Article

Enantioselective Organocatalyzed Michael Addition of Isobutyraldehyde to Maleimides in Aqueous Media

Jae Ho Shim [1,*] iD **, Seok Hyun Cheun** [2] **, Hyeon Soo Kim** [1] **and Deok-Chan Ha** [2]

[1] Department of Anatomy, College of Medicine, Korea University, 73, Goryeodae-ro, Seongbuk-gu, Seoul 02481, Korea; anatomykim@korea.ac.kr
[2] Department of Chemistry, College of Science, Korea University, 145 Anam-ro, Seoul 02481, Korea; eamc2@naver.com (S.H.C.); dechha@korea.ac.kr (D.-C.H.)
[*] Correspondence: shimjh3000@korea.ac.kr; Tel.: +82-2-2286-1125

Abstract: Thiourea was introduced into (*R,R*)-1,2-diphenylethylenediamine as an organocatalyst to promote the reaction between isobutyraldehydes and maleimides. Enantioselective Michael addition reaction was carried out as an eco-friendly method using water as the solvent. As a result of the reaction between isobutyraldehyde and maleimide, ≥97% yield and 99% enantioselectivity were obtained at a low catalyst loading of 0.01 mol%. The solvent effect can be explained by theoretical calculations that indicate the participation of a transition state, in which the CF_3 substituent of the catalyst is a hydrogen bond activated by the surrounding water molecules. This discovery enabled the use of low catalyst loading in the organic reactions of chiral substances for pharmaceutical applications. Furthermore, a solvent effect for Michael reaction of the organocatalysts was proposed, and the organic reaction mechanisms were determined through quantum calculations.

Keywords: organocatalyst; enantioselectivity; Michael addition; aldehydes; succinimides; spironolactone
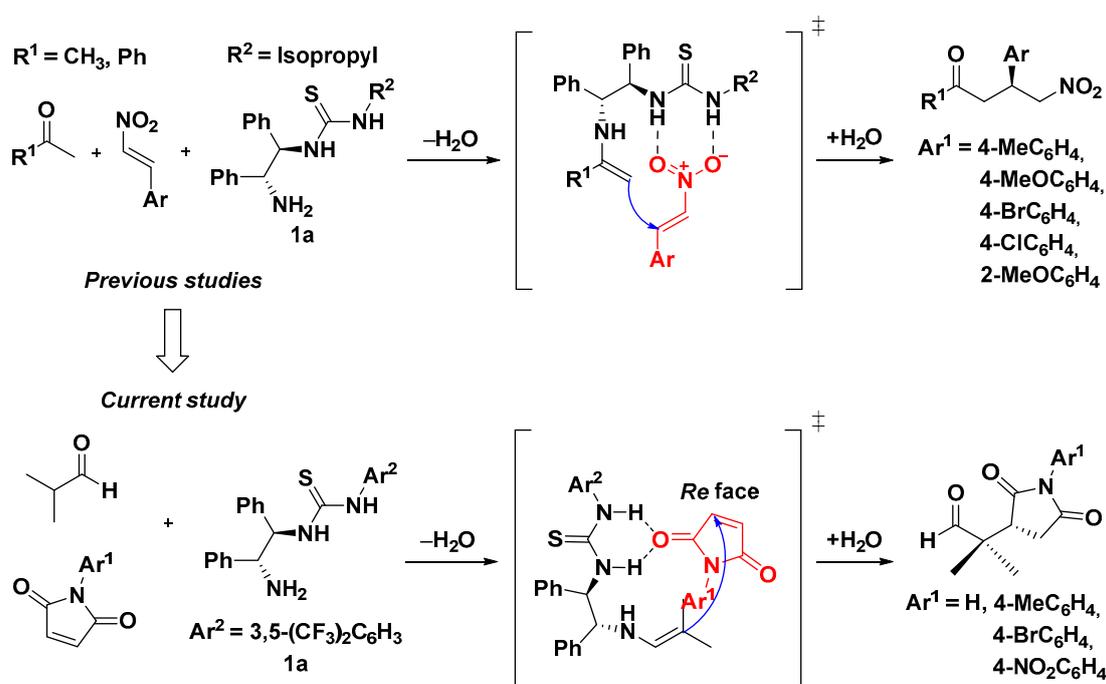
1. Introduction

Organocatalysis using small organic molecules for the asymmetric transformation of organic compounds is a well-known method for synthesizing organic compounds for various purposes [1–6]. In the last two decades, various organocatalysts have emerged as promising solutions to unsolved problems in modern catalysis, providing complementary systems of activation modes; thus, organic catalysts have been classified as one of the main catalyst categories alongside asymmetric, transition metal, and biological catalysts. In general, organocatalysts typically comprise carbon, hydrogen, nitrogen, and sulfur. While the mechanism of organocatalysts is similar to that of metal catalysts, they do not structurally resemble these catalysts that typically comprise metals and ligands. Michael addition is a well-studied organocatalytic transformation that leads to the formation of new C–C bonds in a highly enantioselective manner. In Michael reactions, the addition of α,α-disubstituted aldehydes to maleimides is an attractive modification because the obtained product is considered a valuable synthetic target and a precursor of biologically interesting compounds [7]. Another interesting feature of this transformation is the resulting formation of a quaternary center [8–12]. This reaction is typically promoted by a bifunctional organocatalyst containing a primary amino group and a thiourea motif [13–20].

