

Direct On-Line Method To Monitor the Dynamic Structure of Noncovalent Titanium Complexes in Solution by Using Cold-Spray Ionization Time-of-Flight Mass Spectrometry

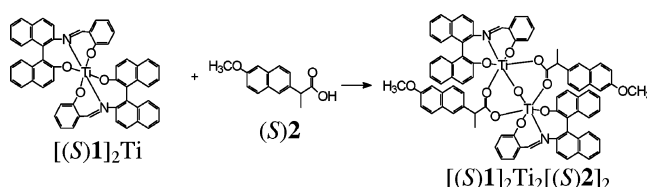
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In this paper, we report the feasibility of using the on-line cold-spray ionization time-of-flight mass spectrometry (CSI-TOFMS) method to monitor directly the labile non-covalent organometallic complexes formed in the substitution reaction between a chiral titanium asymmetric catalyst and organic acid in the toluene solvent. The comparison between the conventional ESI and CSI-TOFMS spectra of $[(S)1]_2Ti_2[(S)2]_2$ in THF indicated that the CSI-TOFMS is an effective method to characterize the structures of labile organometallic complexes in solution. A new strategy was designed so that $[(S)1]_2Ti_2[(S)2]_2$ and organic acid solution were delivered independently to the CSI ion source by two infusion syringe pumps, and they mixed at a triple valve, and then the substitution reaction occurred in the sprayer. The mix and reaction time was ~ 5 s and can be adjusted by the length of the PEEK tube and the flow rate. The reaction products were ionized and detected directly by the CSI-TOFMS. Organic acids, such as formic, acetic, phenylpropionic, anisic, and *para*-methoxyphenylactic acids, were investigated. From the on line CSI-TOFMS spectra, it is observed clearly that one or two (S)2 group(s) can be substituted by the added acid to form new species. The results obtained here demonstrated that the designed strategy with on line CSI-TOFMS is effective and reliable to elucidate the dynamic structure of noncovalent titanium complexes in reaction solution.

Recently, K. Yamaguchi et al. developed cold-spray ionization mass spectrometry (CSI-MS), which allows facile characterization of labile organometallic complexes and biomolecular interactions in high-polarity organic solvents and hydrous solution.^{1–11} Those

Scheme 1. Structures of $[(S)1]_2Ti$ and $[(S)1]_2Ti_2[(S)2]_2$



wonderful works were performed on a double-focused, magnetic mass spectrometer with a CSI ion source. CSI is a variant of electrospray (ESI) operating at low temperature (~ -80 to 20°C). In the CSI-MS spectrum, not only $[M + A]^+$ ($A = \text{H}, \text{Na}, \text{K}, \text{etc.}$) but also $[nM + mA + lS - kH]^{(m-k)+}$ ($S = \text{solvent}$) are usually observed.

Tridentate chiral titanium complexes have the positive nonlinear effect (NLE) in catalytic enantioselective hetero-Diels–Alder and aldol-type reactions.^{12–16} The $[(S)1]_2Ti$ complex was prepared by the reaction of enantiopure (S)1 with titanium(IV) isopropoxide (2:1 molar ratio) in toluene, and the structure was demonstrated as in Scheme 1 by X-ray single-crystal structure analysis. The titanium complex of $[(S)1]_2Ti_2[(S)2]_2$ was obtained from the mixed solution of $[(S)1]_2Ti$ with (S)-naproxen [(S)2] (1:2 molar ratio). X-ray single-crystal structure analysis is a useful method for organometallic complexes, but it is not always available because of the difficulty in getting an appropriate single crystal.

