Rapid Communications in Mass Spectrometry

Received: 10 November 2011 Revised: 21 December 2011 Accepted: 22 December 2011

Rapid Commun. Mass Spectrom. **2012**, *26*, 616–620
(wileyonlinelibrary.com) DOI: 10.1002/rcm.6145

Study on the reactive transient α-λ^3-iodanyl-acetophenone complex in the iodine(III)/PhI(I) catalytic cycle of iodobenzene-catalyzed α-acetoxylation reaction of acetophenone by electrospray ionization tandem mass spectrometry

Hao-Yang Wang*, Juan Zhou and Yin-Long Guo**

Shanghai Mass Spectrometry Center, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai, 200032, P.R. China

RATIONALE: Hypervalent iodine compounds are important and widely used oxidants in organic chemistry. In 2005, Ochiai reported the PhI-catalyzed α-acetoxylation reaction of acetophenone by the oxidation of PhI with *m*-chloroperbenzoic acid (*m*-CPBA) in acetic acid. However, until now, the most critical reactive α-λ^3-iodine alkyl acetophenone intermediate (**3**) had not been isolated or directly detected.

METHODS: Electrospray ionization tandem mass spectrometry (ESI-MS/MS) was used to intercept and characterize the transient reactive α-λ^3-iodine alkyl acetophenone intermediate in the reaction solution.

RESULTS: The trivalent iodine species was detected when PhI and *m*-CPBA in acetic acid were mixed, which indicated the facile oxidation of a catalytic amount of PhI(I) to the iodine(III) species by *m*-CPBA. Most importantly, $\mathbf{3}{\cdot}H^+$ was observed at *m/z* 383 from the reaction solution and this ion gave the protonated α-acetoxylation product $\mathbf{4}{\cdot}H^+$ at *m/z* 179 in MS/MS by an intramolecular reductive elimination of PhI.

CONCLUSIONS: These ESI-MS/MS studies showed the existence of the reactive α-λ^3-iodine alkyl acetophenone intermediate **3** in the catalytic cycle. Moreover, the gas-phase reactivity of $\mathbf{3}{\cdot}H^+$ was consistent with the proposed solution-phase reactivity of the α-λ^3-iodine alkyl acetophenone intermediate **3**, thus confirming the reaction mechanism proposed by Ochiai.

Hypervalent iodine compounds are an important class of reagents and they are efficient alternatives to metal-based oxidants and transition-metal catalysts in many organic transformations.[1–7] Some transformations can be carried out by using hypervalent iodine compounds as catalysts or recyclable reagents under mild conditions with high selectivity and good yield. The most widely used trivalent and pentavalent aryl iodine compounds are shown in Scheme 1.[5]

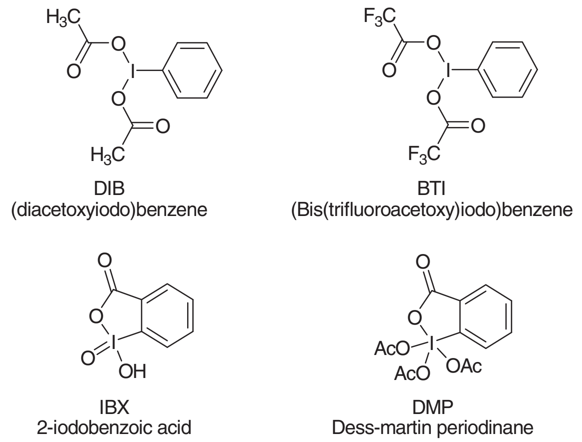
In the past decade, efforts have been made to study the chemical reactivity and the oxidation mechanism of these hypervalent aryl iodine compounds.[1,2,8,9] These studies revealed the presence of some reactive hypervalent iodine species in the reaction solution. In 1995, Sam *et al.* first used electrospray ionization mass spectrometry (ESI-MS) to study of oxidation reaction of PhIO in methanol[10] and they observed reactive λ^3-iodine species: $[PhIOMe]^+$ at *m/z* 235, $[PhIO{+}PhI^+OMe]$ at *m/z* 455 and $[PhI(OMe)_2{+}PhI^+OMe]$ at *m/z* 501 in the ESI-MS spectra. In 1997, Richter *et al.* applied NMR and UV-visible spectroscopy to characterize the active species, $[PhIOH]^+$ and $[PhIOI^+(OH_2)Ph]$, in the aqueous phase of [hydroxy(mesyloxy)iodo]benzene (HMIB) and [hydroxy(tosyloxy)iodo]benzene (HTIB),[11] while Silva and co-workers studied the disproportionation reaction of DIB in acetonitrile and methanol by high-resolution ESI-MS/(MS).[12,13]

