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Mechanistic Investigation of the 2,5-Diphenylpyrrolidine-Catalyzed Enantioselective α-Chlorination of Aldehydes

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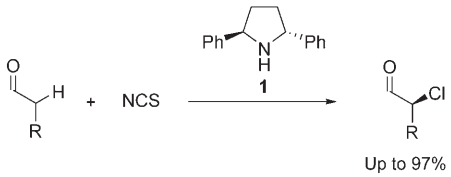
Abstract: The mechanism for the 2,5-diphenylpyrrolidine-catalyzed enantioselective α-chlorination of aldehydes with electrophilic halogenation reagents has been investigated by using experimental and computational methods. These studies have led us to propose a mechanism for the reaction that proceeds through an initial *N*-chlorination of the chiral catalyst–substrate complex, followed by a 1,3-sigmatropic shift of the chlorine atom to the enamine carbon atom. The suggested reaction course is different from previously proposed mechanisms for organocatalytic enamine reactions, in which the carbon–electrophile bond is formed directly. Furthermore, the rate-determining step in the overall reaction was determined and the presence of nonlinear effects was probed.

Keywords: asymmetric catalysis · chlorination · density functional calculations · isotope effects · kinetics · sigmatropic rearrangement

Introduction

The formation of a chiral carbon center next to a carbonyl group in an enantioselective fashion is a transformation of primary importance in organic chemistry, and with the recent emergence of novel organocatalytic processes, the possibilities have never been greater for the synthetic chemist.[1] Among the various reactions developed, those proceeding through an enamine mechanism have proven to be particularly successful leading to the development of highly stereoselective aldol,[2] Mannich,[3] α-amination,[4] α-aminoxylation,[5] α-sulfenylation,[6] and α-fluorination reactions,[7] as well as others.[1] Recently, the organocatalytic enantioselective α-chlorination of aldehydes[8] and ketones[9] have been added to this list by MacMillan et al. and us independently [Eq. (1)]. Previously, optically active α-chlorocarbonyl compounds have been accessed by Lewis acid[10] and cinchona alkaloid[11] mediated methodologies.[12]



(1)

The development of a highly enantioselective α-chlorination of aldehydes clearly complements the previously developed organocatalytic reactions mentioned above, due to the possibilities for further synthetic transformations of the optically active α-chloroaldehydes formed. Thus, these highly versatile compounds can be used for the introduction of a variety of functional groups as both the aldehyde functionality and the chlorine atom are good handles for further chemical transformations.[13] As previously demonstrated, the α-chloroaldehydes are excellent substrates for the synthesis of, for example, optically active amino acid derivatives, epoxides, α-chloroaldehydes, and amino alcohols by a few simple transformations with preservation of the stereochemical information (Scheme 1).[8b]

Due to the evident importance of the α-chloroaldehydes and to obtain further information on the properties of the novel 2,5-diphenylpyrrolidine (**1**) catalyst, we decided to investigate the reaction mechanism and the origin of the asymmetric induction. Here we wish to report the results of our mechanistic investigation into the 2,5-diphenylpyrrolidine-catalyzed α-chlorination of aldehydes [Eq. (1)] by using both experimental and computational methods.[8b]

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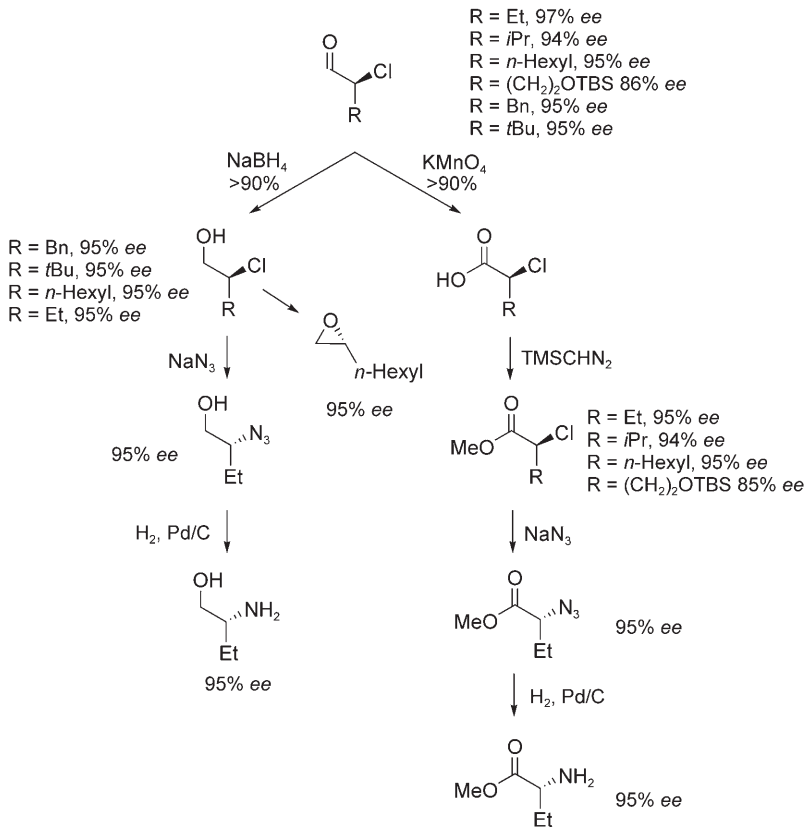
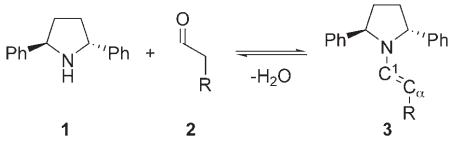


