Protonated Chiral 1,2-Diamine Organocatalysts for \(N\)-Selective Nitroso Aldol Reaction

Jae Ho Shim \(^1,\star\), Ji Yeon Lee \(^2\), Hyeon Soo Kim \(^1\) and Deok-Chan Ha \(^2\)

\(^1\) Department of Anatomy, Korea University College of Medicine, 46, Gaeunsa 2-gil, Seongbuk-gu, Seoul 02842, Korea; anatomykim@korea.ac.kr

\(^2\) Department of Chemistry, Korea University, 145 Anam-ro, Seongbuk-gu, Seoul 02841, Korea; lauren3371@korea.ac.kr (J.Y.L.); dechha@korea.ac.kr (D.-C.H.)

\* Correspondence: shimjh3000@korea.ac.kr; Tel.: +82-2-2286-1125

Abstract: The introduction of nitrogen to carbonyl groups is considered both challenging and highly desirable by those who work in the field of organic synthesis. In this study, a diphenylethylenediamine-derived catalyst demonstrating \(N\)-selectivity was designed using a quantum calculation for the nitroso aldol reaction. The reductive monoalkylation of \((\text{R}, \text{R})-(+)-1,2\)-diphenylethylenediamine afforded an organic chiral diamine catalyst in high yield. The expected reaction mechanism for the nitroso aldol reaction was determined, and the product and solvent conditions were optimized through quantum calculations. The calculation results revealed that the enantioselectivity is determined by the hydrogen bond between the alkyl substituent of the chiral diamine and the oxygen of the aromatic aldehyde on the ammonium moiety. The reaction was found to proceed optimally in the presence of 5 mol % catalyst at \(-10^\circ\text{C}\) in brine. Using these conditions, an eco-friendly nitroso aldol reaction was performed in which the organic catalyst and cyclohexanone formed enamine. Nitrosobenzene, activated by hydrogen bonding with an ammonium catalyst, was used to minimize the steric hindrance between the catalyst and the reactant, resulting in high enantioselectivity. A nitroso aldol product with high \(N\)-selectivity and enantioselectivity (98% ee) was obtained in 95% yield. The catalyst developed in this study provides a less expensive and more environmentally friendly alternative for the nitroso aldol reaction.

Keywords: nitroso aldol reaction; enantioselectivity; regioselectivity; organocatalyst

1. Introduction

Knowledge of the spatial arrangement of atoms constituting a molecule is essential for understanding the fundamental properties. Organic reactions capable of efficiently controlling the stereochemistry of a compound are desirable from an economic and academic standpoint. Numerous efforts to develop stereoselective organic reactions using catalysts are ongoing. Recently, remarkable results have been reported for various stereoselective organic reactions using organic catalysts and chiral metal catalysts. Extensive and promising research on organic stereoselective reactions using metal catalysts has been conducted. However, these reactions are beset by several problems, such as the high cost of metal catalysts, environmental concerns resulting from disposal after use, and contamination of products by residual metals [1].

It is expected that many of the problems associated with metal-catalyzed reactions can be solved by extensive research into organic catalysts [2,3]. In our laboratory, several studies with the aim of developing organic catalysts that can effectively act on stereoselective organic reactions are underway. In this study, we determined the basic information required for stereoselective organocatalytic reactions and simultaneously developed an organic catalyst that can effectively and immediately catalyze the nitroso aldol reaction to control the stereochemistry of the product [4]. The nitroso aldol reaction is an important reaction in organic synthesis for introducing nitrogen to the carbonyl group [5–7]. Until now,
carbonyl group compounds such as ketones and aldehydes were pre-activated or directly used. In this study, we aimed to develop a nitroso aldol reaction using a proline catalyst that proceeds via enamine intermediates with ketones or aldehydes. Although reactions that demonstrate O-selectivity and N-selectivity using organic catalysts are being studied, further research is required [8–29]. The reaction, which uses the enamine form rather than the metal enolate as the nucleophile of nitroso aldol, can exhibit N- or O-selectivity depending on the hydrogen bonds of the catalyst [30]. In addition, unlike metal enolates and enamines, many examples of nitroso aldol reactions using organic catalysts such as proline to produce ketones or aldehydes have been reported [31–34]. The mechanism of nitroso aldol reactions using proline and ketone proceeds as follows: proline and a ketone react to form an enamine, and enamine attacks the oxygen side of the nitroso compound to form an intermediate of the nitroso compound. As water enters, an alpha aminooxy compound is formed, and the proline catalyst is regenerated to catalyze the reaction again [35–38].

