Conference paper

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Recent advances in catalytic Wittig-type reactions based on P(III)/P(V) redox cycling

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Abstract: Numerous organic transformations are based on the use of stoichiometric amounts of phosphorus reagents. The formation of phosphane oxides from phosphanes is usually the thermodynamic driving force for these reactions. The stoichiometric amounts of phosphane oxide which are formed as by-products often significantly hamper the product purification. Organophosphorus catalysis based on P(III)/P(V) redox cycling aims to address these problems. Herein we present our recent advances in developing catalytic Wittig-type reactions. More specifically, we reported our results on catalytic Wittig reactions based on readily available $Bu_3P{=}O$ as pre-catalyst as well as the first microwave-assisted version of this reaction and the first enantioselective catalytic Wittig reaction utilizing chiral phosphane catalysts. Further developments led to the implementation of catalytic base-free Wittig reactions yielding highly functionalized alkylidene and arylidene succinates.

Keywords: ICPC-22; olefination; organic chemistry; organocatalysis; Wittig reaction.

Introduction

Carbon-carbon double bonds are ubiquitous functional groups in organic chemistry. Compounds containing this structural motive can be both feedstock chemicals and synthetic targets. One of the most important methods for the construction of carbon-carbon double bonds is the olefination of carbonyl groups utilizing phosphorus ylides. This reaction was discovered by Wittig and Geissler in 1953 [1, 2]. Over the years the so-called Wittig reaction developed into one of the most recognized methods for the chemo- and regioselective olefination of carbonyl groups. Notably, this reaction has been extensively employed in synthesis [3–6] even on industrial scale [7, 8]. A variety of reagents and modifications have emerged [9–11]. The reaction occurs between carbonyl compounds **1**, usually an aldehyde or ketone, and a carbon–phosphorus ylide **2** to yield the corresponding alkene **3** and a phosphane oxide **4** as a by-product (Scheme 1).

However, the classical Wittig reaction suffers from several drawbacks. For instance the ylide usually needs to be prepared prior to the olefination step. This requires the alkylation of a suitable phosphane **7** and subsequent deprotonation of salt **9** with stoichiometric amounts of a suitable base (Scheme 2) [9–11]. The carbon–phosphorus ylide **10** is then converted with an aldehyde or ketone to generate the alkene and a phosphane oxide as the by-product. Even though the formed alkene is typically around 125 kJ mol^{-1} less stable than the C=O bond of the respective aldehyde or ketone, the remarkable P=O bond strength of approx. 537 kJ mol^{-1} compensates for this and represents the thermodynamic driving force for the reaction. However, the separation of the phosphane oxide by-product can be challenging and sometimes significantly hampers

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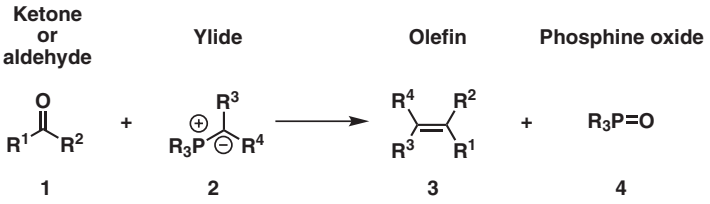
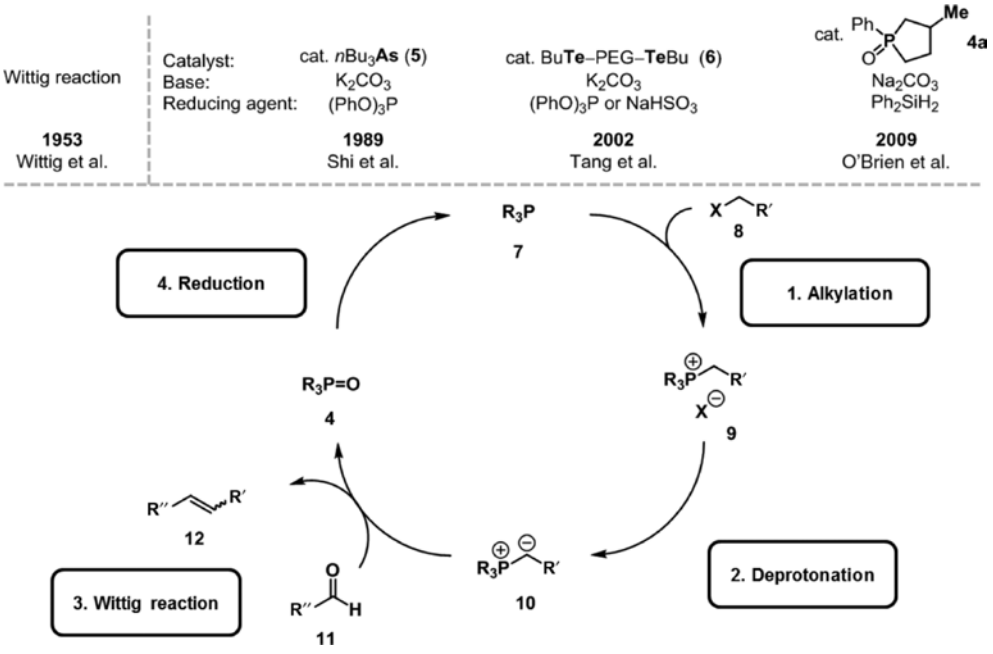


