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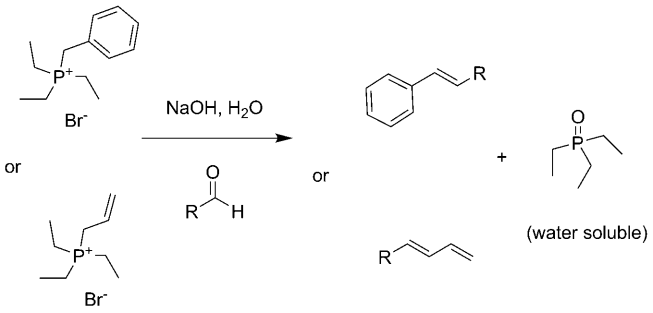
Microwave-Assisted, Aqueous Wittig Reactions: Organic-Solvent- and Protecting-Group-Free Chemoselective Synthesis of Functionalized Alkenes

James McNulty,* Priyabrata Das, and David McLeod[a]

The Wittig olefination reaction[1] is regarded as one of the most strategic, widely applicable carbon–carbon double-bond-forming processes available in organic synthesis.[2–4] The reaction has had an enormous impact on the sophistication of the total synthesis of organic molecules.[5] Some drawbacks of the reaction are the lack of stereocontrol achieved in certain cases, for example, in the synthesis of stilbenes from semistabilised ylides,[6] and the practical issue of phosphane oxide side-product removal. Also, protecting groups are usually required on any acidic protons (OH, NH, etc.) on both the ylide and carbonyl components.

Water is a desirable solvent for organic reactions for environmental, economical, safety and chemical processing reasons.[7,8] It has been used as the reaction medium for Wittig reactions of stabilised ylides to give unsaturated esters.[9] Recently, we reported the first examples of aqueous Wittig reactions of semistabilised ylides derived from trialkylbenzyl and trialkylallyl phosphonium salts.[10a,b] Semistabilised triethylbenzylidenyl and triethylallylidenyl ylides were shown to be formed chemoselectively in water by using sodium or lithium hydroxide and to react with aromatic, unsaturated, aliphatic and even enolisable aliphatic aldehydes in water, yielding a wide array of olefinic products (Scheme 1). These reactions proceeded with high (*E*)-olefin selectivity. The triethylphosphane oxide side-product is readily removed from these processes due to its water solubility and, hence, the Wittig reactions of triethylphosphane-derived, semistabilised ylides encapsulate a single solution to two outstanding problems with Wittig olefinations leading to (*E*)-olefins. This method was applied to the synthesis of valuable *trans*-stilbenes, such as resveratrol and *trans*-3,4,5,4′-tetramethoxystilbene (DMU-212).[11] High-purity *trans*-stilbenes are also the central component in light-emitting diodes (LEDs)[12] and organic-based photovoltaic solar cells.[13]



Scheme 1. Synthesis of stilbenes, alkenes, and dienes (etc.) by using aqueous Wittig chemistry with semistabilised ylides.

In our original work, the phosphonium salts were prepared in the usual fashion, by direct substitution of benzylic or allylic halides with triethylphosphane. Triethylphosphane is a highly odoriferous lachrymator that undergoes rapid oxidation in air and is considered pyrophoric. Allyl and benzyl halides are also known lachrymators and are hydrolytically unstable, generally toxic, alkylating agents. We have now developed a direct alkylation strategy that circumvents these issues, allowing a safe, "off-the-shelf" approach to achieving the above Wittig chemistry. Triethylallyl and triethylbenzyl phosphonium salts are directly available from the reaction of a benzylic or allylic alcohol and air-stable triethylphosphane hydrobromide. We also uncovered a pronounced "microwave effect" in the aqueous olefination reaction, leading to successful Wittig reactions by using weak bases, such as potassium carbonate. The innate reactivity of these ylides in water drew our attention to chemoselectivity issues. We report the unprecedented protecting-group-free, aqueous Wittig reactions of phenols, indoles, pyrroles and ketones, including enolisable substrates.