Therefore, we studied the N-selective synthesis of an alpha hydroxyamino compound, using enolate as a nucleophile to form an N-nitroso aldol product. In addition, a catalyst that drives the reaction using enamine as a nucleophile was designed. The transition state structure is predicted through the mechanism studied based on previous studies [39]. After the catalyst and cyclohexanone formed enamine, the following transition state is proposed as the primary amine moiety of the organic catalyst activates nitrosobenzene (Figure 1).

**Figure 1.** The nitroso aldol reaction via nitrosobenzene and cyclohexanone.

2. Results and Discussion
2.1. Nitroso Aldol Reaction Using DPEN
2.1.1. Effect of Solvents

In previous studies, we performed an aldol reaction using chiral diamine (1b) [15]. With consideration to the results of previous studies, we tested various solvents with the 1b catalyst in this study to determine how the solvent affects the reactivity and stereoselectivity of the product in the nitroso aldol reaction (Table 1). Most solvents demonstrated high N-selectivity and relatively high enantioselectivities (82–94%). However, the yield ranged from 36% to 76%, depending on the polarity of the solvent, indicating that the solvent effect on the reaction is significant. When the experiment was performed using the same equivalent catalyst at room temperature, the solvent that resulted in the highest yield (65%) was brine (Table 1, entry 1). When MeOH, a polar proton solvent (Table 2, entry 4), was used, the yield was as low as 50% because the acid catalyst prevented the activation of nitrosobenzene through hydrogen bonding. Polar aprotic solvents (Table 1, entries 2 and 3) also exhibited low yields because interference with hydrogen bonding was more...
significant than the activation of nitrosobenzene by the solvent (Table 1, entries 7 and 8). Therefore, from the results of the solvent screening in Table 1, brine with the best yield and enantioselectivity of the N-nitroso aldol reaction was determined as the reaction solvent.

**Table 1.** Solvent effects on the nitroso aldol reaction.

| Entry | Solvent | Time  | Yield (%) a | ee (%) b |
|-------|---------|-------|-------------|----------|
| 1     | Brine   | 1 h   | 65          | 94       |
| 2     | DMSO    | 1 h   | 58          | 91       |
| 3     | CH$_3$CN| 1 h   | 52          | 90       |
| 4     | MeOH    | 1 h   | 50          | 90       |
| 5     | -       | 1 h   | 46          | 92       |
| 6     | CH$_2$Cl$_2$ | 1 h | 42 | 81 |
| 7     | THF     | 1 h   | 40          | 94       |
| 8     | Toluene | 15 min| 25          | 86       |

a Isolated yield. b ee values were determined by chiral phase HPLC using the AD-H columns.

**Table 2.** Optimization of the nitroso aldol reaction using (R,R)-1,2-diphenylethylenediamine (DPEN).

| Entry | Cat | Yield (%) a | ee (%) b |
|-------|-----|-------------|----------|
| 1     | 1a  | 82          | 99       |
| 2     | 1b  | 65          | 94       |
| 3     | 1c  | 61          | 96       |
| 4     | 1d  | 53          | 98       |
| 5     | 1e  | 49          | 98       |

a Isolated yield. b ee values were determined by chiral phase HPLC using AD-H columns.

2.1.2. Substituent Effects of DPEN Derivatives

We investigated the effect of a monoalkyl-substituted chiral amine catalyst under the optimized reaction conditions (Figure 2). The yield decreased as the steric hindrance of the alkyl group substituent increased. In particular, the yield of the 1d catalyst was lower than that produced by the 1a catalyst, which suffers from relatively less steric hindrance. However, the stereoselectivity increased slightly. In the case of a chiral amine (1b), which has a similar level of a steric hindrance to that of 1a, there was an unexpectedly large difference in the yield than the 1a catalyst. Therefore, catalyst 1a, which demonstrated the best yield and stereoselectivity, was selected (Table 2).

![Chemical structure](image-url)
entry 4), was used, the yield was as low as 50% because the acid catalyst prevented the activation of nitrosobenzene through hydrogen bonding. Polar aprotic solvents (Table 1, entries 2 and 3) also exhibited low yields because interference with hydrogen bonding was more significant than the activation of nitrosobenzene by the solvent (Table 1, entries 7 and 8). Therefore, from the results of the solvent screening in Table 1, brine with the best yield and enantioselectivity of the \( \text{N} \)-nitroso aldol reaction was determined as the reaction solvent.

