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N-Pyridylmethylephedrine derivatives in the catalytic asymmetric addition of diethylzinc to aldehydes and diphenylphosphinoylimines

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ABSTRACT

N-Pyridylmethyl-substituted *Ephedra* derivatives were synthesized by either direct alkylation or reductive alkylation of (1*R*,2*S*)-norephedrine, (1*S*,2*S*)-pseudo norephedrine, and (1*R*,2*S*)-ephedrine. These derivatives were then employed in asymmetric addition reactions with diethylzinc and aldehydes and diphenylphosphinoylimines. The use of the diastereomers from the *Ephedra* family allowed for a systematic evaluation of the contribution of the *N*-pyridylmethyl.

1. Introduction

Since the pioneering efforts of Oguni and Omi in 1984 in the development of the catalytic asymmetric addition of diorganozinc compounds to aldehydes, there have been many research groups that have explored the preparation and application of structurally diverse ligands.[1,2] Among the ligands that have shown great promise in this field, the *Ephedra* alkaloids ephedrine and norephedrine have been remarkably successful as chiral, non-racemic templates for building a diverse array of ligands (Fig. 1). Soai et al.[2b,3] were instrumental in demonstrating the effectiveness of the *Ephedra* alkaloids by the synthesis and application of a variety of symmetrically substituted *N*,*N*-dialkylnorephedrine derivatives, for example, **1a**–**c**. Mono *N*-alkylnorephedrine derivatives **2a**–**c** have also been prepared and studied,[4,5] although the *N*,*N*-dialkyl derivatives are usually more effective in generating higher enantiomeric ratios when applied in the catalytic asymmetric addition of diorganozinc reagents to carbonyl compounds. Of particular interest were the N,N-disubstituted ephedrine-derived systems, such as **3a**–**c**, where the two *N*-alkyl substituents are of different constitutions, one being a methyl group and the other being a benzyl or substituted benzyl moiety. Despite the dissymmetry of the substituents, these ligands still provide very good enantioselectivities.[6–9]

In the context of these substituted *Ephedra* compounds, Wu et al.[10] have demonstrated that the introduction of a pyridylmethyl substituent, a group that is effectively isosteric with the benzyl substituent, could have a detrimental effect on the enantiomeric ratio observed for the asymmetric addition of diethylzinc to aldehydes (Scheme 1, cf. catalysis with **4**[5] and **5**). In contrast, the use of a highly substituted β-amino alcohol template derived from L-valine demonstrated that the *N*-pyridylmethyl substituent enhanced the level of enantioselection of the reaction over that of the *N*-benzyl substituent (cf. catalysis with **6** and **7**). Wu et al. speculated that the level of substitution on the β-amino alcohol framework was responsible for the high enantioselectivity observed with the application of ligand **7**. It was also proposed that the *N*-pyridylmethyl group only had a limited supporting role in the overall process.[10] There is the possibility that the *N*-pyridylmethyl ligand is more involved in the overall catalysis than originally proposed. Herein, we report on our efforts to study the impact of the *N*-pyridylmethyl group in *Ephedra* ligands in the catalytic asymmetric addition of diethylzinc to aldehydes and the ligand promoted addition of diethylzinc to *N*-(*P*,*P*-diphenylphosphinoyl) imines.

2. Results and discussion

(1*R*,2*S*)-Norephedrine **10** and (1*S*,2*S*)-pseudonorephedrine **11** were reductively alkylated by the reaction with either benzaldehyde, pyridine-2-carboxaldehyde, 5-methylpyridine carboxaldehdye, or quinoline-2-carboxaldehyde followed by treatment with sodium borohydride to afford derivatives **12**–**18** (Scheme 2). These compounds were used as ligands in the catalytic asymmetric addition of diethylzinc to benzaldehyde as a test reaction (Table 1). Ligand **12** is a known compound that has been employed in the asymmetric addition reaction.[5] This ligand is described here for the sake of comparison. The comparative product enantioselectivities generated by ligands **12** and **13** [**12** (84.5:15.5 favoring the (*R*)-enantiomer); **13** (45:55 favoring the (*S*)-enantiomer)] illustrated the different capacity for asymmetric induction exhibited by these diastereomeric derivatives. The opposite configurations observed in the products are believed to be due to the change in configuration at the benzylic position.

Interestingly, when the *N*-benzyl substituent was replaced with an *N*-pyridylmethyl group to afford derivatives **5** and **14**,

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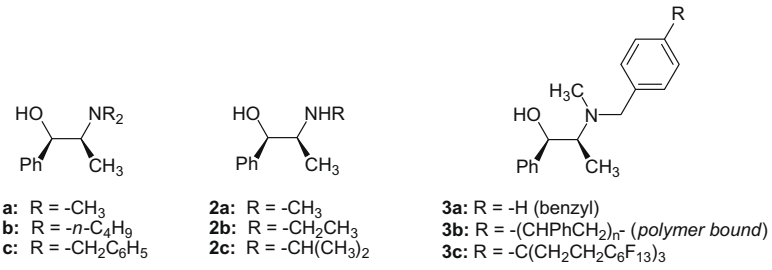
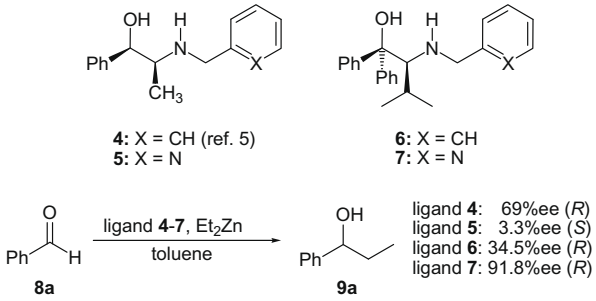


1a: R = -CH_3
1b: R = -*n*-C_4H_9
1c: R = -$CH_2C_6H_5$

2a: R = -CH_3
2b: R = -CH_2CH_3
2c: R = -$CH(CH_3)_2$

3a: R = -H (benzyl)
3b: R = -$(CHPhCH_2)_n$- (*polymer bound*)
3c: R = -$C(CH_2CH_2C_6F_{13})_3$

Figure 1. *Ephedra* derived ligands for asymmetric synthesis.