Asymmetric Michael reactions between maleimides and aldehydes have been studied by several groups. Wang et al. used a primary amine catalyst to promote the Michael addition of aldehydes with *N*-phenylmaleimide [21]. Tao performed a Michael reaction using a small amount of bifunctional thiourea derivative as a catalyst and demonstrated that the use of benzoic acid as an additive resulted in desirable yield and stereoselectivity [22]. Benaglia et al. reported a simple synthesis of a primary amine-containing organocatalyst with a structure similar to that of the Takemoto catalyst and studied Michael addition using the obtained catalyst [23]. Kokotos obtained the (*S*)-configuration product after conducting the

Michael addition of various aldehydes and maleimide with β-phenylalanine as the catalyst and reported that the (*R*)-product was the result when aspartic acid was used as the catalyst. The use of β-phenylalanine and aspartic acid as catalysts resulted in high yields, enantioselectivities, and desirable diastereoselectivities [24]. Chinchilla reported the Michael addition with a monoprotected 1,2-diamine as catalyst and dimethylformamide/H_2O (2:1) as solvent, which afforded the (*R*)-product. However, the use of chloroform or dichloromethane as the solvent resulted in a switch in selectivity and yielded the (*S*)-product [25]. In our recent study, organocatalysis of various reactions using thiourea catalysts derived from (*R,R*)-1,2-diphenylethylenediamine (DPEN) was reported [13–20]. Additionally, the correlation between the reactivity of the organocatalyst and the reaction outcome in water as an eco-friendly reaction solvent was investigated [26,27].

Similar to those used in previous studies, the basic skeleton of the organocatalyst used in this study comprised DPEN; thiourea was used as an additional skeleton. To synthesize a γ-lactone compound, a Michael addition reaction was performed with maleimide and an aldehyde as the electrophile and nucleophile, respectively [26–36]. Here, the correlation between the catalytic reaction and water as solvent was investigated through quantum calculations. Finally, we confirmed the role of water as an eco-friendly solvent in organocatalysis (Figure 1).
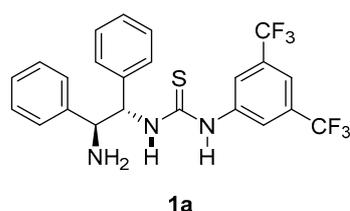

Figure 1. Mechanism of the Michael reaction using a non-covalent organocatalyst in aqueous media.

2. Results and Discussion

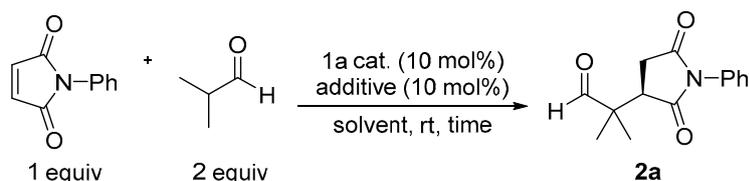### 2.1. Asymmetric Michael Reaction of Maleimide and Aldehydes Using a Thiourea Catalyst

To investigate the effect of the catalyst on the enantioselective Michael reaction of aldehydes and maleimides, reactions between isobutyraldehyde and maleimides were studied. DPEN was used as the basic backbone, and the Michael addition was performed using a catalyst in which thiourea replaced one of the amines. The 3,5-CF_3 benzyl- (**1a**) substituted thiourea catalysts were both evaluated in the Michael reaction (Figure 2).

1a

Figure 2. Catalysts based on DPEN and thiourea.

To examine the effect of the catalyst, CH_2Cl_2 was used as a solvent, and the reaction was performed at room temperature (Table 1). The highest yield and stereoselectivity were obtained using the catalyst substituted with the 3,5-bis(trifluoromethyl) group (**1a**). After confirming that 3,5-bis(trifluoromethyl) (**1a**) exhibited the highest stereoselectivity, an acid additive to further enhance the catalysis was evaluated. In particular, the aldehyde was activated by adding a weak acid additive to promote catalyst function and imine formation. With the addition of benzoic acid, the yield of the reaction increased slightly (entry 4). When the solvent of the reaction was changed to toluene, good yield and stereoselectivity were obtained (entry 6). However, when water was used as the solvent, catalyst **1a** provided the highest reactivity and enantioselectivity with optimal yield and stereoselectivity even in the absence of a weak acid additive (entry 8). In particular, for entry 10 in Table 1, the catalyst loading amount of 0.01 mol% for 12 h resulted in excellent yield and stereoselectivity.
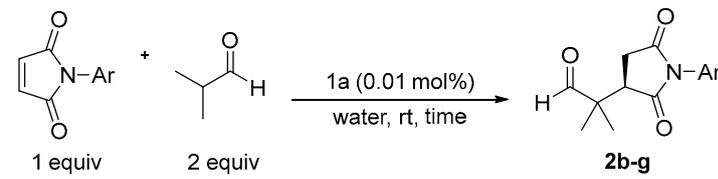
Table 1. Effect of additive and solvent.

