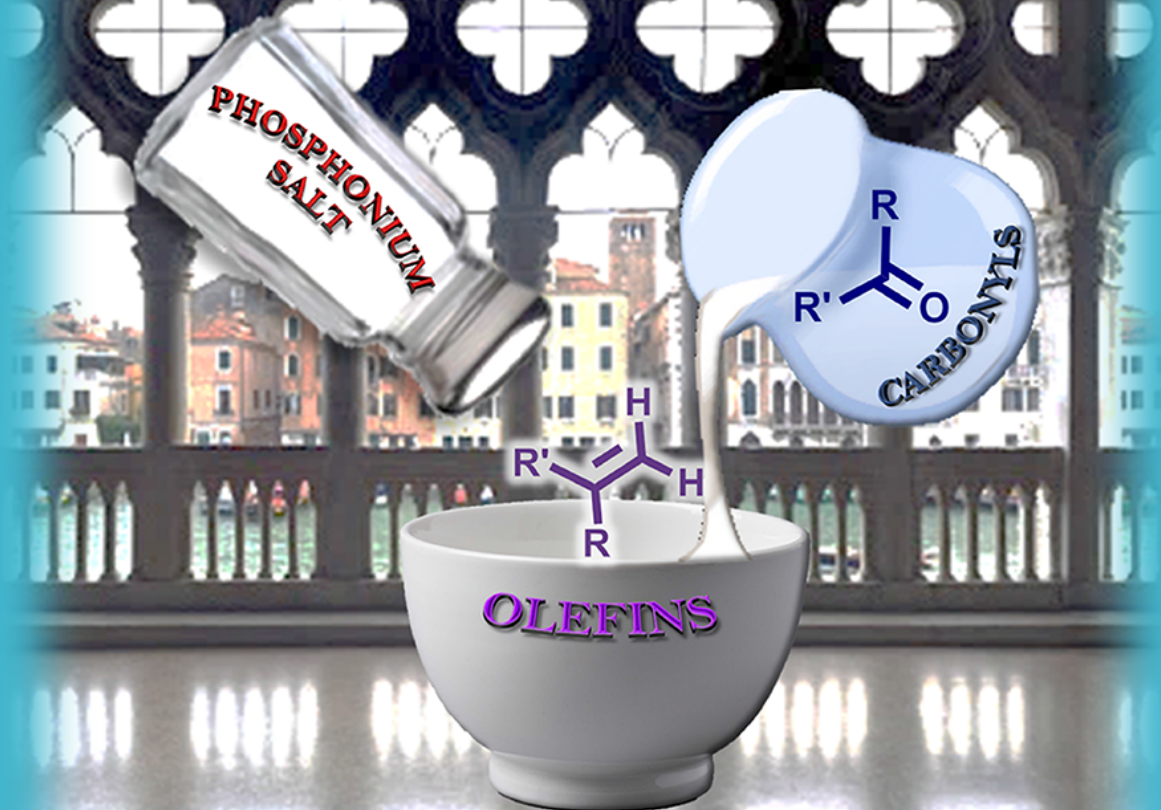


CHEMISTRY & SUSTAINABILITY

CHEM **SUS** CHEM

ENERGY & MATERIALS

Easy Wittig vinylation



23/2015

WILEY-VCH

www.chemsuschem.org

A Journal of



COVER PICTURE

L. Cattelan, M. Noè, M. Selva, N. Demitri,
A. Perosa*



**Methyltriphenylphosphonium
Methylcarbonate, an All-In-One Wittig
Vinylolation Reagent**



The Inside Back Cover picture shows the concept of a simplified vinylolation protocol. A new all-in-one Wittig reagent was developed. Mixed with an aldehyde or a ketone, this phosphonium salt yields the corresponding vinyl derivatives very efficiently simply upon heating in a solvent (no base, no halides, and no inorganic byproducts). Deuterium exchange experiments allowed the synthesis of deuterated olefins and, coupled to XRD studies, explanation of the nature and reactivity of this reagent. Simple green metrics indicate that this phosphonium salt is more efficient for vinylolation than existing reagents. More details can be found in the Communication by Cattelan et al. (DOI: 10.1002/cssc.201500935).