Scheme 1. Transformations of α-chloroaldehydes with preservation of stereochemical information.[8b]



Scheme 2. Formation of the enamine intermediate **3**.

Results and Discussion

To understand the factors controlling the asymmetric induction in the α-chlorination reaction, we commenced our mechanistic investigation using density functional theory (DFT) calculations on catalyst–substrate intermediate **3**, formed by reaction of 2,5-diphenylpyrrolidine (**1**) with aldehyde **2** (Scheme 2).

To our surprise, the DFT-optimized[14] enamine intermediate **3** did not show any appreciable steric shielding of the reacting α-carbon center (Scheme 2 and Figure 1). From a fragment molecular orbital (FMO) point of view, the HOMO N- and C_α-orbital coefficients for **3** are calculated to be 0.312 and 0.253, respectively, indicating that the nitrogen atom has the highest electron density in the HOMO and might be expected to be the most reactive center towards the electrophilic chlorinating reagent.

We hypothesized that the reaction might proceed through an initial, kinetically controlled N–Cl bond formation, whereby the electrophilic chlorine atom reacts first with the nucleophilic enamine nitrogen atom, forming the *N*-chloroammonium ion intermediate **4** (path A, Scheme 3), rather than a direct addition to the enamine carbon atom (path B). The intermediate **4** then rapidly undergoes a 1,3-sigmatropic shift[15] forming the thermodynamically favored catalyst–product iminium ion **5**, which is common to both reaction paths. It should be noted that a peripherally related 1,3-sigmatropic chlorine shift has previously been observed in chlorination reactions of indoles by De Rosa et al.[16]

As the path A mechanism in Scheme 3 is very different from previously proposed mechanisms in which the carbon nucleophile in the enamine intermediate reacts directly with the electrophile (path B, Scheme 3),[17] we set out to fur-

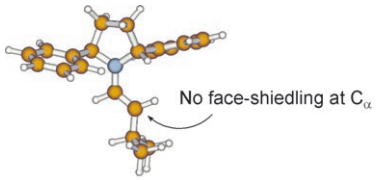
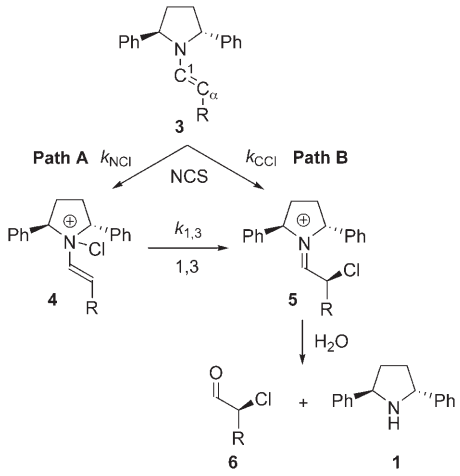


Figure 1. DFT-optimized structure of enamine intermediate **3**, with R = *i*Pr.[14]

