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Highly Efficient Asymmetric [3+2] Cycloaddition Promoted by Chiral Aziridine-Functionalized Organophosphorus Compounds

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Abstract: An asymmetric [3+2] cycloaddition of azomethine ylides generated from the corresponding imino esters to *trans*-β-nitrostyrene catalyzed by chiral aziridine-containing phosphines and phosphine oxides is described. Of the sixteen stereoisomers that could be formed as a result of the title reaction, three were formed, two of which were obtained in an enantiomerically enriched or pure form, and one in a racemic form. One of the products underwent epimerization under basic reaction conditions.

Keywords: asymmetric cycloaddition; aziridines; chiral ligands/catalysts; enantioselective synthesis

1. Introduction

Asymmetric synthesis including organocatalysis is still one of the most important and intensively researched methodologies for creating new carbon-carbon bonds [1]. Within the above methodology, new trends are emerging, including, for example, photocatalysis [2] and asymmetric synthesis using free radicals [3]. Among the very wide variety of asymmetric reactions, stereodifferentiating pericyclic reactions [4], including cycloadditions [5], deserve special mention. Among the products of asymmetric cycloaddition reactions, chiral systems containing a pyrrolidine ring often play a key role in biological and pharmacological research [6]. They may have a wide spectrum of activity - antibacterial, cytotoxic, antifungal, etc. [7]. Examples of substances containing a pyrrolidine motif available on the pharmaceutical market are Telaprevir which is an antiviral agent used in the treatment of chronic hepatitis C virus infection [8], ombitasvir also used as a strong inhibitor of SARS-CoV-2 [8], levetiracetam commonly used in the treatment of focal epilepsy [9], and sunitinib, i.e., a tyrosine kinase inhibitor used in the treatment of gastrointestinal stromal tumor and renal cell carcinoma [8].

Based on our experience in the field of asymmetric synthesis using heteroorganic ligands and organocatalysts [10], and taking into account the significant importance of chiral pyrrolidine systems in several areas of life and science [8], we decided to carry out an asymmetric [3+2] cycloaddition of azomethine ylides to nitrostyrene [6], using chiral, optically pure organophosphorus derivatives of aziridines as catalysts, namely phosphines [11], phosphine oxides [12], and aziridine-containing imines [13a,b]. The purpose of this decision was also to expand the scope of applicability of the chiral catalysts we had previously obtained.

2. Results and Discussion

2.1. Synthesis of the Chiral Catalysts and the Starting Materials

We started from the synthesis of the corresponding chiral catalysts **1-12** (Figure 1). Aziridine phosphines **1-4** were obtained from the corresponding phosphine oxides **5-8** via triethoxysilane and

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titanium(IV) isopropoxide [11]. Aziridine phosphine oxides **5-8** were synthesized starting from *o*-bromoanisole and diphenylphosphinic chloride as described previously [12]. In turn, imines **10-12** were obtained using previously described protocols [13a,b]. Finally, phosphine oxide bearing NH-aziridine subunit **9** was prepared from (S)-2-phenylaziridine and diphenylphosphinic chloride in the presence of sec-BuLi [14].

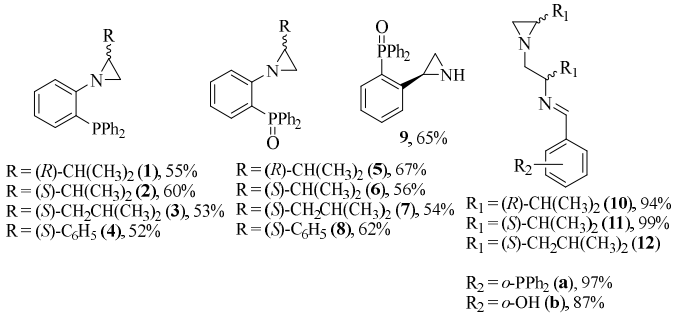


Figure 1. Chiral aziridine-containing catalysts **1-12**.

