

The role of ionic liquids in co-catalysis of Baylis-Hillman reaction: Interception of supramolecular species via electrospray ionization mass spectrometry[†]

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ABSTRACT: The Baylis–Hillman reaction is a general and multifaceted method for C—C bond formation in organic synthesis. Using electrospray ionization mass spectrometry in both the positive and negative ion modes, we performed on-line monitoring of the reaction in the presence of imidazolium ionic liquids. Loosely bonded supramolecular species formed by coordination of neutral reagents, products and the protonated forms of zwitterionic Baylis–Hillman intermediates with cations and anions of ionic liquids were gently and efficiently transferred directly from the solution to the gas phase. Mass measurements and structural characterization of these unprecedented species via collision-induced dissociation in tandem mass spectrometry experiments were performed. The interception of several supramolecular species indicates that ionic liquids co-catalyze Baylis–Hillman reactions by activating the aldehyde toward nucleophilic enolate attack and by stabilizing the zwitterionic species that act as the main BH intermediates. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: Baylis-Hillman; ionic liquids; ESI-MS/MS; mechanism

The Baylis–Hillman (BH) reaction (Scheme 1)¹ is a useful and general σ C—C bond-forming reaction, providing a straightforward single-step synthetic method to form densely functionalized precursors (α -methylene- β -hydroxy derivatives) of a great variety of natural and non-natural products.² The BH mechanism³ is known to proceed by the conjugate reversible addition of a tertiary amine catalyst, usually diazabicyclo[2.2.2]octane (DABCO), to a Michael acceptor to produce an ammonium enolate intermediate (Scheme 1). The nucleophilic addition of this enolate intermediate to an aldehyde⁴ followed by successive intramolecular elimination gives the final BH adduct, an α -methylene- β -hydroxy-ester, regenerating the

tertiary amine catalyst.⁵ Some BH reactions are, however, too slow even in most favorable systems. Therefore, there is a continuous search for more efficient BH catalysts and optimal experimental conditions. Several nitrogen bases such as DABCO, quinuclidine and derivatives,⁶ HMTA (hexamethylenetetramine) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) are commonly used as efficient catalysts in BH, and other, reactions.⁷

The addition of inorganic salts has also been shown to accelerate BH reactions presumably by increasing the concentration of the intermediate enolates.⁸ Physical methods such as high pressure,⁹ microwaves,¹⁰ and ultrasound¹¹ have also been proposed as efficient ways to improve BH reaction rates. More recently, ionic liquids,¹² especially those based on the 1-*n*-butyl-3-methylimidazolium cation (BMI⁺), were found to accelerate BH reactions. Such a catalytic effect has been attributed to the inherent dual ionic-covalent nature of ionic liquids (IL) and the stabilization of the zwitterionic intermediates through different types of H-bonded supramolecular ion pairs, the so-called 'ionic liquid effect'.¹³ Owing to the relatively easy deprotonation of the imidazolium ring,¹⁴ formation of imidazolium-aldehyde adducts as by-products may eventually reduce the overall BH reaction yield,¹⁵ but this side reaction is avoided by using 2-methyl-1,3-dialkylimidazolium salts.¹⁶

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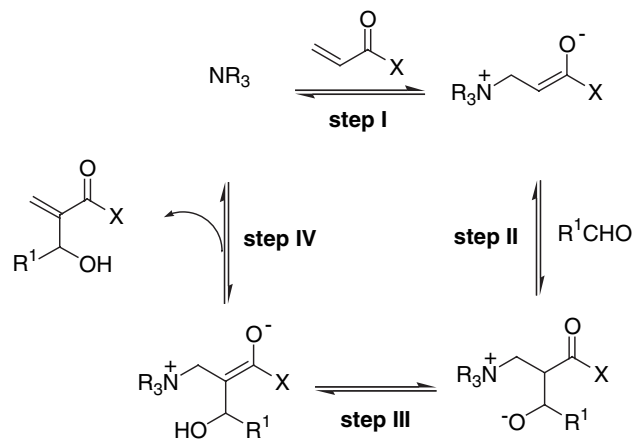
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Scheme 1. The catalytic cycle of the BH reaction

