Organocatalytic Asymmetric Addition of Aldehyde to Nitroolefin by H-δ-Pro-Pro-Glu-NH₂: A Mechanistic Study
Ludovic T. Maillard,*†‡ Hae Sook Park,§ and Young Kee Kang*†§

†Institut des Biomolécules Max Mousseron, UMR CNRS-UM-ENSCM 5247, UFR des Sciences Pharmaceutiques et Biologiques, 15 Avenue Charles Flahault, 34093 Montpellier Cedex 5, France
‡Department of Nursing, Cheju Halla University, Cheju 63092, Republic of Korea
§Department of Chemistry, Chungbuk National University, Cheongju, Chungbuk 28644, Republic of Korea

Supporting Information

ABSTRACT: The mechanism of the asymmetric addition of aldehyde (butanal) to nitroolefin (β-nitrostyrene) catalyzed by H-δ-Pro-Pro-Glu-NH₂ (dPPE-NH₂; I) was explored using density functional theory methods in chloroform. By computational search, it was confirmed that catalyst I and its enamine intermediate adopted a dominant conformation with a β1 structure stabilized by a C10 H-bond between the C=O of δ-Pro1 and C-terminal NH₂ proton and by an additional H-bond between the side chain and the backbone of Glu3. This β1 turn structure was conserved all along the catalytic cycle. Consistently with the kinetic studies, the C–C bond formation between the enamine and electrophile was also confirmed as the rate-determining step. The stereoselectivity results from a re → re prochiral approach of enamine and β-nitrostyrene with a gauche− orientation of the double bonds. Although it was suggested as the possible formation of dihydroxazine oxide species, this process was confirmed to be kinetically less accessible than the formation of acyclic nitronate. In particular, our calculated results supported that the carboxylic acid group of Glu3 in I played a central role by acting as general acid/base all along the catalytic cycle and orienting the asymmetric C–C bond formation.

INTRODUCTION

The advent of organocatalysis has brought the prospect of a mode of catalysis, complementary to organometallic systems, with the potential for savings in cost, time, and energy; easier experimental procedures; and reductions in chemical waste.1 Among environmentally friendly organocatalysts, peptides and peptide-based molecules have emerged as promising candidates (for reviews, see ref 2). Both combinatorial and de novo methods of the catalyst design have been demonstrated successfully to perform a variety of asymmetric conjugate addition reactions including aldol, Mannich, Michael, and Hillman reactions.2a,e,3 From a synthetic perspective, after the recognition of proline’s aptitude in formation of carbon–carbon bond in a stereoselective fashion,4 remarkable efforts have been endorsed in the development of chiral-amine and peptide-based organocatalysts bearing a pyrrolidine moiety.5 It is widely accepted that in such transformations an enamine intermediate is generated by condensing a carbonyl bearing reagent with the catalytic pyrrolidine. Reaction of the enamine then proceeds via addition on an electrophile partner, and the resulting iminium ion is finally hydrolyzed to afford the products. Another less explored possible mechanism involves enol as activated species for addition to the electrophile.6

In such a field, the organocatalytic Michael addition reaction of ketones or aldehydes to nitroolefins has recently attracted considerable attention because of the importance of resultant chiral nitroalkanes as synthetically valuable building blocks.7 Considering activity and selectivity, Wennemers tripeptide H-δ-Pro-Pro-Glu-NH₂ (dPPE-NH₂; peptide 1 in Scheme 1) deserves special mention as a highly active and stereoselective catalyst for Michael conjugate addition of aldehydes to nitroethylene8 and β-monosubstituted nitro-olefins in the protic CHCl₃/PrOH (9:1 v/v) environment9 (Scheme 1). It has noteworthy achieved the highest levels of stereocontrol under the lowest catalyst loading reported to date without significant catalyst deactivation. ESI−MS back-reaction screening experiments support an enamine mechanism because enamine and iminium have been detected as intermediates.10 Considering such a pathway, the catalytic cycle should be divided into four main steps consisting of (i) enamine formation, (ii) reaction with the nitroolefin to yield a new C–C bond, (iii) protonation of the nitronate intermediate, and finally (iv) hydrolysis of the iminium. Kinetic studies provided insights that the reaction of the enamine with the electrophile is rate limiting and highlight a double role of the acidic group. It first orients the reactivity and stereoselectivity and secondly, it improves the reaction rate by promoting protonation of the iminium nitronate.11,12 Although the acid group probably coordinates the nitronate function, its exact role as well as the protonation states along the catalytic pathway are not fully understood. Especially, its presence is not indispensable.

Received: February 19, 2019
Accepted: May 13, 2019
Published: May 22, 2019
Scheme 1. (a) H-d-Pro-Pro-Glu-NH₂-Catalyzed Conjugate Addition Reaction of Butanal to β-Nitrostyrene; (b) Proposed Catalytic Cycle: (i) Enamine Formation, (ii) C–C Bond Formation, (iii) Protonation of the Nitronate and (iv) Hydrolysis

![Reaction diagram](image)

because a powerful catalytic tripeptide without the acid group has been reported for the addition of nitro-Michael between aldehydes and β/β-disubstituted nitro-olefins. Alternative mechanisms have been proposed for the catalysts which do not have acidic hydrogen. As an example, with chiral prololin ether derivatives, cyclic intermediates such as dihydrooxazine and cyclobutane (1-D’ and 1-C’ in Chart 1a, respectively) were identified as resting states of catalysts, and the rate-determining step (rds) of the reaction was suggested to be the protonation of the dihydrooxazine oxide species instead of the iminium (refs 14a,15a) or enamine nitronates (ref 15b). An analogous cyclobutane intermediate has also been found in the reaction of butanal and nitrostyrene with dPPE-NH₂ methyl ester. Hence, even they are not populated to a significant extent, dihydrooxazine and cyclobutane intermediates could not be excluded in dPPE-NH₂ as a catalyst.

Recently, Rigling et al. investigated the conformational preferences of dPPE-NH₂ (1) and its enamine intermediate (1-En’ in Chart 1b) obtained by reaction with phenylacetaldehyde in a solution of CDCl₃/CD₃OH (9:1) using NMR spectroscopy and density functional theory (DFT) methods. In dPPE-NH₂, a strong nuclear Overhauser effect (NOE) was found between the amide NH of Glu3 and one of the C-terminal amide protons, which supports the formation of a β-turn conformation with a H-bond between the carbonyl group of d-Pro1 and the amide proton of the C-terminal group. By the lower vicinal coupling constants (close to 4 Hz) from the Hβ protons to Ha and Hγ’, it was suggested as distinct conformational preferences of the side chain torsion angles χ¹ and χ² of Glu3 at ~60° (g¹) and ~−60° (g²), respectively, which indicates a conformation with the side chain of Glu3 pointing toward d-Pro1. However, it was found that 1-En’ with the s-trans configuration still adopts a β-turn conformation being less populated compared to dPPE-NH₂, by observing a stronger NOE between Ha of d-Pro1 and NH of Glu3 and by a significantly higher temperature dependence of the C-terminal CONHamide proton chemical shift in 1-En’ than in peptide 1. The higher flexibility of the Glu3 side chain and backbone in 1-En’ was suggested to be essential to stereoselectively accommodate the incoming nitroolefin for the C–C bond formation. However, the detailed pathways for the formation of iminium-nitronate, protonation, and hydrolysis were not reported.

