



有机化学反应中间体的质谱分析

王昊阳, 郭寅龙*

上海质谱中心; 中国科学院上海有机化学研究所, 上海 200032

*通讯作者, E-mail: ylguo@sioc.ac.cn

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摘要 有机化学反应中活性中间体的性质各异, 对反应中间体的表征和研究对于阐明和确证反应机理、优化反应条件、筛选催化剂和发现新类型反应至关重要. 近年来, 质谱技术和在线微量采样技术的发展, 极大程度地拓展了质谱学在该领域的应用. 本文总结了近年来本领域发展的新策略、技术和方法, 以及有机质谱技术在反应中间体研究中的应用.

关键词
质谱学
有机化学反应
反应中间体
反应机理

1 引言

20 世纪 80 年代, 发展了电喷雾离子化质谱法(electrospray ionization mass spectrometry, ESI-MS)^[1]和基质辅助激光解吸离子化质谱法(matrix-assisted laser desorption/ionization mass spectrometry, MALDI-MS)^[2, 3], 这两种革命性软离子化技术使得化学家能够对化学反应的溶液进行直接分析, 检测、表征和研究反应中的活性反应中间体, 甚至在表征无机复合物、有机金属化合物和催化剂方面也取得了很大成功^[4]. 反应中间体(或瞬态活性反应中间体)是化学反应中一系列基元反应的产物, 对应于反应势能图中过渡态间相对稳定的物种, 一般活性很高、寿命短、不稳定、难以分离^[5]. 本课题组^[6-9]较早时期便采用电喷雾串联质谱技术开展了多种类型有机化学反应中活泼瞬态中间体的质谱学研究, 如 Pd(0)催化的联烯与有机硼酸加成反应^[6]、Pd(0)催化联烯参与的三组分偶联环化反应^[7]、BINOL/Ti 催化的 4,4'-二甲基-3,5,8-三氧双环[5.1.0]辛烷的不对称环氧开环反应^[8]和铱催化的氢化反应^[9].

近年来, 质谱学的快速发展使得质谱技术在有机化学研究中有了一系列新的应用, 包括在线监测反应并从催化反应溶液中捕获和表征瞬态活性中间

体/复合物、基于质谱学技术的催化剂筛选方法和策略, 气相与液相反应的相关性研究, 以及气相人名反应的研究. 有机化学的发展和研究的深入, 对质谱学研究瞬态活性反应中间体的手段和技术也提出了更高的要求和挑战. 本文总结了近年来有机化学反应中间体质谱分析的一些阶段性成果, 以及有机质谱学在有机化学研究中新的应用.

2 质谱分析反应中间体的新技术和策略

2.1 在线瞬时监测技术与质谱联用

间隔取样 ESI-MS 分析法在研究快速有机反应体系的历程与机理中存在极大的局限性, 因此, 有必要发展在线反应控制技术和微量溶液采样手段^[4], 如微反应器-质谱联用和惰性气体低压进样等, 来解决在这些研究中所遇到的难题^[10]. 微型反应器装置由两个独立的注射器将两种反应溶液由毛细管注入一个三通阀, 该装置能有效地将反应时间控制在 0.1~100 s 区间内, 为捕获和研究活性中间体提供了快速且稳定的时间窗口(图 1). 再帕尔课题组^[11]结合冷喷雾质谱技术, 更大程度地检测瞬态活性中间体物种. 二氯二苯基环丙烯与醇的氯代反应速度极快, 在 1~5 min

