P(III)/P(V) Redox Cycling Catalysis: Advances in Catalytic Wittig and Appel Reactions

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Hiermit versichere ich an Eides statt, dass ich die vorliegende Arbeit selbständig angefertigt und ohne fremde Hilfe verfasst habe. Dazu habe ich keine außer den von mir angegebenen Hilfsmitteln und Quellen verwendet. Die aus den benutzten Werken inhaltlich und wörtlich entnommenen Stellen sind als solche kenntlich gemacht.

Jan Günther Tönjes

Rostock, den 14.04.2024

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Abstract

While phosphorus mediated reactions are ubiquitous in small scale organic synthesis, the ensuing generation of phosphine oxide waste in the reaction leads to multiple problems. On the one hand, phosphine oxides often times prove to be difficult to separate from the product fraction leading to more elaborate purification procedures. On the other hand, these present a significant waste stream, which is problematic especially on larger scale reactions. One approach to solve these problems is the in situ reduction of phosphine oxide with silanes as terminal reductant in P(III)/P(V) redox cycling reactions. This enables the use of phosphines in catalytic amounts, facilitating purification and reducing phosphine oxide waste.

In this work, new methods in the field of P(III)/P(V) redox cycling catalysis were developed. The first part of the work covers the development of a catalytic base-free Wittig (BFW) reaction under environmentally friendly conditions forming highly substituted alkenes. The use of a phosphetane catalyst enabled the use of environmentally friendly poly(methyl-hydrosiloxane) as the terminal reductant and butyl acetate as solvent. Using this method, a library of exocyclic maleimides was synthesized for analysis on their cytostatic activity at the Rostock University Medical Center.

The addition of a sufficiently active electrophile can scavenge an active intermediate of the BFW and similar reactions. Activated alkenes could be brought to reaction with acyl chlorides using catalytic amounts of phosphine, forming an enol ester. Deprotonation and a following intramolecular Wittig or ring closure reaction led to substituted furans with an unusual substitution pattern. Overall, 32 tri- and tetrasubstituted furans were synthesized showing a wide functional group tolerance.

The classic Appel reaction uses stoichiometric amounts of triphenylphosphine and hazardous tetrachloromethane. While the viability for a catalytic reaction was already shown, an excess of a cancerogenous chlorination agent was needed, and the stereospecificity of the reaction showed room for improvement. In the third part of this work, a phosphetane catalyst proved to be exceptionally active in the catalytic Appel chlorination using substoichiometric amounts of hexachloroacetone as the chlorine source. A wide functional group tolerance was shown, and chiral secondary alcohols were converted to the respective chlorides in good to excellent enantiomeric ratios. Also, the dichlorination of epoxides in enantiomeric ratios of up to >99:1 was possible.

Kurzfassung

Während phosphorvermittelte Reaktionen in der organischen Synthese im Labormaßstab weit verbreitet ist, führt die daraus resultierende Erzeugung von Phosphanoxid-Abfällen zu mehreren Problemen. Auf der einen Seite lassen sich Phosphanoxide oft nur schwer von der Produktfraktion abtrennen, was aufwendigere Reinigungsschritte notwendig macht. Auf der anderen Seite stellen diese einen beträchtlichen Abfallstrom dar, was insbesondere bei Reaktionen im größeren Maßstab problematisch ist. Ein Ansatz zur Lösung dieser Probleme ist die in situ-Reduktion von Phosphanoxiden mithilfe von Silanen als terminalen Reduktionsmitteln in P(III)/P(V)-Redoxreaktionen. Dies ermöglicht die Verwendung von Phosphanen in katalytischen Mengen, erleichtert die Reinigung der Produkte und verringert den Phosphanoxid-Abfall.

In dieser Arbeit wurden neue Methoden auf dem Gebiet der P(III)/P(V)-Redoxkatalyse entwickelt. Der erste Teil der Arbeit umfasst die Entwicklung einer katalytischen basenfreien Wittig-Reaktion (BFW) unter umweltfreundlichen Gesichtspunkten, bei der hoch-substituierte Alkene gebildet werden. Der Einsatz eines Phosphetan-Katalysators ermöglicht die Verwendung von umweltfreundlichen Poly(methylhydrosiloxan) als terminalem Reduktionsmittel und Butylacetat als Lösungsmittel. Mit dieser Methode wurde eine Sammlung exozyclischer Maleimide synthetisiert, welche in der Universitätsmedizin Rostock auf ihre zytostatische Aktivität untersucht wurden.

Durch Zugabe eines ausreichend starken Elektrophils kann ein aktives Intermediat der BFW und ähnlicher Reaktionen abgefangen werden. Aktivierte Alkene konnten mit Carbonsäurechloriden unter Verwendung katalytischer Mengen von Phosphanen zur Reaktion gebracht werden, wodurch Enolester gebildet wurden. Eine folgende Deprotonierung und eine anschließende intramolekulare Wittig- oder Ringschlussreaktion führte zu substituierten Furanen mit einem unüblichen Substitutionsmuster. Insgesamt wurden 32 tri- und tetrasubstituierte Furane mit einer hohen Toleranz gegenüber funktionellen Gruppen synthetisiert.

Die klassische Appel-Reaktion verwendet stöchiometrische Mengen an Triphenylphosphan und schädlichem Tetrachlormethan. Die Durchführbarkeit einer katalytischen Reaktion wurde zwar bereits gezeigt, doch war ein Überschuss an krebserregendem Chlorierungsmittel notwendig und die Stereospezifität der Reaktion war verbesserungswürdig. Im dritten Teil dieser Arbeit zeigte sich ein Phosphetan-Katalysator als außergewöhnlich aktiv bei Verwendung substöchiometrischen Mengen von Hexachloraceton als Chlorquelle. Es zeigte sich eine breite Toleranz gegenüber funktionellen Gruppen, und chirale sekundäre Alkohole wurden in guten bis ausgezeichneten Enantiomerenverhältnissen in die entsprechenden Chloride umgewandelt. Auch die Dichlorierung von Epoxiden in Enantiomerenverhältnissen von bis zu >99:1 war möglich.

List of abbreviations

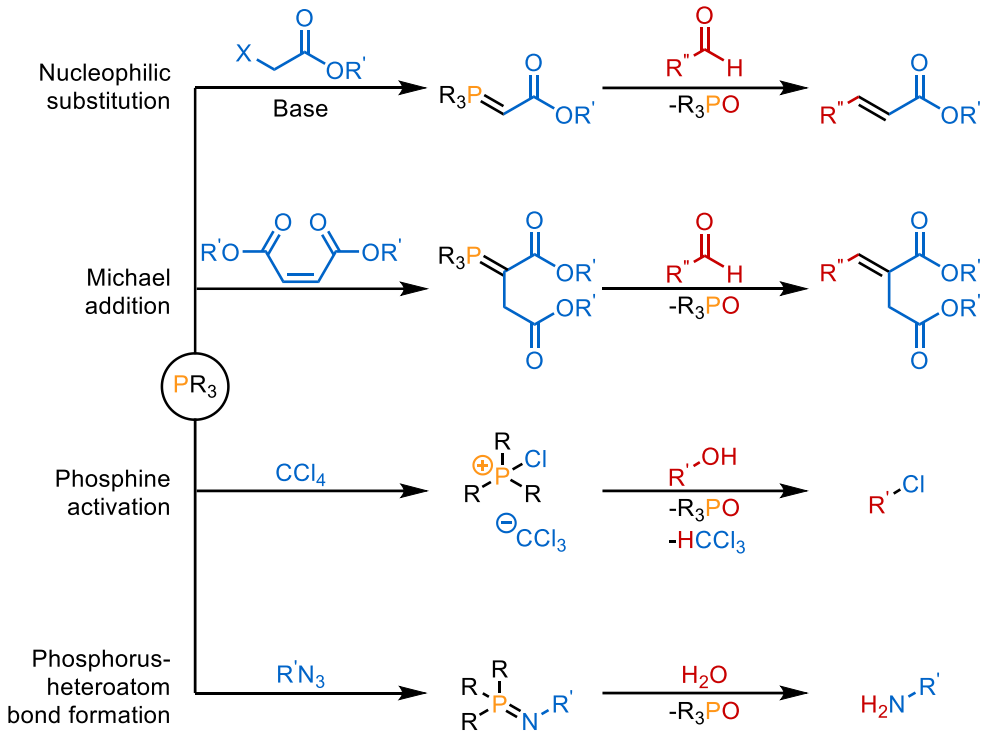
Ac	Acetyl
Alk	Alkyl
Ar	Aryl
BFW	base-free Wittig reaction
Bn	Benzyl
Bu	Butyl
Bz	Benzoyl
cat.	Catalyst
CED	Cumulative energy demand
CPME	Cyclopentyl methyl ether
DEBM	Diethyl bromomalonate
DEMBM	Diethyl 2-bromo-2-methyl-malonate
DFT	Density functional theory
DIPEA	*N*,*N*-Diisopropylethylamine
dr	diastereomeric ratio
ee	enantiomeric excess
er	enantiomeric ratio
equiv	Equivalent
Et	Ethyl
EWG	Electron withdrawing group
FID	Flame ionization detector
GC	Gas chromatography
GHG	Greenhouse gas
*i*Pr	*iso*-Propyl
LCA	Life cycle assessment
Me	Methyl
MeTHF	2-Methyl-tetrahydrofuran
MS	Mass spectrometry
NMR	Nuclear magnetic resonance spectrometry
Nu	Nucleophile
Ph	Phenyl
PMHS	Poly(methylhydrosiloxane)
R	Rest
S_N	Nucleophilic substitution
t	Time
T	Temperature
TBDMS	*tert*-Butyldimethylsilyl
*t*Bu	*tert*-Butyl
THF	Tetrahydrofuran
tol	Toluene

Contents

1 Introduction

1.1 Stoichiometric phosphorus-mediated reactions

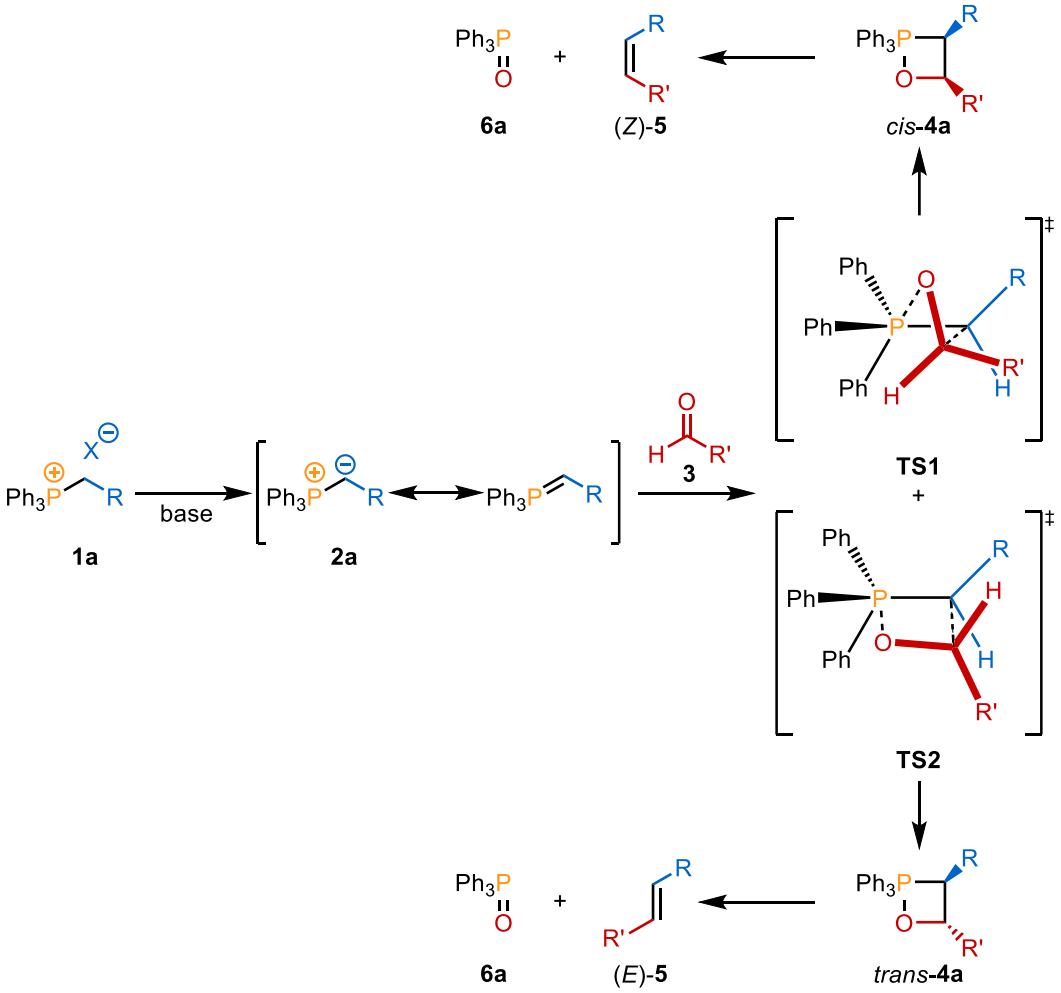
Starting with the development of the Staudinger reaction in 1919 and the Wittig reaction in 1953, trisubstituted phosphines found widespread use as reactants in organic synthesis.[1] The Wittig reaction is one of the most important reactions for the formation of olefins, while the Staudinger reaction opens the possibility to use azides as synthons for primary amines by conducting a mild reduction. Over the years additional methods were developed, such as the Appel reaction, which can be used to halogenate alcohols, or the Cadogan reaction, reducing nitro substituents to nitroso groups or amines in cyclizations.[2] While all these reactions rely on the formation of thermodynamically stable phosphorus-heteroatom double bonds as a driving force, and especially on the formation of highly stable phosphine oxides, these methods can be divided into four groups based on their general reaction mechanism and the first reaction step (Scheme 1).



Scheme 1: Four general groups of phosphine reactivity in phosphine oxide forming reactions.