Scheme 1: The Wittig reaction.



Scheme 2: Proposed catalytic cycle for the Wittig reaction and first reports on catalytic Wittig(-type) reactions.

product purification which reduces the overall efficiency of this reaction [12, 13]. The chemoselective reduction of the P=O bond is a prerequisite for the realization of a catalytic Wittig reaction, beside the formation of the ylide and the subsequent Wittig reaction in one pot. Since the As=O bond is about 108 kJ mol^{-1} weaker compared to the respective P=O bond it is significantly easier to reduce. Thus it is not surprising that the first example on a catalytic Wittig-type reaction has been realized using nBu$_3$As (**5**) as a catalyst by Shi and coworkers in 1989 [14]. Subsequently, Tang et al. reported the use of alkyl tellurides as viable catalysts for this reaction [15, 16]. Notably, in 2009, O'Brien et al. described the first Wittig reaction using catalytic amounts of phosphane and subsequently further elaborated this methodology [17–20].

Results and discussion

Microwave assisted catalytic Wittig reaction

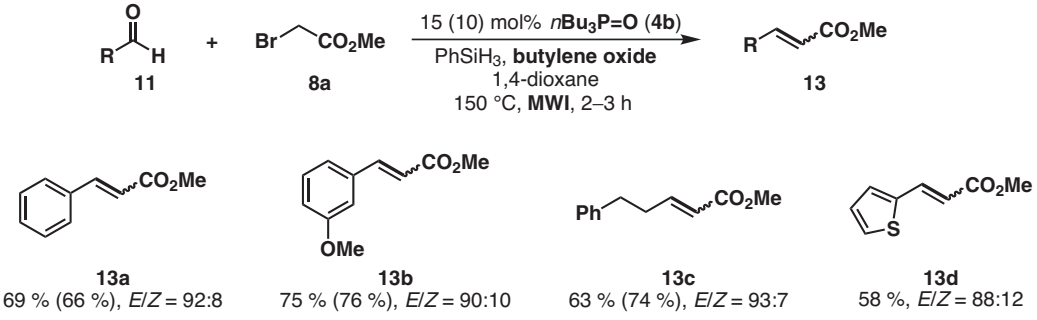
Initially, we envisioned to develop a variant of the catalytic Wittig reaction employing readily available catalysts and pre-catalysts, respectively. Thus, we screened various phosphane oxides as well as phosphanes in the presence of different silane reducing agents and solvents utilizing conventional heating as well as microwave irradiation. In this study nBu$_3$P=O (**4b**, 10–15 mol%) proved to be the most suitable

pre-catalyst while microwave heating gave superior results compared to conventional heating [21, 22]. Under the optimized reaction conditions aromatic (R = Ar), aliphatic (R = alkyl) as well as heteroaromatic (R = HetAr) substrates **11** were converted. The desired products **13** were obtained in moderate to good yields (Scheme 3).