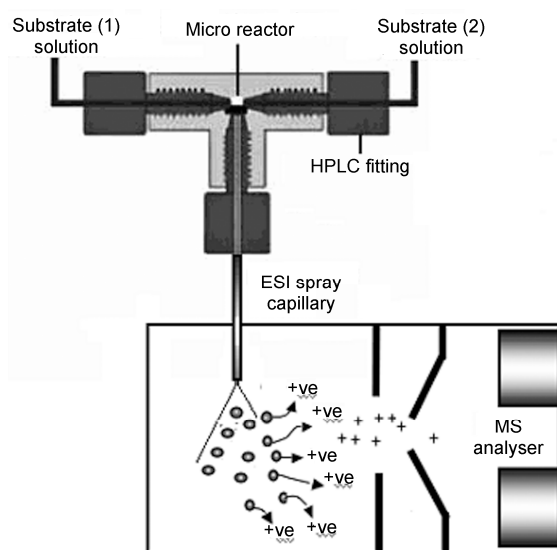


图1 微反应器-电喷雾质谱联用技术示意图

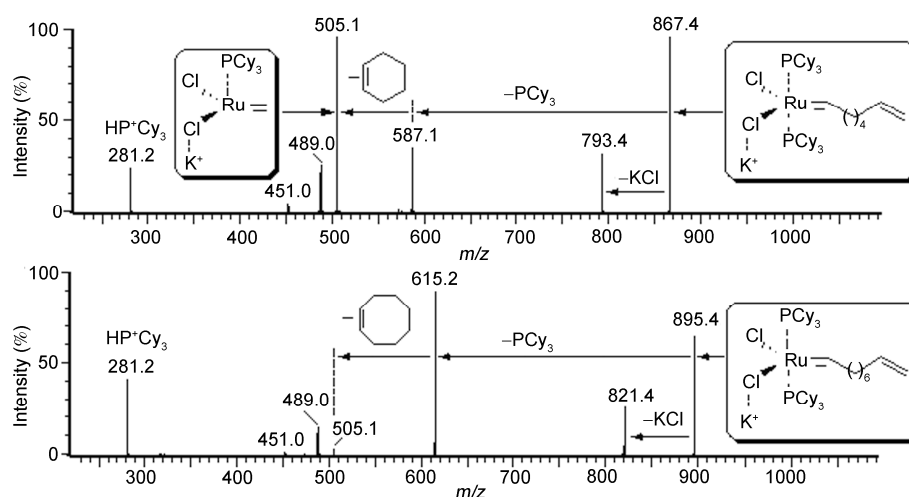
内即可以接近定量的产率完成. 本课题组^[12]利用微反应器监测技术成功捕获到关键的瞬态活性中间体: 氯环丙烯正离子和苄基环丙烯酮正离子. 与微反应器相比, 陈焕文课题组^[13]发展的反应性萃取电喷雾(EESI)技术能提供更短的混合时间. 该技术被用于研究单电子转移引发的茴香脑二聚反应中开环自由基电荷异位中间体离子^[14], 以及吩噻嗪自由基阳离子与脂肪醇、苯酚和苯在常温常压下的反应^[15].

2.2 电荷标记手段

多数情况下, 反应中间体是中性物种, 含量较低

而且难于离子化, 有时离子化过程会破坏其结构和活性. 为解决这一难题, 可以采用电荷标记手段. 电荷标记可以分为永久标记和在线电荷标记. 永久标记是通过化学反应在底物或催化剂的非活性区域上引入电荷标签(如季铵阳离子中心或磺酸阴离子中心); 在线标记是利用中间体的特性临时加入选择性离子化试剂, 实现中性物种的检测, 如碱金属离子化. 电荷标签技术不影响反应的正常进行, 同时能大大提高微量中性活泼中间体的质谱检测效率. Metzger等^[16]用电荷标记的膦配体, 首次运用质谱方法从反应溶液中检测到了亚甲基 Ru 卡宾中间体. 随后, Metzger等^[17]运用碱金属离子与催化剂形成加合离子来追踪溶液中钌卡宾物种的变化, 成功检测到了 1,7-辛二烯和 1,9-癸二烯的关环复分解(ring-closing metathesis, RCM)反应中含有末端双键的钌卡宾中间体. 该两个中间体在气相中首先脱除膦配体(PCy₃)后再发生气相 RCM 反应分别丢失环己烯和环辛烯(图 2). 该研究还表明, 气相条件下六元环化 RCM 反应的活性远远高于八元环化, 与液相中 RCM 反应活性顺序一致.

催化反应中典型的活性反应中间体应体现该催化反应的趋势性, 即该活性中间体在串联质谱过程中所发生的单分子反应或其在气相离子-分子反应中体现该中间体离子特有的反应活性. 质谱学研究活泼中间体可以有三点依据: 离子质荷比、离子同位素丰度和中间体离子的特征气相反应活性. 近期, 本课题组^[18, 19]运用碱金属离子化策略和微反应器技术研

图2 末端双键的钌卡宾活性反应中间体的气相关环复分解(RCM)反应^[17]

究了氮杂钨卡宾催化剂, 以及乙腈促进的 Grubbs 催化剂的降解反应. 同时, 本课题组^[20]发现, 采用硫作为基质, 可以用 MALDI-TOFMS 技术表征 Grubbs 催化剂.