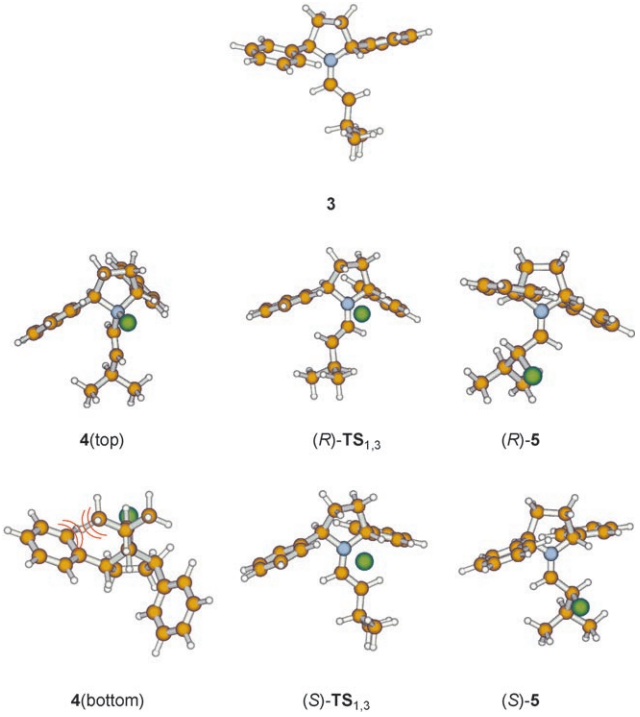


Scheme 3. Possible mechanistic pathways for the organocatalytic enantioselective α-chlorination of aldehydes.

ther test our hypothesis experimentally and computationally.

We initiated our studies by investigating the proposed 1,3-sigmatropic shift of the chlorine atom by DFT calculations[18] at the B3LYP/6-31G(d) level of theory using the system in Scheme 3 with R = *i*Pr. Energies of the gas-phase-optimized DFT structures have also been calculated in solution by means of single-point calculations in 1,2-dichloroethane (DCE). The optimized structures and important calculated results are summarized in Table 1.

Table 1. Optimized structures and electronic energies of the *N*-chloro intermediate **4**, enantiomers (*R*)- and (*S*)-**5**, and transition states (*R*)- and (*S*)-$\mathbf{TS}_{1,3}$ in the gas phase and in solution.



	C–Cl [Å]	N–Cl [Å]	ΔE_{elec} [kcal mol^{-1}] gas phase[a]	ΔE_{elec} [kcal mol^{-1}] 1,2-dichloroethane[a]
4	3.000	1.795	0	0
(*R*)-**5**	1.824	3.685	−43.43	−44.35
(*S*)-**5**	1.830	3.524	−43.96	−44.41
(*R*)-$\mathbf{TS}_{1,3}$	3.193	2.714	16.55	12.16
(*S*)-$\mathbf{TS}_{1,3}$	3.281	2.706	14.09	9.48

[a] ΔE values are given relative to the total energy of **4**: −1329.95260 Hartree in the gas phase and −1329.98854 Hartree in 1,2-dichloroethane.

Similarly to enamine **3** (Figure 1), no steric shielding of the reacting carbon center is observed for the *N*-chloro intermediate **4** (see graphic of **4** (top) in Table 1), because the dihedral angle defined by Cl-N-C_1-C_α (see **3** in Scheme 3) is very close to 0°. We have calculated the potential-energy surface for rotation around this dihedral angle and found that the conformation of **4** depicted in Table 1 represents the lowest energy conformation.

Optimal orbital overlap for the 1,3-sigmatropic shift is expected when the N–Cl bond is orthogonal to the C_α=C_1 double bond. For this to happen, a rotation around the N–C_1 bond must take place. Rotation of the double bond moiety to the right in **4**, followed by the 1,3-sigmatropic shift of chlorine gives (*S*)-**5**, whereas rotation to the left gives (*R*)-**5**. We speculated as to whether there was a preferred rotation of the *N*-chloro intermediate **4** leading to one of the two possible products (*S*)- or (*R*)-**5**. The two transition states have been optimized and the energies calculated (Table 1). These two structures have almost identical N–Cl bond lengths, and only a minor difference in the C–Cl bond lengths. In both gas phase and solution, formation of (*S*)-**5** represents the lowest transition state energy. The computational results reveal that formation of (*S*)-**5** is favored in the gas phase by a difference in activation energies, $\Delta E_{a,gas}$, of 2.5 kcal mol^{-1}, corresponding to 97% *ee* of (*S*)-**5**, which is in very good agreement with the experimentally observed enantiomeric excess of 94% *ee*.[8b] The solvation calculations point in the same direction with $\Delta E_{a,DCE}$ = 2.7 kcal mol^{-1} and thereby a calculated enantiomeric excess of 98% *ee*. Figure 2 shows an energy diagram for the 1,3-sigmatropic shift from the *N*-chloro intermediate **4** to the two possible products (*S*)- and (*R*)-**5**.

