Olefination

DOI: 10.1002/anie.200902525

Recycling the Waste: The Development of a Catalytic Wittig Reaction**

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Dedicated to Avner and Marie O'Brien (née Yang)

The formation of carbon–carbon double bonds is among a select group of key transformations on which much synthetic chemistry is based. This is not surprising, as the fabrication of many natural products and drugs necessitates their assembly via alkenes.[1] Accordingly, numerous processes for their construction have been developed; besides direct elimination[2] there are four widely employed methodologies for the routine and reliable formation of alkenes:[3] 1) the Wittig reaction,[4] 2) the Peterson reaction,[5] 3) the Julia–Lythgoe[6]/Julia–Kocienski[7] olefination reactions, and 4) metathesis.[8] Of the three stoichiometric olefination processes discussed, one that may offer the possibility to evolve to a catalytic process, coupled with selective formation of *E* or *Z* alkenes, is the Wittig reaction.[4] Discovered in 1953 by Georg Wittig, the reaction involves treatment of an aldehyde or ketone with a phosphonium ylide,[4] yielding an alkene with the concomitant generation of phosphine oxide. Since its discovery the Wittig reaction has been used extensively in organic chemistry.[9] Nevertheless, the Wittig reaction suffers from several limitations: The current process is stoichiometric, and complete removal of the phosphine oxide byproduct is not always straightforward. The lack of a catalytic protocol, due to cost/benefit ratio, removes from serious consideration the possibility to control the olefination by alteration of phosphine structure This is unfortunate, as the structure of the phosphine has been shown to have a substantial impact on the stereochemical outcome of the reaction. Therefore a carefully designed phosphine may result in a selective process.[10]

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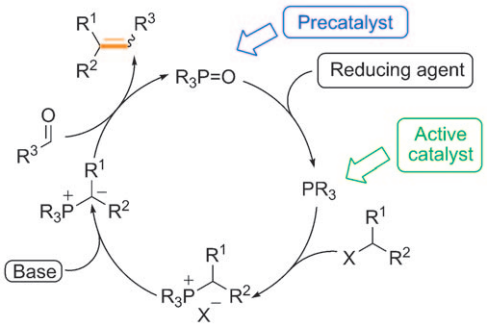
[**] We thank The University of Texas at Arlington (UTA) for funding this work and ThalesNano (Hungary) for their collaborative in-kind donation (in part) of an H-Cube Midi used to synthesize **1**. C.J.O.B. thanks Prof. Daniel W. Armstrong and Edra Dodbiba for separation of **1**. G.A.C. thanks GIOCOMMS for computational resources and CAFMaD (Wales (UK)) for personal support.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200902525.

Yet, the barriers to the development of a catalytic Wittig reaction are formidable, and the successful construction of a catalytic process relies on the completion of four steps (Scheme 1): 1) formation of the phosphonium ylide precursor, typically a phosphonium salt;[9,10] 2) generation of the phosphonium ylide, normally by deprotonation;[9,10] 3) olefination with concomitant generation of phosphine oxide;[9,10] and 4) reduction of the phosphine oxide byproduct producing phosphine to re-enter the catalytic cycle (Scheme 1). The most daunting aspect of the above processes is the requisite chemoselective reduction of the phosphine oxide byproduct to a phosphine in the presence of either aldehyde or ketone starting materials and alkene product. One could ameliorate this problem of chemoselective reduction by the replacement of phosphorus with arsenic,[11] tellurium,[12] or antimony,[13] as their corresponding oxides, owing to bond strength, are appreciably easier to reduce.[14] In fact, such an approach has led to the successful development of catalytic Wittig-type processes employing arsines and tellurides.[15] Unfortunately, significant drawbacks to the broad adoption of the aforementioned methodologies are the intrinsic high toxicity and carcinogenicity of arsenic,[16] tellurium,[17] and antimony compounds;[18] environmental anthropogenic contamination particularly of groundwater would be one concern if these reactions were performed on large-scale.[19] Importantly, the catalytic use of phosphine would not suffer from these issues; therefore a Wittig reaction catalytic in phosphine would find wider employment. Furthermore, this would marry the power of the Wittig olefination protocol to the synthetic benefits of a catalytic reaction without the poisoning issues that can plague transition-metal-catalyzed processes.[10f] Hence, the successful

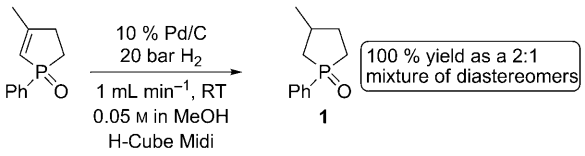


Scheme 1. Proposed catalytic Wittig reaction.

development of a stereoselective Wittig reaction that is catalytic in phosphine would represent a significant advance.

