Tetrahedron 65 (2009) 4968–4976

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Stereoselective synthesis of *N*-heterocycles: application of the asymmetric Cu-catalyzed addition of Et_2Zn to functionalized alkyl and aryl imines

Isabelle Bonnaventure, André B. Charette *

Department of Chemistry, Université de Montréal, PO Box 6128, Station Downtown, Montreal, QC H3C 3J7, Canada

ARTICLE INFO

Article history:
Received 3 February 2009
Received in revised form 30 March 2009
Accepted 1 April 2009
Available online 9 April 2009

Keywords:
α-Chiral amines
Asymmetric catalysis
Chemoselectivity
Heterocycles
Functionalized imines

ABSTRACT

The preparation of *N*-heterocycles from alkyl- and aryl-substituted imines is described. The key step involves a copper-catalyzed addition of diethylzinc to functionalized alkyl-substituted imines that were generated in situ from the sulfinic acid adducts. The nucleophilic addition products were then converted to 2-substituted pyrrolidines and piperidines. Aryl-substituted imines were transformed into enantioenriched 1- and 1,4-substituted tetrahydroisoquinolines.

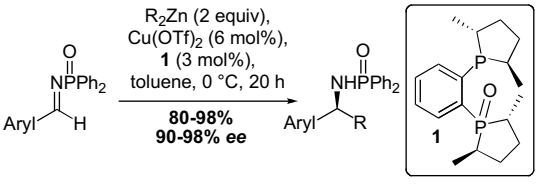
1. Introduction

The nucleophilic addition to imines is a versatile method to access α-chiral amines.[1] These products are important subunits of more complex bioactive molecules,[2] as well as useful building blocks for the synthesis of both chiral ligands[3] and auxiliaries.[4]

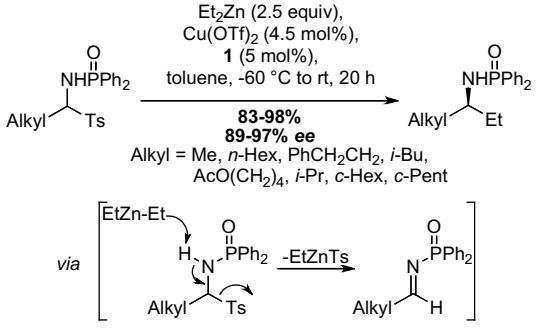
Recently we reported a copper-catalyzed asymmetric addition of diorganozinc reagents to aryl-substituted *N*-phosphinoyl-imines.[5] The corresponding *N*-protected α-chiral amines were generated in high yields (80–98%) and high enantioselectivities (90–98% ee), with the diphosphine monoxide, Me-DuPHOS(O) **1** being a very efficient chiral ligand for this reaction (Eq. 1).[6]

We have also reported that alkyl-substituted imines are also compatible with this reaction. However, these aldimines are highly sensitive to moisture, and thus are prone to facile hydrolysis.[7] Furthermore, they exist as an equilibrium between the imine and the enamine form, which can undergo homo-coupling.[7e,f] To overcome this, the sulfinic acid adducts were used as stable precursors, which were compatible with the Cu·Me–DuPHOS(O) system.[8] We were then able to prepare numerous α-chiral amines from aliphatic aldehydes in excellent yields (83–98%) and enantioselectivities (89–97% ee) (Scheme 1).[9]

Herein, we demonstrate the excellent chemoselectivity of the asymmetric copper-catalyzed diorganozinc addition to imines to prepare suitably functionalized α-chiral amines that could be converted into *N*-heterocycles after simple synthetic steps.



(1)



Scheme 1. Synthesis of *N*-protected α-chiral alkylamines.

* Corresponding author. Fax: +1 514 343 5900.
E-mail address: andre.charette@umontreal.ca (A.B. Charette).

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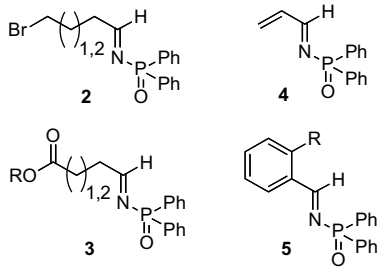
doi:10.1016/j.tet.2009.04.002

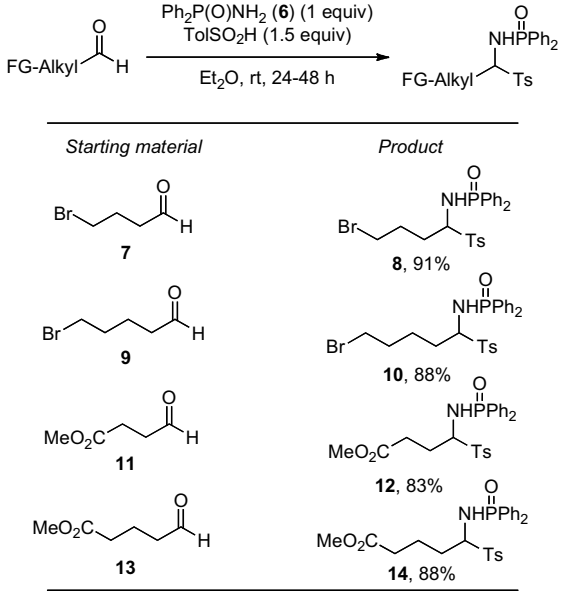
2. Results and discussion

It was envisioned that *N*-heterocycles could be obtained from the corresponding acyclic precursors **2**–**5**. These compounds should provide access to pyrrolidines, pyrrolidinones, piperidines, piperidinones, and tetrahydroisoquinolines.[10–12] The challenge was not only to prepare the imine (or the sulfinic acid imine precursor adduct), but also to determine the degree of functionality compatible with the enantioselective nucleophilic addition (Scheme 2).



Scheme 2. Potential functionalized imines: access to various important α-chiral amines.

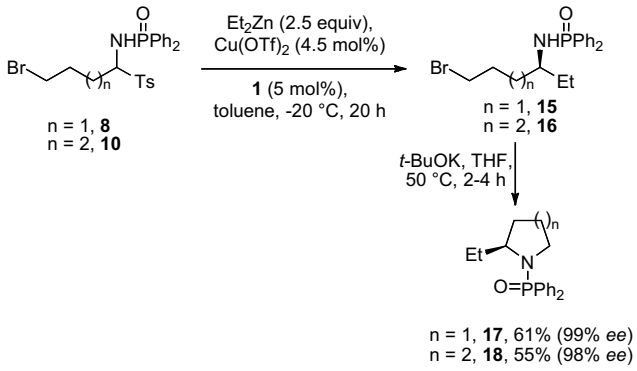
Aldehydes containing bromide and ester were treated with phosphinic amide **6** (1 equiv) and *p*-toluenesulfinic acid (1.5 equiv) at rt in Et_2O to produce the desired sulfinic acid adducts (Scheme 3). In all cases, the sulfinic acid adducts precipitated out of the solution and were isolated by simple filtration as white solids in excellent yields (83–91%).



Scheme 3. Synthesis of functionalized sulfinic acid adducts.

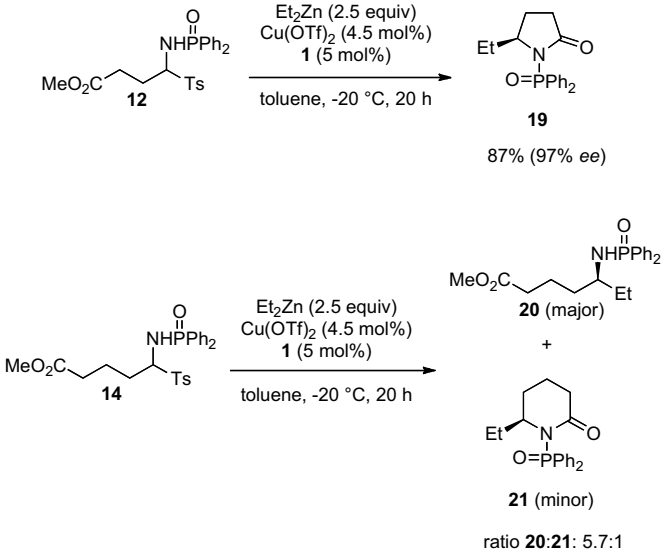
With these substrates in hand, we next examined their compatibility with the catalytic asymmetric reaction. Alkyl bromide substrates are often incompatible with organometallic species, thereby leading to extra protection/deprotection steps.[13] Moreover, there are no reports of the addition to imines in the presence of methyl esters.[14]

The brominated sulfinic acid adducts **8** and **10** were subjected to the conditions for the catalytic asymmetric addition of diethylzinc at −20 °C to give compounds **15** and **16**, which were not isolated (Scheme 4). The crude mixture was directly treated with *t*-BuOK in THF at 50 °C to yield the desired *N*-heterocycles **17** and **18** in good yields (55–61%) and with excellent enantioselectivities (98–99% ee). It is interesting to note that neither cyclized products **17** or **18** nor homocoupling compounds (through enamine formation)[13a] were obtained after the asymmetric addition step, as determined by ^1H NMR.



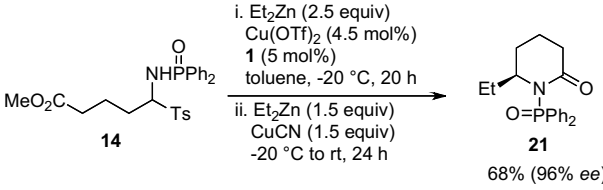
Scheme 4. Application to the synthesis of pyrrolidine **17** and piperidine **18**.

