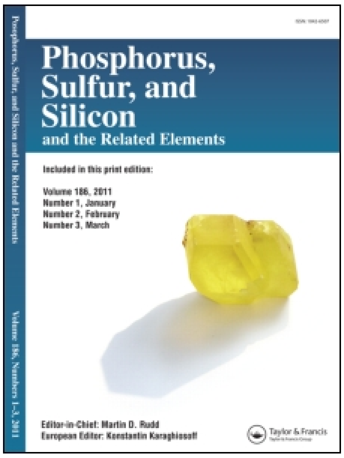
This article was downloaded by:
On: *28 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

New Approaches towards the Synthesis of Alkenes using the Horner-Wadsworth-Emmons (HWE) Reaction as the Key Step

Kerstin Bodman; Shenay Has-Becker; Oliver Reiser

To cite this Article Bodman, Kerstin , Has-Becker, Shenay and Reiser, Oliver(1999) 'New Approaches towards the Synthesis of Alkenes using the Horner-Wadsworth-Emmons (HWE) Reaction as the Key Step', Phosphorus, Sulfur, and Silicon and the Related Elements, 144: 1, 173 — 176

To link to this Article: DOI: 10.1080/10426509908546210

URL: http://dx.doi.org/10.1080/10426509908546210

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Phosphorus, Sulfur and Silicon, 1999, Vol. 144-146, pp. 173-176
Reprints available directly from the publisher
Photocopying permitted by license only

Published by license under the
Gordon and Breach Science Publishers imprint.
Printed in Malaysia

New Approaches towards the Synthesis of Alkenes using the Horner-Wadsworth-Emmons (HWE) Reaction as the Key Step

KERSTIN BODMAN, SHENAY HAS-BECKER and OLIVER REISER

Department of Organic Chemistry, University of Regensburg, Universitätsstr. 31, D-93053 Regensburg

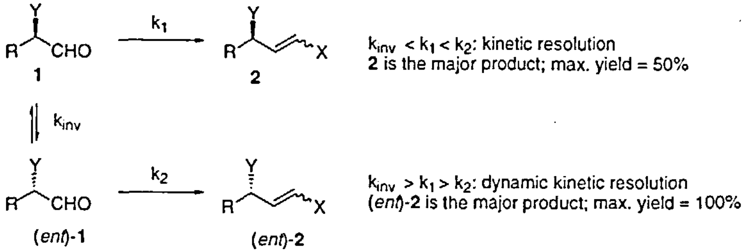
Leading from our work in asymmetric alkene synthesis it was discovered that the alkenylatio of aldehydes with phosphonates proceeds smoothly at room temperature *in the absence of Lewis acid*using triethylamine as the base if the reaction is carried out at a pressure of 8 kbar. Based on this protoco a new domino process was developed, combining the HWE reaction with a Heck coupling, thus allowing the one pot synthesis of trisubstituted alkenes.

Keywords: Horner-Wadsworth-Emmons reaction; Heck reaction; High Pressure Palladium; Alkenes

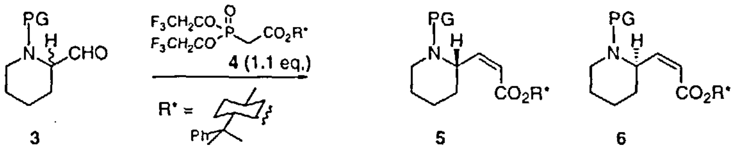
The reaction of aldehydes or ketones with phosphonates – the Horner-Wadsworth-Emmons (HWE) reaction – is one of the most versatile methods for the synthesis of alkenes. Recently, chiral variants[1] of this transformation have been developed, using both strategies being available for rendering a reaction asymmetric if no new stereocenters are formed at the reaction centers:

(1) Using *meso*-aldehydes or *meso*-ketones their symmetry may be broken, thus creating a remote stereocenter, by reaction with a chirally modified phosphonate.

(2) Using racemic aldehydes, enantiomeric enriched product may be formed in a process of kinetic or dynamic kinetic resolution. The key feature in this approach is the ability of the chiral phosphonate to preferentially react with one aldehyde enantiomer leaving the other behind unchanged.

