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Merging Domino and Redox Chemistry: Stereoselective Access to Di- and Trisubstituted β,γ-Unsaturated Acids and Esters

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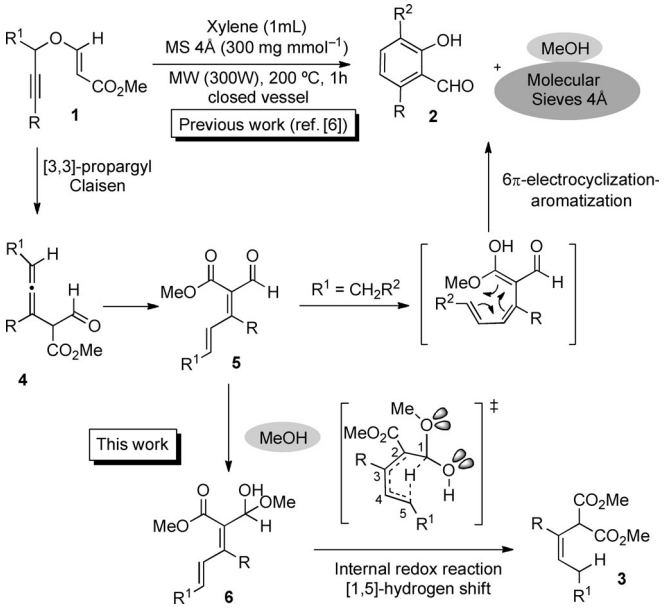
The regio- and stereocontrolled access to multisubstituted alkenes bearing reactive functionalities constitutes a current topic in organic synthesis. These alkenes are appreciated building blocks for molecular construction and versatile platforms for diversity-oriented synthesis.[1] The most developed and used synthetic approaches to these structural motifs comprise the olefination of suitable carbonyl derivatives (carbonyl olefination)[2] and the transition-metal-catalyzed cross-coupling reactions of stereodefined alkenyl derivatives.[3] Whereas carbonyl olefination methodologies present stereochemical limitations and often stereocontrol problems,[4] the transition-metal-catalyzed cross-coupling approach requires the previous access to stereodefined alkenyl derivatives, which adds to the process an extra number of synthetic transformations and a second synthetic challenge, the synthesis of the precursor itself. Modern tendencies in synthetic chemistry demand efficient protocols able to achieve the molecular construction in a fast manner with atom and step economy, in a simple and bench-friendly process.[5] In this sense, the discovery of metal-free, domino manifolds for the regio- and stereocontrolled access to multisubstituted alkenes from easily accessible starting materials constitutes an important challenge.[5] We report herein the discovery and development of a novel approach to this challenge, which is based on the microwave-assisted (MWA) rearrangement of propargyl vinyl ethers (PVEs) **1** and utilizes a [3,3]-propargyl Claisen rearrangement and a [1,5]-hydrogen shift as key chemical transformations.

The chemical foundation for this domino manifold was discovered while exploring the microwave-assisted rearrangement of PVEs **1** leading to salicylaldehydes **2** (Scheme 1).[6] We found that the microwave irradiation of



Scheme 1. Microwave (MW)-assisted rearrangement of PVEs 1.

PVE **1a** (R = Ph; R^1 = *n*Pr) in the presence of molecular sieves (MS 4 Å) directly afforded the corresponding salicylaldehyde derivative **2a** (R = Ph, R^2 = Et; 76%), through a complex domino process involving a sequential [3,3]-propargyl Claisen rearrangement/pseudo-pericyclic [1,3]-H/enolization/6π-electrocyclization and aromatization set of discrete reactions. Overall, the process generated one equivalent of methanol per equivalent of salicylaldehyde produced. In the absence of MS 4 Å (an efficient methanol scavenger), the domino process delivered the corresponding salicylaldehyde **2a** (41%) and the β,γ-unsaturated malonate ester **3a** (50%). We envisioned that the formation of **3a** could be mediated by the formation of the redox active hemiacetal **6a** through a [1,5]-hydrogen shift from the hemiacetal center to the terminus of the conjugated diene with the concomitant rearrangement of the dienic chain. Although examples of formation of activated carboxylates by direct internal redox reactions from α,β,γ,δ-unsaturated aldehydes have been described,[7,8] in only a few cases have they shown some preparative value.[8] Evidently, this is not the case of dienal **5a** whose hydricity[9] is not enough to launch a direct internal redox reaction in the presence of a methanol scavenger (MS 4 Å). Thus, the productive formation of the internal redox reaction product **3a** seems to be strongly related