We next studied the behavior of the sulfinic acid adducts **12** and **14** bearing a methyl ester functional group under the conditions for the asymmetric addition of Et_2Zn (Scheme 5). In the case of **12**, we observed complete conversion to the cyclized compound **19**, which was obtained in 87% yield and excellent enantioselectivities (97% ee). On the other hand, treatment of **14** under the same reaction conditions gave rise to a mixture of the uncyclized product **20** and piperidinone **21** (5.7:1 ratio).



Scheme 5. Application to the synthesis of pyrrolidinones and piperidinones **20** and **21**.

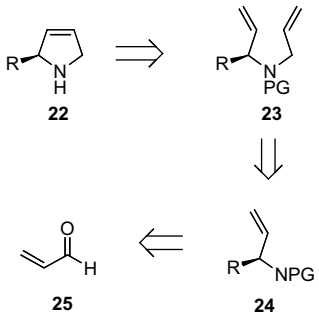
To promote the cyclization we tried heating the reaction mixture, but this did not increase the amount of **21** formed. The addition of Lewis acids ($MgBr_2$, $AlMe_3$[15]) to activate the methyl ester moiety gave very low conversion toward the cyclized product. We finally found that the addition of a mixture of Et_2Zn–CuCN gave satisfactory results. Thus, CuCN and Et_2Zn were added at the end of



(2)

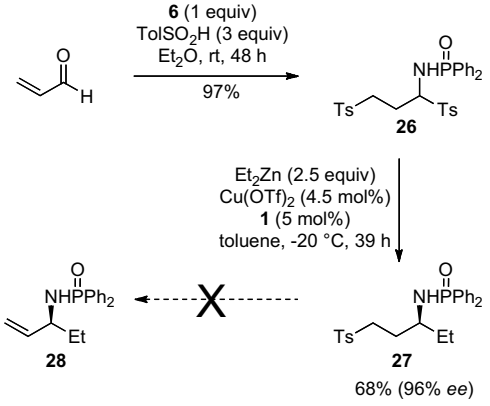
the reaction at −20 °C and the reaction mixture was allowed to stir at rt for 24 h, yielding the desired compound in 68% yield and high enantiomeric excesses (96% ee) (Eq. 2).

Encouraged by the high functional group compatibility of the catalytic system, we next turned our attention to the synthesis of α-chiral allylic amines **24**.[11] These compounds have been shown to be extremely useful precursors to pyrroline derivatives **22** through the use of ring closing metathesis strategies (Scheme 6).[16]



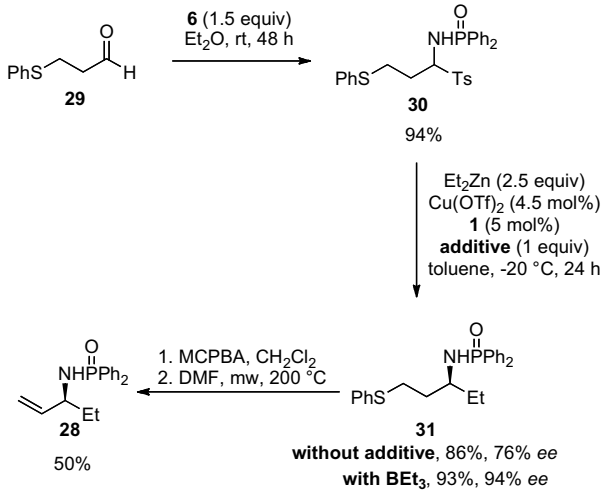
Scheme 6. Strategy for the synthesis of α-chiral allylic amines.

At first, we planned to use a tosyl group as a suitable protecting group for the olefin,[17] the corresponding sulfinic acid adduct **26** would be readily available in one step from acrolein by a double condensation of *p*-toluenesulfinic acid. Thus, we submitted acrolein to the conditions used above but with 3 equiv of *p*-toluenesulfinic acid (Scheme 7).



Scheme 7. Tosyl as a protecting group for α,β-unsaturated system.

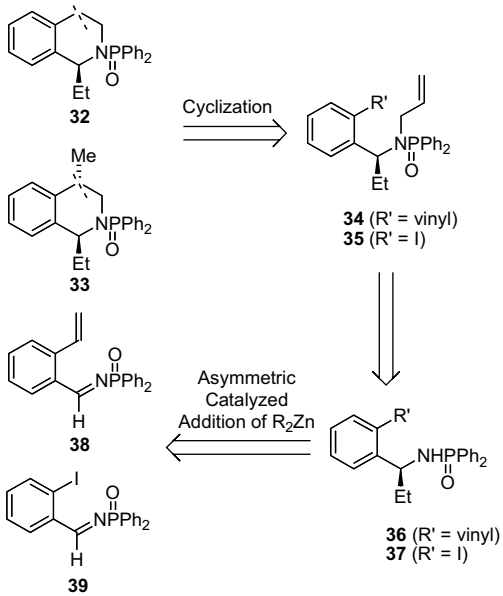
We were pleased to observe that *p*-toluenesulfinic acid was adding cleanly to both the 1,2 and 1,4-positions to yield the desired sulfinic acid adduct **26** in 97% yield. These substrates are generally difficult to prepare, and only 1,4-addition of *p*-toluenesulfinic acid is observed with tosyl amide ($TolSO_2NH_2$).[18] Compound **26** was then reacted under the conditions for the asymmetric addition of Et_2Zn (Scheme 7). The corresponding *N*-protected α-chiral amine **27** was isolated in 68% yield and in high enantioselectivities (96% ee). Unfortunately, all attempts to deprotect the olefin by elimination of the tosyl group failed to yield **28**. We also considered to use a reduction/oxidation sequence of the sulfone to the corresponding sulfoxide, which would be more easily eliminated. However, the reduction step required harsh conditions that led to the cleavage of the phosphinoyl group. The α-chiral amine **27** is still an interesting substrate that could lead to 1,3-substituted compounds by nucleophilic displacement of the tosyl group. We then decided to change the olefin protecting group for a sulfide substituent that would be readily oxidized to the corresponding sulfoxide, a substituent that should be more easily eliminated to generate allylic amine.[19] Consequently, acrolein was treated with PhSH to yield the crude aldehyde **29**,[20] which in turn was transformed to sulfinic acid adduct **30** in 94% yield over the two steps (Scheme 8). The copper-catalyzed asymmetric addition of diethylzinc was then conducted under usual conditions. The conversion to the corresponding *N*-protected amine was high (86%), though a decrease in enantioselectivity (76%) was observed.



Scheme 8. Addition/elimination sequence to generate allylic amine **28**.

We envisioned that sulfur might interfere with the catalyst by complexing either copper or zinc and induce a competitive non-enantioselective intramolecular addition.[21] To circumvent this, a Lewis acid was added to the sulfinic acid adduct that would temporarily block the complexing ability of the sulfur atom during the course of the reaction. We chose BEt_3 as a compatible additive under our reaction conditions.[22] The use of the Lewis acid was efficient, and the desired amine **31** was obtained with high conversion (93%) and excellent enantioselectivity (94% ee) (Scheme 8). Finally, the allylic amine **28** was obtained in 50% yield using a two-step sequence consisting of the oxidation to the sulfoxide and elimination under microwave conditions. No epimerization occurred under these conditions.[23]

We next focused on the application of the enantioselective addition methodology to the preparation of tetrahydroisoquinolines.

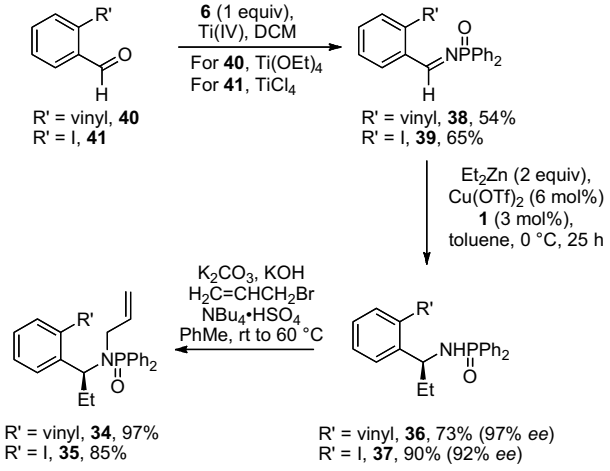


Scheme 9. Strategy for the synthesis of tetrahydroisoquinolines **32** and **33**.

We planned to use the following strategy to access appropriate substrates (Scheme 9).

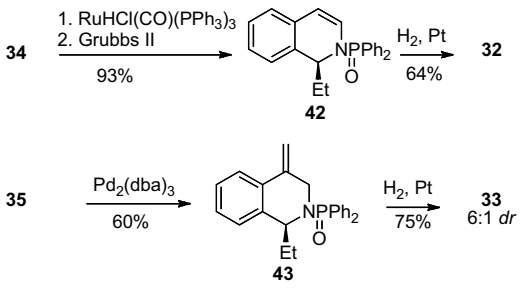
Functionalized imines **38** (R′=vinyl) and **39** (R′=I) were chosen as substrates for the catalyzed asymmetric addition of dialkylzinc. After allylation of the corresponding amines **36** and **37**, a Heck coupling reaction or a tandem isomerization/metathesis followed by hydrogenation would lead to the desired tetrahydroisoquinolines **32** and **33**.

