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Asymmetric Catalytic *N*-Phosphonyl Imine Chemistry: the Use of Primary Free Amino Acids and Et₂AlCN for Asymmetric Catalytic Strecker Reaction

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Abstract

The new asymmetric catalytic Strecker reaction of achiral *N*-phosphonyl imines has been established. Excellent enantioselectivity (95.2–99.7% *ee*) and yields (89–97%) have been achieved by using primary free natural amino acids as catalysts and Et₂AlCN as nucleophile. This work also presents the novel use of non-volatile and inexpensive Et₂AlCN in asymmetric catalysis. The *N*-phosphonyl protecting group enabled simple product purification to be achieved simply by washing the crude products with hexane. It can also be readily cleaved and recycled under mild condition to give a quantitative recovery of *N,N'*-bis(naphthalen-1-ylmethyl)ethane-1,2-diamine. A new mechanism was proposed for this reaction and was supported by experimental observations.

Keywords

N-Phosphonyl imine; Asymmetric Strecker reaction; Diethylaluminum cyanide; Amino acid catalyst

Introduction

Imine chemistry has been one of the most important and active topics in asymmetric catalysis and synthesis due to its importance in drug discovery and development, which heavily depend on the amine functionality.[1–3] *N*-protected imines serve as both electrophiles and dienophiles for many asymmetric reactions;[2–3] they are represented by Ar₂CH-/Bn-, [4] alkoxycarbonyl, [5] Ar₂PO-, [6] Aryl-, [7] and ArSO₂ [8] imines in which the protecting groups are often crucial for controlling regio-, enantio- and chemoselectivity for asymmetric reactions.[9] The search for novel imines of general use for both racemic and asymmetric reactions, particularly, for asymmetric catalysis has been challenging.[1–3] In the past several years, we have established chiral *N*-phosphonyl imine chemistry and successfully utilized it for a variety of asymmetric reactions to produce chiral amino products in good yields and excellent diastereoselectivities.¹⁰ During our continuous study of this project, we envisioned that if achiral *N*-phosphonyl imines are designed and synthesized, they would serve as a new family of C=N electrophiles and dienophiles for general use in advanced synthesis and asymmetric catalysis.

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Supporting Information Available. ¹H and ¹³C NMR spectra of all pure products **1a–1k** and **4a–4k** are available free of charge via the Internet at <http://pubs.acs.org>.

Results and Discussion

N-phosphonyl imines and *N*-phosphoramides have stronger Lewis basicity as compared with their counterparts.[11] During the reaction process, the resulting *N*-phosphoramide species can strongly bind to catalytic centers and thus retard catalytic cycles, which consequently makes it extremely difficult to achieve asymmetric catalysis using *N*-phosphonyl imines as electrophiles. In this report, we would like to describe the new asymmetric catalytic Strecker reaction of *N*-phosphonyl imines under a concise catalytic system (Scheme 1); In fact, this reaction has recently become an active topic due to its practical use for the synthesis of unnatural α -amino acids and their derivatives and its versatility as a superior model reaction for organocatalysis.[2–4,6] The present *N*-phosphonyl imine-based Strecker reaction was conducted by using free primary amino acids as catalysts and Et₂AlCN[12] as nucleophile. Excellent chemical yields (89–97%) and enantioselectivities (95.2–99.7%*ee*) have been achieved by performing the reaction at –78 °C in dry toluene in the presence of 4 Å mol sieves (Scheme 1).

Our new work described here shows several attractive characteristics as compared with previous known systems: (1) the first asymmetric catalytic reaction of achiral *N*-phosphonyl imines; (2) the first use of non-volatile and inexpensive Et₂AlCN as the cyanide source for catalytic Strecker reaction; (3) *N*-phosphonyl group can be readily cleaved under mild conditions without racemization; (4) The new *N*-phosphonyl protection group enabled the pure Strecker products to be obtained simply by washing the crude products with hexane without further purification. (5) The cleaved *N,N*-dialkyl diamine auxiliary can be recovered quantitatively for re-use; (6) free primary natural amino acid catalysts are common commercial chemicals; (7) The modifiable flexibility of C₂-symmetric structure by changing its ring sizes and *N,N*-protection groups can result in various C=N electrophiles with changed reactivity for different catalytic reactions.

The reaction is believed to undergo through the mechanism as shown in Scheme 2. The first step is the reaction of amino acid (**A**) with Et₂AlCN to form the catalytic species (**B**). The evolution of ethane gas and the solubility change of amino acid (which is insoluble in toluene but was dissolved after species (**B**) was formed) are evidenced of this step occurring. The Lewis acidic center can activate oxygen of *N*-phosphonyl group of the substrate before species (**B**) delivers cyanide onto the C=N bond from its *Si*-face to afford intermediate (**C**). During the reaction process, Et₂AlCN reacts with additive *i*-PrOH to give species Et(*i*-PrO)AlCN, its activation of imine nitrogen is also anticipated prior to C=N addition. At the third step, the catalyst (**B**) is regenerated *via* the homotransmetallation between species (**C**) and Et(*i*-PrO)AlCN which is derived from reaction of Et₂AlCN and *i*-PrOH; simultaneously, the actual catalytic complex (**D**) was generated, which was followed by deprotonation and quenching to afford the final product.

i-PrOH has been proven to be a crucial additive for this reaction, which is similar to other asymmetric Strecker process. [6a,12d] A tiny amount of product was formed without the addition of *i*-PrOH in reaction mixture. Usually, in aromatic solvents, Et₂AlCN exists as tetramers or pentamers[6a] that show lower reactivity. However, its coordination with phosphonyl imine followed by conversion to intermediate (**B**) and Et(*i*-PrO)AlCN, which was evidenced by the release of ethane bubbles during the reaction process, led to the present success.

Starting materials, achiral *N*-phosphonyl imines (**1a–k**), were readily prepared by following the procedure which is similar to that developed by our group for asymmetric chiral *N*-phosphonyl imine chemistry.[10] The four-step preparation of *N*-phosphoramides showed quantitative yields for all steps. Products were obtained as white solids without the need of

special purification. The final step of imine formation showed higher yields (76–87%) than the formation of *N*-phosphonyl imine counterparts. It is somewhat surprising that the design and synthesis of achiral *N*-phosphonyl imines have not been well documented in literature so far.

