

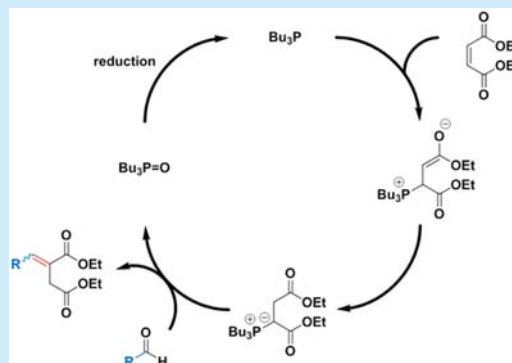
First Base-Free Catalytic Wittig Reaction

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S Supporting Information

ABSTRACT: The first base-free catalytic Wittig reaction utilizing readily available Bu_3P (5 mol %) as an organocatalyst is reported. The initial Michael addition of the phosphine to a suitable acceptor substituted alkene ultimately results in the formation of an ylide which is subsequently converted with an aldehyde. The presented ^1H NMR studies actually reveal evidence for the Michael addition and proposed ylide formation. Under the optimized reaction conditions various maleates and fumarates were converted with aromatic, heteroaromatic, and aliphatic aldehydes to evaluate the scope and limitations of this unprecedented reaction. Notably, maleates and fumarates react in a stereoconvergent fashion. The corresponding products were obtained in up to 95% isolated yield and *E/Z*-selectivities up to 99:1.



Carbon–carbon double bonds are essential and ubiquitous functional groups in chemistry, both as feedstock and as synthetic targets in their own right. One of the most fundamental transformations for their construction is the olefination of carbonyl groups. Since its discovery in 1953 by Wittig and Geissler, the so-called Wittig reaction is probably the most recognized method for the chemo- and regioselective olefination of carbonyl groups.¹ Over the ensuing years this reaction has been extensively studied and employed in synthesis² even on an industrial scale.³ A variety of reagents and modifications have emerged.⁴ The reaction occurs between carbonyl compounds, usually an aldehyde or ketone, and a phosphonium ylide to give the corresponding alkene and a phosphine oxide as a byproduct (Scheme 1).

The classical Wittig reaction suffers from several drawbacks. The ylide is usually prepared prior to the olefination by alkylation of a suitable phosphine and subsequent deprotonation which requires stoichiometric amounts of a base.⁴ Moreover, the separation of the phosphine oxide waste can be challenging and sometimes significantly hampers product purification. This reduces the overall efficiency and atom economy of this reaction.⁵ The first catalytic Wittig-type reactions have been reported based on tributylarsine and dibutyl telluride as viable catalysts.⁶ In 2009, O'Brien et al. described the first catalytic Wittig reaction (CWR, in phosphine) and subsequently further elaborated this methodology.⁷ The catalytic cycle is based on the in situ reduction of the formed phosphine oxide. This reduction strategy has also been applied to the Appel, aza-Wittig, and Staudinger reaction.⁸ Recently, we reported the first asymmetric catalytic Wittig reaction as well as a microwave assisted version.⁹ We envisioned a base-free catalytic Wittig reaction based on a three-step process depicted in Scheme 2. The Michael addition of a phosphine, e.g. Bu_3P , to an acceptor substituted alkene, e.g.

diethyl maleate (**1a**), followed by a [1,2]-H-shift should ultimately lead to the corresponding ylide from nonhalide compounds under base-free conditions.¹⁰ Subsequent conversion with an aldehyde **2** should afford succinates **3** and $\text{Bu}_3\text{P}=\text{O}$ as a byproduct. The in situ reduction of the phosphine oxide regenerating the phosphine would then close the catalytic cycle.

