catalysts

MDPI

Article

Efficient Asymmetric Simmons-Smith Cyclopropanation and Diethylzinc Addition to Aldehydes Promoted by Enantiomeric Aziridine-Phosphines

Aleksandra Buchcic-Szychowska [1], Justyna Adamczyk [1], Lena Marciniak [2], Adam Marek Pieczonka [1], Anna Zawisza [1], Stanisław Leśniak [1] and Michał Rachwalski [1,*]

[1] Department of Organic and Applied Chemistry, University of Lodz, Tamka 12, 91-403 Lodz, Poland; aleksandra.buchcic@edu.uni.lodz.pl (A.B.-S.); justyna.adamczyk@edu.uni.lodz.pl (J.A.); adam.pieczonka@chemia.uni.lodz.pl (A.M.P.); anna.zawisza@chemia.uni.lodz.pl (A.Z.); stanislaw.lesniak@chemia.uni.lodz.pl (S.L.)

[2] The Bio-Med-Chem Doctoral School of the University of Lodz and Lodz Institutes of the Polish Academy of Sciences, University of Lodz, 91-403 Lodz, Poland; lena.marciniak@edu.uni.lodz.pl

* Correspondence: michal.rachwalski@chemia.uni.lodz.pl; Tel.: +48-42-635-5767

Abstract: During an implementation of current research, a set of optically pure chiral aziridines and aziridine imines bearing a phosphine moiety was prepared with high values of chemical yield. The above chiral heteroorganic derivatives were tested for catalytic utility as chiral ligands in asymmetric Simmons-Smith cyclopropanation and asymmetric diethylzinc addition to various aldehydes. Most of the desired products were formed in high chemical yields, with satisfactory values of enantiomeric excess (sometimes more than 90%) and diastereomeric ratios (in case of cyclopropanation reaction).

Keywords: asymmetric synthesis; aziridines; chiral ligands; cyclopropanation; diethylzinc addition

check for updates

Citation: Buchcic-Szychowska, A.; Adamczyk, J.; Marciniak, L.; Pieczonka, A.M.; Zawisza, A.; Leśniak, S.; Rachwalski, M. Efficient Asymmetric Simmons-Smith Cyclopropanation and Diethylzinc Addition to Aldehydes Promoted by Enantiomeric Aziridine-Phosphines. *Catalysts* **2021**, *11*, 968. https://doi.org/10.3390/catal11080968

Academic Editor: Filippo Perna

Received: 31 July 2021
Accepted: 12 August 2021
Published: 13 August 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

The asymmetric construction of chiral non-racemic organic compounds is still an extremely important issue for many research teams around the world. Both the chemical yield and optical purity of the desired products of stereocontrolled synthesis depend on the selection of an appropriate promoter for such a reaction. This role can be played by a chiral ligand [1,2], an organocatalyst [3,4], a chiral auxiliary [5], bifunctional catalysts (molecule possessing two distinct functional groups) [6,7] or another cooperative catalytic system [8].

The asymmetric Simmons-Smith reaction is one of the approaches in the synthesis of cyclopropane derivatives [9]. A cyclopropane ring with unusual electronic and steric properties is present in many natural products [10] and drugs [11–15]. Molecules containing this three-membered motif can be constructed in transformations with or without transition metals [16] in the presence of, e.g., complexes of porphyrin [17], proline derivatives [18,19], chiral phase-transfer catalysts [20] or as demonstrated in our laboratory, using chiral aziridinyl ligands containing sulfinyl moiety [21].

In turn, asymmetric diethylzinc addition to carbonyl compounds (especially aromatic aldehydes) is one of the most exploited test reactions in the chemical literature [22,23]; however, it is still a very simple and effective tool for studying the catalytic activity of chiral ligands. Based on our experience, ligands containing an aziridine fragment show very high efficiency in reactions of this type [23–28].

Chiral systems containing a phosphine group and an aziridine ring within one molecule are not the subject of many reports in the chemical literature [29]. Enriching the current state of knowledge about such chiral junctions, we recently published a successful application of aziridine phosphines in the asymmetric Friedel-Crafts reaction [30].

Taking into consideration all of the aforementioned circumstances, we decided to synthesize a series of optically pure aziridines and aziridine imines possessing phosphine motif in order to check their catalytic activities in the asymmetric Simmons-Smith cyclopropanation and asymmetric diethylzinc addition to aldehydes. Thus, we wanted to show that chiral aziridine-phosphines are universal catalysts operating in various types of asymmetric transformations.

2. Results and Discussion

2.1. Preparation of the Aziridine-Phosphines **1**–**8**

The chiral enantiomeric aziridine-phosphines **1**–**8** (Figure 1) were prepared as previously described [30], through triethoxysilane-mediated reduction of the corresponding phosphine oxides [30].

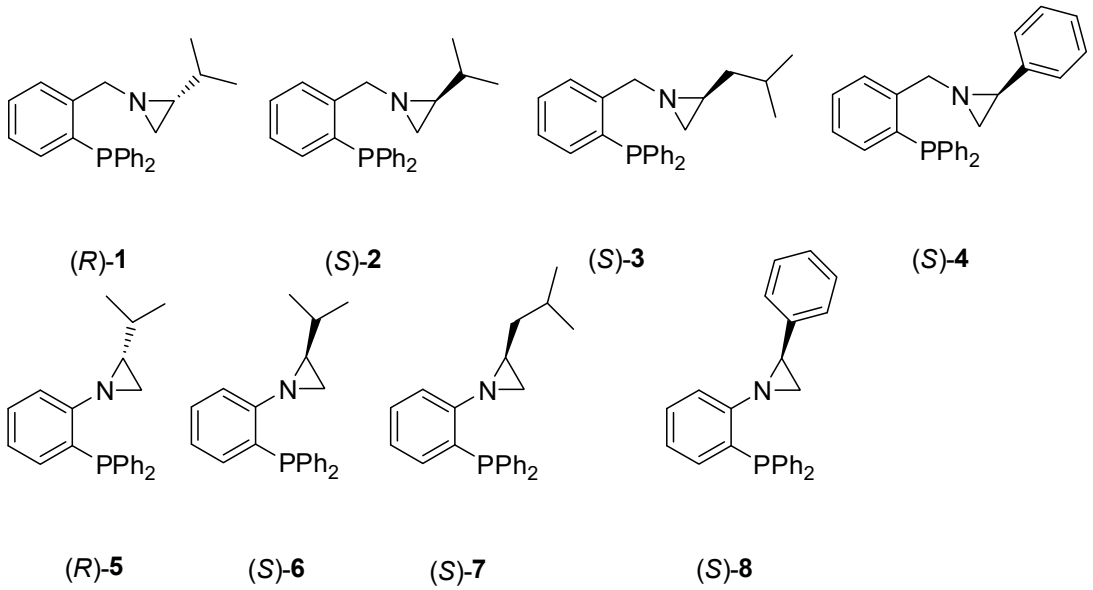
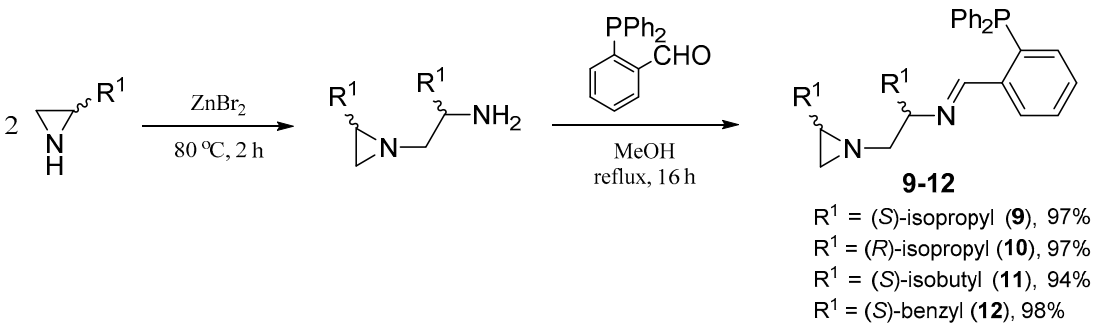