4: X = CH (ref. 5)
5: X = N

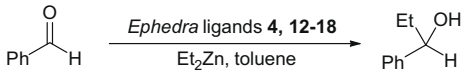
6: X = CH
7: X = N

Scheme 1. *N*-Pyridyl ligands and asymmetric addition.

the diastereoselectivities of the reaction underwent a drastic change. The *Ephedra*-based ligands **5** and **14** afforded the product alcohol in very low enantioselectivies, and in each case, the same (*S*)-configuration was obtained. The *N*-benzyl analogue of **5**, that is, **12**, afforded the (*R*)-configured product as the dominant enantiomer in the asymmetric addition process. This change in configuration suggested that the presence of the *N*-pyridylmethyl substituent is indeed involved in a significant way which diminishes the impact of the benzylic position on the *Ephedra* ligand. Mechanistically, it is proposed that there are equilibria involving multiple species that are capable of yielding the addition product either through coordination in the commonly accepted transition state model[11] **TS-1** or in a transition state that involves the *N*-methylpyridyl ligand **TS-2** (Fig. 2). As depicted in **TS-2**, the interaction with the nitrogen of the pyridyl ring with diethylzinc leads to a transition state in which an eight-membered ring with significant flexibility forms.

The use of *N*-pyridylmethyl derivatives **15** and **16** yielded marginally improved enantioselectivities in the observed products.

Table 1
Catalytic asymmetric addition of diethylzinc with ligands **4** and **12**–**18**

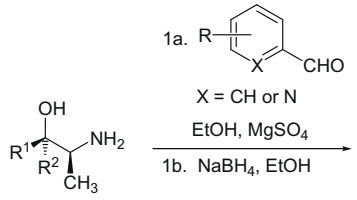


Entry	Ligand[a]	Enantiomeric ratio[b]	% ee[c]
1	**12**	84.5 (*R*):15.5 (*S*)	69 (*R*)
2	**13**	45.0 (*R*):55.0 (*S*)	10 (*S*)
3	**5**[10]	48.4 (*R*):51.6 (*S*)	3.3 (*S*)
4	**14**	47.9 (*R*):52.1 (*S*)	4.2 (*S*)
5	**15**	42.9 (*R*):57.1 (*S*)	14.3 (*S*)
6	**16**	34.3 (*R*):65.7 (*S*)	31.5 (*S*)
7	**17**	62.3 (*R*):37.7 (*S*)	24.6 (*R*)
8	**18**	59.5 (*R*):40.5 (*S*)	19.0 (*R*)

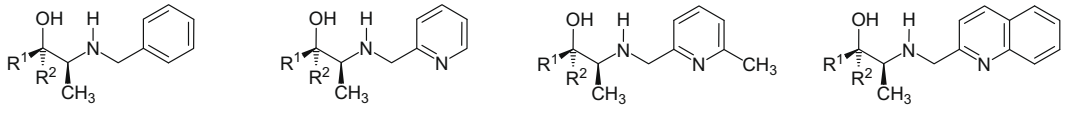
[a] All reactions reached completion as determined by ^{1}H NMR spectroscopy.
[b] Enantiomeric ratios were determined by chiral stationary phase HPLC.
[c] Absolute configuration was determined by comparison of HPLC data with the literature values (see Ref. 3).

Presumably, the presence of the α-methyl ring substituent diminishes the ability of the pyridyl nitrogen to coordinate to the diethylzinc thereby allowing the **TS-1** to make a greater contribution to the stereochemical outcome of the reaction. Finally, the use of the *N*-quinolylmethyl derivatives **17** and **18** afforded the (*R*)-enantiomer as the dominant product. This would suggest that the *N*-quinolylmethyl substituent is even more efficient in diminishing the contribution of the alternate coordinating form **TS-2**.

The collected results from the use of *Ephedra* ligands **5** and **12**–**19** clearly suggest that the introduction of an additional mode of coordination can be detrimental to obtaining good levels of enantioselection in the catalytic asymmetric addition of diethylzinc to



10: R^1 = -Ph; R^2 = -H
11: R^1 = -H; R^2 = -Ph



12: R^1 = -Ph; R^2 = -H (ref. 5)
13: R^1 = -H; R^2 = -Ph (81%)

5: R^1 = -Ph; R^2 = -H (ref. 10)
14: R^1 = -H; R^2 = -Ph (79%)

15: R^1 = -Ph; R^2 = -H (82%)
16: R^1 = -H; R^2 = -Ph (66%)

17: R^1 = -Ph; R^2 = -H (84%)
18: R^1 = -H; R^2 = -Ph (63%)

Scheme 2. Ligand synthesis.

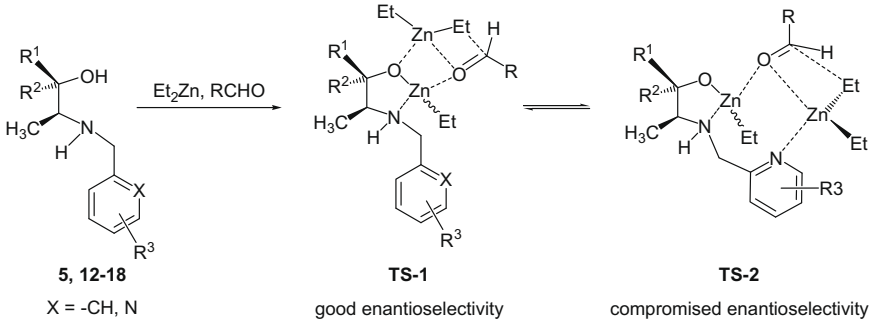


Figure 2. Proposed transition states.

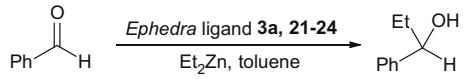
benzaldehyde. There was also an interest in determining if the use of β-tertiary amino alcohols derived from (1*R*,2*S*)-ephedrine **19** and (1*S*,2*S*)-pseudoephedrine **20** might offer improved enantioselection in the asymmetric process and provide greater insight into the contribution of the *N*-pyridylmethyl group. To this end, **19** and **20** were alkylated with either benzyl bromide or with α-bromomethylpyridinium hydrobromide to afford ligands **3a** and **21**–**24** (Scheme 3). For the sake of carrying out a more complete structural comparison, (1*R*,2*S*)-norephedrine **10** was reacted with two equivalents of benzyl bromide to afford the known *N*,*N*-dibenzylnorephedrine derivative **24**[3a,12] in 48% yield after chromatography. With these ligands in hand, we pursued a preliminary study on the asymmetric addition reactions with diethylzinc and benzaldehyde (Table 2).