The Michael addition of propanal to β-nitrostyrene catalyzed by diarylprolinol silyl ether has been the subject of computational studies using DFT methods to investigate the stereoselectivity of the C–C bond formation and mechanistic pathways. In earlier studies, the lowest-energy transition state was obtained for the (R,S) pathway (∆E = 23 kcal mol⁻¹) at the B3LYP/6-31G(d) level of theory. In a recent study, the free energy of the transition state for the (R,S) pathway was computed as 16.2 kcal mol⁻¹ in chloroform by the sum of the free energy at the ωB97X-D/6-31+G(3df,3pd)//ωB97X-D/6-311G(d,p) level of theory and polarizable continuum model (PCM) solvation free energy at the ωB97X-D/6-311G(d,p) level of theory. In particular, the stereoselectivity was suggested to be primarily controlled by the C–C bond formation even though the reaction rate was dictated by the subsequent protonation step.

Here, we explored the plausible pathways of addition of aldehyde (butanal) to nitroolefin (β-nitrostyrene) catalyzed by dPPE-NH₂ in chloroform by DFT calculations. Our results highlight the central role of the carboxylic acid group by acting as a general acid/base all along the catalytic cycle and orienting the asymmetric C–C bond formation.

**RESULTS AND DISCUSSION**

**Preferred Conformations of dPPE-NH₂.** For dPPE-NH₂ (1), we identified 11 local minima with ΔE < 10 kcal mol⁻¹ at the M06-2X/6-31G(d) level of theory in the gas phase. However, there were only four local minima with the relative Gibbs free energy (ΔG) < 10 kcal mol⁻¹ at the ωB97X-D/6-31+G(d,p)//SMD M06-2X/6-31+G(d) level of theory in chloroform. The torsion angles and thermodynamic properties of these local minima in chloroform are listed in Table 1.

The most preferred conformation 1-dPPE-NH₂ was dominantly populated in chloroform (ΔG = 0.0 kcal mol⁻¹).
with a population of 100%) and the next preferred conformers were 2-dPPE-NH₂, 3-dPPE-NH₂, and 4-dPPE-NH₂ with ΔG = 4.1, 5.6, and 6.3 kcal mol⁻¹, respectively (Table 1 and Figure 1). The most preferred conformer 1-dPPE-NH₂ adopted a type β-turn (β/β) structure, which appeared to be stabilized by a C=O H-bond between the C==O of d-Pro1 and the proton of the C-terminal amide NH₂ with a distance of d(C==O···H–N terminus) = 2.01 Å (Figure 1a). In addition, there were two additional H-bonds between the side chain C=O⁻¹ and backbone NH proton of Glu3 with a distance of d(C=O⁻¹···H–N Glu3) = 1.92 Å and between the side chain carboxylic proton of Glu3 and the amide nitrogen of d-Pro1 with a distance of d(O=–H Glu3···N–d-Pro1) = 1.59 Å (Figure 1a).

The backbone torsion angles of the most preferred conformation 1-dPPE-NH₂ in chloroform were calculated as (ψ₁, ψ₂, ψ₃, ψ₄) = (−158°, −16°, −63°, −21°) (Table 1), which are consistent with the mean values of (−152 ± 1°, −36 ± 10°, −66 ± 11°, 2 ± 15°) obtained by simulated annealing calculations with the restraints of NOEs, residual dipolar couplings, and vicinal coupling constants from NMR experiments. In addition, our calculated torsion angles (ψ₁, ψ₂) = (76°, −65°) of the side chain of Glu3 (Table 1) are in accord with the population calculated by the ΔG values at 25 °C.

Table 1. Torsion Angles (°) and Thermodynamic Properties (kcal mol⁻¹) of Local Minima (ΔG < 10 kcal mol⁻¹) for the Catalyst dPPE-NH₂

| conformer | ψ₁   | ψ₂   | ψ₃   | ψ₄   | χ₁   | χ₂   | χ₃   | ΔΔE  | ΔΔH  | ΔΔG  | w   |
|-----------|------|------|------|------|------|------|------|------|------|------|-----|
| 1-dPPE-NH₂| −157.9 | −16.1 | −63.0 | −21.2 | 75.8 | −64.6 | 152.4 | 0.0  | 0.0  | 0.0  | 100 |
| 2-dPPE-NH₂| −147.4 | 61.5  | −111.8 | 156.4 | −52.8 | 78.8  | 45.5  | 5.5  | 5.6  | 4.1  | 0   |
| 3-dPPE-NH₂| −141.2 | 58.8  | −85.4 | 69.7  | −54.0 | 89.0  | −152.4 | 7.2  | 7.2  | 5.6  | 0   |
| 4-dPPE-NH₂| −129.6 | 67.3  | −144.2 | −60.4 | −8.7  | 70.9  | −174.5 | 7.7  | 7.8  | 6.3  | 0   |

“Torsion angles are for the backbone of dPPE-NH₂. Calculated at the ωB97X-D/6-311++(d,p)/SMD M06-2X/6-31+G(d) level of theory in chloroform. ΔΔE, ΔΔH, and ΔΔG stand for relative electronic energy, enthalpy, and Gibbs free energy at 25 °C and 1 atm. The population calculated by the ΔΔG values at 25 °C.”

Table 2. Torsion Angles (°) and Thermodynamic Properties (kcal mol⁻¹) of 12 Local Minima (ΔG < 3 kcal mol⁻¹) for the Enamine Intermediate

| conformer | ψ₁   | ψ₂   | ψ₃   | ψ₄   | χ₁   | χ₂   | χ₃   | ΔΔE  | ΔΔH  | ΔΔG  | w   |
|-----------|------|------|------|------|------|------|------|------|------|------|-----|
| En-01     | −167.4 | −18.5 | −78.2 | −13.7 | 84.7 | −66.0 | 174.8 | 0.0  | 0.0  | 0.0  | 45  |
| En-02     | −40.1  | −16.6 | −82.6 | 70.2  | −58.7 | 86.7  | −178.9 | 3.3  | 2.7  | 0.6  | 17  |
| En-03     | −101.4 | −11.8 | −80.6 | −9.1  | −55.0 | −169.3 | −168.9 | 1.4  | 1.6  | 0.6  | 16  |
| En-04     | −150.4 | 150.2 | −89.6 | 67.4  | −74.9 | 55.6  | −106.0 | 2.9  | 2.8  | 1.0  | 9   |
| En-05     | −153.9 | 66.3  | −145.5 | 17.6  | 70.1  | −65.9 | 125.7  | 1.9  | 1.7  | 1.2  | 6   |
| En-06     | 34.7   | 146.1 | −147.6 | 159.4 | −57.8 | −65.4 | 169.9  | 4.3  | 4.1  | 1.9  | 2   |
| En-07     | −162.4 | 70.5  | −90.0 | 64.9  | −48.5 | −46.2 | −56.2  | 3.3  | 3.1  | 2.0  | 2   |
| En-08     | −94.2  | −10.2 | 79.4  | −51.2 | −54.5 | −71.0 | −172.7 | 3.5  | 3.6  | 2.1  | 2   |
| En-09     | −168.6 | 67.0  | −86.0 | 71.3  | −59.4 | 71.8  | 49.1  | 2.8  | 2.7  | 2.3  | 1   |
| En-10     | −123.1 | 153.1 | −88.8 | 64.3  | −76.4 | 53.4  | −101.6 | 3.1  | 3.1  | 2.6  | 1   |
| En-11     | −106.3 | 142.5 | −158.5 | 166.7 | −99.7 | −67.7 | 179.3  | 5.8  | 5.5  | 2.6  | 1   |
| En-12     | 42.9   | 59.1  | −93.3 | 63.1  | −51.6 | −48.0 | −58.2  | 4.5  | 4.3  | 2.8  | 0   |