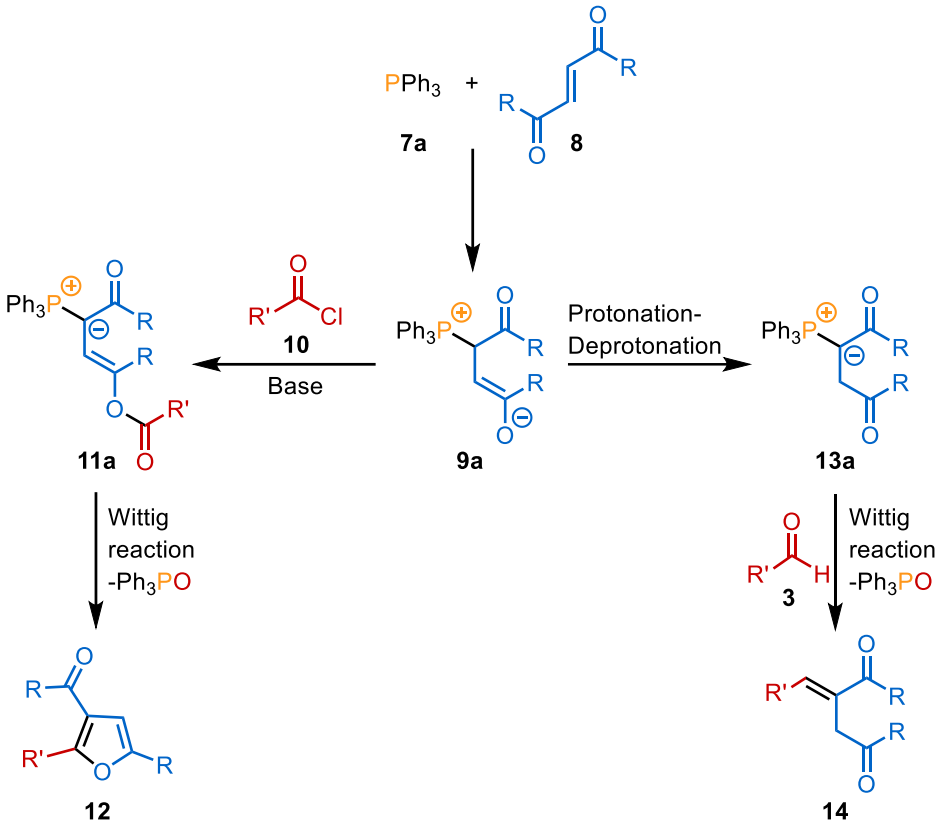
The ylid necessary for the classical Wittig reaction is usually formed by the reaction of a phosphine with an alkyl halide in a nucleophilic substitution, forming the phosphonium salt **1a** (Scheme 2). Deprotonation with a base leads to the ylid **2a**, which in turn can react with an aldehyde **3** towards an olefin **5** via an oxaphosphetane intermediate **4a**. The mechanism of the Wittig reaction has been thoroughly studied.[3] Under lithium salt free conditions, the ylid reacts with an aldehyde in a [2+2] cycloaddition to form the oxaphosphetane **4a**. Depending on both the electronic properties of ylid **2a** and carbonyl compound **3**, as well as the steric

environment, two different transition states are possible. Transition state **TS1** is kinetically favored and reduces the steric interactions between the aldehyde **3** and both the aryl groups on the phosphorus, as well as the substituent R on the ylid **2a**. This leads to the formation of the *cis*-oxaphosphetane *cis*-**4a**, which reacts to the (*Z*)-alkene (*Z*)-**5** and phosphine oxide **6a** in a [2+2] cycloreversion reaction. Transition state **TS2** shows the lowest energy *trans*-selective transition state for unstabilized ylids. Here, the steric interaction of the substituents R and R' is minimized but the carbonyl oxygen is influenced by the aryl groups on the phosphorus. This leads to the formation of the *trans*-oxaphosphetane *trans*-**4a** and subsequently to a (*E*)-alkene (*E*)-**5**. In the classic Wittig reaction, the stereoselectivity largely depends on the substrate used. Stabilized ylids, such as an ylid with a neighboring electron withdrawing group, lead mainly to the formation of the (*E*)-isomer, while alkyl substituted ylids react towards the (*Z*)-isomer. Semi-stabilized ylids often form an isomeric mixture. Various modifications on the classic Wittig reaction were developed to improve the selectivity for either isomer.[4]



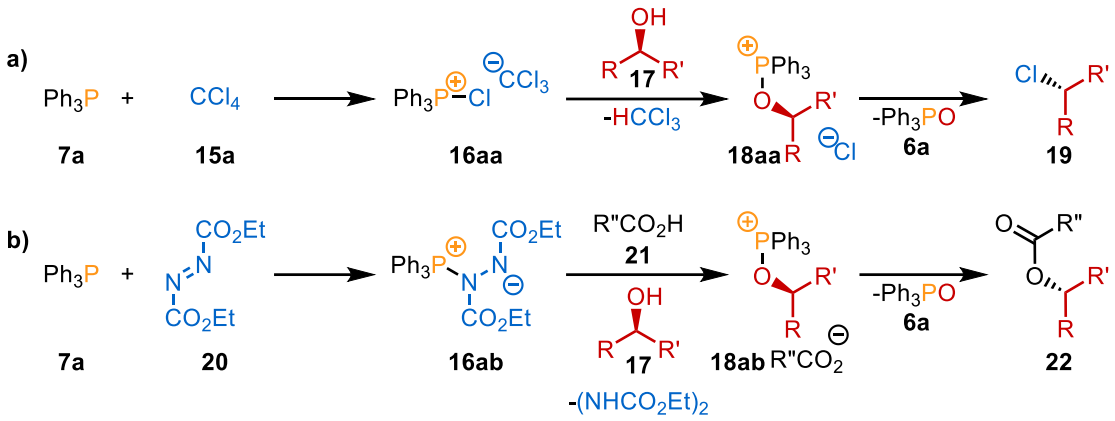
Scheme 2: Reaction pathways of the Wittig reaction.

In the closely related base-free Wittig reaction first published by McCombie and Luchaco, the first reaction step involves the Michael addition of the trisubstituted phosphine **7a** and an activated alkene **8** forming an enolate **9a** (Scheme 3).[5] A protonation/deprotonation step leads to the formation of the stabilized ylid **13a**, which reacts in the same way as the classically generated ylid. For the formation of the ylid no additional base is required. In other methods, such as the formation of heterocycles, the enolate can further react with other electrophiles, which in turn can lead to various reaction cascades, e.g., the reaction of the enolate **9a** with acyl chloride **10** in the presence of an amine base was shown to form furans **12** in an intramolecular Wittig reaction.[6]



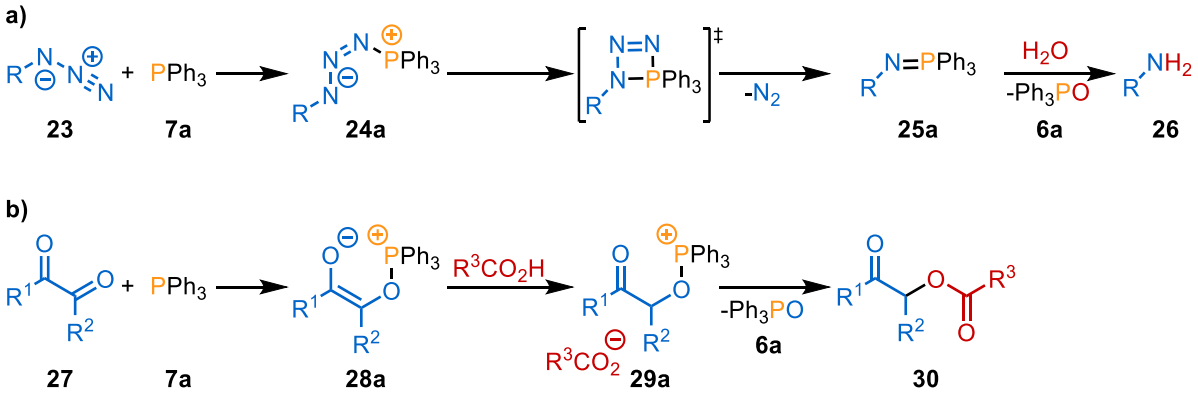
Scheme 3: The base-free Wittig reaction and the furan formation following the SNt of enolate and acyl chloride.

The third general reaction principle involves the prior activation of the phosphine **7**. In the classical Appel reaction tetrachloromethane **15a** reacts with the phosphine **7a** under formation of the chlorophosphonium salt **16aa** (Scheme 4a).[2a] The alcohol **17** is deprotonated by the trichloromethanide and reacts with the phosphonium ion in a nucleophilic substitution, forming an alkoxyphosphonium chloride **18aa**, which in turn can form the alkyl chloride **19**. A similar activation step to a phosphonium salt can be seen in the Mitsunobu reaction, in which the activation of the phosphine **7a** happens by reaction with an azodicarboxylate **20** (Scheme 4b).[7]



Scheme 4: The Appel reaction (**a**) and Mitsunobu reaction (**b**) as examples for the phosphine activation mechanism.

In a fourth reaction principle, the phosphine is reacting under formation of phosphorus-heteroatom bonds. Examples include the Cadogan reaction, the aza-Wittig reaction, the Staudinger reaction, or the Kukhtin-Ramirez reaction.[1a, 2b, 8] In the Staudinger reaction, the phosphine **7a** is reacting with an azide **23** under expulsion of dinitrogen, forming an aza-ylid **25a** (Scheme 5a). This can be hydrolyzed to the respective amine **26** and the phosphine oxide **6a**. Alternatively, aza-ylids can also react with e.g. aldehydes towards imines.[9] In the Kuhktin-Ramirez reaction, the nucleophilic attack of the phosphine **7a** on a carbonyl oxygen of 1,2-dione **27** leads to the formation of enolate **28a** (Scheme 5b).[10] A protonation of this species opens up the activated alcohol **29a** for a nucleophilic attack, forming the ketone **30** and phosphine oxide **6a**.

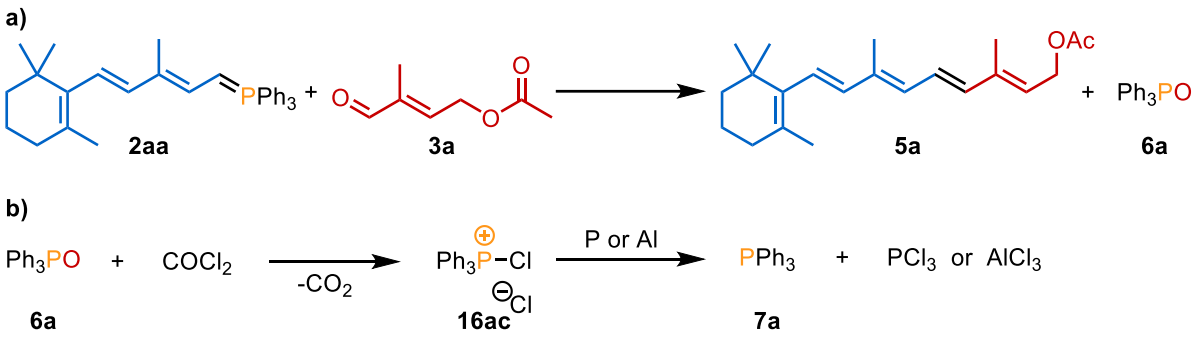


Scheme 5: Staudinger reaction (**a**) and Kukhtin-Ramirez reaction (**b**) as examples for the reactions of phosphines under attack of heteroatoms.

1.2 Separation of phosphine oxides

A common feature of these reaction is the formation of stoichiometric amounts of phosphine oxide of relatively high molecular weight, which can lead to multiple problems. On the one hand work-up of the reaction mixture can lead to separation problems, and even product separation by chromatography can be difficult due to carry-over of the phosphine oxide.

Multiple methods to address this issue have been developed, such as the immobilization of the phosphine, the use of water soluble phosphines, or precipitation of the oxide with $ZnCl_2$.[11] On the other hand, the formed phosphine oxide represents a considerable amount of waste. While on a lab scale the oxide generally is discarded, on an industrial scale this would pose a disadvantage for reactions of this type. Yamamoto et al. developed a method for separation and ex-situ reduction of the phosphine oxide using a phosphine with perfluoroalkyl side-chain and a biphasic reaction mixture with fluorous solvents.[12] Here, after separation, the phosphine oxide is reduced to the phosphine using DIBAL-H and protected by forming a borane complex, which could be reused. The Wittig reaction is used industrially by BASF in a key step in the synthesis of Vitamin A acetate on a scale of 3800 t/a.[13] Ylid **2aa** and aldehyde **3a** react in the final step of the reaction sequence, forming the desired Vitamin **5a** and triphenylphosphine oxide **6a**, which is extracted from the reaction mixture and subsequently activated with phosgene, forming a chlorophosphonium chloride **16ac** (Scheme 6).[14] A reduction is conducted by either elemental phosphorus or aluminum, forming the respective trichlorides as a coupling product and regenerating triphenylphosphine **7a**, which can be reused in the reaction.[15] While this reaction sequence is feasible on an industrial scale, the use of hazardous phosgene makes it unsuitable for smaller scale reactions, while the problem of separation of reaction product and phosphine oxide remain.

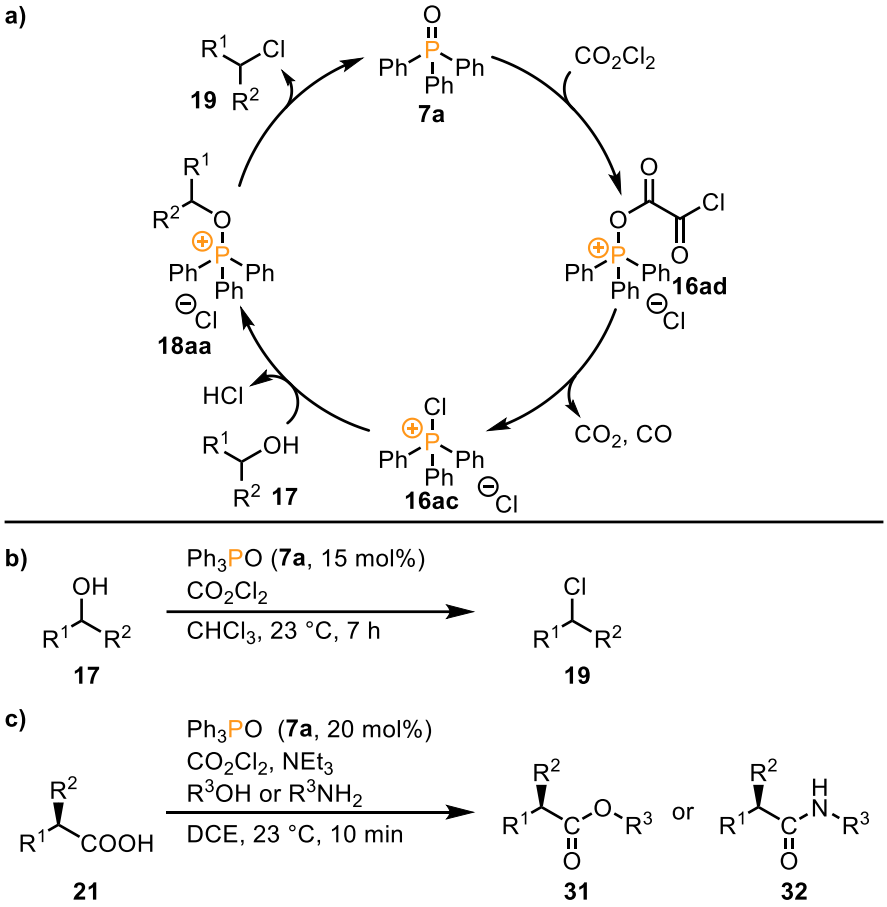


Scheme 6: Wittig reaction in the formation of Vitamin A acetate and subsequent ex-situ reduction of the formed phosphine oxide.

1.3 Redox neutral catalytic methods

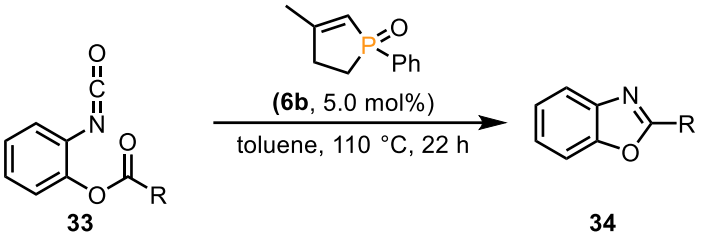
To address these issues, methods for the in situ activation of phosphine oxides were developed for some of the classic reactions mentioned above. Denton et al. could show the feasibility of activating triphenylphosphine oxide **6a** in the reaction mixture with oxalyl chloride, forming chlorophosphonium chloride **16ac**, while expelling carbon monoxide and carbon dioxide (Scheme 7a). This chloride could then react in an Appel type reaction with alcohols, forming the respective alkyl chlorides **19** (Scheme 7b).[16] This in situ activation enabled the use of the phosphine in catalytic amounts. Further development also enabled the conversion of epoxides to 1,2-dichlorides, aldehydes to geminal dichlorides and the activation of carboxylic acids to acid chlorides with subsequent reaction with amines or alcohols to form

esters and amides (Scheme 7c).[17] Exchange of oxalyl chloride with triphosgene by Köring et al. also enabled the formation of imidoyl chlorides from secondary amides.[18] Nevertheless, the use of highly activated and hazardous chlorides, as well as the formation of HCl in the reaction makes these reactions challenging in regards to their functional group tolerance.