In contrast to the secondary β-amino alcohols derived from (1*R*,2*S*)-norephedrine, the tertiary systems, with the exception of ligands **23** and **24**, exhibited significantly higher enantiomeric ratios. The ephedrine-based ligand **3a** yielded an enantiomeric ratio of 88:12 (76% ee) favoring the (*R*)-enantiomer. The *N*-pyridylmethyl ephedrine-based analogue **21** afforded an enantiomeric ratio of 84.5:15.5 (69% ee) favoring the (*R*)-enantiomer as well. This was a considerable change from the results obtained from the use of the *N*-benzyl- and *N*-pyridylmethylnorephedrine derivatives **12** and **5** which yielded the addition products in ratios of 84.5 (*R*):15.5 (*S*) (69% ee) and 48.4 (*R*):51.6 (*S*) (3.3% ee), respectively. In the case of the norephedrine ligand **5** where the nitrogen is secondary, it is presumed that the *N*-pyridylmethyl can readily coordinate with diethylzinc, leading to lower selectivity.

The pseudoephedrine ligands **22** and **23** predominantly afforded the (*S*)-enantiomer of the addition product when employed in the asymmetric addition reaction. The *N*-benzylpseudoephedrine derivative **22** had a moderate enantiomeric ratio of 20:80 (60% ee) favoring the (*S*)-enantiomer. However, the corresponding *N*-pyridylmethyl derivative **23** yielded the product with an enantioselectivity of 45:55 (10% ee) favoring the (*S*)-enantiomer.

For the sake of further comparison, the *N*,*N*-dibenzylnorephedrine ligand **24** was also employed in the asymmetric reaction. It was determined that the system was not effective in inducing asymmetry [53:47 (6% ee) favoring the (*R*)-enantiomer] and that reduction of the aldehyde substrate was a major reaction pathway (>40%). The presence of the reduction product is suggestive of the failure of the catalyst system to properly interact with the substrate. With these results in hand, a tentative model for the catalytic asymmetric addition of diethylzinc to these ligands was developed (Fig. 3).

Table 2
Catalytic asymmetric addition of diethylzinc with **3a** and **21**–**24**

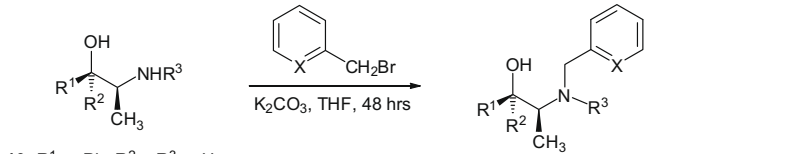


8a **9a**

Entry	Ligand[a]	Enantiomeric ratio[b]	% ee[c]
1	**3a**[d]	88.0 (*R*):12.0 (*S*)	76 (*R*)
2	**21**	84.5 (*R*):15.5 (*S*)	69 (*R*)
3	**22**	20.0 (*R*):80.0 (*S*)	60 (*S*)
4	**23**	45.0 (*R*):55.0 (*S*)	10 (*S*)
5	**24**	53.0 (*R*):47.0 (*S*)	6 (*R*)

[a] All reactions reached completion as determined by ^{1}H NMR spectroscopy.
[b] Enantiomeric ratio was determined by chiral stationary phase HPLC.
[c] Absolute configuration was determined by comparison of HPLC data with the literature values (see Ref. 3).
[d] See Ref. 6.

The enantioselectivity was moderate (60% ee) in the case of the ephedrine derived **3a**, but this was in contrast to the very low enantioselectivity observed for the related *N*,*N*-dibenzylnorephedrine ligand **24**. This ligand differed from **3a** only by the substitution at nitrogen (–CH_2Ph vs –CH_3) but afforded a significantly lower enantiomeric excess when used in the asymmetric addition process. The origin of the lower enantioselectivity is believed to be rooted in the presence of transition states of an acyclic nature (TS–Et_2Zn–**24B**) that diminish the capacity of the norephedrine scaffold to influence the stereochemical outcome of the reaction (Fig. 3).



10: R^1 = -Ph; R^2 = R^3 = -H
19: R^1 = -Ph; R^2 = -H; R^3 = $-CH_3$
20: R^1 = -H; R^2 = -Ph; R^3 = $-CH_3$

3a: R^1 = -Ph; R^2 = -H; R^3 = $-CH_3$; X = -H (82%)
21: R^1 = -Ph; R^2 = -H; R^3 = $-CH_3$; X = -N (51%)
22: R^1 = -H; R^2 = -Ph; R^3 = $-CH_3$; X = -H (78%)
23: R^1 = -H; R^2 = -Ph; R^3 = $-CH_3$; X = -N (41%)
24: R^1 = -Ph; R^2 = -H; R^3 = $-CH_2$Ph; X = -H (48%)

Scheme 3. Ligand synthesis.

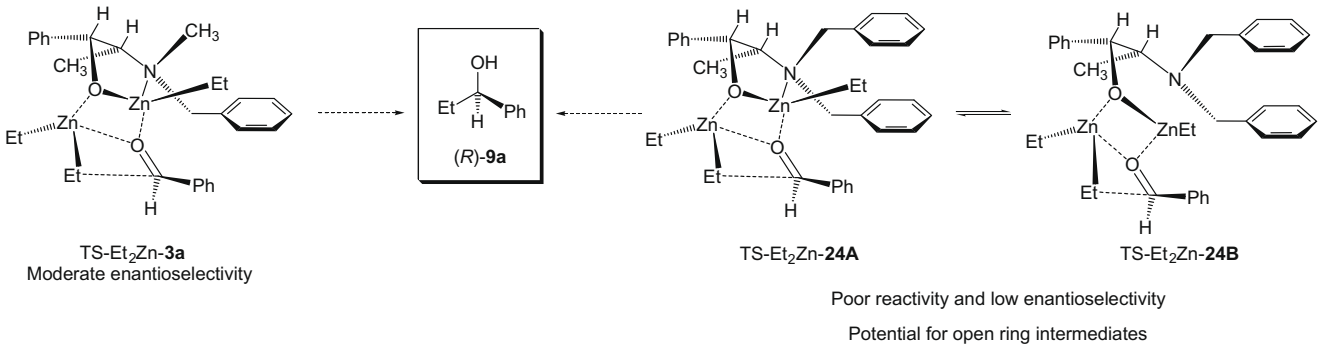


Figure 3. Proposed transition states for the asymmetric addition with **3a** and **24**.

There was an interest in a computational evaluation of the potential intermediates and transition states that might be involved in the overall process. The use of a Semi-empirical PM3 methodological approach was pursued for the study of the interaction of the *Ephedra* ligand **3a** with diethylzinc and benzaldehyde to address the concern of the facial preference (*Re*- or *Si*-face) for the addition reaction (Fig. 4). The transition state shown in Figure 4 correctly predicted that the stereochemical formation of the (*R*)-enantiomer of the addition product would require less energy to form than the (*S*)-enantiomer where the aldehyde would be arranged in the opposite orientation (ΔH_f (*R*-ent) = −143.2 kcal/mol, ΔH_f (*S*-ent) = −138.2 kcal/mol).