Entry	Time (h)	Additive	Solvent	Yield (%) [a]	*ee* (%) [b]
1	24	Trifluoro-acetic acid	CH_2Cl_2	78	98
2	24	Acetic acid	CH_2Cl_2	83	94
3	24	Salicylic acid	CH_2Cl_2	82	94
4	24	Benzoic acid	Toluene	78	99
5	24	Benzoic acid	THF	98	99
6 [c]	0.67	-	Water	99	99
7 [d]	6	-	Water	99	99
8 [e]	12	-	Water	97	99

[a] Isolated yield. [b] Enantiomeric excess (*ee*) values were determined by chiral-phase high-performance liquid chromatography (HPLC) using an OD-H column. Reactions were run with catalyst loading of [c] 1, [d] 0.1, and [e] 0.01 mol%.

The reaction between isobutyraldehyde and various maleimides was carried out under the optimized conditions determined in Table 1. A reactant substituted with the maleimide *N*-phenyl maleimide was used, electron-withdrawing groups 4-Br, 4-NO$_2$, and 4-Me (Table 2, entry 2, 3, 4). Additionally, when the maleimide was not substituted with the phenyl group, the reaction time was shorter than optimal (entry 1). This difference slightly affects the stabilization of maleimide as an electron acceptor when the ketone group of maleimide binds with the thiourea hydrogen of the organocatalyst. So, the thermodynamic energy difference, solvent effect, and mechanism were confirmed through quantum calculations to determine the correlation between the organocatalysts and reactants (Table 2).
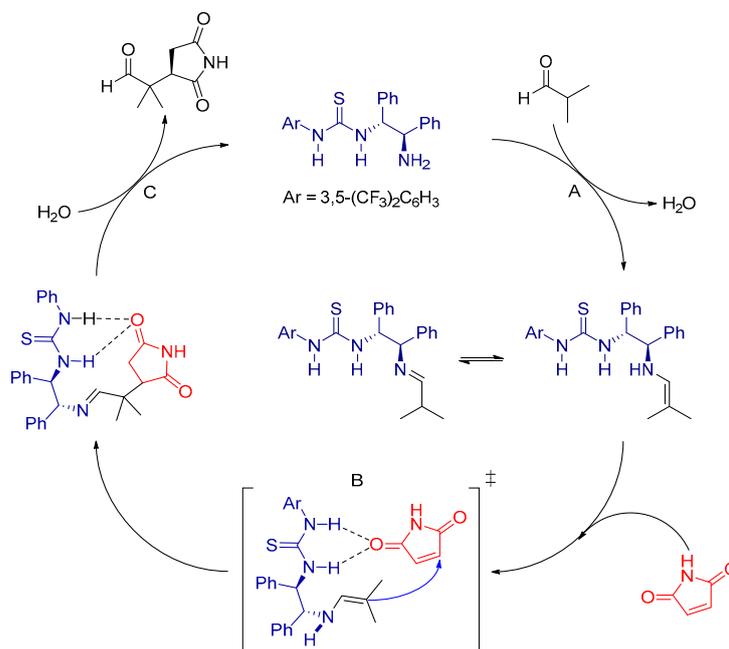
Table 2. Effect of various types of maleimide on the reaction.

Entry	Ar	Time (h)	Yield (%) [a]	*ee* (%) [b]
1	H	10	98	99
2	$4\text{-MeC}_6\text{H}_4$	12	99	99
3	$4\text{-BrC}_6\text{H}_4$	12	98	99
4	$4\text{-NO}_2\text{C}_6\text{H}_4$	12	97	99

[a] Isolated yield. [b] *ee* values were determined by chiral-phase HPLC using OD-H, AD-H, and AS-H columns.
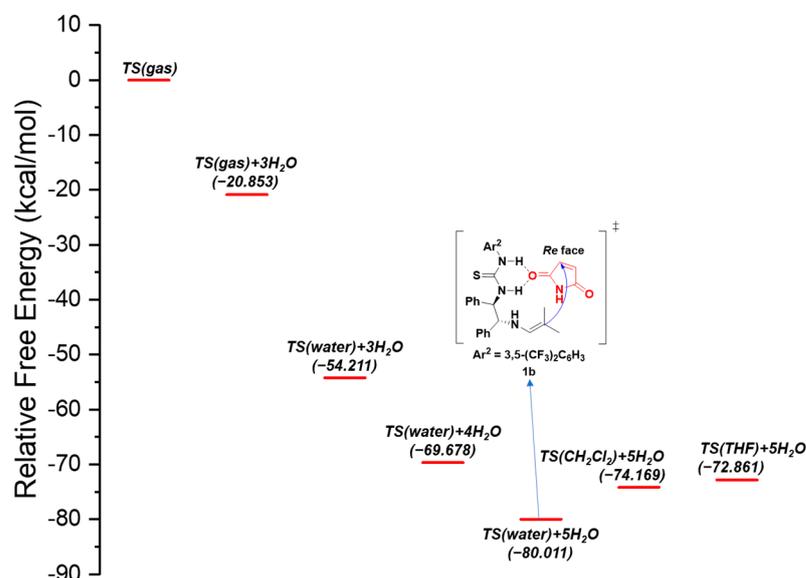
2.2. Reaction Mechanism Inferred through Expected Transition States

In step A, the **1a** catalyst reacts with isobutyraldehyde to form an imine, which forms an enamine. Additionally, the **1a** catalyst and maleimide activate the electrophile through hydrogen bonding with the thiourea of the catalyst. As in step B, a transition state including an activated electrophile is formed. Additionally, the reaction is expected to minimize the steric hindrance of maleimide by the re-face attack. Finally, the catalyst and the product are separated through hydrolysis as in step C. Therefore, it was possible to obtain the (*R*)-enantiomer rather than the (*S*)-enantiomer as the main product (Figure 3).

