Communication

Unsymmetrical E-Alkenes from the Stereoselective Reductive Coupling of Two Aldehydes

Keyhan Esfandiarfard, Juri Mai, and Sascha Ott

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.7b00428 • Publication Date (Web): 10 Feb 2017

Unsymmetrical *E*-Alkenes from the Stereo-selective Reductive Coupling of Two Aldehydes

Keyhan Esfandiarfard, Juri Mai, Sascha Ott*

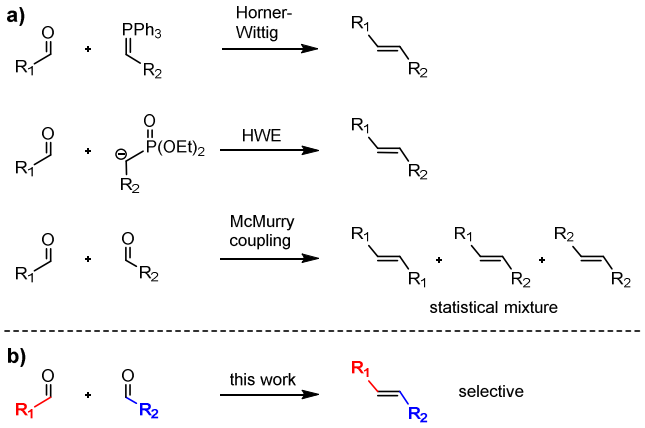
Department of Chemistry – Ångström Laboratory, Box 523, 75120 Uppsala, Sweden.

Supporting Information Placeholder

ABSTRACT: The unprecedented formation of unsymmetrical alkenes from the intermolecular reductive coupling of two different aldehydes is described. In contrast to the McMurry reaction which affords statistical product mixtures, selectivity in the reported procedure is achieved by a sequential ionic mechanism in which a first aldehyde is reacted with a phosphanylphosphonate to afford a phosphaalkene intermediate which, upon activation by hydroxide, reacts with a second aldehyde to the unsymmetrical *E*-alkenes. The described reaction is free of transition metals and proceeds under ambient temperature within minutes in good to excellent overall yields. It is a new methodology to use feedstock aldehydes for the direct production of C=C double bond-containing products, and may impact how chemists think of multistep synthetic sequences in the future.

Carbon-carbon double bonds are the functional groups of alkenes and ubiquitous in Nature and commodity chemicals. They feature in synthetic systems as diverse as plastics, pigments or drugs as well as in biomolecules such as lipids or vitamins. As such, the discovery of novel synthetic methodologies to construct these bonds from readily available starting materials is at the heart of Organic Chemistry. The Wittig reaction,[1-4] as well as the Horner-Wadsworth-Emmons (HWE) reaction are well established procedures that use organophosphorus reagents for the conversion of carbonyl compounds such as aldehydes or ketones to alkenes (Scheme 1a).[5-7] The related Julia-Kocienski olefination,[8-9] enables the preparation of alkenes from sulfone reagents and aldehydes with good *E*-selectivity. At present, the only way to conduct the reductive coupling of *two* carbonyl compounds to form alkenes is the McMurry coupling.[10-11] This reaction is initiated by coordination of the carbonyl compounds to low-valent titanium reagents. Electron transfer from the latter to the former produces most likely radical species that couple to form a pinacolate intermediate which upon subsequent electron transfer steps collapses to the alkene and TiO_2.[12] The McMurry coupling works well for many substrates,[13] but also has severe drawbacks as it is a radical reaction, works under highly reducing conditions and typically requires high temperatures and long reaction times. Thus, substrates with easily reducible groups are hardly compatible with the reaction conditions. Also, the *E*:*Z* selectivity of the McMurry reaction is often limited.[14] Most importantly, the intermolecular coupling of two non-identical carbonyl compounds is unselective and yields at best statistical mixtures of the two symmetric alkenes and the desired unsymmetric product (Scheme 1a, last entry).[15] In other words, the intermolecular coupling of two different carbonyl compounds of similar reactivity to form exclusively the unsymmetrical product is at present not possible. Herein, we disclose a new concept to overcome the limitations of the McMurry coupling. We present a new one-pot reaction that *i*) exhibits a somewhat complementary substrate scope to the McMurry coupling, *ii*) works under mild reaction conditions at room temperature within minutes, *iii*) gives rise to exclusively *E*-alkene products, and, most importantly, *iv*) allows the coupling of two different aldehydes to selectively form unsymmetrical alkenes (Scheme 1b)

