

RCM

Letter to the Editor

To the Editor-in-Chief
Sir,

Transient intermediates of the Tebbe reagent intercepted and characterized by atmospheric pressure chemical ionization mass spectrometry

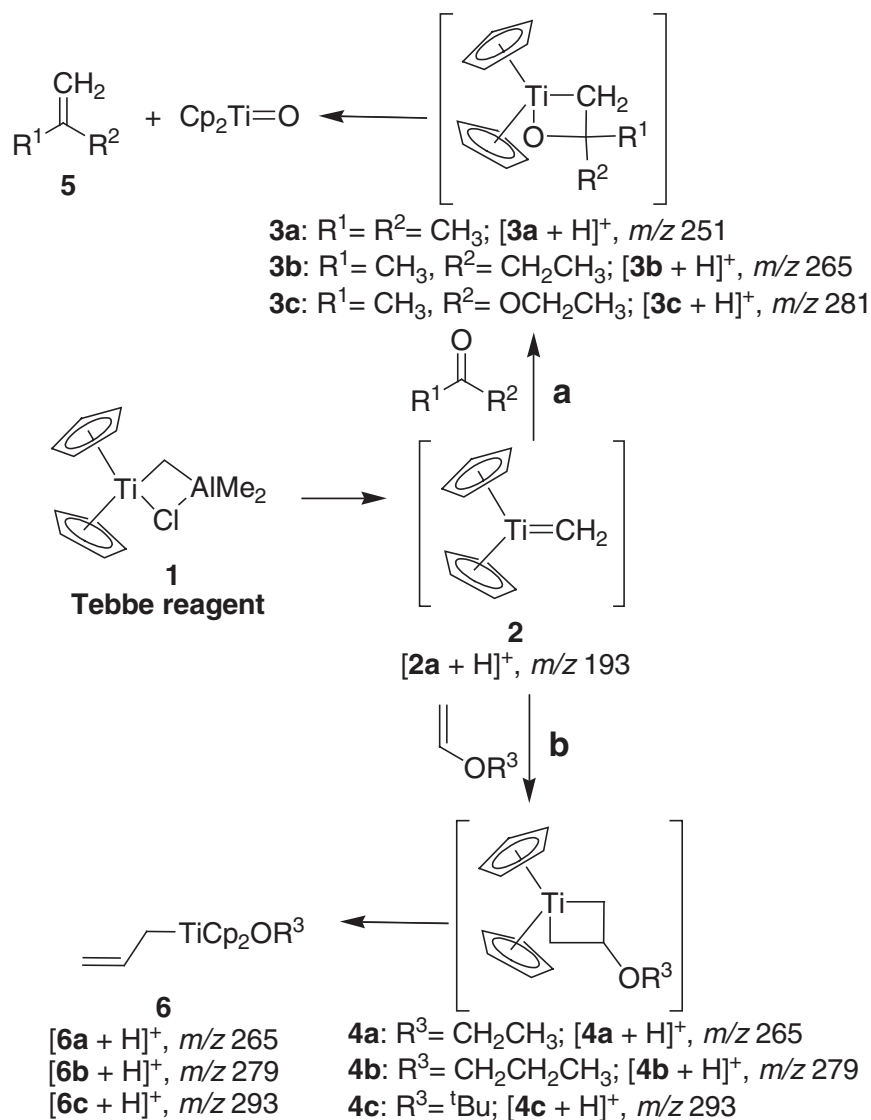
Titanium catalysts or mediators, such as titanium chlorides, are, among group IV metal derivatives, the most attractive for practical use since they are the least expensive and most convenient to handle. In the 1970s, Tebbe discovered the first synthetically important reaction of an organotitanium compound.^{1,2} Under the action of a Lewis base, Tebbe reagent **1** is postulated to form **2** (Scheme 1), which then interacts with organic compounds.¹ However, the transient methylenetitanocene key Tebbe intermediate **2** has never been isolated as a pure compound. In previous work,³ we were able to transfer solvated **2** directly from solution to the gas phase, and characterized gaseous **2** while monitoring Petasis reactions via atmospheric pressure chemical ionization mass (APCI-MS) and tandem mass spectrometry (APCI-MS/MS). We have been successfully using both electrospray (ESI)-MS⁴ and APCI-MS⁵ to 'fish' and characterize key intermediates of organic and organometallic reactions.^{3,6}