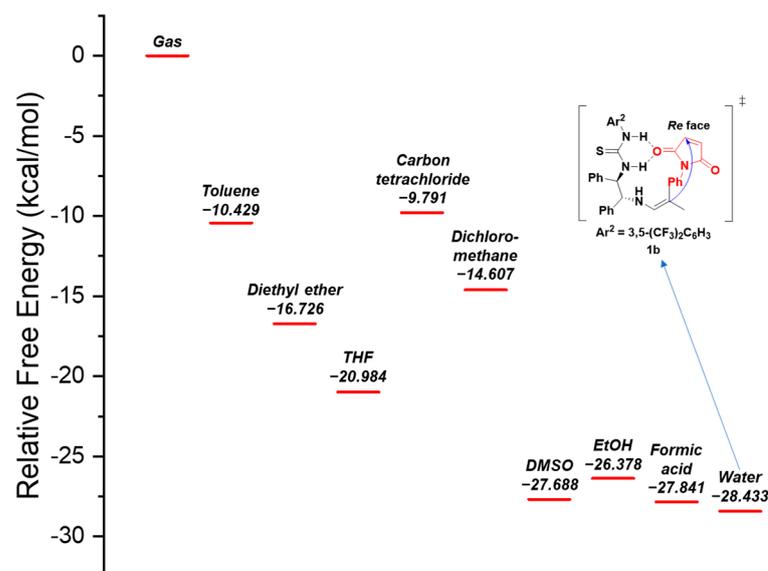**Figure 3.** Catalytic cycle of the Michael reaction and proposed transition states.

To obtain a more accurate prediction of the solvent effect on the catalyst, the relative free energy of the transition states (TS) during the interfacial reaction between the fluorine substituent of trifluorophenyl of catalyst **1b** and water as solvent was calculated in an aqueous binary mixture (H_2O + solvent, Figure 4) in the following manner. The lowest relative free energy of TS was calculated when water was used as solvent. As shown in Figure 4, the fluorine atom of the 3,5-bis(trifluoromethyl)phenyl group of the catalyst is predicted to interact with the proton of the water solvent through hydrogen bonding. In particular, the relative free energy decreases as the number of hydrogen bonds in water increases. In addition, when water is used as the solvent in the Michael addition reactions,

reactivity increases as the stabilization of the relative energy and the hydrophobic effect of the hydration reaction (Figure 4).

Figure 4. Proposed catalytic transition states based on the B3LYP/6-31G (d, p) method. Calculations were performed using water, toluene, and solvent + nH_2O conditions. Relative free energy diagram of the (*R,R*)-1,2-diphenylethylenediamine (DPEN)–thiourea-catalyzed enantioselective Michael reaction.

Hydrophobic non-polar solvents, such as toluene, afford good yields and stereoselectivities in Michael adduct synthesis [37]. However, the solvent effect on the Michael reaction was confirmed in Figure 4; thus, thermodynamic analysis was performed to determine the factors affecting Michael addition with water. To this end, quantum calculations were performed to predict the relative free energy of the interfacial reaction system in the TS of the catalyst (Figure 5).
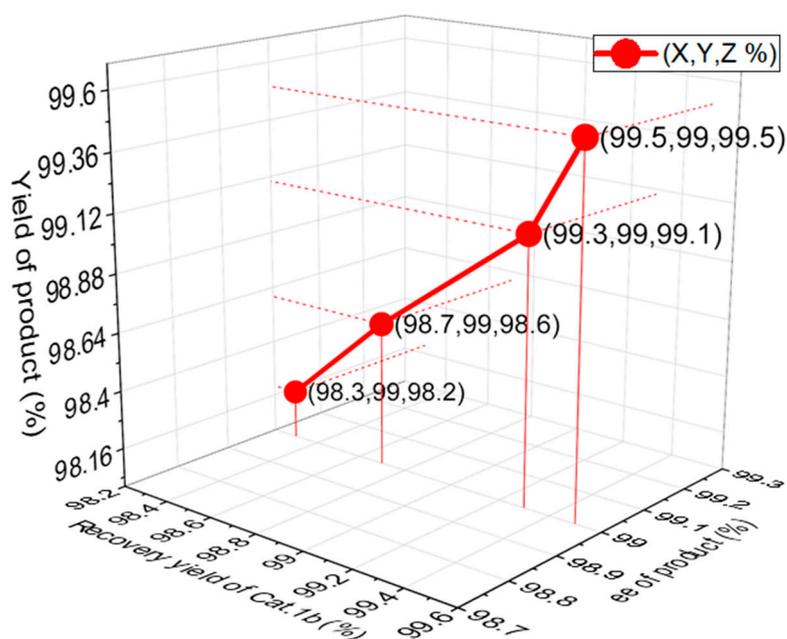
Figure 5. Proposed catalytic transition states based on B3LYP/6-31G (d, p) for the solvent + $5H_2O$ condition calculations and the thermal energy diagram of the (*R,R*)-1,2-diphenylethylenediamine-(DPEN)–thiourea-catalyzed enantioselective Michael reaction.
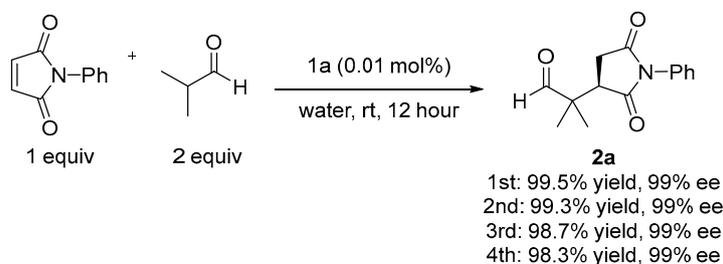
A comparison of the actual reaction findings (Table 1) with the quantum calculation results confirmed that the non-polar solvent toluene exhibited the lowest reactivity. In addition, tetrahydrofuran and CH$_2$Cl$_2$ exhibited similar reactivities in the calculated results. Notably, water showed the best reactivity and stability, with the obtained results exceeding those recorded for polar hydrophilic solvents dimethyl sulfoxide and ethanol and weak acids, such as aqueous formic acid (Figure 5). The optimization structures for DFT calculations mentioned in this article can be found on Supplementary Material page 27–125.