Secondly, the corresponding imino esters **13-15** (Figure 2) being substrates for in situ generation of azomethine ylides were prepared from the appropriate glycine esters and benzaldehyde in the presence of triethylamine according to literature general protocol [15].

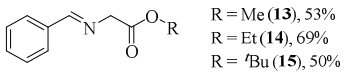
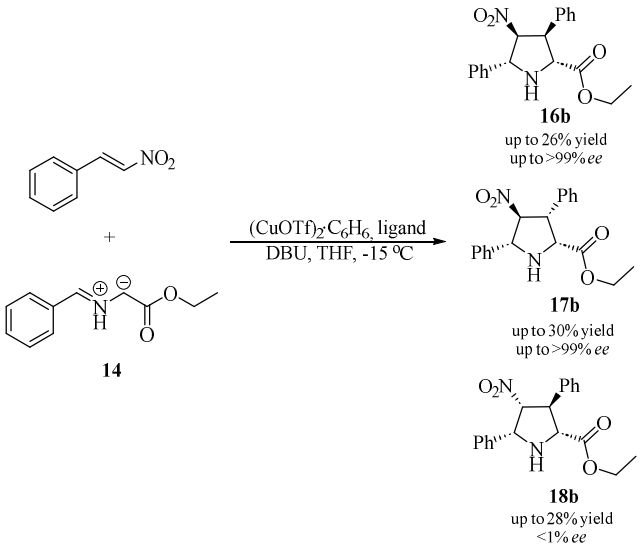


Figure 2. Structures of imino esters **13-15**.

2.2. Asymmetric [3+2]-Cycloaddition Reactions

All the aziridine derivatives **1-12** were examined for catalytic activity in the asymmetric [3+2]-cycloaddition reaction occurring between *trans*-*β*-nitrostyrene and ethyl imino ester **14** (Scheme 1). These reactions were catalyzed by an in situ generated catalytic system consisting of copper triflate, chiral ligand and DBU as a basic additive. After appropriate purification of crude mixtures by column chromatography three diastereomeric products **16-18** were obtained. Two of them were identified based on the literature data as products *exo* **17b** and *endo* **18b** (Scheme 1) [16a-b]. However, compound **16b** has not been described in the literature. The effectiveness of the ligands was determined based on the analysis of the optical purity of the obtained products using the HPLC method on a column with chiral support. The results are summarized in Table 1.



Scheme 1. Asymmetric [3+2]-cycloaddition in the presence of aziridine ligands **1-12**.

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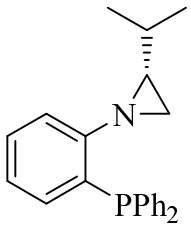
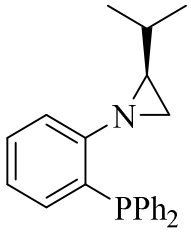
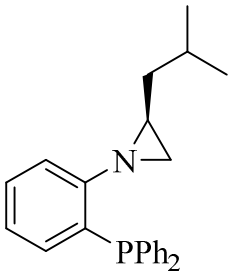
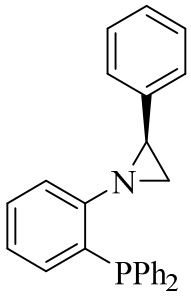
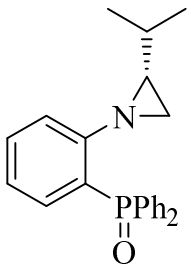
Table 1. Asymmetric [3+2]-cycloaddition of ethyl imino ester **14**.