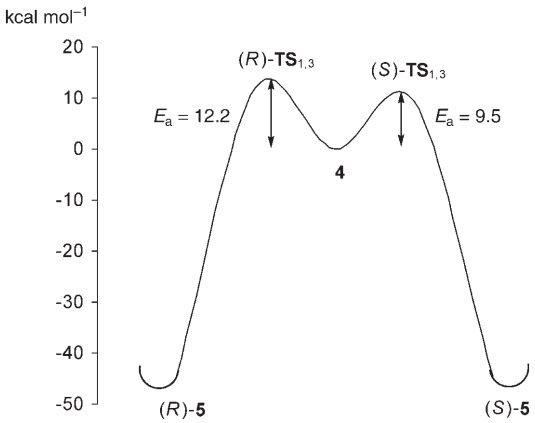
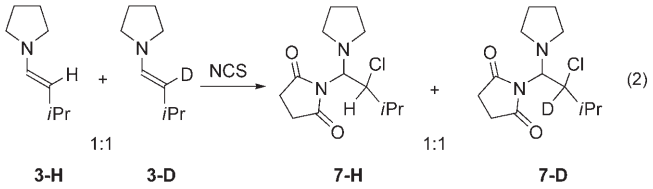


Figure 2. Energy diagram for the 1,3-sigmatropic shift from the *N*-chloro intermediate **4** to the two possible products (*S*)- and (*R*)-**5** in 1,2-dichloroethane.

The optimized structures of the two products (*R*)- and (*S*)-**5** are of similar energy with the latter being favoured by 0.5 kcal mol^{-1} in the gas phase (Table 1), and in solution the energy difference is even less. The preference for (*S*)-$\mathbf{TS}_{1,3}$ can be accounted for by steric repulsion between the phenyl substituent and enamine fragment as indicated in red for **4** (see bottom view) in Table 1, thereby favoring rotation to the right. Thus, not only is the formation of the experimentally observed enantiomer predicted, but also the experimental optical purity is calculated with high accuracy. Therefore, the computational results support our hypothesis that the reaction might take place through an initial *N*-chlorination followed by a very fast enantioselective 1,3-sigmatropic shift (Scheme 3, path A).

We have also attempted to detect *N*-chloro intermediate **4** experimentally using spectroscopic methods. However, this

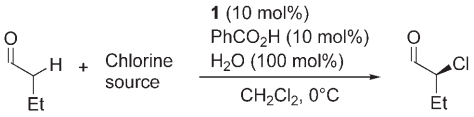
was not possible as the 1,3-sigmatropic shift is a fast process (vide infra) making the population of **4** negligible. Since we were unable to detect **4** we changed strategy and investigated the possibility of detecting a secondary isotope effect using a deuterated model system [Eq. (2)].



(2)

By using a 1:1 mixture of enamine **3-H** and the deuterated analogue **3-D**, a series of ^{1}H NMR spectroscopy experiments were undertaken to determine the relative reaction rates of **3-H** and **3-D**. It should be noted that since the reactions were performed under strictly anhydrous conditions, the products formed are the aminals **7-H** and **7-D**, resulting from addition of the succinimide anion to the iminium ion intermediate **5**. If the reaction proceeds through path B, an inverse secondary isotope effect is expected,[19] that is, $k_H/k_D<1$. On the other hand, no secondary isotope effect is expected if the reaction proceeds through path A and it is assumed that $k_{1,3}\gg k_{NCl}$. We believe this assumption to be reasonable based on the large thermodynamic driving force for the 1,3-sigmatropic shift ($\approx$44 kcal mol^{-1}), as shown by DFT-calculations (Table 1). The reaction [Eq. (2)] was performed at −20, 0, and 20 °C in both CD_2Cl_2 and $CDCl_3$ using four equivalents of the preformed enamine relative to NCS and in none of the experiments did we detect any isotope effect during the reaction, or after all the NCS was consumed. Furthermore, the reaction was repeated using one, two and five equivalents of enamine relative to NCS with identical results. The absence of a secondary isotope effect is only an indication that the reaction might proceed through path A, and cannot be used to entirely exclude path B, as a very small isotope effect, for example, $k_H/k_D=0.99$ is within experimental error.

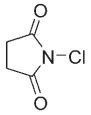
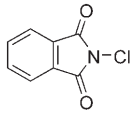
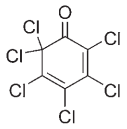
The absence of a secondary isotope effect led us to study the influence of the chlorine source on the enantioselectivity of the reaction. Therefore, we performed the α-chlorination of butanal using NCS, the structurally related *N*-chlorophthalimide (NCP) and 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one, employed by MacMillan et al.[8a] as electrophilic chlorine sources [Eq. (3), Table 2].



(3)

For all three chlorine sources, an optical purity of exactly 95 % *ee* was observed in the α-chlorobutanal formed, and only the reaction rate differed. If the reaction proceeds through path A in Scheme 3, it would be expected that all three chlorine sources should provide α-chlorobutanal with the same optical purity, as the chlorine source is not directly involved in the step where the chiral center is formed. On the other hand, if the chlorine donor is directly involved in the step where the chiral center is formed as in path B in Scheme 3, it is highly unlikely that three structurally different chlorine donors should provide the product in exactly the same optical purity.