The chemistry employed in the direct synthesis of triethylallyl and triethylbenzyl phosphonium salts is outlined in Scheme 2. The synthesis of allylic triphenylphosphonium salts from allylic alcohols and acidic Ph_3P–HBr was first re-

[a] Dr. J. McNulty, Dr. P. Das, D. McLeod
Department of Chemistry and Chemical Biology
McMaster University, 1280 Main Street West
Hamilton, Ontario, L8S 4M1 (Canada)
Fax: (+1) 905-522-2509
E-mail: jmcnult@mcmaster.ca

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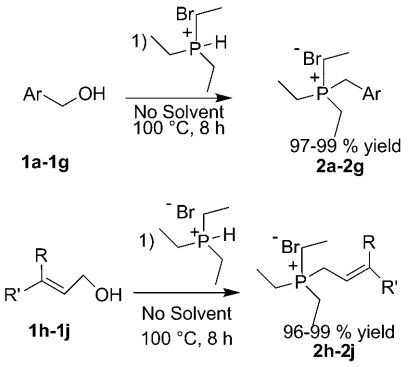
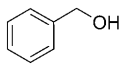
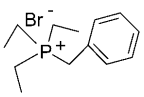
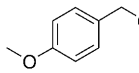
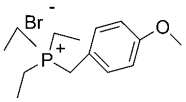
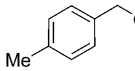
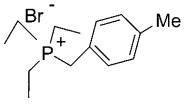
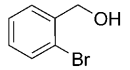
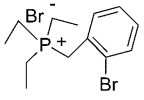
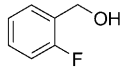
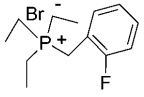
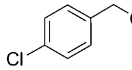
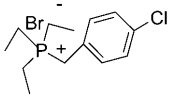
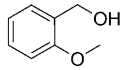
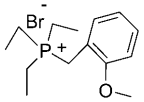
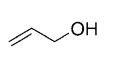
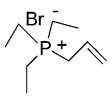
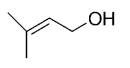
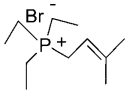
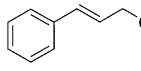
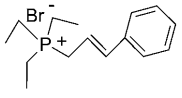


Scheme 2. Direct synthesis of triethylbenzyl and triethylallyl phosphonium bromides from the corresponding alcohols.

ported by chemists at BASF in the late 1950s in their, now classical, Wittig approach to vitamin A and its analogues.[5,14]

Table 1. Synthesis of triethylbenzyl and triethylallyl phosphonium salts directly from the corresponding alcohol using Et_3P–HBr.

Entry	Alcohol		Phosphonium salt		Yield [%]
1		**1a**		**2a**	98
2		**1b**		**2b**	99
3		**1c**		**2c**	99
4		**1d**		**2d**	98
5		**1e**		**2e**	99
6		**1f**		**2f**	97
7		**1g**		**2g**	99
8		**1h**		**2h**	99
9		**1i**		**2i**	96
10		**1j**		**2j**	98

However, it was not evident that triethylphosphane hydrobromide ($pK_a = 8.69$)[14d] would be acidic enough to allow the conversion of a benzylic or allylic alcohol into its corresponding phosphonium salt. Triethylphosphane hydrobromide was prepared directly from triethylphosphane and 47% HBr. The salt proved to be a hygroscopic, colourless, crystalline solid, which is stable to air oxidation upon direct exposure to open laboratory conditions for several weeks. In addition, the salt is almost odourless and proved to be easy to handle.

