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Enantiodivergent Aldol Condensation in the Presence of Aziridine/Acid/Water Systems

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Abstract: A series of novel chiral imines was synthesized from corresponding aldehydes and 1-(2-aminoalkyl)aziridines with good chemical yields. Such imines were tested as catalysts in the direct asymmetric aldol reaction between aromatic aldehydes and acetone/cyclohexanone in the presence of catalytic amounts of water and an acidic additive. The corresponding aldol products were formed in excellent yields and with very high enantioselectivities (98% and 99% *ee*, respectively).

Keywords: asymmetric synthesis; enantiodivergent aldol condensation; diastereodivergent process; aziridines; chiral imines; enantioselectivity

1. Introduction

The stereoselective creation of carbon–carbon bonds using chiral catalysts constitutes one of the most common methods used for the synthesis of optically pure compounds [1]. Among them, the direct asymmetric aldol reaction is one of the most powerful transformations in synthetic organic chemistry [2–4], being one of the synthetic stages in the preparation of various useful substances, such as canthaxanthin (a keto-carotenoid) [5], echinenone (a xanthophylls) [6,7], or citranaxanthin (a carotenoid pigment applied as food coloring additive) [8]. Furthermore, its modification through the use of catalytic amounts of water and a Lewis acid is becoming more popular in modern organic chemistry [9]. Moreover, the procedure allowing for the selective synthesis of each of both enantiomers of a product from identical starting material is known as an enantiodivergent synthesis. Enantiodivergent (enantioselective) processes can be easily achieved by employing a specific enantiomer of chiral catalysts, various solvents, and acidic or basic agents, as well as metal cations and starting from the same substrates [10,11]. Diastereodivergent processes, leading to specific diastereoisomers, are much more challenging [12], but in the literature, there are examples of enantioselective diastereodivergent aldol condensations of cyclohexanone with electron-deficient aryl aldehydes [13,14]. The control of diastereoselectivity can be achieved, e.g., by changing the acidic additives [12].

In nature, direct aldol transformations in water are catalyzed by aldolases of type I or type II. These enzymes affect the coupling of substrates via an enamine (aldolases type I) or enolate formation mechanism (aldolases type II) (Figure 1). Promoted by aldolases, an aldol reaction carried out in water was one of the most inspiring transformations taken from nature. For this reason, chemists are focused on the development of small-molecule catalysts possessing strong and versatile properties that mimic enzymes [9,15].

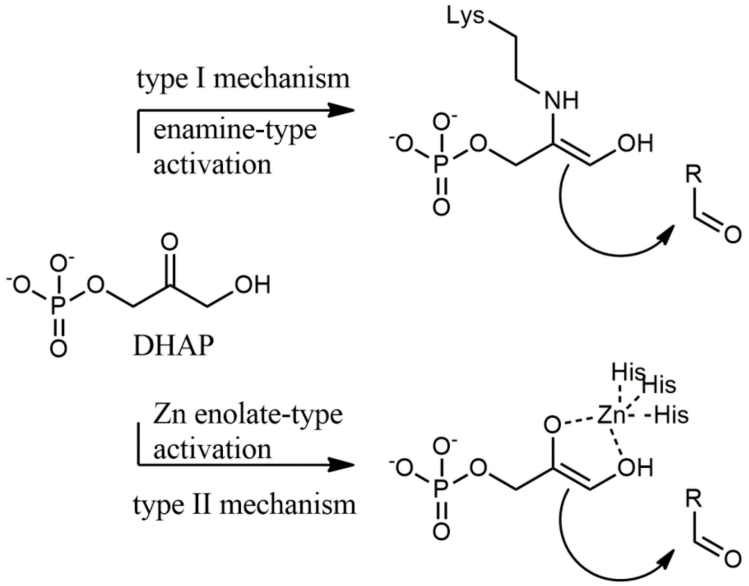


Figure 1. Mechanisms of type I and II aldolases.

We have previously reported a successful direct asymmetric aldol reaction using various aziridine-based catalysts, such as aziridine alcohols and ethers [16], aziridine semicarbazides [17], and recently, aziridine amides [18]. In the combination of water and $Zn(OTf)_2$, the appropriate adducts were formed from acetone and aromatic aldehydes in high yields and also with high enantiomeric excess values.

Based on our experience in the field of asymmetric synthesis using aziridine-containing ligands/organocatalysts [19–22] and achieving very promising preliminary results [23,24], we decided to synthesize a series of chiral, diastereomerically pure imines from 1-(2-aminoalkyl)aziridines and to investigate their catalytic activity in the enantiodivergent and/or diastereodivergent asymmetric aldol reaction in the presence of water. In 2019, Chen et al. [25] prepared chiral aziridine imines and investigated its use in organocatalysis. However, our first report concerning such chiral derivatives appeared in 2017 [23]. As a continuation of the studies, we herein present the synthesis of aziridine ligands with specific configurations by starting from 1-(2-aminoalkyl)aziridines and any carbonyl compound (not only hydroxy-substituted), which is more useful from a synthetic point of view. Moreover, the first use of aziridine-functionalized compounds in a diastereodivergent aldol reaction was reported.

2. Results

Chiral catalysts **1**–**10** (Figure 2) were synthesized using a two-step synthesis from chiral, optically pure NH-aziridines [22] according to a procedure described earlier [23,24]. Two equivalents of enantiomerically pure chiral aziridines reacted with one equivalent of $ZnBr_2$ at 80 °C without solvent. The appropriate 1-(2-aminoalkyl)aziridines **11**–**13** were formed as a result of the Lewis acid $ZnBr_2$-catalyzed self-ring opening of aziridine with good yields in a diastereoselective manner (Scheme 1). The appropriate 1-(2-aminoalkyl)aziridines **11**–**13** were then treated with aromatic aldehydes in boiling methanol over 16 h, producing chiral, diastereomerically pure imines **1**–**10** with very high chemical yields around 95%. All synthetic details are described in Appendix A and Supplementary Materials.