Our initial effort on this reaction was made on the use *N,N*-dibenzyl *N*-phosphonyl imine as the substrate and free primary amino acid,[13] *L*-valine, as the catalyst in dry toluene in the presence of 4 Å MS. The reaction was conducted by using Et₂AlCN (1.5 equiv, 1.0 M in toluene) together with *i*-PrOH (1.0 equiv) as an additive at –78 °C for 5 h, followed by quenching with dilute aq HCl to produce product in 75% yield and poor enantioselectivity (22.6 %*ee*). Next, we attempted to improve the reaction by replacing benzyl with *i*-propyl in *N*-phosphonyl imine substrates, which has been proven to be successful for several chiral *N*-phosphonyl imine-based reactions. However, the resulting *N*-di-*i*-propyl phosphonyl imine was found to be insoluble in toluene at –78 °C and even at r.t. We then utilized *N,N*-naphthalen-1-ylmethyl to replace benzyl, *i.e.*, to use *N,N*-naphthalen-1-ylmethyl *N*-phosphonyl imine (**1a**) as the electrophile. We were pleased to find that not only the solubility problem was solved, but also enantioselectivity and chemical yield were substantially increased to 70 %*ee* and 98 %, respectively.

Several catalysts were then screened under the above conditions. As revealed in Scheme 3, *N*-tosyl *L*-valine resulted in a much lower enantioselectivity of 38 %*ee*, albeit yield remained high. This was somewhat surprising because nearly all successful asymmetric catalytic reactions utilize amino acids that are based on the use of *N*-protected ones.[14] *N*-Tosyl phenylalanine and *N*-tosyl phenylglycine also showed poor enantioselectivities of 28 %*ee* and 36 %*ee*, respectively. We then turned our attention back to free amino acids and found that free *L*-phenylalanine afforded 63 %*ee* and 65% yield. Amazingly, the use of free *L*-phenylglycine (10 mol%) as the catalyst resulted in 99%*ee* and 95% yield under this new catalytic system.

It should be noted that well-activated 4 Å MS are also very important for this reaction. Much lower yields were observed in the absence of 4 Å MS. Other solvents, such as DCM, THF and CHCl₃, proved to be unsuitable for this reaction as they afforded poor yields and %*ee*'s. During the preparation of catalytic species, it is important to allow chiral amino acids to react with Et₂AlCN for at least 15 min at r.t. before the reaction mixture is cooled down to –78 °C. Keeping the reaction at –78 °C was necessary for achieving high enantioselectivity, albeit yield was not affected by temperature. TMSCN was also employed as the nucleophile, but poor yields (<10 %) were obtained.

Having identified the optimal catalyst and catalytic condition, we turned our attention to the substrate scope. As shown in Table 1, the reaction proceeded very well for all eleven substrates that were examined with excellent enantioselectivities (95.2–99.7%*ee*) and chemical yields (89–97 %). Electron-rich substrates (entries 5 and 6) showed nearly the same reaction rates as other substrates and led to similar results. Strong electron-deficient substrates (entries 2 and 7) that sometimes showed less efficiency in chiral *N*-phosphonyl imine-based asymmetric reactions [10] resulted in excellent yields (96 and 94 %, respectively) and enantioselectivity (94 and 96.1 %*ee*, respectively) under the present system. Interestingly, the present *N*-phosphonyl protection group enabled the pure products to be obtained simply by washing with hexane without further purification. It is noteworthy that resulting halogenated Strecker adducts (entries 3, 4, 8 and 9) can be readily converted to a variety of useful synthetic building blocks *via* metal catalyzed coupling reactions.[15] 2-Furyl substrate led to complete enantioselectivity (99%*ee*) and 89% yield, which is important because the furyl functionality can be subjected to other transformations, such as Diels-Alder and oxidative ring opening.[3] Our preliminary results also confirmed that this

asymmetric catalytic system showed promising for aliphatic *N*-dialkoxyphosphoryl imines. [16] More substrates will be under investigation under this system.

The absolute configuration for this asymmetric induction was determined by converting product (**4a**) to an authentic sample.[17] In this conversion, **4a** was subjected to deprotection with 2.0 M aq. HCl at r.t. in methanol followed by *in situ* *t*-Boc protection by treating with (*t*-Boc)₂O in the presence of triethylamine (Scheme 5) to yield product **5**. Optical rotation of this product was confirmed to be consistent with that of the known sample with *S* configuration. During this transformation, the cleaved *N*¹,*N*²-bis(naphthalen-1-ylmethyl)ethane-1,2-diamine was subjected to a one-time extraction with *n*-butanol from the acidic mixture, prior to *t*-Boc protection, to give a quantitative recovery yield.

Based on the assignment of absolute configuration of the resulting products, a working model has been proposed and shown in Figure 1 to explain the possible source of asymmetric induction. In this model, *N*-phosphonyl imine approaches the catalytic nucleophilic source of [−]CN from its less hindered side of hydrogen instead of bulkier phenyl group of the chiral center of the catalyst. Although several conformational arrangements are possible, it is more likely for C=N bond to be arranged on the *anti* position of Al-CN bond as shown in Figure 1.

Conclusion

The new asymmetric catalytic Strecker reaction of achiral *N*-phosphonyl imines has been established. Excellent enantioselectivities and yields have been achieved by using primary free natural primary amino acids as catalysts and Et₂AlCN as the nucleophile. This work presents the new use of non-volatile Et₂AlCN in asymmetric catalysis. *N,N'*-Protection groups on achiral *N*-phosphonyl imine were found to play an important role for the present success. This new protection group enabled simple product purification to be achieved simply by washing the crude products with hexane;¹⁸ it can also be readily cleaved and recycled under mild condition to give a quantitative recovery of *N,N'*-bis(naphthalen-1-ylmethyl)ethane-1,2-diamine. A new mechanism has been proposed that is consistent with experimental observations.

Experimental Section

Typical procedure for the synthesis of achiral *N*-phosphonyl imine (1a–k)

In a dry vial, under inert gas protection, *N,N*-naphthalen-1-ylmethyl phosphoramidate (1.0 equiv.) was taken and dissolved in dry dichloromethane. To the solution, corresponding aldehyde (1.5 equiv.) was added followed by the addition of triethylamine (3.0 equiv.). The reaction was cooled down to 0 °C and titanium (IV) chloride (1.0 M solution in DCM, 0.5 equiv.) was added to the reaction (Scheme 1). The reaction was allowed to stir at room temperature for 36 h and after that the mixture was loaded directly to silica gel. The reaction mixture was purified through column chromatography (Ethyl acetate: Hexane: 1% Et₃N). Pure product was obtained by eluting the reaction mixture with ethyl acetate: hexane: triethylamine (60:40:1mL) as white or pale yellow solid in all of the cases reported.