2.3 准对映体策略

质量标签策略是质谱学研究气相反应途径和机理的传统手段, 也是质谱学表征和研究反应中间体的常用手段. 手性异构体化合物的分子量相同, 因此直接质谱分析难以区分. Pfaltz 课题组^[21]将传统的质量标签策略发展成准对映体(quasienantiomers, QAS)标记策略, 在远离反应位点的地方用同位素标记或差异较小的取代基标记手性异构体. 准对映体标记让原本分子量相同的手性异构体有了质量差异, 可在质谱分析中直接进行辨别, 也可实现手性催化剂的筛选和反应立体选择性的评价^[22]. 此外, 该课题组^[23]通过 ESI-MS 方法检测烯丙基酯动力学拆分反应中的活性中间体, 而不是前体或产物的新方法筛选不对称催化剂. 这些技术和方法使得质谱学为不对称催化系统的对映选择性研究提供了关键的证据, 甚至实现了手性催化剂的筛选.

3 质谱分析有机反应中间体的典型案例

Metzger^[24]、Eberlin^[25]和本课题组^[26]均发表过关于质谱学研究反应机理的综述, 本文主要对最新研究进展进行小结.

3.1 以 Pd 为代表的过渡金属催化反应

1994 年, Canary 等^[27]首次运用 ESI-MS 方法研究 Pd(0)催化的芳基硼酸与溴代吡啶偶联反应, 为机理的研究提供了宝贵的证据, 该工作为质谱表征反应活泼中间体以及反应机理的研究奠定了基础. 本课题组^[28, 29]利用电喷雾质谱法研究了三氟甲基取代烯炔醇环异构化反应和炔基磷酸胺的分子内环化反应. 轴手性产物的 Suzuki 偶联反应在不对称催化研究中具有重要的意义和创新性, 对这一过程进行质谱学研究也具有很大的挑战性. 此外, 我们还采用 ESI-MS/MS 技术对手性双烯氯化钯催化的不对称 Suzuki 偶联反应进行了机理研究^[30], 根据 Pd 的同位素峰簇特征将反应相关的物种和其他物种按质荷比进行质量筛选, 成功地捕获到了目标 Suzuki 反应各阶段的

反应中间体.

目前, Pd(II)/Pd(IV)的催化循环体系是有机化学中新兴的研究领域, 这类高价金属复合物是发生 C-H 键活化和三氟甲基化的重要活性中间体. 本课题组与刘国生课题组^[31~33]合作, 研究了一系列 Pd(IV)催化的有机化学反应, 如钯催化的苯乙烯分子内氨基氟化反应^[31]、钯催化的烯烃的氧化芳基烷基化反应^[32]和钯催化的苯乙烯的氟酯化反应^[33]. 本课题组^[34]近期研究表明, Pd(IV)反应中间体在 MS/MS 条件下, 能发生气相还原偶联反应, 生成相应的偶联产物和 Pd(II)物种(图 3), 这与 Pd(IV)复合物的液相反应活性一致. 同时, 许毓课题组^[35]也报道了 Pd(IV)复合物的相关质谱学研究结果. 由于 ESI-MS 技术能捕获催化循环中的关键反应中间体, 被 Chen^[36]和 Irth^[37]证实是高通量筛选催化剂的一种极具价值的研究工具.

3.2 自由基中间体

中性自由基反应中间体不易被 ESI-MS 检测, Metzger 等^[38]曾利用微反应器-电喷雾质谱联用技术捕获到了单电子转移引发的反式茴香脑二聚反应中的自由基阳离子中间体. 在一些自由基反应中, 一般需 Lewis 酸进行催化, 同时金属 Lewis 酸可与底物或自由基中间体形成复合物, 被质谱检测^[39]. 本课题组^[40, 41]运用 ESI-MS 研究了 Selectfluor 参与的亲电氟化反应和醛的 α -氟化反应, 成功捕捉到了亲电氟化反应过程中的自由基阳离子中间体. 通过向反应体系中加入自由基捕获剂(如 Tempo 和 Dempo 等)^[42], 用质谱捕捉到了自由基捕获剂与反应中的自由基阳离子中间体形成的复合物, 证明了在所选底物的亲电氟化反应过程中确实存在单电子转移过程.