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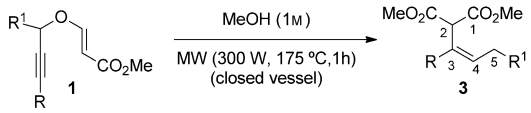
with the capacity of the system to selectively produce hemiacetal **6a**. This issue was experimentally corroborated by performing the microwave-assisted reaction in methanol, a solvent unable to react with the starting PVE but highly reactive toward the intermediate α,β,γ,δ-unsaturated aldehyde **5**. When irradiated in methanol (300 W, 175 °C, 1 h, closed vessel), PVE **1a** cleanly afforded the corresponding β,γ-unsaturated malonate **3a** in 83 % yield with complete regio- and stereoselectivity (**3a** was obtained as the unique isomer; Table 1, entry 1). It deserves to be highlighted how the

Table 1. Stereoselective synthesis of β,γ-unsaturated malonates **3** from PVEs **1**.[a]

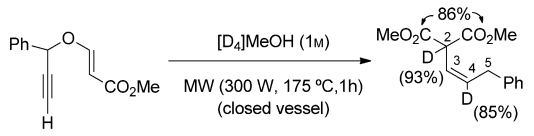


Entry	R	R^1	**3** [%][b]	
1	Ph	*n*Pr	**a**	83
2	H	*n*Pent	**b**	86
3	H	Ph	**c**	90
4	Ph	Ph	**d**	85
5	*n*Bu	Ph	**e**	70
6	*n*Bu	*n*Pr	**f**	91
7	Ph	H	**g**	75[c]
8	CO_2Me	*t*Bu	**h**	93
9	CO_2Me	*m*Xylyl	**i**	94
10	CO_2Me	*c*Hex	**j**	50

[a] See the Experimental Section for details. [b] Isolated material. [c] 3 h.

chemical efficiency of this reaction involves a complete rebuilding of the original carbon–carbon connectivity pattern. The generality and scope of this redox domino reaction was studied using the set of PVEs shown in Table 1.[10] In general, the reaction was tolerant with a broad functional diversity at the propargylic and sp-terminal positions of the PVE units. Different combinations of alkyl/aryl/hydrogen substituents at the propargyl position and ester/alkyl/aromatic/hydrogen at the sp-terminal position uniformly afforded the corresponding di- or trisubstituted β,γ-unsaturated esters **3b–h** in good to excellent yields and with the same stereochemical pattern than **3a** (only the isomers bearing the R and R^1 substituents in a *trans* relationship were observed). Even the PVE **1j** bearing a hydrogen atom at the homopropargylic position and an ester group at the sp-terminal position afforded the corresponding triester **3j** in a convenient 50 % yield (Table 1, entry 10). The combination of these two substituents generates a particular reactivity profile in the intermediate α,β,γ,δ-unsaturated aldehyde **5j** ($R = CO_2Me$; $R^1 = c$Hex), which allows the formation of other redox inactive intermediates,[6] and consequently, it reduces the efficiency of the internal redox reaction (Scheme 1).