2.3. Pharmaceutical Applications Using Gram-Scale Asymmetric Reactions

Next, catalyst **1b** recycling was evaluated (Figures 6 and 7). The results of four-time tests indicated that the DPEN-derived thiourea catalyst (**1b**) was sufficiently recyclable (99.5–98.3%). In addition, the stereoselectivity of the product (99%) was maintained during the four reuse cycles of the catalyst. To synthesize the spironolactone, a physiologically active material, using the recovered catalyst, a gram-scale reaction was performed to add a cyclohexyl group to an aldehyde, as described below.
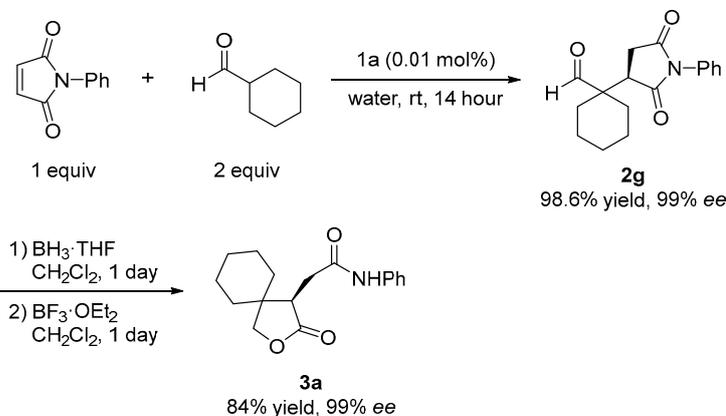

Figure 6. Recycling test for asymmetric Michael addition using chiral (*R,R*)-1,2-diphenylethylene-diamine-derived thiourea catalyst (**1b**).

2a
1st: 99.5% yield, 99% ee
2nd: 99.3% yield, 99% ee
3rd: 98.7% yield, 99% ee
4th: 98.3% yield, 99% ee

Figure 7. Gram-scale reaction of *N*-phenylmaleimide and isobutyraldehyde and catalyst recycling through catalyst recovery.

The Michael addition of isobutyraldehyde to *N*-phenylmaleimide (5 g) was studied; notably, when the reaction was performed using cyclohexanecarboxaldehyde instead of isobutyraldehyde, **2g** of the desired product was obtained in 98.6% yield (8.19 g) with 99%

enantiomeric excess (*ee*). As summarized in Figure 8, spirolactone **3a** was produced by the reaction of this product with $BH_3 \cdot THF$ and $BF_3 \cdot Et_2O$. The spironolactone series are known diuretics with potential medicinal applications (Figure 8) [24].

Figure 8. Gram-scale reaction for the application of spironolactone for the Michael reaction of cyclohexanecarboxaldehyde and *N*-phenylmaleimide.
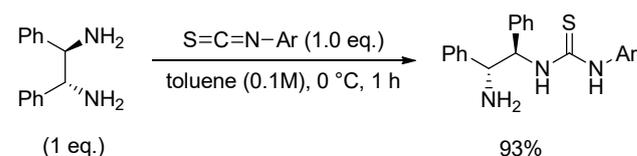
3. Materials and Methods

3.1. Instruments and Reagents

Optical rotation was measured using an auto digital polarimeter, and Fourier transform infrared (FT-IR) spectra were recorded using Nicolet 380 FT-IR spectrophotometer (Thermo Electron Corporation). Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were obtained using Varian Gemini 300 (300, 75 MHz) and Bruker Avance 500 (500, 125 MHz) using tetramethylsilane as internal standard. Low-resolution mass spectrometry profiles were obtained using a JEOL the MStation JMS-700. Chiral high-performance liquid chromatography (HPLC) analysis was performed using a Jasco LC-1500 Series HPLC system. Toluene (CaH_2), tetrahydrofuran (THF) (Na, benzophenone), and CH_2Cl_2 (CaH_2) reaction solvents were purified before use. The reagents used in this study were obtained from Aldrich, Acros, Alfa, Sigma, Merck, Fluka, TCI, and Lancaster, and purified or dried using a known method when necessary. Merck's silica gel 60 (230–400 mesh) was used as the stationary phase in column chromatography.