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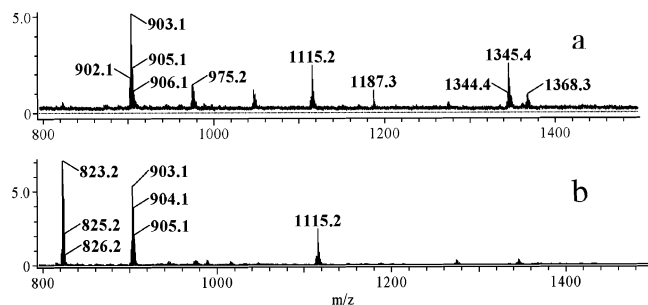


Figure 1. (a) CSI-MS and (b) ESI-MS spectra of $[(S)1]_2Ti_2[(S)2]_2$ dissolved in THF.

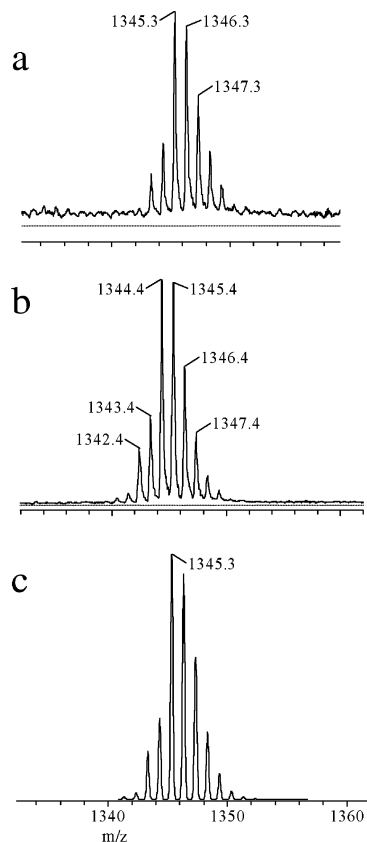


Figure 2. (a) Observed ion distribution of $[M + H]^+$ in THF, (b) observed ion distribution of M^+ in toluene, and (c) theoretical ion distribution of $[M + H]^+$.

A new type of orthogonal acceleration time-of-flight (oa-TOF) mass spectrometer with a CSI ion source, AccuTOF CS, has been introduced. MS has the accuracy of mass measurement, speed of analysis, and small sample quantities, which are advantages over other methods, such as UV/vis spectroscopy, fluorescence spectroscopy, NMR spectroscopy, IR spectroscopy, and X-ray crystallographic analysis. Moreover, due to the attractive features of TOFMS the analyzer, such as a theoretically wide mass range, a very high spectrum acquisition rate, high sensitivity, multiplex detection capacity, and reasonable mass resolution, CSI-TOFMS becomes a powerful instrument to monitor directly the formation of noncovalent complexes in solution, even though the ionization efficiency of these complexes is low at low temperature. The latest reports have demonstrated the ability of CSI-TOFMS as a means of direct observation of specific carbohydrate-related and water–protein complexes in aqueous solution.^{17–18}

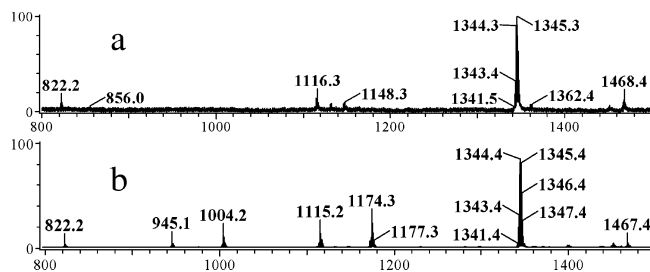


Figure 3. CSI-MS spectra of $[(S)1]_2Ti_2[(S)2]_2$ dissolved in (a) toluene and (b) toluene + 1% acetic acid.

In this paper, we report the novel results on the feasibility of the on line CSI-TOFMS method to monitor directly the labile noncovalent organometallic complexes formed in the substitution reaction between chiral titanium catalyst and organic acid in toluene solvent.