Table 2. Organocatalytic α-chlorination of butanal with various chlorine sources.[a]

Entry	Chlorine source	*t* [min]	Conversion [%][b]	*ee* [%][c]
1		30	>95	95
2		180	>95	95
3		5	>95	95

NCS

NCP

2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one

[a] Reaction conditions: the chlorine source (1.3 equiv) was added to a mixture of 2,5-diphenylpyrrolidine (**1**, 10 mol %), butanal, $PhCO_2H$ (10 mol %) and H_2O (100 mol %) in CH_2Cl_2 at 0 °C. [b] Determined by GC and ^{1}H NMR spectroscopy. [c] Determined by CSP-GC.

We have also studied the overall mechanism. Initially, the possible presence of a nonlinear effect[20] in the reaction was examined as this can provide important mechanistic information. 2,5-Diphenylpyrrolidine (**1**) was prepared as a racemate, and in four different optical purities. The catalytic enantioselective α-chlorination of isovaleraldehyde with NCS as the chlorine source was then investigated and the results are shown in Figure 3.

As shown in Figure 3 the enantiomeric excess of the catalyst clearly correlates linearly with the enantiomeric excess of the α-chloroisovaleraldehyde formed ($R^2=0.99$) in the reaction. Therefore there is clearly *no* nonlinear effect in the reaction and this strongly indicates that only one molecule of **1** is involved in the formation of the chiral center. These results support the proposed catalytic cycle (Scheme 4—the 1,3-sigmatropic shift is not included), in which the reaction proceeds through formation of the chiral enamine **9**, that in turn reacts with NCS as the chlorine source to form the product iminium ion **10**, which upon hydrolysis yields the product and succinimide.

We also speculated if other mechanistic pathways, for example, chlorination of the catalyst to form a chiral chlorine

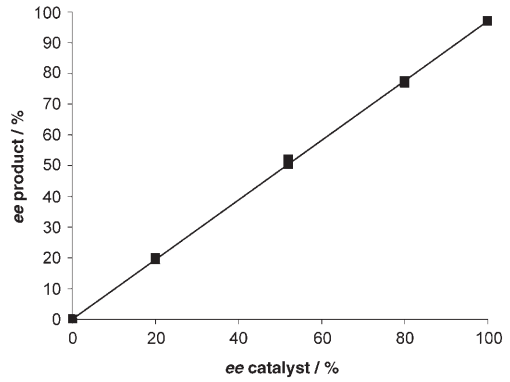
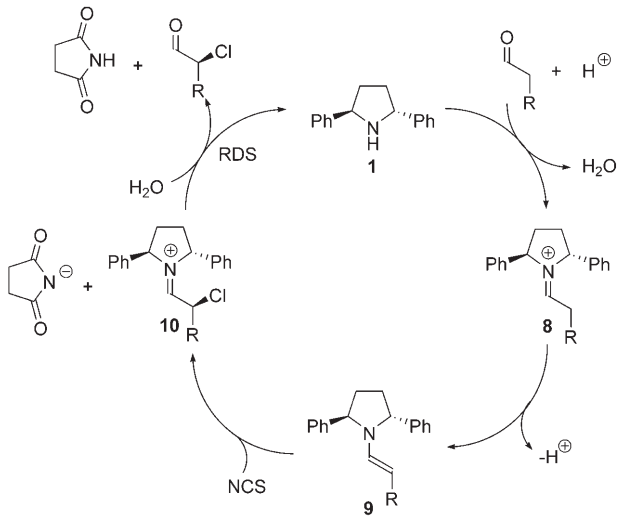


Figure 3. Absence of nonlinear effect in the α-chlorination reaction.



Scheme 4. Proposed catalytic cycle for the **1**-catalyzed α-chlorination of aldehydes (the 1,3-sigmatropic shift is not shown).

donor could be an alternative to the proposed mechanism (Scheme 3 and 4), as this mechanism would also afford α-chloro aldehydes with optical purities independent of the chlorine donor. However, this mechanism is unlikely, as a nonlinear effect would then be expected because two chiral molecules of **1** are involved in the formation of the chiral center. Furthermore, no reaction between **1** and NCS was observed when mixed in CH_2Cl_2 at ambient temperature, rendering this alternative mechanism unlikely.

During our investigation of the mechanism of the **1**-catalyzed α-chlorination of aldehydes with NCS, the rate-determining step and the influence of additives on the reaction rate were also studied. In Figure 4, we show the formation of α-chlorobutanal from butanal and NCS (1.3 equiv) in the presence of 10 mol% **1** in CH_2Cl_2 at 0°C as the reaction progresses [Eq. (3)].

