Published in final edited form as:

Tetrahedron Lett. 2017 April 5; 58(14): 1379–1381. doi:10.1016/j.tetlet.2017.02.051.

Synthesis of olefins via a Wittig reaction mediated by triphenylarsine

Lun Li^a, Jared C. Stimac^a, and Laina M. Geary^{a,*}

^aUniversity of Nevada, Reno 1664 N. Virginia Street, Reno, Nevada, 89557, United States

Abstract

An arsine-mediated Wittig reaction for the synthesis of olefins is described. After heating triphenylarsine in the presence of an activated alkyl bromide for 30 minutes, the resulting arsonium salt condensed with aldehydes in as little as 5 minutes at room temperature, yielding the olefins in high yields. Aromatic, heteroaromatic, and alkyl aldehydes were all suitable substrates for this process.

Graphical abstract

Keywords

Wittig reaction; Olefination; Stereoselective

Carbon-carbon double bonds are ubiquitous in biologically active materials and are useful starting materials for numerous oxidative and reductive transformations into other organic functional groups. Of the de novo olefin synthetic methods,^{1–2} the Wittig reaction is the most common variant employed. First discovered in 1953,^{3–4} it remains among the most common C-C bond forming reactions performed in medicinal chemistry and total synthesis.⁵

The Wittig reaction is exemplified by the application of organophosphines to facilitate condensation of alkyl halides with carbonyl compounds.^{6–7} Less commonly examined are analogous organoarsine-mediated Wittig reactions.^{8–9} The first example of an arsa-Wittig utilized ylides derived from triphenylarsine oxide and organic acids, and only condensed with benzaldehyde at elevated temperatures.¹⁰ A more recent variant reports the need for

*Corresponding author. Tel.: +1-775-682-8308; fax: +1-775-784-6804; lgeary@unr.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Supplementary Material

Experimental details and spectroscopic characterization.

stepwise formation of the arsonium salt, arsonium ylide, and olefin due to disparate reaction temperatures at each step,¹¹ and this is representative of many arsa-Wittig reactions.^{12–21} Arsonium ylides are also used to condense with activated alkenes to yield cyclopropanes.^{22–27}

As part of a broader scope of our research program, we sought to develop more practical conditions for organoarsine mediated Wittig reactions. We first attempted to develop a one-pot Wittig reaction between methyl bromoacetate **1a** and benzaldehyde **2a** as mediated by triphenylarsine. We screened combinations of solvents (toluene, THF, acetonitrile) and bases (potassium carbonate, potassium *tert*-butoxide, triethylamine, diisopropylethylamine, DABCO) at a variety of reaction temperatures. Unfortunately, we could only isolate the olefin in 32% yield under optimized conditions (MeCN, DIPEA, 80 °C). We reasoned that acetonitrile was a better solvent than THF or toluene due to the reduced nucleophilicity of arsine versus phosphine,^{28–30} as polar solvents accelerate the rate of binuclear substitutions. We therefore next investigated a pseudo-one-pot reaction³¹ to both support our hypothesis and improve isolated yields of the olefin (Table 1).

Consistent with the observations of Moorhoff,^{11, 32–33} we found that the generation of the arsonium salt required elevated temperatures, even when combined neat with methyl bromoacetate **1a**. Acetonitrile was generally the best solvent for the reaction (entries 1–3), though non-polar solvents could promote the Wittig reaction once the arsonium salt was formed (entries 4 and 5), consistent with our hypothesis. As was observed in the one-pot reaction, DIPEA was the best base to promote the pseudo one-pot (entry 3). Notably, once the arsonium salt is formed at 80 °C, the actual C-C bond formation is complete within 30 minutes of adding the remaining reagents in acetonitrile at room temperature. The reaction could also be performed open to the atmosphere with no decrease in isolated yield or stereoselectivity (entry 6). Decreasing the equivalents of triphenylarsine from 2 equiv to 1 reduced the isolated yield of **3a** from 81% to 53% (entry 7).