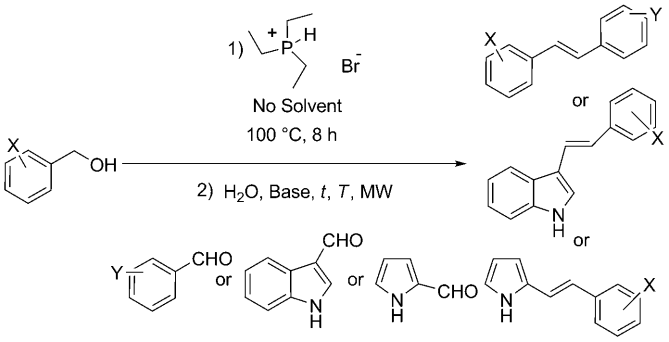
Initial attempts to transform benzyl alcohol into its triethylphosphonium salt were disappointing. No reaction occurs at room temperature in various solvents or solvent free, most likely due to the lower acidity of the salt. Nonetheless, we quickly determined that heating a mixture of benzyl alcohol and triethylphosphane hydrobromide without a solvent, in an oil bath, at 100°C allowed slow conversion to the desired salt, which was completed within 8 h. This process proved to be very general and was successful with *ortho*-substituted benzyl alcohols containing either electron-withdrawing or -donating groups. A wide range of differently substituted benzylic and allylic alcohols (**1a–j**) could be converted safely and efficiently to the desired phosphonium salts (**2a–j**), as summarised in Table 1.

This new approach can readily be applied to the synthesis of *trans*-stilbenes by using the aqueous Wittig reactions previously reported.[10a] Under our original conditions the olefination requires four equivalents of base (10.0 M; NaOH or LiOH) reacting with triethylbenzylphosphonium bromide and an aromatic aldehyde with conventional heating at 70°C for 3 h in order to achieve high conversion. Encouraged by recent reports of microwave-assisted Wittig reactions, mainly employing stabilised ylides, the above aqueous Wittig reaction was subjected to microwave dielectric heating with remarkable results.[15] Under microwave irradiation in a sealed vial, at 75°C, for only 0.5 h (Scheme 3, Table 2), the use of only 1.1 equivalents of base (NaOH or LiOH) resulted in high conversion (>98%). An otherwise identical reaction conducted with thermal heating gave only 15% conversion in 0.5 h. Furthermore, the choice of base can be

Table 2. Comparison of conventional versus microwave-assisted aqueous Wittig reactions by using benzyl alcohol and benzaldehyde.[a]

Base (1.1 equiv)	Oil bath [h]	Conversion [%]	Microwave [min]	Conversion [%]
NaOH	1	20	10	30
NaOH	2	30	20	60
NaOH	3	35	30	98
NaOH	6	81		
LiOH	1	27	15	30
LiOH	2	30	25	65
LiOH	3	40	30	97
LiOH	6	78		
K_2CO_3	1	20	15	32
K_2CO_3	2	33	25	60
K_2CO_3	3	40	30	98
K_2CO_3	6	70		

[a] All reactions were performed at 75°C.



Scheme 3. Microwave-assisted one-pot synthesis of *trans*-stilbenes and heterostilbenes.

successfully extended to the weaker potassium carbonate (1.1 equivalents), which also provides 98% conversion with 0.5 h of microwave heating.

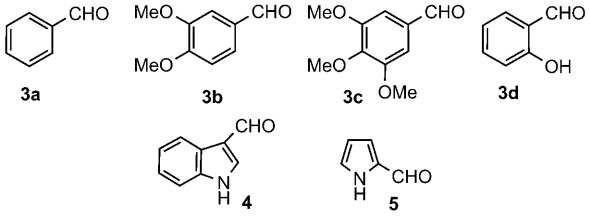
The two steps, that is, formation of the initial triethylphosphonium salt and the aqueous Wittig reaction, can be conveniently conducted as a one-pot process. A microwave vial is charged with the desired benzylic or allylic alcohol and triethylphosphane hydrobromide in a 1:1 ratio. After heating to 100 °C for 8 h, the flask is cooled to room temperature and charged with potassium carbonate, water and the aldehyde. The flask is then re-sealed and subjected to microwave irradiation at 75 °C for 30 min.