The *N*-phosphinoylimines **38** and **39** were synthesized in 54% and 65% yields, respectively, from **6** and the corresponding aldehydes **40** and **41** in the presence of Ti Lewis acids[24] (Scheme 10). The asymmetric addition of diethylzinc was performed at 0 °C and the *N*-protected α-chiral amines **36** and **37** were obtained in good yields (73–90%) and excellent enantioselectivities (92–97% ee). It was interesting to note that the presence of an *ortho* substituent did not affect the reactivity and the level of enantioinduction of the reaction. Moreover, no product resulting from an iodine–zinc exchange was observed.[25] Finally, reaction with allyl bromide[26] afforded compounds **34** and **35** in 97% and 85% yields, respectively (Scheme 10).



Scheme 10. Synthesis of precursors **34** and **35**.

Alkene **34** was then treated sequentially with [RuHCl(CO)(PPh_3)$_3$][27] to perform the isomerization of the allyl moiety and Grubbs catalyst (second generation) led to the cyclized product **42** in 93% yield (Scheme 11). Conversely, Heck coupling conditions were applied to **35** to afford **43** in 60% yield. A final stage of hydrogenation on PtO_2 gave the desired tetrahydroisoquinolines **32** and **33** in 64% and 75% yields, respectively.



Scheme 11. Tetrahydroisoquinoline formation.

3. Conclusion

In conclusion, we have demonstrated the ability to synthesize sulfinic acid adducts as stable precursors of functionalized alkylimines. The catalyzed asymmetric addition of diethylzinc to imines generated in situ was mild and tolerated the presence of primary alkyl bromide and methyl ester substituents for the aliphatic series, iodine, and vinyl substituents were tolerated for the aromatic series. This enabled us to synthesize *N*-heterocycles, such as pyrrolidine/piperidine, pyrrolidinone/piperidinone as well as tetrahydroisoquinolines and allylic amines, which are important subunits for biologically active compounds.

4. Experimental

4.1. General

All non-aqueous reactions were carried out in oven-dried glassware under argon atmosphere. Anhydrous solvents were obtained either by filtration through drying columns (CH_2Cl_2, DMF, PhMe, MeOH), or by distillation over CaH (Et_3N), Ba(OH) (DMA). Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel. Visualization was performed by UV light or aq $KMnO_4$. Flash column chromatography was performed using 230–400 mesh silica of the indicated solvent system according to standard technique. Melting points were obtained on a melting point apparatus and are uncorrected. IR spectra were taken on an FTIR and are reported in reciprocal centimeters (cm^{-1}). NMR spectra (^1H, ^{13}C, ^{31}P, DEPT 135, COSY, HMQC) were recorded on an AV 400 spectrometer. Chemical shifts are reported relative to Me_4Si with the solvent resonance as the internal standard ($CDCl_3$ or C_6D_6). All spectra were obtained with complete proton decoupling. Microwave reactions were run using a Biotage apparatus. Tol-SO_2H,[28a] **6**,[5c] and aldehydes **7**,[28b] **9**,[28c] **11**,[28d] **13**,[28d] **40**,[28e] and **41**[28f] were synthesized according to literature procedures.

4.2. Experimental procedure

*4.2.1. General procedure for the synthesis of the sulfinic acid adducts **8**, **10**, **12**, **14**, **26**, **30***

Aldehyde (6.1–20.0 mmol, 1.5 equiv) was mixed with *P,P*-diphenylphosphinic amide (**6**) (4.0–13.3 mmol, 1 equiv) and *p*-toluenesulfinic acid (6.1–20 mmol, 1.5 equiv) in Et_2O (41–140 mL). The resulting mixture was then stirred at rt for 24–48 h. The white precipitate was then filtered through a fine sintered funnel and washed with Et_2O to give sulfinic acid adduct as a white solid.

*4.2.2. N-{4-Bromo-1-[(4-methylphenyl)sulfonyl]butyl}-P,P-diphenylphosphinic amide (**8**)*

Yield: 1.8 g (91%); mp 117–118 °C; IR (neat): 3214, 1435, 1290, 1191, 1143, 1116, 1087, 983, 874, 750, 721, 692, 664 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=7.77–7.63 (m, 2H), 7.63–7.33 (m, 10H), 7.28 (d, J=8.1 Hz, 2H), 6.42 (t, J=11.9 Hz, 1H), 4.48 (qd, J=10.3, 2.7 Hz, 1H), 3.48–3.37 (m, 2H), 2.36 (s, 3H), 2.19–2.05 (m, 1H), 2.00–1.67 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=144.3, 134.0 (d, J_{C-P}=124.3 Hz), 133.3, 133.1 (d, J_{C-P}=127.3 Hz), 131.6 (d, J_{C-P}=1.9 Hz), 131.4, 131.0 (d, J_{C-P}=9.3 Hz), 130.8 (d, J_{C-P}=9.8 Hz, 2 C), 129.5, 129.0, 128.4 (d, J_{C-P}=12.4 Hz, 2 C), 128.3 (d, J_{C-P}=12.5 Hz, 2 C), 71.4, 33.9, 28.2, 27.5, 21.1; ^{31}P NMR (162 MHz, DMSO-d_6): δ=23.7; MS (APCI, 70 eV): m/z (%)=350.1 (100), 352.1 (100) $[M]^+$; Anal. Calcd for $C_{23}H_{25}BrNO_3PS$: C, 54.55; H, 4.98; N, 2.77; S, 6.33. Found: C, 54.51; H, 4.92; N, 2.93; S, 6.52.

*4.2.3. N-{5-Bromo-1-[(4-methylphenyl)sulfonyl]pentyl}-P,P-diphenylphosphinic amide (**10**)*

Yield: 3.8 g (88%); mp 121–123 °C; IR (neat): 3206, 2952, 1596, 1437, 1289, 1191, 1145, 1124, 1109, 1087, 722, 692, 666 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=7.70 (dd, J=11.9, 8.0 Hz, 2H), 7.59 (d, J=8.0 Hz, 2H), 7.56–7.35 (m, 8H), 7.28 (d, J=8.0 Hz, 2H), 6.35 (t, J=12.1 Hz, 1H), 4.45 (qd, J=10.9, 3.4 Hz, 1H), 3.26 (t, J=6.7 Hz, 2H), 2.36 (s, 3H), 2.06–1.90 (m, 1H), 1.68 (m, 3H), 1.54–1.41 (m, 1H),

1.35–1.19 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=144.1, 134.2 (d, J_{C-P}=123.7 Hz), 133.4, 133.4 (d, J_{C-P}=127.3 Hz), 131.5 (d, J_{C-P}=1.9 Hz), 131.3 (d, J_{C-P}=1.8 Hz), 131.0 (d, J_{C-P}=10.1 Hz, 2 C), 130.9 (d, J_{C-P}=10.4 Hz, 2 C), 129.4, 129.1, 128.2 (d, J_{C-P}=12.4 Hz, 2 C), 127.9 (d, J_{C-P}=12.6 Hz, 2 C), 71.9, 34.2, 31.2, 27.7 (d, J_{C-P}=1.3 Hz), 23.6, 21.1; ^{31}P NMR (162 MHz, DMSO-d_6): δ=23.6; MS (APCI, 70 eV): m/z (%)=364.1 (100), 366.1 (100) $[(M-Ts)+H]^+$; Anal. Calcd for $C_{24}H_{27}BrNO_3PS$: C, 55.39; H, 5.23; N, 2.69; S, 6.16. Found: C, 55.23; H, 5.26; N, 2.79; S, 6.23.

4.2.4. Methyl 4-[(diphenylphosphoryl)amino]-4-[(4-methylphenyl)-sulfonyl]butanoate (**12**)

Yield: 3.8 g (83%); mp 121–123 °C; IR (neat): 3163, 2953, 1732, 1436, 1290, 1189, 1144, 1121, 1085, 968, 720, 695, 669 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ=7.78–7.67 (m, 2H), 7.63–7.45 (m, 6H), 7.45–7.30 (m, 6H), 6.36 (t, J=10.8 Hz, 1H), 4.46 (qd, J=11.2, 3.1 Hz, 1H), 3.51 (s, 3H), 2.48–2.43 (m, 2H), 2.39 (s, 3H), 2.27–2.14 (m, 1H), 1.93–1.77 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=172.3, 144.4, 133.4, 133.6 (d, J_{C-P}=125.9 Hz), 132.5 (d, J_{C-P}=127.4 Hz), 131.6, 131.4, 131.1 (t_{app}, J_{C-P}=9.1 Hz, 2 C), 129.5, 129.0, 128.3 (d, J_{C-P}=12.4 Hz, 2 C), 128.0 (d, J_{C-P}=12.6 Hz, 2 C), 71.5, 51.2, 28.8, 24.4, 21.0; ^{31}P NMR (162 MHz, DMSO-d_6): δ=23.3; HRMS–ESI: m/z $[M+Na]^+$ calcd for $C_{24}H_{26}NNaO_5PS$: 494.11615; found: 494.11394.