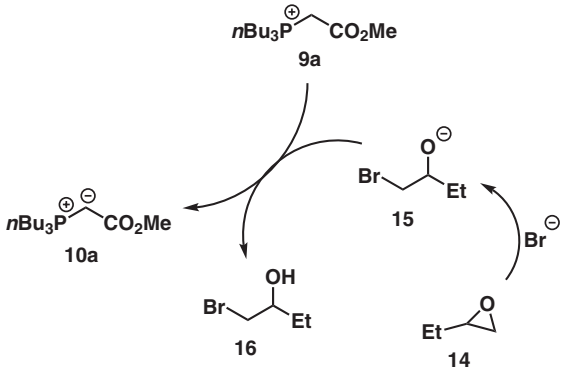
Notably, the use of capped bases (epoxides) namely butylene oxide (**14**) proved to be essential to obtain good results. Based on our experience with phosphonium salts as catalysts for the addition of CO_2 to epoxides a putative mechanism for the formation of the carbon–phosphorus ylide **10a** is shown in Scheme 4 [23–26]. The initial step of the ylide formation is the nucleophilic ring opening of the epoxide **14** by the anion (Br^-) of the in situ formed phosphonium salt **9a**. Subsequent deprotonation of the phosphonium salt **9a** by the formed alkoxide **15** yields the desired ylide **10a**. The formed bromo hydrine **16** was detected by GC-MS from the reaction mixture.

Phospholane catalyzed Wittig reaction

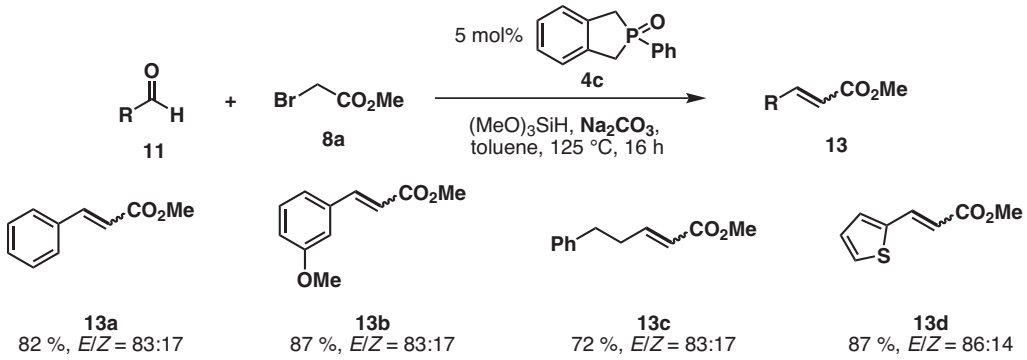
Phospholane-based catalysts are frequently employed in P(III)/P(V) redox cycling [17–20, 27, 28]. In this respect we envisioned easily accessible 2-phenylisophosphindoline oxide (**4c**) to be a promising catalyst for catalytic Wittig reactions [29]. In this case trimethoxysilane proved to be the reducing agent of choice while simple sodium carbonate could be used as base. However, to realize reproducible results it is crucial to use sodium carbonate with a grain size ≤250 µm. Under the optimized reaction conditions good to excellent yields for the desired alkenes **13** were obtained (Scheme 5).



Scheme 3: First microwave assisted catalytic Wittig reaction and selected examples. Yields in parenthesis corresponds to the use of 10 mol% catalyst **4b**.



Scheme 4: Putative mechanism for the ylide formation in the presence of butylene oxide as a capped base.



Scheme 5: Phospholane catalyzed Wittig reaction and selected examples.

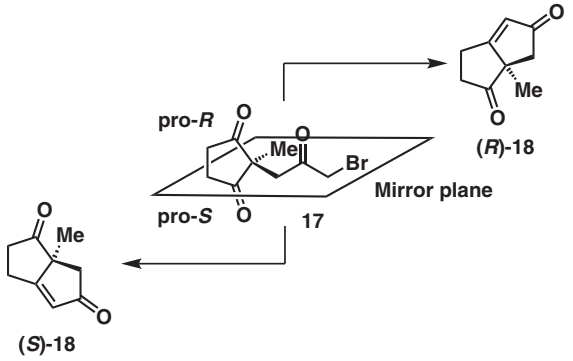
Enantioselective catalytic Wittig reaction

One major advantage of phosphorus-based organocatalysis is the good availability of chiral phosphanes e.g. **7d–7g**, which are commonly used as ligands in transition metal catalysis. Generally it is possible to realize enantioselective Wittig reactions e.g. by converting pro-chiral substrates with chiral ylides which has been reported by Trost and Curran in 1980 namely the intramolecular Wittig reaction of a pro-chiral diketone **17** to form the chiral bicyclic compound **18** (Scheme 6) [30, 31]. We envisioned the use of chiral phosphanes to be suitable catalysts to realize the first enantioselective catalytic Wittig reaction.