The scope of this microwave accelerated synthesis of stilbenes was extended to a range of substituted aldehydes (**3a–d**; Table 3, entry 1–4) that yield *trans*-stilbenes (**6a–c** and **f**) in high yields, similar to those in the original aqueous Wittig report.[10a] The solid stilbenes can be isolated by direct filtration upon cooling and dilution with water. Surprisingly, under these mildly basic aqueous conditions unprotected 2-hydroxybenzaldehyde also entered into the Wittig reaction to yield the hydroxyl-substituted stilbene directly in high yield and with *E* stereocontrol (Table 3, entry 4).

We next attempted the reaction with both indole-3-carboxaldehyde (**4**) and pyrrole-2-carboxaldehdye (**5**) and were delighted to find that both aldehydes readily reacted with a range of ylides, generated under the aforementioned conditions, without requiring NH protection (Table 3, entries 5–15). The heterostilbenes were isolated in good yields in both the indole (**7a–f**) and pyrrole (**8a–e**) series and essentially as the single *E* isomer in all cases.

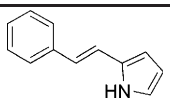
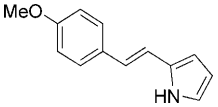
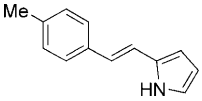
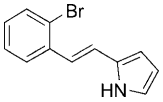
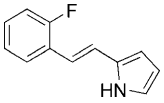
Wittig reactions on substituted indoles typically require prior protection of the NH group and side reactions are known to occur during Wittig reactions on pyrroles with a free NH group.[16] In addition to the wide array of naturally occurring biologically active stilbenes,[11i] heteroatom-containing *trans*-stilbenes include the asthma drug Singulair. Other heterostilbenes have recently been shown to posses potent antibacterial activity against the tuberculosis-causing pathogen[11j] and vinylheterocycles have proven to be valuable intermediates in the synthesis of pharmaceuticals, flavourings and agrochemical agents.[11k] Heterosubstituted stil-

Table 3. Scope of the microwave-assisted synthesis of stilbenes and heterostilbenes in water.



Entry	$ArCH_2OH$	RCHO	Product	Yield [%]	*E*:*Z*
1[a]	**1a**	**3a**	**6a**	98	100:0
2[a]	**1b**	**3b**	**6b**	99	90:10
3[a]	**1f**	**3c**	**6f**	97	95:5
4[b]	**1a**	**3d**	**6c**	83	>99 (*E*)
5[c]	**1a**	**4**	**7a**	75	>99 (*E*)
6[c]	**1b**	**4**	**7b**	75	>99 (*E*)
7[c]	**1c**	**4**	**7c**	77	>99 (*E*)
8[c]	**1d**	**4**	**7d**	83	>99 (*E*)
9[c]	**1e**	**4**	**7e**	82	>99 (*E*)
10[c]	**1f**	**4**	**7f**	80	>99 (*E*)

Table 3. (Continued)

Entry	$ArCH_2OH$	RCHO	Product	Yield [%]	E:Z
11[d]	**1a**	**5**		**8a** 98	>99 (E)
12[d]	**1b**	**5**		**8b** 93	>99 (E)
13[d]	**1c**	**5**		**8c** 93	>99 (E)
14[d]	**1d**	**5**		**8d** 92	>99 (E)
15[d]	**1e**	**5**		**8e** 95	>99 (E)

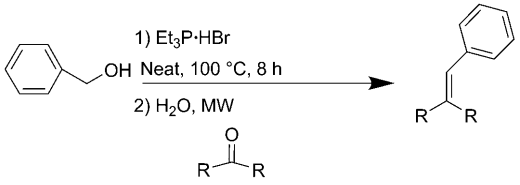
[a] K_2CO_3, 75 °C, 30 min. [b] NaOH, 100 °C, 30 min. [c] K_2CO_3, 100 °C, 30 min. [d] NaOH, 100 °C, 25 min.