3.3 高价碘复合物参与和催化的反应

本课题组^[43]于 2012 年对 PhI 催化芳基酮 α -乙酰

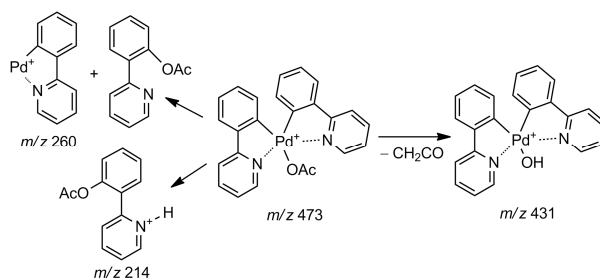


图 3 Pd(IV)反应中间体的气相分子内偶联反应

氧基化反应进行了研究, 捕获了反应中目前未能分离或用其他手段未能直接分析的重要中间体: α - λ^3 -碘烷基酮复合物. 进一步研究质子化的该复合物在串联质谱中的气相裂解行为表明, 最后一步产物的生成经历了分子内五元环过渡态的还原消除过程比分子间 SN2 反应过程更合理. 此外, 我们^[44]还运用质谱法研究了三氟甲基苯基碘鎓阳离子($\text{CF}_3\text{I}^+\text{Ph}$), 发现 PhI^+CF_3 能发生气相分子内三氟甲基迁移反应并脱除碘原子生成 $\text{PhCF}_3^{+\cdot}$, 而 $\text{PhCF}_3^{+\cdot}$ 可进一步丢失 CF_2 生成 $\text{PhF}^{+\cdot}$ (图 4), 该反应能很好地体现高价碘氟化试剂的本质反应活性. 随后, 本课题组^[45]又研究了多氟取代碘苯自由基阳离子, 发现其在气相中特殊的 CF_2 丢失反应, 这体现了多氟取代引发的新型芳环裂解反应.

3.4 气相与液相人名反应相关性的研究

著名质谱学家 Beynon 曾将现代化的有机质谱仪形容为一个“化学实验室”^[46]. 质谱中离子所发生的重排/碎裂方式与化合物的离子形态在液相中相应条件下的反应有一定相似性^[47, 48], 甚至可以“预测”研

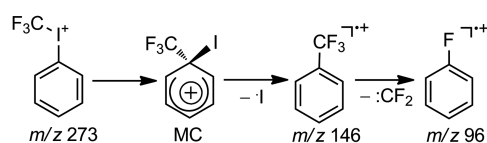


图 4 PhI^+CF_3 的气相分子内三氟甲基迁移反应

究对象在溶液中的化学反应途径. 目前, 气相中的人名反应除麦式重排和逆 Diels-Alder 反应外, 一直鲜有报道. 本课题组^[49-55]系统地研究了嘧啶氧基-*N*-芳基苄胺类除草剂丰富的气相化学反应, 如嘧啶氮引发的苄基迁移反应^[49]、质子酸促进的气相 Smiles 重排反应^[50]、Lewis 酸促进的气相 Smiles 重排反应^[51, 52]、对氨基磺酰基阳离子的重排反应^[53, 54]和芳环的逆-Michael 反应^[55]. 在此基础上, 本课题组^[56]研究发现了类似的溶液相反应, 对研究该类除草剂的代谢及降解途径和环境行为有重要的意义. 2010 年, 本课题组^[57]利用 Favorskii 重排反应顺利实现对该类具有高度环张力的活泼芳香性小环类化合物的气相合成, 还发现了 *N*-苯基甲基丙烯酸酰胺质子化后独特的气相 *N*-Claisen 重排反应^[58]. 潘远江课题组在本领域也做出了很多出色的工作, 如新型的气相 Smiles 重排反应^[59, 60]、逆-Michael 反应^[61]、质子迁移诱导解离^[62]和银离子催化的气相 Diels-Alder 反应^[63]等.

4 结论与展望

现代质谱学为有机反应中间体和反应机理的研究打开了一扇窗. 目前, 有机质谱学的发展应与解决有机化学的核心科学问题相结合, 建立有机化学各种复杂过程中间体研究的方法, 为反应机理研究提供支持. 当代新型质谱分析技术和方法不断涌现, 将大大提升质谱分析在解决相关有机化学问题的能力.