3.2. Experimental Method

3.2.1. Synthesis of *N*-Mono-Thiourea Catalyst

DPEN (0.5 g, 0.235 mmol) was dissolved in toluene (2.50 mL). Then, the solution was added with isothiocyanate (0.35 mL, 0.235 mmol) and stirred for 1 h at 0 °C, and the reaction was terminated with distilled water. The mixture was extracted with ethyl acetate (20 mL × 3 times), dehydrated using $MgSO_4$, filtered, concentrated under reduced pressure, and purified using column chromatography (SiO_2, CH_2Cl_2: *n*-hexane = 1:2) to isolate the product (Scheme 1).

Scheme 1. Synthesis of *N*-mono-thiourea catalyst.

3.2.2. Asymmetric Michael Reaction of Aldehyde and Maleimide Using a Chiral Thiourea Catalyst

At room temperature, an *N*-mono-thiourea catalyst (0.01 mol%) and *N*-phenylmaleimide (2.88 mmol) were placed in a reaction vessel and then dissolved with water (0.1 mL) in

air. Then, aldehyde (2 equiv.) was added to the mixture, which was stirred for 10–13 h. After the reaction was terminated with distilled water, the mixture was extracted with ethyl acetate (0.3 mL × 3 times), dehydrated using MgSO$_4$, filtered, concentrated under reduced pressure, and purified using column chromatography (SiO$_2$, CH$_2$Cl$_2$: *n*-hexane = 1:3) to isolate the product.

3.2.3. Gram-Scale Asymmetric Michael Reaction of Aldehyde and Maleimide Using a Chiral Thiourea Catalyst

At room temperature, an *N*-mono-thiourea catalyst (0.01 mol%) and *N*-phenylmaleimide (288.7 mmol) were placed in a reaction vessel and then dissolved with water (10 mL) in air condition. Then, aldehyde (2 equiv.) was added to the mixture and stirred for 10–13 h. After the reaction was terminated with distilled water, the mixture was extracted with ethyl acetate (30 mL × 3 times), dehydrated using MgSO$_4$, filtered, concentrated under reduced pressure, and purified using column chromatography (SiO$_2$, CH$_2$Cl$_2$: *n*-hexane = 1:3) to isolate the product. Finally, the column chromatography conditions were changed (SiO$_2$, CH$_2$Cl$_2$: *n*-hexane = 1:3) to isolate the catalyst.

3.2.4. General Procedure of the Racemic Michael Addition

N-Phenylmaleimide (0.3 mmol), aldehyde (10 equiv.), and 20 mol% of *DL*-proline were added to toluene (1 mL), and the reaction mixture was stirred at ambient temperature. The reaction conversion was checked by thin-layer chromatography. Upon the completion of the reaction after approximately 12 h, ethyl acetate (0.2 mL) was added to the reaction product. This solution was washed twice with water (2 × 1.0 mL), dried over MgSO$_4$ (anhydrous), and concentrated to yield the desired product. The product was purified by chromatography on a silica gel column eluted with a mixed solvent (CH$_2$Cl$_2$: *n*-hexane = 1:3).

3.3. Results of Density Functional Theory Calculations and Discussion

Density functional theory (DFT) calculations were performed using Gaussian 16 and Gauss-View 6.0 programs. 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 [37]. Single-point calculations for the optimized geometries were then performed by using the 6-31G (d, p) basic set. After the shapes of reactants and transition states (TS) were fully optimized, the thermodynamic functions and parameters (Gibbs free energy G) of reactants were obtained through vibrational frequency calculation. Additionally, 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

Herein, we report the experimental and theoretical analyses of DPEN-based catalysts for use as chiral bifunctional organocatalysts in asymmetric Michael addition to unsaturated maleimides under neutral conditions. The reaction delivered an enantiomeric excess range of 94–99%. Michael addition using the catalyst substituted with the 3,5-bis(trifluoromethyl) group (Figure 2, **1b**) exhibited relatively high enantioselectivity and diastereoselectivity. Owing to the low catalyst loading of 0.01 mol% and the straightforward synthetic methodology, these catalysts offer certain economic prospects. Notably, the reaction proceeds without metals and additives, and can be performed in air using water as the solvent, making the method environmentally friendly. In addition to presenting a pharmaceutical application using gram-scale asymmetric reactions, this study sought to gain insights into organocatalytic transformations with water as the solvent, making the reaction eco-friendly. The Michael addition reaction provided high yields and good stereoselectivity owing to the hydrogen bonding effect of the fluorine atoms with other hydrophobic groups in the catalyst. This catalytic methodology can be applied to various pharmaceutical syntheses

in the future. The development of drugs bearing chiral compounds using these synthetic approaches is underway.

