.1, 127.8 (d, J = 8.8 Hz), 127.7, 126.8 (d, J = 2.4 Hz), 126.5 (d, J = 8.8 Hz), 127.7 (d, J = 10.3 Hz), 73.4, 60.3, 45.1, 44.5, 32.3 (d, J = 9.5 Hz), 26.0, 25.9, 25.4 (3C). ^{31}P NMR: δ 55.18.



Scheme 2: Absolute configuration determination and recovery of auxiliary.

Compound 6l White solid; yield (0.082 g, 76%); mp 158–160 °C, $[\alpha]^{D}_{24}$ = −60.52 (c 0.6, CHCl3); ^{1}H NMR: δ 7.48-7.10 (m, 15H), 4.65 (q, J = 10.5 Hz, 2H), 3.78-3.42 (m, 1H), 3.24-3.05 (m, 1H), 2.65-2.22 (m, 4H), 1.77 (bs, 1H, NH), 1.41 (s, 3H). ^{13}C NMR: δ 142.9 (d, J = 11.8 Hz), 137.1 (d, J = 9.8 Hz), 136.3 (d, J = 10.0 Hz), 129.46, 129.41, 128.9 (d, J = 8.8 Hz), 128.7 (2C), 128.6 (d, J = 2.4 Hz), 128.4 (d, J = 8.8 Hz), 127.7 (d, J = 10.3 Hz), 127.6, 126.8, 124.3 (2C), 84.0, 49.5, 49.3, 48.9, 48.6, 33.5 (d, J = 9.5 Hz), 31.2 (d, J = 8.0 Hz), 27.6 (d, J = 9.8 Hz), 27.3, 27.2. ^{31}P NMR: δ 53.51.

HRMS (ESI): m/z calcd for $C_{25}H_{28}N_2O_3P$ 435.1838 $[M+H]^+$, found: 435.1833.

Determination of absolute configuration

Removal of *N*-phosphinyl group followed by *in situ* *t*-Boc protection

In a 50-mL round-bottomed flask, 0.200 g of aza-Henry product (1.0 equiv.) and 5 mL of methanol were taken. To this solution, 0.8 mL of 48% aq. HBr (1.0 equiv.) was added and the reaction mixture was stirred at room temperature for 10 h. Disappearance of starting material was observed by TLC, then volatiles were evaporated and crude product was dried overnight under vacuum. To the above crude mixture, 10 mL of dichloromethane was added, and this suspension was cooled to 0 °C. At this temperature, 0.42 mL of triethylamine was added slowly. To this resulting mixture, 0.436 g of di-*tert*-butyl dicarbonate was added and stirred at room temperature for 12 h (Scheme 2). After aqueous workup, the crude product was purified by column chromatography to obtain compound (8). $[\alpha]^{24}{}_{D}$ +13.27 (c = 0.8, $CHCl_3$) {Literature value $[\alpha]^{24}{}_{D}$ −20.1 (c = 0.48, $CHCl_3$) for *R* isomer}.

Results and Discussion

The present study was started from the synthesis of chiral *N*-phosphinamide (**3**) as shown in Scheme 1. The starting material, phosphinoic acid (**1**), was prepared *via* an addition reaction of 1,4-biphenyl-1,3-butadiene according to a known procedure (61). Phosphinoic acid (**1**) was next reacted with oxalylchloride to give phosphinic chloride (**2**) that was treated with ammonia at −78 °C to produce **3** in quantitative yield. In fact, the synthesis of **3** has been readily conducted on a 20.0 g-scale to consistently give a quantitative overall yield. *N*-Phosphinamide (**3**) was obtained as a white solid and can be stored at room temperature in the air for more than 2 months without any decomposition as monitored by ^{1}H-NMR determination.

Chiral *N*-phosphinyl imines were then prepared by following a similar procedure for the previous chiral *N*-phosphonamides synthesis (Table 1) (39–46). In this synthesis, aldehydes were reacted with chiral *N*-phosphonamide (**3**) in the presence of triethylamine and $TiCl_4$ in DCM solution. When compared with the previous synthesis of chiral *N*-phosphonyl imines where chemical yields ranged from 62% to 74%, in the present synthesis of *N*-phosphinyl imines, much higher yields were obtained (up to 94%); only in one difficult case (*p*-NO_2-Ph, entry 2, Table 1), yield of 75% was observed. The resulting *N*-phosphinyl imines were found to be stable at room temperature for a long time under inert gas atmosphere. For preparation of the aliphatic imine and ketimine, the use of $TiCl_4$ led to predominant formation of enamines. We found that the use of Ti(*i*-OPr)$_4$ instead of $TiCl_4$ for this synthesis led to efficient formation of imines (entry 11 and 12, Table 1, respectively), but these two imines were found unstable to column chromatographic. Therefore, they were directly subjected to aza-Henry reaction without special purification.