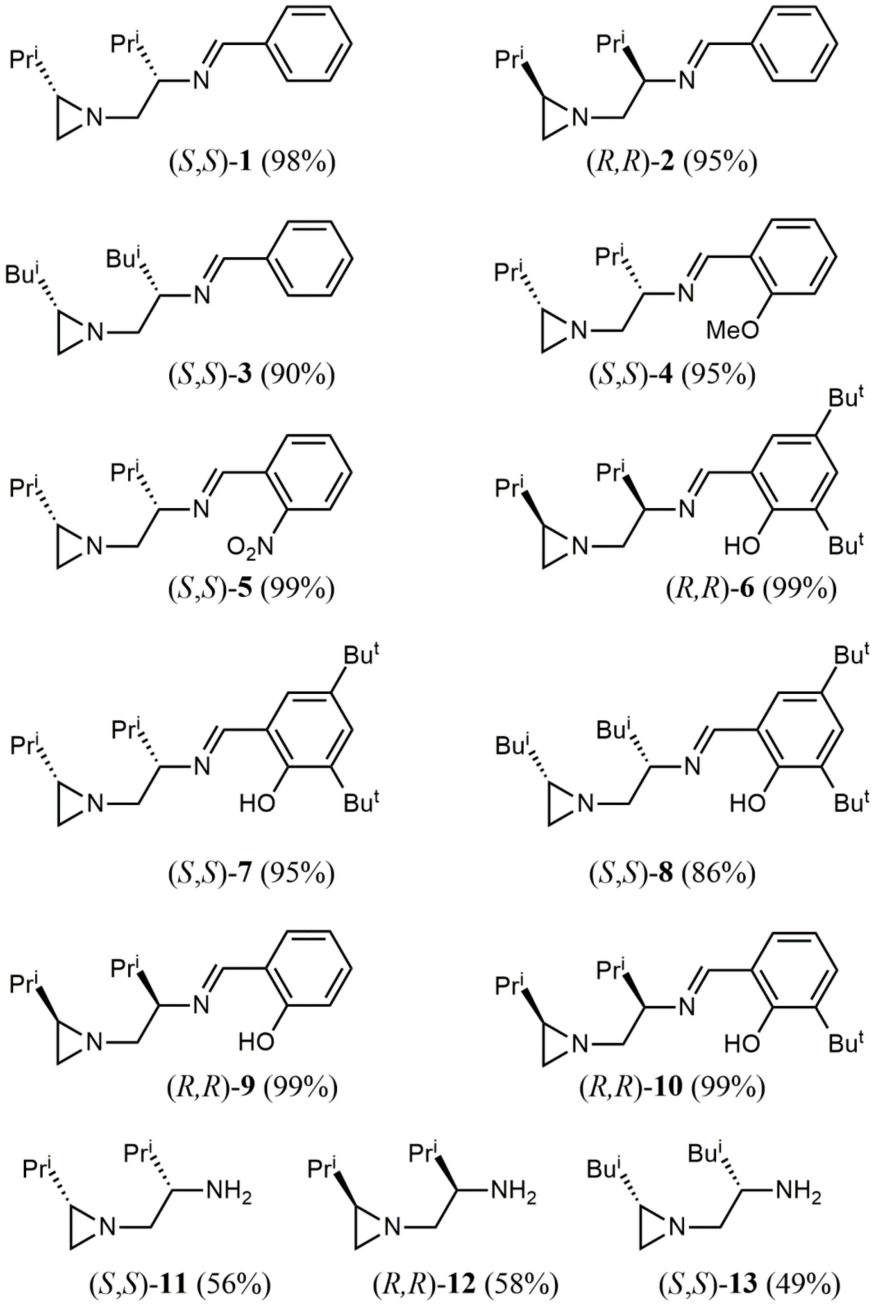
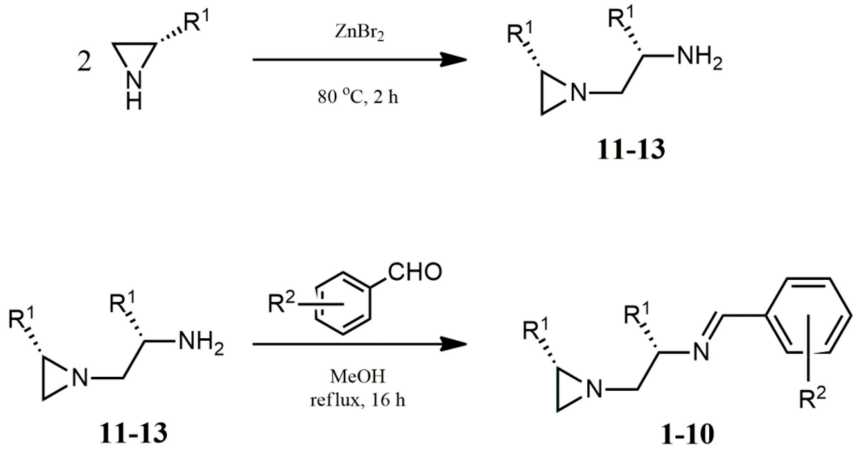
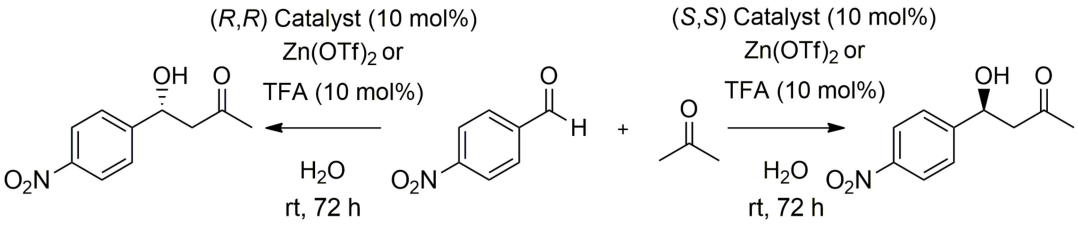


Figure 2. Chiral imines **1**–**10** and 1-(2-aminoalkyl)aziridines **11**–**13**.

In the course of our studies, we decided to investigate the catalytic activity of the new chiral aryl imines **1**–**10** obtained from 1-(2-aminoalkyl)aziridines and 1-(2-aminoalkyl)aziridines **11**–**13** in asymmetric aldol reactions of acetone with 4-nitrobenzaldehyde. The reactions were performed in the presence of 10 mol% of catalyst and 10 mol% of additive ($Zn(OTf)_2$ or TFA, respectively) in an acetone/water (1.8/0.2) mixture (Scheme 2). All the results are collected in Table 1.



Scheme 1. Synthesis of the chiral catalysts.



Scheme 2. Asymmetric aldol transformations that were promoted by chiral aziridines.

Table 1. Aldol reactions of acetone with 4-nitrobenzaldehyde that were promoted by various catalysts.