Compound 1a

White solid; yield (0.172 g, 76%); mp 84–86 °C; ¹H NMR (500 MHz, CDCl₃) δ 9.03 (d, *J* = 33.5 Hz, 1H), 8.28 (d, *J* = 9.0 Hz, 2H), 7.86–7.82 (m, 4H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.53–7.46 (m, 9H), 7.42–7.39 (m, 2H), 4.67–4.64 (m, 2H), 4.55–4.52 (m, 2H), 3.13 (d, *J* = 9.5 Hz, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 173.5 (d, *J* = 7.0 Hz), 139.6, 135.8, 135.6 (2C), 133.7, 133.1, 132.7(2C), 132.6, 131.7 (2C), 129.9 (2C), 128.7 (2C), 128.4, 128.3, 126.7

(2C), 126.2, 125.7, 125.4, 125.0 (2C), 123.8, 120.5, 47.43, 47.40 (d, $J = 7.3$ Hz), 44.9, 42.3. ^{31}P NMR (202 MHz, CDCl_3) δ 24.2.

Compound 1b

White foamy solid; Yield (0.214 g, 82%); mp 68–70 °C; ^1H NMR (500 MHz, CDCl_3) δ 8.87 (d, $J = 32.9$ Hz, 1H), 8.24 (dd, $J = 8.9, 1.8$ Hz, 2H), 7.83–7.76 (m, 6H), 7.52–7.46 (m, 6H), 7.41–7.38 (m, 2H), 7.15 (t, $J = 8.5$ Hz, 2H), 4.66–4.49 (m, 4H), 3.15–3.11 (m, 4H). ^{13}C NMR (125 MHz, CDCl_3) δ 172.3 (d, $J = 6.45$ Hz), 166.8, 164.8, 133.8 (2C), 132.65 (d, $J = 6.94$ Hz, 2C), 132.18 (d, $J = 8.9$ Hz, 2C), 131.7 (2C), 128.5 (2C), 128.4 (2C), 126.8 (2C), 126.3 (2C), 125.8 (2C), 125.1 (2C), 123.9 (2C), 116.1, 115.9, 47.5 (d, $J = 4.9$ Hz, 2C), 45.0 (d, $J = 10.4$ Hz, 2C). ^{31}P NMR (202 MHz, CDCl_3) δ 26.1.

Compound 1c

Pale yellow solid; Yield (0.355 g, 82%); mp 60–62 °C. ^1H NMR (500 MHz, CDCl_3): 8.83 (d, $J = 33.0$ Hz, 1H), 8.24 (d, $J = 8$ Hz, 2H), 7.83 (dd, $J = 2.5$ Hz, 7.5 Hz, 2H), 7.77 (d, $J = 8.0$ Hz, 2H), 7.62 (d, $J = 11$ Hz, 2H), 7.51–7.47 (m, 8H), 7.41–7.38 (m, 2H), 4.64 (dd, $J = 7.5$ Hz, 15.0 Hz, 2H), 4.52 (dd, $J = 5.5$ Hz, 15.0 Hz, 2H), 3.13 (d, $J = 9.0$ Hz, 4H); ^{13}C NMR (125 MHz, CDCl_3): 172.3 (d, $J = 6.9$ Hz); 134.6, 134.4, 133.7 (2C), 132.5 (d, $J = 6.9$ Hz, 2C), 132.0 (2C), 131.7 (2C), 131.5, 131.1 (2C), 128.4 (d, $J = 7.5$ Hz, 2C), 127.9, 126.8 (2C), 126.3 (2C), 125.7 (2C), 125.1 (2C), 123.8 (2C), 47.4 (d, $J = 4.5$ Hz, 2C), 45.0 (d, $J = 10.9$ Hz, 2C); ^{31}P NMR (202 MHz, CDCl_3): 26.0.

Compound 1e

White solid; Yield (0.208 g, 87%); mp 64–66 °C; ^1H NMR (500 MHz, CDCl_3) δ 9.33 (d, $J = 33.3$ Hz, 1H), 8.27 (d, $J = 8.5$ Hz, 2H), 8.02 (d, $J = 8.0$ Hz, 1H), 7.83 (d, $J = 8.0$ Hz, 2H), 7.78 (d, $J = 8.5$ Hz, 2H), 7.53–7.39 (m, 9H), 7.31 (t, $J = 7.5$ Hz, 1H), 7.23 (d, $J = 8.0$ Hz, 1H), 4.66 (d, $J = 7.0$ Hz, 2H), 4.55 (d, $J = 5.0$ Hz, 2H), 3.13 (d, $J = 10.0$ Hz, 4H), 2.49 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 172.5 (d, $J = 12.5$ Hz), 140.6 (2C), 133.7 (2C), 132.8 (d, $J = 7.4$ Hz), 132.6 (2C), 131.7, 131.2 (2C), 129.3 (2C), 128.4 (2C), 128.3 (2C), 126.5 (2C), 126.3 (2C), 126.1, 125.7 (2C), 125.1 (2C), 123.8 (2C), 47.5 (d, $J = 4.7$ Hz, 2C), 45.0 (d, $J = 10.6$ Hz, 2C), 19.4. ^{31}P NMR (202 MHz, CDCl_3) δ 26.4.

Compound 1f

White solid, yield (0.198 g, 87%); mp 64–66 °C; ^1H NMR (500 MHz, CDCl_3) δ 8.98 (d, $J = 33.3$ Hz, 1H), 8.31 (d, $J = 8.4$ Hz, 2H), 7.88–7.79 (m, 6H), 7.57–7.41 (m, 8H), 7.02 (d, $J = 8.7$ Hz, 2H), 4.71–4.53 (m, 4H), 3.92 (s, 3H), 3.13 (d, $J = 9.6$ Hz, 4H). ^{13}C NMR (125 MHz, CDCl_3) δ 173.4 (d, $J = 6.52$ Hz), 164.1 (2C), 134.1 (2C), 133.16 (d, $J = 7.4$ Hz, 2C), 132.4 (2C), 132.1 (2C), 128.7 (2C), 128.6 (2C), 127.0 (2C), 126.6 (2C), 126.0 (2C), 125.4 (2C), 124.2 (2C), 114.4 (2C), 55.8, 47.8 (d, $J = 4.7$ Hz, 2C), 45.3 (d, $J = 10.6$ Hz, 2C). ^{31}P NMR (202 MHz, CDCl_3) δ 26.8

Compound 1g

White solid, Yield (0.214 g, 81%); mp 64–66 °C; ^1H NMR (500 MHz, CDCl_3) δ 9.30 (d, $J = 33.0$ Hz, 1H), 8.32–8.25 (m, 2H), 8.12–8.07 (m, 1H), 7.88–7.56 (m, 5H), 7.59–7.38 (m, 10H), 4.72–4.49 (m, 4H), 3.13–2.92 (m, 4H). ^{31}P NMR (202 MHz, CDCl_3) δ 26.3. HRMS (ESI): m/z calcd for $\text{C}_{31}\text{H}_{28}\text{FN}_3\text{OP}$, 508.1954; found, 508.1983.