The first step toward this aim would be the construction of a phosphine-catalyzed protocol. Initial studies focused on the systematic evaluation of each step in the proposed catalytic Wittig cycle (Scheme 1) and utilized phosphine oxides rather than phosphines to remove ambiguity in the interpretation of results. The generation of product would demonstrate the completion of the steps necessary to achieve a catalytic cycle. This required the first step to be the reduction of phosphine oxide to phosphine. There are few reliable methods to reduce a phosphine oxide;[20–22] most either use harsh reducing agents, such as lithium aluminum hydride[21] or trichlorosilane, with or without an amine base.[20] However, we felt that neither of the aforementioned reduction protocols would be compatible with the overall catalytic process.

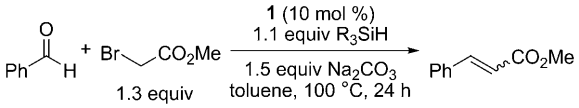
We were also not willing to risk inversion of the phosphorus center, as reduction with loss of stereointegrity would significantly detract from the realization of a catalyzed Wittig protocol with stereocontrol. From the literature we highlighted two possible reducing agents, diphenylsilane and phenylsilane, both known to reduce phosphine oxides with retention of configuration.[23] It was anticipated that the use of silanes would allow chemoselective reduction of the phosphine oxide in the presence of an aldehyde or ketone; it was assumed that hydrosilylation would not occur, as this normally requires a transition-metal catalyst.[24] In order to ensure a reasonable rate of phosphine oxide reduction, we decided to employ 3-methyl-1-phenylphospholane-1-oxide (**1**, Scheme 2) rather than triphenylphosphine oxide, as the former is more easily reduced.[25]



Scheme 2. Synthesis of phosphine oxide precatalyst.

After experimentation we discovered that **1** could be reduced at a reasonable rate (reduction in <30 min) to phosphine by diphenylsilane in toluene at 100 °C. Following optimization of reduction conditions we proceeded to construct the catalytic cycle. As shown in Table 1, the treatment of benzaldehyde with methyl bromoacetate with a 10 mol % loading of **1** in the presence of diphenylsilane and Na_2CO_3 at 100 °C yielded the desired methyl cinnamate in high yield (Table 1, entry 2).[26] Importantly, control experiments in the absence of phosphine oxide yielded no product, also triphenylphosphine oxide was found to be ineffective as a precatalyst, and both resulted in the recovery of aldehyde.[27] The above result represents to the best of our knowledge the first example of a Wittig reaction catalytic in phosphine. Further investigation of silane structure revealed that trimethoxysilane also functioned as an effective reducing agent; however, phenylsilane was less efficient and triphenylsilane was essentially ineffective (Table 1).

Table 1: Effect of the silane on the catalytic Wittig reaction.[a]

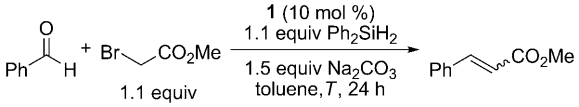


Entry	Silane	Yield [%][b]	E/Z[c]
1	Ph_3SiH	trace	n.d.
2	Ph_2SiH_2	75	>95:5
3	$PhSiH_3$	46	>95:5
4	$(MeO)_3SiH$	61	70:30

[a] Benzaldehyde (1.0 mmol), methyl bromoacetate (1.3 mmol), silane (1.1 mmol), 3.0 M in toluene. [b] Yields were determined by GC/MS/MS against a calibrated internal standard (undecane) and were performed in duplicate. [c] E/Z ratio was determined by GC/MS/MS. n.d. = not determined.

Evaluation of solvent and temperature (Table 2) revealed that altering the solvent and temperature produced little variation in yield. However, reducing the temperature to 80 °C (cf. Table 2, entries 3 and 4) led to significant amounts of

Table 2: Effects of solvent and temperature on the catalytic Wittig reaction.[a]



Entry	Solvent	T [°C]	Yield [%][b]	E/Z[c]
1	DME	100	50	>95:5
2	CH_3CN	100	52	>95:5
3	toluene	100	60	>95:5[d]
4	toluene	80	62	67:33[d]
5	toluene	70	49	67:33
6	toluene	60	33	67:33

[a] Benzaldehyde (1.0 mmol), methyl bromoacetate (1.1 mmol), diphenylsilane (1.1 mmol), 3.0 M in requisite solvent. [b] Yields were determined by GC/MS/MS against a calibrated internal standard (undecane) and were performed in duplicate. [c] E/Z ratio was determined by GC/MS/MS. [d] Identical results were obtained with diastereomerically pure **1** (major diastereomer), separated by HPLC; courtesy of Edra Dodbiba and Prof. Daniel W. Armstrong, UTA. No isomerization was observed during the reaction, indicating that reduction proceeded with retention.