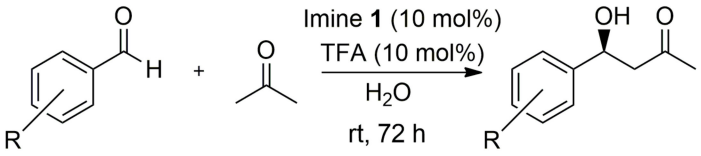
Entry	Catalyst	Additive	Yield (%)	*ee* [a] (%)	Abs. Conf.
1	**1**	$Zn(OTf)_2$	96	99	(*S*)
2	**1**	TFA	98	99	(*S*)
3	**2**	$Zn(OTf)_2$	86	78	(*R*)
4	**2**	TFA	96	99	(*R*)
5	**3**	$Zn(OTf)_2$	85	65	(*S*)
6	**3**	TFA	91	20	(*S*)
7	**4**	$Zn(OTf)_2$	87	69	(*S*)
8	**4**	TFA	87	42	(*S*)
9	**5**	$Zn(OTf)_2$	99	54	(*S*)
10	**5**	TFA	99	53	(*S*)
11	**6**	$Zn(OTf)_2$	98	86	(*R*)
12	**6**	TFA	84	8	(*R*)
13	**7**	$Zn(OTf)_2$	96	64	(*S*)
14	**7**	TFA	91	30	(*S*)
15	**8**	$Zn(OTf)_2$	99	54	(*S*)
16	**8**	TFA	98	50	(*S*)
17	**9**	$Zn(OTf)_2$	94	65	(*R*)
18	**9**	TFA	98	45	(*R*)
19	**10**	$Zn(OTf)_2$	91	36	(*R*)
20	**10**	TFA	99	50	(*R*)
21	**11**	TFA	99	51	(*S*)
22	**12**	TFA	98	50	(*R*)
23	**13**	TFA	93	23	(*S*)
24 [b]	**1**	$Zn(OTf)_2$	96	87	(*S*)

[a] Determined using chiral HPLC on a Chiralpak AD column. [b] Reaction in the presence of 5 mol% of the catalyst and additive.

An inspection of Table 1 reveals that the best results in terms of chemical yield and enantiomeric excess were obtained using chiral imines **1** and **2** in the presence of trifluoroacetic acid. The use of organocatalysts **3** and **8** bearing isobutyl moieties led to adducts with lower *ee* values, which was probably due to steric hindrance (Table 1, entries 5, 6, 15, and 16). An application of imine **5** with an electron-withdrawing group (–NO_2) at the phenyl ring gave very similar amounts of the corresponding product with moderate enantioselectivity (Table 1, entries 9 and 10). The introduction of an electron-donating group (–OMe) into the aromatic ring resulted in a lower chemical yield (Table 1, entries 7 and 8). As an unexpected result, the use of imine **6** in combination with TFA gave a product with dramatically lower enantioselectivity (Table 1, entry 12), although the same catalyst **6** worked very efficiently with $Zn(OTf)_2$ (Table 1, entry 11). In the last experiments (Table 1, entry 21–23), the chiral 1-(2-aminoalkyl)aziridines **11**–**13** (Figure 2) themselves were used as catalysts and produced good yields and moderate enantioselectivity only in the presence of TFA. Experiments performed with $Zn(OTf)_2$ as an additive or without any additive and water did not lead to the expected product. The reduction of the amount of catalyst **1** and additive to 5 mol% led to a product with a decreased enantioselectivity with the same chemical yield (Table 1, entry 24).

The configuration of all the aldol products was established according to optical rotation signs, retention times in HPLC chromatograms, and by comparison with literature data [22–28]. All data are described in Appendix A and chromatograms are included in Supplementary Materials. In all cases, the application of a catalyst with the (*S*,*S*) configuration led to a product with an (*S*) configuration, while an (*R*,*R*)-catalyst gave an (*R*)-aldol product, as we observed in previous contributions [14,15,18].

After establishing the most effective organocatalyst, namely **1**, we decided to test its catalytic activity in the title reaction using other aromatic aldehydes bearing electron-withdrawing groups in the presence of TFA (Scheme 3). The results are summarized in Table 2.



Scheme 3. Asymmetric aldol reaction of other substituted benzaldehydes in the presence of chiral imine **1**.

Table 2. Aldol reactions of acetone with 4-nitrobenzaldehyde in the presence of various catalysts.

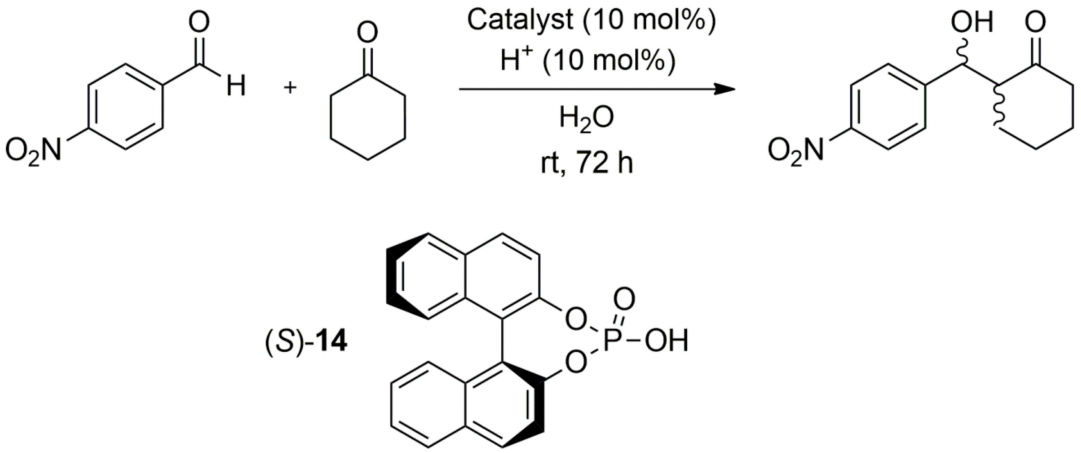
Entry	R	Yield (%)	*ee* [a] (%)	Abs. Conf.
1	2-NO_2	86	82	(*S*)
2	2,4-diNO_2	>99	>99	(*S*)
3	4-CN	98	42	(*S*)
4	4-CF_3	62	38	(*S*)
5	H	24	11	(*S*)

[a] Determined using chiral HPLC on a Chiralpak AD column.

The use of 2-nitrobenzaldehyde as a starting material produced an aldol product with a good chemical yield and *ee* (Table 2, entry 1). However, when 2,4-dinitrobenzaldehyde was applied, the title reaction proceeded much more effectively (Table 2, entry 2). The use of other electron-deficient aldehydes gave corresponding products with lower *ee* values (Table 2, entries 3 and 4). The reaction with benzaldehyde gave an aldol product with dramatically lowered enantioselectivity and chemical yield (Table 2, entry 5).

Thus, it was demonstrated that the use of a specific enantiomer of an imine catalyst could lead to a specific configuration of the product when starting from acetone and 4-nitrobenzaldehyde. An aldol reaction in the presence of an imine catalyst constituted an enantioselective process; in the next step, the enantiodivergence (diastereodivergence) of the aldol reaction between 4-nitrobenzaldehyde and

cyclohexanone was examined (Scheme 4). In this part of the study, imine **9** (*R*,*R*) and its enantiomer **9**-(*S*,*S*) were used (Table 3). As additives, TFA and both enantiomers of 1,1′-binaphthyl-2,2′-diyl hydrogenphosphate **14** were applied. We chose catalyst **9** because in the first case, it gave very good results in terms of reaction yields, but only the average selectivity for both acids was used as an additive (Table 1, entries 17, 18).