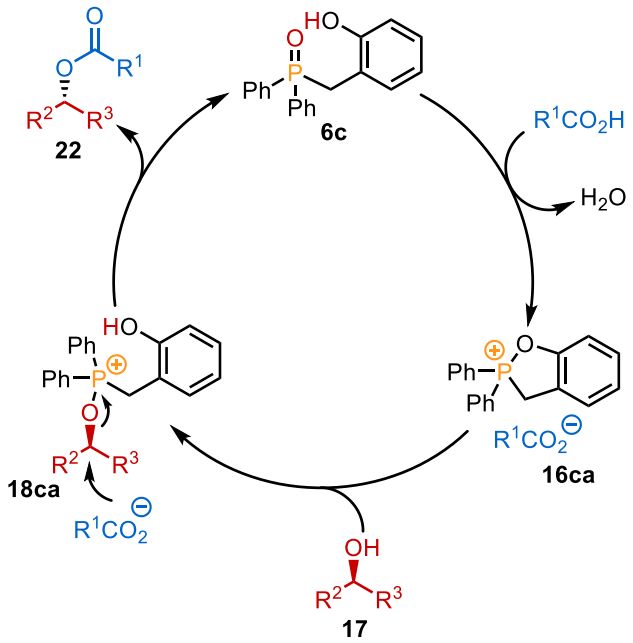
Scheme 7: In situ activation of phosphine oxides with reactive chlorides in the chlorination of alcohols and activation of carboxylic acids.

A different approach towards the activation of phosphine oxides was shown by Marsden, McGonagle and McKeever-Abbas in the reaction of phospholene oxide **6b** with an isocyanate **33**, forming an aza-ylid under release of CO_2 (Scheme 8).[19] This intermediate can subsequently react intramolecularly to the benzoxazole **34**. This approach was also used in the formation of benzodiazepinones, or in an aza-Wittig/Diels-Alder reaction sequence.[20]



Scheme 8: In situ activation of phosphine oxides using isocyanates in a catalytic aza-Wittig cyclization.

The Misunobu reaction is widely used in natural product synthesis when the stereochemistry on a hydroxy group must be inverted.[7a, 21] Here, the phosphine is activated by reaction with an azodicarboxylate forming an activated phosphonium intermediate, which in turn reacts with the alcohol. This hydroxy group usually is then substituted by a carboxylate under inversion of the stereochemistry. Due to the large amounts of reactants needed, this reaction has a very low atom economy. Attempts to recycle the reactions in situ proved to be challenging, since both a reductant and an oxidant were needed to recycle the phosphine oxide and the formed hydrazine.[22] An alternate, redox neutral method was developed by Denton and coworkers.[23] Here, a phosphonium intermediate **16ca** is generated by the intramolecular attack of a phenolic hydroxyl group on a phosphine oxide **6c** under acidic conditions, leading to the release of water (Scheme 9).



Scheme 9: Proposed mechanism of the redox-neutral organocatalytic Mitsunobu reaction.

Activation and substitution of hydroxyl groups under stereoinversion led to the formation of a set of esters **22** with good to excellent enantiomeric ratios. Unsolved problems of this reaction remain the need for high reaction temperatures, long reaction times, strong acids and need for azeotropic distillation to remove the water. The mechanism of this reaction was further explored by DFT calculations by Houk and coworkers.[24] The deoxyhalogenation was

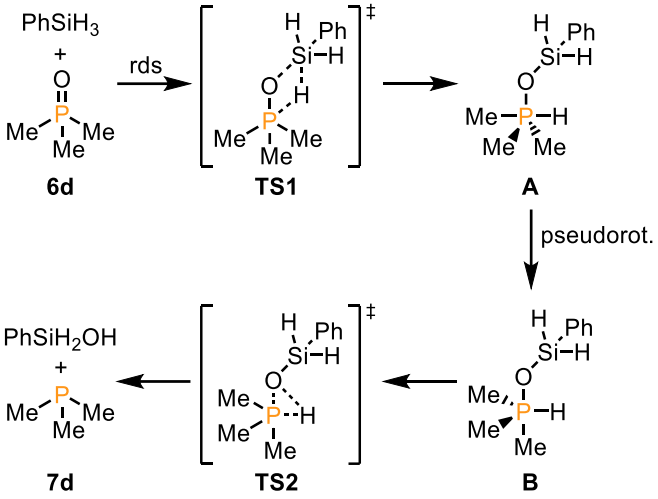
shown to be possible using this general method by Wang et al. with a modified catalyst.[25] At reaction temperatures of 160 °C to 170 °C the iodination and bromination of alcohols was possible, while subsequent substitution of the generated iodides also enabled the formation of chlorides and fluorides. Using a similar reaction principle but on a basis of phosphates instead of phosphines, Movahed et al. could activate carboxylic acids for the formation of amides, as well as amides in the formation of oxazolines.[26]

1.4 The development of P(III)/P(V) redox cycling

1.4.1 Reduction of phosphine oxides

An alternative to the in situ activation of phosphine oxides with highly reactive substrates or harsh reaction conditions would be the reduction of catalytic amounts of phosphine oxide in the reaction mixture. This would open new reaction pathways and substrates that are not available in redox neutral catalytic reactions, such as the broad field of Wittig- or Cadogan-type reactions. In these classical types of phosphine mediated reactions, usually acyclic, tertiary phosphines, such as triphenylphosphine, are used. However, the strength of the P=O bond makes the selective reduction challenging. Traditionally, highly reactive reducing agents or harsh reaction conditions were required, lowering the functional group tolerance on the phosphine substituents and making the reduction incompatible with most subsequent reactions.[27] Silanes were found to be viable for the reduction of acyclic phosphines, but also here high reaction temperatures were needed.[28] Beller and coworkers showed the advantages of using diphenyl phosphoric acid as a catalyst in the reduction of phosphine oxides at 100 °C.[29] Further development showed the viability of perfluorinated aromatic boranes, triflic acid or trityl borates as catalysts for the reduction reaction using organo-silanes.[30] Using a highly active silane and a high loading of phosphoric acid catalyst, even the reduction of triphenylphosphine oxide at room temperature was shown to be possible with a reaction time of 48 h.[31]

Also, the reducibility of cyclic phosphine oxides was shown to be strongly increased.[27d, 32] This reactivity has been rationalized with DFT calculations by Kirk, O'Brien and Krenske (Scheme 10).[33] In a first step, the mechanism in the reaction of trimethylphosphine oxide and phenyl-silane was calculated. The rate determining step of the reaction is the hydride transfer from the silane to the phosphorus with concerted oxygen-silicon bond formation via a four membered transition state **TS1**.[34] The trigonal bipyramidal phosphorane **A** undergoes a pseudorotation, followed by the elimination of silanol via a three membered transition state **TS2**, forming the reduced trimethylphosphine **7d**.



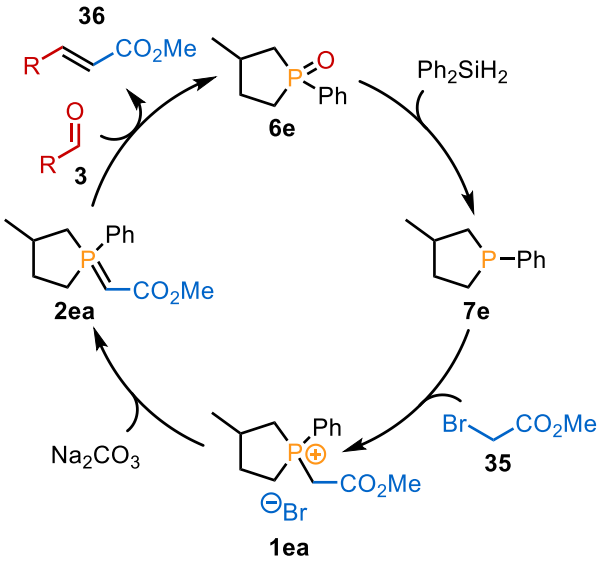
Scheme 10: Proposed mechanism for the reduction of phosphine oxides with organosilanes.

The authors argue that the interaction of the oxygen lone pairs of the phosphine oxide and an [Si]-H antibonding orbital is most influential on the energy on the transition state of the hydride transfer reaction step, thus, making electron rich phosphines easier to reduce. The analysis of five membered cyclic phosphine oxides showed an even higher influence on the transition state energy due to their ground state geometries. With a CPC angle close to 90°, these closely resemble the transition state geometries, thus, limiting the deformation needed for the rate-determining hydride transfer step.

1.4.2 The catalytic Wittig reaction by P(III)/P(V) redox cycling

A general method using an approach more closely related to the classic name reactions was developed by O'Brien et al. in 2009 with the in situ reduction of phosphine oxides in the catalytic Wittig reaction.[35] While catalytic Wittig type reactions were already known using arsenic or antimony catalysts, O'Brien et al. were the first to show the viability to use silanes as terminal reductants for the in situ reduction of cyclic phosphines.[36] With this P(III)/P(V) redox cycling method, activated bromides were converted with a variety of aryl and alkyl aldehydes, forming the corresponding olefins (Scheme 11).

In the first step of the reaction, the phosphine oxide **6e** is reduced in situ by an organosilane to generate the active phosphine **7e**. This reacts in a nucleophilic substitution with an activated bromide **35**, forming a bromophosphonium salt **1ea**. Deprotonation with a base leads to the formation of a stabilized ylid **2ea**, which in turn can react with an aldehyde **3** in a Wittig olefination, regenerating the phosphine oxide **6e**. Based on this reaction principle a set of activated halides **35** were converted with a phospholane catalyst **6e** at a reaction temperature of 100 °C with different alkyl and aryl aldehydes **3**, forming activated alkenes **36** in generally moderate to good yields up to 81%. These activated halides included bromoacetates, bromopropionates and bromoacetonitrile, as well as electron-deficient benzyl bromides.

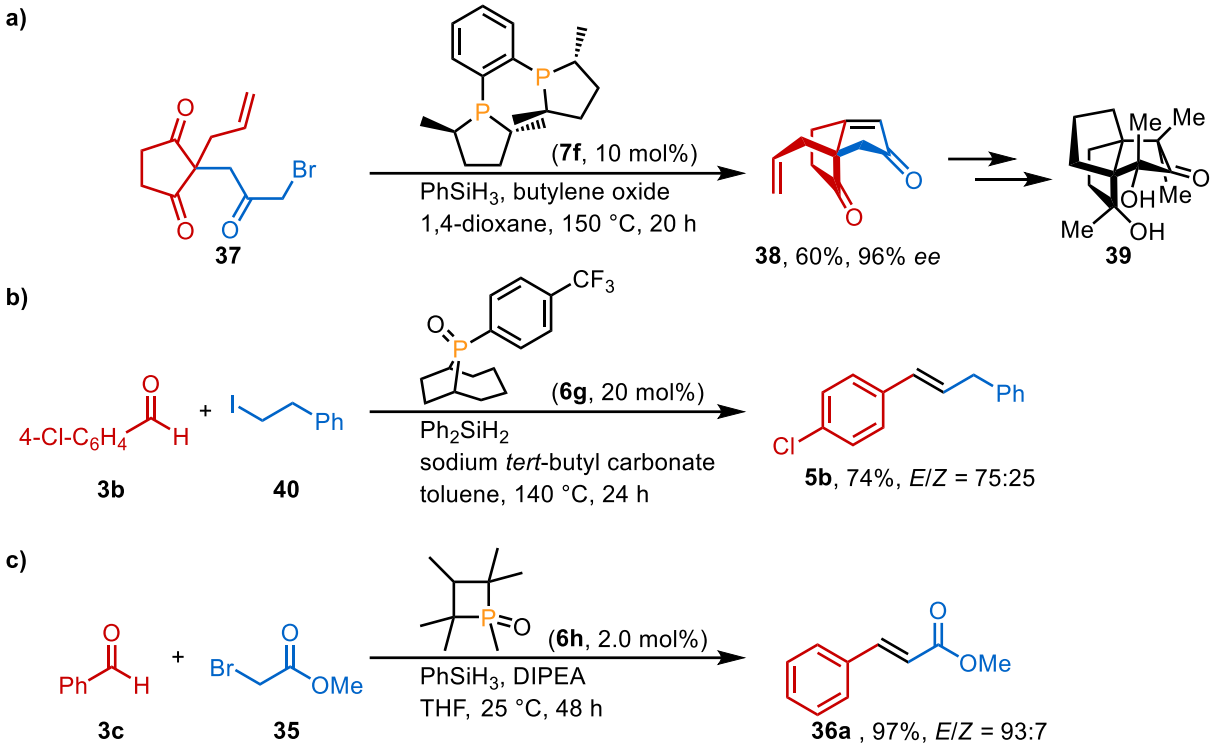


Scheme 11: Reaction mechanism for the catalytic Wittig reaction using diphenylsilane as terminal reductant.

1.5 Further development of the catalytic Wittig reaction

The subsequent development of the catalytic Wittig reaction was shown by O'Brien and coworkers in 2013.[37] While the use of sodium carbonate as a base in toluene at 100 °C led to acceptable yields, the reaction was sensitive to the particle size of the base, and rapid stirring of the reaction mixture was necessary. To alleviate this, the search for a soluble base brought up DIPEA as a viable alternative. Due to its steric bulk and lack of nucleophilicity no additional side reactions were observed, while a lower catalyst loading of 4.0 mol% and a broader scope were made possible by its use. The addition of nitrobenzoic acid as a cocatalyst allowed the reaction to take place at room temperature using a phospholane catalyst while it also enabled the use of trioctylphosphine oxide (**6l**) at 100 °C.[38] Even triphenylphosphine oxide **6a** could be used as a catalyst with an electron poor silane as the terminal reductant. An alternate method for the activation of trialkylphosphine oxides was developed by Werner et al. in the microwave assisted catalytic Wittig reaction.[39] Under microwave dielectric heating to 150 °C tributylphosphine oxide **6i** could be used as a catalyst with a loading of 10 mol% at shortened reaction times of 3 h. To avoid side reactions, butylene oxide was used as a capped base. Under the reaction conditions the formed phosphonium bromide would lead to its ring opening, freeing the alcoholate base. Under similar conditions, employing chiral catalysts, Werner et al. also reported an enantioselective catalytic Wittig reaction, which was later used as a key step in the natural product synthesis of dichrocephones A (**39**) and B by Christmann and coworkers (Scheme 12a).[40] Further studies by Coyle et al. on the catalytic Wittig reaction, including the careful optimization of the catalyst by variation of electron donating and withdrawing substituents, enabled the formation and reaction of semi- and non-stabilized ylids (Scheme 12b).[41] The introduction of a highly active hexamethylphosphetane catalyst **6h** enabled the room temperature catalytic Wittig reaction with low catalyst loadings of 1–2 mol% without the need of an additional cocatalyst (Scheme 12c).[42] At reaction temperatures

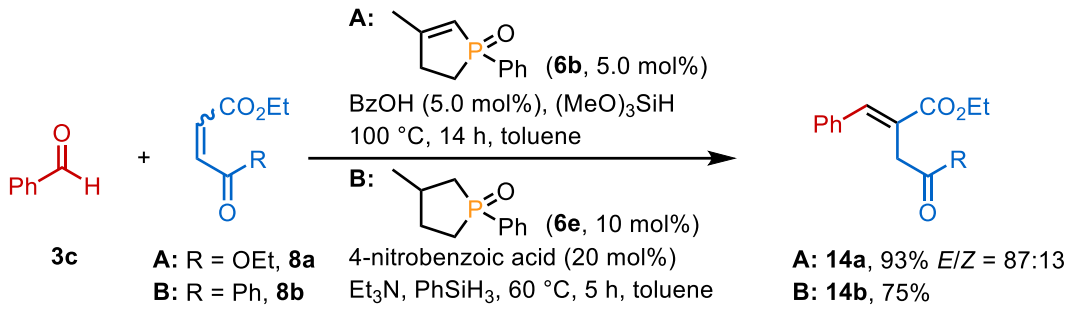
of 100 °C also the use of poly(methylhydrosiloxane) (PMHS) was shown to be a viable alternative. The value in using this non-toxic, environmentally friendly and cheap reductant, which is a waste product of silicone industry, was shown in a life cycle assessment (LCA) by van Kalkeren et al. investigating the cumulative energy demand (CED) and greenhouse gas (GHG) emissions of both (catalytic) Wittig reaction and Appel reaction.[43] While overall less energy is needed in comparison to the classic Wittig reaction, the choice of terminal reductant has the largest influence on CED and GHG emissions in the catalytic Wittig reaction. Thus, the use of PMHS with its relatively low reactivity as a terminal reductant is of significant value.