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参考文献

- 1 Fenn JB, Mann M, Meng CK, Wong SF, Whitehouse CM. Electrospray ionization for mass-spectrometry of large biomolecules. *Science*, 1989, 246: 64-71
- 2 Tanaka K, Waki H, Ido Y, Akita S, Yoshida Y, Yohida T, Matsuo T. Protein and polymer analyses up to m/z 100000 by laser ionization time-of-flight mass spectrometry. *Rapid Commun Mass Spectrom*, 1988, 2: 151-153
- 3 Karas M, Hillenkamp F. Laser desorption ionization of proteins with molecular masses exceeding 10000 daltons. *Anal Chem*, 1988, 60: 2299-2301
- 4 Wang HY, Zhao ZX, Guo YL. Chemical and biochemical applications of MALDI TOF-MS based on analyzing the small organic compounds. *Top Curr Chem*, 2013, 331: 165-192
- 5 Santos LS. *Reactive Intermediates: MS Investigations in Solution*. Weinheim: Wiley-VCH, 2009
- 6 Qian R, Guo H, Liao YX, Guo YL, Ma SM. Probing the mechanism of the palladium-catalyzed addition of organoboronic acids to allenes in the presence of AcOH by ESI-FTMS. *Angew Chem Int Ed*, 2005, 44: 4771-4774
- 7 Guo H, Qian R, Liao YX, Ma SM, Guo YL. ESI-MS studies on the mechanism of Pd(0)-catalyzed three-component tandem double addition-cyclization reaction. *J Am Chem Soc*, 2005, 127: 13060-13064