As compared to typical triphenylphosphine-mediated Wittig reactions,³⁴ neither the arsonium salt or ylide required isolation or purification prior to addition of the aldehyde and base. Moreover, the reaction was generally complete within a total of 45 minutes under mild conditions, as opposed to the more typical 3–24 hours under phosphine-mediated conditions.^{34–35}

We next established the scope of the triphenylarsine mediated Wittig reaction (Table 2). We found that the reaction conditions tolerated electron-rich and electron-poor aromatic aldehydes well; isolated yields were quantitative when the aldehyde was electron poor, and the reaction was complete in as little as 15 minutes. The reactions took a bit longer (30 minutes) with electron-rich aldehydes, but the corresponding olefins (**3h**, **3i**, **3j**, **3k**) were generally isolated in good yields. The substitution pattern on the aryl aldehydes did not appear to have a significant influence, as *ortho*-, *meta*-, and para-chlorobenzaldehyde (**2d**, **2e**, **2f**) each led to the olefin (**3d**, **3e**, **3f**) in comparable times in similar isolated yields. Heteroaromatic aldehydes (**2m**, **2n**, **2o**) could also be employed in this process, as could alkyl aldehydes (**2p**, **2q**, **2r**), and the olefins were produced in good yields and complete stereoselectivity. We also did not detect any cyclopropanation byproducts.

We then established a preliminary scope of the reaction with bromoacetophenone **1b** as the halide (Table 3). After formation of the arsonium salt, the C-C bond formation was complete within 30 minutes at room temperature for both electron-rich and poor aldehydes, and yields were nearly quantitative and produced a single isomer of the olefins **4a–4f**.

We have also examined bromoacetonitrile **1c** as the halide source to generate unsaturated nitriles **5a–5h** (Table 4). In this case, the reactions were complete within as little as 5 minutes after arsonium salt formation, though the olefins were isolated as (*E*):(*Z*) mixtures.

In attempts to improve the stereoselectivity in the synthesis of α,β -unsaturated nitriles, we screened reaction time and temperature. We found that both increasing or decreasing the reaction temperature led to an erosion in diastereoselectivity, and that the room temperature Wittig condensation was optimal (Table 5). Reactions at reduced temperature took up to an hour to complete the C-C bond formation, but the reactions at elevated temperatures were complete within two minutes. Extending reaction times beyond that required for completion did not change the observed diastereoselectivity. We also found that using tris(*p*-methoxyphenyl)arsine in place of triphenylarsine led to the synthesis of **5c** with comparable stereoselectivity. It is common for α,β -unsaturated nitriles synthesized via phosphine-mediated Wittig reactions to be produced with low (*E*):(*Z*) selectivity.^{36–38} Moreover, the arsonium salt could be synthesized in only 30 minutes at 80 °C, whereas Horner-Wadsworth-Emmons cyanomethyl reagents can require up to 6 hours at 150 °C to synthesize.³⁹

To demonstrate application of this chemistry on a larger scale, we performed the reaction between methyl bromoacetate **1a** and benzaldehyde **2a** on a 10 mmol scale. The C=C bond forming reaction completed within the same time frame, and gave a comparable yield to that of the small scale (30 minutes, 78% yield), and 1.27 g of methyl cinnamate **3a** was isolated with >19:1 (*E*):(*Z*) selectivity (equation 1).

(1)

In conclusion, we have developed a triphenylarsine mediated Wittig reaction for the construction of olefins. The mild reaction conditions coupled with the short reaction times are highly attractive, and this method is expected to find wide application in synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Research reported in this publication was partially supported by the National Institute of General Medical Sciences of the National Institutes of Health under award number R15GM120738 and by the University of Nevada, Reno via start-up funds.