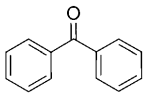
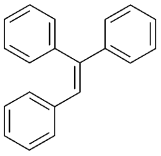
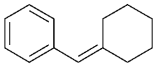
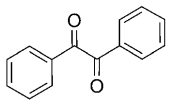
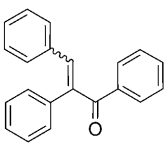
benes are also of interest in the development of the organic components in dye-sensitised solar cells.[13e]

The microwave-assisted Wittig reaction can also be extended to ketones in the presence of sodium or lithium hydroxide. Under these conditions, the ylide derived from triethylbenzylphosphonium bromide reacted with benzophenone and the enolisable ketone cyclohexanone to form compounds **9** and **10** in moderate yields (Table 4, entries 1 and 2). Under similar conditions, 1,2-diphenyl-1,2-ethanedione reacted more efficiently and yielded the phenyl chalcone derivative **11** in near quantitative yield. In contrast to the microwave-assisted Wittig reaction, little or no conversion occurred with these ketones if conventional heating was employed. Recent discussions on the nature of microwave-assisted reactions conclude that microwave-enhanced reactions involve only a thermal effect.[15f,g] We believe that the controlled heating in a sealed, pressurised microwave vial are relevant factors in the remarkable acceleration in this case.

In conclusion, we have shown that triethylallyl and triethylbenzyl phosphonium bromides are formed in quantitative yields from the direct reaction of triethylphosphane hydrobromide with allylic and benzylic alcohols. Triethylphosphane hydrobromide is an air-stable, easy-to-handle solid and this new protocol allows for the use of chemically stable, innocuous allylic or benzylic alcohols in place of their more reactive halide counterparts. This allows a convenient, safer alternative approach to valuable *trans*-stilbenes in very high yield and E stereoselectivity by employing aqueous Wittig chemistry. Furthermore, we also demonstrate a significant microwave-effect on the Wittig reaction if it is conducted with these salts in water. In addition, semi-stabilised ylides can now be generated by using potassium carbonate as the base. The ylides were shown to add to various benzaldehydes as well as aldehydes containing acidic protons, which includes phenols, indoles and pyrroles, demonstrating remarkable chemoselectivity. This new process allows access to a wide range of heterostilbene derivatives and should find applications in the synthesis of a wide range of pharmacologically active stilbenes[11] as well as other derivatives of interest in the design of organic chromophores for LED's and dye-sensitised solar cells.[12,13] Further investigations along these lines are currently being performed in our laboratory.

Table 4. One-pot microwave-assisted synthesis of olefins from ketones.



Entry	$ArCH_2OH$	Ketone	Product	Yield [%]
1[a]	**1a**		 **9**	48
2[a]	**1a**		 **10**	63
3[a]	**1a**		 **11**	99

[a] NaOH, 100 °C, 30 min. [b] LiOH, 100 °C, 35 min.

Experimental Section

The Supporting Information includes general details, synthetic protocols and characterisation data for phosphonium salts and the compounds reported in the Tables. Tables comparing various olefination reactions under conventional thermal versus microwave heating with various bases are also included.

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Keywords: alkenes · chemoselectivity · microwave chemistry · water chemistry · Wittig reactions

[1] G. Wittig, G. Geissler, *Liebigs Ann. Chem.* **1953**, *580*, 44–57.
[2] T. Takeda, *Modern Carbonyl Olefination*, Wiley-VCH, Weinheim, **2004**.