Scheme 4. Asymmetric aldol reaction of cyclohexanone in the presence of chiral imines and chiral acid additives.

Table 3. Aldol reactions of cyclohexanone with 4-nitrobenzaldehyde in the presence of catalyst **9** and various acidic additives.

Entry	Catalyst	Additive	Yield (%)	*dr* [a] (*Syn*/*Anti*)	*ee* [b] *Syn* (%)	*ee* [b] *Anti* (%)
1	**9** (*S*,*S*)	TFA	86	25:75	<2	77 (*S*,*R*)
2	**9** (*R*,*R*)	TFA	83	27:73	<2	80 (*R*,*S*)
3	**9** (*S*,*S*)	**14** (*R*)	93	11:89	11 (*R*,*R*)	91 (*S*,*R*)
4	**9** (*R*,*R*)	**14** (*R*)	95	10:90	8 (*R*,*R*)	93 (*R*,*S*)
5	**9** (*S*,*S*)	**14** (*S*)	90	44:56	40 (*R*,*R*)	70 (*S*,*R*)
6	**9** (*R*,*R*)	**14** (*S*)	88	65:35	33 (*S*,*S*)	45 (*R*,*S*)

[a] Determined using ^{1}H NMR. [b] Determined using chiral HPLC on a Chiralpak AD-H column.

Similar to the previous results, the use of specific enantiomers of the catalyst in the presence of a chiral acid additive led to the appropriate enantiomers of the product (Table 3, entries 1 and 2) with moderate enantioselectivity and diastereoselectivity. The use of the chiral acid additive (*R*)-**14** (Table 3, entries 3 and 4) improved the enantioselectivity and diastereoselectivity of the reaction for both catalysts. On the other hand, the application of the opposite enantiomer (*S*)-**14** in cooperation with the (*S*,*S*)-**9** catalyst led to a product with a lower *ee* value and with a loss of diastereoselectivity. Moreover, when using an (*R*,*R*)-**9** catalyst and (*S*)-**14** (Table 3, entry 6), a reversion of diastereoselectivity was observed and a *syn*-product (*S*,*S*) with 33% enantiomeric excess was obtained as the main product.

As we present in Figure 3, the use of the catalyst (*S*,*S*)-**9** with the acid (*R*)-**14** led exclusively to an (*S*,*R*) configured *anti* product (Table 3, entry 3), while the use of the imine (*R*,*R*)-**9** with the acid (*R*)-**14** led selectively to an *anti*-(*R*,*S*)-configured compound (Table 3, entry 4). When the imine (*R*,*R*)-**9** was used with the acid (*S*)-**14**, an (*S*,*S*) configured *syn* compound was the main product, which had a low 33% *ee* (Table 3, entry 6). A *syn*-(*R*,*R*) product with 40% *ee* in the mixture with an *anti*-(*S*,*R*) diastereoisomer was formed only in the reaction where the imine (*S*,*S*)-**9** and the acid (*S*)-**14** were applied (Table 3, entry 5). Thus, comparing entries 4 and 6, we saw a reversal of selectivity when we used the opposite acid enantiomer. It can be seen that the configuration of the resulting aldol product was influenced not only by aziridine but also by the acid configuration. Thus, the process

was moderately diastereodivergent and allowed for the isolation of a product with a clearly defined configuration using the same starting materials.

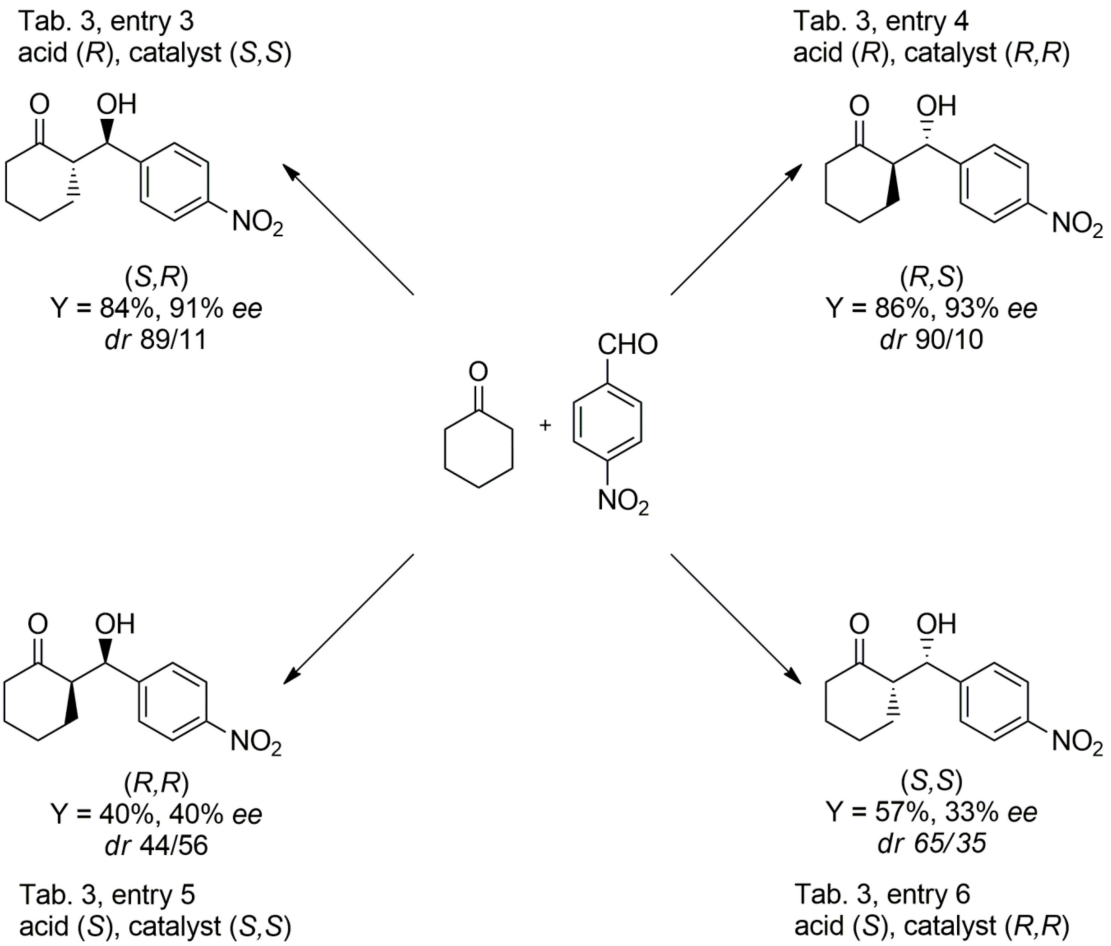


Figure 3. Stereochemistry of obtained products with the yields and enantiomeric excesses of the separated products.

