Kinetic Study of Disulfonimide Catalyzed Cyanosilylation of Aldehyde Using a Method of Progress Rates

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Abstract: Kinetic study of organic reactions, especially multistep catalytic reactions, is crucial to in-depth understanding of reaction mechanisms. Here we report our kinetic study of the chiral disulfonimide catalyzed cyanosilylation of aldehyde, which reveals that two molecules of TMSCN are involved in the rate-determining C-C bond forming step. In addition, the apparent activation energy, enthalpy of activation and entropy of activation were deduced through the study of temperature dependence of the reaction rates. More importantly, a novel and efficient method which makes use of the progress rates was developed to treat the kinetic data obtained from continuous monitoring of the reaction progress with in situ FT-IR.

Key words: kinetic study, progress rates, disulfonimide, cyanation, organocatalysis, initial rates, RPKA

Numerous novel catalysts and organic transformations are being developed nowadays, meanwhile, mechanistic studies of these organic reactions which certainly will facilitate better understanding of the reaction pathways and practical application of them, have been left behind. Although theoretical studies have proved to be a powerful way to depict the mechanistic details of the reactions, experimental kinetic studies which provide concentration dependence of the reactants and catalysts, and give rate and equilibrium constant of the reactions thus help to understand the molecular-level behavior of the reaction, are still essential and irreplaceable to the mechanistic studies.2

Catalytic asymmetric addition of cyanide to carbonyl compounds which produce enantioenriched cyanohydrins is of great importance in organic synthesis, as chiral cyanohydrins are versatile synthetic intermediates for a large number of biologically important compounds, such as α-hydroxy acids, α-amino acids and β-amino alcohols. A large variety of catalysts including enzymes,3 metal-based Lewis acid catalysts,4 organocatalysts5 and metal-organic frameworks6 have been developed in the past decades.5-7 In 2016, List and coworkers reported a very efficient chiral disulfonimide organocatalyst (1a,1b) for asymmetric cyanosilylation of aldehydes (Scheme 1), with catalyst loading down to 50 ppm (0.005 mol%), yield up to 98%, e.r. up to 98:2 and reaction scale up to 156 grams.8 Preliminary mechanistic investigations have been conducted via in situ FT-IR and NMR analysis, revealing that the catalytically active species actually is a silylated disulfonimide Lewis acid organocatalyst and an interesting “dormant period” which is mainly induced by water comes before the real catalytic cycle starts. Although these studies provided a better understanding of the pre-catalytic cycle, the details of the real catalytic cycle are still unknown. Here we report our detailed kinetic study of disulfonimide 1a catalyzed cyanosilylation of 2-naphthaldehyde 2, which may contribute to an in-depth understanding of the reaction mechanism and to future development of new catalysts and transformations.
Experimental kinetic studies were carried out by monitoring of reaction progress with in situ FT-IR (see Supporting Information for details). To determine the reaction orders of all components, several reactions were carried out under identical conditions, only varying the initial concentrations of reactants 2 and 3, and the catalyst 1a, respectively. From the data obtained by in situ FT-IR measurements, concentration of aldehyde [2] vs time profiles with different initial concentrations of TMSCN [3]₀ were obtained as shown in Figure 1a. Profiles of [2] vs time with different initial concentrations of aldehyde [2]₀ and catalyst loading [1a]₀ were also obtained (Figure S13, S16, Supporting Information).

Reaction progress kinetic analysis (RPKA) is a methodology developed and formalized by Blackmond and co-workers. Compared with the classical kinetic approach (method of pseudo-zero-order) where the concentration of one substrate is artificially fixed at a pseudo-constant high value (usually tenfold), RPKA allows reactions to be carried out at synthetically relevant conditions which are closer to standard reaction conditions and more reasonable. One of the key points of RPKA is to determine the reaction orders in “a trial and error procedure” by constructing “graphical rate equations” and seeking “overlay” of them by dividing the rate curves by the concentration of the substrate under study taken to the power of the reaction order. We first evaluated our kinetic data using the method of RPKA.