“Torsion angles are for the backbone of dPPE-NH₂. Calculated at the ωB97X-D/6-311++(d,p)/SMD M06-2X/6-31+G(d) level of theory in chloroform. ΔΔE, ΔΔH, and ΔΔG stand for relative electronic energy, enthalpy, and Gibbs free energy at 25 °C and 1 atm. The population calculated by the ΔΔG values at 25 °C.”
with the conformational preference of the side chain torsion angles $\chi'$ and $\chi''$ of Glu3 at $g'$ and $g''$, respectively, deduced from vicinal coupling constants between protons at $C_\text{r}, C_\beta,$ and $C_\gamma$ in Glu3.

**Preferred Conformations of the Enamine 1-En.** For the enamine intermediate 1-En, we identified 40 local minima with $\Delta E < 10$ kcal mol$^{-1}$ at the M06-2X/6-31G(d) level of theory in the gas phase and 30 local minima with $\Delta G < 5$ kcal mol$^{-1}$ at the oB97X-D/6-311++G(d,p)/SMD M06-2X/6-31+G(d) level of theory in chloroform. The torsion angles and thermodynamic properties of 12 local minima of 1-En with $\Delta G < 3$ kcal mol$^{-1}$ in chloroform are listed in Table 2. All 30 local minima with $\Delta G < 5$ kcal mol$^{-1}$ in chloroform are listed in Table S1 of the Supporting Information.

The conformer En-01 of 1-En (Figure 2a) was the most preferred, as indicated by the $\Delta G$ values with a population of 45%; the next most preferred conformers were En-02, En-03, and En-04 (Figure 2b–d) [\(\Delta G = 0.6, 0.6, \text{and} 1.0\) kcal mol$^{-1}$, respectively (Table 2); populated at 17, 16, and 9%, respectively], confirming the higher flexibility of 1-En compared with dPPE-NH$_2$. The most preferred conformer En-01 adopted a $\beta$I structure stabilized by a C$_\text{10}$ H-bond between the C═O of d-Pro1 and the proton of the C-terminal amide NH$_3$ with a distance of $d(\text{C}═\text{O}_{\text{d-Pro1}}\cdots\text{H}−\text{N}_{\text{C-terminal}}) = 2.02$ Å (Figure 2a). In addition, there was an additional H-bond between the side chain C$′═$O$′$ and the backbone NH proton of Glu3 with a distance of $d(\text{C}′═\text{O}_{\text{Glu3}}\cdots\text{H}−\text{N}_{\text{Glu3}}) = 1.92$ Å (Figure 2a). Although a H-bond between the side chain carboxylic proton of Glu3 and the amide nitrogen of d-Pro1 was lost in En-01 because of the enamine formation, the overall conformation of En-01 with the torsion angles \((\psi_1, \psi_2, \phi_1, \psi_3, \chi_1, \chi_2, \chi_3) = (−167°, −19°, −78°, −14°, 85°, −66°, 175°)\) (Table 2) was quite similar to the most preferred conformer 1-dPPE-NH$_2$ of peptide 1 (Table 1).

The second most preferred conformer En-02 had two H-bonds between the C═O of Pro2 and the proton of the C-terminal amide NH$_2$ with a distance of $d(\text{C}═\text{O}_{\text{Pro2}}\cdots\text{H}−\text{N}_{\text{Glu3}}) = 2.07$ Å and between the side chain C$═$O$′$ and the amide NH of Glu3 with a distance of $d(\text{O}^′\cdots\text{H}−\text{N}_{\text{Glu3}}) = 2.24$ Å (Figure 2b). Conformer En-02 was 2.7 kcal mol$^{-1}$ less favored in $\Delta H$ relative to the most preferred En-01, but the former had more conformational flexibility of $−\Delta TS = −2.1$ kcal mol$^{-1}$ than the latter. The third most preferred conformer En-03 had only one H-bond between the C═O of d-Pro1 and the proton of the C-terminal amide NH$_3$ with a distance of $d(\text{C}═\text{O}_{\text{d-Pro1}}\cdots\text{H}−\text{N}_{\text{C-terminal}}) = 1.99$ Å (Figure 2c). Conformer En-03 was 1.6 kcal mol$^{-1}$ less favored in $\Delta H$ relative to the most preferred En-01, but the former had more conformational flexibility of $−\Delta TS = −1.0$ kcal mol$^{-1}$ than the latter. The fourth most preferred conformer En-04 had two H-bonds between the C═O of Pro2 and the proton of the C-terminal amide NH$_3$ with a distance of $d(\text{C}═\text{O}_{\text{Pro2}}\cdots\text{H}−\text{N}_{\text{C-terminal}}) = 2.17$ Å and between the C═O of d-Pro1 and the side chain carboxylic proton of Glu3 and the C═O of d-Pro1 with a distance of $d(\text{O}^′\cdots\text{H}_{\text{Glu3}}\cdots\text{C}═\text{O}_{\text{Pro1}}) = 1.73$ Å (Figure 2d). Conformer En-04 was 2.8 kcal mol$^{-1}$ less favored in $\Delta H$ relative to the most preferred En-01, but the former had more conformational flexibility of $−\Delta TS = −1.8$ kcal mol$^{-1}$ than the latter. The other conformers En-05 to En-12 exhibited values of $\Delta G = 1.2−2.8$ kcal mol$^{-1}$ and populations less than 6% in chloroform (Table 2).

Our results are in agreement with the NMR data reported by Rigling et al. for the enamine intermediate named 1-En$'$ obtained by condensation of dPPE-NH$_2$ (1) with phenylacetaldehyde. Despite a predominant $\beta$-turn conformation, the enamine intermediates appeared more flexible than the parent catalyst dPPE-NH$_2$. We also predicted that the puckering of d-Pro1 and Pro2 in En-01 are both C$_\gamma$-endo, which are consistent with NMR data for 1-En$'$. The main difference between En-01 and 1-En$'$ relates to the conformation of the Glu3 side chain. While \((\chi_1', \chi_2') = (−71°, 78°)\) for 1-En$'$, it was \((\chi_1', \chi_2') = (85°, −66°)\) for En-01, which is similar to the values calculated for 1-dPPE-NH$_2$. The assignment of the $g'g''$ side chain conformation of Glu3 to 1-En$'$ probably resulted in a clash between the carboxylic group of Glu3 and the C═C bond that did not occur with the butanlan reactant.

**Stereoselective C–C Bond Formation.** We then studied the stereoselective C–C bond formation resulting from the addition of En-01 of 1-En to $\beta$-nitrostyrene. Depending on the relative orientations of the prochiral centers, four different enamine $\rightarrow$ nitrostyrene facial approaches were considered. The $\text{re} \rightarrow \text{re}$, $\text{re} \rightarrow \text{si}$, $\text{si} \rightarrow \text{re}$, and $\text{si} \rightarrow \text{si}$ approaches lead, respectively, to the four possible diastereomers (2S,3R), (2S,3S), (2R,3R), and (2R,3S) for the nitronate 1-Nit (Scheme 2). For each enantiomer, three different orientations [i.e., gauche $^−$ (g$′$), gauche $^+$ (g$''$), and trans (t)] of the double bonds of enamine and nitrostyrene were considered.