**Table 1. Solvent effects on the nitroso aldol reaction.**

| Entry | Solvent | Time | Yield (%) \( a \) | ee (%) \( b \) |
|-------|---------|------|----------------|-------------|
| 1     | Brine   | 1 h  | 65              | 94          |
| 2     | DMSO    | 1 h  | 58              | 91          |
| 3     | \( \text{CH}_3\text{CN} \) | 1 h  | 52              | 90          |
| 4     | MeOH    | 1 h  | 50              | 90          |
| 5     |         | 1 h  | 46              | 92          |
| 6     | \( \text{CH}_2\text{Cl}_2 \) | 1 h  | 42              | 81          |
| 7     | THF     | 1 h  | 40              | 94          |
| 8     | Toluene | 15 min | 25            | 86          |

\( a \) Isolated yield. \( b \) ee values were determined by chiral phase HPLC using the AD-H columns.

2.1.2. Substituent Effects of DPEN Derivatives

We investigated the effect of a monoalkyl-substituted chiral amine catalyst under the optimized reaction conditions (Figure 2). The yield decreased as the steric hindrance of the alkyl group substituent increased. In particular, the yield of the 1d catalyst was lower than that produced by the 1a catalyst, which suffers from relatively less steric hindrance. However, the stereoselectivity increased slightly. In the case of a chiral amine (1b), which has a similar level of steric hindrance to that of 1a, there was an unexpectedly large difference in the yield than the 1a catalyst. Therefore, catalyst 1a, which demonstrated the best yield and stereoselectivity, was selected (Table 2).

![Figure 2. Chiral 1,2-diamine catalysts prepared for use in this study.](image)

2.1.3. Effects of Different Temperatures and Solvent Ratios

As the product is unstable and the yield is low at room temperature, the experiment was performed at a lower temperature. At \(-10^\circ\text{C}\), the yield increased from 82% to 95% instead of demonstrating similar enantioselectivity to that observed at room temperature (Table 3, entries 2 and 3). To examine how the ratio of cyclohexanone to nitrosobenzene reagent affects the nitroso aldol reaction, the reagent quantity was varied. When the reagent ratio was 1:1 (entry 1) and the quantity of catalyst to be added was reduced to 1 mol %, the yield and enantioselectivity decreased (entry 5). In addition, the yield and stereoselectivity decreased when the quantity of the nitrosobenzene reagent was increased (entries 6 and 7). When benzoic acid (5 mol %) was added, the yield of the side product decreased, and the yield improved (entry 8). In the case of entry 8, benzoic acid was added to promote amine catalysis and imine formation through the activation of cyclohexanone. Finally, when the quantity of the catalyst was reduced to 5 mol %, the reaction time needed to be increased to 6 h (entry 4). However, it was possible to confirm the yield of 95% and the enantioselectivity of 99. Thus, the optimal quantity of catalysts was determined. However, when the type of ketones was changed to a type such as 3-pentanone or 2-butanone, it was confirmed through preliminary tests that the stereoselectivity of the product was significantly reduced. Therefore, if the kind of ketones is changed, the stereoselectivity of the product is expected to decrease (Figure S1). So, it is necessary to confirm it by changing the nitroso type in the future.
Section from a research paper on the nitroso aldol reaction:

**2.1.4. Proposed Mechanism including the Expected Transition State**

The chiral diamine reacts with cyclohexanone to form an imine, which in turn forms an enamine. The alkylated chiral diamine and nitroso benzene activate the electrophile through hydrogen bonding with an acid catalyst. A nitroso aldol product is expected after the activated electrophile and enamine react. The product of the nitroso aldol reaction forms a more stable enamine when dehydrated at room temperature (Figure 3). Based on the results in Table 3, the mechanism proceeds as follows: reducing the quantity of ketone causes process (A), which involves the synthesis of an enamine by the reaction of a chiral diamine with cyclohexanone, to proceed slowly (Figure 3). As a result, the reaction rate decreases. In the absence of brine, A proceeds rapidly. However, after the enamine reacts with nitrosobenzene, the hydrolysis from imine to alpha hydroxyamino compound C is slow, which implies that side reactions occur. In particular, when toluene is used as a solvent (Table 1, entry 8), the reaction time is fast, but the side reaction proceeds quickly, which implies that several adducts are generated. Therefore, to increase the reaction yield (Table 3 entry 8), a small volume of benzoic acid is added to prevent the activation of cycloketone and self-aldol condensation, which reduces the number of side reactions. Chiral diamine and cyclohexanone form enamine, and chiral amine and nitrosobenzene are activated through hydrogen bonding. According to the mechanism, the expected transition state occurs when the bond between enamine and nitrosobenzene is formed, and the enamine is formed by reacting with a catalyst. We expect that the reaction proceeds in a way that minimizes the steric hindrance of the phenyl group of nitrosobenzene. Therefore, it was possible to obtain the (S)-enantiomer rather than the (R)-enantiomer as the main product (Figure 3).