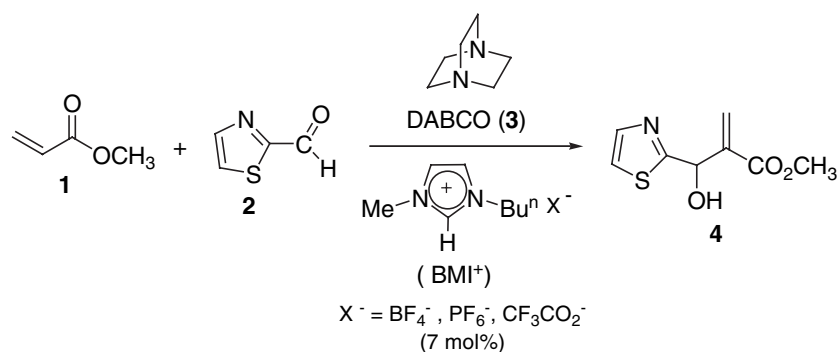
Electrospray ionization (ESI),¹⁷ a powerful ‘ion-fishing’,¹⁸ technique for mass spectrometry (MS) analysis, has been increasingly used in chemistry and biochemistry to probe reaction mechanisms¹⁹ and catalysis.²⁰ Recently,²¹ we used ESI-MS to investigate the BH mechanism in classical organic solvents, being able to intercept and characterize the protonated forms of its zwitterionic intermediates (Scheme 1). We have also demonstrated recently that ESI is able to transfer, gently and efficiently, small to large as well as singly to multiply charged loosely bonded ionic liquid supramolecules to the gas phase for MS detection and characterization.²²

In the reaction of acrylates with aldehydes catalyzed by DABCO (Scheme 2), the role of BMI.X ionic liquids in accelerating the reaction is likely to involve stabilization of the zwitterionic intermediates by supramolecular ion pairing via H-bonds. Therefore, ESI-MS could be used to monitor BH reactions co-catalyzed by ionic liquids in the search for the supramolecular species presumably responsible for the co-catalytic effect of ionic liquids. ESI-MS could allow the unprecedented interception of such supramolecular species in ionic forms by ‘fishing’ them directly from solution to the gas phase for MS analysis and MS/MS characterization. In this communication we report the first interception and characterization of the supramolecular species, which appears to be responsible for the co-catalytic role of ionic liquids in BH reactions.

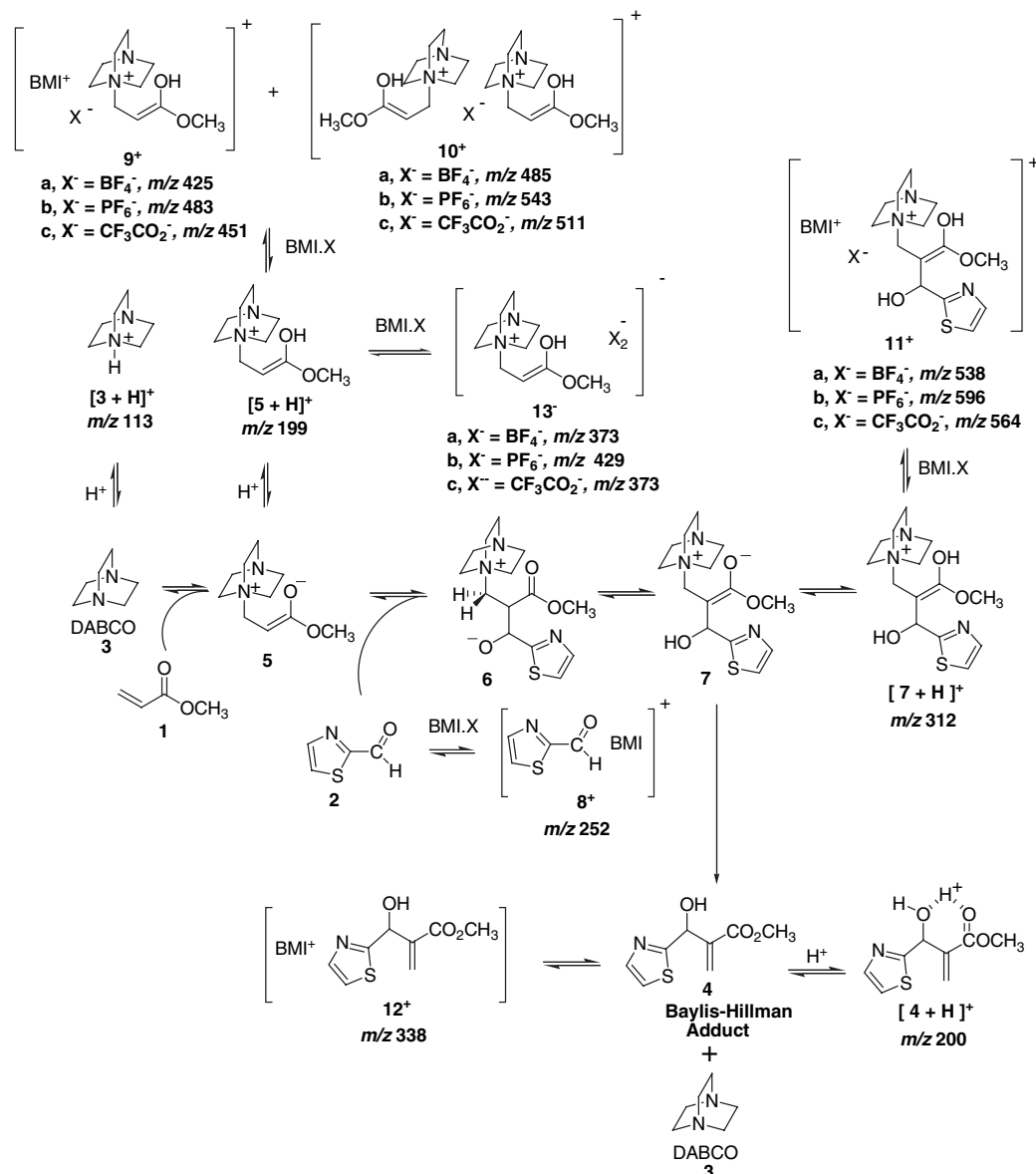
Our search began with the on-line monitoring by ESI-MS²³ of the reaction of 1 equivalent of methyl acrylate (1) with 1 equivalent of 2-thiazolecarboxaldehyde (2) catalyzed by 1 equivalent of DABCO (3) in acetonitrile in the presence of 7 mol % of BMI ionic liquids (Scheme 2).²⁴ The undiluted reaction mixture was directly infused to the ESI source operating in the positive ion mode, and cationic species were continuously screened via MS analysis.