EXPERIMENTAL SECTION

$[(S)1]_2Ti_2[(S)2]_2$ was prepared and diluted to $0.1 \mu\text{g}/\mu\text{L}$ in a solution of THF or toluene, and the solution was delivered to the ion source by an infusion syringe pump at a flow rate of $10 \mu\text{L}/\text{min}$. The CSI-TOFMS spectra were acquired using an AccuTOF CS mass spectrometer (JMS-T100CS, JEOL, Tokyo, Japan). The needle voltage was set at 3200–3650 V; the orifice 1 voltage was set at 40 V; the orifice 2 voltage was 20 V; and the flow rate and temperature of spray gas were 2.5 L/min and -35 to 20°C , respectively.

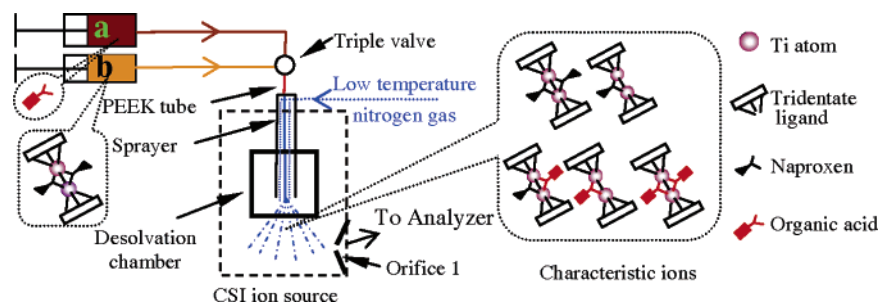
RESULT AND DISCUSSION

As shown in Figure 1, the $[M + H]^+$ ion at m/z 1345 can be observed in the CSI (spray temperature, 20°C) and conventional ESI (desolvation chamber temperature, 250°C) mass spectra of $[(S)1]_2Ti_2[(S)2]_2$ dissolved in THF. The observed and theoretical ion distribution of $[M + H]^+$ are shown in Figure 2; however, the fragment ion $[M + H - (S)2]^+$ at m/z 1115 and the ion at m/z 823, assigned as $\{[(S)1]_2Ti + H\}^+$, can be observed with high abundance in the ESI mass spectrum because of the high desolvation chamber temperature. Thus, CSI-MS was proved to be an effective method to characterize the solution structures of labile organometallic complexes. The ions at m/z 903, 975, 1047, and 1187 are also observed in the CSI mass spectrum, and these ions can be assigned as $[M + H + H_2O - 2(S)2]^+$, $[M + H + H_2O + THF - 2(S)2]^+$, $[M + H + H_2O + 2THF - 2(S)2]^+$, and $[M + H + THF - (S)2]^+$, respectively. Ion distribution pattern on Ti isotopes matched nicely for all assigned peaks, as shown in Figure S-1 of the Supporting Information. To confirm the element composition of these ions, an exact mass measurement was performed by using poly(ethylene glycol) as internal calibrant. The data are attached in Table S-1 of the Supporting Information; the deviation in the measured mass number is <10 ppm for each ion. It should be pointed out that for these low-polarity organometallic complexes, it is impossible to get significant results when high-polarity solvents, such as CH_3OH , CH_3CN , and H_2O are used conventionally in CSI and ESI ionization.

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Scheme 2. Strategy Designed To Monitor the Dynamic Structure of Noncovalent Complexes in the Substitution Reaction between [(S)1]₂Ti₂[(S)2]₂ and Organic Acid by Using on Line CSI-TOFMS



"a" was toluene + 0.2% organic acid; the flow rate was 5 $\mu\text{L}/\text{min}$. "b" was 0.2 $\mu\text{g}/\mu\text{L}$ [(S)1]₂Ti₂[(S)2]₂ in toluene; the flow rate was 5 $\mu\text{L}/\text{min}$.