In recent years, the catalytic hypervalent iodine oxidation reaction has been studied by using co-oxidants.[6,14–18] In this present study the chemical transformation catalyzed by the cycle of ArI(III)XY/ArI(I) (where X and Y are the anionic ligands) in the presence of a co-oxidant has been investigated by electrospray ionization tandem mass spectrometry (ESI-MS/MS). In 2005, Ochiai and co-workers first reported the direct iodobenzene-catalyzed α-acetoxylation of acetophenone by using *m*-chloroperbenzoic acid (*m*-CPBA) in acetic acid as the co-oxidant.[19,20] The speculated step-wise reaction mechanism is shown in Scheme 2: (1) PhI (I) was first oxidized to diacetoxy iodobenzene (DIB) **2** by *m*-CPBA in acetic acid; (2) acetophenone **1** was activated to its enol form in acid conditions; (3) the ligand substitution of an OAc^- moiety on **2** with the enol form of **1** occurred to generate the transient reactive α-λ^3-iodine alkyl acetophenone intermediate **3**; and (4) finally the OAc^- moiety of **3** initiated an intramolecular S_N2 substitution reaction to form the corresponding product of α-acetoxy acetophenone by reductive elimination of PhI.

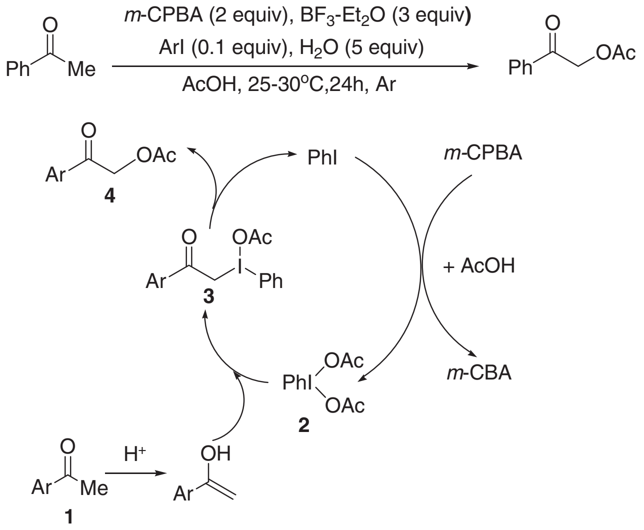
The most critical reaction intermediate, α-λ^3-iodine alkyl acetophenone (**3**), had not previously been isolated or directly detected due to its relatively weak non-covalent bonding and its short lifetime. ESI-MS/MS is a valuable tool for reaction

---

* *Correspondence to:* H.-Y. Wang and Y.-L. Guo, Shanghai Mass Spectrometry Center, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, P.R. China.
E-mail: haoyangwang@mail.sioc.ac.cn; ylguo@mail.sioc.ac.cn



Scheme 1. Hypervalent iodine compounds: DIB, BTI, IBX and DMP.



Scheme 2. The reaction mechanism of iodobenzene-catalyzed α-acetoxylation of acetophenone proposed by Masahito Ochiai.

mechanism studies in solution, with the transient reaction intermediates being transferred from solution to the gas phase. Thus, the reactivity and structures of reactive intermediates can then be further studied by MS/MS in order to investigate and explain the reaction mechanism.[21–26] The direct capture and study of the α-λ^3-iodine alkyl acetophenone intermediate **3** by mass spectrometry would provide valuable confirmation of its existence in the reaction solution and help to understand the reaction mechanism.

EXPERIMENTAL

Materials and chemicals

Acetonitrile (purity of HPLC grade) was purchased from Dikma Technology Inc. (Richmond Hill, ON, Canada). Acetic acid, iodobenzene (PhI), acetophenone, *m*-chloroperbenzoic acid (*m*-CPBA) and $BF_3{\cdot}Et_2O$ were purchased from Sinopharm Chemical Reagent Co. Ltd. (Shanghai, China) and used without further treatment.