A variety of cationic supramolecular species (Scheme 3) likely to be involved in the co-catalytic role of ionic liquids in BH reactions were intercepted by ESI-MS monitoring. As an example, Fig. 1 shows an ESI-MS ‘snapshot’ of the BH reaction co-catalyzed by BMI.PF₆ (Scheme 2) shortly after 1 min of mixing. Protonated forms of DABCO [**3** + H]⁺ of *m/z* 113 as well as of the major BH zwitterionic intermediates [**5** + H]⁺ of *m/z* 199 and [**7** + H]⁺ of *m/z* 312 and the final BH adduct [**4** + H]⁺ of *m/z* 200 are evident, and these species have already been detected and characterized in our previous work.²¹ In the presence of BMI.PF₆, however, additional supramolecular species directly related to BMI.PF₆ (Scheme 3) are also clearly detected: **8**⁺ of *m/z* 252, **9b**⁺ of *m/z* 483, **10b**⁺ of *m/z* 543, **11b**⁺ of *m/z* 596, and **12**⁺ of *m/z* 338, as well as BMI⁺ of *m/z* 139 and the [(BMI)₂.PF₆]⁺ singly charged supramolecule of *m/z* 423. The same BH species, as well as analog BH-BMI(X) supramolecular species, have also been ‘fished’ from the reaction media when using BMI.BF₄ and BMI.CF₃CO₂ as the co-catalysts.

Scheme 3 shows the ionic species with their respective *m/z* ratios which were gently transferred from solution to the gas phase by ESI operating either in the positive or negative ion mode. Each of the intercepted gaseous supramolecular species was then characterized via mass-selection in the quadrupole Q1, followed by collision-induced dissociation (CID) with argon in the collision cell q2, and MS analysis of fragment ions using an orthogonal high-resolution and high-accuracy TOF-MS analyzer. These loosely bonded species show, as expected, relatively low resistance toward CID (5–10 eV energy collisions with argon promote prompt dissociation) and structurally diagnostic dissociation chemistry.