Herein, we prove the feasibility of our proposed reaction sequence and report the first base-free catalytic Wittig reaction. Since we intended to develop a generally easy to apply protocol only commercially available phosphines and phosphine oxides were selected as catalysts and precatalysts, respectively.¹¹

We began our studies with the synthesis of succinate **3a** at defined reaction parameters (Table 1). Most of the employed catalysts and precatalysts showed no conversion while PBu_3 was identified as the most promising candidate (entry 1, see Supporting Information). We increased the reaction temperature and screened various silane reducing agents thereby we kept the hydride equivalents constant (entries 2–5). Phenylsilane proved to be the most efficient, and the desired product **3a** was obtained in 59% yield (entry 5). Final adjustments of the reaction parameters allowed reducing the catalyst amount to 5 mol %, still providing the desired product **3a** in excellent 84% isolated yield (entry 6). Importantly, control experiments in the absence of Bu_3P yielded no product and resulted in the recovery of the starting material.

The above-mentioned results represent to the best of our knowledge the first base-free catalytic Wittig reaction. Moreover it is an easy access to alkylidene and arylidene succinates which are commonly prepared via Heck- or Stobbe-type reactions.¹² Following the protocol optimizations the substrate

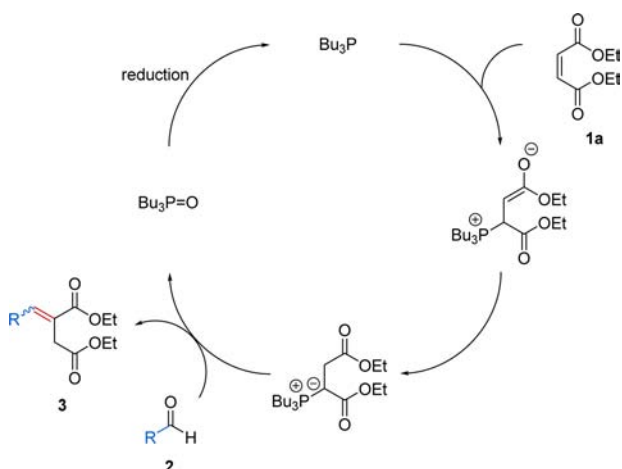
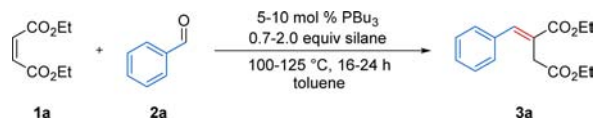
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Scheme 1. Wittig Reaction



Scheme 2. Proposed Reaction Sequence for the Base-Free Catalytic Wittig Reaction

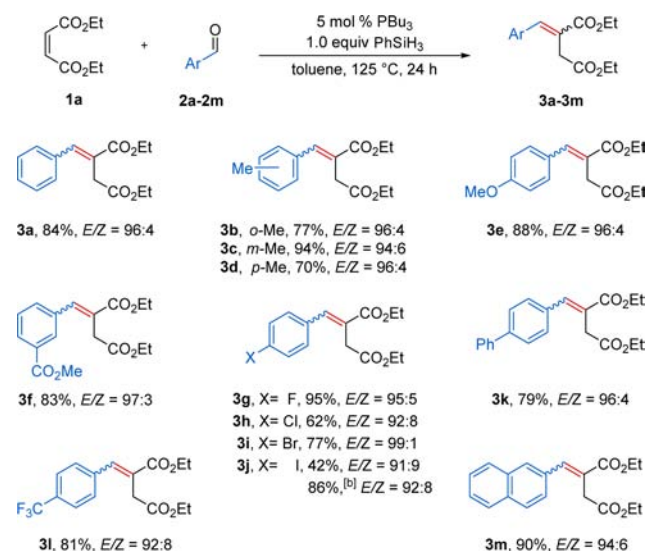
Table 1. Optimization of the Catalytic Base-Free Wittig Reaction^a

entry	Bu ₃ P	silane	equiv	temp (°C)	yield (%) ^b	<i>E/Z</i> ^c
1	10 mol %	HSi(OMe) ₃	2.0	100	22	95/5
2	10 mol %	HSi(OMe) ₃	2.0	125	35	94/6
3	10 mol %	HSi(OEt) ₃	2.0	125	17	94/6
4	10 mol %	Ph ₂ SiH ₂	1.0	125	20	95/5
5	10 mol %	PhSiH ₃	0.7	125	59	93/7
6 ^d	5 mol %	PhSiH ₃	1.0	125	84 ^e	96/4