**Table 3. Effects of temperature and different equivalent conditions on the nitroso aldol reaction.**

| Entry | Cyclohexanone: Nitrobenzene | Temp (°C) | Time (h) | Yield (%) \(^a\) | ee (%) \(^b\) |
|-------|-----------------------------|-----------|----------|----------------|----------|
| 1     | 1:1                         | rt        | 1        | 55             | 92       |
| 2     | 2:1                         | 0         | 1.5      | 88             | 98       |
| 3     | 2:1                         | –10       | 3        | 95             | 99       |
| 4     | 2:1                         | –10       | 6        | 95             | 99       |
| 5     | 2:1                         | –10       | 24       | 52             | 99       |
| 6     | 1:2                         | –10       | 2        | 71             | 82       |
| 7     | 1:5                         | –10       | 2        | 65             | 80       |
| 8     | 2:1                         | –10       | 6        | 98             | 99       |

\(^a\) Isolated yield. \(^b\) ee values were determined by chiral phase HPLC using AD-H columns. \(^c\) Using 5 mol % 1a cat. \(^d\) Using 1 mol % 1a cat. \(^e\) Using 5 mol % benzoic acid and 1a cat.
2.2. Thermodynamic Energy Comparison of Solvent Effect and Mechanism through Quantum Calculations

Comparison of Gibbs Free Energy of Transition State by Catalyst and Type

For each mechanism step, the expected transition states of catalysts 1a and 1b were compared in the gas phase and water phase to investigate the reactivity differences (Table 2). The results of the calculation demonstrate that catalyst 1a was more stable than catalyst 1b in the gas phase by 0.424 kcal/mol. However, for the water phase calculation, the result for catalyst 1a was 13.016 kcal/mol lower than that of catalyst 1b, which was lower than expected (Figure 4).
As the solvent effect on the reaction was confirmed in Table 1, thermodynamic analysis was performed to determine the factors affecting the nitroso aldol reaction of water. To this end, based on the results confirmed in Figure 3, this time, the thermodynamic energies of various solvents were compared for the transition state of catalyst 1a. Based on the results in Figure 3, the thermodynamic energies of various solvents were compared for the transition state of catalyst 1a. A comparison of the experimental results (Table 1) and quantum calculation results confirmed that non-polar solvents such as toluene exhibited the lowest reactivity. Furthermore, using tetrahydrofuran, CH$_2$Cl$_2$, or no solvent resulted in similar reactivity to that indicated by the calculations. In particular, the use of polar solvents such as MeOH, acetonitrile, and DMSO resulted in relatively good reactivity, and the experimental results were similar to the calculation results. However, water demonstrated the best reactivity and stereoselectivity among these solvents (Table 1). In addition, the calculation results confirmed that the transition state of the nitroso aldol reaction is most stable under a water solvent (Figure 5).
Figure 5. Effect of solvent on the transition state of asymmetric nitroso aldol reaction. The calculations were performed using various solvent conditions based on the B3LYP/6-31G(d,p) method.

2.3. Gibbs Free Energy of Each Mechanism

In our proposed reaction cycle, cyclohexanone reacts with a primary amine to form an enamine via an imine, and this enamine reacts with a primary amine to minimize the steric hindrance (Figure 3). An aromatic aldehyde forms hydrogen bonds with ammonium salts to form the transition structure. New C–N bonds are formed through structure TS with the minimal steric hindrance of single bond alkyl groups. Finally, the nitroso aldol product is formed by the hydrolysis of iminium by the water produced in the enamine form and by the solvent water, as shown in Figures 3 and 6.
Figure 6. Proposed catalytic mechanism based on the B3LYP/6-31G(d,p) method. The calculations were performed using water conditions. Relative free energy diagram of the (R,R)-1,2-diphenylethylene diamine (DPEN)-iminium salt catalyzed enantioselective nitroso aldol reaction. The reactants 1, 2, and 3: (1: cyclohexanone, 2: nitrosobenzene, and 3: 1a cat.).