Scheme 2. BH reaction monitored by ESI-MS/MS and co-catalyzed by both DABCO and a BMI.X ionic liquid



Scheme 3. BH reaction of methyl acrylate (**1**) and 2-thiazolecarboxaldehyde (**2**) co-catalyzed by both DABCO (**3**) and an ionic liquid BMI.X (X = BF₄⁻, PF₆⁻, CF₃CO₂⁻)

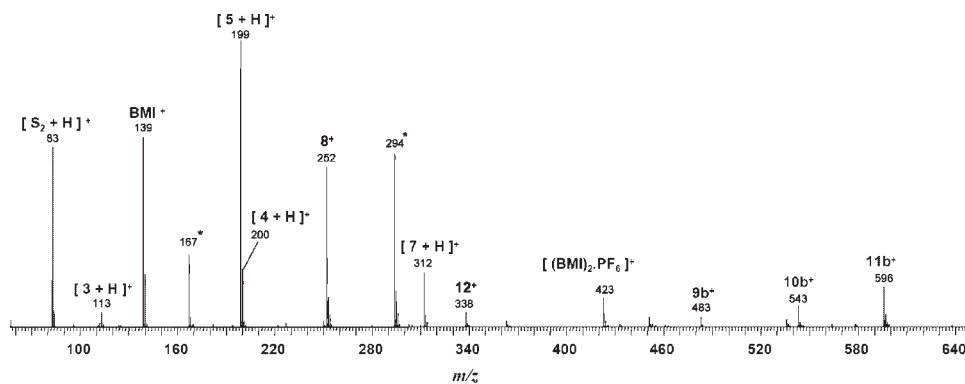


Figure 1. ESI(+) mass spectrum for the BH reaction mixture of methyl acrylate **1** with 2-thiazolecarboxaldehyde **2** co-catalyzed by DABCO **3** and the ionic liquid BMI.PF₆. Note that the unidentified ion of *m/z* 294 has also been detected in the BH reaction performed without the ionic liquid,²¹ and that the ion of *m/z* 167 is likely a fragment of the ion of *m/z* 252, see text. The ion marked as [S₂+H]⁺ is the acetonitrile (S, solvent) proton-bound dimer. The intensity scale has been blown up 20 times to show the peak at *m/z* 596