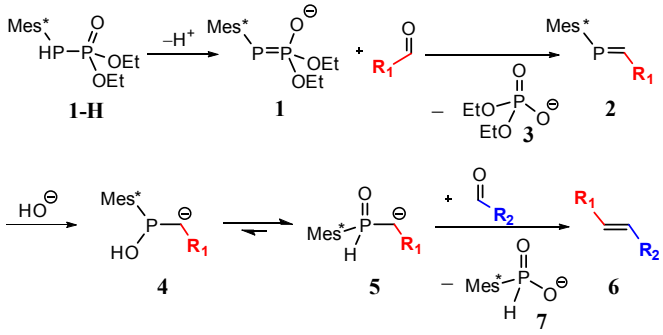
Scheme 1. Synthetic strategies to 1,2-disubstituted alkenes, including the selective aldehyde coupling presented herein.



With the similarities between carbon and low-valent phosphorus,[16] the phosphorus-analogue to the HWE reaction to form phosphaalkenes, *i.e.* compounds with a P=C double bond, has been reported by Mathey and co-workers more than 25 years ago.[17-18] In recent years, we have developed great interest in the reactivity of the thereby used reagents, *i.e.* phosphanylphosphonates, for the construction of *P*-containing π-conjugated materials[19-21] and elucidated the mechanism of the phospha-HWE reaction.[22] While the lone pair of the low-valent *P*-center in these reports is coordinated by a metal fragment, mostly $W(CO)_5$, which stabilizes the products against subsequent reactions, we recently also reported the preparation of the first metal-free phosphanylphosphonate **1-H** (Scheme 2).[23] Compound **1-H** is an air-stable, crystalline material that can be stored for several months at -20 °C without any observable decomposition. It can be prepared on a multi-gram scale, and engages with aldehydes in the phospha-HWE reaction to afford P=C compounds **2** and a diethyl phosphate **3** by-product (Scheme 2, upper row). Interesting to note at this point is that phosphaalkene formation is concomitant with a change in polarity (Umpolung) of the carbon center from δ^+ to δ^-. With the *P*-center being free of any metal fragment, we hypothe-

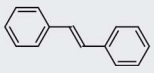
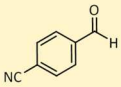
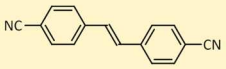
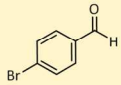
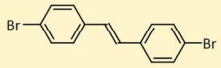
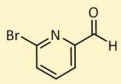
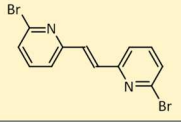
sized that the P=C product **2** could be activated further to increase the nucleophilicity of the *C*-center. Simple addition of hydroxide ions should lead to the hydroxylphosphane **4** which is known to exist in equilibrium with its phosphane oxide tautomer **5**.[24] Compound **5** bears resemblance to classical HWE reagents, and could potentially react with a second equivalent of aldehyde under alkene formation (Scheme 2).

Scheme 2. Envisaged sequence for the reductive coupling of two different aldehydes to dissimilarly disubstituted *E*-alkenes.



To test this hypothesis, two equivalents of benzaldehyde were reacted with compound **1** that is formed by deprotonation of **1-H** with lithium diisopropylamine (LDA). Already after minutes at room temperature, ^{31}P NMR spectroscopy indicates quantitative conversion of **1** to the phosphaalkene product **2**. Tetrabutylammonium hydroxide (TBAOH) is then added to the reaction which rapidly consumes the phosphaalkene **2** under the formation of 1,2-diphenylalkene (stilbene). While the isolated yield of 37% is admittedly modest, it is important to realize that this is the first time that two aldehydes have been reductively coupled under an ionic mechanism and at room temperature. The reaction also proceeds free of transition metals.[25] The reaction is only possible when the *P*-lone pair is not coordinated by a metal fragment, as this stabilization shuts down the nucleophilic attack of the hydroxide ion on the phosphaalkene intermediate and thus prevents the second half of the reaction sequence (bottom row in Scheme 2).