3. Materials and Methods

3.1. Instruments and Reagents

Optical rotation was measured using an auto digital polarimeter and FT-IR spectrum was recorded using NICOLET 380 FT-IR spectrophotometer of Thermo Electron Corporation (Thermo Fisher Scientific Inc., Waltham, MA, USA). $^1$H NMR and $^{13}$C NMR spectra were obtained using Varian Gemini 300 (300, 75 MHz) and Varian Mercury 400 (400, 100 MHz) using TMS as the internal standard (300, 75 MHz, Agilent, Santa Clara, CA, USA), Varian Mercury 400 (400, 100 MHz, Agilent, Santa Clara, CA, USA). Chiral HPLC analysis was performed using a Jasco LC-1500 Series HPLC system (JASCO, 4-21, Sennin-cho 2-chome, Hachioji, Tokyo 193-0835, Japan). Toluene (CaH$_2$), THF (Na, benzophenone), and CH$_2$Cl$_2$ (CaH$_2$) reaction solvents were purified before use. The reagents used in this study were products from Aldrich (Louis, MO, USA), TCI (Tokyo, Japan), and, if necessary, were purified or dried by a known method. Merck’s silica gel 60 (230–400 mech) was used as a stationary phase for column chromatography.

3.2. Experimental Method

3.2.1. Synthesis of Catalysts (1a–e); General Procedure

To a solution of (R, R)-1,2-diphenylethylene diamine (300 mg, 1.41 mmol) in dichloromethane, 141 mL of a carbonyl compound (1.41 mmol) and MgSO$_4$ were added. The mixture was refluxed for 48 h. Then, we removed the MgSO$_4$ via a celite filter and concentrated it in vacuo. NaBH$_4$ (4.0 equiv.) and ethanol 14 mL were added, and the mixture was stirred at room temperature for 3 h, quenched with 1 N NaOH solution, and extracted...
with ethyl acetate 20 mL three times. The combined organic extracts were washed with brine, and MgSO$_4$ was dried and concentrated in vacuo. The product was purified by chromatography on a silica-gel column (methanol/methylene chloride 1:20) to obtain the pure amide product (quantitative yield) as a white foamy solid (Scheme 1).

![Scheme 1](image)

Scheme 1. Synthesis of N-alkylation of DPEN. Reagents and conditions: (a) 1.0 eq. carbonyl compound, MgSO$_4$, toluene (0.1 M), reflux, 48 h. (b) EtOH (0.1 M), excess NaBH$_4$, 3 h (overall yield 81–90%).

3.2.2. Asymmetric Nitroso Aldol Reaction of Nitrosobenzene and Cyclohexanone Using a Chiral DPEN Catalyst

We dissolved the amine catalyst 1a (0.023 mmol) at room temperature in 2 mL of the reaction solvent (Brine:1 N HCl = 1:1) and added cyclohexanone (0.92 mmol). After stirring for about 10 min, we added nitrosobenzene (0.46 mmol). After stirring for 6 h, we washed with brine and extracted it with diethyl ether three times. The organic layer was neutralized with NaHCO$_3$ and dried with anhydrous MgSO$_4$, and the product was obtained by chromatography on a silica-gel column (EA:Hex = 1:10) after being concentrated in vacuo.

3.3. Results of DFT Calculations and Discussion

Density functional theory (DFT) calculations were performed using Gaussian 16 and Gauss-View 6.0 programs (Gaussian, Inc., Wallingford, CT, USA). DFT calculations were performed to show the mechanisms of substrates and catalysts. The optimized geometry was described using the DFT method with the Becke three-parameter Lee–Yang–Parr (B3LYP) level [40]. Single-point calculations for the optimized geometries were then performed using the 6-31G(d,p) basic set [40]. After the shapes of reactants, intermediates (IM), transition states (TS), and products were fully optimized, the thermodynamic functions and parameters (Gibbs free energy) of reactants were obtained through vibrational frequency calculation. At the same level of theory, the minimum or transition state energy was obtained. Enthalpy correction and entropy with temperature were calculated at 298 K and 1 atm pressure.