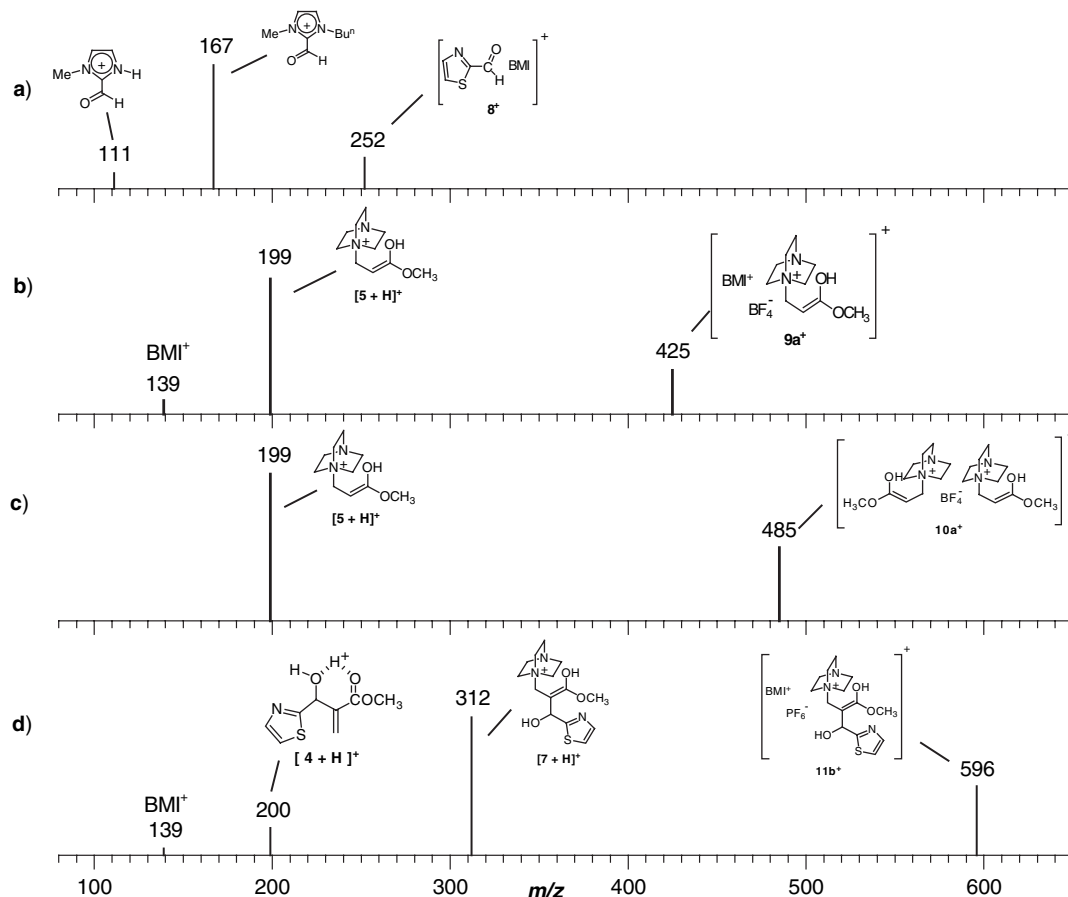


Figure 2. ESI tandem mass spectra of major BH-ionic liquid supramolecular species

Dissociations of $[3 + H]^+$ of m/z 113, $[5 + H]^+$ of m/z 199, and $[4 + H]^+$ of m/z 200 have previously been described and discussed.²¹ The supramolecular species 8^+ of m/z 252 (Fig. 2a) dissociates probably through the loss of a neutral thiazole molecule to form the fragment ion of m/z 167 (most likely a carbon monoxide derivative of BMI^+ whose structure is tentatively assigned in Fig. 2a) which, in turn, dissociates by the loss of a neutral butene molecule to yield its lower homologue of m/z 111. Note that this dissociation route occurring in the ESI source ('in-source CID') is probably what forms the ion of m/z 167 detected in the spectrum of Fig. 1. The BF_4^- bound dimer of BMI^+ and $[5 + H]^+$, that is, $9a^+$ of m/z 425 (Fig. 2a), dissociates to yield both BMI^+ of m/z 139 and $[5 + H]^+$ of m/z 199. The X-bound dimers of $[5 + H]^+$, that is, ions **10** as exemplified for $10a^+$ of m/z 485 in Fig. 2c, give $[5 + H]^+$ of m/z 199 exclusively. The supramolecular species **11**, as exemplified by $11b^+$ of m/z 596 (Fig. 2d), that is, the PF_6^- bound dimer of BMI^+ and $[7 + H]^+$, dissociate predominantly to $[7 + H]^+$ of m/z 312, and to a lesser extent to BMI^+ of m/z 139. Subsequently, the fragment ion $[7 + H]^+$ of m/z 312 loses DABCO to form the protonated BH adduct $[4 + H]^+$ of m/z 200.

A careful analysis of these results permitted us to make some suggestions in order to rationalize the role of the

ionic liquids in the rate of the Baylis–Hillman reaction. Apparently there are synergic associations of effects, which seem to be responsible for the observed increased reaction rate. Based on the intercepted species it is clear to us that ionic liquids participate in almost all steps of the catalytic cycle of the Baylis–Hillman reaction, which could explain the results reported independently by Afonso,^{13b} Kim,^{13d} and Aggarwal.¹⁵ For instance, the interception of 8^+ of m/z 252 (Scheme 3) could be considered as evidence that the ionic liquid acts in the first step of the cycle like a Lewis acid, which complexes with the aldehyde thus contributing to the increase in the electrophilicity of the carbonyl carbon. This effect seems to be more pronounced for aromatic than for aliphatic aldehydes, which is in agreement with the results reported by Afonso.^{13b,16}

The rate of the Baylis–Hillman reaction is likely related to the stabilization of the 'enolate intermediate' resulting from the Michael addition of the tertiary amine on the acrylate activated double bond. Ionic liquids also participate in this step (see species 9^+ and 13^- , Scheme 3) and probably stabilize this intermediate. Both intermediates (5^+ and 9^+) play a fundamental role in the catalytic cycle of the reaction, more specifically in the rate-determining step. Finally, the ionic liquids complex with the product of the reaction which should shift the

equilibrium towards the adduct formation. If we associate the Lewis acid-like effect of the ionic liquids exerted over the aldehyde, the stabilization of the 'intermediate enolate' and the stabilization of the final products, the perceived overall effect is the huge increasing of the reaction rate.