The linear relationship ($R^2 = 0.984$) between conversion and time shows that the reaction rate was constant as the reaction progresses, indicating that the concentration of the reactants did not affect the reaction rate.[21] Therefore, we reasoned that it is likely that neither butanal nor NCS is directly involved in the rate-determining step and focused on the steps directly involving the catalyst (Scheme 4).

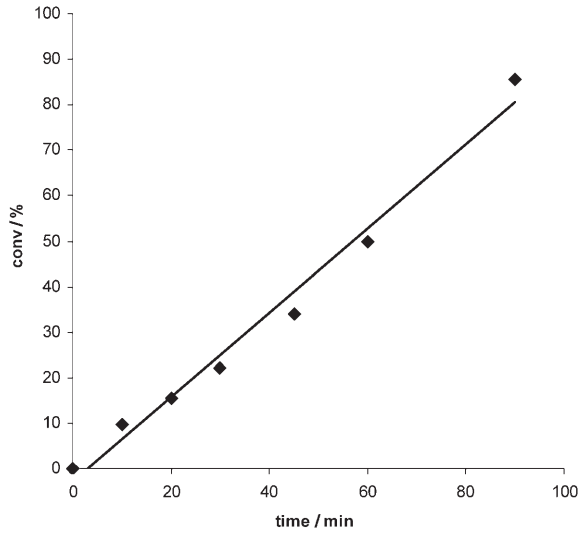


Figure 4. Formation of α-chlorobutanal.

With the above results in hand we hypothesized that the rate-determining step in the catalytic cycle was most likely the hydrolysis of the product iminium ion **10**. To test this hypothesis we investigated how the addition of water and acid influenced the reaction rate, as both additives are known to facilitate imine hydrolysis. The **1**-catalyzed α-chlorination of butanal with NCS was therefore performed in the presence of 10 mol% butyric acid, with and without added water (Figure 5 and Table 3).

It appears from Figure 5 and Table 3 that the addition of 10 mol% butyric acid increased the reaction rate markedly relative to that found for the reaction without additive, and that the reaction rate was increased even further by the addition of water (2.0 equiv).[23] In fact, when both 10 mol%

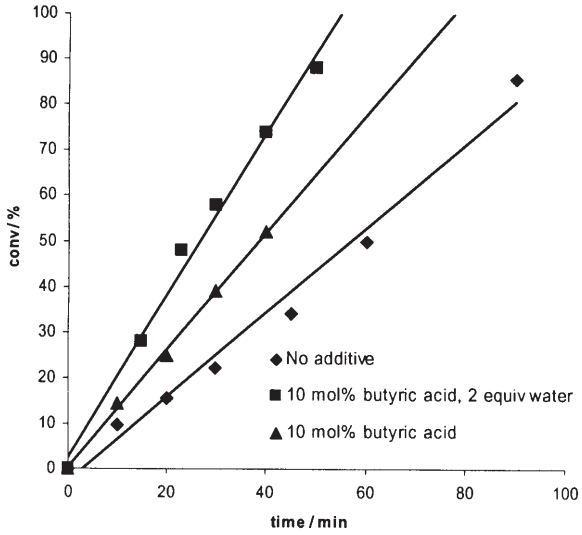


Figure 5. 2,5-Diphenylpyrrolidine (**1**; 10 mol%)-catalyzed formation of α-chlorobutanal, with and without additives.[22]

Table 3. Reaction rate data for **1**-catalyzed (10 mol%) formation of α-chlorobutanal, with and without additives.

Entry	Additive	k	R^2
1	none	0.92	0.98
2	10 mol% butyric acid	1.24	0.99
3	10 mol% butyric acid +2.0 equiv H_2O	1.77	0.99

butyric acid and water were added to the reaction, the reaction rate was almost doubled with respect to the reaction rate without additives. Furthermore, it should be noted that even in the presence of additives, the reaction rate was found to be constant throughout the reaction ($R^2=0.99$), and thus still independent of the concentration of the reactants. These results further support our hypothesis that the rate-determining step in the catalytic cycle is the hydrolysis of product iminium ion **10**. Another possibility for the rate-determining step would be the condensation between the catalyst and the aldehyde, that is, the formation of substrate iminium ion **8** (Scheme 4), and the addition of acid additives would be expected to increase this reaction rate. On the other hand, the addition of water would have a severely detrimental effect on the rate of formation of substrate iminium ion **8**, and since this is contrary to our observations we therefore rule this step out as being the rate-determining step in the catalytic cycle.