References

1. MacMillan, D.W.C. The advent and development of organocatalysis. *Nature* **2008**, *455*, 304. [CrossRef] [PubMed]
2. Dalko, P.I.; Moisan, L. In the golden age of organocatalysis. *Angew. Chem. Int. Ed. Engl.* **2004**, *43*, 5138. [CrossRef]
3. Doyle, A.G.; Jacobsen, E.N. Small-molecule H-bond donors in asymmetric catalysis. *Chem. Rev.* **2007**, *107*, 5713. [CrossRef] [PubMed]
4. Mukherjee, S.; Yang, J.W.; Hoffmann, S.; List, B. Asymmetric enamine catalysis. *Chem. Rev.* **2007**, *107*, 5471. [CrossRef] [PubMed]
5. CDavie, E.A.C.; Mennen, S.M.; Xu, Y.; Miller, S.J. Asymmetric catalysis mediated by synthetic peptides. *Chem. Rev.* **2007**, *107*, 5759. [CrossRef]
6. Ballini, R.; Bosica, G.; Cioci, G.; Fiorini, D.; Petrini, M. Conjugate addition of nitroalkanes to N-substituted maleimides. Synthesis of 3-alkylsuccinimides and pyrrolidines. *Tetrahedron* **2003**, *59*, 3603. [CrossRef]
7. Du, Z.-H.; Qin, W.-J.; Tao, B.-X.; Yuan, M.; Da, C.-S. N-primary-amine tetrapeptide-catalyzed highly asymmetric Michael addition of aliphatic aldehydes to maleimides. *Org. Biomol. Chem.* **2020**, *18*, 6899. [CrossRef] [PubMed]
8. Mase, N.; Tanaka, F.; Barbas, C.F., III. Synthesis of β-hydroxyaldehydes with stereogenic quaternary carbon centers by direct organocatalytic asymmetric aldol reactions. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 2420. [CrossRef]
9. Chowdari, N.S.; Suri, J.T.; Barbas, C.F., III. Asymmetric synthesis of quaternary α- and β-amino acids and β-lactams via proline-catalyzed Mannich reactions with branched aldehyde donors. *Org. Lett.* **2004**, *6*, 2507. [CrossRef]
10. Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C.F., III. Organocatalytic direct Michael reaction of ketones and aldehydes with β-nitrostyrene in brine. *Org. Lett.* **2004**, *6*, 2527. [CrossRef]
11. Chowdari, N.S.; Barbas, C.F., III. Total synthesis of LFA-1 antagonist BIRT-377 via organocatalytic asymmetric construction of a quaternary stereocenter. *Org. Lett.* **2005**, *7*, 867. [CrossRef] [PubMed]
12. Brown, A.R.; Kuo, W.-H.; Jacobsen, E.N. Enantioselective catalytic α-alkylation of aldehydes via an SN1 pathway. *J. Am. Chem. Soc.* **2010**, *132*, 9286. [CrossRef] [PubMed]
13. Shim, J.H.; Nam, S.H.; Kim, B.S.; Ha, D.C. Organocatalytic asymmetric Michael addition of ketones to α, β-unsaturated nitro compounds. *Catalysts* **2020**, *10*, 618. [CrossRef]
14. 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]
15. Shim, J.H.; Lee, M.J.; Lee, M.H.; Kim, B.S.; Ha, D.C. Enantioselective organocatalytic Michael reactions using chiral (*R,R*)-1,2-diphenylethylenediamine-derived thioureas. *RSC Adv.* **2020**, *10*, 31808. [CrossRef]
16. Shim, J.H.; Park, S.J.; Ahn, B.K.; Lee, J.Y.; Kim, B.S.; Ha, D.C. Enantioselective thiolysis and aminolysis of cyclic anhydrides using a chiral diamine-derived thiourea catalyst. *ACS Omega* **2021**, *6*, 34501. [CrossRef]
17. Shim, J.H.; Ahn, B.K.; Lee, J.Y.; Kim, H.S.; Ha, D.C. Organocatalysis for the asymmetric Michael addition of cycloketones and α,β-unsaturated nitroalkenes. *Catalysts* **2021**, *11*, 1004. [CrossRef]

18. Shim, J.H.; Hong, Y.; Kim, J.H.; Kim, H.S.; Ha, D.-C. Organocatalytic asymmetric Michael addition in aqueous media by a hydrogen-bonding catalyst and application for inhibitors of GABA_B receptor. *Catalysts* **2021**, *11*, 1134. [CrossRef]

19. Shim, J.H.; Cheun, S.H.; Kim, H.S.; Ha, D.-C. Organocatalysis for the asymmetric Michael addition of aldehydes and α,β-unsaturated nitroalkenes. *Catalysts* **2022**, *12*, 121. [CrossRef]

20. Shim, J.H.; Lee, J.Y.; Kim, H.S.; Ha, D.-C. Protonated Chiral 1,2-Diamine Organocatalysts for *N*-Selective Nitroso Aldol Reaction. *Catalysts* **2022**, *12*, 435. [CrossRef]

21. Xue, F.; Liu, L.; Zhang, S.; Duan, W.; Wang, W. A simple primary amine thiourea catalyzed highly enantioselective conjugate addition of α,α-disubstituted aldehydes to maleimides. *Chem. Eur. J.* **2010**, *16*, 7979–7982. [CrossRef] [PubMed]

22. Ma, Z.-w.; Liu, Y.-x.; Li, P.l.; Ren, H.; Zhu, Y.; Tao, J.C. A highly efficient large-scale asymmetric Michael addition of isobutyraldehyde to maleimides promoted by a novel multifunctional thiourea. *Tetrahedron Asymmetry* **2011**, *22*, 1740–1748. [CrossRef]

23. Orlandi, S.; Pozzi, G.; Ghisetti, M.; Benaglia, M. Synthesis and catalytic activity of fluorous chiral primary amine-thioureas. *New J. Chem.* **2013**, *37*, 4140. [CrossRef]

24. Kokotos, C.G. An Asymmetric Michael Addition of α,α-Disubstituted Aldehydes to Maleimides Leading to a One-Pot Enantioselective Synthesis of Lactones Catalyzed by Amino Acids. *Org. Lett.* **2013**, *15*, 2406–2409. [CrossRef]

