

Wittig reactions of moderate ylides with heteroaryl substituents at the phosphorus atom

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Received 15 February 2005; accepted 2 May 2005

Abstract—The influence of various heteroaryl substituents at the phosphorus atom to the stereoselectivity of Wittig reactions of allylic and benzylic ylides has been studied. In the case of nitrogen bearing heteroaromatic ligands at the phosphorous atom of benzyliidenephosphoranes high *E*-alkene selectivity's of up to 90:10 could be observed. NMR spectroscopic investigations revealed that substituents at the phosphorus have influences on the reactivity of ylides as well as the stability of reaction intermediates. Indications for chelation of lithium ions with ylides could also be detected and will be discussed in this article.

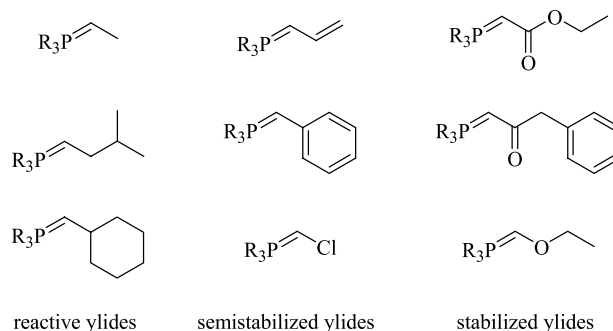
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1. Introduction

The Wittig reaction (Scheme 1) is known for more than 50 years and belongs to the most important carbon–carbon double bond forming reactions in organic chemistry¹ and is also used in large scale in industry.²

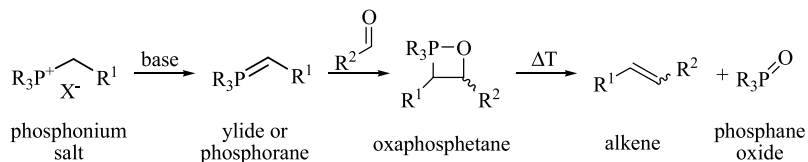
The popularity of the Wittig reaction is mainly due to the regioselective formation of the double bond at the position of the former carbonyl group and the possibility to control the stereoselectivity by applying special reaction conditions.³ The reaction conditions needed for maximum *Z*- or *E*-alkene selectivity's are strongly dependent on the nature of the ylide used (Scheme 2).

For unstabilized, so called 'reactive ylides', the selective formation of *Z*-alkenes is possible by applying 'salt free' reaction conditions.^{4,5} Salt free means performing the reactions in the absence of lithium ions, although other cations (e.g., Na⁺ or K⁺) can be present. In the presence of lithium ions most often reduced alkene selectivity's are



Scheme 2. Examples for different classes of phosphorus ylides.

observed. The negative influence of lithium ions on the stereochemistry of Wittig reactions is concentration dependent⁶ and is attributed to the fact, that lithium salts are at least partially soluble in many organic solvents. Solvated Li⁺ is able to complex the carbonyl compound, which then reacts faster with the ylide. This catalysed pathway of the Wittig reaction is rather unspecific, explaining the reduced selectivity's in the presence of Li⁺.



Scheme 1. General overview of the Wittig reaction.

Keywords: Wittig reactions; NMR spectroscopy; Ylides; Configuration; Low-temperature chemistry.

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The selective formation of *E*-alkenes in the case of reactive ylides is possible using the Schlosser methodology.⁷ For stabilized ylides the selective formation of *E*-alkenes is achieved using phosphorus ylides⁸ or PO-ylides within the Horner–Wadsworth–Emmons reaction.⁹ *Z*-Alkene selective variants of the Horner–Wadsworth–Emmons reaction with stabilized ylides are also known, for example, the Ando-methodology¹⁰ or the Still–Gennari-variant.¹¹ Despite these traditional and well established methods for the selective formation of alkenes using reactive and stabilized ylides, there is still a considerable lack of efficient methods for the selective formation of alkenes in the case of moderate or semistabilized ylides. Schlosser reported a *Z*-alkene selective variant of the Wittig reaction for moderate ylides using ‘methoxymethoxy-armed’ ylides.^{3,12} However, the yields are below 50% in many cases due to the steric demand of the 2-methoxymethoxyphenyl groups. The *E*-alkene selective formation of alkenes in the case of moderate ylides has been reported in some cases.^{13,14,15}

We were interested in the influence of heteroaromatic substituents at the phosphorus center on stereochemistry and reaction mechanism of Wittig reactions. Previously we reported that reactive ylides bearing 2-furyl substituents at the phosphorus atom react with greatly enhanced *Z*-alkene selectivity’s.¹⁶ 2-Pyridyl substituents also increase the *Z*-alkene ratio.¹⁷

Encouraged by this observation we wanted to test, if those and other heteroaromatic substituents have similar effects of increased alkene selectivity in Wittig reactions of moderate ylides.