Conclusion

In summary we have proposed that the 2,5-diphenylpyrrolidine-catalyzed α-chlorination of aldehydes might proceed by an initial *N*-chlorination of the chiral catalyst–substrate complex, followed by a 1,3-sigmatropic shift of the chlorine atom to the enamine carbon atom. This hypothesis was tested by the investigation of the possible presence of isotope effects, nonlinear effects, kinetics, and by DFT calculations. The experimental and computational results presented here support the proposed mechanism, and alternative mechanistic pathways were disproved. Furthermore, the rate-determining step in the reaction was determined to be the hydrolysis of product iminium ion.

Experimental Section

NMR experiments were performed on a Varian Mercury NMR spectrometer at 400 MHz for ^{1}H and 100 MHz for ^{13}C experiments. Deuterated solvents were dried over molecular sieves (4 Å) prior to use. NCS was recrystallized from AcOH before use and dried under high vacuum.

α,α-Dideuterated isovaleraldehyde was prepared from isovaleraldehyde and D_2O by repeating the method of Villieras[24] five times, and was subsequently used for the formation of enamine **3-D**.

1-(2-Deuterio-3-methylbut-1-enyl)pyrrolidine (3-D): Distilled α,α-dideuterated isovaleraldehyde (10.7 mL, 100 mmol) was slowly added to a mixture of distilled pyrrolidine (10.9 mL, 1.3 equiv) and CaH_2 (5.0 g, 1.2 equiv) in cyclohexane under an nitrogen atmosphere and the reaction mixture was stirred for 40 h. After filtration under a nitrogen atmosphere, the solvent was removed, and the **3-D** was purified by distillation (81 °C, 20 mbar) to obtain the pure product. ^{1}H NMR ($CDCl_3$): $\delta=0.97$ (d, $J=6.8$ Hz, 6H), 1.80–1.84 (m, 4H), 2.24 (septet, $J=6.8$ Hz, 1H), 2.92–2.96 (m, 4H), 6.14 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): $\delta=24.4$, 24.8, 29.3, 49.1, 106.7, 106.9, 107.1, 133.4 ppm.

1-(3-Methylbut-1-enyl)pyrrolidine (3-H): This compound was prepared by the same procedure as for **3-D** by using isovaleraldehyde, but the reaction time is only a few hours as no primary deuterium isotope effect is present. ^{1}H NMR ($CDCl_3$): $\delta=0.99$ (d, $J=6.8$ Hz, 6H), 1.81–1.85 (m, 4H), 2.25 (octet, $J=6.8$ Hz, 1H), 2.94–2.98 (m, 4H), 4.14 (dd, $J=6.8$, 16.0 Hz, 1H), 6.16 ppm (d, $J=16.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta=24.5$, 24.8, 29.3, 49.1, 107.2, 133.6 ppm.

General procedure for the NMR competition experiments between 3-H and 3-D: An exact 1:1 mixture of enamine **3-H** and **3-D** (0.05–1.0 M) was prepared under an Ar atmosphere by using flame-dried (under vacuum) Schlenk glassware and strictly anhydrous solvents. The desired amount of the mixture was transferred to a dried NMR tube under Schlenk conditions. The exact 1:1 molar ratio was double checked by ^{1}H NMR spectroscopy and the NMR tube was put in a Schlenk tube under an argon atmosphere and cooled by liquid N_2. A solution of NCS in the desired solvent was prepared under strictly anhydrous conditions and added slowly by syringe to the NMR tube. The NMR tube was then transferred directly to a pre-cooled NMR probe set at the desired temperature (−60 to +20 °C). The reaction progress was monitored by ^{1}H NMR spectroscopy until completion, when all NCS was consumed as determined by ^{1}H NMR spectroscopy. The relative rate of reaction was determined by comparing the amounts of remaining **3-H** and **3-D** by integration of ^{1}H NMR spectra.

1-(2-Chloro-3-methyl-1-pyrrolidin-1-ylbutyl)pyrrolidine-2,5-dione (7H): Formed as a single diastereomer. This compound was not isolated due its highly unstable nature but characterized by NMR spectroscopy (^{1}H, ^{13}C-DEPT, H-H COSY, H-C COSY). ^{1}H NMR ($CDCl_3$): $\delta=0.86$ (d, $J=6.8$ Hz,, 3H; CH_3), 0.99 (d, $J=6.8$ Hz, 3H; CH_3), 1.52–1.67 (m, 4H; pyrrolidine CH_2CH_2), 2.31 (dseptet, $J=1.6$, 6.8 Hz, 1H; $CHMe_2$), 2.47–2.83 (m, 8H; CH_2NCH_2, succinimide CH_2CH_2), 5.06 (d, $J=1.6$ Hz, 1H; C*HCl), 5.07 ppm (s, 1H; aminal CH); ^{13}C NMR ($CDCl_3$): $\delta=14.4$ (CH_3), 20.9 (CH_3), 23.3 (CH_2), 24.2 (CH_2), 27.8 (CH_2), 29.4 (CH_2), 48.5 (NCH_2), 49.5 (NCH_2), 64.8 (CH*Cl), 71.9 (NCHN), 178.8 (CO), 179.0 ppm (CO).