Scheme 12: Further development on the catalytic Wittig reaction.

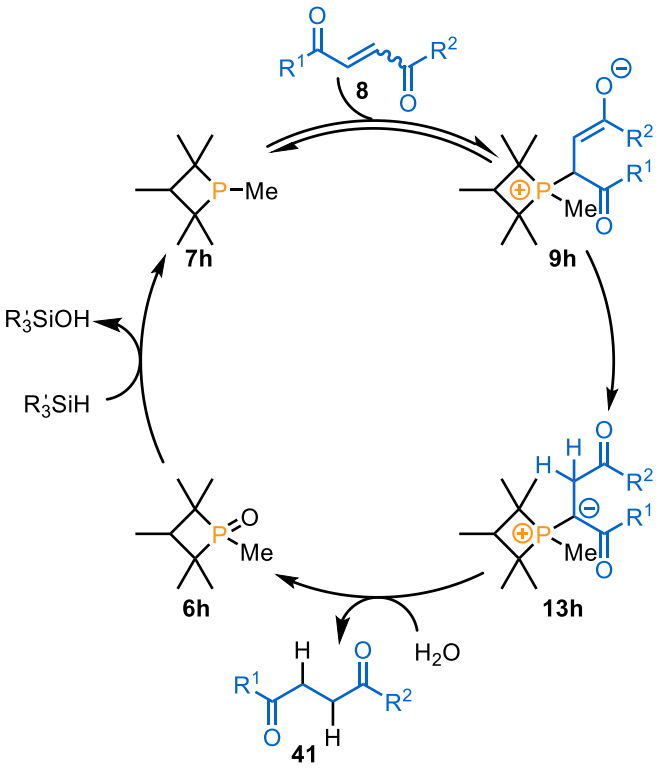
1.6 Catalytic conversion of activated alkenes initiated by Michael addition

The reaction of phosphine catalysts with an activated alkene in a Michael-type reaction can open new reactivities. In the catalytic base-free Wittig reaction (BFW) developed by Schirmer et al. in 2015, tributylphosphine **7i** reacts with a maleate **8a** in a Michael addition at 125 °C, followed by a protonation/deprotonation step forming an ylid.[44] The reaction with an aldehyde **3c** in a Wittig reaction forms an highly substituted alkene **14a**. The use of a phospholane catalyst **6b** in combination with benzoic acid as cocatalyst enabled a shorter reaction time of 14 h at a lower temperature of 100 °C, while broadening the reaction scope (Scheme 13).[45] Tsai and Lin developed a similar method in 2015, which focused on the reaction of benzoylacrylate **8b** with phospholane catalyst **6e** with a nitrobenzoic acid cocatalyst.[46] While the addition of stoichiometric amounts of base was necessary, a lower reaction temperature of 30–60 °C could be used.



Scheme 13: Formation of trisubstituted alkenes in the catalytic (base-free) Wittig reaction.

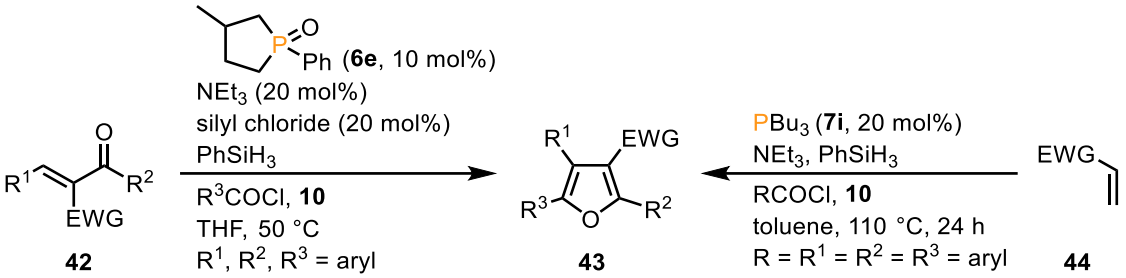
The BFW could also be used in an intramolecular fashion, as shown by Grandane et al. in the synthesis of benzoxepinones.[47] This type of ylid formation could also be used in the phosphetane catalyzed reduction of activated alkenes **8**.[48] The addition of water to the reaction of hexamethylphosphetane **7h** and activated alkenes **8** or alkynes led to the generation of ylids **13h** which were subsequently hydrolyzed, forming alkanes **41** and the phosphine oxide **6h** (Scheme 14). Phenylsilane was shown to be compatible with the reaction conditions at 80 °C, enabling the reduction of the phosphetane oxide **6h**.



Scheme 14: Mechanism for the reduction of activated alkenes by P(III)/P(V) redox cycling catalysis.

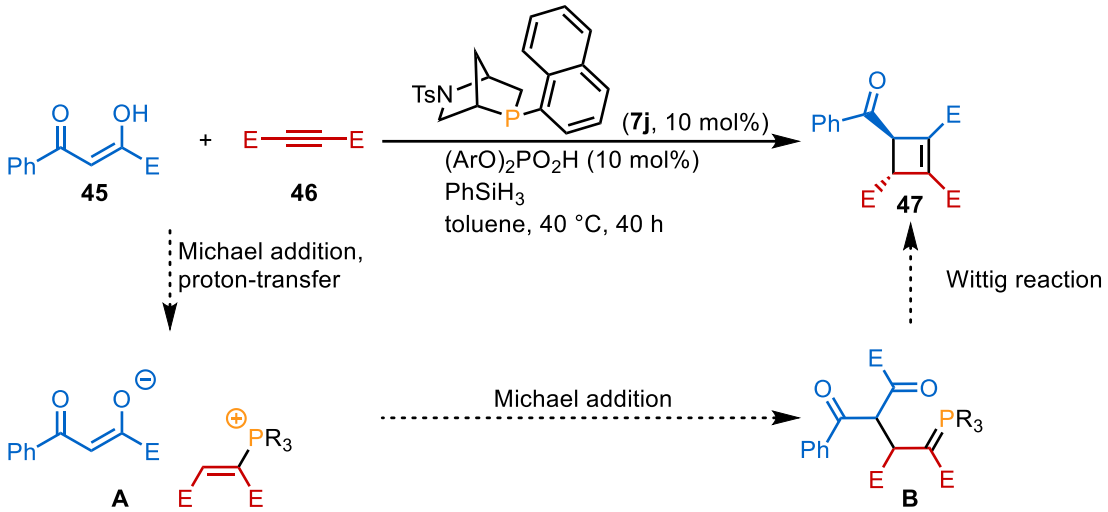
Alternate reaction principles involve the subsequent reaction of the generated enolate **9**. An enolate was formed from an activated, trisubstituted alkene **42** in the furan synthesis by Lee et al. which further reacted with an acyl chloride **10** to form an enol ester (Scheme 15).[49] An added base subsequently led to the formation of a tetrasubstituted, aromatic furan **43** via an intramolecular Wittig reaction. In the phosphine catalyzed furan synthesis starting from

acrylates **44**, Fan et al. showed the reaction with two acyl chlorides **10** in a multicomponent reaction.[50] In a first step the Michael adduct reacts via C-acylation, followed by deprotonation steps and subsequent *O*- and *C*-acylations. An intramolecular Wittig reaction finally generates the tetrasubstituted furan **43**.



Scheme 15: Formation of furans by reaction of activated alkenes with acyl chlorides.

In an intramolecular fashion, acrylates were shown to react in a Rauhut-Currier type reaction, followed by a Wittig reaction, as shown by Lin et al. in their synthesis of pyrroloquinolines.[51] Also, an intramolecular Morita-Baylis-Hillman type reaction followed by intramolecular Wittig reaction was developed by Zheng et al. in the synthesis of quinolinones and coumarins.[52]

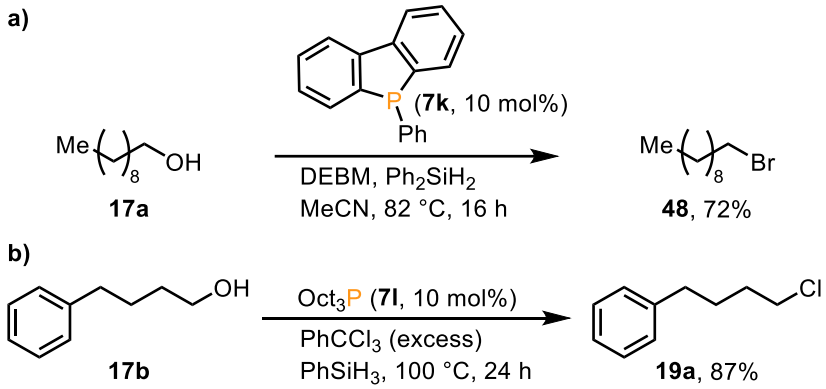


Scheme 16: Formation of cyclobutenes in the reaction of alkynes with 1,3-diones. E = CO_2Et.

The work of Voituriez and coworkers in this field focuses on the addition of phosphines **7** to activated alkynes **46** (Scheme 16). A following protonation step leads to the formation of a vinylphosphonium salt **A**, which in turn can reacts in another Michael addition, followed by a Wittig reaction. When using a chiral phosphine **7j**, this reaction can be conducted stereo-selectively. With this reaction principle, alkynes **46** could be converted with 1,3-diones **45** to form cyclobutenes **47**, and with 4-oxoesters in specific cases to cyclopentene spirocycles (Scheme 16).[53] The reaction with β-aminoaldehydes led to the stereoselective formation of tetrahydropyridines, whereas fluorinated acetyl carbamates were converted to 2-acetines.[54] Zhang et al. showed that ketenes react in a similar fashion via a vinylphosphonium salt. A Michael addition/Wittig reaction sequence led to the formation of dihydroquinolines.[55]

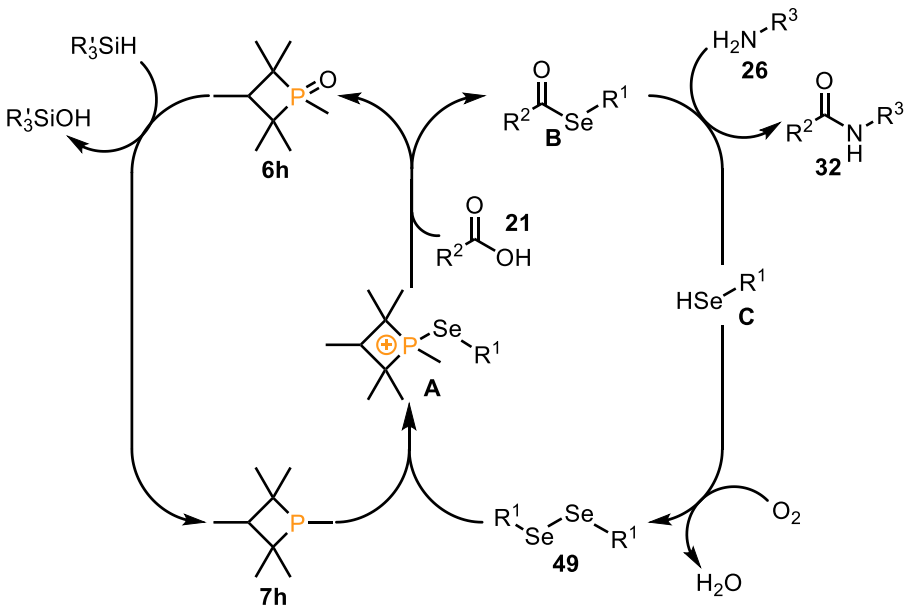
1.7 Catalytic reactions initiated by phosphine activation

Van Kalkeren et al. introduced the first catalytic Appel reaction by P(III)/P(V) redox cycling.[32, 56] Instead of the harsh conditions used by Denton et al. in the catalytic Appel chlorination, in which the phosphine oxide **6** is directly activated by oxalyl chloride, the additional step of the reduction of the phosphine oxide **6** allows for the formation of the phosphonium halide **16** under milder conditions.[16] The bromination of multiple alcohols **17** was conducted with a dibenzophosphole **7k** as the catalyst and diethyl bromomalonate (DEBM) as the bromide source in acetonitrile under reflux conditions (Scheme 17a). A chlorination of a primary alcohol **17** was also investigated, but due to the low nucleophilicity of the catalyst, the respective chloride was only formed in low yields. Further development on this was conducted by Longwitz et al. in an solvent free catalytic Appel chlorination (Scheme 17b).[57] Cheap and readily available trioctylphosphine **7l** could be used as the catalyst with an excess of benzotrichloride as the chloride source and phenylsilane as the terminal reductant. A variety of primary alcohols **17** were converted in good yields with good functional group tolerance, but secondary alcohols could only be isolated in moderate yields. Also, while the Appel reaction is generally stereospecific, when reacting enantiopure alcohols under these conditions the respective chloride could only be afforded in a low enantiomeric ratio.



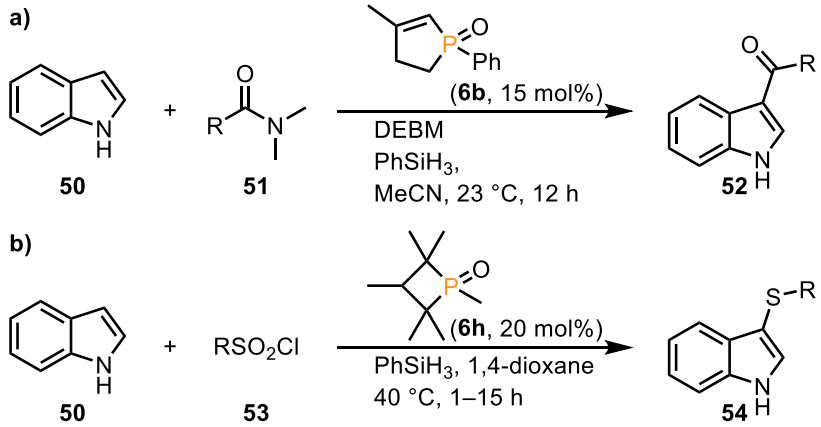
Scheme 17: Two approaches to the organocatalytic Appel halogenation.