References and notes

1. Takeda, T. Modern carbonyl olefination: Methods and applications. Wiley-VCH; 2006. p. 365
2. Muller C, Cokoja M, Kuhn FE. *Sci Synth*. 2014; 2:1–29.
3. Wittig G, Geissler G. *Justus Liebigs Ann Chem*. 1953; 580:44–57.
4. Wittig G, Schollkopf U. *Chem Ber*. 1954; 87:1318–1330.
5. Brown DG, Bostrom JJ. *Med Chem*. 2016; 59:4443–4458.
6. Maryanoff BE, Reitz AB. *Chem Rev*. 1989; 89:863–927.
7. Maercker A. *Org React*. 2011; 14:270–490.
8. Song He H, Chung CWT, But TYS, Toy PH. *Tetrahedron*. 2005; 61:1385–1405.
9. Lloyd D, Gosney I, Ormiston RA. *Chem Soc Rev*. 1987; 16:45–74.
10. Gosney I, Lloyd D. *Tetrahedron*. 1973; 29:1697–1710.
11. Moorhoff CM. *Synlett*. 1997:126–128.
12. Dai W-M, Wu J, Huang X. *Tetrahedron: Asymm*. 1997; 8:1979–1982.
13. Lau KCY, Chiu P. *Tetrahedron*. 2011; 67:8769–8774.
14. Huang Y, Shi L, Yang J. *Tetrahedron Lett*. 1985; 26:6447–6448.
15. Chenault J, Dupin JFE. *Synthesis*. 1987:498–499.
16. Huang Y, Shi L, Li S. *Synthesis*. 1988:975–977.
17. Huang Y, Shi L, Li S, Huang R. *Synth Commun*. 1989; 19:2639–2646.
18. Hon YS, Lee CF. *Tetrahedron*. 2000; 56:7893–7902.
19. Ma D, Sun H. *J Org Chem*. 2000; 65:6009–6016. [PubMed: 10987934]
20. Huang Z-Z, Yu X-C, Huang X. *Tetrahedron Lett*. 2002; 43:6823–6825.
21. Sun RJ, Jiang H, Huang ZZ. *Chin Chem Lett*. 2003; 14:243–244.
22. Jiang H, Sun X-L, Zhu C-Y, Dai L-X, Tang Y. *Tetrahedron*. 2008; 64:5032–5035.
23. Ren Z, Cao W, Tong W, Chen J, Deng H, Wu D. *Synth Commun*. 2008; 38:2200–2214.
24. Ren Z, Cao W, Tong W, Chen J, Wang C. *J Heterocycl Chem*. 2008; 45:85–90.
25. Wang H, Chen Y, Cao W, Ding H, Chen J, Deng H, Shao M. *Synthesis*. 2008:3995–4001.
26. Tong W, Wang C, Zhao W, Chen J, Wu X, Zhang M, Deng H, Shao M, Ren Z, Cao W. *Synth Commun*. 2009; 39:3471–3481.
27. Wang C. *Tetrahedron Lett*. 2012; 53:7003–7005.
28. Davies WC, Lewis WPG. *J Chem Soc*. 1934:1599–1604.
29. Davies WC. *J Chem Soc*. 1935:462–464.
30. Davies WC, Addis HW. *J Chem Soc*. 1937:1622–1627.
31. One-pot phosphine-mediated Wittig reactions are uncommon. For a review see: Byrne PA, Gilheany DG. *Chem Soc Rev*. 2013; 42:6670–6696. and references within. [PubMed: 23673458]
32. Moorhoff CM. *Synth Commun*. 1998; 28:2925–2935.
33. Moorhoff CM. *Recent Res Dev Org Chem*. 2000; 4:239–259.
34. Cao W, Liu X, Peng R, He P, Lin L, Feng X. *Chem Commun*. 2013; 49:3470–3472.
35. Kantam ML, Kumar KBS, Balasubramanyam V, Venkanna GT, Figueras F. *J Mol Catal A*. 2010; 321:10–14.
36. Wu J, Yue C. *Synth Commun*. 2006; 36:2939–2947.
37. OBrien CJ, Nixon ZS, Holohan AJ, Kunkel SR, Tellez JL, Doonan BJ, Coyle EE, Lavigne F, Kang LJ, Przeworski KC. *Chem Eur J*. 2013; 19:15281–15288. [PubMed: 24115040]