4.2.5. Methyl 5-[(diphenylphosphoryl)amino]-5-[(4-methylphenyl)-sulfonyl]pentanoate (**14**)

Yield: 3.8 g (88%); mp 119–121 °C; IR (neat): 3200, 2933, 1732, 1437, 1289, 1191, 1148, 1123, 1109, 1087, 751, 723, 694, 665 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ=7.68 (dd, J=12.0, 7.0 Hz, 2H), 7.62–7.35 (m, 10H), 7.27 (d, J=8.0 Hz, 2H), 6.37 (t, J=12.0 Hz, 1H), 4.46 (qd, J=10.9, 3.2 Hz, 1H), 3.52 (s, 3H), 2.36 (s, 3H), 2.27–2.14 (m, 2H), 2.04–1.90 (m, 1H), 1.79–1.56 (m, 2H), 1.52–1.36 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=172.6, 144.1, 134.2 (d, J_{C-P}=124.0 Hz), 133.4, 133.3 (d, J_{C-P}=127.3 Hz), 131.5 (d, J_{C-P}=2.2 Hz), 131.3 (d, J_{C-P}=2.2 Hz), 131.0 (d, J_{C-P}=9.8 Hz, 2 C), 130.9 (d, J_{C-P}=10.0 Hz, 2 C), 129.4, 129.0, 128.2 (d, J_{C-P}=12.4 Hz, 2 C), 127.9 (d, J_{C-P}=12.7 Hz, 2 C), 71.8, 51.2, 32.3, 27.9 (d, J_{C-P}=1.3 Hz), 21.1, 20.5; ^{31}P NMR (162 MHz, DMSO-d_6): δ=23.7; HRMS–ESI: m/z $[M+Na]^+$ calcd for $C_{25}H_{28}NNaO_5PS$: 508.53180; found: 508.12985.

4.2.6. N-{1,3-Bis[(4-methylphenyl)sulfonyl]propyl}-P,P-diphenylphosphinic amide (**26**)

3 Equiv of sulfinic acid was used. Yield: 7.3 g (97%); mp 124–126 °C; IR (neat): 3154, 1595, 1437, 1312, 1197, 1147, 1118, 724, 692, 663 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ=7.75–7.29 (m, 18H), 6.50 (dd, J=11.3, 9.6 Hz, 1H), 4.57 (qd_{app}, J=11.3, 2.9 Hz, 1H), 3.59–3.45 (m, 1H), 3.36–3.23 (m, 1H), 2.42 (s, 3H), 2.40 (s, 3H), 2.27–2.16 (m, 1H), 2.09–1.95 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=144.7, 144.5, 135.5, 133.3 (d, J_{C-P}=126.1 Hz), 133.0, 131.9 (d, J_{C-P}=127.7 Hz), 131.8 (d, J_{C-P}=2.0 Hz), 131.4 (d, J_{C-P}=1.9 Hz), 131.2 (t_{app}, J_{C-P}=10.6 Hz, 4 C), 129.9, 129.7, 129.1, 128.4 (d, J_{C-P}=12.4 Hz, 2 C), 128.0, 128.0 (d, J_{C-P}=12.6 Hz, 2 C), 127.6, 125.5, 70.4, 51.0, 23.1, 21.1, 21.1; ^{31}P NMR (162 MHz, DMSO-d_6): δ=23.5; HRMS–ESI: m/z $[M+H]^+$ calcd for $C_{29}H_{31}NO_5PS_2$: 568.13758; found: 568.13729.

4.2.7. N[1-[(4-Methylphenyl)sulfonyl]-3-(phenylthio)propyl]-P,P-diphenylphosphinic amide (**30**)

Yield: 6.5 g (94%); mp 134–135 °C; IR (neat): 3117, 2894, 1595, 1437, 1309, 1302, 1190, 1165, 1145, 1125, 967, 736, 723, 661, 581 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ=7.77 (dd, J=11.9, 7.0 Hz, 2H), 7.62–7.09 (m, 17H), 6.48 (t, J=10.9 Hz, 1H), 4.69–4.56 (m, 1H), 3.14–3.02 (m, 1H), 2.96–2.84 (m, 1H), 2.38 (s, 3H), 2.18–1.92 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=144.4, 134.8, 133.8 (d, J_{C-P}=119.8 Hz), 132.5 (d, J_{C-P}=121.5 Hz), 132.2, 131.7 (d, J_{C-P}=2.0 Hz), 131.5 (d, J_{C-P}=2.0 Hz), 131.3 (d, J_{C-P}=4.5 Hz, 2 C), 131.2 (d, J_{C-P}=4.9 Hz, 2 C), 129.6, 129.0, 128.4, 128.3 (d, J_{C-P}=12.4 Hz, 2 C), 128.0 (d, J_{C-P}=12.6 Hz, 2 C), 125.8, 71.2, 28.4, 28.3, 21.1; ^{31}P NMR (162 MHz, DMSO-d_6): δ=23.5; MS (APCI, 70 eV): m/z (%)=366.2 (100) $[M+H]^+$; Anal. Calcd for $C_{28}H_{28}NO_3PS_2$: C, 64.47; H, 5.41; N, 2.69; S, 12.29. Found: C, 64.19; H, 5.58; N, 2.87; S, 12.18.

4.2.8. General procedure for the asymmetric catalyzed addition of diethylzinc to sulfinic acid adducts **8**, **10**, **12**, **14**, **26**, **30**

The general procedure[9a] was followed using (*R*)-**1** (4.8–32.2 mg, 0.015–0.1 mmol, 0.05 equiv), $Cu(OTf)_2$ (5–33.0 mg, 0.014–0.09 mmol, 0.045 equiv), Et_2Zn (79–523 μL, 0.75–5 mmol, 2.5 equiv), sulfinic acid adduct (0.3–2.0 mmol) in dry PhMe (2.7–35 mL) for 19–39 h at −20 °C. The crude material was purified by flash chromatography on silica gel to afford the corresponding amide as a white solid.

For ***17***/***18***. The crude material was dissolved in dry THF (47 mL). *t*-BuOK (53.0 mg, 0.47 mmol) was added and the reaction was heated to 50 °C for 4 h. The resulting mixture was diluted with EtOAc (10 mL), washed with brine (10 mL), and dried over Na_2SO_4. Concentration under vacuum gave the crude material, which was purified by flash chromatography on silica gel eluting with 100% EtOAc to afford the desired compound.

For ***21***. After stirring for 26 h at −20 °C, the reaction was diluted with dry PhMe (10 mL). CuCN (134 mg, 1.5 mmol) and Et_2Zn (160 μL, 1.5 mmol) were then added at −20 °C and the reaction was allowed to warm to rt and stirred for 24 h (monitored by MS). The reaction was quenched with aq satd NH_4Cl (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (4×20 mL). The combined organic layers were dried over Na_2SO_4. Concentration under vacuum gave the crude material, which was purified by flash chromatography on silica gel eluting with 100% EtOAc.

For ***31***. BEt_3 (290 μL, 2 mmol) was added to **26** and the resulting heterogeneous mixture was stirred for 5 min at rt prior to the addition to the catalyst solution at −20 °C.

4.2.9. (2S)-1-(Diphenylphosphoryl)-2-ethylpyrrolidine (**17**)

Enantiomeric excess (99% ee) was determined by SFC analysis (Chiralpak) AD, 180 bar, 2 mL/min, 26 °C, modifier 10% *i*-PrOH: (major enantiomer) t_R=25.9 min, (minor enantiomer) t_R=29.0 min. Yield: 85 mg (61%); colorless oil; $[\alpha]_D^{20}$ −26.0 (*c* 1.2, $CHCl_3$); R_f=0.3 (hexanes–EtOAc, 1:4); IR (neat): 2962, 2872, 1437, 1188, 1116, 1071, 994, 723, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.92–7.83 (m, 4H), 7.51–7.39 (m, 6H), 3.26–3.14 (m, 1H), 3.12–2.94 (m, 2H), 1.84–1.67 (m, 2H), 1.66–1.43 (m, 6H), 0.78 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=132.8 (d, J_{C-P}=129.2 Hz), 132.3 (d, J_{C-P}=9.1 Hz, 2 C), 132.0 (d, J_{C-P}=9.3 Hz, 2 C), 132.6 (d, J_{C-P}=128.5 Hz), 131.4 (d, J_{C-P}=2.6 Hz), 131.3 (d, J_{C-P}=2.6 Hz), 128.3 (d, J_{C-P}=12.3 Hz, 2 C), 128.1 (d, J_{C-P}=12.5 Hz, 2 C), 60.0 (d, J_{C-P}=1.4 Hz), 47.1 (d, J_{C-P}=2.2 Hz), 30.7 (d, J_{C-P}=4.5 Hz), 28.9 (d, J_{C-P}=3.4 Hz), 25.3 (d, J_{C-P}=5.3 Hz), 10.4; ^{31}P NMR (162 MHz, $CDCl_3$): δ=26.6; HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{18}H_{23}NOP$: 300.14990; found: 300.15117.