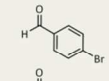
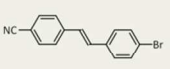
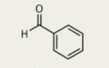
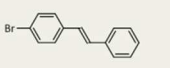
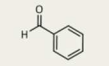
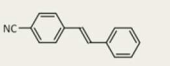
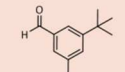
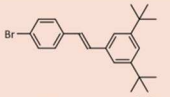
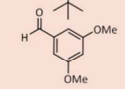
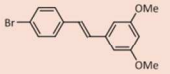
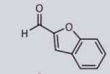
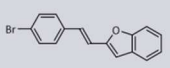
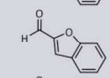
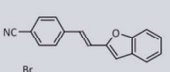
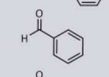
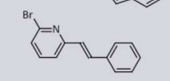
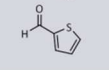
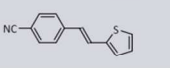
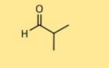
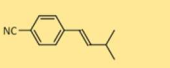
Table 1. Reductive aldehyde coupling to symmetrical 1,2-disubstituted alkenes.[a]

Entry	Aldehyde	Product	Conversion [%] (isolated yield)
1			(37)
2			>80 (75)
3			82 (50)
4			80

[a] Reaction conditions: 1.) phosphanylphosphonate **1-H**, LDA, THF, 20 °C, 2 equivalents of aldehyde, 5 min; 2.) aq. Bu_4NOH (40% wt). Conversions were determined by ^{1}H NMR spectroscopy and isolated yields are given in brackets.[27]

In further studies of the reaction's substrate scope, it emerges that electron-deficient aldehydes that are typically not compatible with the McMurry coupling such as those that carry nitrile substituents[26] can reductively be coupled very efficiently with yields greater than 80% (Table 1).[27] In all cases, only *E*-alkenes could be observed. Benzaldehydes with electron donating substituents react more sluggishly with only trace amounts of products being formed. In all cases, P=C formation is complete after minutes, but the *P*-centers in electron-rich phosphaalkenes exhibit lower electrophilicity, resulting in a higher stability of the P=C bond to hydroxide attack.

Table 2. Unsymmetrically disubstituted *E*-alkenes from the reductive coupling of two different aldehydes.[a]

Entry	1st Aldehyde	2nd Aldehyde	Product	Conversion [%] (isolated yield)
1				91 (72)
2				56 (47)
3				57
4				58
5				74
6				50
7				68
8				48 (36)
9				44
10				60
11				27
12				24
13				37

[a] Reaction conditions: 1.) phosphanylphosphonate **1-H**, LDA, THF, 20 °C, 1st aldehyde, 5 min; 2.) aq. Bu_4NOH (40% wt), 2nd aldehyde. Conversions were determined by ^{1}H NMR spectroscopy and isolated yields are given in brackets.[27]

The reductive aldehyde coupling does not only proceed at favorable reaction conditions, it also offers an additional and entirely new dimension compared to the McMurry coupling. As C=C bond formation occurs sequentially through the phosphaalkene intermediate **2**, the reaction allows for the selective coupling of two *different* aldehydes and offers access to dissimilarly disubstituted *E*-alkenes. Hence, 4-bromobenzaldehyde (BrPhCHO) and 4-

cyanobenzaldehyde (NCPhCHO), the phosphaalkenes of which engage readily in the second half of the reaction (*vide supra*) were coupled to a variety of aldehydes in the presence of TBAOH.

As shown in Table 2, the coupling of BrPhCHO and NCPhCHO with other benzaldehydes proceeds in good to excellent yields. While the coupling of NCPhCHO with BrPhCHO affords the olefinic product in 91% yield,[27] the reaction also tolerates aldehydes in the second step that carry alkoxy-groups at the phenyl ring, with the di-methoxy-containing stilbene (Entry 5) being formed in 74%. The reaction is however not limited to stilbene formations, and substrates other than benzaldehydes are also tolerated. For example, heteroaromatic aldehydes engage in the reaction with BrPhCHO or NCPhCHO (Entry 6-9) with good conversions. Entry 10 describes the reaction with *iso*-butyraldehyde which couples to NCPhCHO in 60% conversion. This is particularly remarkable as the reaction thereby outcompetes the base-catalyzed self-condensation of aldehydes with acidic protons in α-position, *i.e.* the aldol reaction. Even though the yields in Entry 11-13 are relatively low, they are still remarkable considering the bulkiness of some of the substituents, as well as the functional groups that they carry. These examples show that these functional groups are no inherent limitation to the reaction, and we are confident that improved procedures and reagents will result in considerable higher yields for these kinds of substrates. In all cases, the reaction is highly selective for the formation of *E*-alkenes, and isomeric *Z*-alkenes are not observed in any of the examples.