The same reaction principle can be used for the activation of carboxylic acids. In the reaction by Radosevich and coworkers, the phosphine reacts with either DEBM or diethyl methyl-bromomalonate (DEMBM) towards a bromophosphonium salt, which in turn reacts with the carboxylic acid, forming an active ester.[58] Reaction of the activated ester with an amine forms an amide, which in turn reacts with another activated phosphine, forming an imidate. Intra-molecular cyclization leads to the formation of heterocycles, while the reaction with pyridine *N*-oxides and rearrangement forms 2-amidopyridines. A different approach was chosen by Handoko et al. in the organocatalytic peptide bond formation.[59] In the dual catalytic cycle, the phosphine **7h** is activated by a diselenide **49**, forming a selenophosphonium salt **A** (Scheme 18). The reaction with a carboxylic acid **21** generates an activated selenoester **B** and the phosphine oxide **6h**, which can be reduced in situ with phenylsilane as terminal reductant.



Scheme 18: Dual catalytic cycle for the peptide bond formation of Handoko et al.

Reaction of the ester **B** with an amine **26** forms the peptide bond, freeing the selenol **C**, which can be oxidized by air back to the diselenide **49**, closing the second catalytic cycle. Thus, the reduction of the phosphine oxide **6h** with phenylsilane as terminal reductant, and the oxidation of the selenol **C** with air were compatible. These opposing requirements were also a problem for the development of the fully catalytic Mitsunobu reaction via P(III)/P(V) redox cycling. While the phosphine oxide **6** had to be reduced, the formed hydrazine had to be oxidized to regenerate the azo compound. Buonomo and Aldrich showed the general viability of a fully catalytic Mitsunobu reaction under redox conditions by using a phospholane catalyst with phenylsilane as terminal reductant, as well as a phenylhydrazine carboxylate as second catalyst, iron phthalocyanine as a cocatalyst and oxygen as terminal oxidant.[22]



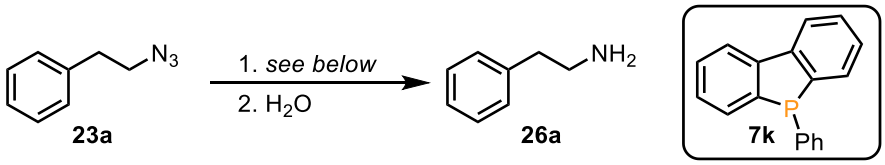
Scheme 19: Electrophilic aromatic substitution of indoles following a phosphine activation mechanism.

Xue et al. could also show that bromophosphonium ions under redox catalytic conditions could be used for the activation of deuterated DMF and other dimethyl amides **51** in a catalytic Vilsmeier-Haack reaction (Scheme 19a).[60] As shown before, the phospholene **6b** reacted with

bromomalonate to form a bromophosphonium intermediate **16**, which in turn could activate the dimethyl amide **51**. In an electrophilic aromatic substitution this intermediate reacted with indole **50** forming the carbonyl-substituted indoles **52** after aqueous workup. Indoles **50** were also brought to reaction in an electrophilic sulfenylation by Ghosh et al. in 2019 (Scheme 19b).[61] Here, the phosphetane catalyst **6h** was activated by the reaction with sulfonyl chlorides **53**, followed by their deoxygenation in multiple steps. Finally, an electrophilic aromatic substitution led to the formation of sulfenylated indoles **54**.

1.8 Phosphorus-heteroatoms bond formation as first step in catalytic transformations

In another general reaction principle, in the first step of the reaction phosphorus-heteroatom bonds are formed. Early work on the catalytic Staudinger reaction was conducted by van Kalkeren et al. using a dibenzophosphole catalyst **7k** and phenylsilane as terminal reductant (Table 1).[62] Here, the phosphine **7** reacts with an azide **23** in an 4-membered transition state to form an aza-ylid under release of nitrogen. The aza-ylid **25** can be reduced directly to the phosphine and a silylamine species, which is hydrolyzed on aqueous workup to form the free amine. Further development was done by Lenstra et al. who could use triphenylphosphine **7a** as the catalyst.[63] Since no exceptionally stable triphenylphosphine oxide **6a** is formed in the reaction mixture, but only the more easily reduced aza-ylid **25**, PMHS could be used as the terminal reductant under reflux conditions in the green solvent CPME. Also, a room temperature catalytic Staudinger reaction with triphenylphosphine **7a** could be shown by Lenstra et al. using the highly active reductant diphenyldisiloxane.[64]



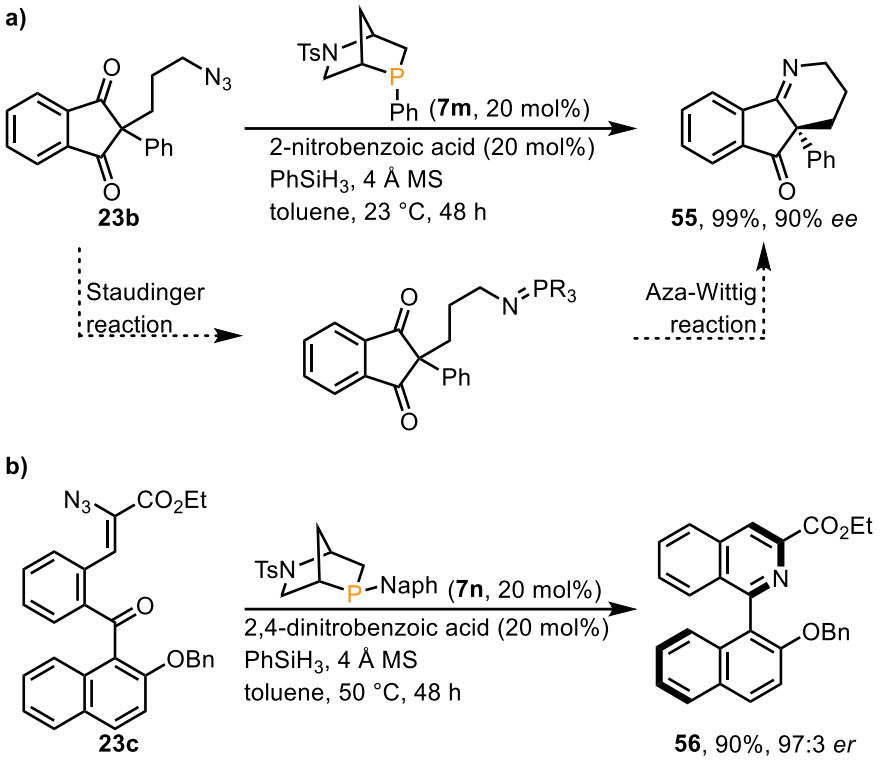
Entry	Conditions	**26a** / %
1	**7k** (5.0 mol%), $PhSiH_3$, 1,4-dioxane, 101 °C, 16 h	71
2	PPh_3 (**7a**, 3.0 mol%), PMHS, CPME, 106 °C, 20 h	97
3	PPh_3 (**7a**, 10 mol%), $(PhSiH_2)_2O$, CPME, 23 °C, 24 h	90[a]

Table 1: Different approaches towards the organocatalytic Staudinger reaction. [a] isolated as hydrochloride.

The aza-ylid formed in the reaction of azides **23** and phosphines **7** can also undergo different conversions in the reaction mixture. In the catalytic Staudinger reaction shown by Kosal et al. the aza-ylid **25** is protonated by a carboxylic acid **21**.[65] It was proposed that the formed carboxylate is then activated by the phosphonium ion, leading to a rearrangement and the formation of an amide **32** and phosphine oxide **6**. Since this proposed mechanism would include the reduction of the formed triphenylphosphine oxide **6a** at unusually low reaction

temperatures of 60 °C to 110 °C, White et al. conducted more thorough investigation of the mechanism and showed that also here the aza-ylid **25** is directly reduced by the silane, forming the amine **26**.[66] The silane is then also involved in the formation of the amide **32**.

A Staudinger/aza-Wittig reaction sequence can be used for the formation of multiple types of nitrogen-containing heterocycles. Early work was conducted by van Kalkeren et al. in the synthesis of benzoxazoles and benzodiazepinones, using a dibenzophosphole catalyst **7k** in dioxane under reflux conditions with diphenylsilane as terminal reductant.[67] The catalyst **7k** reacts with an arylazide **23**, forming the aza-ylid **25**, which in turn reacts intramolecularly under ring closure with an ester in an aza-Wittig reaction. While the formation of benzoxazole worked well in moderate to excellent yields, the formation of benzoxazepinones showed strong substrate dependence. This general method was adapted by Wang et al. for the synthesis of quinazolinones with catalytic amounts of triphenylphosphine.[68] The addition of titanium tetraisopropoxide as a cocatalyst was necessary to aid in the reduction of the formed triphenylphosphine oxide. Kwon and coworkers used this reaction sequence for the desymmetrization of ketones and esters using a chiral phosphine catalyst **7m**. The reaction of prochiral diketone **23b** with bicyclic phosphine **7m** leads to the formation of iminoketone **55** in excellent yield and selectivity at low reaction temperatures with the help of an acidic cocatalyst (Scheme 20a).[69]

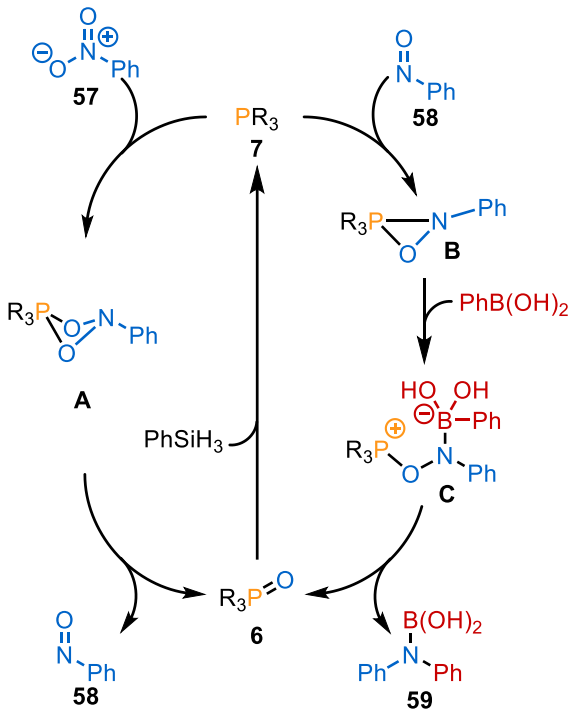


Scheme 20: Desymmetrization of prochiral azides in a Staudinger/aza-Wittig reaction sequence using chiral phosphine catalysts.

Moser, Jana and Sparr recently used a similar system in the atroposelective generation of isoquinoline derivatives **56** (Scheme 20b).[70] A similar bicyclic phosphine also reacts with the

substituted malonate to stereoselectively form the oxindoles using an iridium-based Lewis acid cocatalyst.[71]

Radosevich and coworkers did a thorough investigation on catalytic Cadogan-type reactions. In the catalytic Cadogan cyclization, nitroaryl compounds react intramolecularly with a double bond in form of an imine, alkene or aryl group after reduction to the nitroso compound and subsequent activation by the phosphine to a nitrenoid species.[72] Using the phosphetane oxide catalyst **6h** and phenyl silane as terminal reductant, indazoles can be formed in excellent yields and indoles/carbazoles in moderate to good yields. Further development also showed the reactivity of this nitrenoid species towards boronic acids, leading to a coupling reaction and forming a secondary amine.[73]



Scheme 21: Mechanism for the catalytic reductive C-N coupling.

A thorough optimization and mechanistic investigation was conducted and the scope of the reaction was extended towards the use of nitroalkanes and towards the inclusion of a ring closure step (Scheme 21).[74] In a first reaction step, the nitro compound **57** is reduced by the phosphine **7**, forming an nitroso intermediate **58**. The following (2+1) addition leads to the formation of the nitrenoid species **B**, which reacts under ring opening with a boronic acid. Rearrangement leads to the formation of the product **59** and the phosphine oxide **6**. Also, the formation of primary amines by reaction of an aryl boronic acids and 2-nitropropane via a Nef decomposition under basic conditions was made possible.[75] The reaction of nitroarenes and anilines towards hydrazines uses a different intermediate step. Here, the nitrosoarene reacts with the aniline in a condensation reaction, forming a diazo compound. Activation with the phosphine, protonation and subsequent hydrolysis leads to the hydrazine.[76] This reaction

was investigated in detail with DFT calculations by Zhang et al. which led to the recommendation to use a more electron donating dimethylamine substituted phosphetane catalyst.[77]

1.9 Outlook

Phosphorus mediated reactions forming phosphine oxides, such as the Staudinger reaction, Wittig reaction or Appel reaction have shown their value for organic synthesis for a long time and are widely employed for lab-scale or small-scale synthesis. Still, the formation of stoichiometric amounts of phosphine oxide waste limits their applicability for large scale synthesis of commodity chemicals. Only few examples of this are available, such as the Vitamin A synthesis of BASF, in which the oxides are separated and recycled in an ex-situ process involving highly hazardous phosgene.[14] For a subset of these reactions, the development of redox neutral, catalytic reactions was successful. A catalytic Appel chlorination was made possible with the in situ activation of phosphine oxides using oxalyl chloride, and a Mitsunobu reaction was conducted with a hydroxy-substituted phosphine oxide which could be activated by a cyclization reaction under elevated temperatures.[16, 23] These reactions however are hampered by their relatively harsh reaction conditions, either due to highly reactive activation agents or due to the need for elevated temperatures and long reaction times. The reduction of phosphine oxides was shown to be possible using silanes, which are compatible with many substrates and functional groups. While the reduction of acyclic phosphine oxides still necessitated the use of high reaction temperatures, cyclic phosphine oxides were shown to react at much milder conditions, which opened the possibility for the use as catalyst in P(III)/P(V) redox catalytic systems. Starting with the catalytic Wittig reaction developed by O'Brien et al., a wide variety of classical phosphorus mediated reactions were adapted.[35] While some reactions, such as the Wittig reaction of unstabilized ylids proved to be challenging due to the need of strong bases, many reactions such as the Staudinger reaction proved to be widely compatible.[41, 78] In recent years, the focus shifted towards the improvement of these reactions towards their environmental impact. While the avoidance of phosphine oxide waste is highly valuable, oftentimes still highly active silanes, such was phenylsilane, or high catalyst loadings are necessary. Also, recently a larger number of catalytically enabled cascade reactions were published, such as a Staudinger/aza-Wittig reaction, or a Michael/Michael/Wittig reaction sequence.[54a, 70] Both, the development of reactions under more "green" conditions and the valuation of the P(III)/P(V) reaction principle due to the viability to exploit the innate reactivity of the more complex catalysts in comparison to the previously used commodity phosphines remain a challenge.

Not discussed in this overview are the developments of the electroreduction of phosphine oxides. While until now, the need for large amounts of sacrificial agents or co-reagents do not make this reaction principle a viable alternative to the use of chemical reductants, future developments could lead to the creation of new catalytic procedures.[79]

2 Objectives of this work

The development of P(III)/P(V) redox cycling catalysis enabled the modification of classical, phosphorus mediated reactions, such as the Wittig reaction, towards a higher resource-efficiency while producing less phosphorus waste. Still, challenges remain. These comprise the need for highly active silanes for the in situ reduction of phosphine oxides, high catalyst loadings or the need for acidic cocatalysts. Additionally, the viability to use more complex phosphines in comparison to the classically used PPh_3 opens new reaction pathways towards underexplored product classes.