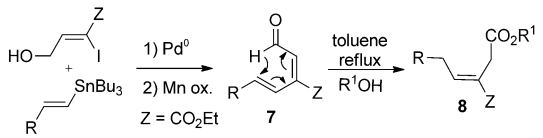
The intermediacy of a [1,5]-hydrogen shift in these reactions was established by isotopic labeling experiments (Scheme 2). Deuterium incorporation from the solvent resulted in the expected labile positions (esters, C2 and C4). Therefore, the deuterium label was not incorporated at the



Scheme 2. Isotopic labeling experiment.

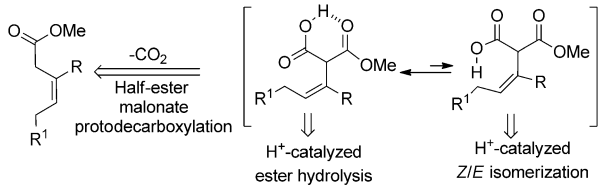
allylic (C5) position. This fact proved that the hydride migrated directly from the hemiacetalic position (C1) onto the conjugated diene (C5). The high acidic methine of the malonate function (C2), which largely incorporated deuterium in the reaction (93 % of D incorporation), suffered a large D/H exchange in the chromatography process, giving an overall 11 % of total deuterium incorporation (see the Supporting Information for details).

From a preparative point of view, the reaction offers the following advantages: 1) the substituted PVEs **1** are readily available;[10] 2) the substituted (*E,E*)-dienals **5** are assembled directly from the corresponding PVEs in a regiocontrolled manner,[11] and 3) the experimental protocol is operationally simple and bench-friendly. These advantages are highlighted when this reaction is compared with the recently described direct oxidation of the dienals **7** to carboxylic esters **8** (Scheme 3),[8b] which requires the previous formation of these dienals by a sequential Pd-catalyzed cross-coupling reaction of stereodefined vinyl iodide derivatives and (*E*)-vinyl stannanes, and the corresponding allylic oxidation to the aldehyde level.



Scheme 3. Direct oxidation of dienal **7** to carboxylic ester **8**.

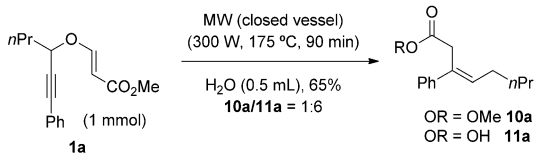
With these results in hand, we envisioned the feasibility to perform this reaction under aqueous conditions to access these valuable synthetic building blocks in a more benign and sustainable manner.[12] It was expected that the dienal molecule **5** should express in water the same reactivity pattern as it exhibits in MeOH, affording the corresponding hydrates,[13] which should oxidize to the corresponding carboxylic acids. In Nature, aldehyde oxidations to carboxylates are performed by the NAD^+-dependent aldehyde dehydrogenases (ALDHs) enzymes. The mechanism of these oxidations involves the transformation of the aldehyde in a more oxidizable thiohemiacetal derivative (ALDHs use cysteine residues to perform this task) and a hydride transfer to the NAD^+ unit, which plays the role of an activated reducible functional group.[14] Although we have not found precedents for the [1,5]-H shift-mediated oxidation of dienals under aqueous conditions, which gives an added value to this study,[15] we were concerned with the possibility that the free carboxylic acid would act as an internal acid catalyst for the



Scheme 4. Acid-catalyzed transformations of the half-ester malonate intermediate.

hydrolysis of the geminal ester and for the *Z*/*E* isomerization of the distal double bond, introducing a certain grade of instability to the redox product (Scheme 4). However, the characteristic protodecarboxylation reaction of the half-ester malonates was also expected to occur under microwave irradiation in water. If this reaction were fast enough, then the side H^+-catalyzed reactions could be inhibited and the expected monoester derivative could be accumulated in the reaction medium without suffering chemical deterioration.