[3] E. Vedejs, M. J. Peterson, *Top. Stereochem.* **1994**, *21*, 1–157.
[4] B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863–927.
[5] K. C. Nicolaou, M. W. Harter, J. L. Gunzer, A. Nadin, *Leibigs Ann.* **1997**, 1283–1301.
[6] a) G. R. Pettit, A. Thornhill, N. Melody, J. C. Knight, *J. Nat. Prod.* **2009**, *72*, 380–388; b) A. Shirali, M. Sriram, J. J. Hall, B. L. Nguyen, R. Guddneppanavar, M. B. Hadimani, J. F. Ackley, R. Siles, C. J. Jelinek, P. Arthasery, R. C. Brown, V. L. Murrell, A. McMordie, S. Sharma, D. J. Chaplin, K. G. Pinney, *J. Nat. Prod.* **2009**, *72*, 414–421; c) F. Orsini, L. Verotta, M. Lecchi, R. Restano, G. Curia, E. Redaelli, E. Wanke, *J. Nat. Prod.* **2004**, *67*, 421–426; d) M. Cushman, N. Dhanapalan, D. Gopal, A. K. Chakraborti, C. M. Lin, E. Hamel, *J. Med. Chem.* **1991**, *34*, 2579–2588; e) D. Simoni, M. Roberti, F. P. Invidiata, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3245–3248.
[7] a) C. J. Li, *Chem. Rev.* **2005**, *105*, 3095–3165; b) U. M. Lindström, *Chem. Rev.* **2002**, *102*, 2751–2772; c) U. M. Lindström, F. Anderson, *Angew. Chem.* **2006**, *118*, 562–565; *Angew. Chem. Int. Ed.* **2006**, *45*, 548–551.
[8] a) S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb, K. B. Sharpless, *Angew. Chem.* **2005**, *117*, 3339–3343; *Angew. Chem. Int. Ed.* **2005**, *44*, 3275–3279; b) J. E. Klijn, J. B. F. N. Engberts, *Nature* **2005**, *435*, 746–747.
[9] a) J. Dambacher, W. Zhao, A. El-Batta, R. Anness, C. Jiang, M. Bergdahl, *Tetrahedron Lett.* **2005**, *46*, 4473–4477; b) J. Wu, D. Zhang, S. Wei, *Synth. Commun.* **2005**, *35*, 1213–1222; c) F. Orsini, G. Sello, T. Fumagalli, *Synlett* **2006**, 1717–1718; d) T. Thiemann, M. Watanabe, Y. Tanaka, S. Mataka, *New J. Chem.* **2006**, *30*, 359–369; e) A. El-Batta, C. Jiang, W. Zhao, R. Anness, A. L. Cooksy, M. Bergdahl, *J. Org. Chem.* **2007**, *72*, 5244–5259; f) S. Tiwari, A. Kumar, *Chem. Commun.* **2008**, 4445–4447; g) G. A. Molander, R. A. Oliveira, *Tetrahedron Lett.* **2008**, *49*, 1266–1269.
[10] a) J. McNulty, P. Das, *Eur. J. Org. Chem.* **2009**, 4031–4035; b) J. McNulty, P. Das, *Tetrahedron Lett.* **2009**, *50*, 5737–5739; for earlier studies employing triphenylphosphane derived semistabilised ylides, see: c) J. J. Hwang, R. L. Lin, R. L. Shieh, J. J. Jwo, *J. Mol. Catal. A* **1999**, *142*, 125–139; d) J. Wu, D. Li, D. Zhang, *Synth. Commun.* **2005**, *35*, 2543–2551; e) S. A. Busafi, W. A. Rawahi, *Ind. J. Chem.* **2007**, *46B*, 370–374.