The reaction of *m*-CPBA with PhI in the presence of HOAc

m-CPBA (235 mg, 3 equiv), PhI (6 μL, 0.1 equiv) and HOAc (2 mL) were added together with stirring.

Iodobenzene-catalyzed α-acetoxylation reaction of acetophenone

m-CPBA (235 mg, 3 equiv) and HOAc (2 mL) were placed in a dry Schlenk flask with stirring, then water (90 μL, 5 equiv), acetophenone (50 μL, 1 equiv), PhI (6 μL, 0.1 equiv) and $BF_3{\cdot}Et_2O$ (0.15 mL, 3 equiv) were added. These reactions were carried out at room temperature.[19]

Mass spectrometry

The ESI-MS and subsequent MS/MS experiments were performed on a Finnigan TSQ Quantum Access™ triple-quadrupole mass spectrometer (Thermo Scientific, San Jose, CA, USA) equipped with a standard ESI ion source. Nitrogen was used as the sheath gas and auxiliary gas, and argon as the collision gas. The basic ESI conditions were: vacuum, 2.8×10^{-6} Torr; spray voltage, 3000 V; capillary temperature, 270°C; sheath gas pressure, 20 arbitrary units; auxiliary gas pressure, 5 arbitrary units; while the selected collision energy depended on the dissociation capability of the precursor ion. Data acquisition and analysis were carried out with the Xcalibur software package (version 2.0, Thermo Scientific).

Study of reactions by ESI-MS/(MS)

A volume of 2 μL of the reaction solution at a certain reaction time was diluted with 98 μL of acetonitrile, and the diluted reaction solutions was injected into the ESI source at a flow rate of 10 μL/min.

RESULTS AND DISCUSSION

ESI-MS/(MS) study of the reaction of *m*-CPBA with PhI in HOAc

Acetonitrile was selected as the solvent for diluting the highly concentrated reaction solution in the ESI-MS/(MS) studies as it is not easily oxidized by trivalent iodine compounds.[13,27,28] In order to verify whether trivalent iodine compounds, such as DIB **2**, were generated by the oxidation of a catalytic amount of PhI with *m*-CPBA, *m*-CPBA and PhI (2:1 equivalent) in acetic acid were mixed. Signals were detected of the trivalent iodine-containing ions: $PhIOH^+$ at *m/z* 221, $[\mathbf{2}–OAc]^+$ at *m/z* 263 and $PhIOOC(m\text{-}ClC_6H_4)^+$ at *m/z* 359 in the acetonitrile-diluted reaction solution of PhI with *m*-CPBA and acetic acid (Fig. 1).

The first important intermediate **2** was detected as $[\mathbf{2}–OAc]^+$ at *m/z* 263. In the MS/MS process, $[\mathbf{2}–OAc]^+$ at *m/z* 263 gave two main product ions: $PhI^{\bullet+}$ at *m/z* 204 by loss of an $\cdot OCOCH_3$ radical and Ph^+ at *m/z* 77 by neutral loss of $IOCOCH_3$ (Fig. 2 and Scheme 3). This information showed that the initiating step of the catalytic reaction was the oxidation of a catalytic amount of PhI(I) to $PhI(OAc)_2$(III) **2** by *m*-CPBA in acetic acid (Scheme 2).

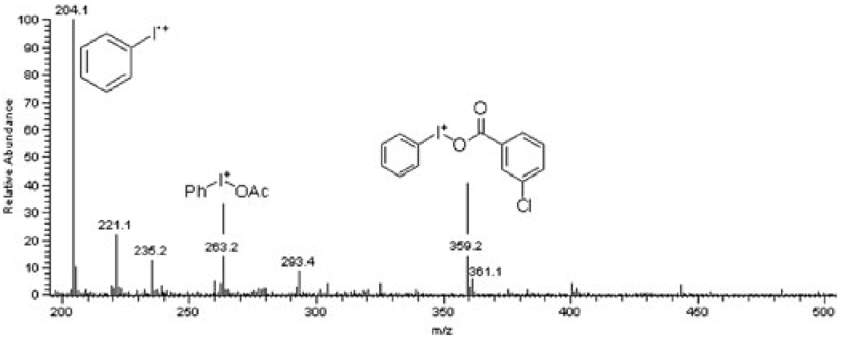


Figure 1. ESI-MS spectrum of the products of the reaction of *m*-CPBA with PhI in HOAc.