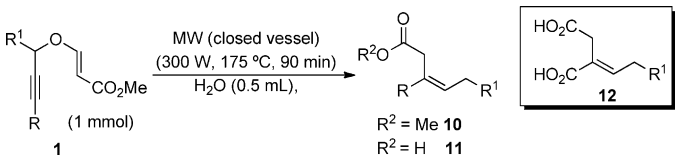
With these concerns in mind, we undertook the study of these reactions under aqueous conditions[16] by using the hydrophobic PVE **1a** as a model. After some trials, a set of reaction conditions were selected for the heterogeneous reaction (Scheme 5). Under these conditions, **1a** was transformed into the 1:6 mixture of trisubstituted β,γ-unsaturated methyl ester **10a** and carboxylic acid **11a** in a combined yield of 65%. Three main characteristics of this reaction deserve to be highlighted: Firstly, the stereoselectivity of the process is good (90% of the *E* isomer); secondly, the expected H^+-catalyzed ester hydrolysis is achieved with a low erosion of the alkene stereochemistry (10%), and thirdly, the expected protodecarboxylation of the half-ester malonate function takes place without significant alkene reordering.



Scheme 5. Microwave-assisted rearrangement of PVE **1a** under aqueous conditions.

Once a proof of concept was established, we studied the scope of this reaction with regard to the nature of the PVE (Table 2). Three conclusions could be extracted from the data of Table 2: 1) the reaction showed good tolerance with regard to the substituents, affording the desired products as mixtures of the carboxylic acids or esters; 2) the stereoselectivity of the reaction is governed by the nature of the alkyne substituent R, which is optimal for R = H or CO_2Me (up to 90%; Table 2, entries 2, 3, and 7–10); and 3) the isolated product yields of the products range from good to excellent. Furthermore, it is worth mentioning that under these reaction conditions, there is no significant double-bond migration to give the corresponding α,β-unsaturated esters/acids. Consequently, this procedure becomes a simple, metal-free stereoselective access to di- and trisubstituted β,γ-unsaturated esters/acids, which are valuable synthetic building blocks.

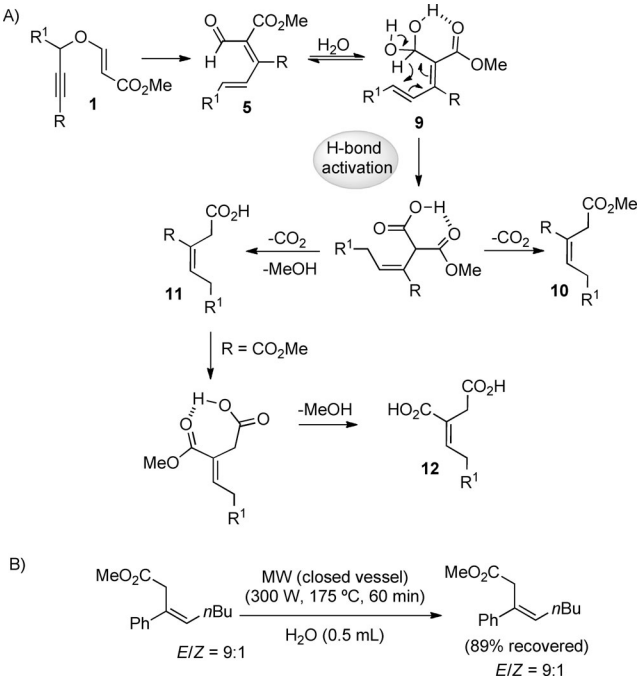
Table 2. Stereoselective synthesis of di- and trisubstituted β,γ-unsaturated esters/acids **10**:**11** under aqueous conditions.[a]



Entry	R	R^1		[%][b]	**10**:**11**	Stereoselectivity
1	Ph	*n*Pr	**a**	65[c]	1:6	9:1
2	H	*n*Pent	**b**	58	3:1	15:1
3	H	Ph	**c**	82	2.6:1	19:1
4	Ph	Ph	**d**	92	1:2.1	3.2:1
5	*n*Bu	Ph	**e**	69	1:1.6	6:1
6	*n*Bu	*n*Pr	**f**	56[d]	1:5.2	3.1:1
7	CO_2Me	*t*Bu	**h**	96	2:1	≥19:1
8	CO_2Me	*m*Xyl	**i**	96	2.4:1	≥19:1
9	CO_2Me	*c*Hex	**j**	68[e]	1:1.7	≥19:1
10	CO_2Me	*n*Bu	**k**	66[f]	1:12	≥19:1
11	*c*Hex	Ph	**l**	57	1:2	6.3:1