Figure 1. The structures of chiral aziridine-phosphines **1**–**8**.

2.2. Synthesis of Imine-Phosphines **9**–**12**

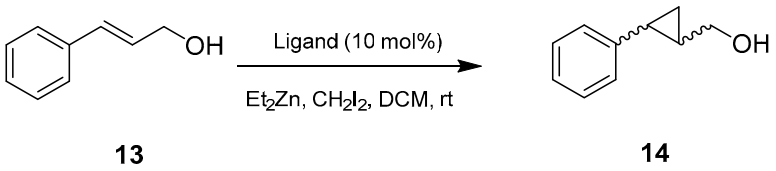
Chiral imine-phosphines **9**–**12** (Scheme 1) were obtained starting from appropriate 1-(2-aminoalkyl)aziridines, which were formed as a result of the zinc bromide-mediated self-ring opening reaction of NH-aziridines, as previously described [31]. The corresponding 1-(2-aminoalkyl)aziridines were then reacted with 2-(diphenylphosphino)benzaldehyde affording 1-(2-iminealkyl)aziridine catalysts functionalized by a phosphine group in excellent yields (Scheme 1).



Scheme 1. Synthesis of chiral imine-phosphines **9**–**12**.

2.3. Asymmetric Simmons-Smith Cyclopropanation Promoted by Aziridine-Phosphines **1–8** *and Imine-Phosphines* **9–12**

Equipped with all optically pure phosphorus-functionalized aziridines **1–12**, we decided to check their utility as chiral ligands catalyzing an asymmetric cyclopropanation reaction of cinnamyl alcohol (**13**) as a model substrate. The transformations were carried out in DCM with 2 equiv. of diethylzinc and 3 equiv. of diiodomethane in the presence of a ligand (10 mol%) (Scheme 2). All the results are presented in Table 1.



Scheme 2. Asymmetric cyclopropanation of alcohol **13** in the presence of catalysts **1–12** leading to cyclopropane derivative **14**.

Table 1. Asymmetric Simmons-Smith cyclopropanation of cinnamyl alcohol catalyzed by aziridines **1–12**.

Entry	Ligand	Product 14			
		Yield (%)	*ee* (%) [a]	*Dr* [b]	Abs. Conf. [c]
1	**1**	70	62	5:1	1*R*,2*R*
2	**2**	72	65	5:1	1*S*,2*S*
3	**3**	63	54	5:1	1*S*,2*S*
4	**4**	65	58	5:1	1*S*,2*S*
5	**5**	90	92	12:1	1*R*,2*R*
6	**6**	93	98	15:1	1*S*,2*S*
7	**7**	90	82	10:1	1*S*,2*S*
8	**8**	91	85	10:1	1*S*,2*S*
9	**9**	85	72	10:1	1*S*,2*S*
10	**10**	83	70	10:1	1*R*,2*R*
11	**11**	79	68	10:1	1*S*,2*S*
12	**12**	80	70	10:1	1*S*,2*S*

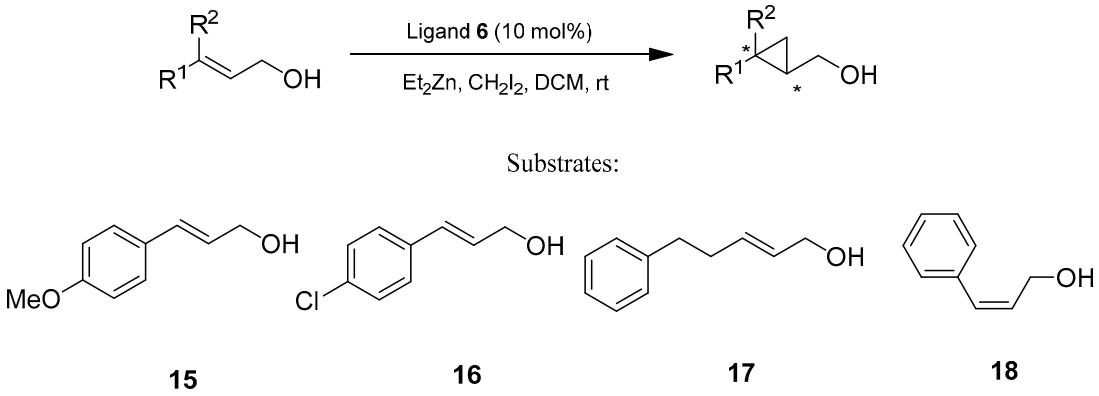
[a] Determined by chiral HPLC using Chiralcel OD-H column (for major product). [b] Determined by ^{1}H NMR of the crude mixture. [c] According to the literature data [21,32]. Conditions: 10 mol% of the ligand, cinnamyl alcohol (0.5 mmol), diethylzinc (1.0 M in hexanes, 1 mmol), diiodomethane (0.6 mmol), DCM (5 mL), 0 °C, 4 h.