- 8 Bao HL, Zhou J, Wang Z, Guo YL, You TP, Ding KL. Insight into the mechanism of the asymmetric ring-opening aminolysis of 4,4-dimethyl-3,5,8-trioxabicyclo[5.1.0]octane catalyzed by titanium/BINOLate/water system: evidence for the $\text{Ti}(\text{BINOLate})_2$ -bearing active catalyst entities and the role of water. *J Am Chem Soc*, 2008, 130: 10116–10127
- 9 Wang DS, Zhou J, Wang DW, Guo YL, Zhou YG. Inhibiting deactivation of iridium catalysts with bulky substituents on coordination atoms. *Tetrahedron Lett*, 2010, 51: 525–528
- 10 Zhao ZX, Wang HY, Guo YL. Studies of heterogeneous/homogeneous ion-molecule reactions by ambient ionization mass spectrometry. *Curr Org Chem*, 2011, 15: 3734–3749
- 11 He JM, Abliz Z, Zhang RP, Liang YX, Ding KL. 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. *Anal Chem*, 2006, 78: 4737–4740
- 12 Zhao ZX, Wang HY, Guo YL. ESI-MS study on transient intermediates in the fast cyclopropenium-activated chlorination reaction of alcohols. *J Mass Spectrom*, 2011, 46: 856–858
- 13 Chen HW, Venter A, Cooks RG. Extractive electrospray ionization for direct analysis of undiluted urine, milk and other complex mixtures without sample preparation. *Chem Commun*, 2006: 2042–2044
- 14 Marquez CA, Wang HY, Fabbretti F, Metzger JO. Electron-transfer-catalyzed dimerization of trans-anethole: detection of the distonic tetramethylene radical cation intermediate by extractive electrospray ionization mass spectrometry. *J Am Chem Soc*, 2008, 130: 17208–17209
- 15 Yao SJ, Wang HY, Zhang L, Zhang J, Guo YL. Study on reactions of long-lived phenoxathiin radical cation with aliphatic alcohols, phenol and phenyl halides in ambient condition by fused-droplet electrospray ionization mass spectrometry. *Eur J Mass Spectrom*, 2011, 17: 385–394
- 16 Wang HY, Metzger JO. 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: 2761–2766
- 17 Wang HY, Yim WL, Klüner T, Metzger JO. 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: 10948–10959
- 18 Wang HY, Yim WL, Guo YL, Metzger JO. ESI-MS studies and calculations on second-generation Grubbs and Hoveyda-Grubbs ruthenium olefin metathesis catalysts. *Organometallics*, 2012, 31: 1627–1634
- 19 Zhao ZX, Wang HY, Guo YL. Studies on CH_3CN -assisted decomposition of 1(st) Grubbs catalyst by electrospray ionization tandem mass spectrometry. *Rapid Commun Mass Spectrom*, 2011, 25: 3401–3410
- 20 Zhu W, Wang HY, Guo YL. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry analyses of Grubbs catalysts and ferrocene derivatives using sulfur as matrix. *J Mass Spectrom*, 2012, 47: 352–354
- 21 Müller CA, Markert C, Teichert AM, Pfaltz A. Mass spectrometric screening of chiral catalysts and catalyst mixtures. *Chem Commun*, 2009: 1607–1618
- 22 赵志雄, 姚胜军, 王昊阳, 郭寅龙. 电喷雾质谱法研究不对称催化反应进展. 有机化学, 2010, 30: 809–815
- 23 Markert C, Pfaltz A. Screening of chiral catalysts and catalyst mixtures by mass spectrometric monitoring of catalytic intermediates. *Angew Chem Int Ed*, 2004, 43: 2498–2500
- 24 Santos LS, Knaack L, Metzger JO. Investigation of chemical reactions in solution using API-MS. *Int J Mass Spectrom*, 2005, 246: 84–104
- 25 Eberlin MN. Electrospray ionization mass spectrometry: a major tool to investigate reaction mechanisms in both solution and the gas phase. *Eur J Mass Spectrom*, 2007, 13: 19–28
- 26 张立, 钱荣, 张祥, 周静, 郭寅龙. 电喷雾质谱法在研究有机反应中间体方面的应用. 有机化学, 2008, 28: 372–380
- 27 Aliprantis AO, Canary JW. Observation of catalytic intermediates in the Suzuki reaction by electrospray mass-spectrometry. *J Am Chem Soc*, 1994, 116: 6985–6986
- 28 Qian R, Guo YL, Lu L. ESI-FTICRMS characterization of the intermediates in cycloisomerization of trifluoromethyl-substituted enynols through changing the protecting group of substrate. *Chin J Chem*, 2009, 27: 123–129
- 29 Zhou J, Tang W, Guo YL, Ding YX. Mechanistic insights into the palladium(II)-catalyzed intramolecular cyclization of *o*-alkynylphenylphosphonamide and *N*-(*o*-alkynylphenyl)acetamide by electrospray ionization mass spectrometry. *Chin J Chem*, 2009, 27: 1733–1740
- 30 He XS, Zhang SS, Guo YL, Wang HY, Lin GQ. Mechanistic investigations of a palladium-diene catalyzed Suzuki-Miyaura cross-coupling reaction. *Organometallics*, 2012, 31: 2945–2948
- 31 Qiu SF, Xu T, Zhou J, Guo YL, Liu GS. Palladium-catalyzed intermolecular aminofluorination of styrenes. *J Am Chem Soc*, 2010, 132: 2856–2857