The procedure to construct the 12 initial 1-Nit structures (only four enantiomers) and the corresponding transition states are described in the Supporting Information. The torsion angles and relative thermodynamic properties of enantiomeric transition states and products for the stereoselective C–C bond formation in chloroform are listed in Table S2 of the Supporting Information. The free-energy profiles for 12 stereoselective C–C bond formations between En-01 and $\beta$-nitrostyrene in chloroform at the oB97X-D/6-311+G(d,p)//SMD M06-2X/6-31+G(d) level of theory are depicted in Figure 3.
Scheme 2. Four Different Approaches of the Prochiral Centers of Enamine 1-En and β-Nitrostyrene to Form the C–C Bond

The torsion angles of the backbone of dPPE-NH₂ moiety in all transition states and products were quite similar to each other. The five lowest energy barriers were obtained for the re → re/t, re → si/g*, re → si/t, si → re/t, and re → re/g⁺ prochiral approaches. Although the barriers of the four first prochiral approaches were 1.6, 2.3, 1.0, and 2.2 kcal mol⁻¹ lower in free energy than that of the re → re/g⁻ one, the corresponding products were less preferred than the (2S,3R)-1-Nit (ΔΔG = 12.4, 4.9, 3.8, and 1.8 kcal mol⁻¹, respectively). The nitronate intermediates resulting from re → re/g⁺ and si → si/g* approaches were lower in free energy (ΔΔG = −1.4 and −1.8 kcal mol⁻¹); however, the energy barriers were found to be 1.4 kcal mol⁻¹ higher than that of the re → re/g⁻ prochiral approach. Hence, the re → re/g⁻ prochiral approach between enamine (1-En) and β-nitrostyrene was kinetically and/or thermodynamically favored and appeared to be the major route for the C–C bond formation, which produced the major (2S,3R)-1-Nit intermediate.

The three re → si/g*, re → si/t, and si → re/t prochiral approaches have the lower ΔΔG⁺ barriers for the C–C bond formation than the re → re/g⁻ approach, and the si → re/g⁺ approach has comparable ΔΔG⁺ barrier to the re → re/g⁻ approach. In addition, these four prochiral approaches resulted in the somewhat higher ΔΔG values for nitronate intermediate (1-Nit) than the re → re/g⁻ approach. Hence, the backward process (i.e., the C–C bond dissociation) from 1-Nit to intermediate I5 is kinetically feasible for these four prochiral approaches as well. The ΔΔG⁺ barriers for backward process were calculated as 12.1, 14.5, 17.7, and 15.3 kcal mol⁻¹ for the re → si/g*, re → si/t, si → re/g⁺, and si → re/t prochiral approaches, respectively, which are 7.2, 4.8, 1.6, and 4.0 kcal mol⁻¹ lower than that of the re → re/g⁻ approach, respectively.

In addition, the possibility of further protonation of nitronate intermediates produced by these four prochiral approaches was investigated. The torsion angles and thermodynamic properties for the protonation in chloroform at the ωB97X-D/6-311++G(d,p)//SMD M06-2X/6-31+G(d) level of theory are listed in Table S7 of the Supporting Information. The free-energy profiles for the protonation are depicted in Figure 4. The ΔΔG⁺ barriers for protonation from

Figure 3. Free-energy profiles for the 12 feasible stereoselective C–C bond formations between En-01 and β-nitrostyrene depending on the relative orientations of the prochiral centers. All free energies are relative to the reaction complex (RC) + β-styrene system.

Figure 4. Free-energy profiles for the C–C bond dissociation (via ts4) and protonation (via ts5) of nitronate intermediate (1-Nit) produced by the four re → si/g*, re → si/t, si → re/g⁺, and si → re/t prochiral approaches. All free energies are relative to the RC + β-styrene system.
The optimized structures of transition states and $\text{1-Nit}$ for $\text{re} \to \text{re}/g^-$ are depicted in Figure 5. Interestingly, the $\text{re} \to \text{re}/g^-$, $\text{re} \to \text{si}/g^-$, and $\text{si} \to \text{si}/g^-$ prochiral approaches produced dihydrooxazines as products (i.e., $\text{1-D}$ in Scheme 1b), but the barriers $\Delta G^\ddagger$ were 1.4, 3.1, and 5.9 kcal mol$^{-1}$ higher than that of the $\text{re} \to \text{re}/g^-$ prochiral approach and those appeared to be kinetically less favored. In the Michael addition of propenal to $\beta$-nitrostyrene catalyzed by diarylprolinol silyl ether, the $\Delta G^\ddagger$ barrier of the most preferred transition state for the C–C bond formation via the $(\text{R},\text{S})$ pathway in chloroform was recently calculated as 16.2 kcal mol$^{-1}$ at the $\omega$B97X-D/6-311++G(3df,3pd)//$\omega$B97X-D/6-311G(d,p) level of theory and the PCM solvation free energy at the $\omega$B97X-D/6-311+G(d) level of theory is 5.7 kcal mol$^{-1}$ lower than that of the $\text{re} \to \text{re}/g^-$ prochiral approaches produced dihydrooxazines as products (i.e., $\text{1-D}$ in Scheme 1b) in the present work.

In addition, we studied the stereoselective C–C bond formation of the next most preferred conformers [i.e., $\text{En-02}, \text{En-03}$, and $\text{En-04}$ shown in Figure 2; populated at 17, 16, and 9%, respectively]. Only the $\text{re} \to \text{re}$ prochiral approach in the $g^-$ orientation of the double bonds was considered for these addition reactions, which resulted the major $(2S,3R)$-1-Nit species. The procedure to construct these initial 1-Nit structures and the corresponding transition states are described in the Supporting Information. The torsion angles and relative thermodynamic properties of transition states and products for these stereoselective C–C bond formation in chloroform at the $\omega$B97X-D/6-311++G(d)//SMD M06-2X/6-31+G(d) level of theory are listed in Table S3 of the Supporting Information.

The free-energy profiles for the C–C bond formation of $\text{En-02}, \text{En-03}$, and $\text{En-04}$ with $\beta$-nitrostyrene via the $\text{re} \to \text{re}/g^-$ prochiral approach in chloroform at the $\omega$B97X-D/6-311++G(d)//SMD M06-2X/6-31+G(d) level of theory are depicted in Figure 6. The torsion angles of the backbone of $\text{dPPE-NH}_2$ moiety in the transition state and 1-Nit of each enamine species were similar to the corresponding values of $\text{En-02}, \text{En-03}$, and $\text{En-04}$, although there were somewhat large changes of $\phi_\beta, \psi_\beta$, and $\chi_\beta^\ddagger$ of $\text{En-03}$, respectively (Table S3 of the Supporting Information). The $\Delta G^\ddagger$ barriers of the $\text{re} \to \text{re}/g^-$ prochiral approaches for $\text{En-02}, \text{En-03}$, and $\text{En-04}$ with $\beta$-nitrostyrene were 9.9, 9.1, and 6.1 kcal mol$^{-1}$ higher than that of En-01, and the corresponding products were much less preferred than En-01 ($\Delta \Delta G = 19.4$, 18.4, and 15.6 kcal mol$^{-1}$, respectively). Hence, the $\text{re} \to \text{re}/g^-$ prochiral approach between $\text{En-01}$ and $\beta$-nitrostyrene was kinetically and thermodynamically favored and appeared to be the major route for the C–C bond formation, which produced the major $(2S,3R)$-1-Nit intermediate.