Methyltriphenylphosphonium Methylcarbonate, an All-In-One Wittig Vinylation Reagent

Lisa Cattelan,^[a] Marco Noè,^[a] Maurizio Selva,^[a] Nicola Demitri,^[b] and Alvis Perosa^{*,[a]}

The methyltriphenylphosphonium methylcarbonate salt $[\text{Ph}_3\text{PCH}_3][\text{CH}_3\text{OCO}_2]$, obtained directly by quaternarization of triphenylphosphine with dimethylcarbonate, is a latent ylide that promotes Wittig vinylation of aldehydes and ketones. Alkenes are obtained simply by mixing $[\text{Ph}_3\text{PCH}_3][\text{CH}_3\text{OCO}_2]$ and the carbonyl and heating in a solvent (no base, no halides, and no inorganic byproducts). Deuterium exchange experiments and the particularly short anion-cation distance measured by XRD in $[\text{Ph}_3\text{PCH}_3][\text{CH}_3\text{OCO}_2]$ allowed to explain the nature and reactivity of this species. Green chemistry metrics (atom economy, mass index, environmental factor) indicate that this vinylation procedure is more efficient than comparable ones. Deuterated $[\text{Ph}_3\text{PCD}_3][\text{CH}_3\text{OCO}_2]$ promoted the synthesis of deuterated olefins.

While its mechanism is still an open topic,^[1] the Wittig reaction^[2] is widely applied in both the academic^[3] and industrial^[4] sectors for the olefination of carbonyl substrates, including formaldehyde,^[5] aldehydes,^[6] and ketones.^[7] Even so, the Wittig reaction suffers from a number of shortcomings, summarized in Figure 1.

In particular, a primary issue is the reaction's low atom economy (AE),^[8] due to the unavoidable formation of phosphine

oxide.^[9] A catalytic alternative, based on in situ reduction of the phosphine oxide with a silane,^[10] still suffers from the co-production of stoichiometric amounts of waste, although life-cycle analysis (LCA) of the process seem to indicate that it is more efficient than traditional procedures.^[11] A second issue is related to the need for organic solvents; this has met with only partial solutions through the use of water,^[12] biphasic systems,^[13] ionic liquids,^[14] and solvent-free conditions.^[15] The third drawback of the Wittig reaction is the need for alkyl halides in the preparation of the phosphonium,^[16] along with the necessity of an external base to generate the ylide. This leads to stoichiometric amounts of halide salts that require separation and disposal. To the best of our knowledge, there are no reports on halide- and base-free Wittig reactions. Likewise, other direct procedures to convert a carbonyl into a methylene group involve complex and expensive reagents such as Tebbe's complex, which is water- and air-sensitive.^[17]

We have previously established the halide-free synthesis of phosphonium and ammonium ionic liquids using dimethylcarbonate ($\text{CH}_3\text{OCO}_2\text{CH}_3$, DMC) as a green methylating agent.^[18] The resulting compounds have the structure $[\text{R}_3\text{QCH}_3][\text{CH}_3\text{OCO}_2]$ ($\text{Q} = \text{N}, \text{P}$) and behave as very efficient basic organo-catalysts.^[19] This catalytic behavior was explained by a cooperative double activation mechanism of the substrate.^[20]

Considering the structures of these methyl-phosphonium compounds from a different perspective (Scheme 1, left box)^[18]