The analysis of the results collected in Table 1 leads to the following conclusions. Ligands **1–4** containing a methylene linker connecting a phenyl ring with an aziridine nitrogen atom were characterized by moderate catalytic efficiency leading to cyclopropyl derivative **14** in chemical yields varying from 63 to 72%, with enantiomeric excess in the range of 53 to 65% and with a moderate diastereomeric ratio of 5:1 (Table 1, entries 1–4). Much better catalytic activity was shown by aziridine-phosphines **5–8** (without methylene subunit). Their use in the asymmetric cyclopropanation allowed us to obtain the desired chiral product **14** in high yields of around 90%, 80–98% of *ee*, and with reasonable diastereoselectivity (10:1–15:1) (Table 1, entries 5–8). In turn, the last group of chiral ligands, namely, imine-phosphines **9–12**, exhibited indirect catalytic activity to systems with and without a methylene linker. In these cases, cyclopropane **14** was formed in 79–85% yields, 68–70% of *ee*, and a 10:1 diastereomeric ratio (Table 1, entries 9–12).

Finally, there is one more interesting aspect to note. The change in the absolute configuration on the carbon atom of the aziridine moiety of the ligand leads to the cyclopropanation product **14** with opposite absolute configuration (Table 1, entries 1, 5 and 10). We observed a similar relationship while conducting research on asymmetric Michael [33], Mannich [34] and Friedel-Crafts [30] reactions. Thus, the application of enantiomeric catalysts provides access to both enantiomers of the cyclopropanation product **14**.

2.4. Asymmetric Simmons-Smith Cyclopropanation Promoted by Aziridine-Phosphine **6**

Considering the highest catalytic activity of ligand **6**, we decided to study the scope of the asymmetric cyclopropanation in the presence of **6** by the application of another allylic alcohol under the same conditions (Scheme 3). All the results are shown in Table 2.



Scheme 3. Asymmetric cyclopropanation reaction of alcohols **15**–**18** catalyzed by aziridine-phosphine **6** (*—stereogenic center).

Table 2. Asymmetric cyclopropanation promoted by aziridine-phosphine **6**.

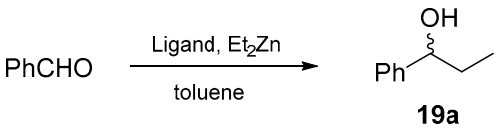
Entry	Substrate	Yield (%)	*ee* (%) [a]	*Dr* [b]	Abs. Conf. [c]
1	**15**	92	95	15:1	(1*S*,2*S*)
2	**16**	94	93	15:1	(1*S*,2*S*)
3	**17**	91	91	15:1	(1*S*,2*S*)
4	**18**	56	40	4:1	(1*R*,2*S*)

[a] Determined by chiral HPLC using Chiralcel OD-H column (for major product). [b] Determined by ^{1}H NMR of the crude mixture. [c] According to the literature data [21,32]. Conditions: 10 mol% of the catalyst **6**, allylic alcohol (0.5 mmol), diethylzinc (1.0 M in hexanes, 1 mmol), diiodomethane (0.6 mmol), DCM (5 mL), 0 °C, 4 h.

The data collected in Table 2 clearly indicate a very high catalytic activity of aziridine-phosphine **6** in the asymmetric Simmons-Smith cyclopropanation of (*E*)-allylic alcohols **15**–**17** using diethylzinc and diiodomethane in the presence of diethylaluminum chloride leading to the appropriate cyclopropyl systems in high chemical yields (up to 90%) with a high degree of enantioselectivity (up to 90% *ee*) and diastereoselectivity (15:1 of *dr*). Lower enantio- and diastereoselectivity in the case of the reaction of (*Z*)-cinnamyl alcohol **18** (Table 2, entry 4) is in accordance with previous studies on the asymmetric cyclopropanation of this system [21].

2.5. Asymmetric Diethylzinc Addition to Benzaldehyde Catalyzed by Aziridine-Phosphines **1**–**8** and Imine-Phosphines **9**–**12**

Based on our experience in the field of asymmetric transformations in the presence of zinc ions catalyzed by aziridine derivatives [35], in the next stage of research, we decided to check the catalytic activity of the chiral systems **1**–**12** in one of the most basic model asymmetric reactions involving zinc ions, namely, asymmetric diethylzinc addition to benzaldehyde (Scheme 4). The results of these tests are shown in Table 3.



Scheme 4. Asymmetric diethylzinc addition to benzaldehyde promoted by ligands **1**–**12**.

Table 3. Asymmetric addition of Et_2Zn to benzaldehyde in the presence of **1**–**12**.

Entry	Ligand	Product 19a		
		Yield (%)	*ee* (%) [a]	Abs. Conf. [b]
1	**1**	75	66	(*R*)
2	**2**	78	68	(*S*)
3	**3**	71	62	(*S*)
4	**4**	72	63	(*S*)
5	**5**	92	96	(*R*)
6	**6**	95	96	(*S*)
7	**7**	91	86	(*S*)
8	**8**	90	85	(*S*)
9	**9**	85	80	(*S*)
10	**10**	83	80	(*R*)
11	**11**	81	73	(*S*)
12	**12**	82	76	(*S*)

[a] Determined by chiral HPLC using Chiralcel OD column. [b] According to the literature data [25,36]. Conditions: 10 mol% of the ligand, benzaldehyde (1 mmol), diethylzinc (1.0 M in hexanes, 3 mmol), toluene (5 mL), 0 °C, 2 h.

The results summarized in Table 3 show that all chiral systems **1**–**12** are capable of catalyzing an asymmetric addition reaction of diethylzinc to benzaldehyde. The best results in terms of chemical yields and enantioselectivities were achieved using aziridine-phosphines **5**–**8** without a methylene linker (Table 3, entries 5–8) with the most active system **6** leading to the desired chiral alcohol **19a** in 95% yield and with 96% *ee*. Ligands **9**–**12** (imines) exhibited lower activity (yield and *ee* around 80%) (Table 3, entries 9–12). In turn, aziridine-phosphines **1**–**4** containing a methylene linker showed only moderate efficiency as chiral ligands (Table 3, entries 1–4), which is in line with our previous observations.

2.6. Asymmetric Addition of Et_2Zn to Aldehydes Promoted by Aziridine-Phosphine **6**

Equipped with the most effective catalyst **6**, we decided to expand the scope of its application using other aldehydes for this purpose (Scheme 5). The results are shown in Table 4.

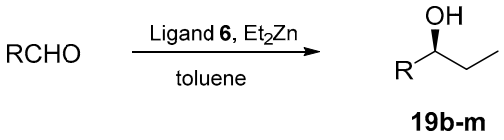
Table 4. Asymmetric addition of Et_2Zn to aldehydes in the presence of **6**.