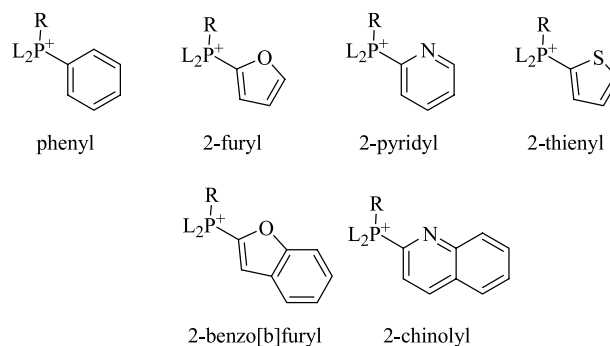
Here we want to report our investigations of the influence of a number of different heteroaromatic substituents at the phosphorus to selectivity and yield of Wittig reactions with moderate ylides. The preparative results will be analysed by means of NMR spectroscopy.

2. Results and discussion

For our studies we chose the well investigated Wittig reaction of benzaldehyde with allylidetriphenylphosphorane or benzylidetriphenylphosphorane in THF. For deprotonation of the corresponding phosphonium salts either NaHMDS or *n*-BuLi was used. We investigated the influence of the heteroaromatic systems at phosphorus by replacing one or all three standard phenyl substituents by

different heteroaromatic systems. The phosphonium salts bearing heteroaromatic substituents at phosphorus are accessible in two to three steps with an overall yield in the range of 50%.

The following heteroaromatic systems have been implemented in phosphonium salts (Scheme 3).



Scheme 3. Overview over the heteroaromatic substituents tested. R denotes allyl or benzyl groups, L represents either a phenyl substituent or a heteroaryl system.

The Wittig reactions with these heteroaromatic systems were repeated two to three times to get reliable results. In the following sections the experimental results of our investigations will be presented, divided in two parts, for the allylic and benzylic Wittig reaction, respectively.

2.1. Results of allylic Wittig reactions

The Wittig reaction of allylidetriphenylphosphorane with benzaldehyde is well investigated and results were published by a number of different authors.^{18,19,20,21} The reported yields vary from 58 to 95% and the stereochemical outcome spread from 44:56 *Z*:*E* to 75:25 *Z*:*E*. The results of our investigations concerning Wittig reactions between allylic ylides bearing heteroaromatic systems and benzaldehyde are presented in Table 1.

The standard reaction with three phenyl substituents at the phosphorus atom is indeed rather unspecific yielding *Z*:*E*-alkene ratios of 55:45 and 73:27 with *n*-BuLi and NaHMDS as base, respectively. The introduction of different heteroaromatic substituents has only minor influences of the stereochemical outcome of allylic Wittig reactions. Interestingly, Wittig reactions with one 2-pyridyl ring at

Table 1. Yield and stereochemical results of Wittig reactions in THF using allylideneheteroaryl-phenylphosphoranes and benzaldehyde with either NaHMDS or *n*-BuLi as base

Compound	<i>n</i> -BuLi		NaHMDS	
	<i>Z</i> : <i>E</i> ^a	Yield (%) ^b	<i>Z</i> : <i>E</i>	Yield (%)
AllylideneP ⁺ Ph ₃	55:45	63	73:27	68
AllylideneP ⁺ (2-thienyl)Ph ₂	66:34	68	74:26	46
AllylideneP ⁺ (2-furyl)Ph ₂	70:30	59	75:25	50
AllylideneP ⁺ (2-furyl) ₃	66:34	63	67:33	68
AllylideneP ⁺ (benzo[b]furyl)Ph ₂	61:39	33	63:37	62
AllylideneP ⁺ (2-pyridyl)Ph ₂	37:63	32	44:56	12
AllylideneP ⁺ (2-pyridyl) ₃	66:34	19	54:46	20

^a *Z*:*E* ratios were determined on isolated products using NMR-spectroscopy and GC.

^b All yields were determined on isolated products.

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