4.2.10. (2S)-1-(Diphenylphosphoryl)-2-ethylpiperidine (**18**)

Enantiomeric excess (98% ee) was determined by SFC analysis (Chiralpak) AS, 180 bar, 2 mL/min, 40 °C, modifier 10% *i*-PrOH: (major enantiomer) t_R=6.6 min, (minor enantiomer) t_R=7.8 min. Yield: 51.5 mg (55%); mp 110–113 °C; $[\alpha]_D^{20}$ −21.0 (*c* 1.0, $CHCl_3$); R_f=0.4 (EtOAc); IR (neat): 3052, 2923, 2847, 1443, 1434, 1203, 1113, 1105, 954, 722, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.92–7.83 (m, 4H), 7.51–7.39 (m, 6H), 3.26–3.14 (m, 1H), 3.12–2.94 (m, 2H), 1.84–1.67 (m, 2H), 1.66–1.43 (m, 6H), 0.78 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=132.5 (d, J_{C-P}=129.9 Hz), 132.4 (d, J_{C-P}=129.7 Hz), 132.3 (d, J_{C-P}=9.0 Hz, 4 C), 131.4 (t_{app}, J_{C-P}=2.2 Hz), 128.4 (d, J_{C-P}=12.3 Hz, 2 C), 128.3 (d, J_{C-P}=12.3 Hz, 2 C), 53.1 (d, J_{C-P}=0.9 Hz), 39.9 (d, J_{C-P}=2.1 Hz), 27.7 (d, J_{C-P}=4.2 Hz), 26.0 (d, J_{C-P}=4.0 Hz), 22.8 (d, J_{C-P}=3.6 Hz), 18.7, 11.3; ^{31}P NMR (162 MHz, $CDCl_3$): δ=28.9; MS (APCI, 70 eV): m/z (%)=314.2 (100) $[M+H]^+$; Anal. Calcd

for $C_{19}H_{24}NOP$: C, 72.82; H, 7.72; N, 4.47. Found: C, 72.65; H, 7.77; N, 4.49.

4.2.11. (5S)-1-(Diphenylphosphoryl)-5-ethylpyrrolidin-2-one (**19**)

Enantiomeric excess (97% ee) was determined by HPLC analysis (Chiralpak) AD-H, 80:20 hexane–*i*-PrOH, 1.0 mL/min: (major enantiomer) t_R=9.3 min, (minor enantiomer) t_R=13.8 min. Yield: 115 mg (87%); mp 166–169 °C; $[\alpha]_D^{20}$ +169.3 (*c* 1.4, $CHCl_3$); R_f=0.3 (hexanes–EtOAc, 1:4); IR (neat): 2963, 1709, 1689, 1438, 1207, 1120, 964, 757, 725, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.98–7.88 (m, 2H), 7.77–7.67 (m, 2H), 7.63–7.39 (m, 6H), 4.44–4.29 (m, 1H), 2.68–2.51 (m, 1H), 2.43–2.19 (m, 2H), 2.02–1.85 (m, 2H), 1.67–1.50 (m, 1H), 0.86 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=178.6 (d, J_{C-P}=1.9 Hz), 132.4 (d, J_{C-P}=3.0 Hz), 132.3 (d, J_{C-P}=3.0 Hz), 131.9 (d, J_{C-P}=11.2 Hz, 2 C), 131.6 (d, J_{C-P}=11.3 Hz, 2 C), 131.0 (d, J_{C-P}=125.9 Hz), 130.7 (d, J_{C-P}=126.2 Hz), 128.3 (d, J_{C-P}=13.8 Hz, 2 C), 128.2 (d, J_{C-P}=13.9 Hz, 2 C), 60.2 (d, J_{C-P}=2.7 Hz), 31.6 (d, J_{C-P}=5.7 Hz), 28.4, 24.4 (d, J_{C-P}=6.2 Hz), 9.7; ^{31}P NMR (162 MHz, $CDCl_3$): δ=27.5; HRMS–ESI: *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{21}NO_2P$: 314.13044; found: 314.13089.

4.2.12. (6S)-1-(Diphenylphosphoryl)-6-ethylpiperidin-2-one (**21**)

Enantiomeric excess (96% ee) was determined by HPLC analysis (Chiralpak) AD-H, 80:20 hexane–*i*-PrOH, 1.0 mL/min: (major enantiomer) t_R=9.3 min, (minor enantiomer) t_R=12.5 min. Yield: 223 mg (68%); mp 104–106 °C; $[\alpha]_D^{20}$ +131.8 (*c* 1.5, $CHCl_3$); R_f=0.4 (hexanes–EtOAc, 1:4); IR (neat): 2968, 1651, 1436, 1392, 1274, 1201, 1122, 1098, 755, 728, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.99–7.88 (m, 2H), 7.73–7.64 (m, 2H), 7.59–7.36 (m, 6H), 4.54–4.39 (m, 1H), 2.51–2.26 (m, 2H), 2.11–2.00 (m, 1H), 2.00–1.73 (m, 4H), 1.65–1.50 (m, 1H), 0.88 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.4, 132.4 (d, J_{C-P}=11.1 Hz, 2 C), 132.1 (d, J_{C-P}=128.1 Hz), 132.0 (d, J_{C-P}=3.0 Hz), 131.8 (d, J_{C-P}=3.0 Hz), 131.3 (d, J_{C-P}=11.2 Hz, 2 C), 131.0 (d, J_{C-P}=126.7 Hz), 128.1 (d, J_{C-P}=13.7 Hz, 2 C), 128.0 (d, J_{C-P}=13.9 Hz, 2 C), 54.3 (d, J_{C-P}=1.4 Hz), 32.5 (d, J_{C-P}=2.9 Hz), 28.2, 24.4 (d, J_{C-P}=3.9 Hz), 15.7, 10.6; ^{31}P NMR (162 MHz, $CDCl_3$): δ=32.1; MS (APCI, 70 eV): *m*/*z* (%)=328.2 (100) $[M+H]^+$; Anal. Calcd for $C_{19}H_{22}NO_2P$: C, 69.71; H, 6.77; N, 4.28. Found: C, 69.37; H, 6.78; N, 4.19.

4.2.13. N-{(1S)-1-Ethyl-3-[(4-methylphenyl)sulfonyl]propyl}-P,P-diphenylphosphinic amide (**27**)

Enantiomeric excess (96% ee) was determined by SFC analysis of the corresponding allyl derivative (Chiralpak) AD, 200 bar, 2 mL/min, 60 °C, modifier 20% *i*-PrOH: (minor enantiomer) t_R=29.3 min, (major enantiomer) t_R=33.5 min. Yield: 600 mg (68%); mp 174–176 °C; $[\alpha]_D^{20}$ −14.6 (*c* 1.1, $CHCl_3$); R_f=0.5 (EtOAc); IR (neat): 3215, 2927, 1593, 1437,1298, 1273, 1190, 1138, 1122, 1107, 1086,750, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.89–7.78 (m, 4H), 7.75 (d, *J*=8.1 Hz, 2H), 7.54–7.36 (m, 6H), 7.33 (d, *J*=8.1 Hz, 2H), 3.52–3.41 (m, 1H), 3.13 (m, 1H), 3.08–2.96 (br, 1H), 2.94–2.83 (br, 1H), 2.43 (s, 3H), 2.03–1.90 (m, 1H), 1.85–1.72 (m, 1H), 1.65–1.46 (m, 2H), 0.85 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=144.4, 136.1, 132.6 (d, J_{C-P}=129.0 Hz), 132.2 (d, J_{C-P}=129.3 Hz, 2 C), 132.1 (d, J_{C-P}=9.5 Hz, 2 C), 131.8 (d, J_{C-P}=35.8 Hz), 131.7 (d, J_{C-P}=9.4 Hz, 2 C), 129.8, 128.4 (d, J_{C-P}=12.5 Hz, 2 C), 128.3 (d, J_{C-P}=12.6 Hz, 2 C), 127.9, 53.1, 51.4 (d, J_{C-P}=1.2 Hz), 30.2 (d, J_{C-P}=4.6 Hz), 28.6 (d, J_{C-P}=4.3 Hz), 21.5, 9.7; ^{31}P NMR (162 MHz, $CDCl_3$): δ=22.5; MS (APCI, 70 eV): *m*/*z* (%)=442.2 (100) $[M+H]^+$; Anal. Calcd for $C_{24}H_{28}NO_3PS$: C, 65.29; H, 6.39; N, 3.17; S, 7.26. Found: C, 65.05; H, 6.24; N, 3.20; S, 7.30.

4.2.14. N-[(1S)-1-Ethyl-3-(phenylthio)propyl]-P,P-diphenylphosphinic amide (**31**)

Enantiomeric excess (94% ee) was determined by HPLC analysis (Chiralpak) AD-H, 80:20 hexane–*i*-PrOH, 1.0 mL/min: (minor enantiomer) t_R=11.6 min, (major enantiomer) t_R=13.5 min. Yield: 772 mg (98%); mp 159–162 °C; $[\alpha]_D^{20}$ −11.5 (*c* 1.1, $CHCl_3$); R_f=0.4 (hexanes–EtOAc, 1:4); IR (neat): 2968, 1651, 1436, 1392, 1274, 1201, 1122, 1098, 755, 728, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.94–7.82 (m, 4H), 7.52–7.36 (m, 6H), 7.31–7.20 (m, 4H), 7.18–7.11 (m, 1H), 3.19–3.05 (br, 1H), 3.07 (ddd, *J*=13.0, 9.1, 5.6 Hz, 1H), 2.93 (ddd, *J*=12.9, 9.1, 6.6 Hz, 1H), 2.88–2.76 (br, 1H), 1.91–1.68 (m, 2H), 1.66–1.50 (m, 2H), 0.87 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.4, 133.4, 133.3, 132.1 (d, J_{C-P}=9.4 Hz, 2 C), 132.1 (d, J_{C-P}=9.3 Hz, 2 C), 131.7 (d, J_{C-P}=2.6 Hz, 2 C), 128.9, 128.8, 128.4 (d, J_{C-P}=12.5 Hz, 2 C), 128.4 (d, J_{C-P}=12.5 Hz, 2 C), 125.8, 52.1 (d, J_{C-P}=1.8 Hz), 35.4 (d, J_{C-P}=5.3 Hz), 30.0, 29.8 (d, J_{C-P}=4.2 Hz), 9.7; ^{31}P NMR (162 MHz, $CDCl_3$): δ=22.2; MS (APCI, 70 eV): *m*/*z* (%)=412.2 (100) $[M(O)+H]^+$; Anal. Calcd for $C_{23}H_{26}NOPS$: C, 69.85; H, 6.63; N, 3.54. Found: C, 69.68; H, 6.52; N, 3.51.