**Exploration of the Nitronate or Dihydrooxazine Pathways.** Whatever the pathway considered, i.e., 1-Nit ($\text{re} \to \text{re}/g^-$) or 1-D ($\text{re} \to \text{re}/g^-$) pathway, the next step of the catalytic cycle requires a water molecule that participates in the protonation of the species. In the 1-D hypothesis, conversion of dihydrooxazine into a cyclobutane adduct should also be considered because this species has been experimentally observed with diphenylprolinol trimethylsilyl ether as catalyst.

Considering the 1-Nit pathway, the initial ts structure was constructed by introducing a water molecule into the $(2S,3R)$-1-Nit model obtained from the most preferred $\text{re} \to \text{re}/g^-$ prochiral approach and was optimized at the SMD M06-2X/6-31+G(d) level of theory in chloroform. The same procedure was used to construct the ts structure for the protonation step of the $(2S,3R)$-1-D dihydrooxazine intermediate. The free energy of each intermediate and transition state in chloroform was calculated at the $\omega$B97X-D/6-311++G(d)//SMD M06-2X/6-31+G(d) level of theory.

The six-membered dihydrooxazine ring in the hydrated $(2S,3R)$-1-D model adopted a boat conformation. However, the structure of $(2S,3R)$-1-D with a half-chair conformation was also considered because such a conformation was proposed in the nitro-Michael addition catalyzed by diphenylprolinol trimethylsilyl ether. Nevertheless, the
later was 3.1 kcal mol$^{-1}$ less stable in chloroform than the corresponding structure in boat conformation. The $\Delta G^\ddagger$ barriers for the protonation step of (2S,3R)-1-D and (2S,3R)-1-D in boat conformation were calculated to be 12.4 and 14.3 kcal mol$^{-1}$ (see Figure 7a). Again, this confirms the $re \rightarrow re/g^*$ prochiral approach as the most preferred pathway.

The structure of the hydrated (2S,3R)-1-D (Figure 7b). In addition, the structure of (2S,3R)-1-C was 5.5 kcal mol$^{-1}$ more stable than (2S,3R)-1-D, indicating that, when formed, the dihydrooxazine oxide species (1-D) should readily convert to cyclobutane adduct. Because I was never observed experimentally with dPPE-NH$_2$ as catalyst, the 1-D pathway involving the $re \rightarrow re/g^*$ prochiral approach should be excluded.

In the Michael addition of propenal to $\beta$-nitrostyrene catalyzed by diarylprolinol silyl ether, the $\Delta G^\ddagger$ barriers for the transition of dihydrooxazine oxide species D into the cyclobutane adduct and for the C–C bond formation and protonation of dihydrooxazine oxide species D in the presence of p-nitrophenol were calculated as 11.9, 15.9, and 18.1 kcal mol$^{-1}$, respectively, at the $\omega$B97X-D/6-311+G(3df,3pd)//$\omega$B97X-D/6-311G(d,p) level of theory and the PCM solvation free energy at the $\omega$B97X-D/6-311G(d,p) level of theory.

The $\Delta G^\ddagger$ barrier for the D $\rightarrow$ C transition is quite similar to 11.3 kcal mol$^{-1}$ for the transition of (2S,3R)-1-D to (2S,3R)-1-C in chloroform in the present work. However, the $\Delta G^\ddagger$ barriers for the C–C bond formation and protonation of dihydrooxazine oxide species D were 6.0 kcal mol$^{-1}$ lower and 3.8 kcal mol$^{-1}$ higher, respectively, than those of the $re \rightarrow re/g^*$ prochiral approaches produced dihydrooxazines as products (i.e., 1-D in Scheme 1b) in the present work.

**Plausible Organocatalytic Cycle by dPPE-NH$_2$.** The procedure to construct the initial structures for the plausible organocatalytic cycle catalyzed by dPPE-NH$_2$ was described in the Computational Methods. The plausible pathway for the addition of butanal to $\beta$-nitrostyrene catalyzed by dPPE-NH$_2$ (I) obtained at the $\omega$B97X-D/6-311+G(d,p)///$\omega$M06-2X/6-31+G(d) level of theory is depicted in Figure 8 (reactant complex, transition state, intermediate, and product complex are abbreviated as RC, ts, I, and PC, respectively). Their corresponding thermodynamic properties are shown in Table 3. All the $\Delta G$ values were calculated with respect to the total Gibbs free energy of the reactant complex system formed by dPPE-NH$_2$ and $\beta$-nitrostyrene. The torsion angles of dPPE-NH$_2$ for reactant, transition states, intermediates, and product for the organocatalytic addition of butanal to $\beta$-nitrostyrene by dPPE-NH$_2$ are listed in Table S7 of the Supporting Information. The free-energy profile for the organocatalytic cycle is depicted in Figure 9. The essential reaction species such as ts3 for the enamine formation, I4 (the enamine intermediate En), ts5 for the protonation of nitroanion, ts7 for hydrolysis, and the final PC are shown in Figure 10. All other structures of RC, transition state, intermediate, and PC optimized in chloroform are depicted in Figure S1 of the Supporting Information.

All intermediates and transition states of the catalytic cycle adopted a $\beta$ structure similar to that found for peptide 1 (see 1-dPPE-NH$_2$ in Figure 1a). The structures are stabilized by a $C\equiv O$ H-bond between the $C\equiv O$ of $\alpha$-Pro1 and the C-terminal amide NH$_2$ [distance $d(C\equiv O_{\alpha\text{-Pro1}}\cdots H\cdots N_{\text{terminal}}) = 1.97\pm 0.09$ Å]. A second H-bond involving the $C\equiv O_1$ and NH proton of Glu3 was also conserved all along the catalytic pathway [$d(C\equiv O_{\text{Glu3}}\cdots H\cdots N_{\text{Glu3}}) = 1.75\pm 1.95$ Å].

In the first step of the catalytic cycle, peptide 1 and butanal $[d(C\equiv O_{\text{Glu3}}\cdots H\cdots O_{\text{butanal}}) = 1.64$ Å] proceed to a first carbinol amine intermediate I1 via the transition state ts1 [$d(N_{\alpha\text{-Pro1}}\cdots C\equiv O_{\text{butanal}}) = 2.29$ Å and $d(C\equiv O_{\text{butanal}}\cdots H\cdots O_{\text{Glu3}}) = 1.60$ Å] with a barrier $\Delta G^\ddagger = 6.2$ kcal mol$^{-1}$. The carbonyl amine I2 results from the prototropy of the $\alpha$-Pro1 NH to the carbonylate of Glu3. Dehydration of I2 under the control of Glu COOH leads to the iminium species I3 via the transition state ts2 ($\Delta G^\ddagger = 8.5$ kcal mol$^{-1}$). The water molecule abstracts a proton from the CH$_3\beta$ of iminium I3 in the transition state ts3 (Figure 10a) with $\Delta G^\ddagger = 17.5$ kcal mol$^{-1}$, which yields the enamine intermediate I4 (Figure 10b). In particular, I4 adopts a structure identical to the most preferred conformer En-01 (Figure 2a), except that a water molecule bound to the side chain carboxyl H–O$^\ddagger$ of Glu3 in I4 [$d(O_{\text{water}}\cdots H\cdots O_{\text{Glu3}}) = 1.71$ Å].