In the next step, the ratio of imine/acidic additive in the experiments with 0.5 eq. and 2 eq. of acid co-catalyst was examined. A change in the ratio of acid and aziridine caused fluctuations in the enantioselectivity; however, a loss of diastereoselectivity took place, so further experiments were conducted in a 1:1 ratio. Moreover, the imines (*R*,*R*)-**2** and (*R*,*R*)-**6** were applied in combination with both enantiomers of acid **14** to examine the influence of substituents in the imine catalyst on the stereoselectivity of the reaction; it was found that the use of those catalysts generally led to an *anti* product (Table 4). Similar to the previous results, an (*R*,*R*)-configured catalyst led to the (*R*,*S*)-*anti* product but the use of an opposite enantiomer of acidic additive did not increase the quantity of *syn* product.

To broaden our knowledge about diastereoselective aldol reactions, we set up a series of experiments with two other aldehydes, namely 2,4-dinitrobenzaldehyde and 2-nitrobenzaldehyde. We also decided to investigate aldol condensation with hydroxyacetone as a ketone component with 4-nitrobenzaldehyde. All experiments were performed with both enantiomers of imine catalyst **9** and both enantiomers of acid **14** (Table 5). In the case of reactions with 2-nitrobenzaldehyde, similar to the previous entries (Table 3), catalyst (*S*,*S*)-**9** led to an (*S*,*R*)-configured *anti* product (Table 5, entry 1 and 3), while the use of imine (*R*,*R*)-**9** led to an (*R*,*S*)-configured compound (Table 5, entry 2 and 4). Only in the reaction where the imine (*S*,*S*)-**9** and the acid (*S*)-**14** were applied, a *syn* (*R*,*R*)-product with

72% *ee* (similar to the reaction with 4-nitrobenzaldehyde, entry 5, Table 3) was formed but with lower diastereoselectivity (Table 5, entry 3).

Table 4. Aldol reactions of cyclohexanone with 4-nitrobenzaldehyde in the presence of different catalysts.

Entry	Catalyst	Additive	Yield (%)	*dr* [a] (*Syn*/*Anti*)	*ee* [b] *Syn* (%)	*ee* [b] *Anti* (%)
1	**9** (*R*,*R*)	**14** (*R*)	95	10:90	8 (*R*,*R*)	93 (*R*,*S*)
2	**9** (*R*,*R*)	**14** (*S*)	88	65:35	33 (*S*,*S*)	45 (*R*,*S*)
3	**2** (*R*,*R*)	**14** (*R*)	35	15:85	10 (*R*,*R*)	94 (*R*,*S*)
4	**2** (*R*,*R*)	**14** (*S*)	99	19:81	14 (*S*,*S*)	95 (*R*,*S*)
5	**6** (*R*,*R*)	**14** (*R*)	99	17:83	24 (*S*,*S*)	94 (*R*,*S*)
6	**6** (*R*,*R*)	**14** (*S*)	99	24:76	30 (*S*,*S*)	92 (*R*,*S*)

[a] Determined using ^{1}H NMR. [b] Determined using chiral HPLC on a Chiralpak AD-H column.

Table 5. Aldol reactions of cyclohexanone with 4-nitrobenzaldehyde in the presence of different catalysts.

Entry	Substrate 1	Substrate 2	Catalyst	Additive	Yield (%)	*dr* [a] (*Syn*/*Anti*)	*ee* [b] *Syn* (%)	*ee* [b] *Anti* (%)
1	2-NO_2	Cyclohexanone	**9** (*S*,*S*)	**14** (*R*)	47	10:90	20 (*R*,*R*)	94 (*S*,*R*)
2	2-NO_2	Cyclohexanone	**9** (*R*,*R*)	**14** (*R*)	46	28:72	52 (*R*,*R*)	92 (*R*,*S*)
3	2-NO_2	Cyclohexanone	**9** (S,S)	**14** (*S*)	99	17:83	72 (*R*,*R*)	96 (*S*,*R*)
4	2-NO_2	Cyclohexanone	**9** (*R*,*R*)	**14** (*S*)	99	18:82	48 (*R*,*R*)	92 (*R*,*S*)
5	2,4-diNO_2	Cyclohexanone	**9** (*S*,*S*)	**14** (*R*)	62	1:99	64 (*S*,*S*)	94 (*R*,*S*)
6	2,4-diNO_2	Cyclohexanone	**9** (*R*,*R*)	**14** (*R*)	99	12:88	41 (*R*,*R*)	96 (*S*,*R*)
7	2,4-diNO_2	Cyclohexanone	**9** (*S*,*S*)	**14** (*S*)	65	2:98	32 (*S*,*S*)	92(*R*,*S*)
8	2,4-diNO_2	Cyclohexanone	**9** (*R*,*R*)	**14** (*S*)	99	33:67	85 (*R*,*R*)	96 (*S*,*R*)
9	4-NO_2	OH-acetone	**9** (*S*,*S*)	**14** (*R*)	99	87:13	92 (*R*,*S*)	26 (*R*,*R*)
10	4-NO_2	OH-acetone	**9** (*R*,*R*)	**14** (*R*)	99	89:11	92 (*S*,*R*)	34 (*S*,*S*)
11	4-NO_2	OH-acetone	**9** (*S*,*S*)	**14** (*S*)	99	89:11	90 (*R*,*S*)	32 (*R*,*R*)
12	4-NO_2	OH-acetone	**9** (*R*,*R*)	**14** (*S*)	99	91:9	96 (*S*,*R*)	36 (*S*,*S*)

In the reactions with 2,4-dinitrobenzaldehyde, the use of the catalyst (*S*,*S*)-**9** led exclusively to (*R*,*S*)-configured *anti* products with high *ee* values and diastereomeric ratios (Table 5, entry 5 and 7), while the use of the imine (*R*,*R*)-**9** led to (*S*,*R*)-configured compounds (Table 5, entry 6 and 8). In the reaction catalyzed by the imine (*R*,*R*)-**9** and the acid (*S*)-**14**, a minor *syn* (*R*,*R*)-product with 85% *ee* (similar to the reaction with 4-nitrobenzaldehyde, entry 6, Table 3) and with a diastereomeric ratio of 33:67 was formed. Again, it can be seen that besides the aziridine catalyst configuration, the configuration of chiral acid used was also very important for the configuration of the obtained aldol product.

Aldol condensation with hydroxyacetone and 4-nitrobenzaldehyde generally led to the *syn* products. The use of the catalyst (*S*,*S*)-**9** led selectively to (*R*,*S*)-configured products (Table 5, entry 9 and 11), while the use of the imine (*R*,*R*)-**9** resulted in the formation of (*S*,*R*)-configured compounds (Table 5, entry 10 and 12). All the products were obtained with high *ee* values and a diastereomeric ratio of about 9:1. The application of different enantiomers of acid did not affect the stereoselectivity.