4.2.15. N-[(1S)-1-Ethylprop-2-enyl]-P,P-diphenylphosphinic amide (**28**)

Chiral amine **31** (270 mg, 0.68 mmol) was dissolved in dry CH_2Cl_2 (6.8 mL). *m*-CPBA (141 mg, 0.82 mmol) was added at rt and the reaction was stirred for 2 h. The reaction was then quenched by a slow addition of aq satd Na_2SO_3 (5 mL), extracted with CH_2Cl_2 (3×10 mL), and dried over Na_2SO_4. Concentration under vacuum gave the crude material, which was purified by flash chromatography on silica gel eluting with the following gradient: 100% EtOAc then MeOH–EtOAc (1:19) to afford the corresponding sulfoxide as a white solid (210 mg, 75%). The sulfoxide (188 mg, 0.46 mmol) was charged in a microwave vial with dry DMF (4.5 mL). The microwave was set as the following: 200 °C, high absorption, 20 min. The resulting brown mixture was diluted with EtOAc (20 mL), washed with brine (3×20 mL), and dried over Na_2SO_4. Concentration under vacuum gave the crude material, which was purified by flash chromatography on silica gel eluting with 100% EtOAc to afford **28** as a white solid (85 mg, 66%). Enantiomeric excess (97% ee) was confirmed by SFC analysis of the corresponding allyl derivative (Chiralpak) AD, 180 bar, 2 mL/min, 40 °C, modifier 5% *i*-PrOH: (minor enantiomer) t_R=8.8 min, (major enantiomer) t_R=10.3 min. Mp 122–123 °C; $[\alpha]_D^{20}$ +11.6 (*c* 1.1, $CHCl_3$); R_f=0.4 (EtOAc); IR (neat): 3118, 2967, 2870, 1437, 1198, 1182, 1107, 1069, 1014, 904, 720, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.96–7.84 (m, 4H), 7.52–7.38 (m, 6H), 5.79 (ddd, *J*=17.1, 10.3, 6.0 Hz, 1H), 5.14 (dt_{app}, *J*=17.2, 1.4 Hz, 1H), 5.09 (dt_{app}, *J*=10.4, 1.3 Hz, 1H), 3.56 (br, 1H), 2.88 (br, 1H), 1.71 (m, 1H), 1.65–1.53 (m, 1H), 0.88 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=140.0 (d, J_{C-P}=6.1 Hz), 133.0 (d, J_{C-P}=128.7 Hz), 132.3 (d, J_{C-P}=9.4 Hz, 2 C), 131.9 (d, J_{C-P}=9.4 Hz, 2 C), 132.5 (d, J_{C-P}=130.7 Hz), 131.7 (t_{app}, J_{C-P}=2.3 Hz, 2 C), 128.4 (d, J_{C-P}=12.5 Hz, 2 C), 128.3 (d, J_{C-P}=12.6 Hz, 2 C), 114.7, 55.0 (d, J_{C-P}=1.1 Hz), 30.4 (d, J_{C-P}=4.2 Hz), 9.8; ^{31}P NMR (162 MHz, $CDCl_3$): δ=22.5; HRMS-ESI: *m*/*z* $[M+Na]^+$ calcd for $C_{17}H_{20}NNaOP$: 308.11747; found: 308.11799.

4.2.16. P,P-Diphenyl-N-[(1Z)-(2-vinylphenyl)methylene]phosphinic amide (**38**)

Compound **38** was synthesized according to literature procedure[24c] using 2-vinylbenzaldehyde (**40**) (1.1 g, 8.3 mmol), **6** (1.6 g, 7.6 mmol), and distilled $Ti(OEt)_4$ (3.8 g, 16.6 mmol). Purification by flash chromatography on silica gel eluting with the following gradient: EtOAc–hexane (1:1) then (4:1) afforded 3**8** as a white solid (1.3 g, 54%). Mp 108–110 °C; R_f=0.3 (hexanes–EtOAc, 1:1.5); IR (neat): 3056, 1610, 1588, 1437, 1201, 1122, 1106, 837, 747, 723, 691 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ=9.88 (d, J_{H-P}=32.0 Hz, 1H), 8.22–8.15 (m, 4H), 8.05 (dd, *J*=7.7, 1.3 Hz, 1H), 7.13–6.92 (m, 10H), 5.29 (dd, *J*=17.3, 1.3 Hz, 1H), 5.04 (dd, *J*=11.0, 1.3 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6): δ=172.2 (d, J_{C-P}=7.4 Hz), 141.4, 134.7 (d, J_{C-P}=125.8 Hz, 2 C), 133.5, 133.2, 133.0, 132.0 (d, J_{C-P}=8.9 Hz, 4 C), 131.6 (d, J_{C-P}=2.7 Hz), 129.2, 128.7 (d, J_{C-P}=12.3 Hz, 4 C), 128.3, 127.3, 118.9; ^{31}P NMR (162 MHz, C_6D_6): δ=23.3; HRMS-ESI: *m*/*z* $[M+H]^+$ calcd for $C_{21}H_{19}NOP$: 332.11988; found: 332.11934.

4.2.17. *N-[(1E)-(2-Iodophenyl)methylene]-P,P-diphenylphosphinic amide (**39**)*

Compound **39** was synthesized according to literature procedure[24b] using 2-iodobenzaldehyde (**41**) (920 mg, 4.0 mmol), **6** (869 mg, 4.0 mmol), $TiCl_4$ (242 μL, 1.7 mmol), and distilled Et_3N (1.7 mL, 3.0 mmol). Purification by flash chromatography on silica gel eluting with 70% EtOAc in hexane afforded **39** as a white solid (1.1 g, 65%). Mp 135–137 °C; R_f=0.3 (hexanes–EtOAc, 1:1.5); IR (neat): 1601, 1437, 1266, 1192, 1126, 1105, 1017, 825, 754, 727, 693 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ=9.74 (d, J_{H-P}=31.0 Hz, 1H), 8.19–8.08 (m, 4H), 8.00 (dd, J=7.8, 1.7 Hz, 1H), 7.43 (d, J=7.9 Hz, 1H), 7.11–7.00 (m, 6H), 6.86–6.79 (m, 1H), 6.52–6.45 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6): δ=176.9 (d, J_{C-P}=6.3 Hz), 140.5, 136.8 (d, J_{C-P}=24.7 Hz), 134.3 (d, J_{C-P}=125.6 Hz, 2 C), 134.1, 132.1 (d, J_{C-P}=9.0 Hz, 4 C), 131.7 (d, J_{C-P}=2.5 Hz, 2 C), 130.1, 128.7 (d, J_{C-P}=12.3 Hz, 4 C), 128.2, 103.1; ^{31}P NMR (162 MHz, C_6D_6): δ=25.1; MS (APCI, 70 eV): m/z (%)=432.0 (100) $[M+H]^+$; Anal. Calcd for $C_{19}H_{15}INOP$: C, 52.92; H, 3.51; N, 3.25. Found: C, 52.88; H, 3.44; N, 3.18.

4.2.18. *Asymmetric addition of diethylzinc to aromatic imines **38** and **39***

General procedure was followed using (*R*)-**1** (9.7–22 mg, 0.03–0.07 mmol, 3 mol %), $Cu(OTf)_2$ (21.7–49.5 mg, 0.06–0.14 mmol, 6 mol %), Et_2Zn (210–477 μL, 2.0–4.6 mmol, 2 equiv), and imine (1.0–2.3 mmol) in PhMe (10–23 mL) for 25 h at 0 °C. The crude material was purified by flash chromatography on silica gel eluting with 100% EtOAc to afford the desired compound as a white solid.

4.2.19. *P,P-Diphenyl-N-[(1S)-(2-vinylphenyl)propyl]phosphinic amide (**36**)*

Enantiomeric excess (97% ee) was determined by HPLC analysis (Chiralpak) AD-H, 90:10 hexane–*i*-PrOH, 1.0 mL/min: (minor enantiomer) t_R=16.1 min, (major enantiomer) t_R=26.8 min. Yield: 264 mg (73%); mp 117–120 °C; $[\alpha]_D^{20}$ +85.1 (*c* 2.5, PhH); R_f=0.3 (EtOAc); IR (neat): 3154, 3057, 2965, 2930, 2873, 1437, 1196, 1182, 1108, 899, 751, 720, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.93–7.85 (m, 2H), 7.76–7.68 (m, 2H), 7.55–7.19 (m, 10H), 6.58 (dd, J=17.2, 10.9 Hz, 1H), 5.41 (dd, J=17.2, 1.4 Hz, 1H), 5.12 (dd, J=10.9, 1.40 Hz, 1H), 4.53–4.40 (m, 1H), 3.43–3.30 (m, 1H), 2.03–1.75 (m, 2H), 0.82 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=141.3 (d, J_{C-P}=5.4 Hz), 136.3, 134.3, 133.2 (d, J_{C-P}=127.8 Hz), 132.6 (d, J_{C-P}=9.7 Hz, 2 C), 131.9 (d, J_{C-P}=9.6 Hz, 2 C), 131.9 (d, J_{C-P}=130.9 Hz), 131.8 (d, J_{C-P}=2.7 Hz), 131.6 (d, J_{C-P}=2.7 Hz), 128.5 (d, J_{C-P}=12.5 Hz, 2 C), 128.3 (d, J_{C-P}=12.7 Hz, 2 C), 128.1, 127.0, 126.5, 125.8, 116.8, 52.7, 32.8 (d, J_{C-P}=3.4 Hz), 10.7; ^{31}P NMR (162 MHz, C_6D_6): δ=22.9; MS (APCI, 70 eV): m/z (%)=362.2 (100) $[M+H]^+$; Anal. Calcd for $C_{23}H_{24}NOP$: C, 76.43; H, 6.69; N, 3.88. Found: C, 76.10; H, 6.59; N, 3.83.