Ligand No.	Ligand	Yield [%]	Ratio 16b/17b/18b	*Ee* [%] 16b	*Ee* [%] 17b	*Ee* [%] 18b
(*R*)-1		52	1.0/4.5/2.2	**67**	63	1
(*S*)-2		41	1.4/7.6/1.0	74	98	8
(*S*)-3		62	1.0/3.1/3.6	95	95	5
(*S*)-4		57	1.0/3.2/4.1	67	97	6
(*R*)-5		51	1.0/1.5/1.3	78	>99	2

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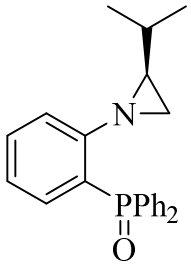
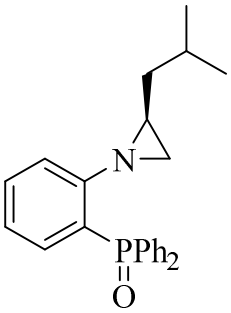
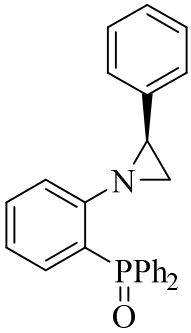
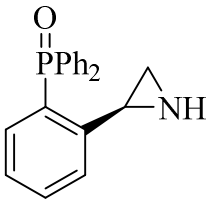
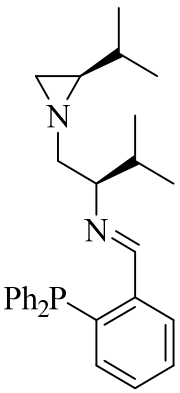
(*S*)-6		59	1.1/1.2/1.0	95	99	6
(*S*)-7		54	1.0/2.4/1.6	94	99	4
(*S*)-8		54	1.0/2.3/1.9	21	88	2
(*S*)-9		45	1.0/2.8/3.9	26	96	4
(*R,R*)-10a		66	1.0/1.2/1.5	95	42	1

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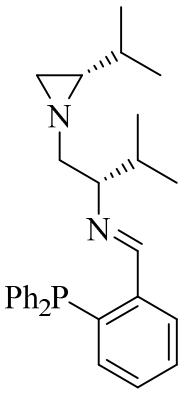
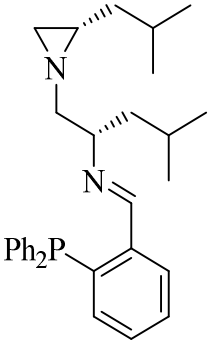
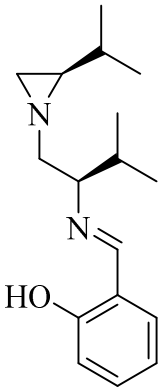
(*S*,*S*)-11a		37	1.3/1.4/1.0	>99	94	5
(*S*,*S*)-12a		64	1.0/1.2/1.0	3	98	5
(*R*,*R*)-10b		71	1.2/1.5/1.0	83	72	4

The analysis of the results showed that the use of structurally similar aziridine ligands led to similar outcomes. The highest chemical yield of the asymmetric [3+2]-cycloaddition, up to 71%, was achieved using ligands with an imine group however, the products were formed without significant diastereoselectivity. Aziridine phosphine ligands resulted in the formation of diastereomeric products in a similar ratio, with only the aziridine-phosphine ligand **2** shifting the equilibrium towards the formation of product *exo* **17b** additionally with excellent enantioselectivity (up to 98% *ee*). In all cases, products **16b** and **17b** were formed in enantiomerically enriched forms, while compound **18b** always formed racemic mixtures. Unexpectedly, the use of ligand **9** containing an NH-aziridine group led to the formation of racemic product *endo* **18b** predominating over products **16b** and **17b**.