4. Conclusions

A chiral diamine catalyst was synthesized using the derivative obtained by the reductive mono-N-alkylation of DPEN. The reaction was N-selective and produced a nitroso aldol compound from an alpha hydroxyamino ketone in good yield with high enantioselectivity. When the nucleophilic enamine was formed using chiral diamine and cyclohexanone, it demonstrated high enantioselectivity. Further studies should focus on attempting the reaction with various aldehyde-based reagents to determine the scope of the asymmetric nitroso aldol reaction. In this laboratory, additional in-depth research on the nitroso aldol reaction in water is in progress.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/catal12040435/s1, Figure S1. Results to changes in ketone types under optimized experimental conditions. Compound Characterization Data, Copy of NMR and MASS Spectra, Copy of HPLC Chromatograms, DFT Calculations for all Calculated Structures of the compounds mentioned in the text.
Author Contributions: Conceptualization, J.H.S. and D.-C.H.; Data curation, J.H.S. and J.Y.L.; Funding acquisition, J.H.S.; Investigation, J.Y.L. and D.-C.H.; Methodology, D.-C.H.; Project administration, J.H.S.; Resources, H.S.K.; Software, H.S.K.; Supervision, J.H.S.; Validation, J.Y.L.; Writing—original draft, J.H.S.; Writing—review and editing, J.H.S. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported by the National Research Foundation (NRF) and funded by the Korean government (MSIT) (2021R1A6A3A01087948). This research was supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) and funded by the Korean government (MSIT) (2021M3A9G1097744). In addition, this study was supported by a Korea University grant.

Acknowledgments: We are grateful for the financial support provided by K. H. Kim.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