Entry	R	Products 19b–m		
		Yield (%)	*ee* (%) [a]	Abs. Conf. [b]
1	*n*-Pr	90	89	(S)
2	2-MeC_6H_4	91	90	(*S*)
3	4-MeC_6H_4	90	93	(*S*)
4	2-$MeOC_6H_4$	93	93	(*S*)
5	4-$MeOC_6H_4$	93	95	(S)
6	2-BrC_6H_4	91	90	(*S*)
7	4-BrC_6H_4	93	92	(*S*)
8	4-$CF_3C_6H_4$	91	93	(*S*)
9	Vi	87	85	(*S*)
10	4-$O_2NC_6H_4$	0	Nd [c]	Nd [c]
11	C_4H_3S	70	68	(*S*)
12	C_4H_3O	0	Nd [c]	Nd [c]

[a] Determined by chiral HPLC using Chiralcel OD column. [b] According to the literature data [37–39]. [c] Not determined. Conditions: 10 mol% of the ligand, aldehyde (1 mmol), diethylzinc (1.0 M in hexanes, 3 mmol), toluene (5 mL), 0 °C, 2 h.

As shown in Table 4, aziridine-phosphine **6** is prone to efficiently catalyzing an asymmetric addition of diethylzinc to aldehydes in most cases. The use of *n*-butyraldehyde (Table 4, entry 1), 2- and 4-methyl, methoxy-, bromo- and 4-trifluoromethylbenzaldehydes (Table 4, entries 2–8) led to the corresponding chiral alcohols in chemical yields with enantioselectivities up to 90%. Slightly worse results in terms of yield and *ee* were obtained

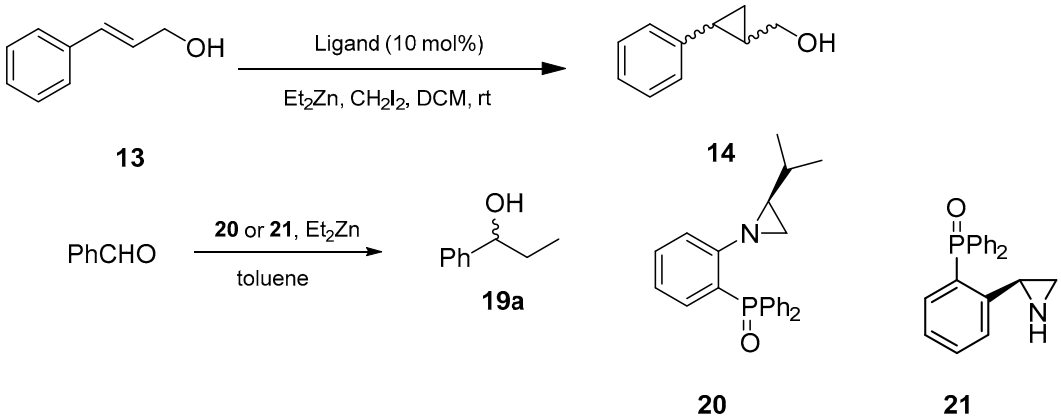
for cinnamaldehyde (Table 4, entry 9) and thiophene-2-carbaldehyde (Table 4, entry 11). Disappointingly, no additional product was observed in the case of 4-nitrobenzaldehyde (Table 4, entry 10) and furan-2-carbaldehyde (Table 4, entry 12).



Scheme 5. Asymmetric diethylzinc addition to aldehydes catalyzed by ligand **6**.

2.7. Asymmetric Cyclopropanation of Cinnamyl Alcohol and Diethylzinc Addition to Benzaldehyde Catalyzed by Aziridine-Phosphine Oxides

Finally, we decided to check whether the presence of the phosphine group is important for the course of both title asymmetric reactions. To this end, we carried out the cyclopropanation of cinnamyl alcohol and the addition of diethylzinc to benzaldehyde under the same conditions as before using two enantiomerically pure phosphinoyl-aziridines **20** and **21**, which were prepared as previously described [33,34] (Scheme 6). The results are summarized in Tables 5 and 6.



Scheme 6. Cyclopropanation of 13 and addition of Et_2Zn to benzaldehyde in the presence of phosphinoyl-aziridines.

Table 5. Cyclopropanation of cinnamyl alcohol catalyzed by phosphine oxides **20** and **21**.

Entry	Ligand	Product 14			
		Yield (%)	*ee* (%) [a]	*Dr* [b]	Abs. Conf. [c]
1	**20**	50	41	5:1	(1*S*,2*S*)
2	**21**	55	52	5:1	(1*S*,2*S*)

[a] Determined by chiral HPLC using Chiralcel OD-H column (for major product). [b] Determined by ^{1}H NMR of the crude mixture. [c] According to the literature data [21,32]. Conditions: 10 mol% of the ligand, cinnamyl alcohol (0.5 mmol), diethylzinc (1.0 M in hexanes, 1 mmol), diiodomethane (0.6 mmol), DCM (5 mL), 0 °C, 4 h.

Table 6. Diethylzinc addition to benzaldehyde catalyzed by phosphine oxides **20** and **21**.

Entry	Ligand	Product 19a		
		Yield (%)	*ee* (%) [a]	Abs. Conf. [b]
1	**20**	60	56	(*S*)
2	**21**	68	62	(*S*)

[a] Determined using chiral HPLC using Chiralcel OD column. [b] According to the literature data [25–36]. Conditions: 10 mol% of the ligand, benzaldehyde (1 mmol), diethylzinc (1.0 M in hexanes, 3 mmol), toluene (5 mL), 0 °C, 2 h.

The inspection of Tables 5 and 6 clearly indicates that the presence of the phosphine group in the structure of the chiral ligand has a very strong influence on the efficient course of both asymmetric transformations. The application of two chiral ligands bearing phosphinoyl (P=O) moiety instead of phosphine produced cyclopropyl derivative **14** and the chiral alcohol **19a** only in moderate chemical yields and with moderate enantiomeric excess and diastereoselectivity.

3. Materials and Methods

3.1. Materials

Dichloromethane was dried over calcium hydride. Toluene and diethyl ether were distilled from sodium benzophenone ketyl radical. All the NMR spectra were accomplished using a Bruker(Bruker, Billerica, MA, USA) instrument at 600, 150 and 243 MHz, respectively, with $CDCl_3$ as a solvent and TMS as an internal standard. Data are presented as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad singlet (br. s). Column chromatography was performed using Merck 60 silica gel. TLC was accomplished on Merck 60 F_{254} silica gel plates (Merck Group (Merck KGaA), Darmstadt, Germany). The plates were visualized using UV light (254 nm). The enantiomeric excess (*ee*) values were determined by HPLC with chiral support (Chiralcel OD-H or OD columns). The corresponding chiral phosphine-aziridines **1**–**8** were synthesized according to general procedures reported in our group [30].