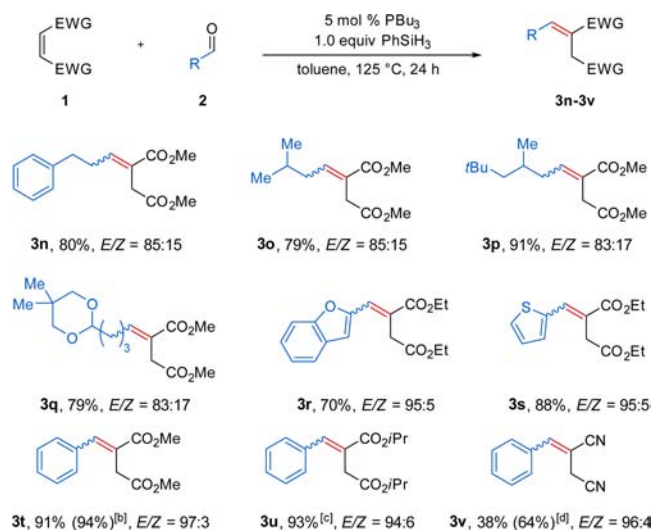
^a1a (1.2 mmol), 2a (1.0 mmol), toluene (2.0 mL), 16 h. ^bYield determined by GC methods using *n*-hexadecane as an internal standard. ^c*E/Z* ratios were determined by GC/FID. ^d1a (1.1 mmol), 24 h. ^eIsolated yield.

scope and limitation had been evaluated. Initially we converted aromatic aldehydes **2a–2m** with diethyl maleate (**1a**) in the presence of 5 mol % Bu₃P as the catalyst and 1 equiv of phenylsilane as the reducing agent at 125 °C for 24 h (Scheme 3). Under these conditions various donor and acceptor substituted aldehydes **2a–2m** with different substitution patterns could be converted into the corresponding succinates **3a–3m**. The products were obtained in good to excellent yields and very high *E*-selectivities. Interestingly, *p*-iodide derivative **3j** was obtained in only 42% yield. However, upon addition of 5 mol % benzoic acid as a cocatalyst the yield could be improved to 86%. We assume that the addition of the Brønsted acid on the one hand activates the aldehyde **2** and on the other hand facilitates the in situ reduction of the phosphine oxide.¹³

Subsequently, we studied the conversion of aliphatic **2n–2q** and heteroaromatic aldehydes **2r** and **2s** (Scheme 4). Aliphatic

Scheme 3. Conversion of Aromatic Aldehydes **2a–2m** with Diethyl Maleate (**1a**) under Base-Free Wittig Conditions^a

^aReaction conditions: **1a** (1.1 mmol), **2a–2m** (1.0 mmol), Bu₃P (5 mol %), PhSiH₃ (1.0 mmol), toluene (2.0 mL), 125 °C, 24 h. Isolated yields are given. *E/Z* ratios were determined by GC/FID. ^b5 mol % benzoic acid was added as cocatalyst.

Scheme 4. Conversion of Various Aldehydes **2** with Acceptor Substituted Alkenes **1** under Base-Free Catalytic Wittig Conditions^a

^aReaction conditions: **1** (1.1 mmol), **2** (1.0 mmol), Bu₃P (5 mol %), PhSiH₃ (1.0 mmol), toluene (2.0 mL), 125 °C, 24 h. Isolated yields are given. *E/Z* ratios were determined by GC/FID. ^bDimethyl fumarate (**1c**). ^cDiisopropyl fumarate (**1d**). ^dBu₃P (10 mol %), 48 h.

substrates **2n–2q** were reacted with dimethyl maleate **1b** giving the desired products **3n–3q** in good to excellent yields up to 91%. These products were obtained in comparable *E/Z*-selectivities which were slightly lower than those observed for aromatic products **3a–3m**.