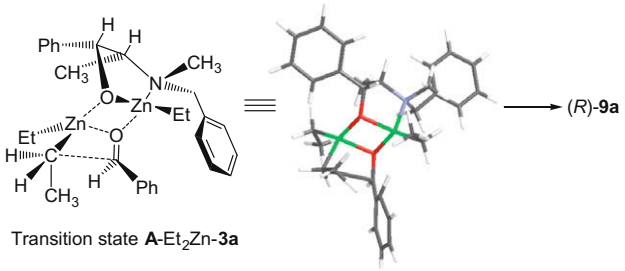
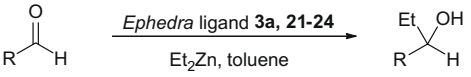


Figure 4. Putative transition state for ligand **3a** and Et_2Zn (PM3 semi-empirical calculations: red = oxygen; blue = nitrogen; and green = zinc).

Based on the fact that ligand **3a** catalyzed the asymmetric addition of diethylzinc to benzaldehyde with a ratio of 88.0 (*R*):12.0 (*S*) and that ligand **21** catalyzed the same reaction to a similar degree, it is possible that both ligands might be undergoing similar reaction pathways. The slightly lower enantioselectivity observed in the application of **21** might be due to the competitive pathways wherein the pyridyl nitrogen becomes an active participant.

At this stage, the more successful ligands derived from (1*R*,2*S*)-norephedrine and (1*R*,2*S*)-ephedrine were reacted with a variety of aldehyde substrates to determine if the reactivity trends would remain the same (Table 3). Thus, the application of the *N*-benzylephedrine in the asymmetric addition reaction afforded the product in an enantiomeric ratio of 91:9 (82% ee) with the (*R*)-configuration dominating. More importantly, we learnt that the *N*-pyridylmethylephedrine ligand **21** yielded a comparable level of enantioselection when employed in the addition reaction [87.7:12.2 favoring the (*R*)-enantiomer]. This suggested that the *N*-pyridylmethyl substituent did not have a detrimental effect on the reaction as was the case with the *N*-pyridylmethylnorephedrine ligand **5** (Scheme 1). The application of the *N*,*N*-dibenzylnorephedrine ligand **21** afforded the target product in addition to a significant reduction of the 2-naphthaldehyde substrate. The asymmetric addition reaction with *trans*-cinnamaldehyde exhibited a more pronounced difference in the enantioselection when comparing the products of the reactions employing **3a** and **21** as catalysts.

Table 3
Catalytic asymmetric 1,2-addition of diethylzinc with **3a** and **21**–**24**



8b: R = -2-(C_8H_7)
8c: R = -CH=CHPh
8d: R = -CH_2OCH_2Ph

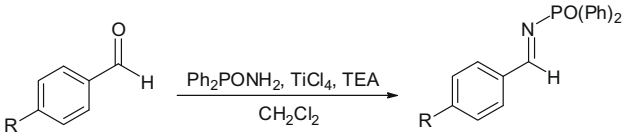
9b: R = -2-(C_8H_7)
9c: R = -CH=CHPh
9d: R = -CH_2OCH_2Ph

Entry	RCHO	Ligand	Yield[a]	Enantiomeric ratio (*R*:*S*), (ee)	Config.[d]
1	2-$C_{10}H_7$–	**3a**	88	91.1:8.9 (82)[b]	(*R*)
2	2-$C_{10}H_7$–	**21**	79	87.7:12.2 (76)[b]	(*R*)
3	2-$C_{10}H_7$–	**24**	82	Reduction[c]	nd[e]
4	*trans*-PhCH=CH–	**3a**	82	84.9:15.1 (70)[b]	(*R*)
5	*trans*-PhCH=CH–	**21**	60	74.4:25.6 (49)[b]	(*R*)
6	*trans*-PhCH=CH–	**24**	72	60.8:39.2 (22)[b]	(*R*)
7	$BnOCH_2$–	**3a**	73	52.9:47.1 (5)	nd[e]
8	$BnOCH_2$–	**21**	96	39.6:60.4 (21)	nd[e]
9	$BnOCH_2$–	**24**	35	46.9:53.1 (6)	nd[e]

[a] Isolated yield after flash chromatography.
[b] Enantiomeric ratio was determined by CSP HPLC with a chiralcel OD column.
[c] ^1H NMR spectrum indicated the formation of 2-naphthylmethyl alcohol.
[d] The absolute configuration was determined by comparison with order of elution values from the literature (see Ref. 3).
[e] The absolute configuration was not determined.

This may be due to the difference in the steric demands of the *trans*-cinnamaldehyde and 2-naphthaldehyde. Finally, the use of the benzyloxyacetaldehyde in the asymmetric process afforded poor enantioselectivities with all ligands presumably due to the coordination of the aldehyde with diethylzinc to create multiple species with stereochemically divergent pathways. Surprisingly, the *N*-pyridylmethyl ligand **21** gave the best result; the origin for this result is unknown but speculation is focused on the *N*-pyridylmethyl substituent.

These collected results proved to be interesting but there was also an interest in employing these systems in the asymmetric addition of diethylzinc to *N*-(*P*,*P*-diphenylphosphinoyl)imines[13] to further attempt to understand the contribution of the *N*-pyridylmethyl group. This work began with the synthesis of a series of phosphinoylimines using the method of Jennings and Lovely (Scheme 4).[14] With the requisite imines **25a**–**d** in hand, the ephedrine-based ligands **3a**, **21**, and **24** were employed in the addition reaction (Table 4).

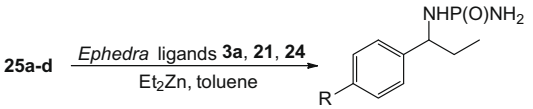


8a: R = -H
8b: R = -F
8c: R = -Cl
8d: R = -OMe

25a: R = -H (43%)
25b: R = -F (54%)
25c: R = -Cl (43%)
25d: R = -OMe (85%)

Scheme 4. Diphenylphoshinoylimine synthesis.