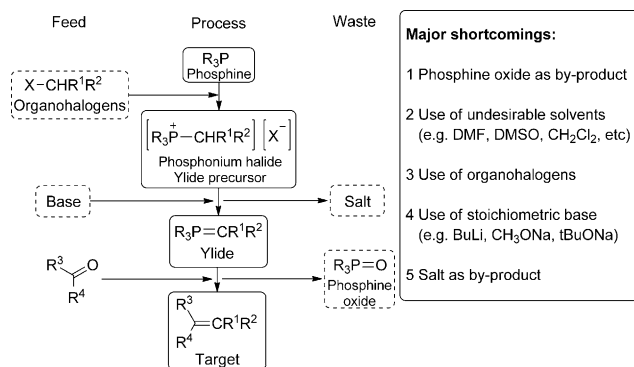
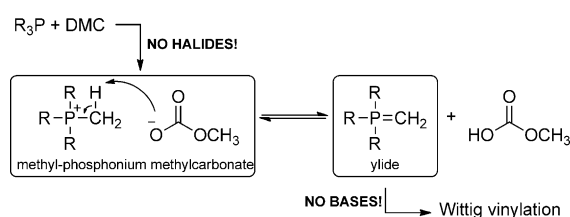


Figure 1. Major shortcomings of the traditional Wittig reaction protocol.



Scheme 1. Phosphonium-ylide equilibrium.

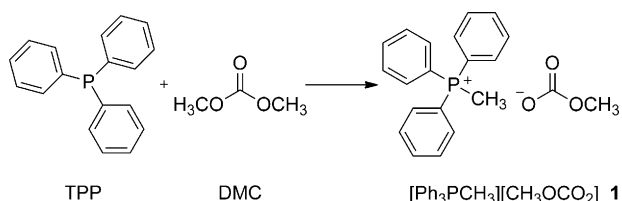
suggests that they incorporate both the basic and phosphonium moieties indispensable for the preparation of phosphorous ylides. We therefore imagined that the methylcarbonate anion might be able to generate the ylide in situ, as shown in Scheme 1, and thus give access to a new Wittig vinylation protocol.

Because methyltriphenylphosphonium is one of the most commonly reported Wittig ylide precursors, we started by developing its synthesis by methylation of triphenylphosphine (TPP) with DMC as a generalization of our previous results with trialkylphosphines (Scheme 2).^[18] Optimization of the reaction

[a] L. Cattelan, Dr. M. Noè, Prof. M. Selva, Prof. A. Perosa
Dipartimento di Scienze Molecolari e Nanosistemi
Università Ca' Foscari Venezia
Dorsoduro 12137, 30123 Venezia (Italy)
E-mail: alvis@unive.it

[b] N. Demitri
Elettra—Sincrotrone Trieste, S.S. 14 Km 163.5 in Area
Science Park, 34149 Basovizza—Trieste (Italy)

Supporting Information and ORCIDs from the authors of this article are available on the WWW under <http://dx.doi.org/10.1002/cssc.201500935>.



Scheme 2. Synthesis of **1** from TPP and DMC.

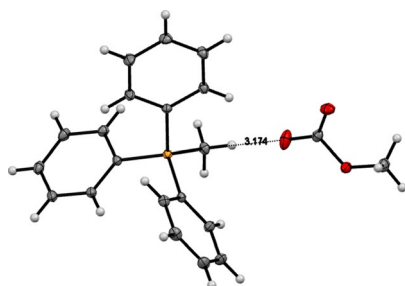


Figure 2. X-ray crystal structure (50% probability ellipsoids) of **1** (100 K, C: grey, P: yellow, O: red, H: white).

conditions by ^1H NMR monitoring (TPP: 89.6 mmol, DMC: 617 mmol, CH_3OH : 52 mL, N_2 atmosphere, 140°C for 24 h) led to an 89% yield of **1** as a white powder. Recrystallization yielded **1** suitable for crystal structure determination by X-ray diffraction (XRD) (Figure 2).

The crystal structure of **1** (Figure 2) highlighted a short distance between the methylcarbonate oxygen and the P– CH_3 methyl group (3.174 Å at 100 K), suggesting significant hydrogen-bonding in the solid state.^[21] Comparison with the distances between the P– CH_3 methyl group and the anion in other $[\text{Ph}_3\text{PCH}_3][\text{X}]$ salts (Supporting Information, Table S1 and references therein) further supports this peculiar proximity. This offers strong evidence for the possibility of “counterion mediated” deprotonation, as hypothesized in Scheme 1, and therefore in favor of the existence of a latent ylide able to promote Wittig olefination.