Compound 1h

Pale yellow solid; Yield (0.362 g, 79%); mp 54–56 °C. ^1H NMR (500 MHz, CDCl_3) δ 9.32 (d, $J = 32.5$ Hz, 1H), 8.27 (d, $J = 8.5$ Hz, 2H), 8.15–8.13 (m, 1H), 7.83 (d, $J = 8.25$ Hz, 2H), 7.77 (d, $J = 8.0$ Hz, 2H), 7.62–7.60 (m, 1H), 7.54–7.44 (m, 6H), 7.42–7.36 (m, 4H), 4.71 (dd,

$J = 7.0$ Hz, 15.0 Hz, 2H), 4.56 (dd, $J = 5.0$ Hz, 14.5 Hz, 2H), 3.12 (d, $J = 10.0$ Hz, 4H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.4 (d, $J = 5.4$ Hz), 134.23, 133.9, 133.8, 133.4, 132.6 (d, $J = 7.0$ Hz, 2C), 131.7 (2C), 129.6, (2C), 128.4 (d, 11.2 Hz, 2C), 127.6 (2C), 127.5 (2C), 126.6 (2C), 126.4 (2C), 125.8 (2C), 125.1 (2C), 123.8 (2C), 47.5 (d, $J = 4.5$ Hz, 2C), 44.9 (d, $J = 10.7$ Hz, 2C); ^{31}P NMR (202 MHz, CDCl_3) δ 26.0

Compound 1i

White foamy solid, Yield (0.225 g, 85%); mp 66–68 °C; ^1H NMR (500 MHz, CDCl_3) δ 9.39 (d, $J = 32.7$ Hz, 1H), 8.43–8.14 (m, 2H), 7.88–7.75 (m, 5H), 7.58–7.29 (m, 11H), 4.74–4.52 (m, 4H), 3.14–2.85 (m, 4H). ^{13}C NMR (125 MHz, CDCl_3) δ 167.0 (d, $J = 5.7$ Hz), 135.1 (d, $J = 8.9$ Hz), 134.0 (2C), 132.8 (d, $J = 6.8$ Hz), 131.9 (2C), 128.8, 128.7 (2C), 128.6 (2C), 128.5 (2C), 126.9 (2C), 126.5 (2C), 126.5, 126.0 (2C), 125.4, 125.3 (2C), 124.6, 124.0 (2C), 123.9, 116.4, 47.6 (d, $J = 4.8$ Hz, 2C), 45.1 (d, $J = 10.9$ Hz, 2C). ^{31}P NMR (202 MHz, CDCl_3) δ 26.2. HRMS (ESI): m/z calcd for $\text{C}_{31}\text{H}_{28}\text{ClN}_3\text{OP}$, 524.1659; found, 524.0652.

Compound 1j

Pale yellow solid; Yield (0.284 g, 82%); mp 62–64 °C. ^1H NMR (500 MHz, CDCl_3): 9.62 (d, $J = 33.5$ Hz, 1H), 8.29 (d, $J = 8.0$ Hz, 2H), 7.82–7.76 (m, 6H), 7.53–7.38 (m, 10H), 4.69 (dd, $J = 7.0$ Hz, 15.0 Hz, 2H), 4.54 (dd, $J = 5.0$ Hz, 14.5 Hz, 2H), 3.08 (d, $J = 10.0$ Hz, 4H), 2.04 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): 169.8 (d, $J = 5.4$ Hz), 134.7 (2C), 133.6 (2C), 132.8 (d, $J = 7.3$ Hz, 2C), 131.6 (2C), 128.3 (2C), 128.2 (2C), 128.0 (2C), 126.4, (2C), 126.2 (2C), 125.8 (2C), 125.1 (2C), 123.8 (2C), 120.4, 111.1, 47.3 (d, $J = 4.5$ Hz, 2C), 44.8 (d, $J = 10.7$, 2C), 14.0; ^{31}P NMR (202 MHz, CDCl_3) δ 25.8.

Compound 1k

Yellow color solid; Yield (0.216 g, 90%), mp 68–70 °C; ^1H NMR (500 MHz, CDCl_3) δ 8.85 (d, $J = 34.2$ Hz, 1H), 8.29 (d, $J = 7.8$ Hz, 2H), 7.86–7.78 (m, 4H), δ 7.71 (s, 1H), 7.57–7.41 (m, 8H), 7.07 (d, $J = 3.6$ Hz, 1H), 6.62–6.61 (m, 1H), 4.71–4.64 (m, 2H), 4.56–4.49 (m, 2H), 3.22–3.09 (m, 4H). ^{13}C NMR (125 MHz, CDCl_3) δ 161.2 (d, $J = 5.9$ Hz), 152.1, 151.8, 147.4, 133.7 (2C), 132.6 (d, $J = 7.3$ Hz), 131.7 (2C), 128.4 (d, $J = 13.7$ Hz, 2C), 126.7 (2C), 126.3 (2C), 125.7 (2C), 125.1 (2C), 123.8 (2C), 121.2 (2C), 112.7 (2C), 47.2 (d, $J = 5.0$ Hz, 2C), 44.8 (d, $J = 10.3$ Hz, 2C). ^{31}P NMR (202 MHz; CDCl_3) δ 26.4. HRMS (ESI): m/z calcd for $\text{C}_{29}\text{H}_{27}\text{N}_3\text{O}_2\text{P}$, 480.1841; found, 480.1839.

Typical procedure for the synthesis of *N,N*-naphthalen-1-ylmethyl *N*-phosphonyl imine substituted α -aminonitriles

In a dry vial, under inert gas protection, 4 Å MS and the chiral amino acid (**3**) was added followed by loading dry toluene. A turbid solution was obtained in which diethylaluminium cyanide (**2**, 1.0 M solution in toluene, 1.50 mmol) was added followed by the addition of *i*-PrOH (1.0 mmol). The reaction was stirred for 15 min at room temperature, and then cooled to –78 °C. The resulting mixture was stirred at –78 °C for 30 min followed by the addition of achiral *N*-phosphonyl imine which was dissolved in 3 mL of toluene. The reaction mixture was stirred for 5 h at this temperature before it was quenched by aq. 0.05 M HCl, followed by addition of ethylacetate (10 mL) and water (10 mL). The reaction mixture was filter off through celite. Organic layer was separated (3×10 mL of ethyl acetate) and dried over anhydrous sodium sulfate. Sodium sulfate was filtered off, and organic phase was evaporated to obtain crude product, which upon washings with hexane afforded the pure product as white solid without further purification.