Table 4
Asymmetric 1,2-addition of diethylzinc to diphenylphosphinoylimines **25a**–**d**



26a-d

Entry	Imine	Ligand	Yield[a]	Enantiomeric ratio, (|*R*–*S*|)	Config.
1	**25a**	**3a**	92	94.2:5.8 (88)[b]	(*R*)
2	**25a**	**21**	68	45.3:54.7 (9)[b]	(*S*)
3	**25a**	**24**	67	74.4:25.7 (49)[b]	(*R*)
4	**25b**	**3a**	89	95.9:4.1 (92)[c]	(*R*)
5	**25b**	**21**	77	38.0:62.0 (24)[c]	(*S*)
6	**25b**	**24**	58	90.7:9.3 (81)[c]	(*R*)
7	**25c**	**3a**	46	95.0:5.0 (90)[c]	(*R*)
8	**25c**	**21**	48	44.9:55.2 (10)[c]	(*S*)
9	**25c**	**24**	67	86.3:13.7 (73)[c]	(*R*)
10	**25d**	**3a**	42	97.2:2.8 (94)[b]	(*R*)
11	**25d**	**21**	Inc.[d]	nd[e]	(*S*)
12	**25d**	**24**	48	96.5:3.5 (93)[b]	(*R*)

[a] Isolated Yield after flash chromatography.
[b] Enantiomeric excess was determined by CSP HPLC with a chiralcel AD column.
[c] Enantiomeric excess was determined by CSP HPLC (AS column).
[d] The absolute configuration was determined by comparison with order of elution values from the literature (see Ref. 3).
[e] The absolute configuration was not determined.

The *N*-benzylephedrine ligand **3a** performed well in these trial experiments as described in earlier literature and afforded products **26a**–**d** in very good enantiomeric excess.[6] In contrast, the addition of diethylzinc mediated by the *N*-pyridylmethyl ligand **21** to the phosphinoylimines yielded the corresponding amine products **26a**–**d** in very low enantiomeric excess. It is proposed that the two ligands, **3a** and **21**, potentially catalyze the addition reaction through dissimilar transition states (Fig. 5). The use of the PM3 Semi-empirical computational method suggested that

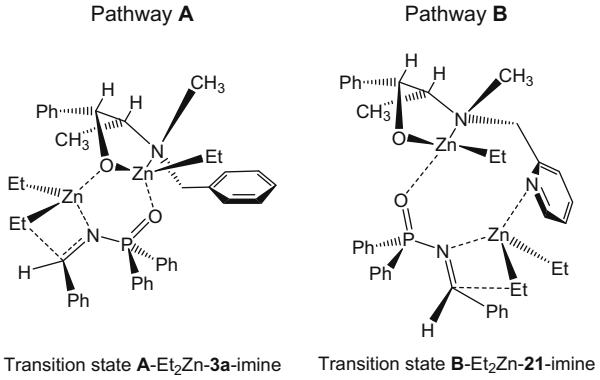


Figure 5. Putative transition states for ligand **3a** and **21** with Et_2Zn (PM3 semi-empirical calculations).

both pathways illustrated in Figure 5 were possible. This does not preclude the existence of other transition states not depicted here. The low enantiomeric excess observed from the use of **21** makes a reasonable determination of a proposed comprehensive mechanism not viable.

3. Conclusion

The ligands prepared in this work strongly suggest that the presence of the *N*-pyridylmethyl on the *Ephedra* scaffold leads to diminished levels of enantioselection in the asymmetric addition of diethylzinc to aldehydes. The effect is even more pronounced in the case of the asymmetric reaction with diethylzinc and diphenylphosphinoylimines. It is proposed that the nitrogen of the *N*-pyridylmethyl group allows for alternate transition states that compromise the capacity of the *Ephedra* component of the ligand to transmit asymmetry.

4. Experimental section

4.1. General remarks

Diethylzinc solutions (1 M in hexanes), dry toluene, and (1*R*,2*S*) norephedrine were purchased from Sigma–Aldrich. Pyridine-2-carboxaldehyde, 6-methyl pyridine-2-carboxaldehyde, and quinoline-2-carboxaldehyde were purchased from Alfa Aesar. (1*S*,2*S*)-Pseudonorephedrine was synthesized by established procedures. Calculations of intermediate and transition state optimized geometries and energies were carried out by the Semi-empirical PM3 methodology using the Spartan'02 for Linux molecular modeling software package. Optimized structures were confirmed as minima or transition states by vibrational frequency analysis. All reactions were performed under an inert nitrogen atmosphere. All NMR spectra were collected using either a 500 MHz Bruker NMR (125 MHz for $^{13}C\{^1H\}$ spectroscopy), 400 MHz Varian NMR (100 MHz for $^{13}C\{^1H\}$ spectroscopy) or 300 MHz Oxford NMR (75 MHz for $^{13}C\{^1H\}$ spectroscopy) spectrometer with all spectra recorded in $CDCl_3$ (δ = 77.0 ppm ^{13}C) and reported in parts per million (δ scale) with tetramethylsilane as an internal standard (δ = 0 ppm ^1H) and was used for ^1H and ^{13}C spectroscopy unless otherwise stated. On some ^1H NMR spectra, the OH and NH peaks on the spectrum were not observed due to broadening. Infrared data were acquired using a PerkinElmer Spectrum BX FT-IR spectrophotometer on KBr plates and reported in reciprocal centimeters (cm^{-1}). Optical rotation data were gathered on a Jasco P-2000 polarimeter operating at 589 nm in an 8 × 100 mm cylindrical cell. HPLC information was gathered on a Shimadzu HPLC SCL-10AVP instrument with a UV–vis detector operating at 254 nm. Melting points

were determined using a Laboratory Devices Mel-Temp apparatus and are uncorrected. Compound **5** was previously prepared by Wu et al.[10] Compounds **9a–c** and **12** were previously prepared by Parrott and Hitchcock.[5] Diphenylphosphinoylimines **25a**, **25c**, and **25d** have been prepared and characterized by Jennings and Lovely.[14] The amine products **26a**, **26c**, and **26d** have been prepared and characterized by Gong, Mi, et al.[15]

4.2. General procedure for alkylation

In a flame-dried, nitrogen-purged flask 1.0 g of (1*S*,2*S*)-pseudonorephedrine or (1*R*,2*S*)-norephedrine was dissolved in 20 mL of absolute ethanol. To this solution was added a portion of anhydrous $MgSO_4$ followed by the addition of 1.05 equiv of the aldehyde. The reaction mixture was allowed to react for 14–18 h at which time the reaction vessel was cooled in an ice bath and the Schiff's base was reduced with the addition of 1.5 equiv of $NaBH_4$. The subsequent reduction was allowed to progress for 2 h after which the reaction was quenched by the addition of a 1 M NaOH solution. The ethanol was removed under vacuum and the product was extracted with ethyl acetate and washed with brine.