4.2.20. *N-[(1S)-1-(2-Iodophenyl)propyl]-P,P-diphenylphosphinic amide (**37**)*

Enantiomeric excess (92% ee) was determined by HPLC analysis (Chiralpak) AD-H, 90:10 hexane–*i*-PrOH, 1.0 mL/min: (minor enantiomer) t_R=23.0 min, (major enantiomer) t_R=27.0 min. Yield: 946 mg (90%); mp 153–155 °C; $[\alpha]_D^{20}$ +51.5 (*c* 1.2, $CHCl_3$); R_f=0.4 (EtOAc); IR (neat): 3139, 2868, 1452, 1437, 1196, 1180, 1124, 1108, 1058, 1005, 903, 747, 721, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.92–7.82 (m, 2H), 7.75–7.68 (m, 3H), 7.52–7.26 (m, 8H), 6.91 (ddd, J=7.9, 6.8, 2.2 Hz, 1H), 4.42–4.32 (m, 1H), 3.55–3.42 (br, 1H), 1.89–1.73 (m, 2H), 0.93 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=146.0, 139.5, 132.7 (d, J_{C-P}=128.1 Hz), 132.5 (d, J_{C-P}=9.7 Hz, 2 C), 131.8 (d, J_{C-P}=9.8 Hz, 2 C), 131.7, 131.6 (d, J_{C-P}=1.90 Hz), 131.4 (d, J_{C-P}=131.0 Hz), 128.5 (d, J_{C-P}=13.7 Hz, 2 C), 128.4 (d, J_{C-P}=12.8 Hz, 2 C), 128.4, 128.2, 127.4, 98.7, 60.4, 32.3, 10.5; ^{31}P NMR (162 MHz, $CDCl_3$): δ=22.8; MS (APCI, 70 eV): m/z (%)=462.1 (100) $[M+H]^+$; Anal. Calcd for $C_{21}H_{21}INOP$: C, 54.68; H, 4.59; N, 3.04. Found: C, 54.53; H, 4.55; N, 3.01.

4.2.21. *General procedure for the allylation reaction*

The general procedure[26] was followed using chiral amine (0.87–1.1 mmol), K_2CO_3 (150–191 mg, 1.1–1.4 mmol), KOH (147–187 mg, 2.6–3.3 mmol), $NBu_4 \cdot HSO_4$ (30–38 mg, 0.09–0.1 mmol), distilled allyl bromide (100–120 μL, 1.1–1.4 mmol) in PhMe (11–14 mL) at 60 °C for 5–13 h. The crude material was purified by flash chromatography on silica gel to afford the allylic amine.

4.2.22. *N-Allyl-P,P-diphenyl-N-[(1S)-(2-vinylphenyl)-propyl]phosphinic amide (**34**)*

Yield: 431 mg (97%); colorless oil; $[\alpha]_D^{20}$ +111.0 (*c* 3.4, PhH); R_f=0.4 (hexanes–EtOAc, 1:1.5); IR (neat): 3057, 2967, 2874, 1736, 1436, 1200, 1118, 1104, 915, 890, 746, 722, 697 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ=7.95–7.85 (m, 2H), 7.83–7.75 (m, 2H), 7.57 (dd, J=17.2, 10.9 Hz), 7.52–7.45 (m, 2H), 7.13–6.96 (m, 8H), 5.51 (dd, J=17.2, 1.6 Hz, 1H), 5.56–5.44 (m, 1H), 5.29 (q_{app}, J=8.0 Hz, 1H), 5.15 (dd, J=10.9, 1.6 Hz, 1H), 4.66–4.58 (m, 2H), 3.59–3.34 (m, 2H), 2.25 (p_{app}, J=7.5 Hz, 2H), 0.73 (t, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ=138.7 (d, J_{C-P}=90.1 Hz), 138.2, 137.0 (d, J_{C-P}=5.1 Hz), 135.8, 134.0 (d, J_{C-P}=123.9 Hz), 134.6 (d, J_{C-P}=123.1 Hz), 132.8 (d, J_{C-P}=8.5 Hz, 2 C), 132.7 (d, J_{C-P}=8.9 Hz, 2 C), 131.5 (d, J_{C-P}=2.8 Hz), 131.4 (d, J_{C-P}=2.7 Hz), 128.8, 128.4 (d, J_{C-P}=12.3 Hz, 2 C), 128.6 (d, J_{C-P}=12.4 Hz, 2 C) 127.9, 127.5, 126.8, 116.3, 115.4, 57.2 (d, J_{C-P}=3.3 Hz), 47.5 (d, J_{C-P}=5.0 Hz), 27.8, 11.7; ^{31}P NMR (162 MHz, C_6D_6): δ=30.6; HRMS-ESI: m/z $[M+Na]^+$ calcd for $C_{26}H_{29}NOP$: 402.19813; found: 402.19848.

4.2.23. *N-Allyl-N-[(1S)-1-(2-iodophenyl)propyl]-P,P-diphenylphosphinic amide (**35**)*

Yield: 370 mg (85%); mp 77–79 °C; $[\alpha]_D^{20}$ +56.3 (*c* 1.3, $CHCl_3$); R_f=0.4 (hexanes–EtOAc, 1:9); IR (neat): 3056, 2968, 1463, 1437, 1199, 1118, 1104, 1009, 922, 749, 723, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.86–7.76 (m, 4H), 7.73–7.66 (m, 2H), 7.54–7.30 (m, 7H), 6.92 (td, J=7.6, 1.6 Hz, 1H), 5.57 (ddt, J=16.8, 10.5, 6.4 Hz, 1H), 4.91–4.76 (m, 2H), 4.54 (ddd, J=10.9, 9.9, 5.7 Hz, 1H), 3.69–3.41 (m, 2H), 2.35–2.06 (m, 2H), 0.75 (t, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=143.4 (d, J_{C-P}=4.0 Hz), 139.7, 136.5, 133.0 (d, J_{C-P}=126.4 Hz), 132.9 (d, J_{C-P}=126.1 Hz), 132.5 (d, J_{C-P}=10.0 Hz, 2 C), 132.4 (d, J_{C-P}=9.8 Hz, 2 C), 131.6 (d, J_{C-P}=2.4 Hz), 131.5 (d, J_{C-P}=2.4 Hz), 130.1, 129.0, 128.2, 128.2 (d, J_{C-P}=12.6 Hz, 4 C), 116.5, 102.5, 67.7, 49.5 (d, J_{C-P}=5.0 Hz), 28.7, 11.5; ^{31}P NMR (162 MHz, $CDCl_3$): δ=32.9; MS (APCI, 70 eV): m/z (%)=502.2 (100) $[M+H]^+$; Anal. Calcd for $C_{24}H_{25}INOP$: C, 57.50; H, 5.03; N, 2.79. Found: C, 57.36; H, 5.05; N, 2.84.

4.2.24. *(1S)-2-(Diphenylphosphoryl)-1-ethyl-1,2-dihydroisoquinoline (**42**)*

$RuH(CO)(PPh_3)_3$ (10 mg, 0.010 mmol) was added to a solution of **34** (300 mg, 0.75 mmol) in PhMe (38 mL). The resulting mixture was warmed to 115 °C for 9 h and three other portions of $RuH(CO)(PPh_3)_3$ (10 mg) were added every 2 h during that time. After completion of the isomerization (monitored by TLC), Grubbs (II) catalyst (32 mg, 0.037 mmol) was added in one portion to the same flask at 115 °C. The reaction was then stirred at 115 °C for 2 h (monitored by MS). After cooling to rt, the reaction was concentrated under vacuum. The crude material was purified by flash chromatography on silica gel (dry pack) eluting with 65% EtOAc in hexane to afford **42** as a colorless oil (251 mg, 93%). $[\alpha]_D^{20}$ +552.8 (*c* 2.2, PhH); R_f=0.3 (hexanes–EtOAc, 1:2); IR (neat): 3057, 2964, 2873, 1618, 1437, 1211, 1120, 1043, 930, 773, 725, 701, 680 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ=7.94–7.71 (m, 4H), 7.09–6.84 (m, 9H), 6.55 (d, J=7.40 Hz, 1H), 6.20–6.12 (m, 1H), 5.59 (dd, J=7.4, 1.8 Hz, 1H), 4.80

(q_{app}, J=7.1 Hz, 1H), 2.12–1.87 (m, 2H), 0.78 (t, J=7.5 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ=132.8 (d, J_{C-P}=127.0 Hz), 132.8 (d, J_{C-P}=9.7 Hz, 2 C), 132.8 (d, J_{C-P}=9.7 Hz, 2 C), 132.0 (d, J_{C-P}=2.1 Hz, 2 C), 131.9 (d, J_{C-P}=124.2 Hz), 131.5, 129.2 (d, J_{C-P}=5.9 Hz), 128.7 (d, J_{C-P}=12.5 Hz, 2 C), 128.3, 127.7, 126.6 (d, J_{C-P}=16.6 Hz, 2 C), 124.4, 107.4 (d, J_{C-P}=8.1 Hz), 58.3 (d, J_{C-P}=3.3 Hz), 28.5, 10.4; ^{31}P NMR (162 MHz, C_6D_6): δ=25.4; HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{23}H_{23}NOP$: 360.15118; found: 360.15264.