3.2. Methods

3.2.1. Synthesis of Imine-Phosphines **9**–**12**—General Procedure

The appropriate 1-(2-aminoalkyl)aziridines were prepared as previously described [31]. A solution of the 1-(2-aminoalkyl)aziridine (1 mmol) and 2-(diphenylphosphino)benzaldehyde (1 mmol) in methanol (10 mL) was refluxed for 16 h. After this time, the solvent was evaporated in vacuo, and the crude product was purified via flash chromatography (silica gel and hexane/ethyl acetate in gradient) to afford the appropriate chiral imine-phosphines as colorless viscous oils. Copies of NMR spectra of compounds **9**–**12** are included in the Supplementary Materials.

(E)-1-(2-(diphenylphosphaneyl)phenyl)-N-((S)-1-((S)-2-isopropylaziridin-1-yl)-3-methylbutan-2-yl)methanimine 9

Colorless oil, 97% yield; $[\alpha]_D^{20}$ = +4.83 (c 0.5, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 0.58 (d, *J* = 6.9 Hz, 1H); 0.75–0.81 (m, 9H, 3xCH_3); 0.82–0.86 (m, 3H, CH_3); 0.87–0.89 (m, 1H); 0.95–1.01 (m, 2H); 1.04–1.08 (m, 2H); 1.12–1.19 (m, 1H); 1.44 (d, *J* = 3.4 Hz, 1H); 1.73 (dd, J_1 = 7.0 Hz, J_2 = 12.0 Hz, 1H); 1.89–1.95 (m, 1H); 2.84 (dd, J_1 = 5.4 Hz, J_2 = 11.9 Hz, 1H); 3.08 (m, 1H); 6.87–6.91 (m, 1H); 7.25–7.31 (m, 9H); 7.32–7.37 (m, 6H); 7.38–7.43 (m, 1H); 7.95–7.98 (m, 1H); 8.81 (d, *J* = 4.62 Hz, 1H) ppm;

^{13}C NMR (150 MHz, $CDCl_3$): δ = 17.70 (**C**H_3), 19.13 (**C**H_3), 20.00 (**C**H_3), 20.69 (**C**H_3), 30.98 (**C**H), 31.53 (**C**H_2), 31.89 (**C**H), 46.63 (**C**H), 64.46 (**C**H_2), 77.60 (**C**H), 128.37 (**C$_{arom.}$**), 128.59 (**C$_{arom.}$**), 128.72 (**C$_{arom.}$**), 129.90 (**C$_{arom.}$**), 133.38 (**C$_{arom.}$**), 134.11 (**C$_{arom.}$**), 137.03 (**C$_{arom.}$**), 137.33 (**C$_{arom.}$**), 139.57 (**C$_{arom.}$**), 159.13 (d, *J* = 72.0 Hz, **C$_{imine}$**) ppm;

^{31}P NMR (243 MHz, $CDCl_3$): δ = −13.2 ppm;

Anal. Calcd. for $C_{29}H_{35}N_2P$; C, 78.70; H, 7.97; N, 6.33; P, 7.00; Found: C, 78.72; H, 7.95; N, 6.32; P, 7.01.

(E)-1-(2-(diphenylphosphaneyl)phenyl)-N-((R)-1-((R)-2-isopropylaziridin-1-yl)-3-methylbutan-2-yl)methanamine 10

Colorless oil, 97% yield; $[\alpha]_D^{20}$ = −4.80 (*c* 0.5, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 0.58 (d, *J* = 6.9 Hz, 1H); 0.75–0.81 (m, 9H, 3xCH_3); 0.82–0.86 (m, 3H, CH_3); 0.87–0.89 (m, 1H); 0.95–1.01 (m, 2H); 1.04–1.08 (m, 2H); 1.12–1.19 (m, 1H); 1.44 (d, *J* = 3.4 Hz, 1H); 1.73 (dd, J_1 = 7.0 Hz, J_2 = 12.0 Hz, 1H); 1.89–1.95 (m, 1H);

2.84 (dd, J_1 = 5.4 Hz, J_2 = 11.9 Hz, 1H); 3.08 (m, 1H); 6.87–6.91 (m, 1H); 7.25–7.31 (m, 9H); 7.32–7.37 (m, 6H); 7.38–7.43 (m, 1H); 7.95–7.98 (m, 1H); 8.81 (d, J = 4.62Hz, 1H) ppm;

^{13}C NMR (150 MHz, $CDCl_3$): δ = 17.70 (**C**H_3), 19.13 (**C**H_3), 20.00 (**C**H_3), 20.69 (**C**H_3), 30.98 (**C**H), 31.53 (**C**H_2), 31.89 (**C**H), 46.63 (**C**H), 64.46 (**C**H_2), 77.60 (**C**H), 128.37 (**C$_{arom.}$**), 128.59 (**C$_{arom.}$**), 128.72 (**C$_{arom.}$**), 129.90 (**C$_{arom.}$**), 133.38 (**C$_{arom.}$**), 134.11 (**C$_{arom.}$**), 137.03 (**C$_{arom.}$**), 137.33 (**C$_{arom.}$**), 139.57 (**C$_{arom.}$**), 159.13 (d, J = 72.0 Hz, **C$_{imine}$**) ppm;

^{31}P NMR (243 MHz, $CDCl_3$): δ = -13.2 ppm;

Anal. Calcd. for $C_{29}H_{35}N_2P$; C, 78.70; H, 7.97; N, 6.33; P, 7.00; Found: C, 78.72; H, 7.95; N, 6.32; P, 7.01.