25. Ferrandiz, J.F.; Bengoa, E.G.; Chinchilla, R. Solvent-induced reversal of enantioselectivity in the synthesis of succinimides by the addition of aldehydes to maleimides catalysed by carbamate-monoprotected 1,2-diamines. *Eur. J. Org. Chem.* **2015**, *6*, 1218. [CrossRef]

26. Qiaoa, Y.; Headley, A.D. A simple and highly effective water-compatible organocatalytic system for asymmetric direct Michael reactions of linear aldehydes to maleimides. *Green Chem.* **2013**, *15*, 2690–2694. [CrossRef]

27. Kolcsára, V.J.; Szőllősi, G. Chitosan as a chiral ligand and organocatalyst: Preparation conditions–property–catalytic performance relationships. *Catal. Sci. Technol.* **2021**, *11*, 7652–7666. [CrossRef]

28. Du, Z.-H.; Qin, W.-J.; Tao, B.-X.; Yuan, M.; Da, C.-S. Silver-catalyzed direct C–H oxidative carbamoylation of quinolines with oxamic acids. *Org. Biomol. Chem.* **2020**, *18*, 6899. [CrossRef]

29. Landeros, J.M.; Cruz-Hernandez, C.; Juaristi, E. α-amino acids and α,β-dipeptides intercalated into hydrotalcite: Efficient catalysts in the asymmetric Michael addition reaction of aldehydes to N-substituted maleimides. *Eur. J. Org. Chem.* **2021**, *37*, 5117. [CrossRef]

30. Avila, A.; Chinchilla, R.; Najera, C. Enantioselective Michael addition of α,α-disubstituted aldehydes to maleimides organocatalyzed by chiral primary amine-guanidines. *Tetrahedron Asymmetry* **2012**, *23*, 1625. [CrossRef]

31. Nugent, T.C.; Sadiq, A.; Bibi, A.; Heine, T.; Zeonjuk, L.L.; Vankova, N.; Bassil, B. Noncovalent bifunctional organocatalysts: Powerful tools for contiguous quaternary-tertiary stereogenic carbon formation, scope, and origin of enantioselectivity. *Chem. Eur. J.* **2012**, *18*, 4088. [CrossRef] [PubMed]

32. Vazquez-Chavez, J.; Luna-Morales, S.; Cruz-Aguilar, D.-A.; Díaz-Salazar, H.; Narváez, W.E.V.; Silva-Gutiérrez, R.S.; Hernández-Ortega, S.; Rocha-Rinza, T.; Hernández-Rodríguez, M. The effect of chiral N-substituents with methyl or trifluoromethyl groups on the catalytic performance of mono- and bifunctional thioureas. *Org. Biomol. Chem.* **2019**, *17*, 10045. [CrossRef] [PubMed]

33. de Simone, N.A.D.; Meninno, S.; Talotta, C.; Gaeta, C.; Neri, P.; Lattanzi, A. Solvent-free enantioselective Michael reactions catalyzed by a calixarene-based primary amine thiourea. *J. Org. Chem.* **2018**, *83*, 10318. [CrossRef]

34. Torregrosa-Chinillach, A.; Moragues, A.; Pérez-Furundarena, H.; Chinchilla, R.; Gómez-Bengoa, E. Enantioselective Michael addition of aldehydes to maleimides organocatalyzed by a chiral primary amine-salicylamide. *Molecules* **2018**, *23*, 3299. [CrossRef] [PubMed]

35. Schiza, A.; Spiliopoulou, N.; Shahu, A.; Kokotos, C.G. Combining organocatalysis with photoorganocatalysis: Photocatalytic hydroacylation of asymmetric organocatalytic Michael addition products. *New J. Chem.* **2018**, *42*, 18844. [CrossRef]

36. Muramulla, S.; Ma, J.-A.; Zhao, J.C.-G. Michael addition of ketones and aldehydes to maleimides catalyzed by modularly designed organocatalysts. *Adv. Synth. Catal.* **2013**, *355*, 1260. [CrossRef]

37. 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]

38. Miura, T.; Masuda, A.; Ina, M.; Nakashima, K.; Nishida, S.; Tada, N.; Itoh, A. Asymmetric Michael reactions of α, α-disubstituted aldehydes with maleimides using a primary amine thiourea organocatalyst. *Tetrahedron Asymmetry* **2011**, *22*, 1605–1609. [CrossRef]

39. Bai, J.F.; Peng, L.; Wang, L.L.; Wang, L.X.; Xu, X.Y. Chiral primary amine thiourea promoted highly enantioselective Michael reactions of isobutylaldehyde with maleimides. *Tetrahedron* **2010**, *66*, 8928–8932. [CrossRef]

40. Yu, F.; Jin, Z.; Huang, H.; Ye, T.; Liang, X.; Ye, J. A highly efficient asymmetric Michael addition of α, α-disubstituted aldehydes to maleimides catalyzed by primary amine thiourea salt. *Org. Biomol. Chem.* **2010**, *8*, 4767–4774. [CrossRef]

41. Ma, Z.W.; Liu, X.F.; Liu, J.T.; Liu, Z.J.; Tao, J.C. Highly enantioselective Michael addition of α, α-disubstituted aldehydes to maleimides catalyzed by new primary amine-squaramide bifunctional organocatalysts. *Tetrahedron Lett.* **2017**, *58*, 4487–4490. [CrossRef]