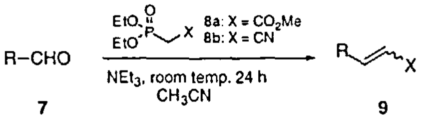


The latter strategy has been extensively studied in our laboratories in collaboration with T. Rein, University of Copenhagen[2-5]. Both, kinetic resolutions (α-alkoxy- and α-aminoaldehydes) and dynamic kinetic resolutions (α-aminoaldehydes) have been achieved using phosphonate esters such as 4 bearing –(8)-phenylmenthol as the chiral auxiliary. Moreover, it has been demonstrated that the major aldehyde enantiomer being selected by the chiral phosphonate can be controlled by modifying the *achiral* reaction conditions.

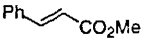


PG = Ts	(2.2 eq.)	1.0 eq. KHMDS; 5 eq. 18-cr-6	90	*Z*/*E* = 85:15	10
PG = Ts	(1.3 eq.)	1.2 eq. KHMDS; 5 eq. 18-cr-6	94	*Z*/*E* = 85:15	06
X = $P(O)Ph_2$	(2.2 eq.)	1.0 eq. KHMDS; 5 eq. 18-cr-6	>99	*Z*/*E* = 87:13	<01
X = $P(O)Ph_2$	(2.2 eq.)	1.0 eq. NaHMDS	02	*Z*/*E* = 72:28	98

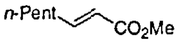
The major drawback of all strategies described here is that the overall transformation is stochiometric both in metal base and in the chiral information being employed. We therefore investigated the possibility of creating a catalytic alkenylation process. Based on the discovery by Roush an Masamune[6] that a HWE-reaction proceeds in the presence of stochiometric amounts of triethylamine and lithium chloride serving as a Lewis acid, we were screening for metal complexes which would carry out the alkenylation catalytically. Unfortunately, we had only limited success in this endeavor so far, finding no metal which would give significant turn over of >3-4. Since we had previously demonstrated that turn over cycles in palladium catalyzed cross coupling reactions can be dramatically increased by applying pressures of 8 to 10 kbar in solution[7], we also applied this technique in HWE reactions. Interestingly, we discovered that HWE reactions of aldehydes with phosphonate 8a when carried out at 8 kbar in the presence of triethylamine smoothly gave rise exclusively to the (*E*)-alkenes 9 *at room temperature in the absence of any Lewis acid.* No reaction at normal pressure is observed under these conditions.



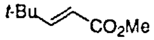
Aromatic (7a → 9a) and α-alkoxylaldehydes (7d → 9d) react particularly well under these reaction conditions, while aliphatic aldehydes give somewhat lower yields (7b → 9b, 7c → 9c). Ketones react sluggishly at room temperature but undergo alkenylation under this protocol if the reaction temperature is raised to 50–80°C.



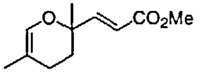
9a (79%)



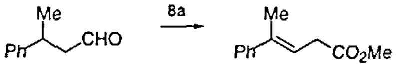
9b (54%)



9c (37%; 90% with DBU instead of NEt_3)



9d (88%)



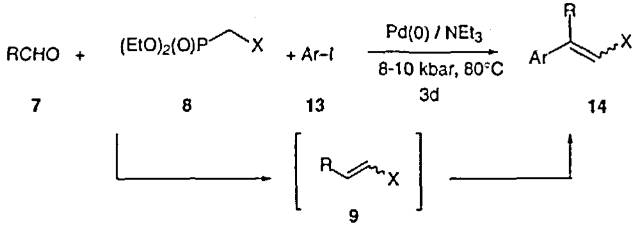
10

11 (54%)

12 (76%, $E/Z = 85{:}15$)

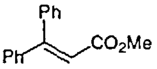
If there is the possibility of isomerization of the alkene initially formed to a trisubstituted alkene the deconjugated alkene is often formed as a byproduct or may even become the major product. Thus, in the reaction of **10** the deconjugated alkene **11** is formed as the only regio- and diastereomer. Using phosphonates with smaller substituents such as **8b**, the (*Z*)-alkene is also obtained (*cf.* **12**).