[11] a) B. B. Aggarwal, A. Bhardwaj, R. S. Aggarwal, N. P. Seeram, S. Shishodia, Y. Takada, *Anticancer Res.* **2004**, *24*, 2783–2840; b) P. Saiko, A. Szakmary, W. Jaeger, T. Szekres, *Mutat. Res.* **2008**, *658*, 68–94; c) S. Sale, R. D. Verschoyle, D. Boocock, D. J. L. Jones, N. Wilsher, K. C. Ruparelia, G. A. Potter, P. B. Farmer, W. P. Steward, A. J. Geschr, *Br. J. Cancer* **2004**, *90*, 736–744; d) J. A. Baur, D. A. Sinclair, *Nat. Rev.* **2006**, *5*, 493–506; e) S. Sale, R. G. Tunstall, K. C. Ruparelia, G. A. Potter, W. P. Steward, A. J. Gescher, *Int. J. Cancer* **2005**, *115*, 194–201; f) B. Stankoff, Y. Wang, M. Bottlaender, M. S. Aigrot, F. Dolle, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 9304–9309; g) C. Wu, D. Tian, Y. Feng, P. Polak, J. Wei, *J. Histochem. Cytochem.* **2006**, *54*, 997–1004; h) C. Wu, J. Wei, D. Tian, Y. Feng, R. H. Miller, Y. Wang, *J. Med. Chem.* **2008**, *51*, 6682–6688; i) T. Shen, X. N. Wang, H. X. Lou, *Nat. Prod. Rep.* **2009**, *26*, 916–935; j) M. Pieroni, A. Lilienkampf, B. Wan, Y. Wang, S. G. Franzblau, A. P. Kozikowski, *J. Med. Chem.* **2009**, *52*, 6287–6296; k) D. Albanese, C. Ghidoli, M. Zeoni, *Org. Process Res. Dev.* **2008**, *12*, 736–739.
[12] S. Xun, Q. Zhou, H. Li, D. Ma, L. Wang, X. Jing, F. Wang, *J. Polym. Sci. Part A* **2008**, *46*, 1566–1576.
[13] a) C. Kim, H. Choi, S. Kim, C. Baik, K. Song, M. S. Kang, S. O. Kang, J. Ko, *J. Org. Chem.* **2008**, *73*, 7072–7079; b) R. A. Kerr, R. F. Service, *Science* **2005**, *309*, 101; c) M. K. Nazeeruddin, F. De Angelis, S. Fantacci, A. Selloni, G. Viscardi, P. Liska, S. Ito, B. Takeru, M. Grätzel, *J. Am. Chem. Soc.* **2005**, *127*, 16835–16847; d) M. Grätzel, *Nature* **2001**, *414*, 338–344; e) Q. Li, L. Lu, C. Zhong, J. Huang, Q. Huang, J. Shi, X. Jin, T. Peng, J. Qin, Z. Li, *Chem. Eur. J.* **2009**, *15*, 9664–9668.
[14] a) W. Sarnecki, H. Pommer, German Patent, 1046046, **1958**; b) W. Sarnecki, H. Pommer, German Patent, 1060386, **1959**; c) C. Wegner, J. Paust, J. Lambsheim, United States Patent, US 6,433,226 B1, **2002**; d) W. A. Henderson, C. A. Streuli, *J. Am. Chem. Soc.* **1960**, *82*, 5791–5794.
[15] For prior reports on microwave-assisted Wittig and related reactions, see: a) G. Sabitha, M. M. Reddy, D. Srinivas, J. S. Yadov, *Tetrahedron Lett.* **1999**, *40*, 165–166; b) J. Westman, *Org. Lett.* **2001**, *3*, 3745–3747; c) J. Wu, L. Sun, W. M. Dai, *Tetrahedron* **2006**, *62*, 8360–8372; d) J. R. Duvall, F. Wu, B. B. Snider, *J. Org. Chem.* **2006**, *71*, 8579–8590; e) C. R. Su, Y. C. Shen, P. C. Kuo, Y. L. Leu, A. G. Damu, Y. H. Wang, T. S. Wu, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6155–6160; f) M. A. Herrero, J. M. Kresmsner, C. O. Kappe, *J. Org. Chem.* **2008**, *73*, 36–47; g) D. Obermayer, B. Gutmann, C. O. Kappe, *Angew. Chem.* **2009**, *121*, 8471–8474; *Angew. Chem. Int. Ed.* **2009**, *48*, 8321–8324.
[16] a) R. A. Jones, T. Pojarlieva, R. J. Head, *Tetrahedron* **1968**, *24*, 2013–2017; b) W. Hinz, R. A. Jones, T. Anderson, *Synthesis* **1986**, 620–623; c) S. Hibino, E. Sugino, T. Kuwada, N. Ogura, Y. Smintani, K. Satoh, *Chem. Pharm. Bull.* **1991**, *39*, 79–80.

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