(E)-1-(2-(diphenylphosphaneyl)phenyl)-N-((S)-1-((S)-2-isobutylaziridin-1-yl)-4-methylpentan-2-yl)methanimine 11

Colorless oil, 94% yield; $[\alpha]_D^{20}$ = +4.76 (*c* 0.5, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 0.65 (d, J = 6.3 Hz, 3H, CH_3); 0.69 (d, J = 6.8 Hz, 1H); 0.73 (d, J = 6.5 Hz, 3H, CH_3); 0.79 (d, J = 9.2 Hz, 3H, CH_3); 0.84 (d, J = 1.0 Hz, 3H, CH_3); 0.96–1.0 (m, 4H); 1.21 (d, J = 6.0 Hz, 1H); 1.39–1.42 (m, 1H); 1.43 (d, J = 3.8 Hz, 1H); 1.81 (dd, J_1 = 7.5 Hz, J_2 = 11.6 Hz, 1H); 2.78 (dd, J_1 = 4.8 Hz, J_2 = 11.7 Hz, 1H); 3.43–3.48 (m, 1H); 6.86–6.89 (m, 1H); 7.22–7.27 (m, 3H); 7.29–7.31 (m, 1H); 7.32–7.37 (m, 8H); 7.38–7.43 (m, 3H); 7.92–8.0 (m, 1H); 8.92 (d, J = 4.86 Hz, 1H) ppm;

^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.06 (**C**H_3), 21.32 (**C**H), 22.53 (**C**H_3), 22.86 (**C**H_3), 23.57 (**C**H_3), 27.00 (**C**H), 33.84 (**C**H_2), 39.09 (**C**H), 42.08 (**C**H_2), 42.81 (**C**H), 67.01 (**C**H_2), 70.02 (**C**H_2), 127.99 (**C$_{arom.}$**), 128.65 (**C$_{arom.}$**), 129.11 (**C$_{arom.}$**), 130.07 (**C$_{arom.}$**), 130.70 (**C$_{arom.}$**), 133.22 (**C$_{arom.}$**), 134.07 (**C$_{arom.}$**), 136.13 (**C$_{arom.}$**), 136.69 (**C$_{arom.}$**), 137.38 (**C$_{arom.}$**), 139.48 (**C$_{arom.}$**), 158.91 (d, J = 78.0 Hz, **C$_{imine}$**) ppm;

^{31}P NMR (243 MHz, $CDCl_3$): δ = −13.41 ppm;

Anal. Calcd. for $C_{31}H_{39}N_2P$ C, 79.11; H, 8.35; N, 5.95; P, 6.58; Found: C, 79.21; H, 8.30; N, 5.90; P, 6.58.

(E)-N-((S)-1-((S)-2-benzylaziridin-1-yl)-3-phenylpropan-2-yl)-1-(2-(diphenylphosphaneyl) phenyl)methanimine 12

Colorless oil, 98% yield; $[\alpha]_D^{20}$ = +3.90 (*c* 0.5, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.23 (d, J = 5.8 Hz, 1H); 1.50 (d, J = 3.2 Hz, 1H); 1.57–1.59 (m, 1H); 1.82 (dd, J_1 = 7.8 Hz, J_2 = 11.5 Hz, 1H); 2.21–2.27 (m, 1H); 2.58–2.64 (m, 1H); 2.70 (dd, J_1 = 4.2 Hz, J_2 = 13.4 Hz, 2H); 2.86–2.91 (m, 1H); 3.52–3.56 (m, 1H); 6.99–7.01 (m, 3H); 7.21–7.24 (m, 4H); 7.28–7.35 (m, 17H); 8.62 (d, J = 4.4 Hz, 1H) ppm;

^{13}C NMR (150 MHz, $CDCl_3$): δ = 33.33 (**C**H_2), 39.40 (**C**H_2), 40.83 (**C**H_2), 42.08 (**C**H_2), 41.23 (**C**H), 65.50 (**C**H_2), 73.80 (**C**H), 125.95 (**C$_{arom.}$**), 126.13 (**C$_{arom.}$**), 126.43 (**C$_{arom.}$**), 128.06 (**C$_{arom.}$**), 128.29 (**C$_{arom.}$**), 128.60 (**C$_{arom.}$**), 128.77 (**C$_{arom.}$**), 129.14 (**C$_{arom.}$**), 129.53 (**C$_{arom.}$**), 130.01 (**C$_{arom.}$**), 133.75 (**C$_{arom.}$**), 133.93 (**C$_{arom.}$**), 134.04 (**C$_{arom.}$**), 134.16 (**C$_{arom.}$**), 137.14 (**C$_{arom.}$**), 137.54 (**C$_{arom.}$**), 137.68 (**C$_{arom.}$**), 138.85 (**C$_{arom.}$**), 139.37 (**C$_{arom.}$**), 159.52 (d, J = 69.60 Hz, **C$_{imine}$**) ppm;

^{31}P NMR ($CDCl_3$, 243 MHz): δ = −13.10 ppm;

Anal. Calcd. for $C_{37}H_{35}N_2P$ C, 82.50; H, 6.55; N, 5.20; P, 5.75; Found: C, 82.42; H, 6.58; N, 5.26; P, 5.74.

3.2.2. Asymmetric Simmons–Smith Cyclopropanation—General Procedure

The corresponding allylic alcohols (substrates) were prepared using the literature protocols [40,41]. The solution of chiral ligand in anhydrous CH_2Cl_2 (5 mL) was cooled to 0 °C and alcohol (0.5 mmol), diethylzinc (1.0 M in hexanes, 1 mmol) and CH_2I_2 (0.6 mmol) were added. The resulting mixture was stirred for 4 h at room temperature. The reaction was quenched by adding a 2 M aqueous solution of NaOH, the phases were separated and the aqueous layer was extracted with dichloromethane (3 × 10 mL). Combined layers were dried with $MgSO_4$ and evaporated in vacuo. The pure product was obtained by purification via column chromatography on silica gel (hexane:ethyl acetate 2:1). The spectroscopic data

of products were consistent with the literature data [21]. Selected HPLC chromatograms of the cyclopropanation products are included in the Supplementary Materials.

3.2.3. Asymmetric Addition of Diethylzinc to Aldehydes—General Procedure

Diethylzinc (1.0 M in hexanes, 3 mmol) was added to the solution of the chiral ligand (0.1 mmol) in toluene (5 mL) at 0 °C. The mixture was stirred for 30 min at this temperature, and an aldehyde (1 mmol) was added. The resulting solution was stirred for 2 h at 0 °C, then overnight at room temperature. The reaction was quenched by adding 5% aqueous solution of HCl. The layers were separated, and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The crude product was purified by column chromatography on silica gel (hexane:ethyl acetate 5:1) [42]. The NMR spectra of the products were consistent with the literature data [37–39]. Selected HPLC chromatograms of the addition products are included in the Supplementary Materials.

4. Conclusions

The chiral aziridine-phosphines exhibited a very high catalytic activity in the asymmetric Simmons-Smith cyclopropanation of allylic alcohols and in the asymmetric addition of diethylzinc to aldehydes. The corresponding cyclopropanation and addition products were achieved in satisfactory chemical yields and with a high level of enantioselectivity and diastereoselectivity. The absolute configuration of a carbon atom of aziridine has a crucial influence on the stereochemical outcome of both title reactions. Moreover, the presence of the phosphine moiety in the structure of the chiral ligand has a very strong influence on the efficient course of both asymmetric transformations.