The first aim of this work is the development of a more environmentally benign method for the catalytic base-free Wittig reaction. For this, highly active silanes such as phenylsilane and trimethoxysilane should be replaced by PMHS as a cheap reducing agent with low GHG emissions and CED, while also employing renewable solvents. The lower reactivity of PMHS should be counteracted by newer developments in catalyst design. Additionally, care should be taken regarding the *E*/*Z*-selectivity of the reaction.

In recent years multiple endocyclic maleimides showed promising cytostatic activity, and interesting differences physiological activity for exocyclic maleimides were expected.[80] In a second step, using the newly developed method, a library of exocyclic maleimides should be synthesized, followed by an investigation on their biological activity on multiple cancer cell lines in cooperation with the Rostock University Medical Center.

Our third aim was the development of a new catalytic method for the synthesis of furans with an unusual and underexplored substitution pattern. For this, an intermediate of the BFW should be intercepted using a sufficiently strong electrophile, such as acyl chloride. An intramolecular Wittig reaction can then lead to the formation of the heterocycle.

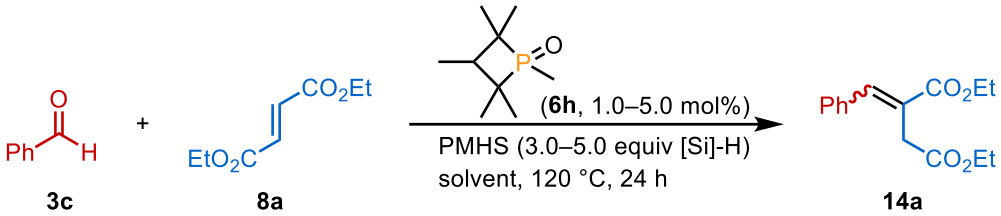
The applicability of the first catalytic Appel chlorination is limited by a high catalyst loading and the need to use an excess of carcinogenic benzotrichloride.[57] Additionally, the conversion of secondary alcohols to the respective secondary chloride proved problematic regarding their stereospecificity. Thus, the fourth aim of this work is the development of a catalytic, stereospecific Appel chlorination procedure, while also improving the efficiency regarding the catalyst loading and the amount of chlorine source needed.

3 Results and Discussion

3.1 Poly(methylhydrosiloxane) as a reductant in the catalytic base-free Wittig reaction[81]

The development of highly strained, small ring phosphetane oxides made the use of less reactive terminal reductants possible. The first goal of this work was the development of a new, more environmentally benign variant of the catalytic base-free Wittig reaction using poly(methylhydrosiloxane) as the terminal reductant. This silane is a by-product of the silicone industry and is not only inexpensive and readily available, but it is also stable to moisture and air and shows low toxicity.[82] Its lower reactivity remains a disadvantage though and it can only be utilized for the reduction of most phosphine oxides at elevated temperatures or with additional catalysts.[28, 83]

Table 2: Selected examples for the reaction optimization.



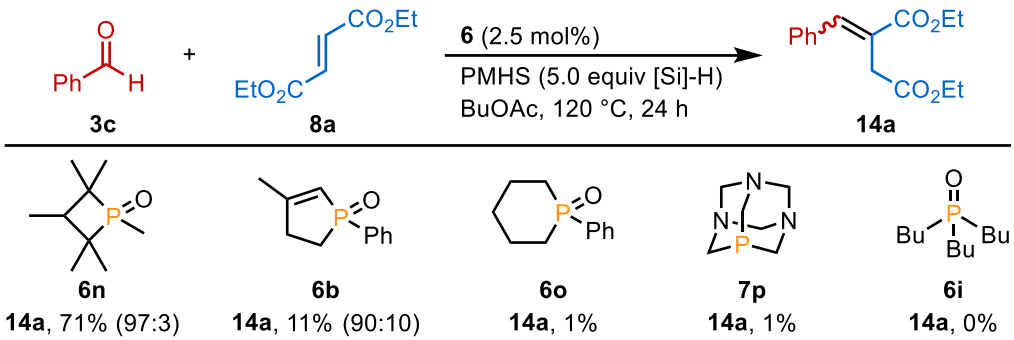
Entry	Solvent	**6h** / mol%	PMHS / equiv [Si]-H	**14a** / %[a]
1	Cymene	5.0	5.0	67
2	Limonene	5.0	5.0	69
3	BuOAc	5.0	5.0	86
4	CPME	5.0	5.0	88
5	Solvent free	5.0	3.0	77
6	BuOAc	2.5	5.0	71
7	BuOAc	1.0	5.0	31
8	BuOAc	5.0	3.0	62
9[b]	BuOAc	5.0	5.0	53
10[c]	BuOAc	5.0	5.0	69

Reaction conditions: 1.0 equiv **3c** (0.5 mmol), 1.5 equiv **8a** (0.75 mmol), 1.0–5.0 mol% catalyst **6h**, 3.0–5.0 equiv [Si]-H of PMHS (1.5–2.5 mmol), 1.5 ml solvent, 120 °C, 24 h. [a] Yield determined by GC-FID with hexadecane as internal standard, [b] 100 °C, [c] additional 5.0 mol% $PhCO_2H$.

Based on the previous work, the reaction of benzaldehyde (**3c**) and diethyl fumarate (**8a**) was chosen as a model.[44-45, 48] Using the phosphetane oxide **6h** as a catalyst, the viability of more

sustainable solvents was investigated.[84] The bio-based, non-polar solvents *p*-cymene and limonene led to a mediocre yield of 67% and 69%, respectively (Table 2, entry 1, 2). Little difference in yield could be seen when using polar-aprotic solvents such as esters or ethers. For instance, *n*-butyl acetate gave a yield of 86% and cyclopentyl methyl ether (CPME) a yield of 88% (entry 3, 4). The reaction could also be conducted under solvent-free conditions in good yields of 77%, although the formation of a silicone-like polymer was detrimental to the reproducibility (entry 5). In all cases an excellent *E*/*Z*-selectivity of 97:3–98:2 could be achieved. For the following studies *n*-BuOAc was chosen due to its good evaluation as a green solvent and the good yield. Lower catalyst loadings of 2.5 mol% or 1.0 mol% led to reduced yields of 71% and 31%, respectively (entry 6, 7). Also, the use of lower amounts of terminal reductant gave a lower yield of 62% (entry 8), while at a lower reaction temperature of 100 °C the product **14a** could only be obtained in a yield of 53%. The addition of an acid-based cocatalyst proved advantageous in previous studies.[45] Here, the addition of previously used benzoic acid (5 mol%) resulted in a lower yield of 69% (entry 10).

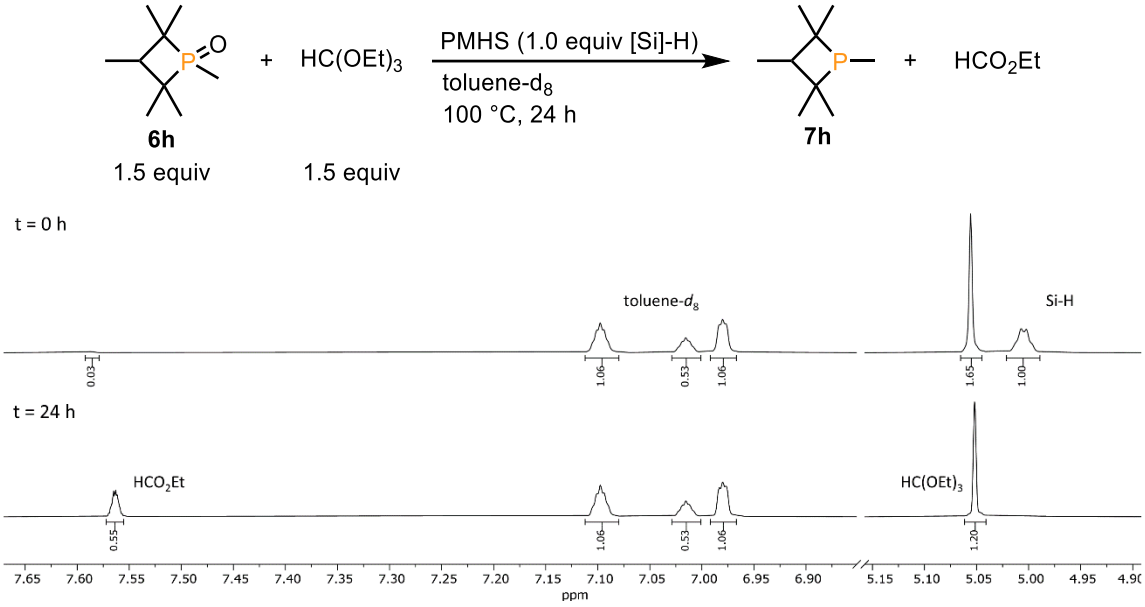
When changing the catalyst to the previously used phospholene oxide **6b** at a catalyst loading of 2.5 mol%, a stark difference in reactivity became visible. When using the phosphetane catalyst **6n**, the trisubstituted olefin **14a** could be afforded in a yield of 71% with excellent *E*/*Z*-selectivity (Scheme 22). Under the same reaction conditions, using the phospholene catalyst **6b**, only 11% of the product **14a** a lower selectivity of 90:10 was afforded. Also, neither phosphinane **6o**, triazaphosphaadamantane **7p** nor tributylphosphine oxide **6i** led to an appreciable yield. Additionally, phosphetane catalysts bearing different substituents, i.e., *i*-propyl, phenyl, and benzyl, were investigated, but none of them led to product formation.



Scheme 22: Catalyst comparison for the base-free Wittig reaction under environmentally friendly conditions.

Previous investigations showed the reduction of activated alkenes **8** using the phosphetane catalyst **6n**, water and a terminal reductant.[48] Thus, it was unexpected to see the formation of diethyl succinate **41a** as a persistent side reaction during the optimization, although no significant amount of water could be found in the starting materials. As a method of in situ water formation we proposed the condensation of two silanols under formation of siloxanes, which is largely unreported in literature. Petit et al. reported a water formation in a titanium-catalyzed reduction with tetramethylsiloxane, but generally, when silanols are formed in the

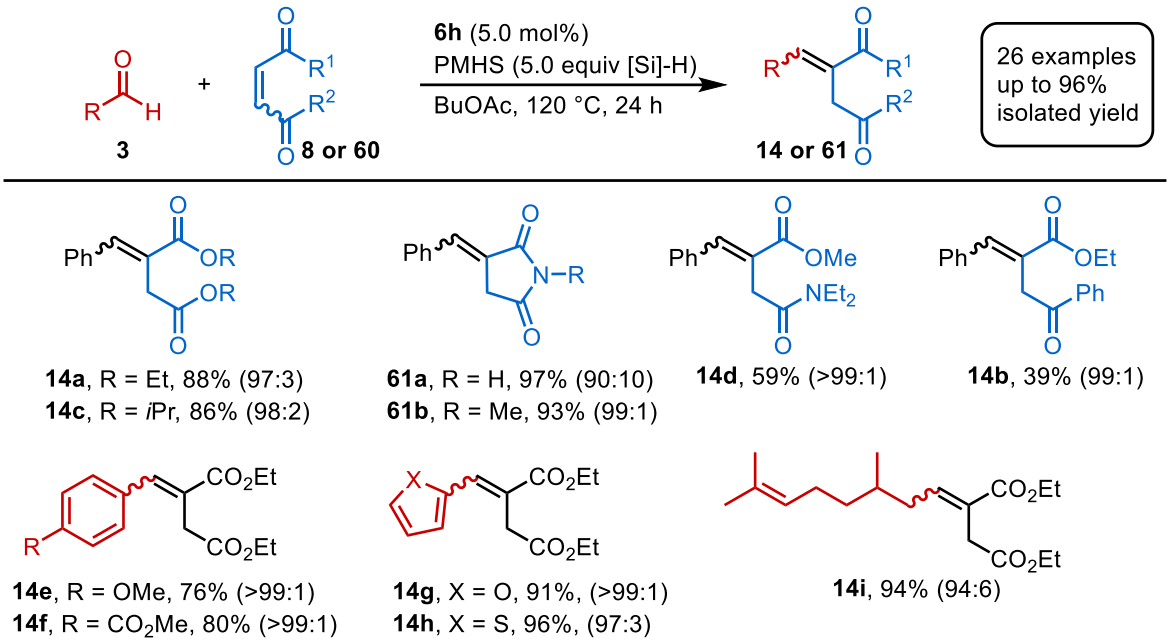
presence of silanes, a siloxane formation under generation of hydrogen is assumed.[85] Since the water formation could not be visualized directly, multiple indirect approaches were conducted. The influence of water scavengers was investigated in a test reaction using a smaller excess of diethyl fumarate (**8a**, 1.1 equiv). Under these reaction conditions the product **14a** could be afforded in a yield of 72%. The addition of the drying agents Na_2SO_4 (30 wt%) or triethyl orthoformate (2.5 equiv) led to a small increase in yield to 78% and 80%, respectively. The water formation could also be visualized indirectly by NMR experiments. Here, an excess of phosphetane oxide **6h** was reduced in the presence of an excess of triethyl orthoformate with 1.0 equivalent of PMHS. The formed silanol led to the formation of 0.5 equivalents of water by condensation, which in turn reacted with the orthoformate, forming 0.5 equivalents of ethyl formate (Scheme 23). Further test reactions could show that this effect was also present with the more active phenylsilane.



Scheme 23: ^{1}H NMR experiment for the detection of water formation with triethyl orthoformate as scavenger.

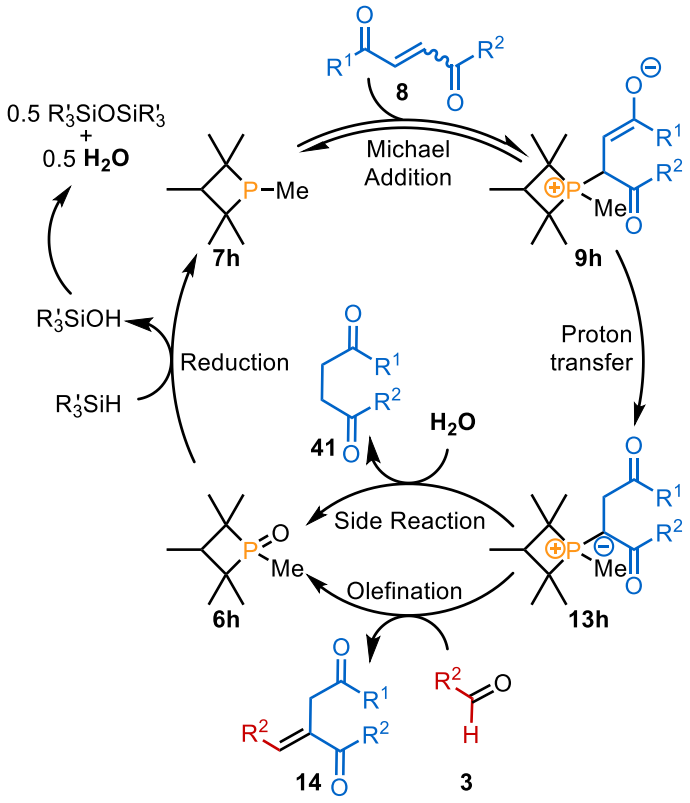
Using the optimized reaction conditions, the model product **14a** could be isolated in a good yield of 88% and a *E*/*Z*-selectivity of 97:3 (Scheme 24). Reactions with different fumarates gave similar product yields and selectivities, such as the isopropyl derivative **14c** which was obtained in 86% yield. Conversion of maleimides **60** to the free maleimide **61a** and the *N*-methyl derivative **61b**, worked in good to excellent yields of 97% and 93%, respectively, although with a slightly reduced *E*/*Z*-selectivity of 90:10 in case of the free maleimide **61a**. The use of less activated alkenes, led to lower yields for the amide derivative **14d** or the ketoester **14b** of 59% and 39% respectively. Furthermore, a variety of aldehydes was converted under optimized conditions. Both, activated and deactivated benzaldehydes gave the respective products in good yields. The methoxy substituted alkene **14e** be obtained in a yield of 76% and the carboxylate **14f** in a yield of 80%. Heteroaromatic carbaldehydes were well tolerated,

giving yields of up to 96%. Also, aliphatic aldehydes could be converted, e.g., citronellal, which formed the trisubstituted alkene **14i** in a yield of 94%.