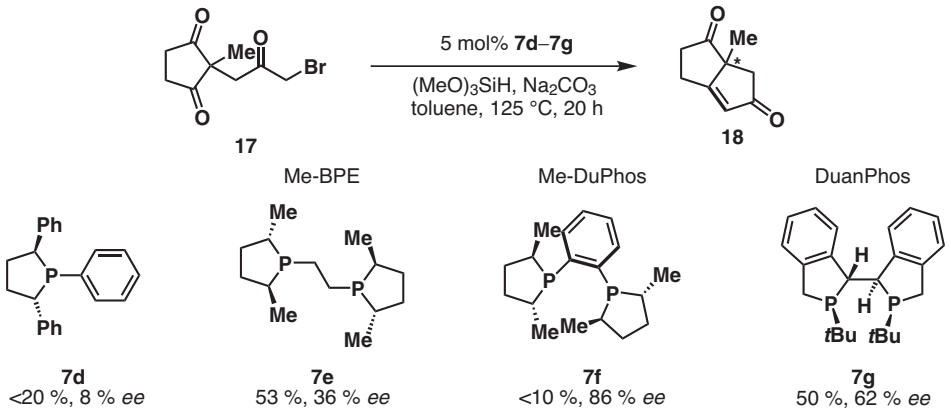
We tested various chiral phosphanes in the asymmetric synthesis of **18** from **17** as potential catalysts under the reaction conditions for catalytic Wittig reactions that have previously established in our group (Scheme 7) [29, 32]. Notably, chiral bisphosphane catalysts **7e–7g**, bearing phospholane substructures proved to be most promising. When DuanPhos **7g** was employed as the catalyst, a yield of 50 % and *ee* of 62 % were obtained. A higher enantioselectivity of over 80 % was observed for Me-Duphos **7f**, but an unsatisfying yield <10 % was achieved.

Base-free catalytic Wittig reaction

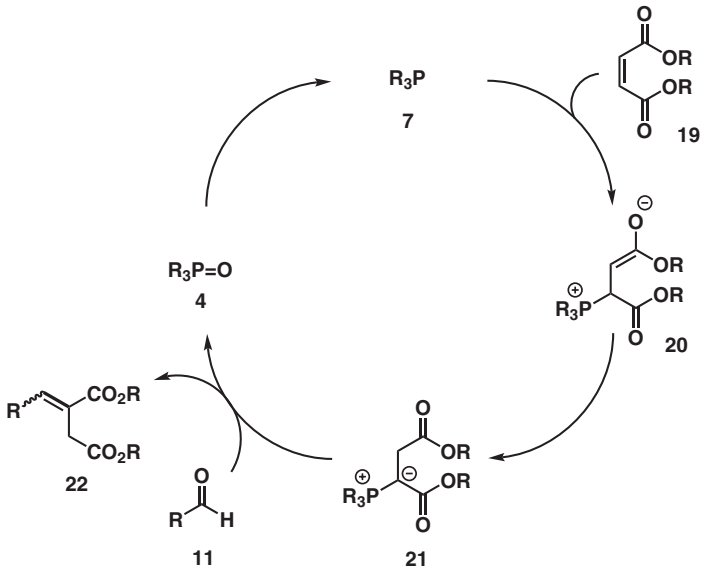
The formation of a carbon–phosphorus ylide **10** usually requires stoichiometric amounts of a base for the deprotonation of the respective phosphonium salt **9** (Scheme 2). However, we could show that a Brønsted base is not required when acceptor substituted alkenes **19** are utilized as substrates instead of alkyl halides (Scheme 8) [33–35]. The initial step is a Michael addition of the phosphane to the acceptor substituted double bond [36]. Subsequent intermolecular deprotonation or a 1,2-proton shift leads to the formation of the ylide



Scheme 6: Intramolecular Wittig reaction of pro-chiral diketones lead to chiral products.