Compound 4a

Yield (0.246 g, 92%); mp 112–114 °C; $[\alpha]_D^{24} = +2.52$ (c 1.0, CHCl₃). ¹H-NMR (500 MHz, CDCl₃) δ 8.22 (d, *J* = 9.5 Hz, 2H), 8.15 (d, *J* = 7.5 Hz, 2H), 7.86 (t, *J* = 7.0 Hz, 2H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.51–7.45 (m, 5H), 7.44–7.39 (m, 4H), 7.35–7.34 (m, 2H), 5.42 (t, *J* = 9.0 Hz, 1H), 4.65–4.55 (m, 4H), 3.44 (t, *J* = 9.5 Hz, 1H), 3.05–3.01 (m, 4H); ¹³C-NMR (125 MHz, CDCl₃) δ 135.36, 135.31, 133.8, 133.7, 132.37, 132.31, 131.6 (d, *J* = 8.0 Hz, 2C), 128.6 (d, *J* = 7.3 Hz, 2C), 128.5, 128.4, 128.3, 126.7, 126.6, 126.5, 126.4, 126.3, 125.9, 125.8, 125.24, 125.20, 123.4, 123.3 (2C), 119.98, 119.92, 47.5, 46.8 (d, *J* = 7.3 Hz), 44.6 (d, *J* = 7.8 Hz), 44.0, 43.9. ³¹P-NMR (202 MHz, CDCl₃) δ 22.9. HRMS (ESI): *m/z* calcd for C₃₂H₃₀N₄OP, 517.2152; found, 517.2156. 99.7 %ee, retention time = 6.77 (major), flow rate = 0.60 ml/min, OD-H chiral column (hexane:*i*-PrOH, v/v = 3:7).

Compound 4b

Off-white solid, Yield (0.172g, 96%); mp: 126–128 °C, $[\alpha]_D^{24} = +7.0$ (c 0.8, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 8.16 (dd, *J* = 9.2, 27.2 Hz, 2H), 7.82 (dd, *J* = 8.0, 36.0 Hz, 4H), 7.51–7.44 (m, 6H), 7.40 (q, *J* = 8.2 Hz, 2H), 7.33 (q, *J* = 5.1 Hz, 2H), 6.95 (t, *J* = 8.5 Hz, 2H), 5.36 (t, *J* = 9.0 Hz, 1H), 4.67–4.52 (m, 4H), 3.82 (q, *J* = 9.8 Hz, 1H, NH), 3.12–3.02 (m, 4H). ¹³C NMR (125 MHz, CDCl₃) δ 163.9, 161.9, 133.8 (d, *J* = 8.9 Hz, 2C), 132.3 (d, *J* = 2.5 Hz), 132.2, 131.5 (d, *J* = 9.9 Hz), 131.2, 128.7 (d, *J* = 6.9 Hz, 2C), 128.6 (2C), 128.5, 128.4, 126.7, 126.4 (d, *J* = 12.4 Hz, 2C), 126.3, 125.9 (d, *J* = 9.9 Hz, 2C), 125.2 (d, *J* = 3.9 Hz, 2C), 123.3 (d, *J* = 12.9 Hz, 2C), 119.7 (d, *J* = 3.5 Hz), 116.14 (d, *J* = 21.8 Hz, 2C), 46.84 (d, *J* = 3.9 Hz), 46.82, 46.1 (d, *J* = 4.9 Hz), 44.8 (d, *J* = 12.4 Hz), 44.0 (d, *J* = 13.4 Hz). ³¹P NMR (202 MHz, CDCl₃) δ 22.1. HRMS (ESI): *m/z* calcd for C₃₂H₂₈FN₄OPNa, 557.1877; found, 557.1884. Ee: 94% (retention time = 6.49 (minor) and 7.17 (major), flow rate = 0.60 ml/min, OD-H chiral column (7:3 hexane:IPA solvent system).

Compound 4c

White solid; Yield (0.13 5g, 97%); mp 138–140 °C; $[\alpha]_D^{25} = +8.0^\circ$ (c 0.6, CHCl₃). ¹H NMR (500 MHz, CDCl₃): 8.14 (dd, *J* = 7.5 Hz, 16.5 Hz, 2H), 7.86 (d, *J* = 7.5 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.51–7.45 (m, 6H), 7.43–7.36 (m, 4H), 7.20 (d, *J* = 8.0 Hz, 2H), 5.32 (t, *J* = 9.0 Hz, 1H), 4.66–4.49 (m, 4H), 3.90 (q, *J* = 6.5 Hz, 1H), 3.11–3.05 (m, 4H); ¹³C NMR (125 MHz, CDCl₃): 134.4 (d, *J* = 5.9 Hz), 133.8 (d, *J* = 7.9 Hz), 132.3 (2C), 132.2, 131.6 (d, *J* = 8.4 Hz), 128.7 (d, *J* = 3.5 Hz, 2C), 128.5 (2C), 128.4 (2C), 128.3 (2C), 126.6 (2C), 126.4 (d, *J* = 7.9 Hz, 2C), 126.2 (2C), 125.9 (d, *J* = 7.5 Hz, 2C), 125.2 (d, *J* = 2.9 Hz, 2C), 123.4, 123.3 (d, *J* = 12.8 Hz), 119.5 (d, *J* = 3.5 Hz), 46.9, 46.8 (d, *J* = 4.4 Hz), 46.1 (d, *J* = 4.9 Hz), 44.8 (d, *J* = 12.2 Hz), 44.1 (d, *J* = 13.4 Hz); ³¹P NMR (202 MHz, CDCl₃): 23.0. HRMS (ESI): *m/z* calcd for C₃₂H₂₉BrN₄OP, 595.1257; found, 595.1262. Ee: 96% (retention time = 6.41 (minor) and 6.84 (major), flow rate = 0.60 ml/min, OD-H chiral column (7:3 hexane:IPA solvent system).