After showing that the methylenetitanocene **2** does indeed participate in Petasis reactions, we decided to investigate related reactions for which there is no conclusive mechanistic data. This is the case for Tebbe olefination reactions (Scheme 1). To study these reactions, we again used APCI-MS to 'fish' the transient Tebbe intermediates from the reaction solution and APCI-MS/MS to characterize the gaseous species. We also investigated the proposal^{7,8} that allylic titanocene com-

plexes are generated from non-allylic starting materials (vinyl ethers derivatives) in a related Tebbe-like reaction (Scheme 1b).

The three carbonylic compounds selected for this study (acetone, 2-butanone, and ethyl acetate) and tetrahydrofuran (THF) were HPLC grade. Vinylic ethers (ethyl, propyl, *n*-butyl, *i*-butyl, and *t*-butyl vinyl ethers) and the Tebbe reagent were commercially available from Aldrich. The Tebbe reagent **1** (1.0 mol L⁻¹ toluene solution) was added to an excess of the reactant carbonylic compounds. THF (10.0 μL) was also added to this solution to function as the base. A microsyringe

pump was used to deliver the reaction solution to the APCI source at a flow rate of 10 μL min⁻¹. The mass spectrometer used was a hybrid quadrupole orthogonal time-of-flight (o-TOF) instrument with a hexapole collision cell (Q-ToF, Micromass, Manchester, UK). The temperature of the nebulizer was 20°C. APCI-MS was performed in the positive ion mode using a pin potential of +3000 V for the corona discharge. The cone and extractor potentials were set to +30 and 0 V, respectively. The scan range was typically in the *m/z* 50–1000 range. To enhance sensitivity, spectra were sometimes acquired across narrow



Scheme 1. Tebbe reagent used in (a) olefination and (b) allylation reactions.

m/z ranges to favor the detection of specific transient Ti species. APCI-MS/MS was performed via Q mass-selection of the desirable product ion, collision-induced dissociation (CID) with argon in the hexapole collision cell, and *o*-TOF mass analysis of the CID product ions. The collision energy ranged from 10–25 eV, depending on the stability of the precursor ion undergoing CID.

In APCI,⁴ neutral molecules evaporate from the drying spray droplets, and the gaseous molecules are ionized at atmospheric pressure via electron abstraction, protonation or deprotonation (or a combination of these processes) due to a cascade of ion/molecule reactions initiated by corona discharge. Therefore, the set of ions detected by APCI-MS normally reflects the solution composition of neutral species, and the gentle evaporation process helps to preserve labile species such as organometallic species and their coordination spheres. Reagents, intermediates, and products of Tebbe reactions may therefore be transferred intact from solution to the gas phase, to be ionized gently and mass analyzed during APCI-MS of the reaction solution. We chose to use APCI-MS in the positive ion mode since we

expected that the reaction intermediates **3** and **4** would be protonated efficiently in the gas phase (Scheme 1).

According to Tebbe,¹ generates **2**, which then reacts with the ketone to yield the oxatitanacyclic intermediates **3a–c** (Scheme 1a). It is proposed that decomposition of **1** provides the active species **2** by the loss of ClAlMe₂.⁹ APCI-MS screening of Tebbe olefination reactions was therefore performed. Titanium has five isotopes, ⁴⁶Ti (8.0%), ⁴⁷Ti (7.3%), ⁴⁸Ti (73.8%), ⁴⁹Ti (5.5%), and ⁵⁰Ti (5.4%), and therefore its multi-isotopic nature facilitates MS assignment of Ti intermediates. As Fig. 1 exemplifies for acetone, in the reaction of **1** with the selected ketones, APCI-MS unequivocally detects [3+H]⁺ as a characteristic cluster of Ti-isotopologue ions, the most abundant (for ⁴⁸Ti) being those of m/z 251 for [3a+H]⁺, m/z 265 for [3b+H]⁺, and m/z 281 for [3c+H]⁺. The isotopic pattern of each [3a–c+H]⁺ species matches that predicted for Ti-containing ions.