[a] See the Experimental Section for details. [b] Isolated material. [c] H_2O (1 mL), **2a** (10%). [d] **2f** (12%). [e] **12j** (8%). [f] **12k** (7%).

A mechanistic proposal for this reaction is outlined in Scheme 6A. Three experimental evidences confirm this mechanistic picture. Firstly, the intermediacy of a [1,5]-H migration in these reactions was again established by isotopic labeling experiments when the reaction was carried out in

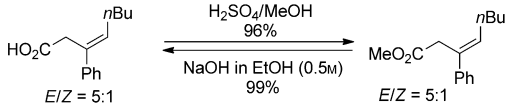


Scheme 6. Microwave-assisted domino-redox rearrangement of PVE **1** under aqueous conditions.

D_2O (see the Supporting Information for details). Secondly, the allylic ester functionality is stable to hydrolysis in the absence of a geminal carboxylic acid (Scheme 6B). Lastly, the isolation of diacids **12j** and **12k** (Table 2, entries 9 and 10) establishes that the allylic ester needs to be hydrolyzed before the protodecarboxylation reaction of the geminal carboxylic acid takes place to give the monoacid **11** (H^+-catalyzed ester hydrolysis). The free carboxylic acid in **11** could catalyze the hydrolysis of the vinylic ester to render the diacid **12**.

The efficiency of this transformation is highlighted when we take into account that it enables a domino process consisting of a [3,3]-propargyl Claisen rearrangement/pseudopericyclic [1,3]-H shift reaction/diene *E/E* to *E/Z* isomerization/water addition/redox [1,5]-H shift/ester hydrolysis and protodecarboxylation.

Finally, the ester–acid mixture (**10**/**11**) can be selectively converted in just one of the two derivatives by the chemical transformation shown in Scheme 7.



Scheme 7. Controlled acid–ester interconversion of the acid–ester mixture **10**/**11**.

In summary, we have shown how the coupling of a MWA domino reaction and an internal neutral redox reaction constitutes an excellent manifold for the stereoselective synthesis of di- and trisubstituted olefins featuring a malonate unit, an ester, or a free carboxylic acid at the allylic position. These reactive functionalities can be used as convenient chemical handles for the development of enantioselective transformations at the double bond or for the chemical homologation of these unsaturated platforms. The reaction utilizes simple starting materials (propargyl vinyl ethers), methanol or water as solvents, and a very simple and bench-friendly experimental protocol. The reaction in methanol is highly efficient, rendering the β,γ-unsaturated malonate with complete stereoselectivity. The use of water as the reaction medium changes the chemical outcome of the reaction to give the corresponding trisubstituted β,γ-unsaturated acid (ester) with high stereoselectivity (up to 19/1).

Experimental Section

Representative procedure for the microwave-assisted reaction of propargyl vinyl ether in methanol: Synthesis of β,γ-unsaturated malonates **3**: Propargyl vinyl ether **1a** (1.00 mmol) and methanol (1 mL) were placed in a microwave-special closed vial and the solution was irradiated for 1 hour in a single-mode microwave oven (300 Watt, 175 °C). After removing the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, appropriate mixtures of *n*-hexane/EtOAc) to yield **3a** (83 %).