Using this alkenylation protocol, a new domino process could be designed for the synthesis of trisubstituted alkenes by combining a HWE and a Heck reaction. Thus, subjecting a mixture of an aldehyde **7**, a phosphonate **8** and an aryl iodide **13** in the presence of triethylamine and catalytic amounts (3 mol%) of palladium acetate to 8 kbar pressure at 80°C, **14a-g** can be obtained in good yields.

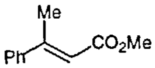


Pressure proved to be beneficial not only for the alkenylation step but also for the subsequently following arylation *via* a Heck reaction, since disubstituted alkenes are generally considerably less reactive in such coupling reactions than monosubstituted ones. The pressure protocol used here compares well to reported protocols of the Heck reaction on disubstituted alkenes at normal pressure with respect to reaction temperature, catalyst loading and yield[8,9]. However, in the case of R≠Ar, mixtures of (*E*)/(*Z*) isomers are formed, as was also noted in Heck reactions with cinnamic esters under normal pressure conditions. In case of the cinnamic nitriles, the Heck reaction proceeds stereospecific at 8 kbar as well as under normal pressure[9], however, the initial alkene formation with **8b** results in a mixture of *E* / *Z* isomers.

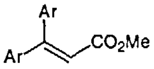
Such domino reactions might be interesting for combinatorial processes, especially given the fact that multiple high pressure reactions can be carried out at the same time by individually sealing the reaction mixtures in small teflon bags[10].



14a (79%)

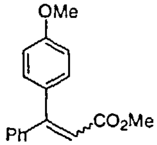


14b (56%, only *E*)

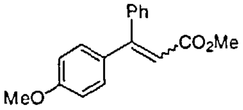


Ar = 4-OMe-Ph

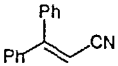
14c (73%)



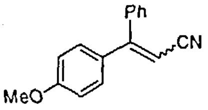
14d (80%, *E*/*Z* 23:77)



14e (90%; *E*/*Z* = 70:30)



14f (79%)



14g (89%; *E*/*Z* = 80:20)

In conclusion, new protocols could be developed allowing the combination of the HWE reaction with a palladium catalyzed coupling reaction. Further investigations of this concept are currently under way in our laboratories.

Acknowledgment

This work was supported by the Volkswagenstiftung (AZ 68/870), the Deutsche Forschungsgemeinschaft (RE948-1/4), the Fonds der Chemischen Industrie, Hoechst AG, Bayer AG and Degussa AG. OR is indebted to the Winnacker foundation for a fellowship (Winnacker award 1997).

References

[1] *Leading review:* T. Rein, O. Reiser, *Acta. Chem. Scand.*, **50**, 369 (1996).
[2] R. Kreuder, T. Rein, O. Reiser, *Tetrahedron Lett.*, **38**, 9035 (1997).
[3] T. Rein, J. Anvelt, A. Soone, R. Kreuder, C. Wulff, O. Reiser, *Tetrahedron Lett.*, **36**, 2302 (1995).
[4] T. Rein, R. Kreuder, P. v. Zezschwitz, C. Wulff. O. Reiser, *Angew. Chem.*, **107**, 1099 (1995).
[5] T. Rein, N. Kann, R. Kreuder, B. Gangloff, O. Reiser, *Angew. Chem.*, **106**, 597 (1994).
[6] M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld. S. Masamune, W. R. Roush, T. Sakai, *Tetrahedron Lett.*, **25**, 2183 (1984).
[7] S. Hillers, S. Saratori, O. Reiser, *J. Am. Chem. Soc.*, **118**, 2077 (1996).
[8] M. Moreno-Manas, R. Pleixats, A. Roglans, *Synlett*, **1997**, 1157.
[9] M. Moreno-Manas, M. Perez, R. Pleixats, *Tetrahedron Lett.*, **41**, 7449 (1996).
[10] *Recent reviews on organic high pressure chemistry.* (a) O. Reiser, *Topics in Catalysis*, **5**, 105 (1998) (b) M. Ciobanu, K. Matsumoto, *Liebigs Ann.*, **1997**, 623. (c) G. Jenner, *Tetrahedron*, **53**, 2669 (1997).