4.2.1. (1*S*,2*S*)-2-(Benzylamino)-1-phenyl-1-propanol 13

The compound was obtained from the reductive alkylation of (1*S*,2*S*) pseudonorephedrine with benzaldehyde as white crystals in 81% yield after recrystallization with diethyl ether and hexanes. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (3H, d, J = 6.3 Hz), 2.76 (1H, dq, J = 6.3 Hz, J = 7.8 Hz), 3.67 (1H, d, J = 13.3 Hz), 3.88 (1H, d, J = 13.3 Hz), 4.18 (1H, d, J = 7.8 Hz), 7.23–7.35 (10H, m). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$, due to coincidental overlap, some peaks in the aromatic region are missing) δ 16.3, 51.0, 59.1, 77.5, 126.9, 127.0, 127.5, 128.0, 128.1, 139.9, 142.2. FT-IR (Nujol) 3100, 1600, 1584, 1041, 1025, 759, 698. Mp. 66–68 °C. $[\alpha]_D^{24} = +128.9$ (c 1, CH_2Cl_2). HRMS (M+H$^+$) calcd for $C_{16}H_{20}NO$: 242.1545, found: 242.1551.

4.2.2. (1*S*,2*S*)-1-Phenyl-2-(2-pyridylmethylamino)-1-propanol 14

The compound was obtained from the reductive alkylation of (1*S*,2*S*)-pseudonorephedrine with 2-pyridine carboxaldehyde as a light yellow oil in 79% yield after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, d, J = 6.6 Hz), 2.84 (1H, dq, J = 6.6 Hz, J = 8.2 Hz), 3.81 (1H, d, J = 14.3 Hz), 3.87 (1H, br s), 4.05 (1H, d, J = 14.3 Hz), 4.30 (1H, d, J = 8.2 Hz), 7.16 (1H, dd, J = 5.1 Hz, J = 7.4 Hz), 7.25–7.35 (6H, m), 7.63 (1H, t, J = 7.4 Hz, 8.49 (1H, d, J = 5.1 Hz). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 16.5, 52.0, 59.6, 77.6, 122.0, 122.2, 126.9, 127.5, 128.1, 136.5, 142.3, 148.9, 159.2. FT-IR (neat) 702, 757, 1045, 1149, 1592, 3298. $[\alpha]_D^{25} = +92.1$ (c 1, CH_2Cl_2). HRMS (M+1) calcd for $C_{15}H_{19}N_2O$: 243.1497, found: 243.1498.

4.2.3. (1*R*,2*S*)-2-((6-Methyl-2-pyridyl)methylamino)-1-phenyl-1-propanol 15

The compound was obtained from the reductive alkylation of (1*R*,2*S*)-norephedrine with 6-methyl-2-pyridinecarboxaldehyde as a light yellow oil in 82% yield after flash chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, d, J = 6.6 Hz), 2.55 (3H, s), 2.98 (1H, dq, J = 3.8, 6.6 Hz), 3.97 (1H, d, J = 14.6 Hz), 4.05 (1H, d, J = 14.6 Hz), 4.80 (1H, d, J = 3.8 Hz), 7.04 (1H, d, J = 7.7 Hz), 7.07 (1H, d, J = 7.7 Hz), 7.23–7.36 (5H, m), 7.54 (1H, t, J = 7.7 Hz). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 14.5, 24.2, 52.1, 58.6, 73.0, 118.9, 121.4, 125.9, 126.6, 127.7, 136.6, 141.6, 157.7, 158.7. FT-IR (neat) 3303, 3062, 1594, 1578, 1118, 1028, 749, 701. $[\alpha]_D^{25} = +12.8$ (c 1, CH_2Cl_2). HRMS (M+1) calcd for $C_{16}H_{21}N_2O$: 257.1654, found: 257.1645.

4.2.4. (1*S*,2*S*)-2-((6-Methyl-2-pyridyl)methylamino)-1-phenyl-1-propanol 16

The compound was obtained from the reductive alkylation of (1*S*,2*S*)-pseudonorephedrine with 6-methyl-2-pyridinecarboxaldehyde as a white solid in 66% yield after trituration with diethyl ether. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (3H, d, J = 6.6 Hz), 2.55 (3H, s), 2.82 (1H, dq, J = 6.6 Hz, J = 8.2 Hz), 3.84 (1H, d, J = 14.3 Hz), 4.02 (1H, d, J = 14.3 Hz), 4.55 (1H, d, J = 8.2 Hz), 7.03 (1H, d, J = 7.7 Hz), 7.08 (1H, d, J = 7.7 Hz), 7.25–7.36 (5H, m), 7.54 (1H, t, J = 7.7 Hz). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 16.6, 24.1, 51.8, 59.6, 77.6, 118.9, 121.3, 126.8, 127.3, 127.9, 136.6, 142.5, 157.6, 158.9. FT-IR (Nujol) 3070, 1593, 1578, 1226, 1045, 784, 767, 706. Mp 107–109 °C. $[\alpha]_D^{25} = +112.5$ (c 1, CH_2Cl_2). HRMS (M+1) calcd for $C_{16}H_{21}N_2O$: 257.1654, found: 257.1653.

4.2.5. (1*R*,2*S*)-1-Phenyl-2-(2-quinolylmethylamino)-1-propanol 17

The compound was obtained from the reductive alkylation of (1*R*,2*S*) norephedrine with quinoline-2-carboxaldehyde as a yellow solid in 84% yield after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, d, J = 6.3 Hz), 3.01 (1H, dq, J = 3.5 Hz, J = 6.3 Hz), 4.14 (1H, d, J = 15.6 Hz), 4.23 (1H, d, J = 15.6 Hz), 4.8 (1H, d, J = 3.5 Hz), 7.22 (1H, d, J = 7.0 Hz), 7.28–7.35 (6H, m), 7.48 (1H, t, J = 7.0 Hz), 7.66 (1H, dt, J = 7.0, 8.2 Hz), 7.75 (1H, d, J = 8.2 Hz), 8.05 (1H, d, J = 8.6 Hz) ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, due to coincidental overlap, some peaks in the aromatic region are missing) δ 14.5, 52.7, 59.0, 73.3, 120.2, 126.0, 126.1, 126.7, 127.4, 127.8, 128.6, 129.5, 136.5, 141.5, 147.3, 160.0. FT-IR (Nujol) 3100, 1617, 1598, 1267, 1152, 1083, 989, 830, 761, 696. Mp 87–89 °C. $[\alpha]_D^{25} + 34.9$ (c 1, CH_2Cl_2). HRMS (M+H)$^+$ calcd for $C_{19}H_{21}N_2O$: 293.1654, found: 293.1647.