From Table 2, it is clear that the substrate scope for the second step of the reaction is larger than that of the first. This difference is demonstrated by the reaction of benzaldehyde with BrPhCHO. Employing the electron deficient BrPhCHO in the first step of the reaction followed by benzaldehyde in the second, good 56% conversion is achieved, while the reverse use of the two aldehydes results in considerably lower yields.

^{31}P NMR spectroscopy is an invaluable technique to follow all transformations discussed herein, and to prove the mechanism of the reductive aldehyde coupling sequence as depicted in Scheme 2. As shown representatively for the homocoupling of NCPhCHO in Figure 1, deprotonation of the phosphanylphosphonate **1-H** by LDA leads to a shift of the ^{31}P NMR resonances from -90 and 34 ppm to -119 and 69 ppm. Addition of *two* equivalents of aldehyde leads to the formation of the phosphaalkene **2** (281 ppm) as well as the diethyl phosphate side product **3** (1 ppm, Fig. 1c). Addition of an aqueous TBAOH solution at this point leads to the consumption of the phosphaalkene **2**, and the emergence of a new resonance at 11 ppm that stems from the phosphinate **7** that is left behind upon formation of the alkene (Fig. 1d). Upon aqueous work-up, the phosphinate **7** can be isolated from the reaction as the phosphinic acid **7-H** and characterized independently (see ESI). In the absence of a second equivalent of aldehyde, the nucleophilic attack of HO^- at the phosphaalkene-*P* can be followed by ^{31}P NMR spectroscopy which reveals a phosphane oxide **5-H** that stems from an equilibrium reaction with a primarily formed hydroxylphosphane **4** (not observed) as another intermediate (see ESI). Phosphane oxide **5-H** is in acid/base equilibrium with its anionic form **5** which is converted to the alkene product upon addition of the second aldehyde, thereby proving that the phosphaalkene is a true intermediate in the reaction mechanism.

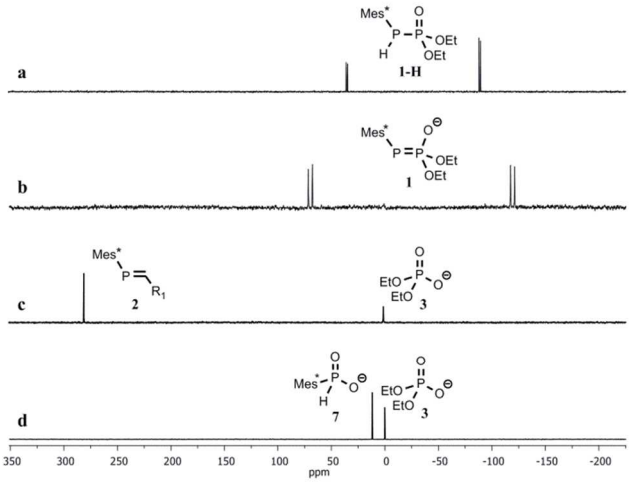


Figure 1. ^{31}P NMR spectroscopic investigation of the individual reaction steps, showing the deprotonation of phosphanylphosphonate **1-H** (a→b), followed by the phospha-HWE reaction to form a phosphaalkene **2** and the diethyl phosphate by-product **3** (b→c). Last step is the conversion of the phosphaalkene **2** to the alkene product under simultaneous formation of the Mes*-phosphinate by-product **7** (c→d).

In conclusion, we have reported the first reaction that enables the selective intermolecular reductive coupling of two different aldehydes to dissimilarly 1,2-disubstituted alkenes. This is a vast improvement to the McMurry coupling where at best statistical product mixtures are obtained. The reaction is highly *E*-selective, free of transition metals and proceeds within minutes at ambient temperature. In addition, the ionic mechanism of the transformation allows a different substrate scope than the McMurry coupling. Crucial to the reaction is the phosphanylphosphonate **1-H** which functions as both reducing agent and oxygen acceptor. The observed selectivity stems from the fact that the one-pot procedure is sequential. In a phosphorus version of the HWE reaction, the first aldehyde is initially converted to a phosphaalkene **2** which reacts further to a phosphane oxide **5** upon addition of hydroxide. The phosphane oxide **5** bears resemblance to classical HWE reagents and thus has the capacity to convert a second aldehyde to the corresponding alkene.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental Details (PDF)

AUTHOR INFORMATION

Corresponding Author

Sascha.Ott@kemi.uu.se

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

Financial support from the Swedish Research Council is gratefully acknowledged.

REFERENCES

(1) The 1979 Nobel Prize in Chemistry. http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1979/press.html

(2) Maryanoff, B. E.; Reitz, A. B., *Chem. Rev.* **1989,** *89* (4), 863-927.