In the next stage, it was decided to conduct an asymmetric [3+2]-cycloaddition reaction, but instead of ethyl imino ester **14**, methyl imino ester **13** was used. The second substrate and the other reaction conditions remained unchanged (Scheme 2) (Table 2). (*S*)-Isopropyl aziridine phosphine oxide **6** was used as the ligand. In this reaction, two diastereomeric products were achieved and also identified based on the literature-described ^{1}H-NMR spectra as the *exo* **17a** product [16a], which was formed with a 70% enantiomeric excess. Based on the ^{1}H-NMR spectrum, the second of the formed diastereomers was also identified as the *4-epi-endo* **16a** product [6]. However, the third *endo* product, formed in the previous reaction with ethyl imino ester **14**, was not obtained this time.

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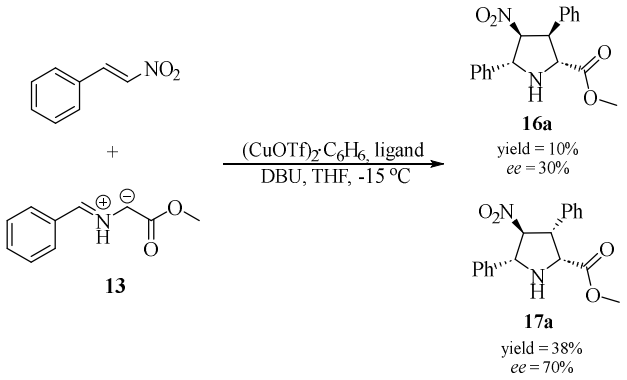
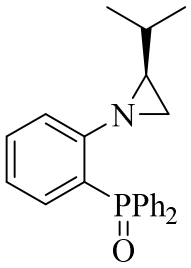
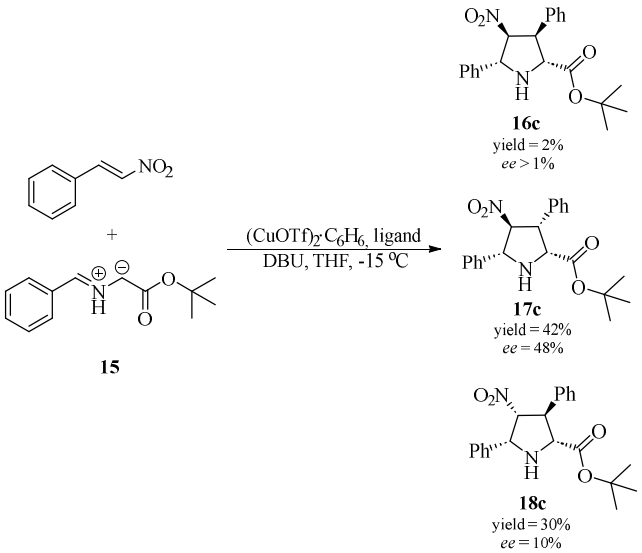


Scheme 2. Asymmetric [3+2]-cycloaddition of methyl imino ester **13**.

Table 2. Asymmetric [3+2]-cycloaddition of methyl imino ester **13**.

Ligand No.	Ligand	Yield [%]	Ratio 16a/17a	*Ee* [%] 16a	*Ee* [%] 17a
(*S*)-6		48	1.0/3.8	30	70

In the next approach, the reaction was carried out using *tert*-butyl ester **15** as the substrate (Scheme 3). In this reaction, three diastereomeric products **16**-**18** were obtained again, and their configuration was determined based on the literature data as *4-epi-endo* **16c**, *exo* **17c**, and *endo* **18c**.[17] Interestingly, in this reaction, product **16c** was formed in a small amount racemic form (Table 3).



Scheme 3. Asymmetric [3+2]-cycloaddition of tert-butyl imino ester **15**.