Compound 4d

Pale yellow color solid, Yield (0.128 g, 95%); mp 134–136 °C, $[\alpha]_D^{24} = +8.60$ (c 0.6, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 8.15 (dd, *J* = 8.3, 23.4 Hz, 2H), 7.86 (d, *J* = 7.8 Hz, 2H), 7.78 (d, *J* = 8.1 Hz, 2H), 7.51–7.45 (m, 6H), 7.40 (q, *J* = 7.8 Hz, 2H), 7.28–7.22 (m, 4H), 5.35 (t, *J* = 9.0 Hz, 1H), 4.66–4.51 (m, 4H), 3.77 (bs, 1H, NH), 3.12–3.03 (m, 4H). ¹³C NMR (125 MHz, CDCl₃) δ 135.2, 133.85, 133.81, 133.7, 132.27, 132.25, 132.21, 131.5 (d, *J* = 9.9 Hz), 129.3 (2C), 128.7 (d, *J* = 4.9 Hz, 2C), 128.5 (d, *J* = 17.9 Hz, 2C), 127.9 (2C), 126.7, 126.4 (d, *J* = 9.9 Hz, 2C), 126.3, 125.9 (d, *J* = 8.4 Hz, 2C), 125.3 (d, *J* = 2.9 Hz, 2C), 123.2 (d, *J* = 14.4 Hz, 2C), 119.5 (d, *J* = 3.5 Hz), 46.9, 46.8 (d, *J* = 4.5 Hz), 46.1 (d, *J* = 5.4 Hz), 44.8 (d, *J* = 11.9 Hz), 44.1 (d, *J* = 13.4 Hz). ³¹P NMR (202 MHz, CDCl₃) δ 22.6. HRMS (ESI): *m/z* calcd for C₃₂H₂₉ClN₄OP, 551.1761; found, 551.1768. Ee: 95.2%

(retention time = 6.27 (minor) and 6.72 (major flow rate = 0.60 ml/min, OD-H chiral column (7:3 hexane:IPA solvent system)).

Compound 4e

White solid, Yield (0.110 g, 94%); mp 176–178 °C, $[\alpha]_{\text{D}}^{24} = +7.45$ (c 0.7, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 8.20 (d, *J* = 7.0 Hz, 1H), 8.15 (d, *J* = 7.5 Hz, 1H), 7.87–7.85 (m, 2H), 7.79 (d, *J* = 5.0 Hz, 1H), 7.31 (d, *J* = 7.0 Hz, 7H), 7.12 (d, *J* = 7.0 Hz, 6H), 5.37 (t, *J* = 8.5 Hz, 1H), 4.66–4.48 (m, 4H), 3.67 (t, *J* = 10.0 Hz, 1H, NH), 3.07–2.99 (m, 4H), 2.30 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 139.2, 133.7 (d, *J* = 8.4 Hz), 132.5 (d, *J* = 6.5 Hz), 132.4 (d, *J* = 5.5 Hz), 132.3 (d, *J* = 6.0 Hz), 131.6 (d, *J* = 8.4 Hz), 129.8 (2C), 128.6 (2C), 128.5 (2C), 128.4 (2C), 128.3, 126.5 (2C), 126.4 (d, *J* = 6.4 Hz), 126.3, 125.8 (2C), 125.7 (2C), 125.2 (d, *J* = 4.0 Hz), 123.3 (d, *J* = 7.5 Hz), 120.0 (d, *J* = 4.0 Hz), 47.2, 46.6 (d, *J* = 4.5 Hz), 46.1 (d, *J* = 5.4 Hz), 44.6 (d, *J* = 11.9 Hz), 44.0 (d, *J* = 12.9 Hz), 21.0. ³¹P NMR (202 MHz, CDCl₃) δ 22.5. HRMS (ESI): *m/z* calcd for C₃₃H₃₁N₄O₂PNa, 569.2077; found, 569.2070. Ee: 98.8% (retention time = 6.82 (major), flow rate = 0.60 ml/min, OD-H chiral column (7:3 hexane:IPA solvent system)).

Compound 4f

White solid, Yield (0.132 g, 93%); mp 182–184 °C, $[\alpha]_{\text{D}}^{24} = +1.45$ (c 1.1, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 8.23–8.19 (m, 1H), 8.16–8.14 (m, 1H), 7.89–7.84 (m, 2H), 7.80–7.78 (m, 2H), 7.52–7.47 (m, 6H), 7.43–7.39 (m, 2H), 7.32–7.28 (m, 2H), 6.83–6.79 (m, 2H), 5.34 (t, *J* = 8.7 Hz, 1H), 4.66–4.52 (m, 4H), 3.75 (s, 3H), 3.50 (t, *J* = 9.6 Hz, 1H, NH), 3.09–3.00 (m, 4H). ¹³C NMR (125 MHz, CDCl₃) δ 160.2, 133.8 (d, *J* = 8.4 Hz), 132.4 (d, *J* = 6.5 Hz), 131.6 (d, *J* = 8.4 Hz, 2C), 128.7 (2C), 128.6 (2C), 128.5 (2C), 128.3 (2C), 128.0 (2C), 127.5 (d, *J* = 6.4 Hz), 126.6, 126.4, 126.3, 125.9 (2C), 125.8 (2C), 125.2 (d, *J* = 4.0 Hz), 123.4 (d, *J* = 7.5 Hz), 120.1 (d, *J* = 4.0 Hz), 114.5 (2C), 55.3, 46.9, 46.7 (d, *J* = 4.5 Hz), 46.1 (d, *J* = 5.4 Hz), 44.7 (d, *J* = 11.9 Hz), 44.0 (d, *J* = 12.9 Hz). ³¹P NMR (202 MHz, CDCl₃) δ 22.5. HRMS (ESI): *m/z* calcd for C₃₃H₃₁N₄O₂PNa, 569.2077; found, 569.2070. Ee: 97.6% (retention time = 6.06 (minor) and 6.88 (major), flow rate = 0.60 ml/min, OD-H chiral column (7:3 hexane:IPA solvent system)).