The concentration of aldehyde [2] vs time profiles (Figure 1a) with different initial concentrations of TMSCN [3]₀ were converted to rate vs [2] profiles (Figure 1b) which clearly indicate a positive reaction order in [3] as the rate significantly increased upon increasing the concentration of 3. Then the rate vs [2] profiles (Figure 1b) were converted to rate/[3] vs [2] profiles (Figure S8, Supporting Information), however no sign of “overlay” between these “graphical rate equations” was observed. When the rate vs [2] profiles (Figure 1b) were further converted to rate/[3]² vs [2] profiles as shown in Figure 1c, the “graphical rate equations” got much closer to each other especially in the middle range of the reaction progress ([2] = 0.075 – 0.15 M), while it is still difficult to judge whether these “graphical rate equations” overlay or not.

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**Scheme 1** Chiral disulfonimides catalyzed asymmetric cyanosilylation of 2-naphthaldehyde 2.
Although RPKA has been proved to be a powerful method\textsuperscript{3-9} to deduce the reaction orders (mainly integer numbers such as 0 and 1) of the components participated in the reaction and to determine whether there is catalyst activation or deactivation, substrate or product inhibition or acceleration, it doesn’t work quite well when the reaction mechanism is more complex and the reaction equation is more complicated (the orders could be non-integer even negative if the overall rate expression for the reaction is written in power-law form). As already mentioned by Blackmond,\textsuperscript{9} in some reactions “it may be found that none of the plots of graphical rate equations result in all the curves falling on top of one another”. In 2016, Burés developed a very simple and practical graphical method using a normalized time scale, to determine the order in catalyst.\textsuperscript{10} However, this method is limited to the order in the catalyst concentration which is not a thermodynamic driving force of the reaction. Besides it, the orders of the reactants also are supposed to be determined in most kinetic studies.

Seeking to make full use of the kinetic data obtained from the steady state catalytic cycles of the entire reaction progress, and deduce the reaction orders of all components in a more efficient and convenient way, we developed a novel method to treat the kinetic data. Taking the determination of the order of TMSCN \( [3] \) as an example, the detailed procedures of this method are illustrated as follows (see Supporting Information for details):

**Step 1. Obtain the rate vs [reactant A] profiles.** Several reactions were carried out under identical conditions only varying the initial concentrations of reactant B, whose order is to be determined (TMSCN 3 in this case). The profiles of rate vs aldehyde concentration Figure 1b (rate vs \([2]\)) were obtained from the \([2]\) vs time profiles, which were deduced from the data sets of in situ FT-IR measurements.

**Step 2. Fit the rate vs [reactant A] profiles and get the functions.** An accurate function (such as high order polynomial function) was used to fit the curves of each reaction in the rate vs \([2]\) profiles (Figure 2a, blue lines).

**Step 3. Obtain the data sets of (rate, [reactant B]).** A series of concentrations of \( [2] \) (reactant A) with a fixed interval (here 0.01 M) and within a selected range (here 0.08-0.16 M), were used to calculate the instant progress rates from the fitting functions and the instant concentrations of \( [3] \) (reactant B) corresponding to each \([2]\). The obtained data sets of (rate, \([3]\)) were shown as red squares in Figure 2a.

**Step 4. Obtain the order of [reactant B] via double logarithmic plot and linear regression of rate vs [reactant B] for each [reactant A].** A profile of log (rate) vs log \([3]\) was plotted for each \([2]\) (Figure 2b, when \([2]=0.16\) M). Linear regression of this profile results a function whose slope corresponds to the order of \([3]\) at this concentration of \([2]\). Thus, data sets of \{order of \([3]\), \([2]\)\} were obtained.

**Step 5. Plot the profile of (order of [reactant B]) vs [reactant A].** The profile of (order of \([3]\)) vs \([2]\) was plotted (Figure 2c), which not only shows an approximate value for (order of \([3]\)) but also indicate changes in reaction order as a function of changing substrate concentrations.

![Figure 2](image-url) Determination of the order of TMSCN \([3]\) using a novel method which makes use of the progress rates. 2a) Rate vs \([2]\) profiles with different initial concentration of \([3]\) (fitted with high order polynomial functions shown as blue lines) and obtained data sets of (rate, \([3]\)) shown as red squares; 2b) Double logarithmic plot and linear regression of rate vs \([3]\) when \([2]=0.16\) M (the deduced order of \([3]\) corresponds to the slope 1.8635); 2c) The profile of (order of \([3]\)) vs \([2]\) in the selected range of \([2]\) (0.08-0.16 M).
This method may look complex when described in steps, while actually all fitting and data processing can easily be done using standard office software such as Excel and Origin. The average value for the order of [3] was calculated to be 1.94 (nearly second order). Thus, the apparent rate order of 3 in power-law form reaction rate equation was obtained. The reaction order of approximately 2 in TMSCN suggests that two molecules of this substrate are involved in a step which has a significant influence on the rate.