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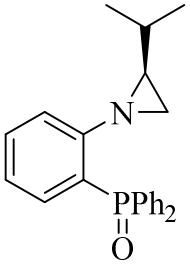
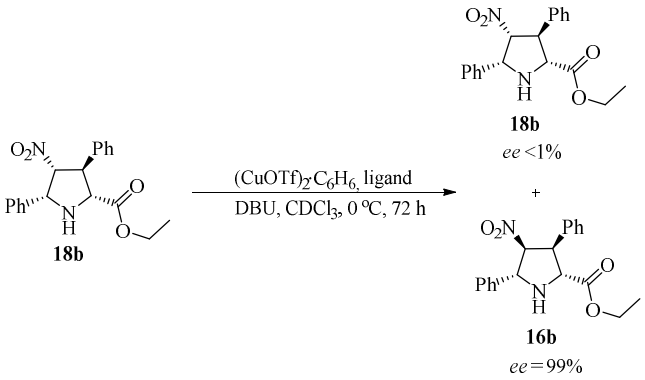
Table 3. Asymmetric [3+2]-cycloaddition of *tert*-butyl imino ester **15**.

Ligand No.	Ligand	Yield [%]	Ratio 16c/17c/18c	*Ee* [%] 16c	*Ee* [%] 17c	*Ee* [%] 18c
(*S*)-6		74	1.0/19.0/13.0	>1	48	10

In summary, after identifying all three products, it was concluded that the reaction proceeds according to a concerted mechanism resulting initially in the formation of two products with *exo* **17** and *endo* **18** configurations. The formation of an additional diastereomeric product **16** should be impossible when *trans*-*β*-nitrostyrene is used as a substrate. Therefore, based on the literature reports, it is believed that product **18** undergoes epimerization under basic conditions (the aziridine ring exhibits basic character). Epimerization involves a change in the configuration of a substituent at a single stereogenic center and is a process described in the literature [6] for both methyl and *tert*-butyl imino esters (e.g., involving triethylamine). It is assumed that the aziridine ligands act as chiral bases, causing selective epimerization of product **18** to product **16**. Methyl derivatives are most susceptible to this change - no *endo* product was observed because the entirety underwent epimerization. However, *tert*-butyl derivatives are the most resistant to epimerization - only trace amounts of product **16c** were observed. Differences in the quantity of product formed during the epimerization process may result from steric hindrance present in individual compounds.

To confirm the epimerization process, an additional experiment was conducted involving the reaction of pure product **18b** with the in situ generated catalytic system consisting of aziridine chiral ligand, copper triflate, and DBU (Scheme 4). The reaction was conducted under analogous conditions to the cycloaddition reaction. This test confirmed that the mixture contained the *4-epi-endo* product **16b** along with the initial *endo* compound **18b** in a ratio of 0.6:1.0, demonstrating that the formation of product **16b** occurred under the influence of the utilized catalytic system and confirming the previously assumed theory of epimerization.



Scheme 4. Base-promoted epimerization of the product **18b**.

4. Materials and Methods

4.1. General Information

All reagents were used as obtained from commercial suppliers, unless otherwise noted. The corresponding chiral catalysts **1-12**, exactly, aziridine phosphines [11], aziridine phosphine oxides [12], phosphine oxide containing NH-aziridine subunit [14], and aziridine-containing imines [13a, b]

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were prepared according to literature report. Also, imino esters **13-15**, being substrates for in situ generation of azomethine ylides were obtained using general protocol [15]. NMR spectra for solutions in deuterated chloroform ($CDCl_3$) were recorded at 600 MHz (^1H NMR) and 150 MHz (^{13}C NMR) on a Bruker Avance III spectrometer, using the solvent as an internal standard. The following abbreviations were used to describe NMR spectra: δ, chemical shift (ppm); *J*, coupling constants (Hz); s, singlet; br.s, broad singlet; d, doublet; dd, double-doublet; t, triplet; q, quartet and m, multiplet. Column chromatography was performed on silica gel using a solvent mixture of hexane/ethyl acetate as eluents (9:1). The enantiomeric excess (*ee*) values were determined by high-performance liquid chromatography (HPLC) on a chiral packed column (Chiralcel OD-H) using hexane and isopropanol as the mobile phase.