38. Choudary BM, Mahendar K, Kantam ML, Ranganath KVS, Athar T. Adv Synth Catal. 2006; 348:1977–1985.
39. Ando K, Okumura M, Nagaya S. Tetrahedron Lett. 2013; 54:2026–2028.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

- Room temperature reactivity under an air atmosphere
- Rapid reaction times (5–60 minutes) and high yields (most reactions have >90% yield)
- Complete *E*-selectivity for the synthesis of α,β -unsaturated esters and ketones

Table 1Optimization of a pseudo one-pot triphenylarsine mediated synthesis of acrylates.^a

Entry	Solvent	Base	(<i>E</i>):(<i>Z</i>) ^b	Yield% ^a
1	MeCN	K_2CO_3	>19:1	65
2	MeCN	TEA	>19:1	53
3	MeCN	DIPEA	>19:1	80
4	CHCl_3	DIPEA	>19:1	67
5	DCM	DIPEA	>19:1	65
6	MeCN	DIPEA	>19:1	81 ^c
7	MeCN	DIPEA	>19:1	53 ^{c,d}

^aDiastereoselectivity was determined by ^1H NMR analysis of the crude reaction material.^bYields of isolated, analytically pure material after column chromatography.^cBoth steps were performed under an open atmosphere.^dOnly 2.5 equiv of methylbromoacetate and 1 equiv of triphenylarsine were used.

Table 2

Scope of a one-pot triphenylarsine mediated synthesis of acrylates.^a

2a , R = Ph	2b , R = <i>p</i> -C ₆ H ₄ NO ₂	2c , R = <i>p</i> -C ₆ H ₄ CF ₃
2d , R = <i>o</i> -C ₆ H ₄ Cl	2e , R = <i>m</i> -C ₆ H ₄ Cl	2f , R = <i>p</i> -C ₆ H ₄ Cl
2g , R = <i>p</i> -C ₆ H ₄ Br	2h , R = <i>p</i> -C ₆ H ₄ OMe	2i , R = <i>o</i> -C ₆ H ₄ OMe
2j , R = <i>p</i> -C ₆ H ₄ Me	2k , R = <i>p</i> -C ₆ H ₄ NMe ₂	2l , R = (<i>E</i>)-CH=CHPh
2m , R = <i>p</i> -C ₆ H ₄ N	2n , R = <i>o</i> -C ₆ H ₄ N	2o , R = 2-furyl
2p , R = <i>c</i> -C ₆ H ₁₁	2q , citronellal	2r , R = <i>n</i> -(CH ₂) ₈ CH ₃
3a , 80%, 30 min	3b , 96%, 15 min	3c , 100%, 15 min
3d , 99%, 15 min	3e , 96%, 15 min	3f , 92%, 15 min
3g , 95%, 15 min	3h , 68%, 30 min	3i , 92%, 1 h
3j , 84%, 30 min	3k , 36%, 24 h at 80 °C	3l , 81%, 1 h
3m , 87%, 15 min	3n , 94%, 15 min	3o , 83%, 30 min
3p , 70%, 30 min	3q , 72%, 30 min	3r , 83%, 30 min

^aYields of isolated, analytically pure material after column chromatography. Olefins were isolated in >19:1 (*E*):(*Z*) ratios (determined by ¹H NMR analysis).

Table 3Scope of a one-pot triphenylarsine mediated synthesis of chalcones.^a

2a , R = Ph 2i , R = <i>o</i> -C ₆ H ₄ OMe	2b , R = <i>p</i> -C ₆ H ₄ NO ₂ 2f , R = <i>p</i> -C ₆ H ₄ Cl	2c , R = <i>p</i> -C ₆ H ₄ CF ₃ 2g , R = <i>p</i> -C ₆ H ₄ Br
 4a , 98%, 30 min	 4b , 95%, 15 min	 4c , 100%, 15 min
 4d , 98%, 30 min	 4e , 97%, 15 min	 4f , 98%, 15 min

^aYields of isolated, analytically pure material after column chromatography. Olefins were isolated in >19:1 (*E*):(*Z*) ratios (determined by ¹H NMR spectroscopy).