Compound 4g

Off-white solid, Yield (0.101 g, 94%); mp 180–182 °C, $[\alpha]_{\text{D}}^{24} = +3.30$ (c 1.1, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 8.21 (d, *J* = 8.2 Hz, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.86–7.83 (m, 2H), 7.79–7.76 (m, 2H), 7.54–7.29 (m, 10H), 7.13–7.05 (m, 2H), 5.64 (t, *J* = 9.8 Hz, 1H), 4.66–4.39 (m, 4H), 3.95 (t, *J* = 10.0 Hz, 1H, NH), 2.99 (d, *J* = 10.7 Hz, 4H). ¹³C NMR (125 MHz, CDCl₃) δ 160.9, 158.9, 133.72 (d, *J* = 4.9 Hz, 2C), 132.29 (d, *J* = 6.9 Hz), 132.23 (d, *J* = 8.4 Hz), 131.6 (d, *J* = 8.9 Hz), 131.3 (d, *J* = 8.4 Hz), 128.7 (d, *J* = 2.5 Hz), 128.6 (d, *J* = 3.5 Hz, 2C), 128.4 (d, *J* = 12.4 Hz, 2C), 126.6, 126.4 (2C), 126.3, 126.2 (2C), 125.8 (d, *J* = 6.9 Hz, 2C), 125.1 (d, *J* = 4.9 Hz, 2C), 125.0 (d, *J* = 3.5 Hz), 123.3 (d, *J* = 10.9 Hz, 2C), 116.2 (d, *J* = 20.3 Hz), 46.3 (d, *J* = 4.9 Hz), 46.1 (d, *J* = 4.9 Hz), 44.1 (dd, *J* = 20.3, 12.9 Hz, 2C), 42.6. ³¹P NMR (202 MHz, CDCl₃) δ 22.0. HRMS (ESI): *m/z* calcd for C₃₂H₂₈FN₄OPNa, 557.1877; found, 557.1886. Ee: 96.1% (retention time = 6.52 (minor) and 7.04 (major), flow rate = 0.60 ml/min, OD-H chiral column (7:3 hexane:IPA solvent system)).

Compound 4h

White solid; Yield (0.135 g, 94%); mp 128–130 °C; $[\alpha]_{\text{D}}^{25} = +7.7^{\circ}$ (c 1.1, CHCl₃). ¹H NMR (500 MHz, CDCl₃): 8.19 (d, *J* = 8.5 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 7.5 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.60–7.57 (m, 2H), 7.54–7.37 (m, 8H), 7.33–7.30 (m, 1H), 7.21–7.18 (m, 1H), 5.77 (t, *J* = 9.5 Hz, 1H), 4.64 (dd, *J* = 6.5 Hz, 14.5 Hz, 1H), 4.57 (t, *J* = 6

Hz, 2H), 4.36 (dd, $J = 6.5$ Hz, 15 Hz, 1H), 3.88 (t, $J = 10$ Hz, 1H), 3.03-2.94 (m, 4H); ^{13}C NMR (125 MHz, CDCl_3): 135.0 (d, $J = 5.0$ Hz), 133.8 (d, $J = 8.9$ Hz, 2C), 132.4, 132.3 (d, $J = 3.4$ Hz), 132.2, 131.6 (d, $J = 6.4$ Hz), 130.9 (s, 2C), 129.3 (s, 2C), 128.6 (d, $J = 1.4$ Hz, 2C), 128.4 (t, $J = 3.0$ Hz, 2C), 126.5 (d, $J = 4.9$ Hz, 2C), 126.3 (s, 2C), 125.8 (d, $J = 5.4$ Hz, 2C), 125.2 (d, $J = 9.9$ Hz, 2C), 123.4 (d, $J = 5.5$ Hz, 2C), 122.6, 118.8 (d, $J = 5.4$ Hz), 47.8 (d, $J = 2$ Hz), 46.4 (t, $J = 5.9$ Hz, 2C), 44.2 (dd, $J = 6.0$ Hz, 12.9 Hz, 2C); ^{31}P NMR (202 MHz, CDCl_3): 22.1. HRMS (ESI): m/z calcd for $\text{C}_{32}\text{H}_{29}\text{BrN}_4\text{OP}$, 595.1257; found, 595.1253. Ee: 97% (retention time = 6.49 (minor) and 6.95 (major), flow rate = 0.60 ml/min, OD-H chiral column (7:3 hexane:IPA solvent system)).

Compound 4i

White solid, Yield (0.146 g, 90%); mp 220–222 °C, $[\alpha]_{\text{D}}^{24} = +4.50$ (c 1.1, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 8.19 (d, $J = 8.2$ Hz, 1H), 8.10 (d, $J = 8.3$ Hz, 1H), 7.84 (d, $J = 7.8$ Hz, 2H), 7.77 (d, $J = 8.1$ Hz, 2H), 7.60 (dd, $J = 2.0, 7.2$ Hz, 1H), 7.53-7.37 (m, 9H), 7.28-7.22 (m, 2H), 5.76 (t, $J = 9.8$ Hz, 1H), 4.63 (dd, $J = 6.5, 14.8$ Hz, 1H), 4.55 (d, $J = 6.3$ Hz, 2H), 4.36 (dd, $J = 6.2, 14.8$ Hz, 1H), 4.13 (t, $J = 10.0$ Hz, 1H, NH), 3.04-2.96 (m, 4H). ^{13}C NMR (125 MHz, CDCl_3) δ 133.72 (d, $J = 1.5$ Hz), 133.44 (d, $J = 4.9$ Hz), 132.7, 132.3 (d, $J = 6.9$ Hz), 132.2 (d, $J = 7.4$ Hz), 131.6 (d, $J = 6.9$ Hz), 130.6 (d, $J = 32.3$ Hz, 2C), 129.1 (2C), 128.6 (2C), 128.4 (d, $J = 5.4$ Hz, 2C), 127.8 (2C), 126.4 (2C), 126.3 (d, $J = 20.8$ Hz, 2C), 125.8 (d, $J = 4.9$ Hz, 2C), 125.2 (d, $J = 9.4$ Hz, 2C), 123.3 (d, $J = 7.9$ Hz, 2C), 118.8 (d, $J = 5.5$ Hz), 46.4 (d, $J = 4.9$ Hz), 46.2 (d, $J = 4.9$ Hz), 45.6 (d, $J = 2.5$ Hz), 44.2 (d, $J = 2.9$ Hz), 44.1 (d, $J = 2.9$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 22.3. HRMS (ESI): m/z calcd for $\text{C}_{32}\text{H}_{29}\text{ClN}_4\text{OP}$, 551.1761; found, 551.1757. Ee: 95.2% (retention time = 6.28 (minor) and 6.82 (major), flow rate = 0.60 ml/min, OD-H chiral column (7:3 hexane:IPA solvent system)).