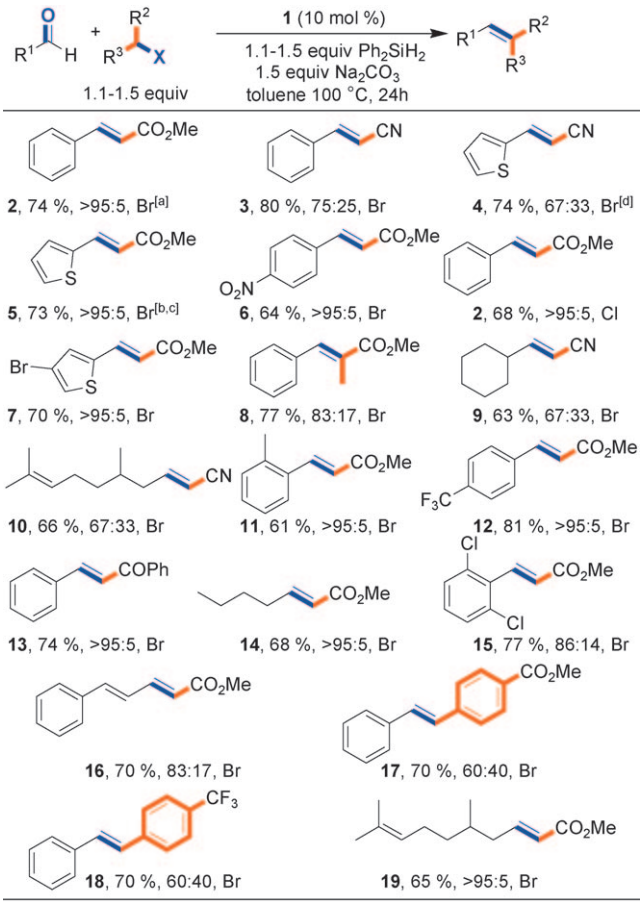
the Z product. This hints at a post-olefination isomerization event, possibly phosphine-mediated. To provide evidence for this hypothesis Z-methyl cinnamate was treated with the phosphine derived from **1** in [D_6]benzene at 100 °C (sealed tube). Complete isomerization to the E isomer was observed. The lack of a selective process when trimethoxysilane was employed (Table 1, entry 4) may result from insufficient rate of phosphine formation to effect the complete isomerization of the product after aldehyde consumption.

In order to understand the differing reactivity of **1** and triphenylphosphine and to set design rules for protocol improvement we conducted preliminary theoretical charac-

terizations[28] by a standardized methodology.[29] These calculations showed near-identical P=O/P–Ph bond lengths (1.509/1.830 Å, 1.509/1.830 Å, 1.507/1.830 Å, respectively) and O=P–Ph bond angles (113.5, 112.0, 112.3, respectively); AIM analyses[28] reiterated this, showing little difference in the electronic structure of the phosphorus–oxygen bond; bond critical points were $\rho_b = 0.2127$, $\rho_b = 0.2127$, $\rho_b = 0.2138$, respectively. This supports the suggestion that **1** is easier to reduce than triphenylphosphine oxide owing to the relief of ring strain, optimization of which may lead to more efficient catalyst recycling.[25]

Following protocol optimization, a substrate evaluation was undertaken (Scheme 3). Notable results were that heterocyclic aldehydes could be employed, with **5** and **7** produced in high yield with diastereocontrol (*E*/*Z*); also the synthesis of **10** and **19** from citronellal, and stilbenes **17** and **18** from the corresponding benzyl bromides proceeded in high yields. As anticipated, the use of methyl chloroacetate did not affect the yield (68% versus 74%). Of particular interest is the utilization of a secondary alkyl bromide that yielded a trisubstituted alkene in high yield with moderate *E*/*Z* control (product **8** in Scheme 3). The selectivity of the reaction diminished when benzyl bromides and bromoacetonitrile were utilized (compare products **3** and **18** to **2** in Scheme 3). In these cases the phosphine isomerization pathway could be significantly reduced or shut down; selectivity would then be governed by the preceding Wittig reaction.[10]

In conclusion, the first Wittig reaction catalytic in phosphine has been developed. A variety of heteroaryl, aryl, and alkyl aldehydes could be efficiently converted to the corresponding alkenes in moderate to high yield with the utilization of the phosphine oxide precatalyst **1**. This protocol also facilitated the synthesis of practical quantities of alkene, as 3.39 g of **5** was produced (67% yield) with 4 mol% loading of **1** (product **5** in Scheme 3, see footnote [c]). These results permit the development of catalytic phosphine-controlled stereoselective Wittig reactions with their ensuing synthetic benefits; such protocols and related processes are being pursued.



Scheme 3. Substrate study. For each product the compound number, yield, *E*/*Z* ratio, and halide are given. The reactions were performed in duplicate; see the Supplementary Information for details. [a] When the reaction was performed with 4 mol% of **1**, the yield was 73%. [b] When the reaction was performed on a 10.67 mmol scale with 10 mol% of **1**, the yield was 63%. [c] When the reaction was performed on a 30 mmol scale with 4 mol% of **1**, 90°C, 48 h, the yield was 67%. [d] A single reaction employing 2 equiv $(MeO)_3SiH$ resulted in 85% yield.

Received: May 12, 2009
Published online: August 17, 2009

Keywords: alkenes · homogeneous catalysis · olefination · Wittig reactions

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