In the second step of the catalytic cycle, the $re \rightarrow re/g^*$ prochiral approach of $\beta$-nitrostyrene is assisted by the Glu COOH that binds the nitro group. The bimolecular intermediate I5 proceeds to the nitronic acid I6, in which the carboxylic hydrogen is transferred to the nitronate group [$d(\text{NO}_{\text{HNO2}}\cdots O_{\text{Glu3}}) = 1.55$ Å]. The transition state ts4 described in Figure 4a has the highest barrier of the catalytic cycle ($\Delta G^\ddagger = 20.5$ kcal mol$^{-1}$) and the stereoselective (2S)-C–(3R)-C bond formation is thermodynamically and/or thermodynamically controlled.
The third step of the catalytic cycle consists in the protonation of the nitronic acid. A second bimolecular species \( I_7 \) is formed by introduction of a water molecule that is doubly coordinated to the \( \beta \)-nitronate group and the carboxylic group of Glu3. In the transition state \( ts_5 \) (Figure 10c), the nitronate picks up a proton from the water molecule with the assistance of the Glu COOH group to form \( I_8 \). The protonation step is recognized as the second highest barrier of the reaction pathway (\( \Delta G^\ddagger = 19.6 \text{ kcal mol}^{-1} \)).

The final step consists of the iminium hydrolysis. The water molecule shifts in close proximity of the iminium moiety. Intermediate \( I_9 \) then proceeds to the carbinal amine \( I_{10} \) via the transition state \( ts_6 \) with a relatively low energy barrier (\( \Delta G^\ddagger = 5.8 \text{ kcal mol}^{-1} \)). In \( ts_6 \), the water molecule bridges both the iminium \( \text{C}_\alpha \) and the carboxylate group. Prototropy of acid proton, that is initially H-bonded to the nitrate group in \( I_{10} \), to the nitrogen atom of d-Pro1 leads to \( I_{11} \). \( I_{11} \) is stabilized by a new H-bond between the OH group of carbinal amine and the carboxylate of Glu3 in \( I_{11} \). Finally, the abstraction of the proton of the hydroxyl group by the Glu3 carboxylate as highlighted in Figure 10d \( [ts_7: d(N_{\text{d-Pro1}}\cdots\text{C}=\text{O}_{\text{product}}) = 2.09 \text{ Å and } d(\text{C}=\text{O}_{\text{product}}\cdots\text{H}\cdots\text{O}_{\text{Glu3}}^\delta) = 1.58 \text{ Å}] \) facilitates the breaking of the C–N bond and the recycling of the catalyst. This elementary step requires a relatively low \( \Delta G^\ddagger = 9.5 \text{ kcal mol}^{-1} \). The final product complex, in which the product and catalyst are H-bonded \( [d(\text{C}=\text{O}_{\text{product}}\cdots\text{H}\cdots\text{O}_{\text{Glu3}}^\delta) = 1.67 \text{ Å}], \) is 1.2 kcal mol\(^{-1}\) more stable in \( \Delta G \) than the RC + \( \beta \)-nitrostyrene system.

According to the calculated \( \Delta G^\ddagger \) values with respect to the total Gibbs free energy of the RC + \( \beta \)-nitrostyrene system, \( ts_4 \) for the C–C bond formation and \( ts_5 \) for the protonation of the nitronic acid intermediate exhibited higher barriers of \( \Delta G^\ddagger = 20.5 \text{ and } 19.6 \text{ kcal mol}^{-1}, \) respectively. Hence, it confirms that the C–C bond formation between the enamine and the electrophile is the rds. However, the protonation of nitronic acid requires energy comparable with the C–C bond formation. These calculated results are consistent with the kinetic studies, which provided insights that not the enamine formation but the reaction of the enamine with the electrophile is rate limiting in case of catalysts bearing an acid group in a position that allows for coordination of the nitrate.

---

**Figure 8.** Plausible pathways for the H-d-Pro-Pro-Glu-NH\(_2\)-catalyzed conjugate addition reaction of butanal to \( \beta \)-nitrostyrene into \((2S,3R)-2\text{-ethyl}-4\text{-nitro-3-phenylbutanal}\) in chloroform. The C–C bond formation was confirmed as the rds. The corresponding thermodynamic properties are listed in Table 3. H-Bonds are represented by dotted lines. All optimized structures are shown in Figure S1 of the Supporting Information.
Table 3. Relative Thermodynamic Properties (kcal mol\(^{-1}\)) of Reactant, Transition States, Intermediates, and Products for the Addition of Butanal to β-Nitrostyrene Catalyzed by dPPE-NH\(_2\) (1) in Chloroform\(^{19}\)

| chemical species | \(\Delta E^b\) | \(\Delta H^\circ\) | \(\Delta G^\circ\) |
|------------------|----------------|----------------|----------------|
| RC + nitrostyrene| 0.0            | 0.0            | 0.0            |
| ts1 + nitrostyrene| 2.8           | 2.7            | 6.2            |
| I1 + nitrostyrene| -9.4           | -7.7           | -3.2           |
| I2 + nitrostyrene| -5.1           | -4.2           | -0.9           |
| ts2 + nitrostyrene| 6.0           | 4.9            | 8.5            |
| I3 + nitrostyrene| -2.2           | -2.4           | -0.9           |
| ts3 + nitrostyrene| 19.3          | 14.6           | 17.5           |
| I4 (En) + nitrostyrene| 1.4            | 1.3            | 2.4            |
| I5 + water       | 2.0            | 0.7            | 5.2            |
| ts4 (C–C bond formation) + water| 13.5          | 11.9           | 20.5           |
| I6 + water       | -8.3           | -8.6           | 1.2            |
| I7               | -12.9          | -11.1          | 7.2            |
| ts5 (protonation) | 2.4            | 0.0            | 19.6           |
| I8               | -24.6          | -21.5          | -3.5           |
| I9               | -21.8          | -18.6          | -0.9           |
| ts6 (carbinol amine) | -16.4         | -14.3          | 5.8            |
| I10              | -23.0          | -19.2          | 0.6            |
| I11              | -19.2          | -14.0          | 7.3            |
| ts7 (hydrolysis) | -14.2          | -11.3          | 9.5            |
| PC               | -21.3          | -18.2          | -1.2           |

\(^{19}\)Calculated at the \(\omega\)B97X-D/6-311+G(d,p)//SMD M06-2X/6-31+G(d) level of theory. \(^{\circ}\)\(\Delta E\), \(\Delta H\), and \(\Delta G\) stand for relative electronic energy, enthalpy, and Gibbs free energy at 25°C and 1 atm.

**Figure 9.** Free-energy profiles for the conjugate addition reaction of butanal and β-nitrostyrene catalyzed by H-D-Pro-Pro-Glu-NH\(_2\) in chloroform: (a) the enamine formation and (b) C–C bond formation, protonation, and hydrolysis. The relative Gibbs free energies to the RC + β-nitrostyrene system were calculated at the \(\omega\)B97X-D/6-311+G(d,p)//SMD M06-2X/6-31+G(d) level of theory in chloroform.