To evaluate the difference in the catalytic properties of each ionic liquid, a reaction using a mixture of three BMI ionic liquids (Scheme 2) was also monitored (5 mol% of each co-catalyst). The goal of this competitive experiment was to evaluate the co-catalysis efficiency by determining which ionic liquid would best stabilize the BH intermediates. ESI-MS snapshots (not shown) show, for the peaks corresponding to ions **9** and **11**, the following relative abundance order: **9c** > **9a** >> **9b** and **11c** > **11a** >> **11b** (see Scheme 3 for structures), which indicates the following order of co-catalysis efficiency: BMI.CF₃CO₂ > BMI.BF₄ >> BMI.PF₆. Interestingly, this order is the same as that observed for the relative strengths of the hydrogen bond between the imidazolium cation and these anions,²² but it is the opposite to that observed by Afonso^{13b} and Kim^{13d} in solution. In these cases BMI.PF₆ was the most efficient catalyst for the Baylis–Hillman reaction. Since our data is influenced by factors governing ion transfer from solution to the gas phase, this inversion of the co-catalyst efficiency may be due to a missing additional stabilizing interaction, which could occur easily in the liquid phase.

On-line monitoring of the same BH reactions by ESI-MS in the negative ion mode produce not so clear results since the spectra (not shown) were essentially dominated by the negatively charged ionic liquid supramolecules [(BMI)_n(X)_{m+1}]⁻.²² However, the supramolecular species **13**⁻ (Scheme 3) were clearly and consistently detected.

In conclusion, in the search for the supramolecular species responsible for the co-catalytic role of ionic liquids, we performed on-line monitoring of Baylis–Hillman reactions by ESI-MS. The search was successful as we were able to gently 'fish' from solution to the gas phase as well as to detect and characterize, via MS analysis and MS/MS dissociation, several supramolecular species formed by coordination of reagents and products as well as protonated BH zwitterionic intermediates with both the cations and anions of the ionic liquids. Via competitive experiments, we found that the order of BH co-catalysis efficiency is: BMI.CF₃CO₂ > BMI.BF₄ >> BMI.PF₆, which is the opposite to that observed by Afonso^{13b} in the liquid phase. Based on the interception of these unprecedented supramolecular species, we propose that 1,3-dialkylimidazolium ionic liquids function as efficient co-catalysts for the BH reaction:

- (i) by activating the aldehyde toward nucleophilic attack via BMI⁺ coordination (species **8**⁺) and
- (ii) by stabilizing the zwitterionic species that act as the main BH intermediates through supramolecular coordination (species **9**⁺, **10**⁺, **11**⁺, and **12**⁻).