Representative procedure for the microwave-assisted reaction of propargyl vinyl ether in water. Synthesis of β,γ-unsaturated carboxylic esters/acids (**10**/**11**): Propargyl vinyl ether **6i** (1.00 mmol) and water (0.5 mL) were placed in a microwave-special closed vial and the solution was irradiated for 90 min in a single-mode microwave oven (300 Watt, 175 °C). The products were extracted with CH_2Cl_2 and the solvent was removed at reduced pressure. The products were purified by flash column chromatography (silica gel, appropriate mixtures of *n*-hexane/EtOAc) to yield **10i**/**11i** (2.4:1) (96 %).

(E)-dimethyl 2-(2-(2,6-dimethylphenyl)ethylidene)succinate (***10i***): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) : δ = 2.28 (s, 6H), 3.52 (d, ^3J(H,H) = 6.8, 2H), 3.52 (s, 2H), 3.71 (s, 3H), 3.72 (s, 3H), 6.82 (t, ^3J(H,H) = 6.8, 1H), 7.01–7.08 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 20.0, 29.5, 32.4, 51.9, 52.0, 125.8, 126.6, 128.3, 135.2, 136.4, 143.5, 167.1, 171.0 ppm; IR ($CHCl_3$) $\tilde{\nu}$ = 3027.6, 2952.7, 1736.8, 1710.9, 1469.1, 1332.5, 1306.7, 1267.4 cm^{-1}; MS (70 eV): *m*/*z* (%): 244 (8.6) [$M^+ - CH_3OH$], 230 (49), 201 (18), 184 (30), 157 (100), 143 (54), 142 (35), 141 (24), 128 (24), 115 (17), 91 (16); elemental analysis calcd (%) for $C_{16}H_{20}O_4$: C 69.54, H 7.30; found: C 69.35, H 7.10.

(E)-5-(2,6-dimethylphenyl)-3-(methoxycarbonyl)pent-3-enoic acid (***11i***): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.27 (s, 6H), 3.54 (d, ^3J(H,H) = 6.8, 2H), 3.56 (s, 2H), 3.72 (s, 3H), 6.84 (t, ^3J(H,H) = 6.8, 1H), 7.01–7.08 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 20.1, 29.6, 32.6, 52.1, 125.3, 126.7, 128.4, 135.1, 136.5, 144.0, 167.4, 175.9 ppm; IR ($CHCl_3$) $\tilde{\nu}$ = 3024.0, 2952.2, 1712.9, 1437.5, 1296.9, 1266.8, 1200.8 cm^{-1}. MS (70 eV): *m*/*z* (%): 262 (5.6) [M^+], 230 (37), 201 (25), 184 (31), 157 (100), 143 (56), 142 (49), 141 (30), 128 (30), 115 (28), 91 (26); HRMS calcd for $C_{15}H_{18}O_4$: 262.1205; found: 262.1205.

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Keywords: alkenes · domino reactions · redox chemistry · stereoselectivity · water

[1] For a concept article, see: K. Itami, J.-I Yoshida, *Chem. Eur. J.* **2006**, *12*, 3966–3974.
[2] *Modern Carbonyl Olefination. Methods and Applications* (Ed.: T. Takeda), Wiley-VCH, Weinheim, **2004**.
[3] a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd completely revised and enlarged edition, Vol.1 and 2 (Eds.: A. de Meijere, F. Diederich), Wiley-VCH: Weinheim, **2004**; for recent and selected reviews, see: b) W. Shi, C. Liu, A. Lei, *Chem. Soc. Rev.* **2011**, *40*, 2761–2776; c) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, *111*, 1780–1824; d) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, *111*, 1417–1492.
[4] L. Kürti, B. Czakó in *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier Academic Press, Amsterdam, **2005**.
[5] For selected reviews, see: a) N. Z. Burns, P. S. Baran, R. W. Hoffmann, *Angew. Chem.* **2009**, *121*, 2896–2910; *Angew. Chem. Int. Ed.* **2009**, *48*, 2854–2867; b) P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40–49.
[6] D. Tejedor, G. Méndez-Abt, L. Cotos, M. A. Ramirez, F. García-Tellado, *Chem. Eur. J.* **2011**, *17*, 3318–3321.
[7] a) P. Schiess, P. Radimerski, *Angew. Chem.* **1972**, *84*, 345–346; *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 288–289 and references cited therein; b) A. Smit, J. G. J. Kok, H. W. Geluk, *Chem. Commun.* **1975**, 513–514.