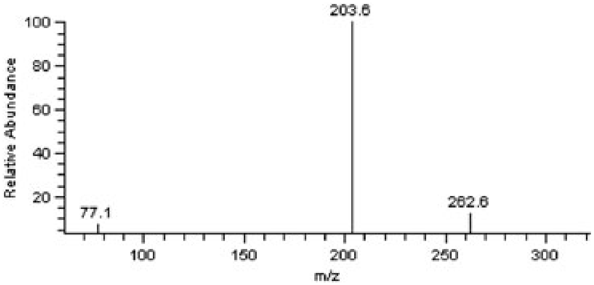
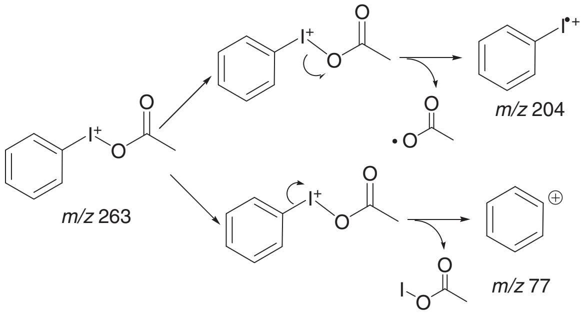


Figure 2. ESI-MS/MS spectrum of [**2**–OAc]$^+$ at *m/z* 263 with a collision energy (in the lab frame) of 10 eV.



Scheme 3. The proposed dissociation pathways of [**2**–OAc]$^+$ at *m/z* 263.

ESI-MS/(MS) study of the iodobenzene-catalyzed α-acetoxylation reaction of acetophenone

The solution of PhI-catalyzed α-acetoxylation reaction was then monitored by ESI-MS/(MS) and a signal was found of protonated α-λ^3-iodine alkyl acetophenone **3**·H$^+$ at *m/z* 383 together with signals of other trivalent iodines: [**2**–OAc]$^+$ at *m/z* 263 and PhIOOC(*m*-ClC_6H_4)$^+$ at *m/z* 359. The ESI-MS spectrum of the reaction solution at a reaction time of 10 min is shown in Fig. 3. MS/MS of the **3**·H$^+$ ion at *m/z* 383 was performed to assign its structure and probe its gas-phase reactivity (Fig. 4), and this showed that **3**·H$^+$ could easily dissociate even without applying extra collision energy (Fig. 4(a)). The proposed structure of **3**·H$^+$ at *m/z* 383 is shown in Scheme 4 as a six-membered ring hydrogen-bonding complex with a proton connecting the O atom of the OAc$^-$ group and the O atom of CO-Ph. The proposed fragmentation pathways of **3**·H$^+$ at *m/z* 383 are shown in Scheme 4.

When the collision energy was 0 eV, the main dissociation pathway of **3**·H$^+$ was the initiation by the OAc$^-$ moiety of a gas-phase intramolecular S_N2 substitution reaction to the corresponding protonated α-acetoxy acetophenone **4**·H$^+$ at *m/z* 179 by reductive elimination of a molecule of PhI (Fig. 4(a)). The formation of **4**·H$^+$ at *m/z* 179 from **3**·H$^+$ at *m/z* 383 might proceed via a five-membered ring transition state (Scheme 4). Interestingly, the gas-phase chemistries of **3**·H$^+$ at *m/z* 383 were consistent with the proposed solution-phase reactivity of α-λ^3-iodine alkyl acetophenone **3**, which could further undergo an intramolecular S_N2 substitution reaction

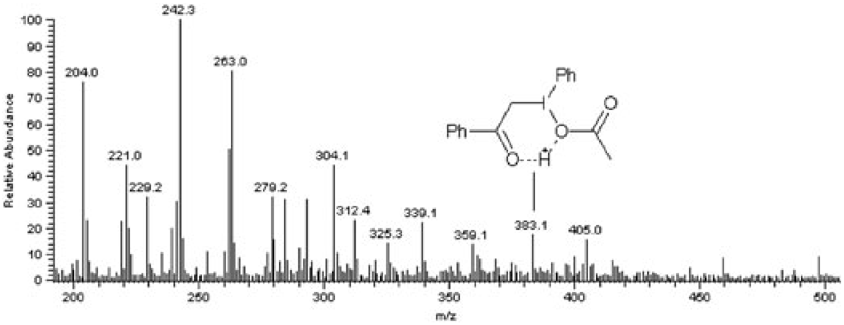


Figure 3. ESI-MS spectrum of the products of the iodobenzene-catalyzed α-acetoxylation reaction of acetophenone.