3. Conclusions

The chiral imines constructed from 1-(2-aminoalkyl)aziridines are compounds that were easy to synthesize and were found to be effective catalysts for asymmetric aldol reactions. Aldol reactions of aromatic aldehydes bearing electron-withdrawing substituents in the presence of water and catalytic amounts of acidic additive led to expected products with moderate to excellent stereocontrol. In all cases, the use of enantiomeric catalysts led to the products with opposite absolute configurations, which allowed for obtaining the desired product in the enantioselective process. The use of an appropriate chiral acidic additive in the reactions of cyclohexanone could improve the stereocontrol of the reaction up to 93% *ee* and the ratio of the diastereoisomers up to 9:1. Moreover, the use of

a suitable combination of chiral aziridine and chiral acid led to the formation of the appropriate enantiomer of the product using the same starting compounds. It can be seen that the configuration of the resulting aldol product was influenced not only by aziridine but also by the acid configuration. Thus, the process was moderately diastereodivergent and allowed for isolation of a product with a clearly defined configuration.

Furthermore, the use of hydroxyacetone as the substrate interfered with the catalytic system. It is likely that the OH group of hydroxyacetone was blocking the diastereodivergent process.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-8994/12/6/930/s1: copies of the NMR spectra of compounds **1**–**10** and selected HPLC chromatograms for the aldol adducts.

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

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

Appendix A

A.1. Materials and Methods

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III instrument (Bruker, Billerica, MA, USA) at 600 MHz and 150 MHz, respectively, with $CDCl_3$ as the solvent and TMS as the internal standard. Data are reported as s—singlet, d—doublet, t—triplet, q—quartet, m—multiplet, and br. s—broad singlet. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter (PerkinElmer, Inc., Waltham, Mass. United States) with a sodium lamp at room temperature. All reagents and solvents are commercially available reagents (Merck Polska) and were used as received. Column chromatography was carried out using Merck 60 silica gel (Merck Group (Merck KGaA), Darmstadt, Germany). TLC was performed on Merck 60 F_{254} silica gel plates (Merck Group (Merck KGaA), Darmstadt, Germany). Visualization was accomplished with UV light (254 nm) or using iodine vapours. The enantiomeric excess (*ee*) values were determined using chiral HPLC (Chiralcel AD-H column; Daicel Corporation, Osaka, Japan). In some cases, the achievement of the baseline resolution was not possible. The valley-to-valley method of integration of the peaks was applied. A Knauer HPLC chromatograph (Knauer, Wissenschaftliche Geräte GmbH, Berlin, Germany) with a smartline pump 1000 was used for the HPLC analysis.

*A.2. Synthesis of Chiral Imines **1**–**10**—General Procedure [23]*

A solution of the corresponding 1-(2-aminoalkyl)aziridine [23] (1 mmol) and aromatic aldehyde (1 mmol) in MeOH (10 mL) was refluxed for 16 h. After this time, a solvent was evaporated and the product was purified using flash chromatography (silica gel, hexane/AcOEt in gradient) to afford the corresponding chiral imines **1**–**10** as colorless, viscous oils.

(E)-N-[(1S)-1-[[(2S)-2-Isopropylaziridin-1-yl]methyl]-2-methyl-propyl]-1-phenyl-methanimine **1**. ^{1}H and ^{13}C NMR spectra were in agreement with Pieczonka et al. [23], yield 98%, 0.253 g. $[\alpha]_D^{23}$ + 4.0 (c 0.2; chloroform).

(E)-N-[(1R)-1-[[(2R)-2-Isopropylaziridin-1-yl]methyl]-2-methyl-propyl]-1-phenyl-methanimine **2**. ^{1}H and ^{13}C NMR spectra were in agreement with Pieczonka et al. [24], yield 95%, 0.245 g. $[\alpha]_D^{23}$ − 4.5 (c 0.2; chloroform).

(E)-N-[(1S)-1-[[(2S)-2-Isobutylaziridin-1-yl]methyl]-3-methyl-butyl]-1-phenyl-methanimine **3**. Colorless oil, yield 90%, 0.257 g, $[\alpha]_D$ (c = 0.2, $CHCl_3$) + 7. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.67, 0.76 (6H, 2d, *J* 6.6 Hz,

$2CH_3$); 0.90–0.94 (8H, m); 1.30 (1H, d, *J* 3.0 Hz); 1.36–1.39 (3H, m); 1.48 (1H, dd, *J'* 7.2 Hz, *J''* 12.0 Hz); 1.61–1.66 (2H, m); 2.01 (1H, dd, *J'* 4.8 Hz, *J''* 12.0 Hz); 2.97 (1H, dd, *J'* 6.0 Hz, *J''* 12.0 Hz); 3.60–3.65 (2H, m); 7.43–7.44 (3H, m, 3 arom. H); 7.78–7.79 (2H, m, 2 arom. H); 8.39 (1H, s, CH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.5, 22.5, 22.6, 23.5 ($4CH_3$); 24.5, 26.7 (2CH); 33.9 (CH_2); 33.9 (CH); 42.3, 42.9, 66.9 ($3CH_2$); 70.6 (CH); 123.8, 128.5, 128.8 (CH arom.); 141.9 (Cq arom.); 160.0 (CH=N). HR-EI-MS: 286.2408 (M^+, $C_{19}H_{30}N_2{}^+$; calcd. 286.2408). $[\alpha]_D{}^{23}$ + 7.0 (c 0.2; chloroform).

(E)-N-[(1S)-1-[[(2S)-2-Isopropylaziridin-1-yl]methyl]-2-methyl-propyl]-1-(2-methoxyphenyl)methanimine ***4***. ^{1}H and ^{13}C NMR spectra were in agreement with Pieczonka et al. [24], yield 95%, 0.274 g. $[\alpha]_D{}^{23}$ + 3.0 (c 0.2; chloroform).

(E)-N-[(1S)-1-[[(2S)-2-Isopropylaziridin-1-yl]methyl]-2-methyl-propyl]-1-(2-nitrophenyl)methanimine ***5***. ^{1}H and ^{13}C NMR spectra were in agreement with Pieczonka et al. [24], yield 99%, 0.3 g. $[\alpha]_D{}^{23}$ + 1.0 (c 0.2; chloroform).