Moreover furane **3r** and thiophene **3s** derivatives could be obtained in 70% and 88% yield, respectively. For both products the *E/Z*-selectivities were similar to those obtained for the aryl compounds **3a–3m**. Besides, we tested various acceptor substituted alkenes **1b–1e** in the conversion with **2a** to yield

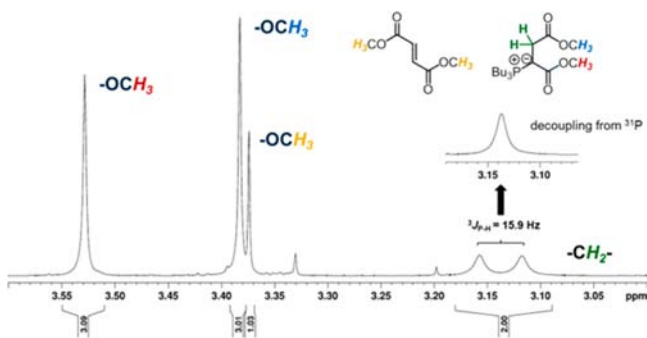


Figure 1. Segment of the ^1H NMR spectra of a 1:1 mixture Bu_3P (3.0 mmol) and **1b** (3.0 mmol) in toluene- d_8 at 23 $^\circ\text{C}$.

3t–3v. While maleates as well as fumarates generally proved to be suitable substrates, acrylates could not be converted under these conditions. Noteworthy, dimethyl maleate (**1b**) and fumarate (**1c**) react in a stereoconvergent fashion both leading to **3t** in >90% yield and identical *E/Z*-selectivity of 97:3. The diisopropyl fumarate (**1d**) gave also excellent results while fumaronitrile (**1e**) gave the desired product **3v** in only 38% yield. However, by increasing the catalyst amount and reaction time, the yield could be significantly improved to 64%.

The fact that the conversion of dimethyl maleate (**1b**) as well as fumarate **1c** with **2a** yields **3t** in identical *E/Z*-selectivity is evidence for the proposed Michael addition of the phosphine in the first step of the reaction (Scheme 2). ^1H NMR experiments revealed that in the presence of Bu_3P the maleate **1b** isomerizes rapidly to the corresponding fumarate **1c** in <15 min. Moreover, we obtained evidence for the proposed formation of a ylide. A 1:1 mixture of Bu_3P and dimethyl maleate (**1b**) showed two sets of signals in the ^1H NMR, one for the formed dimethyl fumarate (**1c**) and one for the generated ylide. Figure 1 shows the spectra between 3.0 and 3.6 ppm. The characteristic doublet at 3.14 ppm for the methylene protons show a specific $^3J_{\text{P-H}}$ coupling constant of 15.9 Hz. By decoupling from ^{31}P the doublet collapsed into a single resonance with the identical chemical shift.

In conclusion, we reported the first base-free catalytic Wittig reaction. Readily available Bu_3P (5 mol %) proved to be an efficient catalyst for this reaction. Evidence for the proposed ylide formation was obtained by ^1H NMR. The scope of the reaction was evaluated by converting various aldehydes with maleates and fumarates to the corresponding succinates under the optimized conditions. In total, 22 succinate derivatives were obtained in good to excellent isolated yields up to 95%. For aromatic and heteroaromatic compounds, very good *E/Z*-selectivities, typically around 95:5, were obtained while the selectivity for aliphatic products was slightly lower.

■ ASSOCIATED CONTENT

Supporting Information

General procedures, (pre)catalyst screening, compound characterization, and NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01352.

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Notes

The authors declare no competing financial interest.

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