4.2.6. (1*S*,2*S*)-1-Phenyl-2-(2-quinolylmethylamino)-1-propanol 18

The compound was obtained from the reductive alkylation of (1*S*,2*S*)-pseudonorephedrine with quinoline-2-carboxaldehyde as white crystals in 63% yield after trituration with diethyl ether. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (3H, d, J = 6.6 Hz), 2.89 (1H, dq, J = 6.6 Hz, J = 8.2 Hz), 4.08 (1H, d, J = 15.2 Hz), 4.23 (1H, d, J = 15.2 Hz), 4.33 (1H, d, J = 8.2 Hz), 7.24–7.38 (7H, m), 7.51 (1H, t, J = 7.0 Hz), 7.69 (1H, dt, J = 7.0 Hz, J = 8.6 Hz), 7.79 (1H, d, J = 7.8 Hz), 8.09 (1H, t, J = 8.6 Hz). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, due to coincidental overlap, some peaks in the aromatic region are missing) δ 17.0, 52.5, 60.0, 77.9, 120.3, 126.2, 126.9, 127.4, 127.5, 128.2, 128.7, 129.6, 136.6, 142.5, 147.4, 160.1. FT-IR (Nujol) 3060, 1604, 1222, 1045, 833, 742, 695. Mp 137–139 °C. $[\alpha]_D^{25} = +132.5$ (c 1, CH_2Cl_2). HRMS (M+1) calcd for $C_{19}H_{21}N_2O$: 293.1654, found: 293.1646.

4.2.7. (1*R*,2*S*)-2-(Methyl(2-pyridylmethyl)amino)-1-phenylpropan-1-ol 21

In a 250 mL round-bottomed flask were added (1*R*,2*S*)-ephedrine (2.0 g, 12 mmol), THF (40 mL), K_2CO_3 (5.00 g, 36.3 mmol), and 2-bromoethylpyridine.HBr (3.06 g, 12.1 mmol). The temperature of the reaction mixture was raised to reflux and was allowed to run overnight (18 h). The reaction mixture was cooled to room temperature. Next, NaOH (1 M, 100 mL) was added to the reaction mixture, after which THF was evaporated from the reaction mixture via rotary evaporation. The residue was extracted with NaOH solution (1 M, 50 mL × 2) and EtOAc (50 mL × 2). The organic layer was washed with brine (100 mL) and dried over $MgSO_4$. The solvent was evaporated via rotary evaporation. The resultant residue was purified by flash chromatography using hexanes/EtOAc (55:45) and triethylamine and the product was recovered as a colorless oil (51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (3H, d, J = 7.1 Hz), 2.28 (3H, s), 2.95 (1H, dq, J = 4.4 Hz, J = 7.1 Hz), 3.73 (1H, d, J = 14.8 Hz), 3.89 (1H, d, J = 14.8 Hz), 4.89 (1H, d, J = 4.4 Hz),

7.10–7.35 (7H, m), 7.58 (1H, dt, J = 6.1 Hz, J = 7.7 Hz), 8.46 (1H, d, J = 4.9 Hz). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 9.3, 39.1, 59.3, 64.1, 73.7, 121.6, 122.4, 126.0, 126.4, 127.6, 136.3, 143.4, 148.3, 160.0. FT-IR (neat) 3227, 1594, 1569, 1045, 159, 701. $[\alpha]_D^{25} = -40.9$ (c 1, CH_2Cl_2). HRMS (M+1) calcd for $C_{16}H_{21}N_2O$: 257.1654, found: 257.1665.

4.2.8. (1*S*,2*S*)-2-(Benzyl(methyl)amino)-1-phenyl-1-propanol 22

The compound was obtained from the alkylation of (1*S*,2*S*)-pseudoephedrine with benzyl bromide (1.1 equiv) dissolved in refluxing anhydrous THF and potassium carbonate (3 equiv) in 78% yield as a colorless oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (3H, d, J = 6.6 Hz), 2.21 (3H, s), 2.73 (1H, dq, J = 6.6 Hz, J = 9.7 Hz), 3.48 (1H, d, J = 12.9 Hz), 3.73 (1H, d, J = 12.9 Hz), 4.30 (1H, d, J = 9.7 Hz), 4.86 (1H, br s), 7.24–7.34 (10H, m). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, due to coincidental overlap, some peaks in the aromatic region are missing) δ 7.0, 35.4, 57.8, 64.6, 74.4, 127.0, 127.1, 127.4, 127.9, 128.2, 128.6, 138.4, 141.8. FT-IR (neat) 3334, 1601, 1585, 1093, 1024, 944, 759, 702. $[\alpha]_D^{23} = +110.7$ (c 1, CH_2Cl_2). HRMS (M+1) calcd for $C_{17}H_{22}NO$: 256.3627, found: 256.3633.

4.2.9. (1*S*,2*S*)-2-(Methyl(2-pyridylmethyl)amino)-1-phenyl-1-propanol 23

The compound was obtained from the alkylation of (1*S*,2*S*) pseudoephedrine with 2-(bromomethyl) pyridinium hydrobromide (1.1 equiv) dissolved in refluxing anhydrous THF and potassium carbonate (3 equiv) in 41% yield as a colorless oil after flash chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (3H, d, J = 6.6 Hz), 2.33 (3H, s), 2.77 (1H, dq, J = 6.6 Hz, J = 9.3 Hz), 3.65 (1H, d, J = 14.3 Hz), 3.93 (1H, d, J = 14.3 Hz), 4.34 (1H, d, J = 9.3 Hz), 7.19 (1H, dt, J = 4.9 Hz, J = 6.1 Hz), 7.25–7.35 (5H, m), 7.43 (1H, d, J = 7.7 Hz), 7.69 (1H, dt, J = 6.1 Hz, J = 7.7 Hz), 8.57 (1H, d, J = 4.9 Hz). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 7.5, 36.4, 58.8, 64.9, 74.7, 121.9, 122.5, 127.0, 127.3, 127.8, 136.3, 141.7, 148.9, 158.7. FT-IR (neat) 3357, 1590, 1570, 1073, 757, 702. $[\alpha]_D^{24} = +98.2$ (c 1, CH_2Cl_2). HRMS (M+1) calcd for $C_{16}H_{21}N_2O$: 257.1654, found: 257.1643.