2,4-Ditert-butyl-6-[(E)-[(1R)-1-[[(2R)-2-isopropylaziridin-1-yl]methyl]-2-methyl-propyl]iminomethyl]phenol ***6***. Yellow oil, yield 99%, 0.382 g, $[\alpha]_D$ (c = 0.2, $CHCl_3$) − 20. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.81, 0.82 (6H, 2d, *J* 6.6 Hz, $2CH_3$); 0.95–0.99 (6H, m, $2CH_3$); 1.20–1.24 (3H, m); 1.34 (9H, m, $3CH_3$); 1.48 (9H, m, $3CH_3$); 1.57 (1H, d, *J* 3.0 Hz); 2.15–2.16 (1H, m); 2.17 (1H, dd, *J'* 7.2 Hz, *J''* 12.0 Hz); 2.92 (1H, dd, *J'* 4.8 Hz, *J''* 12.0 Hz); 3.23–3.25 (1H, m); 7.13 (1H, m, 1 arom. H); 7.40 (1H, s, 1 arom. H); 8.38 (1H, s, CH); 13.85 (1H, s, OH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 17.6, 19.0, 20.0, 20.5 ($4CH_3$); 29.4, 31.9 (*t*-Bu CH_3); 30.9 (CH); 31.1 (CH_2); 35.0 (C_q); 31.5, 47.3 (2CH); 64.7 (CH_2); 76.0 (CH); 125.8, 126.6 (CH arom.); 118.0, 136.6, 139.9, 158.2 (4 Cq arom.); 165.7 (CH=N). HR-EI-MS: 386.3296 (M^+, $C_{25}H_{42}N_2O^+$; calcd. 386.3296). $[\alpha]_D{}^{23}$ − 20.0 (c 0.2; chloroform).

2,4-Di-tert-butyl-6-[(E)-[(1S)-1-[[(2S)-2-isopropylaziridin-1-yl]methyl]-2-methyl-propyl]iminomethyl]phenol ***7***. Yellow oil, yield 95%, 0.366 g, $[\alpha]_D$ (c = 0.2, $CHCl_3$) + 19.5. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.81, 0.82 (6H, 2d, *J* 6.6 Hz, $2CH_3$); 0.95–0.99 (6H, m, $2CH_3$); 1.20–1.24 (3H, m); 1.34 (9H, m, $3CH_3$); 1.48 (9H, m, $3CH_3$); 1.57 (1H, d, *J* 3.0 Hz); 2.15–2.16 (1H, m); 2.17 (1H, dd, *J'* 7.2 Hz, *J''* 12.0 Hz); 2.92 (1H, dd, *J'* 4.8 Hz, *J''* 12.0 Hz); 3.23–3.25 (1H, m); 7.13 (1H, m, 1 arom. H); 7.40 (1H, s, 1 arom. H); 8.38 (1H, s, CH); 13.85 (1H, s, OH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 17.6, 19.0, 20.0, 20.5 ($4CH_3$); 29.4, 31.9 (*t*-Bu CH_3); 30.9 (CH); 31.1 (CH_2); 35.0 (C_q); 31.5, 47.3 (2CH); 64.7 (CH_2); 76.0 (CH); 125.8, 126.6 (CH arom.); 118.0, 136.6, 139.9, 158.2 (4 Cq arom.); 165.7 (CH=N). HR-EI-MS: 386.3297 (M^+, $C_{25}H_{42}N_2O^+$; calcd. 386.3296). $[\alpha]_D{}^{23}$ + 19.5 (c 0.2; chloroform).

2,4-Di-tert-butyl-6-[(E)-[(1S)-1-[[(2S)-2-isobutylaziridin-1-yl]methyl]-3-methyl-butyl]iminomethyl]phenol ***8***. Yellow oil, yield 86%, 0.356 g, $[\alpha]_D$ (c = 0.2, $CHCl_3$) + 14. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.60, 0.72 (6H, 2d, *J* 6.6 Hz, $2CH_3$); 0.91–0.95 (8H, m); 1.25 (1H, d, *J* 3.0 Hz); 1.34 (9H, m, $3CH_3$); 1.47 (9H, m, $3CH_3$); 1.48–1.53 (6H, m); 1.97 (1H, dd, *J'* 7.2 Hz, *J''* 12.0 Hz); 2.98 (1H, dd, *J'* 6.0 Hz, *J''* 12.0 Hz); 3.57–3.60 (1H, m); 7.14 (1H, br.s, 1 arom. H); 7.40 (1H, br.s, 1 arom. H); 8.45 (1H, s, CH); 13.86 (1H, s, OH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.6, 22.5, 22.7, 23.4 ($4CH_3$); 24.6, 26.7 (2CH); 34.0 (CH_2); 33.9 (CH); 42.4, 42.8, 70.0 ($3CH_2$); 70.6 (CH); 125.8, 126.6 (CH arom.); 118.1, 136.6, 140.1, 158.1 (4 Cq arom.); 164.5 (CH=N). HR-EI-MS: 414.3607 (M^+, $C_{27}H_{46}N_2O^+$; calcd. 414.3609). $[\alpha]_D{}^{23}$ + 14.0 (c 0.2; chloroform).

2-[(E)-[(1R)-1-[[(2R)-2-Isopropylaziridin-1-yl]methyl]-2-methyl-propyl]iminomethyl]phenol ***9***. Yellow oil, yield 99%, 0.271 g, $[\alpha]_D$ (c = 0.2, $CHCl_3$) − 18. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.80, 0.85 (6H, 2d, *J* 6.6 Hz, $2CH_3$); 0.96–0.97 (6H, m, $2CH_3$); 1.19–1.24 (3H, m); 1.57 (1H, d, *J* 3.0 Hz); 2.05–2.06 (1H, m); 2.19 (1H, dd, *J'* 7.2 Hz, *J''* 12.0 Hz); 2.89 (1H, dd, *J'* 4.8 Hz, *J''* 12.0 Hz); 3.25–3.27 (1H, m); 6.90–7.00 (2H, m, 2 arom. H); 7.29–7.35 (2H, m, 2 arom. H); 8.38 (1H, s, CH); 13.65 (1H, s, OH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 17.6, 19.0, 19.9, 20.5 ($4CH_3$); 30.9 (CH); 31.2 (CH_2); 31.8, 47.3 (2CH); 64.6 (CH_2); 76.0

(CH); 116.9, 118.4, 131.1 (CH arom.); 132.0, 161.3 (C_q arom.); 164.7 (CH=N). HR-EI-MS: 274.2042 (M^+, $C_{17}H_{26}N_2O^+$; calcd. 274.2044). $[\alpha]_D^{23}$ −18.0 (c 0.2; chloroform).