1-(2-Chloro-2-deuterio-3-methyl-1-pyrrolidin-1-ylbutyl)pyrrolidine-2,5-dione (7D): Formed as a single diastereomer. This compound was not isolated due its highly unstable nature but characterized by NMR spectroscopy (^{1}H, ^{13}C-DEPT, H-H COSY, H-C COSY). ^{1}H NMR ($CDCl_3$): $\delta=0.86$ (d, $J=6.8$ Hz, 3H; CH_3), 0.99 (d, $J=6.8$ Hz, 3H; CH_3), 1.52–1.67 (m, 4H; pyrrolidine CH_2CH_2), 2.31 (septet, $J=6.8$ Hz, 1H; $CHMe_2$), 2.47–2.83 (m, 8H; CH_2NCH_2, succinimide CH_2CH_2), 5.07 ppm (s, 1H; aminal CH); ^{13}C NMR ($CDCl_3$): $\delta=14.4$ (CH_3), 20.9 (CH_3), 23.3 (CH_2), 24.2 (CH_2), 27.8 (CH_2), 29.4 (CH_2), 48.5 (NCH_2), 49.5 (NCH_2), 64.2, 64.5, 64.7 (CD*Cl), 71.9 (NCHN), 178.8 (CO), 179.0 ppm (CO).

Procedure for the organocatalytic α-chlorination of butyraldehyde using different chlorine sources: (*R*,*R*)-2,5-Diphenylpyrrolidine (0.05 mmol, 10 mol%), butyraldehyde (0.50 mmol, 1.0 equiv), and benzoic acid (0.05 mmol, 10 mol%) were stirred in CH_2Cl_2 (1.0 mL) and water (100 mol%) at 0 °C. The chlorine donor (0.65 mmol, 1.3 equiv) was added and the reaction mixture was stirred at 0 °C until the aldehyde was completely consumed as determined by ^{1}H NMR spectroscopy of the reaction mixture and confirmed by GC analysis. The enantiomeric excess was determined by GC on a Chrompak CP-Chirasil Dex CB-column. Temperature program: 55 °C isotherm for 9 min. R_t: 6.7 (*R* enantiomer), 6.9 min (*S* enantiomer).

Computational methods: All quantum chemical calculations were carried out by using the Gaussian 98[18a] or Gaussian 03[18b] suite of programs. Using Gaussian 98, initial structures were computed at the HF/6-31G level of theory and were used as starting geometries for all production calculations, which were computed at the B3LYP/6-31G(d) level of theory. Transition state structures for the 1,3-sigmatropic shift of chlorine

were localized by using the Synchronous Transit-guided Quasi Newton[25] technique as implemented in Gaussian03.

Frequency analysis was performed for all stationary points, and the number of imaginary frequencies was zero and exactly one for all minima and transition state structures, respectively. To confirm that the located transition states in fact corresponded to the transfer of chlorine, the imaginary frequency for each saddle point was analyzed by the Molden program.[26] In addition, the intrinsic reaction coordinate (IRC)[27] paths were traced in order to verify the energy profiles connecting each transition state structure to the two associated minima of the 1,3-chlorine shift.

Assuming that the gas-phase optimized structures do not change much on going to the solution phase, the energies of the gas-phase-optimized DFT structures were calculated in solution by means of single-point solvation calculations. We believe that this represents a satisfactorily approximation, as the gas-phase-optimized geometry of **4** and a fully B3LYP(COSMO)/6-31G(d) optimized geometry of **4** superimpose with a RMS of only 0.015 Å. Continuum solvation effects were modeled by using the implementation of the conductor-like screening solvation model[28] (COSMO) in Gaussian 03. The medium was chosen to be 1,2-dichloroethane (DCE), with a dielectric constant of $\varepsilon = 10.36$, as the *S* product was formed in 94% *ee* in that solvent.[8b] The energies computed for structures in the solvent DCE were thereby calculated at the B3LYP-(COSMO)/6-31G(d)//B3LYP/6-31G(d) level of theory and included the electronic energy from the COSMO[28] solvation model.

Absolute energies and Cartesian coordinates of fully gas phase optimized geometries for the structures **3**, **4**, (*R*)-**5**, (*S*)-**5**, (*R*)-**TS**$_{1,3}$, and (*S*)-**TS**$_{1,3}$ in the gas phase at the B3LYP/6-31G(d) level of theory are listed in Supporting Information.

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