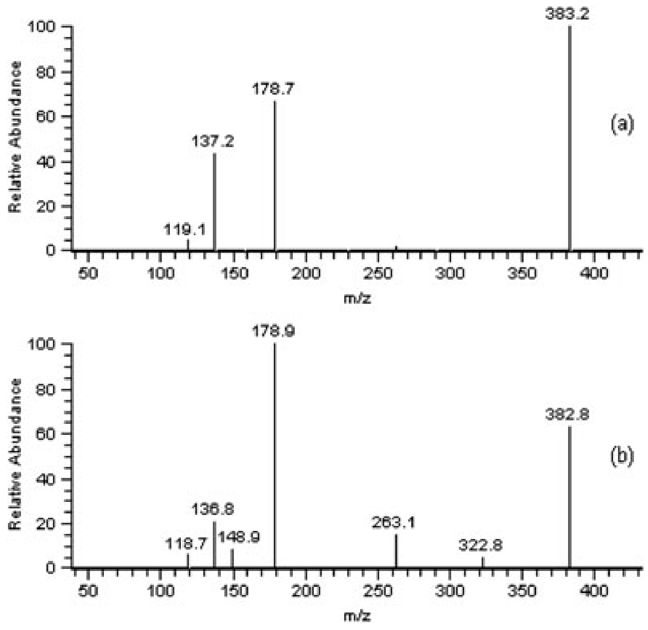
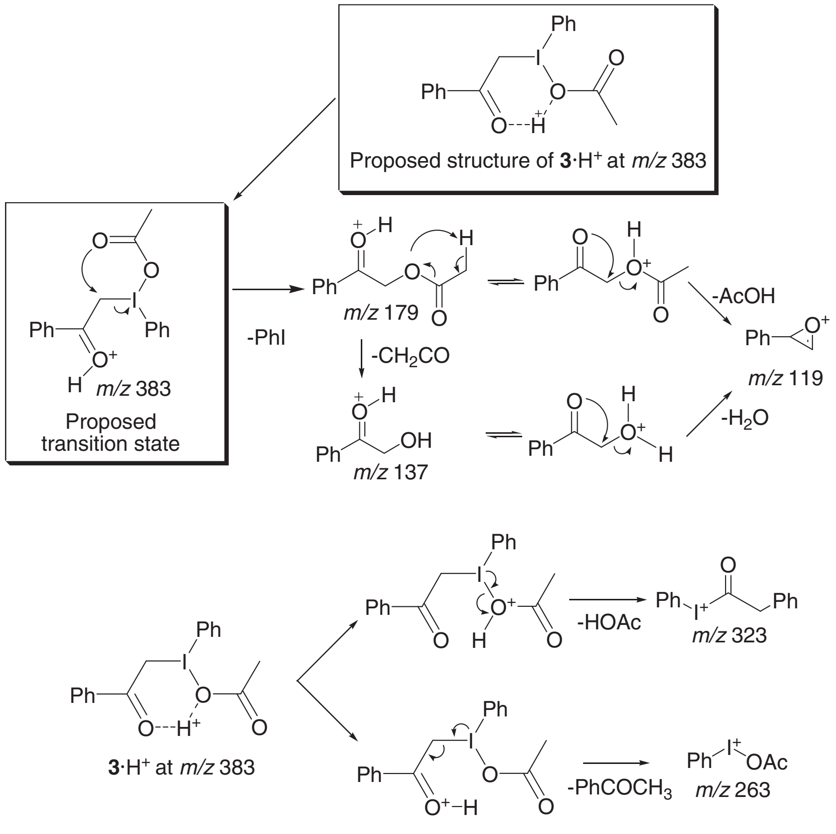


Figure 4. ESI-MS/MS spectra of protonated α-λ^3-iodine alkyl acetophenone, **3**·H$^+$ at *m/z* 383, with collision energies (in the lab frame) of: (a) 0 eV and (b) 5 eV.