^1H NMR analysis of **1** provided additional evidence of the latent ylide intermediate postulated in Scheme 1. Specifically, ^1H NMR of **1** in the resonance region of the P– CH_3 protons (3.29–3.39 ppm) collected in $[\text{D}_6]\text{DMSO}$ showed a doublet ($J = 14.79$ Hz) as expected, due to coupling of the methyl protons with ^{31}P (Supporting Information, Figure S7). Instead, the same spectral region collected in CDCl_3 as solvent showed a time-dependent disappearance of the P– CH_3 protons signal (Figure 3). This disappearance is attributed to hydrogen–deuterium exchange between the P– CH_3 protons ($\text{p}K_{\text{a}} > 20$) in **1** and deuterium in CDCl_3 ($\text{p}K_{\text{a}} = 25$), in analogy to other studies^[22] and with the methylcarbonate anion acting as the base.^[23]

H/D exchange was further supported by treating the phosphonium **1** with a 15-fold molar excess of CDCl_3 that yielded quantitatively (1.34 g) the deuterated analog $[\text{Ph}_3\text{PCD}_3][\text{CH}_3\text{OCO}_2] \mathbf{1-d}_3$. The equilibrium postulated in Scheme 1 triggers complete H/D exchange by successive steps (Scheme 3), in analogy to what was previously described for hindered

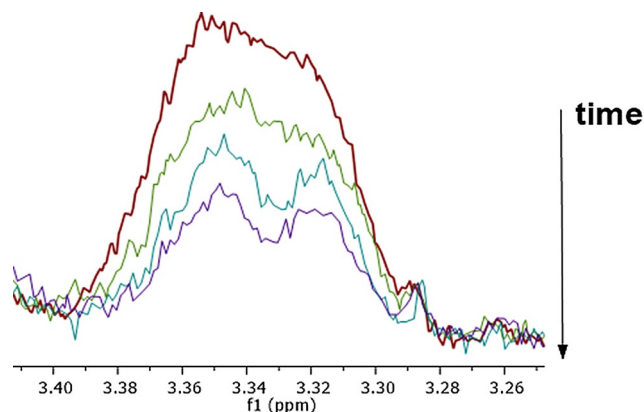
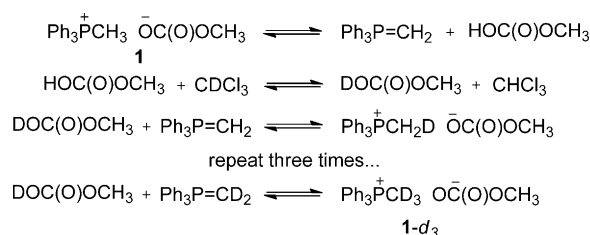


Figure 3. ^1H NMR spectra of $[\text{Ph}_3\text{PCH}_3][\text{CH}_3\text{OCO}_2] \mathbf{1}$ in the P– CH_3 region acquired in CDCl_3 at 10 min time intervals.

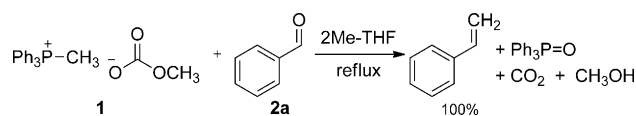


Scheme 3. Hydrogen–deuterium exchange mechanism.

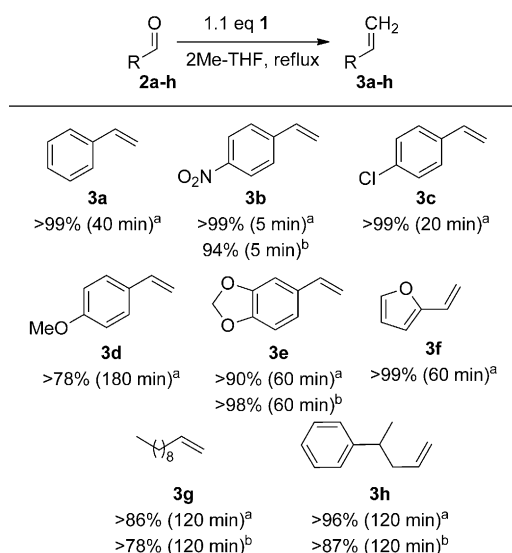
phosphoranes.^[22,24] Others have explained a similar carbonate-induced deprotonation of a phosphonium by invoking a preceding decarboxylation of the alkylcarbonate.^[23b] In our opinion, the available data points towards deprotonation occurring first. In the reverse process, **1-d**₃ was dissolved in CHCl_3 to yield **1** back again.