Scheme 7: First enantioselective catalytic Wittig reaction and selected examples of chiral catalysts.

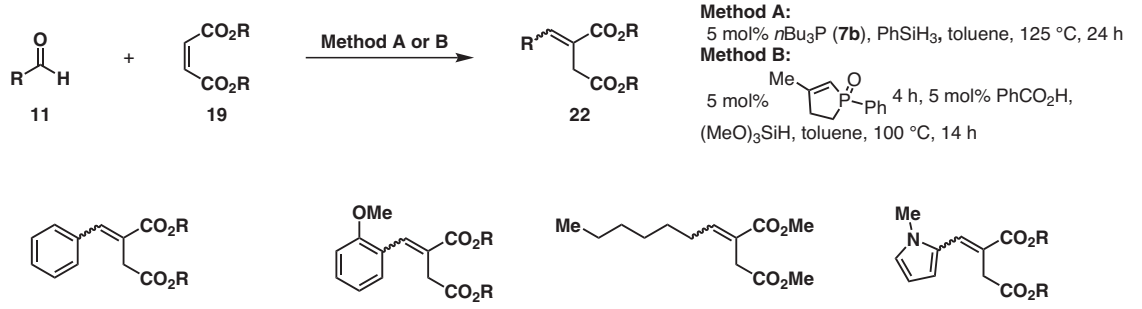


Scheme 8: Proposed mechanism for the base-free catalytic Wittig reaction.

21 which reacts with an aldehyde **11** identical to the classic Wittig reaction to liberate alkylidene or arylidene succinates **22**. Notably, these compounds have a similar substructures compared to Stobbe condensation products [37]. The in situ reduction of the formed phosphane oxide **4** to the phosphane **7** is finally closing the catalytic cycle.

We investigated two different catalytic systems utilizing simple tributyl phosphane (**7b**) as well as a phospholene-based catalyst **4h** (Scheme 9). Notably, both catalysts are readily available from commercial sources. The utilization of tributyl phosphane (**7b**) allows the conversion of differently substituted aldehydes **11** under the optimized reaction conditions to yield the respective succinate derivatives **22** in moderate to good yield [35]. However, the results could be significantly improved by employing 3-methyl-1-phenyl-2-phospholene oxide (**4h**) as the pre-catalyst [34]. In this case the addition of a Brønsted acid, specifically benzoic acid, proved to be beneficial most probably facilitating the reduction of the phosphane oxide **4h** [38].

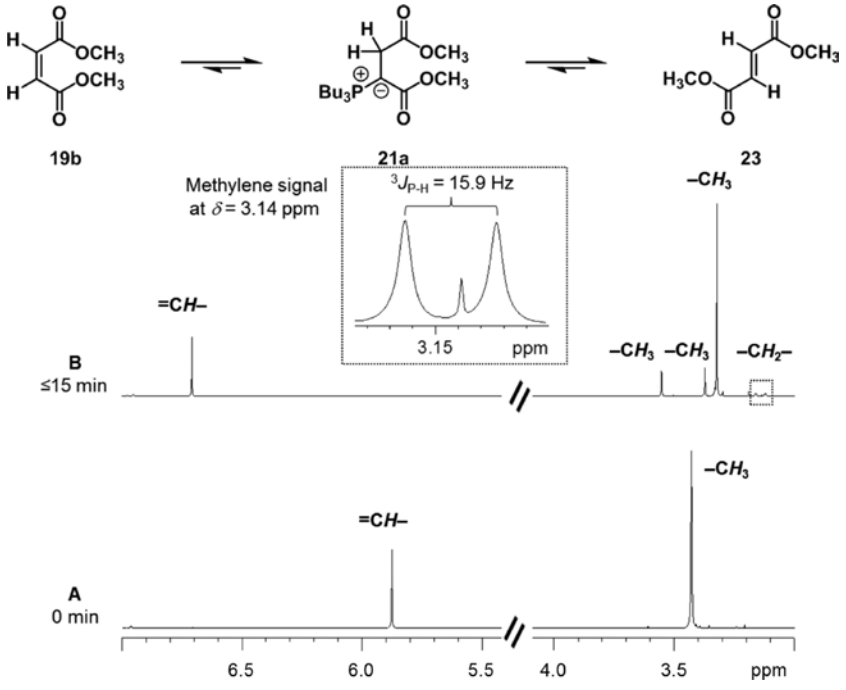
Kinetic studies indicate that the reduction of the phosphane oxide is the rate determining step of the catalytic cycle. Moreover NMR spectroscopic investigations support the Michael addition to the acceptor substituted alkene to be the initial step. Scheme 10 shows a section of the substrate **19b** (dimethyl maleate) ^{1}H NMR (0 min, spectra A). The maleate **19b** was isomerized to the fumarate **23** in less than 15 min by a Michael addition/elimination sequence in the presence of phosphane (R = *n*Bu, spectrum B). Furthermore, a second