2-Tert-butyl-6-[(E)-[(1R)-1-[[(2R)-2-isopropylaziridin-1-yl]methyl]-2-methyl-propyl]iminomethyl]phenol ***10***. Yellow oil, yield 99%, 0.326 g, $[\alpha]_D$ (c = 0.2, $CHCl_3$) − 9.5. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.79, 0.83 (6H, 2d, *J* 6.6 Hz, $2CH_3$); 0.96–0.99 (6H, m, $2CH_3$); 1.23 (3H, s); 1.46–1.48 (9H, m, $3CH_3$); 1.59 (1H, d, *J* 3.0 Hz); 2.04–2.07 (1H, m); 2.17 (1H, dd, *J*′ 7.2 Hz, *J*″ 12.0 Hz); 2.98 (1H, dd, *J*′ 4.8 Hz, *J*″ 12.0 Hz); 3.26–3.27 (1H, m); 6.83–6.85 (1H, m, 1 arom. H); 7.15–7.16 (1H, m, 1 arom. H); 7.34–7.36 (1H, m, 1 arom. H); 8.38 (1H, s, CH); 14.1 (1H, s, OH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 17.8, 18.9, 19.9, 20.4 ($4CH_3$); 29.4 (*t*-Bu CH_3); 30.8 (CH); 31.2 (CH_2); 34.8 (C_q); 31.6, 47.5 (2CH); 64.6 (CH_2); 76.0 (CH); 117.6, 129.6 (CH arom.); 129.1, 137.3, 160.6 (C_q arom.); 165.4 (CH=N). HR-EI-MS: 330.2669 (M^+, $C_{21}H_{34}N_2O^+$; calcd. 330.2670). $[\alpha]_D^{23}$ −9.5 (c 0.2; chloroform).

A.3. Asymmetric Aldol Reaction—General Procedure

Acetone (1.8 mL) and H_2O (0.2 mL) were added to a vial containing the catalyst (0.05 mmol) and appropriate additive (0.05 mmol; $Zn(OTf)_2$, TFA, or 1,1′-binaphthyl-2,2′-diyl hydrogenphosphate **14**). After vigorous stirring at rt for 15 min, aromatic aldehyde (0.5 mmol) was added, and the resulting mixture was stirred at rt and monitored using TLC. Following the reaction's completion (usually after 72 h), the solvent was evaporated and the aldol product was purified using flash column chromatography (hexane/EtOAc in gradient). The spectroscopic data of all the products were in agreement with the literature data.

(4S)-Hydroxy-4-(4-nitrophenyl)-butan-2-one. ^{1}H and ^{13}C NMR spectra were in agreement with Zhou and Shan [29]. The enantiomeric excess was determined using chiral HPLC (Chiral AD-H, EtOH/*n*-hexane 10/90, flow: 1 mL/min, λ = 254 nm): t_R = 14.35 min (minor), t_R = 14.80 min (major). White solid, yield 98%, m.p. 59–60 °C.

(4S)-Hydroxy-4-(2-nitrophenyl)-butan-2-one. ^{1}H and ^{13}C NMR spectra were in agreement with Zhou and Shan [29]. The enantiomeric excess was determined using chiral HPLC (Chiral AD-H, EtOH/*n*-hexane 10/90, flow: 1 mL/min, λ = 254 nm): t_R = 12.13 min (major), t_R = 13.13 min (minor). Yellow oil, yield 86%.

(4S)-Hydroxy-4-(2,4-dinitrophenyl)-butan-2-one. ^{1}H and ^{13}C NMR spectra in agreement with Subba Reddy et al. [30]. The enantiomeric excess was determined using chiral HPLC (Chiral AD-H, EtOH/*n*-hexane 10/90, flow: 1 mL/min, λ = 254 nm): t_R = 22.22 min (major), t_R = 20.62 min (minor). Yellow oil, yield 99%.

(4S)-Hydroxy-4-(4-cyanophenyl)-butan-2-one. ^{1}H and ^{13}C NMR spectra were in agreement with Shah and Soni [26]. The enantiomeric excess was determined using chiral HPLC (Chiral AD-H, iPrOH/*n*-hexane 30/70, flow: 1 mL/min, λ = 254 nm): t_R = 5.55 min (minor), t_R = 6.55 min (major). Yellow solid, yield 98%, m.p. 59–60 °C.

(4S)-Hydroxy-4-(4-(trifluorometyl)phenyl)-butan-2-one. ^{1}H and ^{13}C NMR spectra were in agreement with Shah and Soni [26]. The enantiomeric excess was determined using chiral HPLC (Chiral AD-H, iPrOH/*n*-hexane 10/90, flow: 1 mL/min, λ = 254 nm): t_R = 11.55 min (minor), t_R = 12.54 min (major). White solid, yield 62%.

(4S)-Hydroxy-4-phenyl-butan-2-one. ^{1}H and ^{13}C NMR spectra were in agreement with Zhou and Shan [29]. The enantiomeric excess was determined using chiral HPLC (Chiral AD-H, EtOH/*n*-hexane 10/90, flow: 1 mL/min, λ = 254 nm): t_R = 14.35 min (minor), t_R = 14.80 min (major). Colorless oil, yield 21%.

(2S)-2-[(R)-hydroxy-(4-nitrophenyl)methyl]cyclohexanone. ^{1}H and ^{13}C NMR spectra were in agreement with References [31,32]. The enantiomeric excess was determined using chiral HPLC (Chiral AD-H,

iPrOH/*n*-hexane 15/85, flow: 1 mL/min, λ = 254 nm): t_R = 22.26 min (*syn* major), t_R = 26.18 min (*syn* minor), t_R = 29.36 min (*anti* minor), t_R = 40.68 min (*anti* major). Colorless oil, yield 95%.

(2S)-2-[(R)-hydroxy-(2-nitrophenyl)methyl]cyclohexanone. ^{1}H and ^{13}C NMR spectra were in agreement with Li and Gou [33]. The enantiomeric excess was determined using chiral HPLC (Chiral AD-H, iPrOH/*n*-hexane 15/85, flow: 1 mL/min, λ = 254 nm): t_R = 14.75 min (*syn* major), t_R = 16.40 min (*syn* minor), t_R = 23.42 min (*anti* major), t_R = 25.99 min (*anti* minor). Colorless oil, yield 99%.

(2R)-2-[(S)-hydroxy-(2,4-dinitrophenyl)methyl]cyclohexanone. ^{1}H and ^{13}C NMR spectra were in agreement with References [34,35]. The enantiomeric excess was determined using chiral HPLC (Chiral AD-H, iPrOH/*n*-hexane 15/85, flow: 1 mL/min, λ = 254 nm): t_R = 24.98 min (*syn* minor), t_R = 32.72 min (*syn* major), t_R = 39.46 min (*anti* minor), t_R = 44.81 min (*anti* major). Colorless oil, yield 99%.

(3R,4S)-3,4-dihydroxy-4-(4-nitrophenyl)butan-2-one. ^{1}H and ^{13}C NMR spectra were in agreement with References [34–36]. The enantiomeric excess was determined using chiral HPLC (Chiral AD-H, iPrOH/*n*-hexane 15/85, flow: 1 mL/min, λ = 254 nm): t_R = 23.21 min (*anti* major), t_R = 25.55 min (*anti* minor), t_R = 30.99 min (*syn* minor), t_R = 43.69 min (*syn* major). Colorless oil, yield 99%.

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