Next, benzaldehyde **2a** was chosen as the model carbonyl substrate to test the Wittig olefination with **1**.^[25] Prescreening of different solvents (Supporting Information, Figure S3) indicated that in biobased 2Me-THF^[26] the reaction was extremely effective both in terms of conversion and selectivity, notwithstanding that **1** is only sparingly soluble in all the tested solvents. By simply mixing **1** and **2a** at the reflux temperature of 2Me-THF (80°C), total conversion of benzaldehyde **2a** to yield styrene was observed after 20 min, with 100% selectivity (Scheme 4).

The scope of this procedure was extended by reacting a series of aldehydes (4-nitro-benzaldehyde, **2b**; 4-chloro-benzaldehyde, **2c**; 4-methoxy-benzaldehyde, **2d**; piperonal, **2e**; furfural **2f**, 1-decanal **2g**; 3-phenylbutanal **2h**) with **1** in 2Me-THF to obtain the corresponding vinyl derivatives **3b–3h** (Scheme 5).



Scheme 4. Wittig reaction between benzaldehyde and $[\text{Ph}_3\text{PCH}_3][\text{CH}_3\text{OCO}_2] \mathbf{1}$.



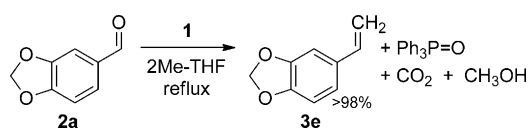
Scheme 5. Wittig vinylation products obtained from different aldehydes (%yields and reaction time are indicated), conditions: 80 °C, 1 atm. N₂, 5 mL 2Me-THF, **1**: substrate ratio = 1.1. [a] Yield as determined by GC at 100% selectivity. [b] Isolated yield.

Reactivity followed the order **2d** < **2g** < **2h** < **2e** < **2f** < **2a** < **2c** < **2b**. Aromatic aldehydes with electron-withdrawing groups (EWGs) reacted faster than ones with electron-donating groups (EDGs) and aliphatic aldehydes required longer reaction times. Notably, aliphatic aldehydes **2g** and **2h** did not show any competing aldol-type condensation reactions despite the basicity of **1**. To confirm the mass balance a selection of products including 4-NO₂-styrene **3b**, methylene-dioxystyrene **3e**, 1-undecene **3g** and 3-phenyl-pent-1-ene **3h** were isolated, purified, fully characterized, and obtained in 94%, >98%, 78% and 87% yields, respectively.

Methylene-dioxystyrene **3e**, a pharmaceutical intermediate,^[26] was selected to compare the efficiency of the present protocol with classic Wittig ones. The reported synthesis of **3e** involves the Wittig reaction of [Ph₃PCH₃][X] with BuLi at 0 °C followed by the addition of piperonal **2e**. In our case, by simply mixing **1** and **2e** in 2Me-THF and heating at reflux, >98% isolated yield of methylene-dioxystyrene **3e** was obtained on a multigram scale (~3 g, 20 mmol), without formation of halide salts (Scheme 6).

In order to take a snapshot of the potential environmental impact, we then compared the efficiency of our protocol with three existing methods for the synthesis of **3e** by using simple green chemistry metrics:^[28] AE,^[29] environmental factor (EF),^[30] and mass index (MI). The results are listed in Table 1.

AE is always low due to the formation of triphenylphosphine oxide (TPPO), nonetheless our procedure is still slightly more



Scheme 6. Synthesis of **3e** from piperonal **2e** in the presence of **1**.