Scheme 24: Selected products formed in the catalytic base-free Wittig reaction. Reaction conditions: 1.0 equiv **3** (0.5 mmol), 1.5 equiv **8** or **60** (0.75 mmol), 5.0 mol% catalyst **6h** (25 µmol), 5.0 equiv [Si]-H of PMHS (2.5 mmol), 1.5 ml BuOAc, 120 °C, 24 h.

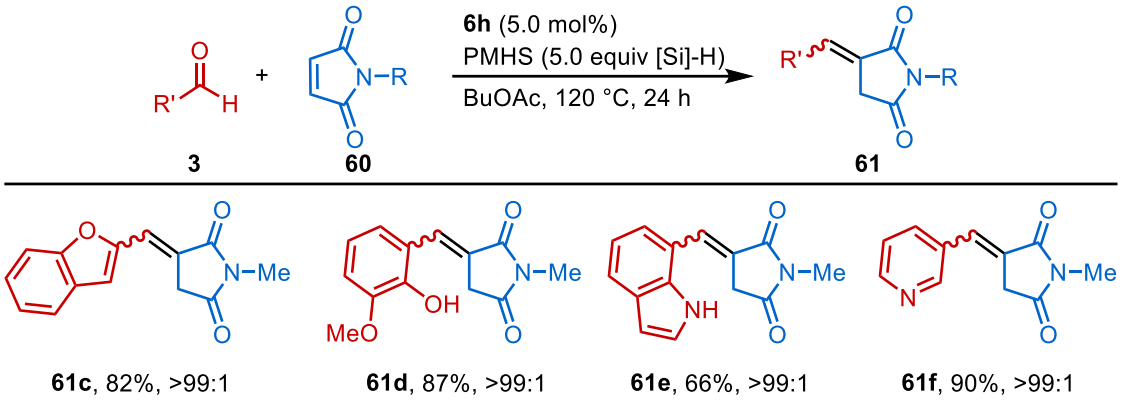
Deuterium labeling experiments were conducted to get insight into the ylid-formation step of the reaction. If the ylid was formed by an intramolecular proton shift, a total retention of deuterium would have been visible. The observed partial loss of deuterium instead hints towards a protonation/deprotonation step. On this basis and using our previous observations a mechanism for the catalytic base free Wittig reaction can be proposed (Scheme 25). In the first step, the reduced phosphetane **7h** reacts in a Michael addition with the activated alkene **8**. A protonation/deprotonation step leads to the formation of the ylid **13h**, which can react with the aldehyde **3** in a Wittig olefination, forming the trisubstituted alkene **14** and the phosphetane oxide **6h**, which gets reduced by the terminal reductant. Water can be formed by condensation of the silanols, which in turn can hydrolyze the ylid **13h** in a side reaction, forming succinate **41** as a byproduct.



Scheme 25: Reaction mechanism for the catalytic base-free Wittig reaction

3.1.1 Synthesis of exocyclic maleimides for studies on biological activity

As part of our investigation of the activity of exocyclic maleimides in cooperation with the University Medical Center Rostock, the previously shown method was used for the synthesis of a library of exocyclic maleimides with various functional groups. In addition to the 6 maleimide derivatives presented in the publication, a library of 16 maleimides was synthesized and characterized, focusing on the various functional group on the aldehyde (Scheme 26). These functional groups included various heterocycles, such as the benzophenone derivative **61c**, which was obtained in a yield of 82%, or substituted phenyl groups, such as the vanillin derived maleimide **61d**, in a yield of 87%. Also, various basic aldehydes were converted, forming products, such as the indole substituted derivative **61e** or the pyridine substituted derivative **61f** in yields of 66% and 90%, respectively. A subset of exocyclic maleimides was chosen by Hamsah Aiash at the University Medical Center Rostock and an evaluation on their cytotoxic and anti-proliferative effects was conducted as part of her Master thesis.[86] Initially, a screening on the RS4;11 cell line was conducted, followed by tests of subsets of the library on further cell lines, showing no significant effect on proliferation, metabolic activity, or biomass.[86] Also experiments on the combinational treatment with Gemcitabine showed no effect. The antibiotic effect of a subset of substrates was tested on E. faecalis, S. pyogenese, S. aureus, K. pneumoniae and E. coli. Also, in these reactions no effect was observed, leaving us without a reasonable pathway for the optimization of the tested substrates.



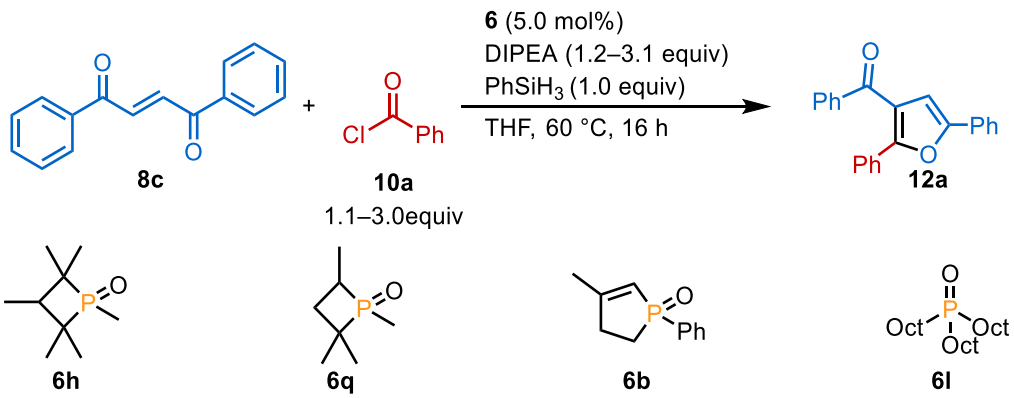
Scheme 26: Subset of the library of 22 maleimides synthesized for testing on biological activity.

3.2 Synthesis of Trisubstituted Furans from Activated Alkenes by P(III)/P(V) Redox Cycling Catalysis

The reaction of activated alkenes with phosphine catalysts in a Michael-addition, followed by a protonation/deprotonation step to form an ylid in the base free Wittig reaction was shown in the previous chapter. After the Michael-addition, other reaction pathways are possible. Here, the formed enolate reacts with an acyl chloride towards an enol ester, which in turn reacts in an intramolecular Wittig reaction, forming a furan. Furans have a wide occurrence in natural products and show versatile reactivity, making them an interesting synthon for natural product synthesis. Despite this, the formation of trisubstituted furans from 1,2-diacylethenes or 3-acylacrylates even under stoichiometric conditions has been underexplored.[6, 87]

In a first step the reactivity of different phosphine oxide catalysts **6** was investigated. At 5.0 mol% catalyst loading and using phenylsilane as terminal reductant, the bisbenzoylethene **8c** could be converted to the trisubstituted furan **12a** using benzoyl chloride **10a** as electrophile and DIPEA as base. Interestingly, only the electron-rich hexamethylphosphetane **6h** led to a good yield of 71% (Table 3, entry 1). The less sterically demanding tetramethyl-phosphetane **6q**, recently introduced by Radosevich and coworkers, only led to low yields of 24% (entry 2), whereas with the classically used phospholene catalysts **6b** or trioctylphosphine oxide **6l** only very low amounts or traces of furan **12a** were obtained (entry 3, 4).[74c] The low yield obtained by using the phospholene catalyst **6b** was especially surprising, since it generally shows good activity and wide use in P(III)/P(V) redox cycling catalysis. Neither lower (40 °C) nor higher (80 °C) reaction temperatures were advantageous (entry 5, 6), but an increase in loading of benzoyl chloride **10a** and DIPEA to 2.0 equiv and 2.1 equiv, respectively, resulted in a nearly quantitative yield (entry 7). A larger excess of reactants did not lead to better results (entry 8). Lower reaction times of 4 h proved to be viable for the model substrate **8c**, but further test reactions showed the necessity for longer reaction times of 16 h for a broader applicability of the method. No product **12a** was formed in the absence of either catalyst or reductant, and only traces of product were obtained without the use of a base.

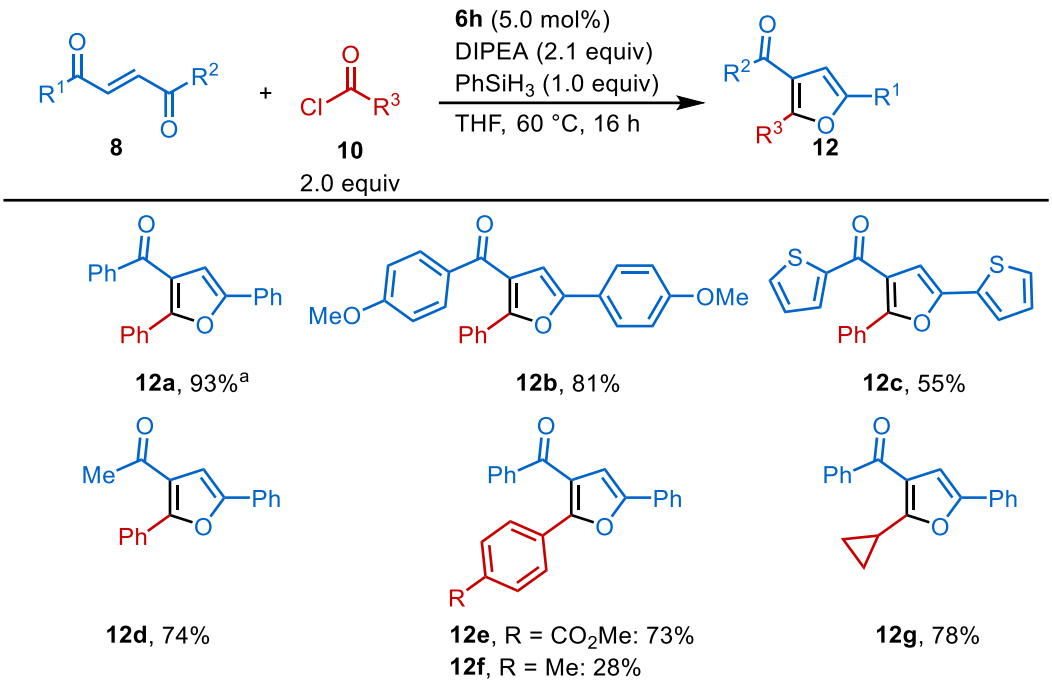
Table 3: Subset of the reaction optimization for the synthesis of furan **12a** from bisbenzoylethene (**8c**).



Entry	Cat.	**10a** /equiv	DIPEA / equiv	**12a** / %[a]
1	**6h**	1.1	1.2	71
2	**6q**	1.1	1.2	24
3	**6b**	1.1	1.2	7
4	**6l**	1.1	1.2	3
5[b]	**6h**	1.1	1.2	13
6[c]	**6h**	1.1	1.2	66
7	**6h**	2.0	2.1	99
8	**6h**	3.0	3.1	94

Reaction conditions: 1.0 equiv **8c** (0.50 mmol), 1.1–3.0 equiv BzCl (**10a**, 0.55–1.5 mmol), 1.2–3.1 equiv DIPEA (0.60–1.55 mmol), 5.0 mol% catalyst **6** (25 µmol), 1.0 equiv $PhSiH_3$ (0.50 mmol), 1.5 ml solvent, 60 °C, 16 h. [a] Yield determined by GC-FID with hexadecane as internal standard, [b] reaction temperature: 40 °C, [c] reaction temperature: 80 °C.

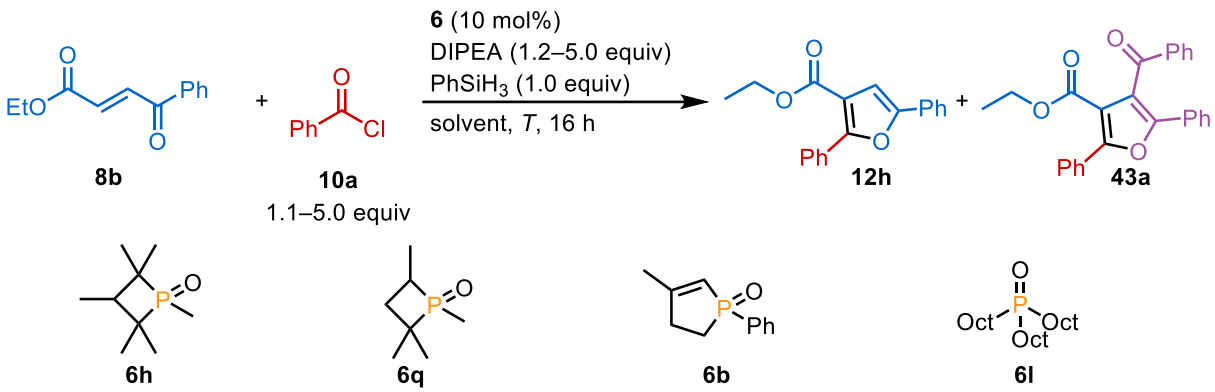
The model substrate **8c** was converted to the triphenylfuran **12a** in an isolated yield of 93% after only 4 h (Scheme 27). The more electron rich dimethoxy derivative was converted to the respective furans **12b** in a good yield of 81% after 16 h. Also, the thiophene substituted diketone was largely compatible with the reaction conditions, leading to the heterocycle-substituted furan **12c** in acceptable yields of 55%. When using asymmetric bisacylethenes **8**, a substrate-specific product ratio is formed. In case of the acetyl benzoyl ethene the diphenylfuran **12d** is formed as a main product in a yield of 74% with less than 7% of the regioisomer formed. Also, the acyl chloride **10** can be exchanged. When using electron-poor derivatives of benzoyl chloride, such as the methyl carboxyl derivative, a good yield of 73% is of furan **12e** achievable. Electron-rich derivatives are less compatible though. Methylbenzoyl chloride led to a lower yield of toluyl-substituted furan **12f** of 28%. Cyclopropylcarbonyl chloride on the other hand formed the furan **12g** in a surprisingly good yield of 78%.



Scheme 27: Selected examples for the synthesis of trisubstituted furans **12** from bisacylethenes **8** and acid chloride **10**. Reaction conditions: 1.0 equiv **8** (1.0 mmol), 2.0 equiv acid chloride **10** (2.0 mmol), 2.1 equiv DIPEA (2.1 mmol), 5.0 mol% catalyst **6h** (50 µmol), 1.0 equiv $PhSiH_3$ (1.0 mmol), 3.0 ml THF, 60 °C, 16 h. [a] reaction time 4 h.