APCI-MS/MS was therefore performed to characterize these key Tebbe intermediates. As Fig. 1(b) exemplifies for [3a+H]⁺, the ions were found to dissociate in a structurally diagnostic fashion. Oxatitanacyclic [3a+H]⁺, for

instance, dissociates by two main routes: (a) by retro-addition that forms the reactants, i.e. the ion of m/z 193 and neutral acetone of 58 Da, and (b) to Tebbe products, i.e. to the ion of m/z 195 and the final olefinic neutral product 2-methylpropene of 56 Da. Similar behavior was observed for [3b+H]⁺ and [3c+H]⁺ (spectra not shown). Note therefore that this dissociation behavior matches the postulated Tebbe reaction equilibrium in solution involving reagents and products. The APCI-MS and APCI-MS/MS data just described provide evidence therefore that the key oxatitanacyclic intermediates **3a–c** postulated by Tebbe¹ have indeed been fished from the solution and the gaseous species characterized accordingly (Scheme 1).

We then investigated the Tebbe-like [2+2] reaction of **1** with vinyl ethers, which is known to afford allyl titanocenes **6** (Scheme 1b). This reaction was performed by dissolving 1.0 mL of a solution of **1** (1.0 mol L⁻¹ toluene solution) directly into an excess of the pure vinyl ether, and then by spraying the reaction solution through the APCI source. No solvents were used since we aimed to intercept possible transient intermediates **2** or **4**, or both, whose concentrations in the reaction mixture were expected to be very low. Figure 2 shows the partial APCI-MS spectra of solutions in which reactions of **1** with vinyl ethers were in progress. Note that the expected Ti intermediates [4a–c+H]⁺ are unambiguously detected by characteristic clusters of Ti-containing ions, the most abundant isotopologues being those of m/z 265 for [4a+H]⁺, m/z 279 for [4b+H]⁺, and m/z 293 for [4a–c+H]⁺.

Figure 3 shows two APCI-MS/MS spectra acquired to characterize the titanacyclic intermediates [4a–c+H]⁺ via CID. Figure 3(a) shows that [4a+H]⁺ dissociates in a predictable and structurally diagnostic fashion that again matches the postulated solution equilibrium (Scheme 1b). That is, [4a+H]⁺ of m/z 265 loses an ethyl radical to form the product ion of m/z 236, a molecule of ethanol to form m/z 219 (a Ti-allylic cation), via retro-addition (loss of ethyl vinyl ether) to form the protonated intermediate [2+H]⁺ of m/z 193, and to a ligand-free titanocene cation [Cp₂Ti]⁺ of m/z