11 19 22

22a, A: 84 %, E/Z = 96:4, (R = Et)
22b, B: 87 %, E/Z = 96:4, (R = Me)
22c, A: 61 %, E/Z = 93:7, (R = Et)
22d, B: 93 %, E/Z = 89:11, (R = Me)
22e, A: 44 %, E/Z = 87:13
22e, B: 81 %, E/Z = 76:24
22f, A: 30 %, E/Z = 92:8, (R = Et)
22g, B: 51 %, E/Z = 88:12, (R = Me)

Scheme 9: Base-free catalytic Wittig reactions and selected examples.



Scheme 10: Isomerization of dimethyl maleate (**19b**) to fumerate **23** and the respective carbon–phosphorus ylide **21a**. SpectrumA: section of the ^{1}H NMR spectra of dimethyl maleate (**19b**). Spectrum B: section of the ^{1}H NMR of a 1:1 mixture of nBu$_3$P/dimethyl maleate (1:1) in toluene-d8 at 296 K after a reaction time of ≤15 min.

compound was identified in ^{1}H NMR of the mixture. The doublet for the CH_2–group at 3.14 ppm showed a typical ^3J-coupling constant of 15.9 Hz indicating the formation of the proposed ylide **21a**. This signal collapsed to a singlet upon decoupling from phosphorus.

Conclusion

The implementation of catalytic Wittig reactions is a challenging task which requires the careful choice and evaluation of the reagents and reaction conditions to obtain the desired products in satisfying yields and to avoid unwanted side reactions. Herein, we reported our recent efforts in the development of catalytic Wittig(-type) reactions based on P(III)/P(V) redox cycling. Initially, the first microwave assisted catalytic

Wittig reaction has been realized. Subsequently, we established a protocol based on 2-phenylisophosphindoline oxide as the pre-catalyst. This was of particular interest for the development of an asymmetric version of this reaction since many chiral phosphanes comprise a similar (phospholane) substructure. Consequently, the first enantioselective catalytic Wittig reaction by means of the desymmetrization of a prochiral diketone was realized. In the presence of DuanPhos, a yield of 50 % and *ee* of 62 % was obtained which highlights the feasibility of this concept. Furthermore, a base-free variant of the catalytic Wittig reaction was established using acceptor substituted alkenes as the substrates. Additional studies revealed that this methodology could be improved by adding a Brønsted acid co-catalyst. The proposed mechanism was supported by mechanistic investigations e.g. evidence for the initial Michael addition of the phosphane catalyst as well as the formation of the phosphorus ylide were obtained by ^{1}H NMR spectroscopy. The potential of the intermolecular base-free catalytic Wittig reaction is by far not fully recognized and currently under further investigation in our group e.g. the obtained alkylidene and arylidene succinates are highly functionalized building blocks which allow a wide variety of subsequent functionalization. Moreover, we are currently developing an intramolecular version of this reaction for the synthesis of heterocycles. With regard to the classical catalytic Wittig reactions the conversion of ketones as substrates, the use of cheap reducing agents such as polymethylhydrosiloxane or even hydrogen, or general protocols for the conversion of non-stabilized ylides remain unsolved challenges which surely will be paid attention to in the future.

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