Scheme 3. Structures and Noncovalent Product Ions (m/z) in the Reaction Solution Monitored by on Line CSI-TOF MS

AC-COOH	HCOOH	CH ₃ COOH	H ₃ CO-C ₆ H ₄ -COOH	C ₆ H ₅ -CH ₂ -COOH	C ₆ H ₅ -CH ₂ -COOH	
R ₁ =AC	931	945	1067	1051	1065	
R ₁ =R ₂ =AC	976	1004	1218	1186	1214	
R ₁ =S	1115	1115	1115	1115	1115	
R ₁ =AC R ₂ =S	1160	1174	1266	1250	1264	
R ₁ =R ₂ =S	1345	1345	1345	1345	1345	

Figure 3 shows the CSI-MS spectra of [(S)1]₂Ti₂[(S)2]₂ dissolved in toluene (3a) and toluene + 1% acetic acid (3b). The molecular ion M⁺ at m/z 1344 is predominant under this condition. The ion distribution pattern on Ti isotopes matched nicely for the M⁺ ion, as shown in Figure 2. It should be noted that the acetic acid could replace (S)2 to form a new species when it was added into the [(S)1]₂Ti₂[(S)2]₂ solution, and the reaction was so quick that the intensity of the peak corresponding to [(S)1]₂Ti₂[(S)2]₂ decreased rapidly within 2 min when 1% acetic acid was added. The CSI-MS spectra at different reaction times are shown in Figure S-2 of the Supporting Information. Therefore, a strategy shown in Scheme 2 was designed to monitor directly the dynamic structure of noncovalent products and reactants synchronously in the substitution reaction between [(S)1]₂Ti₂[(S)2]₂ and the organic acid by using on line CSI-TOFMS.

The sprayer has an inside diameter of 0.1 mm and a length of 110 mm, so the mixing and reaction time will be ~ 5 s if the flow rate is 10 $\mu\text{L}/\text{min}$, and the reaction time can be adjusted by the flow rate and the length of the PEEK tube connecting the sprayer and the triple valve. Under these conditions, molecular ion M⁺ at m/z 1344 is the base peak in the mass spectrum. Additionally, m/z 945, 1004, 1115, and m/z 1174 are also observed, as shown in Figure 2b. These ions could be assigned as [M + AC - (S)2]⁺, [M + 2AC - 2(S)2]⁺, [M - (S)2]⁺, and [M + AC - (S)2]⁺ (AC = acetic acid), respectively. The structure and observed ion distribution pattern are shown in Figure S-3. Other organic acids such as formic, phenylpropionic, anisic, and *para*-

methoxyphenylacetic acids were also investigated under these conditions, and the organic acid substitution products were observed clearly, as shown in Scheme 3 and Supporting Information Figure S-3, and the isotope pattern of all assigned ions is matched nicely with theoretical ion distribution. On the basis of the results that increasing the reaction time would increase markedly the relative intensity of peaks corresponding to the products (see Figure S-2), it is sure that the substitution reaction occurs before spraying. From the CSI-TOFMS spectra, it is concluded obviously that one or two (S)2 group(s) can be substituted by the added acid to form new species. The results obtained above demonstrate that the designed strategy with CSI-TOFMS is powerful to elucidate the dynamic structure of noncovalent products in the substitution reaction.

This is the first demonstration of a new strategy to monitor directly the dynamic structure of the labile noncovalent complexes in solution by using on line CSI-TOFMS. The substitution reaction between five organic acids and [(S)1]₂Ti₂[(S)2]₂ was investigated with this method, and it was proved to be effective and reliable. The designed strategy might promote a theoretical explanation on the NLE in asymmetric catalysis.

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SUPPORTING INFORMATION AVAILABLE

Experimental details for the measurement of CSI-TOFMS spectra, exact mass measurement data of [(S)**1**]₂Ti₂[(S)**2**]₂ in THF solution, the comparison between the theoretical ion distribution

and observed ion distribution of ions, and the CSI-TOFMS spectra of the substitution reaction. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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