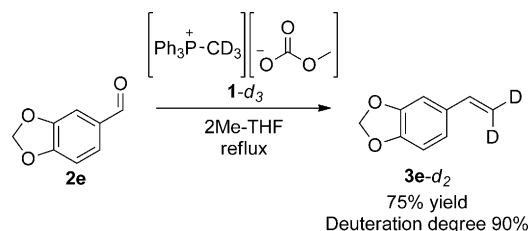
Table 1. Calculated green metrics for the conversion of 2e into 3e . ^[a]			
Reference	Atom economy (AE)	Environmental factor (EF)	Mass index (MI)
[31]	22.9%	4.34	15.85
[27]	25.9%	2.99	15.70
[32]	25.9%	3.90	19.31
This work	29.5%	3.82	9.60

[a] Metrics were calculated by using the method developed by Andraos.^[33] For details see Figures S21–S23 (Supporting Information).

atom efficient (29.5%) due to the absence of halides and of added base. Sheldon's EF is favored in Aslam's procedure due to a staggering 97% yield using purely stoichiometric amounts (1.0 equiv) of phosphonium salt and BuLi. On the contrary, the MI of our protocol was significantly more advantageous (9.60) than the other three (15.70–19.31). This was due to the very high conversion and selectivity achieved with a low amount of solvent (**2e**/2Me-THF = 0.150 g mL⁻¹) that also favored the reaction rate. In all cases, chromatography solvents were not included in the calculation.

A complete evaluation in terms of efficiency and environmental impact would require a full life-cycle analysis (LCA), as was shown elsewhere.^[11] However, the complexity of such an investigation is meaningful for specific industrial processes, and is therefore rather beyond the scope of the present work.

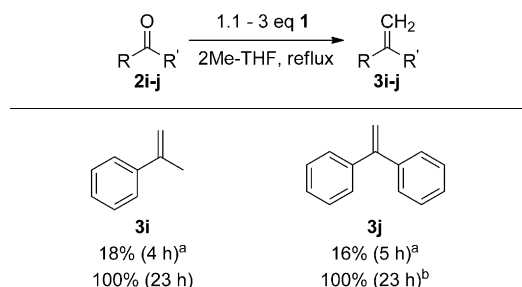
With deuterated [Ph₃PCD₃][CH₃OCO₂] **1-d₃** in hand, we applied our protocol to the synthesis of 2,2-dideutero-methylene-dioxystyrene **3e-d₂**, which was obtained in 75% yield and 90% isotopic purity (by NMR) (Scheme 7).



Scheme 7. Preparation of deuterated **3e-d₂** by reaction of **2e** with **1-d₃**.

The scope of the new Wittig vinylation reaction was further expanded by testing the reactivity of **1** with two representative ketones: acetophenone **2i** and benzophenone **2j**. The results are summarized in Scheme 8. The vinylation of ketones required to increase the molar ratio **1**/ketone up to 3 in order to achieve 100% conversion and 100% selectivity toward the desired products (Scheme 8). A third representative ketone, cyclohexanone, did not undergo Wittig olefination, affording only unidentifiable acyclic products.

In summary, the phosphonium salt **1**—prepared by a halide-free procedure—is a latent ylide able to perform Wittig-type vinylation reactions simply by heating it at reflux with a variety of carbonyls. The solvent of choice was biobased 2Me-THF, but



Scheme 8. Wittig reaction between $[\text{Ph}_3\text{PCH}_3][\text{CH}_3\text{OCO}_2]$ **1** and ketones **2i-j** [a] molar ratio 1/ketone = 1.1 [b] molar ratio 1/ketone = 3. Conditions: 80 °C, 1 atm. N_2 , 5 mL 2Me-THF; conversion as determined by GC.

the reaction was shown to proceed also in dimethylcarbonate (DMC), EtOAc, cyclopentylmethyl ether, toluene and in a 2Me-THF/EtOH mixture. The absence of halides throughout the whole process guaranteed the lack of formation of inorganic halide salts. The vinylation products were isolated from the crude reaction mixture by a simple filtration over silica to remove triphenylphosphine oxide (TPPO) and residual **1**. Synthesis of deuterated **1-*d*₃** confirmed formation of the ylide intermediate through “counterion-mediated” deprotonation and allowed us to prepare deuterated olefins using CDCl_3 as an inexpensive and readily available deuterium source. The straightforward synthesis of **1** and its simple handling should enable the use of this new vinylation reagent in academic and industrial research and development laboratories, as well as in advanced teaching laboratories.