4.2.10. (1*R*,2*S*)-2-(Dibenzylamino)-1-phenylpropan-1-ol 24

In a 250 mL round-bottomed flask were added (1*R*,2*S*)-norephedrine (2.00 g, 13.3 mmol), THF (45 mL), K_2CO_3 (7.3 g, 53.0 mmol), and benzyl bromide (3.20 mL,26.5 mmol). The temperature of the reaction mixture was raised to reflux and allowed to run overnight (18 h). The reaction mixture was cooled to room temperature. NaOH (100 mL) was added to the reaction mixture, after which THF was evaporated from the reaction mixture via rotary evaporation. The residue was extracted with aqueous NaOH solution (1 M, 50 mL × 2) and EtOAc (50 mL × 2). The organic layer was washed with brine (100 mL) and dried over $MgSO_4$. The solvent was evaporated via rotary evaporation. The resultant residue was purified by flash chromatography using hexanes/EtOAc (8:2). Colorless oil (48%). $[\alpha]_D^{24.4} = -40.4$ (c 1.38, $CHCl_3$). IR (Nujol): 3421, 1602, 747. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.10 (d, J = 6.7 Hz, 3H), 2.71 (br s, 1H), 3.08 (p, J = 6.6 Hz, 1H), 3.42 (d, J = 14.0 Hz, 2H), 3.64 (d, J = 14.0 Hz, 2H), 4.62 (d, J = 6.6 Hz, 1H), 7.10–7.22 (m, 15H). ^{13}C NMR (125 MHz, $CDCl_3$): 8.9, 54.5, 58.4, 75.6, 126.6, 126.7, 127.1, 127.8, 128.1, 128.6, 139.8, 143.2. ESI-HRMS calcd for $C_{23}H_{26}NO$ ($M+H^+$): 332.2014, found: 332.2002.

4.3. General procedure for the addition of diethylzinc to aldehyde

In a flame-dried, nitrogen-purged flask 0.33 mmol of the ligand was added and dissolved in 13 equiv of dry toluene. To this solution was added 3.0 equiv of diethylzinc followed by a 20–30 min reaction time after which 1.0 equiv of redistilled benzaldehyde was added and allowed to react for 18–20 h. The reaction was quenched with the dropwise addition of ammonium chloride. Extraction consisted of treatment of the reaction mixture with 30 mL of ethyl acetate and washing the organic portion with 1 M HCl and brine solutions followed by drying with anhydrous magnesium sulfate and solvent removal.

4.3.1. (*R*)-1-(Benzyloxy)butan-2-ol 9d

In a 100 mL round-bottomed flask were added the ligand (0.085 g, 0.332 mmol), toluene (17 mL), and Et_2Zn (10.0 mL, 10.0 mmol). The reaction mixture was stirred for 30 min at room temperature. To the reaction mixture was added benzyloxyacetaldehyde (0.5 g, 3.32 mmol). The reaction mixture was allowed to run for 18 h at room temperature and the reaction was quenched with HCl (1 M, 50 mL). The reaction mixture was extracted with EtOAc (50 mL). The organic layer was washed with brine (50 mL) and dried over $MgSO_4$. The solvent was evaporated via rotary evaporation and the product was purified by flash chromatography (hexanes/EtOAc, 99:1). Colorless oil (73%). $[\alpha]_D^{25.0} = +0.3$ (c 1.7, $CHCl_3$). IR (Nujol): 3435, 2964, 1098, 738, 698. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.91 (t, J = 7.5 Hz, 3H), 1.44 (p, J = 7.5, 2H), 3.03 (s, 1H), 3.29 (dd, J = 9.0 Hz, J = 2.7 Hz, 1H), 3.42 (dd, J = 9.0 Hz, J = 2.7 Hz, 1H), 3.65–3.70 (m, 1H), 4.48 (s, 2H), 7.28–7.30 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): 9.6, 25.9, 71.3, 72.9, 74.1, 127.3, 127.4, 128.0, 137.8. ESI-HRMS calcd for $C_{11}H_{16}O_2Na$ ($M+H^+$): 203.1048, found: 203.1046.

4.4. *N*-Benzylidene-*P*,*P*-diphenylphosphinic amide

In a 250 mL round-bottomed flask were added diphenylphosphinamide (3.00 g, 13.8 mmol) and dichloromethane (56 mL) and cooled to 0 °C. Then triethylamine (5.80 mL, 41.3 mmol), titanium tetrachloride (0.90 mL, 8.3 mmol), and benzaldehyde (1.40 mL, 13.8 mmol) were added. The reaction mixture was allowed to warm to ambient room temperature, stirred for 1.5 h, and then gravity filtered to remove titanium dioxide. The filtrate was collected and the solvent was removed by rotary evaporation. The residue was treated with diethyl ether (40 mL) and filtered to remove triethylammonium chloride. The filtrate from this process was collected and the solvent was removed. The resultant yellow residue was recrystallized using dichloromethane and hexanes.

4.4.1. *P*,*P*-Diphenylphosphinoylimine of 4-fluorobenzaldehyde 25b

White solid (54%). Mp: 110–112 °C. IR (Nujol): IR (Nujol): 1626, 1238, 729, 702 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.15–7.47 (m, 10H), 7.93–8.03 (m, 4H), 9.29 (d, J = 32 Hz, 1H). ESI-HRMS calcd for $C_{19}H_{15}NOPF$ ($M+H^+$): 324.0954, found: 324.0952.

4.5. Diethylzinc reaction with diphenylphosphinoylimines

In a 100 mL round-bottomed flask were placed toluene (13.0 mL), (1*R*,2*S*)-*N*-benzylephedrine (0.167 g, 0.66 mmol), *N*-benzylidene-*P*,*P*-diphenylphosphinic amide (0.20 g, 0.66 mmol), and diethylzinc (3.3 mL, 3.3 mmol). The reaction mixture was stirred for 48 h and then the reaction was quenched by the addition of an aqueous solution of ammonium chloride (50 mL). The organic layer was diluted with ethyl acetate (50 mL), washed with brine (50 mL), and dried ($MgSO_4$). The solvents were removed via rotary evaporation and the product was purified by flash chromatography (hexanes/EtOAc, 4:6). Colorless oil (53%).

4.5.1. (*R*)-*P*,*P*-Diphenyl-*N*-(1(4-fluorophenylbutyl)phosphinic amide 26b

Mp: 133–135 °C. $[\alpha]_D^{24.0} = +19.0$ (c 1.0, $CHCl_3$). IR (Nujol): 3161, 1224, 1056, 760, 722 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm):

0.79 (t, J = 7.4 Hz, 3H), 1.795–1.84 (m, 1H), 1.94–2.02 (m, 1H), 3.29 (t, 1H), 4.09 (m, 1H), 6.93–6.97 (m, 2H) 7.10–7.13 (m, 2H), 7.30–7.34 (m, 2H), 7.41–7.48 (m, 4H), 7.71–7.75 (m, 2H), 7.83–7.87 (m, 2H). ESI-HRMS calcd for $C_{21}H_{22}NOFP$ ($M+H^+$): 354.1423, found: 354.1432.

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