(3) Kolodiazhnyi, O. I., The Wittig Reaction. In *Phosphorus Ylides*, Wiley-VCH Verlag GmbH: 2007; pp 359-538.

(4) Maryanoff, B. E.; Reitz, A. B.; Mutter, M. S.; Whittle, R. R.; Olofson, R. A., *J. Am. Chem. Soc.* **1986,** *108* (24), 7664-7678.

(5) Boutagy, J.; Thomas, R., *Chem. Rev.* **1974,** *74* (1), 87-99.

(6) Wadsworth, W. S., Synthetic Applications of Phosphoryl-Stabilized Anions. In *Organic Reactions; Synthetic Applications of Phosphoryl-Stabilized Anions*, John Wiley & Sons, Inc.: 2004; pp 73-253.

(7) Al Jasem, Y.; El-Esawi, R.; Thiemann, T., *J. Chem. Res.* **2014,** *38*, 453-463.

(8) Julia, M.; Paris, J-M.; *Tetrahedron Lett.* **1973,** *14*, (49) 4833-4836.

(9) Kocienski, P.; *Phosphorus Sulfur* **2006,** *24*, 97-127.

(10) McMurry, J. E.; Fleming, M. P., *J. Am. Chem. Soc.* **1974,** *96* (14), 4708-4709.

(11) McMurry, J. E., *Chem. Rev.* **1989,** *89* (7), 1513-1524.

(12) Ephritikhine, M., *Chem. Commun.* **1998,** (23), 2549-2554.

(13) Fürstner, A.; Bogdanović, B., *Angew. Chem. Int. Ed.* **1996,** *35* (21), 2442-2469.

(14) McMurry, J. E.; Fleming, M. P.; Kees, K. L.; Krepski, L. R., *J. Org. Chem.* **1978,** *43* (17), 3255-3266.

(15) McMurry, J. E.; Krepski, L. R., *J. Org. Chem.* **1976,** *41* (24), 3929-3930.

(16) Dillon, K. B.; Mathey, F.; Nixon, J. F., *Phosphorus: The Carbon Copy*. John Wiley & Sons: Chichester, 1998.

(17) Marinetti, A.; Mathey, F., *Angew. Chem. Int. Ed.* **1988,** *27*, 1382-1384.

(18) Marinetti, A.; Bauer, S.; Ricard, L.; Mathey, F., *Organometallics* **1990,** *9*, 793-798.

(19) Arkhypchuk, A. I.; Santoni, M.-P.; Ott, S., *Angew. Chem. Int. Ed.* **2012,** *51*, 7776-7780.

(20) Arkhypchuk, A. I.; Orthaber, A.; Mihali, V. A.; Ehlers, A.; Lammertsma, K.; Ott, S., *Chem. Eur. J.* **2013,** *19*, 13692-13704.

(21) Arkhypchuk, A. I.; Mijangos, E.; Lomoth, R.; Ott, S., *Chem. Eur. J.* **2014,** *20* (49), 16083-16087.

(22) Arkhypchuk, A. I.; Svyaschenko, Y. V.; Orthaber, A.; Ott, S., *Angew. Chem. Int. Ed.* **2013,** *52*, 6484-6487.

(23) Esfandiarfard, K.; Arkhypchuk, A. I.; Orthaber, A.; Ott, S., *Dalton Trans.* **2016,** *45* (5), 2201-2207.

(24) Hoge, B.; Garcia, P.; Willner, H.; Oberhammer, H., *Chem. Eur. J.* **2006,** *12* (13), 3567-74.

(25) During the writing of this manuscript, a "silane-version" of the McMurry coupling was reported in:. Moxter, M.; Tillmann, J.; Fuser, M.; Bolte, M.; Lerner, H. W.; Wagner, M., Chem. Eur. J. 2016, 10.1002/chem.201603720. The reaction is mechanistically very similar to the classic McMurry coupling, requires heating to 160 ºC for 60-72 hours and does not allow the selective formation of unsymmetrical alkenes.

(26) Dams, R.; Malinowski, M.; Geise, H. J., *Recl. des Trav. Chim. Pays-Bas* **1982,** *101* (3), 112-114.

(27) Many of the olefinic products exhibit poor solubility in organic solvents, thereby impeding purification and compromising isolated yields. For this reason, yields are based on NMR spectra of crude products. See ESI for details.

SYNOPSIS TOC