REFERENCES

1. (a) Baylis AB, Hillman MED. German Patent 2155113, 1972; *Chem. Abstr.* 1972; **77**: 34174q. (b) Morita K, Suzuki Z, Hirose H. *Bull. Chem. Soc. Jpn.* 1968; **41**: 2815–2815. (c) Basavaiah D, Rao AJ, Satyanarayana T. *Chem. Rev.* 2003; **103**: 811–891. (d) Almeida WP, Coelho F. *Quim. Nova* 2000; **23**: 98–101; *Chem. Abstr.* 2000; **132**: 236562. (e) Ciganek E. *Org. React.* 1997; **51**: 201–350. (f) Basavaiah D, Rao PD, Hyma RS. *Tetrahedron* 1996; **52**: 8001–8062.
2. (a) Silveira GPC, Coelho F. *Tetrahedron Lett.* 2005; **46**: 6477–6481. (b) Mateus CR, Coelho F. *J. Braz. Chem. Soc.* 2005; **16**: 386–396 (available free of charge at http://jbcs.sbq.org.br/online/2005/vol16_n3A/11-238-04.pdf). (c) Porto RS, Coelho F. *Synth. Commun.* 2004; **34**: 3037–3046. (d) Almeida WP, Coelho F. *Tetrahedron Lett.* 2003; **44**: 937–940. (e) Feltrin MA, Almeida WP. *Synth. Commun.* 2003; **33**: 1141–1146. (f) Rossi RC, Coelho F. *Tetrahedron Lett.* 2002; **42**: 2797–2800. (g) Mateus CR, Feltrin MP, Costa AM, Coelho F, Almeida WP. *Tetrahedron* 2001; **57**: 6901–6908. (h) Iwabuchi Y, Furukawa M, Esumi T, Hatakeyama S. *Chem. Commun.* 2001; 2030–2031. (i) Iwabuchi Y, Sugihara T, Esumi T, Hatakeyama S. *Tetrahedron Lett.* 2001; **42**: 7867–7871. (j) Masunari A, Trazzi G, Ishida E, Coelho F, Almeida WP. *Synth. Commun.* 2001; **31**: 2100–2109. (k) Ameer F, Drewes SE, Houston-McMillan MS, Kaye PT. *S. Afr. J. Chem.* 1986; **39**: 57–63; *Chem. Abstr.* 1986; **105**: 114809. (l) Hofmann HMR, Rabe J. *Helv. Chim. Acta* 1984; **67**: 413–415. (m) Hofmann HMR, Rabe J. *J. Org. Chem.* 1985; **50**: 3849–3859. (n) Drewes SE, Emslie ND. *J. Chem. Soc., Perkin Trans. 1* 1982; 2079–2083.
3. (a) Hill JS, Isaacs NS. *J. Phys. Org. Chem.* 1990; **3**: 285–290. (b) Hoffman HMR, Rabe J. *Angew. Chem. Int. Ed.* 1983; **22**: 796–797. (c) Fort Y, Berthe M-C, Caubère P. *Tetrahedron* 1992; **48**: 6371–6384.
4. Double aldehyde addition has been recently proposed from kinetic measurements in aprotic solvents, see: (a) Price KE, Broadwater SJ, Jung HM, McQuade DT. *Org. Letters* 2005; **7**: 147–150. (b) Aggarwal VK, Fulford SY, Lloyd-Jones GC. *Angew. Chem. Int. Ed.* 2005; **44**: 1706–1708. (c) Price KE, Broadwater SJ, Walker BJ, McQuade DT. *J. Org. Chem.* 2005; **70**: 3980–3987.
5. (a) Drewes SE, Njamela OL, Emslie ND, Ramesar N, Field JS. *Synth. Commun.* 1993; **23**: 2807–2815. (b) Bode ML, Kaye PT. *Tetrahedron Lett.* 1991; **32**: 5611–5614.
6. Aggarwal VK, Mereu A. *Chem. Commun.* 1999; 2311–2312.
7. (a) de Souza ROMA, Meireles BA, Aguiar CS, Vasconcelos MLAA. *Synthesis* 2004; 1595–1600. (b) Russowsky D, Neto BAD. *Tetrahedron Lett.* 2003; **44**: 2923–2926. (c) Russowsky D, Neto BAD. *Tetrahedron Lett.* 2004; **45**: 1437–1440.
8. See for example: (a) Kawamura M, Kobayashi S. *Tetrahedron Lett.* 1999; **40**: 1539–1542. (b) Aggarwal VK, Tarver GJ, McCague R. *Chem. Commun.* 1996; 2713–2714. (c) Kataoka T, Iwama T, Tsujiyama S. *Chem. Commun.* 1998; 197–198.
9. (a) Hayashi Y, Okado K, Ashimine I, Shoji M. *Tetrahedron Lett.* 2002; **43**: 8683–8686. (b) Jenner G. *High Press. Res.* 1999; **16**: 243–252. (c) Markó IE, Gilles PR, Hindley NJ. *Tetrahedron* 1997; **53**: 1015–1024. (d) Schuurman RJW, Linden AVD, Grimbergen RPF, Nolte RJM, Scheeren HW. *Tetrahedron* 1996; **52**: 8307–8314. (e) Oishi T, Oguri H, Hirama M. *Tetrahedron: Asymmetry* 1995; **6**: 1241–1244. (f) Gilbert A, Heritage TW, Isaacs NS. *Tetrahedron: Asymmetry* 1991; **2**: 969–972. (g) Hill JS, Isaacs NS. *Tetrahedron* 1986; **27**: 5007–5010.
10. Kundu MK, Mukherjee SB, Balu N, Padmakumar R, Bhat SV. *Synlett* 1994; 444.
11. (a) Almeida WP, Coelho F. *Tetrahedron Lett.* 1998; **39**: 8609–8612. (b) Coelho F, Almeida WP, Mateus CR, Veronese D, Lopes ECS, Silveira GPC, Rossi RC, Pavam CH. *Tetrahedron* 2002; **58**: 7437–7447.
12. (a) Wasserscheid P, Keim W. *Angew. Chem. Int. Ed.* 2000; **39**: 3773–3789. (b) Dupont J, de Souza RF, Suarez PAZ. *Chem. Rev.* 2002; **102**: 3667–3691.
13. (a) Dupont J. *J. Braz. Chem. Soc.* 2004; **15**: 341–350. (b) Rosa JN, Afonso CAM, Santos AG. *Tetrahedron* 2001; **57**: 4189–4193. (c) Kumar A, Pawar SS. *J. Mol. Catal. A-Chem.* 2003; **208**: 33–37. (d) Kim EJ, Ko SY, Song CE. *Helv. Chim. Acta* 2003; **86**: 894–899. (e) Pegot B, Vo-Thanh G, Gori D, Loupy A. *Tetrahedron Lett.*