By carrying out these asymmetric reactions, we showed that aziridine-phosphines are versatile catalysts; thus, it is certainly necessary to continue research on their effectiveness in asymmetric synthesis.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/catal11080968/s1: copies of NMR spectra of compounds **9**–**12** and selected HPLC chromatograms for Simmons-Smith cyclopropanation and diethylzinc addition products.

Author Contributions: Conceptualization and methodology, S.L. and M.R.; software, A.M.P., A.Z. and M.R.; investigation, A.B.-S., A.Z., J.A., L.M., A.M.P. and M.R.; writing—original draft preparation, M.R.; writing—review and editing, S.L. and M.R.; supervision, M.R. and S.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the National Science Centre (NCN) (grant no. 2016/21/B/ST5/00421 for M.R.). The scientific grant InterChemMed No. POWR.03.02.00-00-00-I029/16 to A.B. is also acknowledged.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Carroll, M.P.; Guiry, P.J. P,N ligands in asymmetric catalysis. *Chem. Soc. Rev.* **2014**, *43*, 819–833. [CrossRef]
2. Li, Y.-M.; Kwong, F.-Y.; Yu, W.-Y.; Chan, A.S.C. Recent advances in developing new axially chiral phosphine ligands for asymmetric catalysis. *Coord. Chem. Rev.* **2007**, *251*, 2119–2144. [CrossRef]
3. Gaunt, M.J.; Johansson, C.C.C.; McNally, A.; Vo, N.T. Enantioselective organocatalysis. *Drug Discov. Today* **2007**, *12*, 8–27. [CrossRef] [PubMed]
4. Han, B.; He, X.-H.; Liu, Y.-Q.; He, G.; Peng, C.; Li, J.-L. Asymmetric organocatalysis: An enabling technology for medicinal chemistry. *Chem. Soc. Rev.* **2021**, *50*, 1522–1586. [CrossRef] [PubMed]
5. Diaz-Muñoz, G.; Miranda, I.L.; Sartori, S.K.; De Rezende, D.C.; Nogueira Diaz, M.A. Use of chiral auxiliaries in the asymmetric synthesis of biologically active compounds: A review. *Chirality* **2019**, *31*, 776–812. [CrossRef] [PubMed]
6. Dixon, D.J. Bifunctional catalysis. *Beilstein J. Org. Chem.* **2016**, *12*, 1079–1080. [CrossRef] [PubMed]
7. Yuan, Y.-H.; Han, X.; Zhu, F.-P.; Tian, J.-M.; Zhang, F.-M.; Zhang, X.-M.; Tu, Y.-Q.; Wang, S.-H.; Guo, X. Development of bifunctional organocatalysts and application to asymmetric total synthesis of naucleofficine I and II. *Nat. Commun.* **2019**, *10*, 3394. [CrossRef] [PubMed]