4.2. Asymmetric [3+2]-Cycloaddition Reaction Catalyzed by Aziridine Derivatives 1-12 – General Procedure

A copper triflate $(CuOTf)_2{\cdot}C_6H_6$ (0.1 mmol) and ligand (0.1 mmol) were placed in a flask, the whole mixture was cooled to 0 °C, then DBU (12 μL) and anhydrous THF (4 mL) were added. The catalytic system was generated for 4 hours at 0 °C. The mixture was cooled to -15 °C and imino ester (0.5 mmol) was added, stirred for 10 minutes, after which trans-β-nitrostyrene (0.5 mmol) was added. The resulting mixture was stirred for 48 hours at low temperature and then the solvent was evaporated *in vacuo*. The crude products were separated via column chromatography on silica gel (hexane:ethyl acetate 9:1). All the aziridine derivatives **1-12** were examined for catalytic activity in the asymmetric [3+2]-cycloaddition of ethyl imino ester **14**. In the asymmetric [3+2]-cycloaddition of methyl imino ester **13** and *tert*-butyl imino ester **15** only catalyst **6** was examined.

Characterization of Compounds 16a-c, 17a-c, and 18b-c

(2*R*,3*S*,4*S*,5*R*)-Ethyl 4-Nitro-3,5-diphenylpyrrolidine-2-carboxylate (*4-epi-endo*) **16b**; yellow sticky oil, 45 mg, 26%

^1H NMR (600 MHz, $CDCl_3$) δ: 7.58 – 7.56 (m, 2H), 7.45 – 7.43 (m, 2H), 7.39 – 7.33 (m, 4H), 7.29 – 7.28 (m, 2H), 5.16 (dd, *J* = 3.7 Hz, *J* = 7.6 Hz, 1H), 5.10 (d, *J* = 3.7 Hz, 1H), 4.70 (d, *J* = 3.7 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 4.07 – 4.05 (m, 1H), 2.93 (br.s, 1H), 1.24 (t, *J* = 7.1 Hz, 3H).

$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ: 172.5, 140.2, 133.2, 129.0, 128.8, 128.4, 128.2, 126.8, 96.5, 65.8, 63.3, 61.6, 52.6, 14.0.

Anal. Calcd. for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23; O, 18.80; Found: C, 66.85; H, 5.75; N, 8.09; O, 19.31.

(2*R*,3*R*,4*S*,5*R*)-Ethyl 4-Nitro-3,5-diphenylpyrrolidine-2-carboxylate (*exo*) **17b** [16a]; yellow sticky oil, 51 mg, 30%

^1H NMR (600 MHz, $CDCl_3$) δ: 7.60 – 7.59 (m, 2H), 7.47 – 7.41 (m, 3H), 7.34 – 7.29 (m, 5H), 5.24 (t, *J* = 8.2 Hz, 1H), 4.79 (br.s, 1H), 4.51 (d, *J* = 9.0 Hz, 1H), 4.42 (t, *J* = 8.2 Hz, 1H), 3.89 – 3.83 (m, 1H), 3.76 – 3.70 (m, 1H), 2.77 (br.s, 1H), 0.85 (t, *J* = 7.1 Hz, 3H).

$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ: 171.4, 137.7, 136.2, 129.1, 129.0, 128.8, 128.1, 128.0, 126.9, 95.3, 67.6, 64.2, 61.1, 53.8, 13.5.

(2*R*,3*S*,4*R*,5*R*)-Ethyl 4-Nitro-3,5-diphenylpyrrolidine-2-carboxylate (*endo*) **18b** [16b]; yellow sticky oil, 48 mg, 28%

^1H NMR (600 MHz, $CDCl_3$) δ**:** 7.45 – 7.33 (m, 10H), 5.33 (dd, *J* = 3.8 Hz, *J* = 6.5 Hz, 1H), 4.96 (br.s, 1H), 4.37 – 4.25 (m, 2H), 4.24 (dd, *J* = 3.8 Hz, *J* = 7.5 Hz, 1H), 4.16 – 4.15 (m, 1H), 3.39 (br.s, 1H),1.29 (t, *J* = 7.5 Hz, 3H).