The asymmetric aza-Henry reaction using **4a** as the electrophile was studied under a condition similar to the chiral *N*-phosphonyl imine-based system. The reaction of **4a** with lithium nitronate, which was generated by treating nitromethane with LiHMDS, was smoothly finished at −78 °C in 8 h (45). Excellent yield of 96% and diastereoselectivity of 94%*de* were achieved. Other strong bases, such as *n*-BuLi, LDA and KHMDS, resulted in either low yields or poor diastereoselectivity. Also, similar to the previous aza-Henry reaction (45), THF was proven to be the best solvent while diethyl ether gave slightly lower diastereoselectivity, but DCM led to no product formation at all. The present chiral *N*-phosphinyl imines showed higher reactivity toward lithium nitronate when compared with their *N*-phosphonyl imine counterparts that required the reaction temperature to be raised to −10 °C to reach complete consumption of imine starting materials.

Results of asymmetric aza-Henry reaction were summarized in Table 2. The reaction showed wide substrate scope in which aromatic and aliphatic aldehyde-derived imines and ketimines all worked well. For five cases, 2, 3, 5, 9, and 12 in Table 2, complete diastereoselectivities and almost quantitative yields were achieved. Even in the cases of aliphatic imine and ketimine (entries 11 and 12, Table 2), excellent yields (96% and 94%, respectively) and diastereoselectivities (96%*de* and >99%*de*, respectively) were obtained. The reaction of **4b** with lithium nitronate was completed at −78 °C within 4 h, which is because of the electron withdrawing effect of *p*-NO_2-Ph group (entry 2, Table 2). In contrast, *p*-methoxy-substituted aromatic imine, **4j**, was reacted with lithium nitronate at a slower rate, and the reaction took 9 h to completion (entry 10, Table 2).

Another attractive characteristic of the present aza-Henry reaction was shown by the fact that the product purification was conducted simply by washing the crude product with ethylacetate and hexane. This reaction joined a family of asymmetric reactions in that achiral and chiral *N*-phosphonyl groups as well as the present chiral *N*-phosphinyl group enabled the product purification to be achieved by washing (39–46). The recovery of auxiliary for reuse can be performed easily in high yields. The flexibility of these auxiliaries by changing their C_2-substituents would be anticipated to give greener synthesis and reactions. In fact, as mentioned earlier, we have defined this phenomenon as the GAP synthesis or GAP chemistry (40), which would encourage the synthetic community to search for more environmentally friendly syntheses and reactions to shorten preparation period and to minimize the use of manpower and energy.

The absolute stereochemistry of this asymmetric aza-Henry reaction has been unambiguously assigned by removing the chiral *N*-phosphinyl group of the product **6a** *via* treatment with HBr followed by *t*-Boc protection of resulting free amine group (Scheme 2). The absolute configuration of the newly generated chiral center was assigned as '*S*' by comparing the optical rotation of compound **8** with the literature value (62). This process also shows the auxiliary precursor of phosphinoic acid can be efficiently cleaved and recycled for reuse.

The asymmetric induction model is proposed in Figure 2. Lithium Lewis acidic center coordinates with the nitrogen of imine and acts as the anchor to bring two reaction partners together to form a transition state of chair confirmation. As anticipated, this stable transition state is responsible for the resulting excellent diastereoselectivity. The nitromethane anion approaches chiral *N*-phosphinyl imine from its *Re* face.

In conclusion, novel chiral *N*-phosphinamide and *N*-phosphinyl imines were designed, synthesized, and successfully applied to asymmetric aza-Henry reaction. This new class of imines of C_2-symmetry can be prepared in good to excellent yields and showed high stability. The reaction showed wide substrate scope in which aromatic and aliphatic aldehyde- and ketone-derived *N*-phosphinyl imines can all be employed as electrophilic substrates. Excellent yields and diastereoselectivities have been achieved for twelve examples, five of them showed complete diastereoselectivities. The present reaction

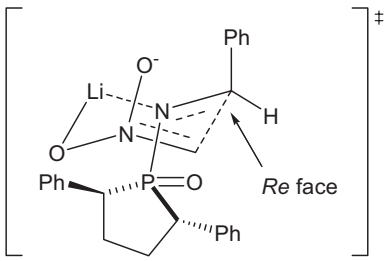


Figure 2: Proposed transition state involved in aza-Henry reaction.

belongs to GAP chemistry (Group-Assistant-Purification chemistry) that enables easy workup simply by washing the crude products with common organic solvents. The auxiliary can be cleaved easily under mild condition to regenerate the free amines and phosphinoic acid precursor for reuse. More applications of this new chiral reagents will be applied for other asymmetric reactions in the near future.

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