- 32 Mu X, Wu T, Wang HY, Guo YL, Liu GS. Palladium-catalyzed oxidative aryltrifluoromethylation of activated alkenes at room temperature. *J Am Chem Soc*, 2012, 134: 878–881
- 33 Peng HH, Yuan ZL, Wang HY, Guo YL, Liu GS. Palladium-catalyzed intermolecular fluoroesterification of styrenes: exploration and mechanistic insight. *Chem Sci*, 2013, 4: 3172–3178
- 34 Zhu W, Wang HY, Peng HH, Liu GS, Guo YL. Study of the transient reactive Pd(IV) intermediate in the Pd(OAc)₂-catalyzed oxidative coupling reaction system by electrospray ionization tandem mass spectrometry. *Chin J Chem*, 2013, 31: 371–376
- 35 Guo LJ, Xu Y, Wang XJ, Liu WJ, Lu DP. Investigation of the mechanisms of palladium-catalyzed C–H acetoxylation and methoxylation by electrospray ionization mass spectrometry. *Organometallics*, 2013, 32: 3780–3783
- 36 Chen P. Electrospray ionization tandem mass spectrometry in high-throughput screening of homogeneous catalysts. *Angew Chem Int Ed*, 2003, 42: 2832–2847
- 37 Martha CT, Elders N, Krabbe JG, Kool J, Niessen WMA, Orru RVA, Irth H. Online screening of homogeneous catalyst performance using reaction detection mass spectrometry. *Anal Chem*, 2008, 80: 7121–7127
- 38 Fürmeier S, Metzger JO. Detection of transient radical cations in electron transfer-initiated Diels-Alder reactions by electrospray ionization mass spectrometry. *J Am Chem Soc*, 2004, 126: 14485–14492
- 39 Fürmeier S, Griep-Raming J, Hayen A, Metzger JO. Chelation-controlled radical chain reactions studied by electrospray ionization mass spectrometry. *Chem Eur J*, 2005, 11: 5545–5554
- 40 Zhang X, Liao YX, Qian R, Wang HY, Guo YL. Investigation of radical cation in electrophilic fluorination by ESI-MS. *Org Lett*, 2005, 7: 3877–3880
- 41 Zhang X, Guo YL. Electrospray ionization mass spectrometric study on the alpha-fluorination of aldehydes. *Rapid Commun Mass Spectrom*, 2006, 20: 3477–3480
- 42 Zhang X, Wang HY, Guo YL. Interception of the radicals produced in electrophilic fluorination with radical traps (Tempo, Dmpo) studied by electrospray ionization mass spectrometry. *Rapid Commun Mass Spectrom*, 2006, 20: 1877–1882
- 43 Wang HY, Zhou J, Guo YL. Study on the reactive transient a-λ³-iodanyl-acetophenone complex in the iodine(III)/PhI(I) catalytic cycle of iodobenzene-catalyzed a-acetoxylation reaction of acetophenone by electrospray ionization tandem mass spectrometry. *Rapid Commun Mass Spectrom*, 2012, 26: 616–620
- 44 Wang HY, Xiang Z, Liu GS, Guo YL. Study of the gas-phase intramolecular aryltrifluoromethylation of phenyl(trifluoromethyl)iodonium by ESI-MS/MS. *J Am Soc Mass Spectrom*, 2013, 24: 761–767
- 45 Wang HY, Gao Y, Zhang F, Yu CT, Xu C, Guo YL. Mass spectrometric study of the gas-phase difluorocarbene expulsion of polyfluorophenyl cations via F-atom migration. *J Am Soc Mass Spectrom*, 2013, 24: 1919–1926
- 46 Porter CJ, Beynon JH, Ast T. The modern mass-spectrometer: a complete chemical laboratory. *Org Mass Spectrom*, 1981, 16: 101–114
- 47 Eichinger PCH, Dua S, Bowie JH. A comparison of skeletal rearrangement reactions of even-electron anions in solution and in the gas-phase. *Int J Mass Spectrom*, 1994, 133: 1–12
- 48 Zhang JT, Wang HY, Zhu W, Guo YL. Mass spectrometry: insightful window for organic chemistry. *Org Chem Curr Res*. 2012, 1: 1000e116
- 49 Wang HY, Guo YL, Lu L. Studies of rearrangement reactions of protonated and lithium cationized 2-pyrimidinyl-oxy-*N*-arylbenzylamine derivatives by MALDI-FT-ICR mass spectrometry. *J Am Soc Mass Spectrom*, 2004, 15: 1820–1832
- 50 Wang HY, Zhang X, Guo YL, Tang QH, Lu L. Using tandem mass spectrometry to predict chemical transformations of 2-pyrimidinyl-oxy-*N*-arylbenzyl amine derivatives in solution. *J Am Soc Mass Spectrom*, 2006, 17: 253–263
- 51 Xu C, Wang HY, Zhu FJ, Guo YL, Lu L. Studies of gas-phase reactions of cationic iron complexes of 2-pyrimidinyl-oxy-*N*-arylbenzylamines by electrospray ionization tandem mass spectrometry. *Rapid Commun Mass Spectrom*, 2011, 25: 169–178
- 52 Wang HY, Xu C, Zhang L, Tang QH, Guo YL, Lu L. Investigation of coordination of Mg(II) cations to 2-pyrimidinyl-oxy-*N*-arylbenzylamines by electrospray mass spectrometry: insights for Mg(II) catalyzed Smiles rearrangement reactions. *Eur J Mass Spectrom*, 2011, 17: 145–157
- 53 Wang HY, Zhang X, Guo YL, Dong XC, Tang QH, Lu L. Sulfonamide bond cleavage in benzenesulfonamides and rearrangement of the resulting *p*-aminophenylsulfonyl cations: application to a 2-pyrimidinyl-oxybenzylaminobenzenesulfonamide herbicide. *Rapid Commun Mass Spectrom*, 2005, 19: 1696–1702
- 54 Wang HY, Zhang X, Qian R, Guo YL, Lu L. Gas-phase sulfonyl-sulfinate rearrangement of protonated 4,6-dimethoxy-2-(methylsulfonyl)pyrimidine. *Rapid Commun Mass Spectrom*, 2006, 20: 2773–2776
- 55 Wang HY, Zhang X, Guo YL, Lu L. Mass spectrometric studies of the gas phase retro-*Michael* type fragmentation reactions of 2-