[8] a) S. E. Steinhardt, J. S. Silverston, C. D. Vanderwal, *J. Am. Chem. Soc.* **2008**, *130*, 7560–7561; b) T. Sakaguchi, Y. Okuno, Y. Tsutsumi, H. Tsuchikawa, S. Katsumura, *Org. Lett.* **2011**, *13*, 4292–4295.

[9] a) M. Alajarin, B. Bonillo, M.-M. Ortin, P. Sanchez-Andrada, A. Vidal, *Eur. J. Org. Chem.* **2011**, 1896–1913 and references cited therein; for a theoretical study of the rearrangement of (5-(dialkylamino)-2,4-pentadienals, see: b) R. S. Paton, S. E. Steinhardt, C. D. Vanderwal, K. N. Houk, *J. Am. Chem. Soc.* **2011**, *133*, 3895–3905.

[10] PVEs **1a–g** were synthesized from the corresponding propargylic alcohols:D. Tejedor, G. Méndez-Abt, F. García-Tellado, *Chem. Eur. J.* **2010**, *16*, 428–431. PVEs **1h–j** were synthesized by the ABB′ three-component reaction of aldehydes and methyl propiolate in the presence of triethylamine, see: D. Tejedor, F. García-Tellado, J. J. Marrero-Tellado, P. de Armas, *Chem. Eur. J.* **2003**, *9*, 3122–3131. For a definition of the ABB′ 3CR notation, see: D. Tejedor, F. García-Tellado, *Chem. Soc. Rev.* **2007**, *36*, 484–491.

[11] We have shown that under controlled conditions, these dienals can be isolated in good yields from the corresponding PVEs (see Ref. [6])

[12] For selected reviews on this topic, see: a) V. Polshettiwar, R. S. Varma, *Acc. Chem. Res.* **2008**, *41*, 629–639; b) D. Dallinger, C. O. Kappe, *Chem. Rev.* **2007**, *107*, 2563–2591.

[13] For a discussion of formation of hydrates in water, see: a) E. T. Urbansky, *J. Chem. Educ.* **2000**, *77*, 1644–1647 and references cited therein; for selected theoretical studies, see: b) B. Wang, Z. Cao, *Angew. Chem.* **2011**, *123*, 3324–3328; *Angew. Chem. Int. Ed.* **2011**, *50*, 3266–3270; c) R. Gómez-Bombarelli, M. González-Pérez, M. T. Pérez-Prior, E. Calle, Julio Casado, *J. Phys. Chem. A* **2009**, *113*, 11423–11428; d) S. H. Hilal, *QSAR Comb. Sci.* **2005**, 24,631–638; e) P. Guthrie, *J. Am. Chem. Soc.* **2000**, *122*, 5529–5538; f) J. P. Guthrie, V. Pitchko, *J. Am. Chem. Soc.* **2000**, *122*, 5520–5528.

[14] For a discussion on this topic, see: S. Marchal, S. Rahuel-Clermont, G. Branlant, *Biochemistry* **2000**, *39*, 3327–3335.

[15] For an example of aerobic oxidation of aldehydes in aqueous conditions, see: N. Shapiro, A. Vigalok, *Angew. Chem.* **2008**, *120*, 2891–2894; *Angew. Chem. Int. Ed.* **2008**, *47*, 2849–2852.

[16] Although the PVEs are not soluble in water and we observed two phases in the reaction vessel at the end of the reaction, we think that "under aqueous conditions" is the best description for these reaction conditions (closed vessel, microwave irradiation (300 W) and high temperature (150 °C)) because it includes a wide range of processes spanning from "in water" (one homogeneous phase) to "on water" processes (aqueous emulsion).

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