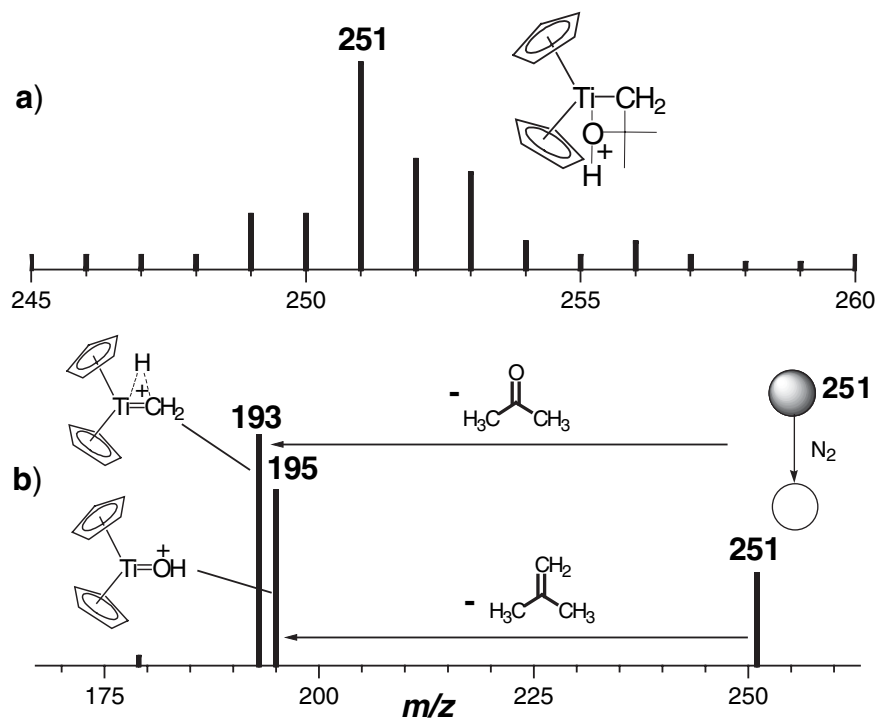


Figure 1. (a) Partial APCI-MS spectrum for the Tebbe olefination reaction of **1** with acetone and (b) APCI-MS/MS spectrum of [3a+H]⁺ of m/z 251.

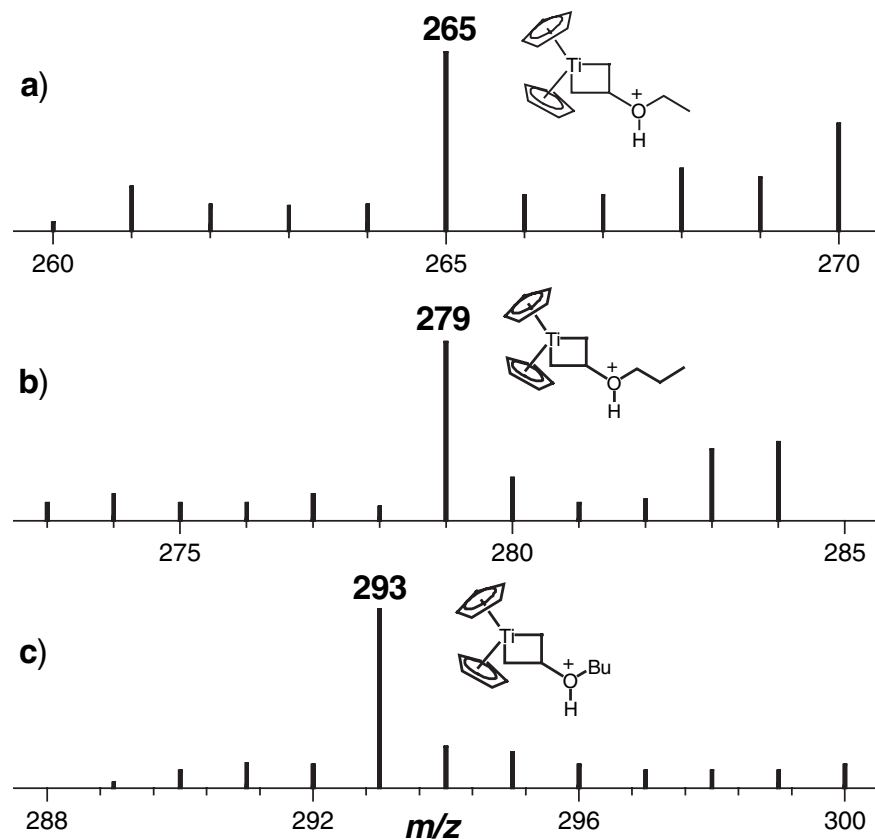


Figure 2. Partial APCI-MS spectra for Tebbe-like reactions of **1** with (a) ethyl vinyl ether; (b) propyl vinyl ether; and (c) butyl vinyl ether.