- hydroxybenzyl-*N*-pyrimidinylamine derivatives. *J Am Soc Mass Spectrom*, 2005, 16: 1561–1573
- 56 Wang HY, Liao YX, Guo YL, Tang QH, Lu L. Interesting acid-catalyzed O-N-type Smiles rearrangement reactions of 2-pyrimidinyl-oxy-*N*-arylbenzylamine derivatives. *Synlett*, 2005: 1239–1242
- 57 Zhao ZX, Wang HY, Xu C, Guo YL. Gas-phase synthesis of hydrodiphenylcyclopropenylum via nonclassical Favorskii rearrangement from alkali-cationized α,α' -dibromodibenzyl ketone. *Rapid Commun Mass Spectrom*, 2010, 24: 2665–2672
- 58 Wang HY, Xu C, Zhu W, Liu GS, Guo YL. Gas phase decarbonylation and cyclization reactions of protonated *N*-methyl-*N*-phenylmethacrylamide and its derivatives via an amide Claisen rearrangement. *J Am Soc Mass Spectrom*, 2012, 23: 2149–2157
- 59 Zhou YP, Pan YJ, Cao XJ, Wu J, Jiang KZ. Gas-phase Smiles rearrangement reactions of deprotonated 2-(4,6-dimethoxypyrimidin-2-ylsulfanyl)-*N*-phenylbenzamide and its derivatives in electrospray ionization mass spectrometry. *J Am Soc Mass Spectrom*, 2007, 18: 1813–1820
- 60 Zhang J, Chai YF, Wang W, Shang W, Pan YJ. Gas-phase Smiles rearrangement of sulfonylurea herbicides in electrospray ionization mass spectrometry. *Chin J Chem*, 2012, 30: 2383–2388
- 61 Zhang J, Chai YF, Jiang KZ, Yang HM, Pan YJ, Sun CR. Gas phase retro-Michael reaction resulting from dissociative protonation: fragmentation of protonated warfarin in mass spectrometry. *J Mass Spectrom*, 2012, 47: 1059–1064
- 62 Guo C, Jiang KZ, Yue L, Xia ZM, Wang XX, Pan YJ. Intriguing roles of reactive intermediates in dissociation chemistry of *N*-phenylcinnamides. *Org Biomol Chem*, 2012, 10: 7070–7077
- 63 Sun HZ, Chai YF, Wang L, Jiang KZ, Pan YJ. Nazarov cyclization and oxo-Diels-Alder reaction of chalcones induced by the naked silver cation in gas phase. *Organometallics*, 2013, 32: 3385–3390

Intermediates in organic reactions by mass spectrometry

WANG HaoYang, GUO YinLong*

Shanghai Mass Spectrometry Center; Shanghai Institute of Organic Chemistry, Chinese Academy of Science, Shanghai 200032, China

*Corresponding author (email: ylguo@sioc.ac.cn)

Abstract: Different organic reactions contain reactive intermediates with diverse natures, the characterizations and studies of reaction intermediates are important for the elucidation and confirmation of the reaction mechanism, optimization of the reaction conditions, screening new types of catalysts and exploration of new organic reactions. In recent years, the developments of mass spectrometric techniques and online micro-sampling techniques promoted the applications of mass spectrometry in such research field. In this paper, we summarize the new strategies, technologies and methods developed recently and their applications in the study of reaction intermediates.

Keywords: mass spectrometry, organic chemical reaction, reaction intermediates, reaction mechanism