Compound 4j

White solid, Yield (0.152 g, 92%); mp 204–206 °C, $[\alpha]_{\text{D}}^{24} = +3.50$ (c 1.1, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 8.31 (d, $J = 7.2$ Hz, 1H), 8.18 (d, $J = 8.0$ Hz, 1H), 7.88-7.78 (d, $J = 7.8$ Hz, 7H), 7.50-7.26 (m, 10H), 5.56 (t, $J = 9.8$ Hz, 1H), 4.46-4.14 (m, 4H), 3.52 (t, $J = 10.0$ Hz, 1H, NH), 3.04-2.96 (m, 4H), 2.41 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 135.6, 133.7 (d, $J = 4.9$ Hz), 132.3, 131.7 (d, $J = 6.9$ Hz), 131.4 (2C), 129.4 (2C), 128.6 (2C), 128.4 (d, $J = 5.4$ Hz, 2C), 128.2, 126.9 (d, $J = 7.5$ Hz, 2C), 126.6 (2C), 126.4 (d, $J = 20.8$ Hz, 2C), 126.3 (d, $J = 4.9$ Hz, 2C), 125.8, 125.1 (d, $J = 9.0$ Hz, 2C), 123.6, 123.4, 123.3, 46.9 (d, $J = 4.9$ Hz), 46.6 (d, $J = 4.9$ Hz), 46.3 (d, $J = 2.5$ Hz), 44.3 (t, $J = 2.9$ Hz), 43.9 (d, $J = 3.0$ Hz), 19.0. ^{31}P NMR (202 MHz, CDCl_3) δ 22.3. Ee: 98.9% (retention time = 6.13 (minor) and 6.68 (major), flow rate = 0.60 ml/min, OD-H chiral column (7:3 hexane:IPA solvent system)).

Compound 4k

White solid; yield (0.156 g, 89%), mp 148–150 °C $[\alpha]_{\text{D}}^{25} = +1.74$ (c 1.1, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 8.25 (d, $J = 8.5$ Hz, 1H), 8.19-8.17 (m, 1H), 7.88-7.84 (m, 2H), 7.79 (t, $J = 7.0$ Hz, 2H), 7.55-7.47 (m, 6H), 7.43-7.39 (m, 2H), 7.37-7.36 (m, 1H), 6.46-6.45 (m, 1H), 6.35-6.34 (m, 1H), 5.60 (t, $J = 9.5$ Hz, 1H), 4.65-4.53 (m, 4H), 3.62 (t, $J = 10.0$ Hz, 1H), 3.03-2.93 (m, 4H); ^{13}C NMR (125 MHz, CDCl_3) δ 147.5 (d, $J = 6.4$ Hz), 143.8, 133.8 (d, $J = 7.8$ Hz), 132.3, 131.7 (d, $J = 7.3$ Hz), 128.7, 128.4, 126.9, 126.5 (d, $J = 13.4$ Hz), 125.9 (d, $J = 7.8$ Hz), 125.2 (d, $J = 5.9$ Hz), 123.4 (d, $J = 9.3$ Hz), 117.9 (d, $J = 4.4$ Hz), 46.6 (d, $J = 5.0$ Hz), 46.1 (d, $J = 5.3$ Hz), 44.4 (d, $J = 12.8$ Hz), 43.9 (d, $J = 13.3$ Hz), 41.9 (d, $J = 1.0$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 21.6. HRMS (ESI): m/z calcd for $\text{C}_{30}\text{H}_{27}\text{N}_4\text{O}_2\text{PNa}$, 529.1764; found, 529.1761. Ee: 99% (retention time = 6.55 (minor) and 6.83 (major), flow rate = 0.60 ml/min, OD-H chiral column (7:3 hexane:IPA solvent system)).

Absolute Configuration Determination

The absolute configuration for this asymmetric induction was determined by converting a product (**4a**) to an authentic sample.[2] In this conversion, **4a** was subjected to deprotection with 2.0 M aq. HCl at r.t. in methanol followed by *in situ* *t*-Boc protection by treating with (*t*-Boc)₂O in the presence of Et₃N to give product **5**. The optical rotation of this product was confirmed to be consistent with that of the known sample with *S* configuration. During this transformation, the cleaved *N*¹, *N*²-bis(naphthalen-1-ylmethyl)ethane-1,2-diamine (**6**) was extracted with *n*-butanol from the acidic mixture prior to *t*-Boc protection to give a quantitative yield. $[\alpha]_{24}^D = -1.71$ (*c* = 1.2, CHCl₃) {Literature value $[\alpha]_{24}^D -1.82$ (*c* = 1.1, CHCl₃)}.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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16. An aliphatic *N*-phosphonyl substituted imine was prepared in situ and subject to asymmetric strecker reaction using the optimized conditions.

Yellow oil, yield (0.090g, 92%); $[\alpha]_D^{24} = +12.0$ (c 0.8, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 4.16–4.08 (m, 4H), 3.96–3.84 (m, 3H), 3.35 (bs, 1H), 1.32 (t, $J = 5.5$ Hz, 1H), 1.25 (s, 3H), 1.07 (s, 3H), 0.93 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 128.7, 76.3 (2C), 68.0, 45.5, 38.5, 21.5, 21.49, 21.43, 20.8, 19.9. ^{31}P NMR (202 MHz, CDCl_3) δ 22.1. Ee: 92% (retention time = 5.43 (major) and 5.86 (minor), flow rate = 0.60 ml/min, OD-H chiral column (7:3 hexane:IPA solvent system). HPLC conditions need to be further optimized (peaks' overlapping still exists).

17. Kuo C-W, Zhu J-L, Wu J-D, Chu C-M, Yao CF, Shia K-S. Chem Comm. 2007; 3:301–303. [PubMed: 17299646]
18. We tentatively define this observation as the “GAP” synthesis (group-assisted-precipitation synthesis) since both achiral and chiral *N*-phosphonyl groups, and chiral *N*-phosphinyl group have resulted in similar simple purification and recovery of auxiliary quantitatively for re-use for several reactions.

Figure 1.

Working model of asymmetric induction in which the nucleophilic species of CN^- attacks *N*-phosphonyl imine from its *Si* face

Scheme 1.

Scheme 2.

Scheme 3.
Results of screening catalysts

Scheme 4.

Scheme 5.

Table 1Results of the synthesis of *N*-phosphonyl substituted chiral α -aminonitriles **4a–k**^a

Entry	Substrate	R ₁	Product	Yield(%) ^b	ee ^c
1	1a	H	4a	95	99.7
2	1b	<i>p</i> -fluoro	4b	96	94
3	1c	<i>p</i> -bromo	4c	97	96
4	1d	<i>p</i> -chloro	4d	95	95.2
5	1e	<i>p</i> -methyl	4e	94	98.8
6	1f	<i>p</i> -methoxy	4f	93	97.6
7	1g	<i>o</i> -fluoro	4g	94	96.1
8	1h	<i>o</i> -bromo	4h	92	97
9	1i	<i>o</i> -chloro	4i	90	95.2
10	1j	<i>o</i> -methyl	4j	92	98.9
11	1k	<i>o</i> -furyl	4k	89	99

^a All reactions were carried out at –78 °C in 0.06 M solution of imine in toluene.^b Combined yields of both isomers.^c Enantiomeric ratio has been determined by using chiral HPLC OD-H column (3:7 IPA:Hexane), flow rate = 0.60 ml/min.