References
1. Fubini, B.; Otero Areán, C. Chemical Aspects of the Toxicity of Inhaled Mineral Dusts. Chem. Soc. Rev. 1999, 28, 373–381. [CrossRef]
2. Dalko, P.I.; Moisan, L. Enantioselective Organocatalysis. Angew. Chem. Int. Ed. Engl. 2001, 40, 3726–3748. [CrossRef]
3. Taylor, M.S.; Jacobsen, E.N. Asymmetric Catalysis by Chiral Hydrogen-Bond Donors. Angew. Chem. Int. Ed. 2006, 45, 1520–1543. [CrossRef] [PubMed]
4. Raj, M.; Vishnumaya, V.; Ginotra, S.K.; Singh, V.K. Highly Enantioselective Direct Aldol Reaction Catalyzed by Organic Molecules. Angew. Chem. Int. Ed. 2001, 40, 3726–3748. [CrossRef]
5. Ji-Mao, L.; Ben-Sheng, L. A Practical Method for the Preparation of Trimethylsilyl Enol Ethers. Tetrahedron 2001, 57, 4570–4581. [CrossRef]
6. Martinez, I.; Alford, P.E.; Ovaska, T.V. First Approach to the Frondosin C Ring System via a Tandem Cyclization/Claisen Rearrangement Sequence. Org. Lett. 2005, 7, 1133–1135. [CrossRef] [PubMed]
7. Momiyama, N.; Yamamoto, H. Catalytic Enantioselective Synthesis of α-Aminoxy and α-Hydroxy Ketone Using Nitro so benzene. J. Am. Chem. Soc. 2003, 125, 6038–6039. [CrossRef]
8. Momiyama, N.; Yamamoto, H. Lewis Acid Promoted, O-Selective, Nucleophilic Addition of Silyl Enol Ethers to N=O Bonds. Angew. Chem. Int. Ed. Engl. 2002, 41, 2986–2988. [CrossRef]
9. Mukaiyama, T.; Uchiro, H.; Kobayashi, S. A New Efficient Chiral Catalyst System. Combined Use of Tin(II) Oxide, Trime thylsilyl Triflate and Chiral Diamine in the Asymmetric Aldol Reaction. Chem. Lett. 1990, 19, 1147–1150. [CrossRef]
10. Hollis, T.K.; Bosnich, B. Homogeneous Catalysis. Mechanisms of the Catalytic Mukaiyama Aldol and Sakurai Allylation Reactions. J. Am. Chem. Soc. 1995, 117, 4570–4581. [CrossRef]
11. Surman, M.D.; Miller, M.J. Regio- and Stereocontrolled Formation of Hydroxamic Acid Containing Anti- or Syn-1,4-Cyclocalkenols from Acylnitroso-Derived Diels-Alder Adducts. J. Org. Chem. 2001, 66, 2466–2469. [CrossRef] [PubMed]
12. Adam, W.; Bottke, N. Hydroxy-Group Directivity in the Nitroso Ene Reaction: Diastereo- and Regioselective Amination of Chiral Allylic Alcohols. J. Am. Chem. Soc. 2000, 122, 9846–9847. [CrossRef]
13. Shim, J.H.; Park, S.J.; Byung, K.A.; Lee, J.Y.; Kim, K.H.; Ha, D.C. Enantioselective Thiolyis and Aminolysis of Cyclic Anhydrides Using a Chiral Diamine-Derived Thiourea Catalyst. ACS Omega 2021, 6, 34501. [CrossRef] [PubMed]
14. Morales, M.R.; Momiyama, N.; Yamamoto, H. Metal-induced reactions of O-nitroso aldol products. Synlett 2006, 5, 705–708. [CrossRef]
15. Momiyama, N.; Yamamoto, H. Enantioselective O- and N-Nitroso Aldol Synthesis of Tin Enolates. Isolation of Three BINAP-Silver Complexes and Their Role in Regio- and Enantioselectivity. J. Am. Chem. Soc. 2004, 126, 5360–5361. [CrossRef] [PubMed]
16. Bui, T.; Candeias, N.R.; Barbas, C.F. III. Dimeric Quinidine-Catalyzed Enantioselective Aminoxygenation of Oxindoles: An Organocatalytic Approach to 3-Hydroxoxindole Derivatives. J. Am. Chem. Soc. 2010, 132, 5574–5575. [CrossRef] [PubMed]
17. Zhang, T.; Cheng, L.; Liu, L.; Wang, D.; Chen, Y.J. Asymmetric Organocatalytic N-Nitroso-Aldol Reaction of Oxindoles. Tetrahedron Asymmetry 2010, 21, 2800–2806. [CrossRef]
18. Shen, K.; Liu, X.H.; Wang, G.; Lin, L.L.; Feng, X.M. Facile and Efficient Enantioselective Hydroxymamination Reaction: Synthesis of 3-Hydroxyamino-2-Oxindoles Using Nitrosoureines. Angew. Chem. Int. Ed. 2011, 50, 4684–4688. [CrossRef]
19. Jia, L.N.; Huang, J.; Peng, L.; Wang, L.L.; Bai, J.F.; Tian, F.; He, G.Y.; Xu, X.Y.; Wang, L.X. Asymmetric Hydroxyamination of Oxindoles Catalyzed by Chiral Bifunctional Tertiary Amine Thiourea: Construction of 3-Amino-2-Oxindoles with Quaternary Stereocenters. Org. Biomol. Chem. 2012, 10, 236–239. [CrossRef]
20. Companyo, X.; Valero, G.; Pineda, O.; Calvet, T.; Font-Bardia, M.; Moyano, A.; Rios, R. Enantioselective Organocatalytic Oxyamination of Unprotected 3-Substituted Oxindoles. Org. Biomol. Chem. 2012, 10, 431–439. [CrossRef]
21. Mailhol, D.; Castillo, J.C.; Mohanan, K.; Abonia, R.; Coqueler, Y.; Rodriguez, J. Practical and Efficient Organocatalytic Enantioselective α-Hydroxyamination Reactions of β-Ketoamides. ChemCatChem 2013, 5, 1192–1199. [CrossRef]
22. Sun, Q.S.; Zhu, H.; Chen, Y.J.; Yang, X.D.; Sun, X.W.; Lin, G.Q. Squaramide-Catalyzed Synthesis of Enantioenriched Spirocyclic Oxindoles via Ketimine Intermediates with Multiple Active Sites. *Angew. Chem. Int. Ed.* 2015, 54, 13253–13257. [CrossRef] [PubMed]

23. Wu, M.Y.; He, W.W.; Liu, X.Y.; Tan, B. Asymmetric Construction of Spirooxindoles by Organocatalytic Multicomponent Reactions Using Diazooxindoles. *Angew. Chem. Int. Ed.* 2015, 54, 9409–9413. [CrossRef] [PubMed]

24. Mouri, S.; Chen, Z.H.; Mitsunuma, H.; Furutachi, M.; Matsunaga, S.; Shibasaki, M. Catalytic Asymmetric Synthesis of 3-Aminooxindoles: Enantiofacial Selectivity Switch in Bimetallic vs Monometallic Schiff Base Catalysis. *J. Am. Chem. Soc.* 2010, 132, 1255–1257. [CrossRef]