to α-acetoxy acetophenone by loss of PhI.[19] The other product ion of **3**·H$^+$ at *m/z* 137 was generated by loss of CH_2CO (ketene) from **4**·H$^+$ at *m/z* 179. The ion at *m/z* 119 could be formed by loss of H_2O from *m/z* 137 or by direct loss of AcOH from **4**·H$^+$ at *m/z* 179 (Scheme 4). When the higher collision energy of 5 eV was applied, the **3**·H$^+$ ion yielded other two product ions (Fig. 4(b)): [**2**–OAc]$^+$ at *m/z* 263 and an ion at *m/z* 323. The [**2**–OAc]$^+$ ion at *m/z* 263 could originated from **3**·H$^+$ by the retro-formation of α-λ^3-iodine alkyl acetophenone **3**·H$^{+[19]}$ by the coupling of acetophenone with [**2**–OAc]$^+$ at *m/z* 263 (Schemes 2 and 4). The product ion at *m/z* 323 was formed by neutral loss of HOAc from **3**·H$^+$ (Scheme 4).

CONCLUSIONS

The direct interception and unambiguous characterization by ESI-MS/(MS) of the reactive α-λ^3-iodine alkyl acetophenone intermediate in the catalytic cycle of the PhI-catalyzed α-acetoxylation reaction provided valuable evidence for the existence of these reactive species in solution and enabled the reaction mechanism to be elucidated. Interestingly, the MS/MS results revealed that the intrinsic gas-phase reactivity of **3**·H$^+$ at *m/z* 383 is essential in the product-formation step to the protonated α-acetoxy acetophenone **4**·H$^+$ at 179. This occurred by the reductive elimination of PhI via an intramolecular five-membered-ring transition state, which was consistent with the proposed reactivity of the α-λ^3-iodine alkyl acetophenone intermediate **3**. The information generated from this study confirmed the reaction mechanism proposed by Ochiai and co-workers.[19] Moreover, our results demonstrate two important driving forces in such a reaction: (1) PhI is a good leaving group and



Scheme 4. The proposed structure and the dissociation pathways of protonated α-λ^3-iodine alkyl acetophenone **3**·H$^+$.

the reductive elimination of PhI from the α-λ^3-iodine alkyl acetophenone intermediate was the key step in the catalytic cycle of λ^3-iodines(III)/PhI(I); (2) the facile regeneration of λ^3-iodine(III) compounds, such as **2**, was achieved by oxidation of a catalytic amount of PhI(I) with *m*-CPBA co-oxidant in acetic acid.

Acknowledgements

The authors acknowledge financial support from the SRF for ROCS of SEM, NSFC (20875097, 20902104, 21072215, 21172250), Innovation Method Fund of China (2010IM030900) and CAS (YZ200938, YG2010056).

REFERENCES

[1] Y. H. Yang, F. Diederich, J. S. Valentine. Lewis acidic catalysts for olefin epoxidation by iodosylbenzene. *J. Am. Chem. Soc.* **1991**, *113*, 7195.

[2] P. J. Stang, V. V. Zhdankin. Organic polyvalent iodine compounds. *Chem. Rev.* **1996**, *96*, 1123.

[3] E. D. Matveeva, M. V. Proskurnina, N. S. Zefirov. Polyvalent iodine in organic chemistry: Recent developments, 2002–2005. *Heteroatom Chem.* **2006**, *17*, 595.

[4] V. V. Zhdankin, P. J. Stang. Chemistry of polyvalent iodine. *Chem. Rev.* **2008**, *108*, 5299.

[5] T. Dohi. Development of environmentally benign oxidations using hypervalent iodine (III) reagents. *Yakugaku Zasshi-J. Pharm. Soc. Jpn.* **2006**, *126*, 757.

[6] T. Dohi, Y. Kita. Hypervalent iodine reagents as a new entrance to organocatalysts. *Chem. Commun.* **2009**, 2073.

[7] A. Varvoglis. Polyvalent iodine compounds in organic synthesis. *Synthesis* **1984**, 709.

[8] L. F. Silva Jr. Hypervalent iodine-mediated ring contraction reactions. *Molecules* **2006**, *11*, 421.

[9] Z. Li, Z. H. Tang, X. X. Hu, C. G. Xia. Insight into the mechanism of oxidative kinetic resolution of racemic secondary alcohols by using manganese(III) (salen) complexes as catalysts. *Chem. Eur. J.* **2005**, *11*, 1210.

[10] J. W. Sam, X. J. Tang, R. S. Magliozzo, J. Peisach. Electrospray mass spectrometry of iron bleomycin II: Investigation of the reaction of Fe(III)-bleomycin with iodosylbenzene. *J. Am. Chem. Soc.* **1995**, *117*, 1012.