**Figure 10.** Essential reaction species for addition of butanal to β-nitrostyrene catalyzed by H-D-Pro-Pro-Glu-NH\(_2\) in chloroform: (a) ts3 for the enamine formation, (b) I4 (the enamine intermediate En), (c) ts5 for the protonation of nitronate, (d) ts7 for hydrolysis, and (e) the final PC. H-Bonds are represented by dotted lines and in Å.

**CONCLUSIONS**

By conformational search, it was confirmed that the catalyst H-D-Pro-Pro-Glu-NH\(_2\) (dPPE-NH\(_2\); 1) and its enamine intermediate (1-En) adopted a dominant conformation with a βI structure stabilized by a C\(_{10}\) H-bond between the C═O of ω-Pro1 and the C-terminal NH\(_2\) proton and with an additional H-bonds between the side chain and the backbone of Glu3. The βI structure is conserved along the catalytic cycle. The stereoselective (2S)-C=(3R)-C bond formation between enamine (1-En) and β-nitrostyrene proceeds via the re → re prochiral approach with the gauche* orientation of the double bonds of reactants. Although it was suggested the possible formation of dihydroxazine oxide species (I-D), this process was confirmed to be kinetically less accessible than the acyclic nitronate pathway.

By exploring the pathways for addition of butanal to β-nitrostyrene catalyzed by catalyst dPPE-NH\(_2\) using DFT methods in chloroform, the C–C bond formation between the enamine and the electrophile (β-nitrostyrene) was confirmed as the rds. However, the protonation by a water molecule to nitronic acid requires energy comparable to the C–C bond formation. These calculated results are consistent with the kinetic studies. In particular, our calculated results supported that the central role of the carboxylic acid group of Glu3 in dPPE-NH\(_2\) by acting as general acid/base all along the catalytic cycle and orienting the asymmetric C–C bond formation.

**COMPUTATIONAL METHODS**

**DFT Calculations.** All Hartree–Fock (HF) and density functional calculations were performed using the Gaussian 09 programs.\(^{20}\) All density functional calculations of optimizations and vibrational frequencies were carried out using the M06-2X functional\(^{21}\) and the solvation model based on density (SMD) method.\(^{22}\) GaussView\(^{23}\) was used to generate and edit the structures of all intermediates and transition states. The M06-2X is a hybrid-meta-GGA functional with the improved medium-range correlation energy and showed good performance in predicting noncovalent interactions of small molecules and structures and relative stabilities of biological compounds such as peptides.\(^{24}\)
For all reactants, intermediates, transition states, and products optimized at the SMD M06-2X/6-31+G(d) level of theory in chloroform, the relative energy (ΔE) of each local minimum in chloroform was calculated as the sum of the relative single-point energy (ΔE_p) using the ωB97X-D functional\textsuperscript{25} with the 6-311+G(d,p) basis set and the relative solvation free energy (ΔG_solv) at the SMD M06-2X/6-31+G(d) level of theory in chloroform. For all local minima and transition states, vibrational frequencies were calculated at the SMD M06-2X/6-31+G(d) level of theory in chloroform at 298 K and 1 atm to confirm the nature of the stationary points and to obtain relative enthalpies and Gibbs free energies of intermediates and transition states at the same level of theory. The scale factor used was 0.9440 at the SMD M06-2X/6-31+G(d) level of theory in chloroform, the relative energy (ΔE) for all local minima and transition states at the same level of theory. Using GaussView,\textsuperscript{23} which were involved in the formation and dissociation of the bonds in the corresponding reactant and product. Notably, consistent with CD and NMR experiments, the ωB97X-D functional exhibited better performance than double-hybrid functionals DSD-BLYP, B2GPPLYPD, and B2PYP with dispersion corrections with respect to the benchmark CCSD(T)/CBS-limit energies of Dien−Alder reactions (the DARC set\textsuperscript{26}).

**Conformational Search.** We investigated the conformational preferences of dPPE-NH\textsubscript{2} and its enamine intermediate (1 and 1-En in Scheme 1, respectively) obtained by reaction with butanal. The initial structure of peptide 1 was constructed by using the X-ray structure of H-d-Pro-Pro-Asp-NH\textsubscript{2}\textsuperscript{2b} and optimized at the M06-2X/6-31+G(d) level of theory. Then, the initial structure of the enamine 1-En in the s-trans configuration was constructed from the optimized structure of peptide 1 and optimized at the same level of theory. Using these optimized structures, 157 and 189 initial structures for 1 and 1-En, respectively, were generated by the systematic search of the Discovery Studio package\textsuperscript{31} using the CHARMM force field with the maximum systematic conformations = 1000 and the energy threshold = 10 kcal mol\textsuperscript{-1}. In the conformational search of 1 and 1-En, a systematic variation of each of the torsion angles ψ\textsubscript{1}, ψ\textsubscript{2}, φ\textsubscript{α}, and ϕ\textsubscript{β} of the backbone and χ\textsubscript{1}, χ\textsubscript{2}, and χ\textsubscript{3} of the side chain of Glu3 was done using steps of 60°. These initial structures were then optimized at the HF/3-21G(d) level of theory, and we obtained 21 and 57 local minima with the relative energy ΔE < 10 kcal mol\textsuperscript{-1}, respectively, which were reoptimized at the M06-2X/6-31G(d) level of theory and further optimized at the SMD M06-2X/6-31+G(d) level of theory in chloroform.

**Construction of Organocatalytic Cycle.** The most preferred conformations 1-dPPE-NH\textsubscript{2} of peptid 1 (Table 1 and Figure 1a) and En-01 of 1-En (Table 2 and Figure 2a) obtained by the conformational search were used to construct the initial structures in the organocatalytic cycle. In particular, the C−C bond formation between enamine (1-En) and β-nitrostyrene was considered by the re → re/g prochiral approach, which was kinetically and/or thermodynamically favored, as described earlier. In addition, the initial structures of intermediates and transition states for addition of butanal to β-nitrostyrene catalyzed by 1 were constructed using the structures of intermediates and transition states suggested by Clemente and Houk\textsuperscript{25} for the enamine mechanism of intramolecular aldol reactions catalyzed by proline as a reference, which involves an enamine intermediate with concerted C−C bond formation and proton transfer from the carboxylic acid group to the carbonyl acceptor. The overall reaction mechanism of intramolecular aldol reactions catalyzed by proline appears to be quite similar to the addition reaction of butanal to β-nitrostyrene catalyzed by dPPE-NH\textsubscript{2}, except for the protonation step being not necessary for the intramolecular aldol reactions.
98. (e) Akagawa, K.; Kudo, K. Development of Selective Peptide Catalysts with Secondary Structural Frameworks. Acc. Chem. Res. 2017, 50, 2429–2439.

(3) (a) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. Asymmetric Enamine Catalysis. Chem. Rev. 2007, 107, 5471–5569.
(b) Romney, D. K.; Colvin, S. M.; Miller, S. J. Catalysis Control over Regio- and Enantioselectivity in Baeyer-Villiger Oxidations of Functionalized Ketones. J. Am. Chem. Soc. 2014, 136, 14019–14022.