Acknowledgements

Dr. Marco Bortoluzzi is gratefully acknowledged for help with ^2H NMR spectra.

Keywords: green chemistry • halides • phosphorus • Wittig reactions • ylides

- [1] D. G. Gilheany, *Chem. Rev.* **1994**, *94*, 1339–1374.
[2] G. Wittig, G. Geissler, *Justus Liebigs Ann. Chem.* **1953**, *580*, 44–57.
[3] a) Z. Chen, Y. Nieves-Quinones, J. R. Waas, D. A. Singleton, *J. Am. Chem. Soc.* **2014**, *136*, 13122–13125; b) P. A. Byrne, D. G. Gilheany, *Chem. Soc. Rev.* **2013**, *42*, 6670–6696; c) G. W. Wong, C. R. Landis, *Angew. Chem. Int. Ed.* **2013**, *52*, 1564–1567; *Angew. Chem.* **2013**, *125*, 1604–1607; d) P. A. Byrne, *Investigation of Reactions Involving Pentacoordinate Intermediates*, Springer, **2012**, pp. 1–92; e) P. A. Byrne, D. G. Gilheany, *J. Am. Chem. Soc.* **2012**, *134*, 9225–9239; f) J. McNulty, P. Das, D. McLeod, *Chem. Eur. J.* **2010**, *16*, 6756–6760; g) J. J. Cao, F. Zhou, J. Zhou, *Angew. Chem. Int. Ed.* **2010**, *49*, 4976–4980; *Angew. Chem.* **2010**, *122*, 5096–5100; h) A. Maercker, *The Wittig reaction*, Wiley, **1965**.
[4] a) H. Pommer, *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 423–429; *Angew. Chem.* **1977**, *89*, 437–443; b) H. J. Bestmann, L. Kiesilowski, W. Distler, *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 298–299; *Angew. Chem.* **1976**, *88*, 297–298; c) H. Yokoyama, P. Calif, *Carotene derivative and use thereof*. 3321315, **1967**.
[5] a) A. Streitwieser, R. S. McDowell, *THEOCHEM* **1986**, *138*, 89–95; b) F. Volatron, O. Eisenstein, *J. Am. Chem. Soc.* **1987**, *109*, 1–14.
[6] a) A. El-Batta, C. Jiang, W. Zhao, R. Anness, A. L. Cooksy, M. Bergdahl, *J. Org. Chem.* **2007**, *72*, 5244–5259; b) M. Schlosser, B. Schaub, *J. Am. Chem. Soc.* **1982**, *104*, 5821–5823.
[7] a) Z. Huang, R. Sun, *J. Chem. Res.* **2003**, 40–41; b) D. Enders, M. Bartsch, D. Backhaus, J. Runsink, G. Raabe, *Synthesis* **1996**, 1438–1442; c) S. Park, D. Yang, K. T. Kim, H. B. Jeon, *Tetrahedron Lett.* **2011**, *52*, 6578–6580.
[8] M. Eissen, R. Mazur, H. G. Quebbemann, K. H. Pennemann, *Helv. Chim. Acta* **2004**, *87*, 524–535.
[9] M. B. Smith, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, Wiley, **2013**.
[10] C. J. O'Brien, J. L. Tellez, Z. S. Nixon, L. J. Kang, A. L. Carter, S. R. Kunkel, K. C. Przeworski, *Angew. Chem. Int. Ed.* **2009**, *48*, 6836–6839; *Angew. Chem.* **2009**, *121*, 6968–6971.
[11] H. A. van Kalker, A. L. Blom, F. P. J. T. Rutjes, M. A. J. Huijbregts, *Green Chem.* **2013**, *15*, 1255–1263.
[12] G. Molander, R. Oliveira, *Tetrahedron Lett.* **2008**, *49*, 1266–1268.