- 2004; **45**: 6425–6428. (f) Mi XL, Luo SZ, Cheng JP. *J. Org. Chem.* 2005; **70**: 2338–2341.
14. Dupont J, Spencer J. *Angew. Chem. Int. Ed.* 2004; **43**: 5296–5297.
15. Aggarwal VK, Emme I, Mereu A. *Chem. Commun.* 2002; 1612–1613.
16. Hsu J-C, Yen Y-H, Chu Y-H. *Tetrahedron Lett.* 2004; **45**: 4673–4676.
17. (a) Whitehouse CM, Dreyer RN, Yamashita M, Fenn JB. *Anal. Chem.* 1985; **57**: 675–679. (b) Fenn JB, Mann M, Meng CK, Wong SF, Whitehouse CM. *Science* 1989; **246**: 64–71. (c) Cole RB. In *Electrospray Ionization Mass Spectroscopy*, John Wiley & Sons Inc.: New York, 1997.
18. Sabino AA, Machado AHL, Correia CRD, Eberlin MN. *Angew. Chem. Int. Ed.* 2004; **43**: 2514–2518.
19. (a) Cooks RG, Zhang DX, Koch KJ, Gozzo FC, Eberlin MN. *Anal. Chem.* 2001; **73**: 3646–3655. (b) Griep-Raming J, Meyer S, Bruhn T, Metzger JO. *Angew. Chem. Int. Ed.* 2002; **21**: 2738–2742. (c) Domingos JB, Longhinotti E, Brandão TAS, Santos LS, Eberlin MN, Bunton CA, Nome F. *J. Org. Chem.* 2004; **69**: 7898–7905. (d) Meyer S, Metzger JO. *Anal. Bioanal. Chem.* 2003; **377**: 1108–1114. (e) Domingos JB, Longhinotti E, Brandão TAS, Bunton CA, Santos LS, Eberlin MN, Nome F. *J. Org. Chem.* 2004; **69**: 6024–6033. (f) Raminelli C, Prechtl MHG, Santos LS, Eberlin MN, Comasseto JV. *Inorg. Chem.* 2004; **23**: 3990–3996. (g) Ferraz HMC, Pereira FLC, Gonçalo ERS, Santos LS, Eberlin MN. *J. Org. Chem.* 2004; **70**: 110–114. (h) Cassera MB, D'Alexandri FL, Merino EF, Peres VJ, Almeida IC, Gozzo FC, Eberlin MN, Wunderlich G, Wiesner J, Kimura EA, Katzin AM. *J. Biol. Chem.* 2004; **279**: 51749–51759.
20. (a) Hilderling C, Adlhart C, Chen P. *Angew. Chem. Int. Ed.* 1998; **37**: 2685–2689. (b) Chen P. *Angew. Chem. Int. Ed.* 2003; **42**: 2832–2847.
21. Santos LS, Pavam CH, Almeida WP, Coelho F, Eberlin MN. *Angew. Chem. Int. Ed.* 2004; **43**: 4330–4333.
22. (a) Gozzo FC, Santos LS, Augusti R, Consorti CS, Dupont J, Eberlin MN. *Chem. Eur. J.* 2004; **10**: 6187–6193. (b) Neto BAD, Ebeling G, Gonçalves RS, Gozzo FC, Eberlin MN, Dupont J. *Synthesis* 2004; **8**: 1155–1158.
23. ESI mass and tandem mass spectra in the positive ion mode were acquired using a Micromass (Manchester, UK) QToF instrument of ESI-QqToF configuration with 7.000 mass resolution and 50 ppm mass accuracy in the TOF mass analyzer. The following typical operating conditions were used: 3 kV capillary voltage, 40 V cone voltage and desolvation gas temperature of 100°C. Tandem ESI-MS/MS were collected after 5 eV collision induced dissociation (CID) of mass-selected ions with argon. Mass-selection was performed by Q1 using a unitary m/z window, and collisions were performed in the rf-only quadrupole collision cell, followed by mass analysis of product ions by the high-resolution orthogonal-reflectron TOF analyzer.
24. Suarez PAZ, Dullius JE, Einloft S, DeSouza RF, Dupont J. *Polyhedron* 1996; **15**: 1217–1219.