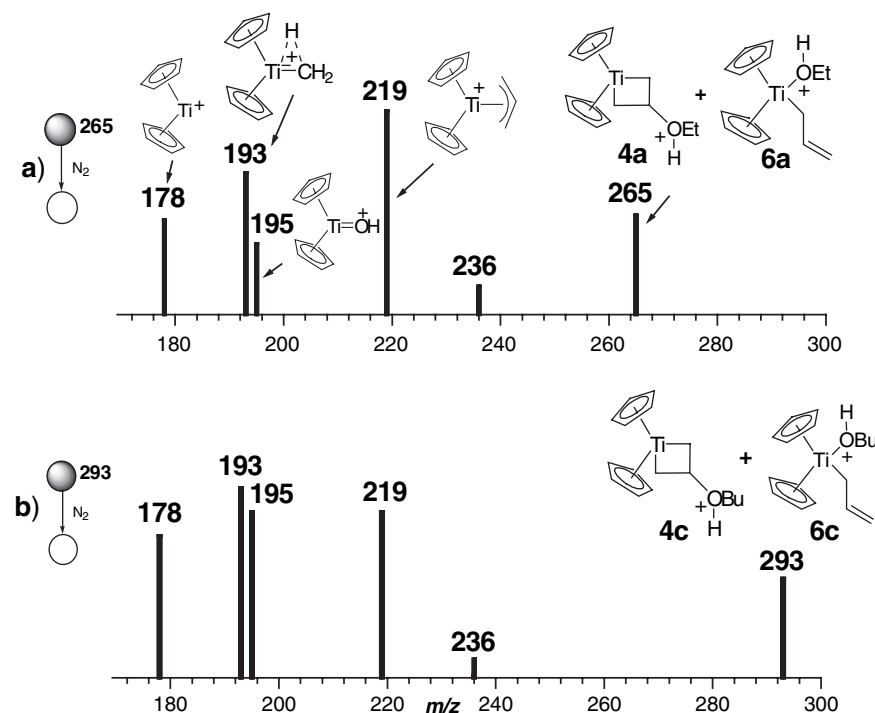
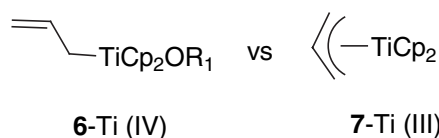


Figure 3. APCI(+)-MS/MS spectra of intermediates of (a) m/z 265 and (b) m/z 293.



Scheme 2. Proposed allyl-Ti complexes **6** and **7**.

178, formally a 14 π -electron species. The product ion of m/z 195 is interesting since its Ti-O connectivity indicates that the precursor ion of m/z 265 may be constituted of a mixture of $[\mathbf{4a}+\text{H}]^+$ and $[\mathbf{6a}+\text{H}]^+$. The presence of $[\mathbf{6a}+\text{H}]^+$ was further indicated by the APCI-MS/MS spectrum of the crude product. The protonated molecule $[\mathbf{6a}+\text{H}]^+$ dissociates to the same set of ions as those seen in Fig. 3(a) except for the $[\mathbf{2}+\text{H}]^+$ ion of m/z 193. Similar dissociation behavior was observed for $[\mathbf{4b}+\text{H}]^+$ (spectrum not shown) and $[\mathbf{4c}+\text{H}]^+$ (Fig. 3b).

An intrinsic characteristic of Ti is that two stable valence states of allylic titanocene derivatives are known: σ -allylic Ti(IV) complexes **6** and π -allylic Ti(III) complexes **7**.^{10,11} Both **6** and **7** are known to react with carbonyl compounds to afford homoallylic alcohols. However, **7** is known to be destroyed by treatment with CH_2Cl_2 , while **6** remains intact.¹⁰ We therefore added a few drops of CH_2Cl_2 to the reaction solution before APCI-MS monitoring and observed no decomposition of the intermediates for both Tebbe reactions. This result suggests therefore that we have indeed intercepted and characterized Ti(IV) species **6** (Scheme 2).

The APCI-MS interception and APCI-MS/MS characterization of key titanacycle intermediates **3** and **4** from reaction solutions support the classical mechanism of Ti-mediated Tebbe olefination reactions as properly postulated by Tebbe,¹ as well as the mechanism for the Tebbe-like [2+2] reaction postulated by Hanzawa *et al.*¹² In addition, the present study further illustrates the broad potential of atmospheric pressure ionization mass spectrometry to elucidate mechanisms of organic reactions via the highly efficient (high sensitivity and speed) 'fishing' of key intermediates and their proper gas phase MS characterization,^{3,6} a vast but still little explored field.¹³

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