

Olefination

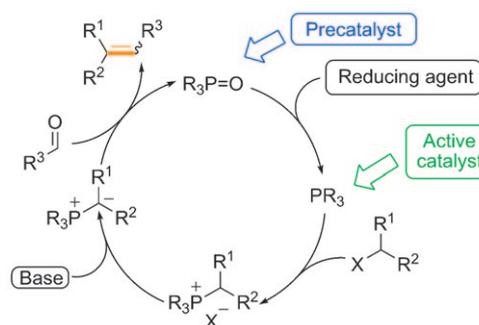
Recycling the Waste: The Development of a Catalytic Wittig Reaction**

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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]

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,



Scheme 1. Proposed catalytic Wittig reaction.

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.^[10] Hence, the successful

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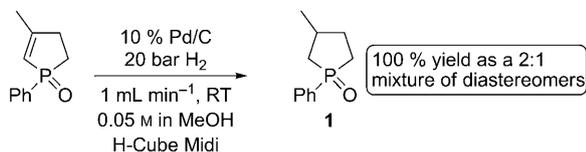
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development of a stereoselective Wittig reaction that is catalytic in phosphine would represent a significant advance.

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 Na₂CO₃ 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] | <i>E/Z</i> ^[c] |
|-------|----------------------------------|--------------------------|---------------------------|
| 1 | Ph ₃ SiH | trace | n.d. |
| 2 | Ph ₂ SiH ₂ | 75 | > 95:5 |
| 3 | PhSiH ₃ | 46 | > 95:5 |
| 4 | (MeO) ₃ SiH | 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 | <i>T</i> [°C] | Yield [%] ^[b] | <i>E/Z</i> ^[c] |
|-------|--------------------|---------------|--------------------------|---------------------------|
| 1 | DME | 100 | 50 | > 95:5 |
| 2 | CH ₃ CN | 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 [D₆]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-

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