[13] Y. Moussaoui, K. Said, R. B. Salem, *Arkivoc* **2006**, *12*, 1–22.
[14] V. Le Boulle, R. Grée, *Chem. Commun.* **2000**, 2195–2196.
[15] V. Balema, J. Wiench, M. Pruski, *J. Am. Chem. Soc.* **2002**, *124*, 6244–6245.
[16] V. K. Aggarwal, J. N. Harvey, R. Robiette, *Angew. Chem. Int. Ed.* **2005**, *44*, 5468–5471; *Angew. Chem.* **2005**, *117*, 5604–5607.
[17] S. H. Pine, G. S. Shen, H. Hoang, *Synthesis* **1991**, 165–167.
[18] M. Fabris, V. Lucchini, M. Noè, A. Perosa, M. Selva, *Chem. Eur. J.* **2009**, *15*, 12273–12282.
[19] M. Selva, A. Caretto, M. Noè, A. Perosa, *Org. Biomol. Chem.* **2014**, *12*, 4143–4155.
[20] V. Lucchini, M. Noè, M. Selva, M. Fabris, A. Perosa, *Chem. Commun.* **2012**, *48*, 5178–5180.
[21] G. Adamová, R. L. Gardas, M. Nieuwenhuyzen, A. V. Puga, L. P. N. Rebelo, A. J. Robertson, K. R. Seddon, *Dalton Trans.* **2012**, *41*, 8316–8332.
[22] I. Szele, S. J. Kubisen, F. H. Westheimer, *J. Am. Chem. Soc.* **1976**, *98*, 3533–3536.
[23] a) L. Jedinak, L. T. Rush, M. Lee, D. Hessek, J. F. Fisher, B. Boggess, B. C. Noll, S. Mobashery, *J. Org. Chem.* **2013**, *78*, 12224–12228; b) E. E. Coyle, B. J. Doonan, A. J. Holohan, K. A. Walsh, F. Lavigne, E. H. Krenske, C. J. O'Brien, *Angew. Chem. Int. Ed.* **2014**, *53*, 12907–12911; *Angew. Chem.* **2014**, *126*, 13121–13125.
[24] D. Phillips, I. Szele, F. H. Westheimer, *J. Am. Chem. Soc.* **1976**, *98*, 184–189.
[25] H. Yamataka, K. Nagareda, K. Ando, T. Hanafusa, *J. Org. Chem.* **1992**, *57*, 2865–2869.
[26] V. Pace, P. Hoyos, L. Castoldi, P. D. de Maria, A. R. Alcántara, *ChemSusChem* **2012**, *5*, 1369–1379.
[27] S. N. Aslam, P. C. Stevenson, S. J. Phythian, N. C. Veitch, D. R. Hall, *Tetrahedron* **2006**, *62*, 4214–4226.
[28] Green Chemistry Metrics, R. K. Henderson, D. J. C. Constable, C. Jiménez-González in *Green Chemistry in the Pharmaceutical Industry*, Wiley-VCH, Weinheim, **2010**.
[29] Atom economy is defined as: $\text{AE} = [\text{MW}(\text{g mol}^{-1})\text{product}] / [\sum \text{MW}(\text{g mol}^{-1}) \text{ of all reagents}] \times 100$. See also B. M. Trost, *Science* **1991**, *254*, 1471–1477.
[30] R. A. Sheldon, *Green Chem.* **2007**, *9*, 1273–1283.
[31] Y. Le Bigot, M. Delmas, A. Gaset, *Synth. Commun.* **1982**, *12*, 107–112.
[32] C. A. Faler, M. M. Joullie, *Org. Lett.* **2007**, *9*, 1987–1990.
[33] a) J. Andraos, M. Sayed, *J. Chem. Educ.* **2007**, *84*, 1004–1010; b) J. Andraos, *Org. Process Res. Dev.* **2009**, *13*, 161–185.

Received: July 10, 2015

Published online on September 18, 2015