$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ: 171.3, 138.7, 134.6, 129.3, 128.8, 128.1, 127.6, 126.5, 97.1, 67.8, 67.6, 61.7, 55.6, 14.1.

(2*R*,3*S*,4*S*,5*R*)-Methyl 4-Nitro-3,5-diphenylpyrrolidine-2-carboxylate (*4-epi-endo*) **16a** [6]; yellow sticky oil, 4 mg, 2%

^1H NMR (600 MHz, $CDCl_3$) δ: 7.35 – 7.34 (m, 2H), 7.34 – 7.33 (m, 2H), 7.33 – 7.32 (m, 4H), 7.29 – 7.27 (m, 2H), 5.14 (dd, *J* = 3.7 Hz, *J* = 8.2 Hz, 1H), 5.07 (d, *J* = 3.7 Hz, 1H), 4.57 (d, *J* = 9.3 Hz, 1H), 3.91 (t, *J* = 8.2 Hz, 1H), 2.84 (br.s, 1H), 1.39 (s, 9H).

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$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ: 171.7, 140.2, 133.4, 129.0, 128.7, 128.4, 128.3, 126.8, 96.7, 82.2, 65.9, 64.1, 53.5, 27.9.

(2*R*,3*R*,4*S*,5*R*)-*Tert*-butyl 4-Nitro-3,5-diphenylpyrrolidine-2-carboxylate (*exo*) **17c** [6]; yellow sticky oil, 72 mg, 42%

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.40 – 7.39 (m, 2H), 7.34 – 7.29 (m, 8H), 5.17 (t, *J* = 7.7 Hz, 1H), 4.75 (d, *J* = 6.7 Hz, 1H), 4.43 (d, *J* = 8.9 Hz, 1H), 4.35 – 4.32 (m, 1H), 2.74 (br.s, 1H), 1.08 (s, 9H).

$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ: 170.0, 137.8, 137.2, 129.1, 128.9, 128.8, 128.4, 128.0, 126.9, 96.0, 81.9, 67.4, 64.6, 53.4, 27.4.

(2*R*,3*S*,4*R*,5*R*)-*Tert*-butyl 4-Nitro-3,5-diphenylpyrrolidine-2-carboxylate (*endo*) **18c** [6]; yellow sticky oil, 51 mg, 30%

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.37 – 7.28 (m, 10H), 5.33 – 5.32 (m, 1H), 4.94 (br.s, 1H), 4.14 – 4.12 (m, 1H), 4.03 (br.s, 1H), 3.36 (br.s, 1H), 1.48 (s, 9H).

$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ: 170.5, 138.8, 134.7, 129.2, 128.8, 128.7, 128.0, 127.6, 126.5, 97.1, 82.5, 68.2, 67.8, 56.1, 28.0.

5. Conclusions

In summary, the obtained ligands containing both arylphosphine or arylphosphinyl groups, an imine group, and an optically pure chiral aziridine ring proved to be efficient catalysts for the asymmetric [3+2]-cycloaddition reaction. The use of the aforementioned catalysts led to the formation of three products: *4-epi-endo* **16**, *exo* **17**, and *endo* **18**, of which products *4-epi-endo* **16** and *exo* **17** typically were formed in enantiomerically enriched forms. Meanwhile, product *endo* **18** always forms as a racemic mixture. Compounds **17** and **18** were the products of a reaction occurring according to a concerted mechanism, whereas the formation of product **16** can be explained by the epimerization of product **18** under catalytic reaction conditions, which was confirmed by an independently conducted experiment. Differences in the quantity of the product formed during the epimerization process may result from steric hindrance present in different compounds.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, copies of NMR spectra, and HPLC chromatograms.

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