Table 4Scope of a one-pot triphenylarsine mediated synthesis of α,β -unsaturated nitriles.^a

$\text{Br}-\text{CH}_2-\text{CN}$ 1c (5 equiv)		$\xrightarrow[\text{80 } ^\circ\text{C, air, 30 min}]{\text{AsPh}_3 \text{ (2 equiv)}}$	$\xrightarrow[\text{DIPEA (2 equiv), air, MeCN (0.1M), rt}]{\text{ArCHO 2 (1 equiv)}}$	 5a-5h
2a , R = Ph	2b , R = <i>p</i> -C ₆ H ₄ NO ₂	2d , R = <i>o</i> -C ₆ H ₄ Cl	2f , R = <i>p</i> -C ₆ H ₄ Cl	
2m , R = <i>p</i> -C ₅ H ₄ N	2g , R = <i>p</i> -C ₆ H ₄ Br	2h , R = <i>p</i> -C ₆ H ₄ OMe	2j , R = <i>p</i> -C ₆ H ₄ Me	
<hr/>				
5a , 95%, 15 min (<i>E</i>):(<i>Z</i>) = 2.4:1 ^c	5b , 98%, 5 min (<i>E</i>):(<i>Z</i>) = 1.5:1 ^b	5c , 92%, 15 min (<i>E</i>):(<i>Z</i>) = 1.9:1 ^b	5d , 89%, 15 min (<i>E</i>):(<i>Z</i>) = 2.2:1 ^c	
5e , 99%, 15 min (<i>E</i>):(<i>Z</i>) = 1.7:1 ^c	5f , 92%, 15 min (<i>E</i>):(<i>Z</i>) = 1.7:1 ^b	5g , 93%, 15 min (<i>E</i>):(<i>Z</i>) = 2.5:1 ^b	5h , 95%, 15 min (<i>E</i>):(<i>Z</i>) = 4.7:1 ^c	

^aYields of isolated, analytically pure material. (*E*):(*Z*) ratios were determined by ¹H NMR analysis of the crude reaction material.^b(*E*) and (*Z*) isomers were separable by chromatography and ¹H and ¹³C NMR data are reported for both isomers in the SI.^c(*E*) and (*Z*) isomers were not separable by chromatography and ¹H NMR data for the mixture are reported in the SI.

Table 5Temperature dependence on the observed stereoselectivity in the synthesis of unsaturated nitriles.^a

$ \begin{array}{c} \text{Br}-\text{CH}_2-\text{CN} \\ \mathbf{1c} \\ (5 \text{ equiv}) \end{array} \xrightarrow[80^\circ\text{C}, 30 \text{ min}]{\text{AsPh}_3 (2 \text{ equiv})} \xrightarrow[\text{DIPEA (2 equiv), MeCN (0.1M), } T^\circ\text{C}]{\text{ArCHO } \mathbf{2d} (1 \text{ equiv})} \begin{array}{c} \text{C}_6\text{H}_4\text{Cl}-\text{CH}=\text{CH}-\text{CN} \\ \mathbf{5c} \end{array} $		
-40 °C (<i>E</i>):(<i>Z</i>) = 1.5:1	-20 °C (<i>E</i>):(<i>Z</i>) = 1.5:1	0 °C (<i>E</i>):(<i>Z</i>) = 1.5:1
20 °C (<i>E</i>):(<i>Z</i>) = 1.9:1	40 °C (<i>E</i>):(<i>Z</i>) = 1.6:1	80 °C ^b (<i>E</i>):(<i>Z</i>) = 1.2:1

^a (*E*):(*Z*) ratios were determined from crude ¹H NMR data.^b Reaction was performed in *n*-PrCN in place of MeCN.