25. Liu, L.W.; Wang, F.Y.; Tian, F.; Peng, L.; Wang, L.X. An Improved and Enantioselective Preparation of the Telaprevir Bicyclic [3.3.0] Proline Intermediate and Reuse of Unwanted Enantiomer. *Org. Process Res. Dev.* 2016, 20, 320–324. [CrossRef] [PubMed]

26. Liu, Y.L.; Zhou, J. Organocatalytic Asymmetric Cyanation of Isatin Derived N-Boc Ketoimines. *Chem. Commun.* 2013, 49, 4421–4423. [CrossRef]

27. Fu, J.Y.; Wang, Q.L.; Gui, Y.Y.; Wang, L.X. Direct Enantioselective Amination of α-Ketoester Catalyzed by Tertiary Amine Thiourea: A New Approach to Chiral α-Hydroxy-β-Amino Acid. *Tetrahedron Letters*. 2015, 56, 4220–4223. [CrossRef]

28. Zhang, H.; Zhang, S.J.; Zhou, Q.Q.; Dong, L.; Chen, Y.C. Organocatalytic Asymmetric Allylic Amination of Morita-Baylis-Hillman Carbonates of Isatins. *Beilstein J. Org. Chem.* 2012, 8, 1241–1245. [CrossRef]

29. Payette, J.N.; Yamamoto, H. Nitrosobenzene-Mediated C-C Bond Cleavage Reactions and Spectral Observation of an Oxazetidin-4-One Ring System. *J. Am. Chem. Soc.* 2008, 130, 12276–12278. [CrossRef]

30. Momiyama, N.; Yamamoto, H. Bronsted Acid Catalysis of Achiral Enamine for Regio- and Enantioselective Nitroso Aldol Synthesis. *J. Am. Chem. Soc.* 2005, 127, 1080–1081. [CrossRef]

31. Córdova, A. The Direct Catalytic Asymmetric Mannich Reaction. *Acc. Chem. Res.* 2004, 37, 102–112. [CrossRef] [PubMed]

32. List, B.; Lerner, R.A.; Barbas, C.F., III. Proline-catalyzed direct asymmetric aldol reactions. *J. Am. Chem. Soc.* 2000, 122, 2395–2396. [CrossRef]

33. Seayad, J.; List, B. Asymmetric Organocatalysis. *Org. Biomol. Chem.* 2005, 3, 719–724. [CrossRef]

34. Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C.F. Organocatalytic Direct Asymmetric Aldol Reactions in Water. *J. Am. Chem. Soc.* 2006, 128, 734–735. [CrossRef] [PubMed]

35. Momiyama, N.; Torii, H.; Saito, S.; Yamamoto, H. O-Nitroso Aldol Synthesis: Catalytic Enantioselective Route to α-Aminooxy Carbonyl Compounds via Enamine Intermediate. *Proc. Natl. Acad. Sci. USA* 2004, 101, 5374–5378. [CrossRef] [PubMed]

36. Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Hibino, K.; Shoji, M. Direct Proline-Catalyzed Asymmetric Alpha-Aminooxylation of Aldehydes and Ketones. *J. Org. Chem.* 2004, 69, 5966–5973. [CrossRef] [PubMed]

37. Córdova, A.; Sundén, H.; Bøgevig, A.; Johansson, M.; Himo, F. The Direct Catalytic Asymmetric Alpha-Aminooxylation Reaction: Development of Stereoselective Routes to 1,2-Diols and 1,2-Amino Alcohols and Density Functional Calculations. *Chemistry 2004*, 10, 3673–3684. [CrossRef]

38. Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Sumiya, T.; Urushima, T.; Shoji, M.; Hashizume, D.; Koshino, H. A Highly Active 4-Siloxyproline Catalyst for Asymmetric Synthesis. *Adv. Synth. Catal.* 2004, 346, 1435–1439. [CrossRef]

39. Shim, J.H.; Kim, M.J.; Lee, J.Y.; Kim, K.H.; Ha, D.C. Organocatalytic Asymmetric Aldol Reaction Using Protonated Chiral 1,2-Diamines. *Tetrahedron Lett.* 2020, 61, 152295. [CrossRef]

40. Boys, S.F.; Bernardi, F. Ab Initio Calculation of Vibrational Absorption and Circular Dichroism Spectra Using Density Functional Force Fields. *Mol. Phys.* 1970, 19, 55341. [CrossRef]