8. Peters, R. (Ed.) *Cooperative Catalysis: Designing Efficient Catalysts for Synthesis*; Wiley-VCH Verlag GmbH & Co. KgaA: Weinheim, Germany, 2015; pp. 1–456.
9. Werth, J.; Uyeda, C. Regioselective Simmons-Smith-type cyclopropanations of polyalkenes enabled by transition metal catalysis. *Chem. Sci.* **2018**, *9*, 1604–1609. [CrossRef]
10. Časar, Z. Synthetic Approaches to Contemporary Drugs that Contain the Cyclopropyl Moiety. *Synthesis* **2020**, *52*, 1315–1345. [CrossRef]
11. Ezawa, T.; Kawashima, Y.; Noguchi, T.; Jung, S.; Imai, N. Convenient synthesis of memantine analogues containing a chiral cyclopropane skeleton as a sigma-1 receptor agonist. *Tetrahedron Asymmetry* **2017**, *28*, 266–281. [CrossRef]
12. Sun, M.; Li, W.-D.Z.; Qiu, F.G. Asymmetric Synthesis of the DEFG Rings of Solanoeclepin A. *Org. Lett.* **2019**, *21*, 644–647. [CrossRef]
13. Talele, T.T. The "Cyclopropyl Fragment" is a Versatile Player that Frequently Appears in Preclinical/Clinical Drug Molecules. *J. Med. Chem.* **2016**, *59*, 8712–8756. [CrossRef] [PubMed]
14. Chawner, S.J.; Cases-Thomas, M.J.; Bull, J.A. Divergent Synthesis of Cyclopropane-Containing Lead-Like Compounds, Fragments and Building Blocks through a Cobalt Catalyzed Cyclopropanation of Phenyl Vinyl Sulfide. *Eur. J. Org. Chem.* **2017**, 5015–5024. [CrossRef] [PubMed]
15. Novakov, I.A.; Babushkin, A.S.; Yablokov, A.S.; Nawrozkij, M.B.; Vostrikova, O.V.; Shejkin, D.S.; Mkrtchyan, A.S.; Balakin, K.V. Synthesis and structure—activity relationships of cyclopropane-containing analogs of pharmacologically active compounds. *Russ. Chem. Bull. Int. Ed.* **2018**, *67*, 395–418. [CrossRef]
16. Wu, W.; Lin, Z.; Jiang, H. Recent advances in the synthesis of cyclopropanes. *Org. Biomol. Chem.* **2018**, *16*, 7315–7329. [CrossRef] [PubMed]
17. Berkessel, A.; Ertürk, E.; Neudörfl, J.M. Asymmetric cyclopropanation of olefins catalyzed by a chiral cobalt(II) porphyrin. *Org. Commun.* **2017**, *10*, 79–89. [CrossRef]
18. Meazza, M.; Ashe, M.; Shin, H.Y.; Yang, H.S.; Mazzanti, A.; Yang, J.W.; Rios, R. Enantioselective Organocatalytic Cyclopropanation of Enals Using Benzyl Chlorides. *J. Org. Chem.* **2016**, *81*, 3488–3500. [CrossRef]
19. Dočekal, V.; Petrželová, S.; Císařová, I.; Veselý, J. Enantioselective Cyclopropanation of 4-Nitroisoxazole Derivatives. *Adv. Synth. Catal.* **2020**, *362*, 2597–2603. [CrossRef]
20. Herchl, R.; Waser, M. Asymmetric cyclopropanation of chalcones using chiral phase-transfer catalysts. *Tetrahedron Lett.* **2013**, *54*, 2472–2475. [CrossRef]
21. Rachwalski, M.; Kaczmarczyk, S.; Leśniak, S.; Kiełbasiński, P. Highly Efficient Asymmetric Simmons-Smith Cyclopropanation Promoted by Chiral Heteroorganic Aziridinyl Ligands. *ChemCatChem* **2014**, *6*, 873–875. [CrossRef]
22. Pu, L.; Yu, H.-B. Catalytic Asymmetric Organozinc Additions to Carbonyl Compounds. *Chem. Rev.* **2001**, *101*, 757–824. [CrossRef]
23. Rachwalski, M.; Jarzyński, S.; Leśniak, S. Aziridine ring-containing chiral ligands as highly efficient catalysts in asymmetric synthesis. *Tetrahedron Asymmetry* **2013**, *24*, 421–425. [CrossRef]
24. Pieczonka, A.M.; Leśniak, S.; Jarzyński, S.; Rachwalski, M. Aziridinylethers as highly enantioselective ligands for the asymmetric addition of organozinc species to carbonyl compounds. *Tetrahedron Asymmetry* **2015**, *26*, 148–151. [CrossRef]
25. Leśniak, S.; Rachwalski, M.; Sznajder, E.; Kiełbasiński, P. New highly efficient aziridine-functionalized tridentate sulfinyl catalysts for enantioselective diethylzinc addition to carbonyl compounds. *Tetrahedron Asymmetry* **2009**, *20*, 2311–2314. [CrossRef]
26. Rachwalski, M.; Jarzyński, S.; Jasiński, M.; Leśniak, S. Mandelic acid derived a-aziridinyl alcohols as highly efficient ligands for asymmetric additions of zinc organyls to aldehydes. *Tetrahedron Asymmetry* **2013**, *24*, 689–693. [CrossRef]
27. Leśniak, S.; Rachwalski, M.; Jarzyński, S.; Obijalska, E. Lactic acid derived aziridinyl alcohols as highly effective catalysts for asymmetric additions of an organozinc species to aldehydes. *Tetrahedron Asymmetry* **2013**, *24*, 1336–1340. [CrossRef]
28. Rachwalski, M. Limonene oxide derived aziridinyl alcohols as highly efficient catalysts for asymmetric additions of organozinc species to aldehydes. *Tetrahedron Asymmetry* **2014**, *25*, 219–223. [CrossRef]
29. Doğan, Ö.; Çağli, E. PFAM catalyzed enantioselective diethylzinc addition to imines. *Turk. J. Chem.* **2015**, *39*, 290–296. [CrossRef]
30. Buchcic, A.; Zawisza, A.; Leśniak, S.; Rachwalski, M. Asymmetric Friedel-Crafts Alkylation of Indoles Catalyzed by Chiral Aziridine-Phosphines. *Catalysts* **2020**, *10*, 971. [CrossRef]
31. Pieczonka, A.M.; Misztal, E.; Rachwalski, M.; Leśniak, S. Synthesis of chiral 1-(2-aminoalkyl)aziridines via a self-opening reaction of aziridine. *Arkivoc* **2017**, *2017*, 223–234. [CrossRef]
32. Shitama, H.; Katsuki, T. Asymmetric Simmons-Smith Reaction of Allylic Alcohols with Al Lewis Acid/N Lewis Base Bifunctional Al(Salalen) Catalyst. *Angew. Chem. Int. Ed.* **2008**, *47*, 2450–2453. [CrossRef]
33. Wujkowska, Z.; Zawisza, A.; Leśniak, S.; Rachwalski, M. Phosphinoyl-aziridines as a new class of chiral catalysts for enantioselective Michael addition. *Tetrahedron* **2019**, *75*, 230–235. [CrossRef]
34. Buchcic, A.; Zawisza, A.; Leśniak, S.; Adamczyk, J.; Pieczonka, A.M.; Rachwalski, M. Enantioselective Mannich reaction promoted by chiral phosphinoyl-aziridines. *Catalysts* **2019**, *9*, 837. [CrossRef]
35. Leśniak, S.; Rachwalski, M.; Pieczonka, A.M. Optically Pure Aziridinyl Ligands as Useful Catalysts in the Stereocontrolled Synthesis. *Curr. Org. Chem.* **2014**, *18*, 3045–3065. [CrossRef]
36. Zhang, C.-H.; Yan, S.-J.; Pan, S.-Q.; Huang, R.; Lin, J. Highly Enantioselective Addition of Diethylzinc to aldehydes Catalyzed by Novel Chiral *tert*-Amino Alcohols. *Bull. Korean Chem. Soc.* **2010**, *31*, 869–873. [CrossRef]

37. Cere, V.; Peri, F.; Pollicino, S. Regio- and Stereospecific Me_3SiI-Promoted Intramolecular Displacement of Hydroxy Group by Sulfide. 2. Polyhydroxylated Thiepane Ring Contraction to Thiolane or Thiane Derivatives. Synthesis of Enantiopure Polyalcohols. *J. Org. Chem.* **1997**, *62*, 8572–8574. [CrossRef] [PubMed]
38. Dilek, Ö.; Tezeren, M.A.; Tilki, T.; Ertürk, E. Chiral 2-(hydroxyaryl)alcohols (HAROLs) with a 1,4-diol scaffold as a new family of ligands and organocatalysts. *Tetrahedron* **2018**, *74*, 268–286. [CrossRef]
39. Lombardo, M.; Chiarucci, M.; Trombini, C. The first enantioselective addition of diethylzinc to aldehydes in ionic liquids catalysed by a recyclable ion-tagged diphenylprolinol. *Chem. Eur. J.* **2008**, *14*, 11288–11291. [CrossRef] [PubMed]
40. Dieckmann, M.; Jang, Y.-S.; Cramer, N. Chiral cyclopentadienyl iridium(III) complexes promote enantioselective cycloisomerizations giving fused cyclopropanes. *Angew. Chem. Int. Ed.* **2015**, *54*, 12149–12152. [CrossRef] [PubMed]
41. Ando, K. Highly selective synthesis of (Z)-unsaturated esters by using new Horner-Emmons reagents, ethyl (diarylphosphono)acetates. *J. Org. Chem.* **1997**, *62*, 1934–1939. [CrossRef] [PubMed]
42. Rachwalski, M.; Kwiatkowska, M.; Drabowicz, J.; Kłos, M.; Wieczorek, W.M.; Szyrej, M.; Sieroń, L.; Kiełbasiński, P. Enzyme-promoted desymmetrization of bis(2-hydroxymethylphenyl)sulfoxide as a route to tridentate chiral catalysts. *Tetrahedron Asymmetry* **2008**, *19*, 2096–2101. [CrossRef]