(4) (a) Eder, U.; Sauer, G.; Wiercht, R. New Type of Asymmetric Cyclization to Optically Active Steroid CD Partial Structures. Angew. Chem., Int. Ed. 1971, 10, 496–497. (b) Hajo, Z. G.; Parrish, D. R. Stereocontrolled synthesis of trans-hydrindan steroidal intermediates. J. Org. Chem. 1973, 38, 3239–3243. (c) Hajo, Z. G.; Parrish, D. R. Asymmetric Synthesis of Bicyclic Intermediates of Natural Product Chemistry. J. Org. Chem. 1974, 39, 1615–1621. (d) List, B.; Lerner, R. A.; Barbas, C. F. Proline-Catalyzed Direct Asymmetric Aldol Reactions. J. Am. Chem. Soc. 2000, 122, 2395–2396.

(5) Notz, W.; Tanaka, F.; Barbas, C. F. Enamine-Based Organo-catalysis with Proline and Diamines: The Development of Direct Catalytic Asymmetric Aldol, Mannich, Michael, and Diels–Alder Reactions. Acc. Chem. Res. 2004, 37, 580–591.

(6) (a) Hajo, Z. G.; Parrish, D. R. Asymmetric Synthesis of Bicyclic Intermediates of Natural Product Chemistry. J. Org. Chem. 1974, 39, 1615–1621. (b) Wong, C. T. A theoretical investigation on the mechanism of the α,α-diphenylprolinol trimethylsilyl ether-catalyzed oximation reaction. Tetrahedron Lett. 2009, 50, 811–813. (c) Wong, C. T. Mechanism of the α,α-Diarylprolinol Trimethylsilyl Ether-Catalyzed Enantioselective C–C, C–N, C–F, C–S, and C–Br Bond Forming Reactions. Tetrahedron 2009, 65, 7491–7497.

(7) (a) Berner, O. M.; Tedeschi, L.; Enders, D. Asymmetric Michael Additions to Nitroalkanes. Eur. J. Org. Chem. 2002, 2002, 1877–1894.
(b) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petriti, M. Conjugate Additions of Nitroalkanes to Electron-Poor Alkenes: Recent Results. Chem. Rev. 2005, 105, 933–972. (c) Ballini, R.; Petriti, M.; Rosini, G. Nitroalkanes as Central Reagents in the Synthesis of Spiroketals. Molecules 2008, 13, 319–330. (d) Ballini, R.; Gabrielli, S.; Palmieri, A.; Petriti, M. Nitroalkanes as Key Compounds for the Synthesis of Amino Derivatives. Curr. Org. Chem. 2011, 15, 1482–1506. (e) Ballini, R.; Palmieri, A. Synthetic Procedures for the Preparation of Nitroalkanes. Adv. Synth. Catal. 2018, 360, 2240–2266.

(8) Wiesner, M.; Revell, J. D.; Tonazzi, S.; Wennemers, H. Peptide Catalyzed Asymmetric Conjugate Addition Reactions of Aldehydes to Nitroethylene-A Convenient Entry into α,β-Unsaturated α,β-Diarylprolinol Trimethylsilyl Ether-Catalyzed Cross-Coupling Reactions. J. Am. Chem. Soc. 2008, 130, 5610–5611.

(9) (a) Wiesner, M.; Revell, J. D.; Wennemers, H. Tripeptides as Efficient Asymmetric Catalysts for 1,4-Addition Reactions of Aldehydes to Nitroalkene-Catalyst A Rational Approach. Angew. Chem., Int. Ed. 2008, 47, 1871–1874. (b) Wiesner, M.; Neuberger, M.; Wennemers, H. Tripeptides of the Type H-D-Pro-Pro-Xaa-NH2 as Catalysts for Asymmetric 1,4-Addition Reactions: Structural Requirements for High Catalytic Efficiency. Chem.–Eur. J. 2009, 15, 10103–10109. (c) Wiesner, M.; Upert, G.; Angelici, G.; Wennemers, H. Enamine Catalysis with Low Catalyst Loadings - High Efficiency via Kinetic Studies. J. Am. Chem. Soc. 2010, 132, 6–7.

(10) Bächle, F.; Duschmalé, J.; Ebner, C.; Pflätz, A.; Wennemers, H. Organocatalytic Asymmetric Conjugate Addition of Aldehydes to Nitroalkenes: Identification of Catalytic Intermediates and the Stereoselectivity-Determining Step by ESI-MS. Angew. Chem., Int. Ed. 2013, 52, 12619–12623.

(11) Duschmalé, J.; West, J.; Wiesner, M.; Wennemers, H. Effects of Internal and External Carboxylic Acids on the Reaction Pathway of Organocatalytic 1,4-Addition Reactions between Aldehydes and Nitroalkenes. Chem. Sci. 2013, 4, 1312–1318.
(21) Zhao, Y.; Truhlar, D. G. The M06 Suite of Density Functionals for Main Group Thermochemistry, Thermochemical Kinetics, Noncovalent Interactions, Excited States, and Transition Elements: Two New Functionals and Systematic Testing of Four M06-Class Functionals and 12 Other Functionals. Theor. Chem. Acc. 2008, 120, 215–241.

(22) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. J. Phys. Chem. B 2009, 113, 6378–6396.

(23) Frisch, A.; Hratchian, H. P.; Dennington, R. D.; Keith, T. A.; Millam, J. GaussView, Version 5.0; Gaussian: Wallingford, CT, 2009.

(24) Zhao, Y.; Truhlar, D. G. Applications and Validations of the Minnesota Density Functionals. Chem. Phys. Lett. 2011, 502, 1–13.

(25) Chai, J.-D.; Head-Gordon, M. Long-range corrected hybrid density functionals with damped atom-atom dispersion corrections. Phys. Chem. Chem. Phys. 2008, 10, 6615–6620.

(26) Kang, Y. K. Ab Initio MO and Density Functional Studies on Trans and Cis Conformers of N-Methylacetamide. J. Mol. Struct.: THEOCHEM 2001, 546, 183–193.

(27) (a) Gonzalez, C.; Schlegel, H. B. An Improved Algorithm for Reaction Path Following. J. Chem. Phys. 1989, 90, 2154–2161. 
(b) Gonzalez, C.; Schlegel, H. B. Reaction Path Following in Mass-Weighted Internal Coordinates. J. Phys. Chem. 1990, 94, 5523–5527.

(28) Kang, Y. K.; Byun, B. J. Assessment of Density Functionals with Long-Range and/or Empirical Dispersion Corrections for Conformational Energy Calculations of Peptides. J. Comput. Chem. 2010, 31, 2915–2923.

(29) Johnson, E. R.; Mori-Sánchez, P.; Cohen, A. J.; Yang, W. Delocalization errors in density functionals and implications for main-group thermochemistry. J. Chem. Phys. 2008, 129, 204112.

(30) Goerigk, L.; Grimme, S. A Thorough Benchmark of Density Functional Methods for General Main Group Thermochemistry, Kinetics, and Noncovalent Interactions. Phys. Chem. Chem. Phys. 2011, 13, 6670–6688.

(31) Discovery Studio, Version 2.5; Accelrys Software, Inc.: San Diego, CA, 2009.

(32) Clemente, F. R.; Houk, K. N. Computational Evidence for the Enamine Mechanism of Intramolecular Aldol Reactions Catalyzed by Proline. Angew. Chem., Int. Ed. 2004, 43, 5766–5768.