With the method described above, the average reaction order of aldehyde 2 was determined to be only 0.17 which nearly is zero order. The average value for the order of catalyst 1a was calculated to be 1.23 which is close to first order (see Supporting Information for details). Taking the average reaction orders determined by our method, the power-law form of the rate equation, which reflects the molecular-level behavior of the reaction as an empirical approximation, can be stated as shown in equation (1). The low reaction order in 2 suggests that the step involving its activation is significantly faster than the addition of cyanide and a catalyst species associated with aldehyde 2 is possibly involved in the rate-limiting step.

\[ \text{rate} = k \cdot [1a]^{1.23} \cdot [2]^{0.17} \cdot [3]^{1.94} \]  

(1)

The temperature dependence of the reaction rates was studied in the range of 273.15 – 303.15 K under otherwise identical conditions. The apparent activation energy of the reaction was deduced to be 41 kJ mol\(^{-1}\) (9.9 kcal mol\(^{-1}\)) according to the Arrhenius equation by plotting ln k vs 1/T (Figure S20,21, Supporting Information), which implies that the reaction is relatively sensitive to temperature. The enthalpy of activation \(\Delta H^\ddagger\) was deduced to be 39 kJ mol\(^{-1}\) (9.3 kcal mol\(^{-1}\)) and the entropy of activation \(\Delta S^\ddagger\) was deduced to be –81 J mol\(^{-1}\) K\(^{-1}\) (–19 cal mol\(^{-1}\) K\(^{-1}\)) according to the Eyring equation by plotting ln \((k/T)\) vs 1/T. The Gibbs energy of activation \(\Delta G^\ddagger\) was calculated to be 61 kJ mol\(^{-1}\) (15 kcal mol\(^{-1}\)) at 273.15 K (Figure S22–24, Supporting Information).

Based on these studies, we propose a catalytic cycle for the disulfonimide catalyzed asymmetric cyanosilylation of aldehydes (Scheme 2). After a long dormant period, which is up to a few hours, the pre-catalytic cycle ends. Then the Bronsted acid pre-catalyst 1a reacts with TMSCN to generate the catalytically active Lewis acid organocatalyst 1a-TMS which interacts with the aldehyde 2 to generate activated species 5. The low reaction order in 2 suggests possible saturation kinetics in [2], indicating that the formation of 5 is significantly faster than the reverse reaction and the addition of cyanide. Subsequently, two molecules of TMSCN interact with 5, possibly forming the new C-C bond via aggregated cyclic transition state as shown in 6, to produce species 7 and regenerate one molecule of TMSCN, which is proposed to be the rate-determining step. This is similar to the well-known Grignard reaction, which proceeds through an aggregated six-membered ring transition state bridged by a dimeric di-cation of Grignard reagent. A study of the relationship between the enantimetric excess of the product and the enantiomeric excess of the catalyst revealed that there is no nonlinear effect in this reaction (Figure S27, Supporting Information), which is consistent with the involvement of only a single catalyst molecule in the stereo-determining step. At last, product 4 is quickly released from 7 and active catalyst 1a-TMS is regenerated.

![Scheme 2 Proposed catalytic cycle. Two molecules of TMSCN are possibly involved in the rate-determining C-C bond forming step.](Image)

In summary, kinetic investigation of disulfonimide catalyzed cyanosilylation of aldehydes was conducted and the orders of the reactants and catalyst for a power-law form of rate equation were obtained. An aggregated cyclic transition state with two molecules of TMSCN involved, was proposed. A novel and efficient method which makes use of the progress rates to deduce orders of both reactants and catalyst, was developed to treat the kinetic data obtained from continuous monitoring of the reaction process, and is expected to attract widespread attention. We predict that these studies may not only facilitate in-depth understanding of the reaction mechanism, but also benefit the future design and application of powerful organocatalysts.

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