[11] H. W. Richter, B. R. Cherry, T. D. Zook, G. F. Koser. Characterization of species present in aqueous solutions of [hydroxy(mesyloxy)iodo]benzene and [hydroxy(tosyloxy)iodo]benzene. *J. Am. Chem. Soc.* **1997**, *119*, 9614.

[12] L. F. Silva Jr, N. P. Lopes. A study on the species present in solutions of hypervalent iodine(III) reagents by electrospray ionization mass spectrometry. *Tetrahedron Lett.* **2005**, *46*, 6023.

[13] L. F. Silva Jr, R. S. Vasconcelos, N. P. Lopes. Application of high-resolution electrospray mass spectrometry for the elucidation of the disproportionation reaction of iodobenzene diacetate. *Int. J. Mass Spectrom.* **2008**, *276*, 24.

[14] R. D. Richardson, T. Wirth. Hypervalent iodine goes catalytic. *Angew. Chem. Int. Ed.* **2006**, *45*, 4402.

[15] V. V. Zhdankin. Hypervalent iodine(III) reagents in organic synthesis. *Arkivoc* **2009**, *i*, 1.

[16] T. Wirth. Hypervalent iodine chemistry in synthesis: Scope and new directions. *Angew. Chem. Int. Ed.* **2005**, *44*, 3656.

[17] T. Dohi, A. Maruyama, M. Yoshimura, K. Morimoto, H. Tohma, M. Shiro, Y. Kita. A unique site-selective reaction of ketones with new recyclable hypervalent iodine (III) reagents based on a tetraphenylmethane structure. *Chem. Commun.* **2005**, 2205.

[18] C. L. Hill. Homogeneous catalysis-controlled green oxidation. *Nature* **1999**, *401*, 436.

[19] M. Ochiai, Y. Takeuchi, T. Katayama, T. Sueda, K. Miyamoto. Iodobenzene-catalyzed alpha-acetoxylation of ketones. In situ generation of hypervalent (diacyloxyiodo)benzenes using m-chloroperbenzoic acid. *J. Am. Chem. Soc.* **2005**, *127*, 12244.

[20] T. Dohi, A. Maruyama, M. Yoshimura, K. Morimoto, H. Tohma, Y. Kita. Versatile hypervalent-iodine(III)-catalyzed oxidations with *m*-chloroperbenzoic acid as a cooxidant. *Angew. Chem. Int. Ed.* **2005**, *44*, 6193.

[21] M. N. Eberlin. Electrospray ionization mass spectrometry: a major tool to investigate reaction mechanisms in both solution and the gas phase. *Eur. J. Mass Spectrom.* **2007**, *13*, 19.

[22] L. S. Santos. Online mechanistic investigations of catalyzed reactions by electrospray ionization mass spectrometry: A tool to intercept transient species in solution. *Eur. J. Org. Chem.* **2008**, *2*, 235.

[23] L. S. Santos. *Reactive Intermediates: MS Investigations in Solution*. Wiley-VCH, Weinheim, **2010**.

[24] H. Y. Wang, J. O. Metzger. ESI-MS study on first-generation ruthenium olefin metathesis catalysts in solution: Direct detection of the catalytically active 14-electron ruthenium intermediate. *Organometallics* **2008**, *27*, 2761.

[25] H. Y. Wang, W. L. Yim, T. Klüner, J. O. Metzger. ESIMS studies and calculations on alkali-metal adduct ions of ruthenium olefin metathesis catalysts and their catalytic activity in metathesis reactions. *Chem. Eur. J.* **2009**, *15*, 10948.

[26] Z. X. Zhao, H. Y. Wang, Y. L. Guo. ESI-MS study on transient intermediates in the fast cyclopropenium-activated chlorination reaction of alcohols. *J. Mass Spectrom.* **2011**, *46*, 856.

[27] H. Tohma, S. Takizawa, T. Maegawa, Y. Kita. Facile and clean oxidation of alcohols in water using hypervalent iodine(III) reagents. *Angew. Chem. Int. Ed.* **2000**, *39*, 1306.

[28] H. Tohma, Y. Kita. Hypervalent iodine reagents for the oxidation of alcohols and their application to complex molecule synthesis. *Adv. Synth. Catal.* **2004**, *346*, 111.