4.2.25. (1S)-2-(Diphenylphosphoryl)-1-ethyl-4-methylene-1,2,3,4-tetrahydroisoquinoline (**43**)

Compound **35** (137 mg, 0.27 mmol), $Pd_2(dba)_3$ (12.5 mg, 0.014 mmol), (±)-BINAP (16.8 mg, 0.027 mmol), and K_2CO_3 (75 mg, 0.54 mmol) were mixed together in dry dimethylacetamide (6 mL). The mixture was then heated to 90 °C and stirred for 17 h. The reaction was then allowed to cool to rt, diluted with Et_2O (12 mL) and distilled H_2O (12 mL), and HCl (10%) was added. The organic layer was separated and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4. Concentration under vacuum gave the crude material, which was purified by flash chromatography on silica gel eluting with 90% EtOAc in hexane to afford **43** as an air sensitive colorless oil (60 mg, 60%). $[\alpha]_D^{20}$ −69.5 (*c* 3.4, PhH); R_f=0.3 (hexanes–EtOAc, 1:9); IR (neat): 3057, 2965, 1438, 1203, 1120, 1107, 1058, 754, 724, 699, 630 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ=8.05–7.96 (m, 2H), 7.94–7.86 (m, 2H), 7.53 (d, J=7.8 Hz, 1H), 7.08–6.90 (m, 8H), 6.55 (dd, J=7.5, 0.8 Hz, 1H), 5.38 (s, 1H), 4.47 (s, 1H), 4.34 (q_{app}, J=6.5 Hz, 1H), 4.06–3.90 (m, 2H), 1.92 (m, 1H), 1.59–1.44 (m, 1H), 1.02 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ=139.2 (d, J_{C-P}=6.0 Hz), 138.3 (d, J_{C-P}=5.2 Hz), 133.4 (d, J_{C-P}=129.4 Hz), 133.1 (d, J_{C-P}=9.2 Hz, 2 C), 133.0 (d, J_{C-P}=9.3 Hz, 2 C), 133.2 (d, J_{C-P}=127.0 Hz), 132.0, 131.5 (t_{app}, J_{C-P}=2.1 Hz, 2 C), 128.5 (d, J_{C-P}=12.3 Hz, 2 C), 128.5 (d, J_{C-P}=12.3 Hz, 2 C), 127.3, 127.0, 124.5, 107.8, 58.4 (d, J_{C-P}=2.4 Hz), 44.3 (d, J_{C-P}=3.4 Hz), 28.6 (d, J_{C-P}=1.5 Hz), 12.0; ^{31}P NMR (162 MHz, C_6D_6): δ=26.6; HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{24}H_{25}NOP$: 374.15955; found: 374.16693.

4.2.26. General procedure for the hydrogenation reaction

Compound **42**/**43** (118/43 mg, 0.33/0.11 mmol), PtO_2 (30/12 mg, 0.4 equiv), and anhydrous AcOH/MeOH (3/1 mL) were mixed. The reaction was stirred under H_2 pressure (400 psi/1 atm) for 24 h at rt. H_2 was then evacuated and the reaction was filtered through a pad of Celite®. For **32**, the filtrate was diluted with CH_2Cl_2 and transferred to a separatory funnel. The organic layer was washed with distilled H_2O (10 mL) and dried over Na_2SO_4. Concentration under vacuum gave the crude material, which was purified by flash chromatography on silica gel to afford the tetrahydroisoquinoline as a colorless oil.

4.2.27. (1S)-2-(Diphenylphosphoryl)-1-ethyl-1,2,3,4-tetrahydroisoquinoline (**32**)

Yield: 76.3 mg (64%); elution with EtOAc–hexane (1.5:1) then 100% EtOAc; $[\alpha]_D^{20}$ −14.6 (*c* 4.7, MeOH); R_f=0.3 (EtOAc); IR (neat): 3056, 2929, 2872, 1734, 1437, 1197, 1117, 1104, 1061, 933, 755, 723, 696 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ=8.05–7.93 (m, 4H), 7.09–6.86 (m, 9H), 6.59 (d, J=7.6 Hz, 1H), 4.37–4.26 (m, 1H), 3.36–3.22 (m, 1H), 3.21–3.07 (m, 1H), 2.98–2.84 (m, 1H), 2.15 (dd, J=16.7, 3.7 Hz, 1H), 1.96–1.82 (m, 1H), 1.62–1.48 (m, 1H), 0.99 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ=139.2 (d, J_{C-P}=5.0 Hz), 134.1, 134.0 (d, J_{C-P}=128.6 Hz), 133.6 (d, J_{C-P}=127.5 Hz), 133.5 (d, J_{C-P}=8.9 Hz, 2 C), 133.3 (d, J_{C-P}=9.0 Hz, 2 C), 131.9 (d, J_{C-P}=2.6 Hz), 131.8 (d, J_{C-P}=2.6 Hz), 129.7, 129.0 (d, J_{C-P}=12.2 Hz, 2 C), 128.9 (d, J_{C-P}=12.3 Hz, 2 C), 127.2, 126.7, 125.8, 57.1 (d, J_{C-P}=2.2 Hz), 37.6 (d, J_{C-P}=2.3 Hz), 30.4 (d, J_{C-P}=2.8 Hz), 28.4 (d, J_{C-P}=3.6 Hz), 12.1; ^{31}P NMR (162 MHz, C_6D_6): δ=26.3; HRMS-ESI: m/z $[M+Na]^+$ calcd for $C_{23}H_{24}NNaOP$: 384.14877; found: 384.14847.

4.2.28. (1S)-2-(Diphenylphosphoryl)-1-ethyl-4-methyl-1,2,3,4-tetrahydroisoquinoline (**33**)

Yield: 32.4 mg (75%), isolated as a 6:1 mixture; elution with EtOAc–hexane (4:1) then (9:1); R_f=0.36 (hexanes–EtOAc, 1:9). (*) stands for the minor isomer; IR (neat): 3056, 2963, 2929, 2873, 2217, 1438, 1197, 1119, 1023, 931, 724, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.92–7.78 (m, 4H), 7.55–7.36 (m, 6H), 7.33–7.25 (m, 2 H, H*), 7.24–7.15 (m, 2H), 7.11 (td, J=7.2, 1.7 Hz, 1H), 6.90 (d, J=7.2 Hz, 1H), 6.86 (d, J=7.2 Hz, 1H*), 4.26 (m, 1H), 4.14 (m, 1H*), 3.63 (ddd, J=12.6, 6.4, 5.1 Hz, 1H), 3.46–3.36 (m, 1H*), 3.13–2.97 (m, 1H, H*), 2.94–2.84 (m, 1H), 2.16–1.88 (m, 1H, H*), 1.88–1.66 (m, 1H, H*), 1.18 (d, J=7.1 Hz, 3H), 1.15 (d, J=7.1 Hz, 3H*), 0.97 (t, J=7.5 Hz, 3H*), 0.81 (t, J=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=139.2 (d, J=1.0 Hz), 138.7 (C*), 138.2 (d, J=4.9 Hz, C*), 137.1 (d, J=6.6 Hz), 132.7 (d, J=9.1 Hz), 132.6 (d, J=9.3 Hz), 132.4 (C*), 132.3 (C*), 131.7 (d, J=2.6 Hz), 131.5 (d, J=2.7 Hz), 132.2 (d, J=129.9 Hz, C*), 132.1 (d, J=129.0 Hz), 131.0, 128.5 (d, J=12.4 Hz), 128.2 (d, J=12.6 Hz), 128.4 (d, J=12.4 Hz, C*), 128.2 (C*), 128.1, 127.5 (C*), 127.0, 126.8, 126.7 (C*), 125.3, 57.5 (d, J=2.7 Hz), 57.3 (d, J=2.4 Hz, C*), 45.1 (d, J=1.8 Hz), 44.7 (d, J=1.9 Hz, C*), 31.8 (d, J=5.2 Hz), 31.2 (d, J=3.3 Hz, C*), 30.6 (d, J=1.5 Hz), 30.0 (d, J=2.8 Hz, C*), 21.9, 18.6 (C*), 11.8 (C*), 11.6; ^{31}P NMR (162 MHz, $CDCl_3$): δ=28.7, 28.3 (P*); HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{24}H_{27}NOP$: 376.18248; found: 376.18217.

Acknowledgements

This work was supported by the National Science and Engineering Research of Canada (NSERC) and the Université de Montréal. I.B. thanks the Université de Montréal for a postgraduate fellowship.

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