In the second step, the reactivity of more activated ethyl benzoylacrylate **8b** was investigated. To our surprise, under reaction conditions comparable to the previous one, not just the expected trisubstituted furan **12h** was formed, but also the tetrasubstituted furan **43a**. The ratio between those two products proved to be dependent on the employed catalyst. The very electron-rich phosphetane catalyst **6h** was the only catalyst tested, which showed a clear preference for the formation of tetrasubstituted furan **43a** (Table 4, entry 1). The less sterically hindered tetramethylphosphetane **6q** led to a nearly even distribution of products **12h** and **43a** with 27% and 22% yield, respectively (entry 2). The phospholene catalyst **6b** gave a high ratio in favor of the formation of trisubstituted furan **12h**, whereas the trioctylphosphine oxide (**6l**) only formed traces of product (entry 3, 4). Higher temperatures of 100 °C proved to be advantageous for the formation of trisubstituted furan using the phospholene catalyst **6b**, and with a slight increase in used benzoyl chloride (**10a**, 1.5 equiv) and DIPEA (1.6 equiv) the trisubstituted furan **12h** was obtained in a yield of 80% (entry 5, 6). A further increase in the amount of reactants only led to more side product (entry 7). The reaction time could be shortened to 4 h without obtaining a lower yield, but at 2 h a drop in yield of trisubstituted furan **12h** to 67% was observed (entry 8, 9). Also, the reaction forming the tetrasubstituted furan **43a** was optimized. Using the phosphetane catalyst **6h** the best yields were obtained when using an excess of benzoyl chloride (**10a**, 5.0 equiv) and DIPEA (5.0 equiv) in toluene as the solvent at 60 °C and 16 h reaction time (entry 10).

Table 4: Subset of the optimization for the synthesis of furans **12h** and **43a** from ethyl benzoylacrylate (**8b**).

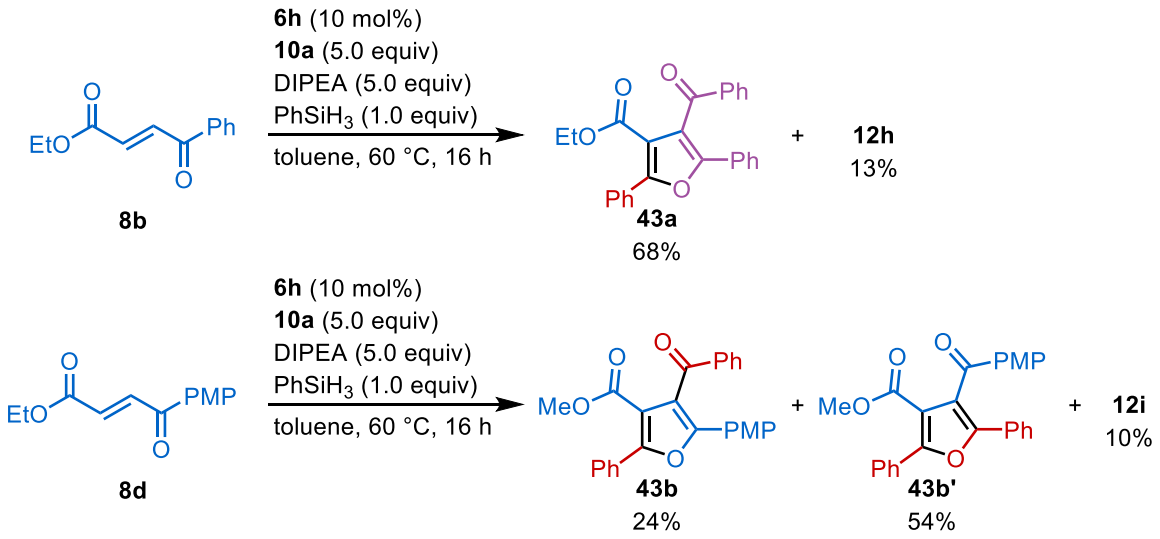


Entry	Cat.	**10a** / equiv	DIPEA / equiv	Solvent	*T* / °C	**12h**[a] / %	**43a**[a] / %	**12h/43a**
1	**6h**	1.1	1.2	THF	60	11	25	31:69
2	**6q**	1.1	1.2	THF	60	27	22	55:45
3	**6b**	1.1	1.2	THF	60	48	5.9	89:11
4	**6b**	1.1	1.2	THF	60	2.1	0.2	91:9
5	**6b**	1.1	1.2	Tol.	100	74	8.0	90:10
6	**6b**	1.5	1.6	Tol.	100	80	9.9	89:11
7	**6b**	2.0	2.1	Tol.	100	81	12	87:13
8[b]	**6b**	**1.5**	**1.6**	**Tol.**	**100**	**82**	**10**	**89:11**
9[c]	**6b**	1.5	1.6	Tol.	100	67	8.9	88:12
10	**6h**	**5.0**	**5.0**	**Tol.**	**60**	**14**	**71**	**16:84**

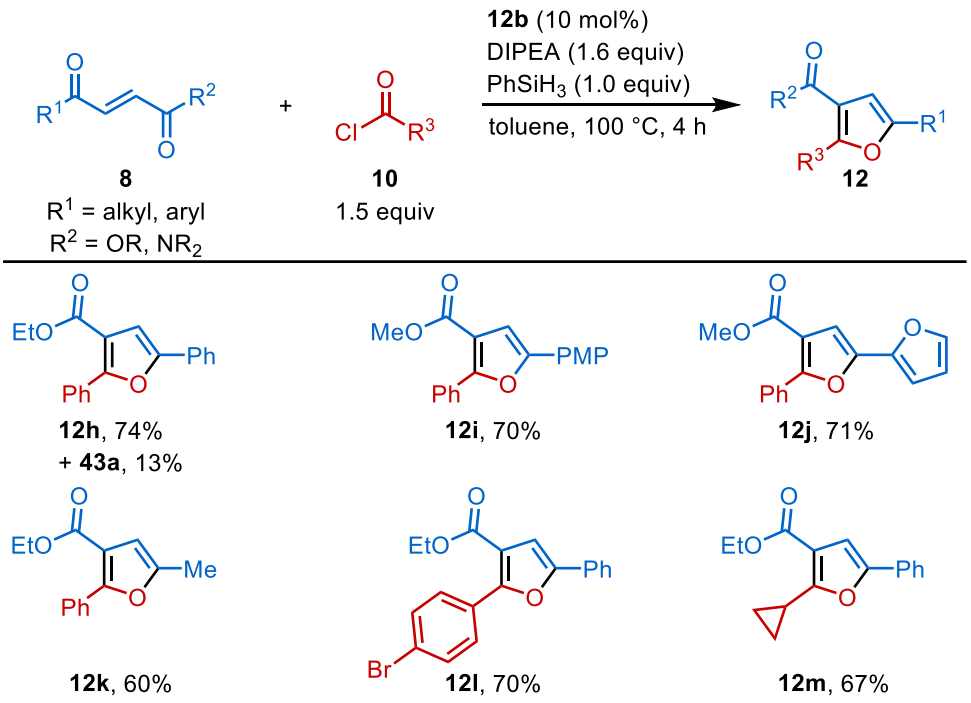
Reaction conditions: 1.0 equiv **8b** (0.50 mmol), 1.1–5.0 equiv BzCl (**10a**, 0.55–2.5 mmol), 1.2–5.0 equiv DIPEA (0.60–2.5 mmol), 10 mol% catalyst **6** (50 µmol), 1.0 equiv $PhSiH_3$ (0.50 mmol), 1.5 ml solvent, 60–100 °C, 4–16 h. [a] Yield determined by GC-FID with hexadecane as internal standard [b] reaction time: 4 h, [c] reaction time: 2 h.

The reaction of the model substrate under the conditions optimized to the formation of tetrasubstituted furan **43a**, using the phosphetane catalyst **6h** led to the formation of the product **43a** in a yield of 68% with 13% of the trisubstituted furan **12h** as the side product (Scheme 28). The reaction of *p*-methoxyphenyl substituted alkene **8d** showed a selectivity problem which was previously concealed due to the choice of reactants. Whenever the substituents of the acyl chloride **10** and the acyl acrylates **8** were different, two isomers of the tetrasubstituted furan **43** were formed in a substrate specific ratio due to a symmetrization step in the reaction mechanism. In case of the methoxy derivative **8d**, this led to the formation

of the diphenylfuran **43b'** in a yield of 54%, and the formation of phenyl methoxyphenyl furan **43b** in a yield of 24%, which made this reaction less synthetically valuable.



Scheme 28: Selected examples for the synthesis of tetrasubstituted furans **43** from acylacrylates **8**. Reaction conditions: 1.0 equiv **8** (1.0 mmol), 5.0 equiv BzCl (**10a**, 5.0 mmol),5.0 equiv DIPEA (5.0 mmol), 10 mol% catalyst **6h** (0.10 mmol), 1.0 equiv $PhSiH_3$ (1.0 mmol), 3.0 ml toluene, 60 °C, 16 h; PMP: *p*-methoxyphenyl.

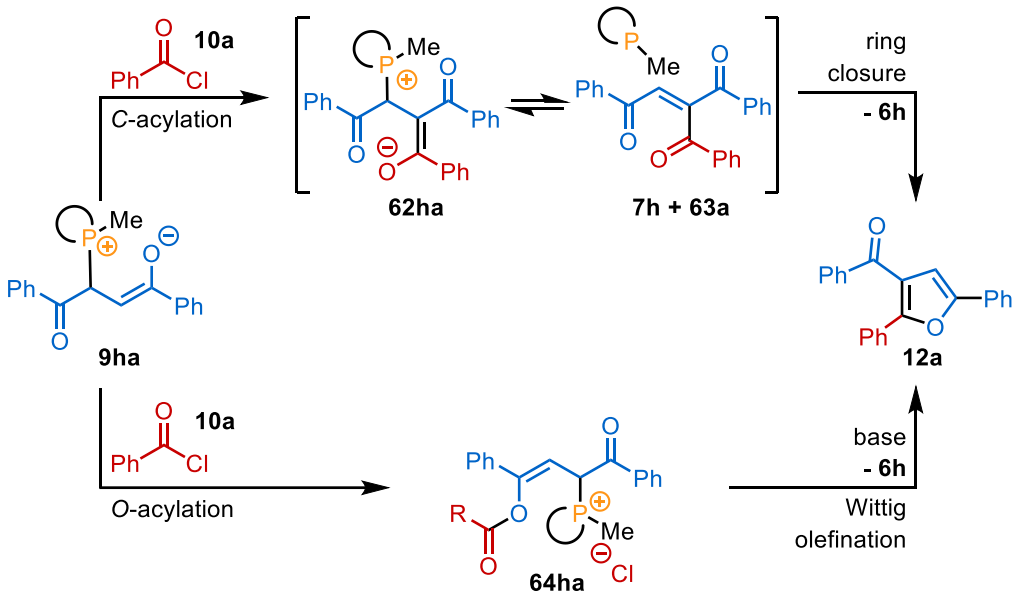


Scheme 29: Selected examples for the synthesis of trisubstituted furans **12** from acylacrylates **8** and acid chlorides **10**. Reaction conditions: 1.0 equiv **8** (1.0 mmol), 1.5 equiv acid chloride **10** (1.5 mmol), 1.6 equiv DIPEA (1.6 mmol), 10 mol% catalyst **6b** (0.10 mmol), 1.0 equiv $PhSiH_3$ (1.0 mmol), 3.0 ml toluene, 100 °C, 4 h; PMP: *p*-methoxyphenyl.

Using the phospholene catalyst **6b** under optimized reaction conditions, the trisubstituted model compound **12h** was isolated in a yield of 74%, while 13% of the tetrasubstituted side product **43a** was obtained (Scheme 29). A similar result was obtained in the synthesis of the

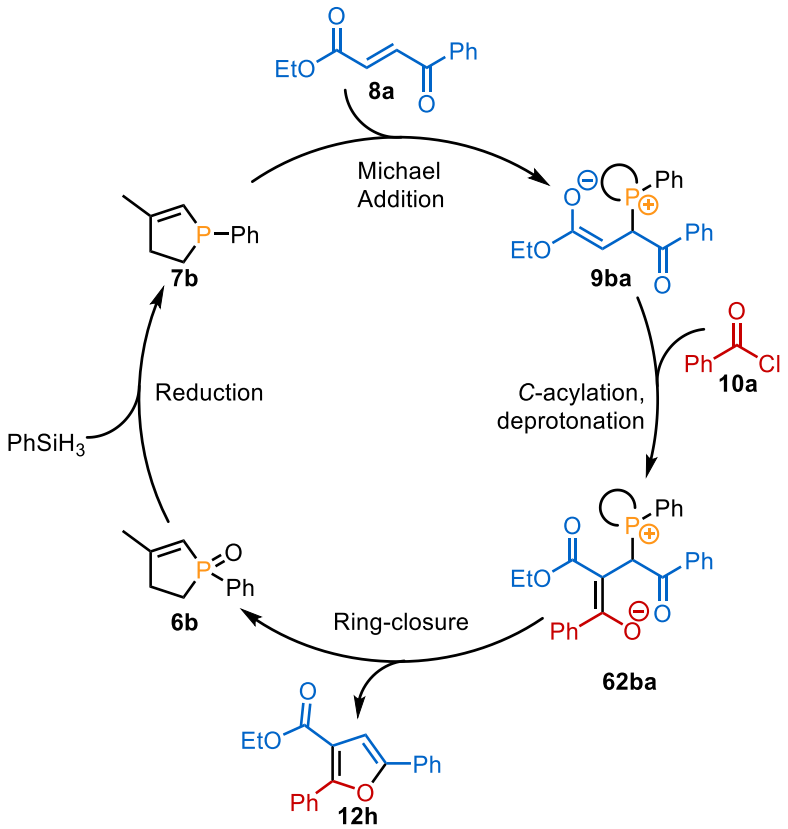
trisubstituted methoxy derivative **12i**, which was obtained in a yield of 70%. The furan moiety was well tolerated, leading to the formation of trisubstituted bifuran **12j** in a yield of 71%. Also, an acetyl acrylate was converted in a yield of 60% to the respective furan **12k**. The use of bromobenzoyl chloride and cyclopropyl carbonyl chloride led to the formation of trisubstituted furans **12l** and **12m** in good yields of 67% and 70%, respectively. Interestingly, the selectivity shifts when acrylamides are converted, due to the different electronic properties on the double bond. Here, the formation of the trisubstituted derivatives is preferred under both reaction conditions using phosphetane **6h** or phospholene catalyst **6b**.

Two general mechanistic pathways were viable in the formation of trisubstituted furans **12** from diacylethenes **8**. After the Michael addition, the formed enolate **9** could react with the acyl chloride **10** in an acylation on the α-carbon, followed by a nucleophilic attack on the opposed carbonyl group and a subsequent deoxygenation in a ring closure mechanism (Scheme 30). Alternatively, the acylation could happen on the oxygen, leading to the formation of an enol ester **64**, followed by a deprotonation step and an intramolecular Wittig reaction. The possible intermediate of the ring closure mechanism **63** was synthesized and brought to reaction with catalytic amounts of phosphetane **6h** and phenylsilane. The ring closure was shown to be a viable reaction, but on addition of benzoyl chloride **10a** and DIPEA, the main product of the reaction was shown to be a tetrasubstituted furan, which was not observed previously. This reaction is largely comparable to the formation of tetrasubstituted furans by Lee et al. starting from trisubstituted olefins.[49] Additionally, while the ring closure mechanism should be possible without the need of an added base, the optimized reaction was non-productive without the addition of DIPEA.



Scheme 30: Two possible mechanistic pathways for the formation of furans **12a** from bisbenzoylethene **8** using phosphetane catalyst **6h**.

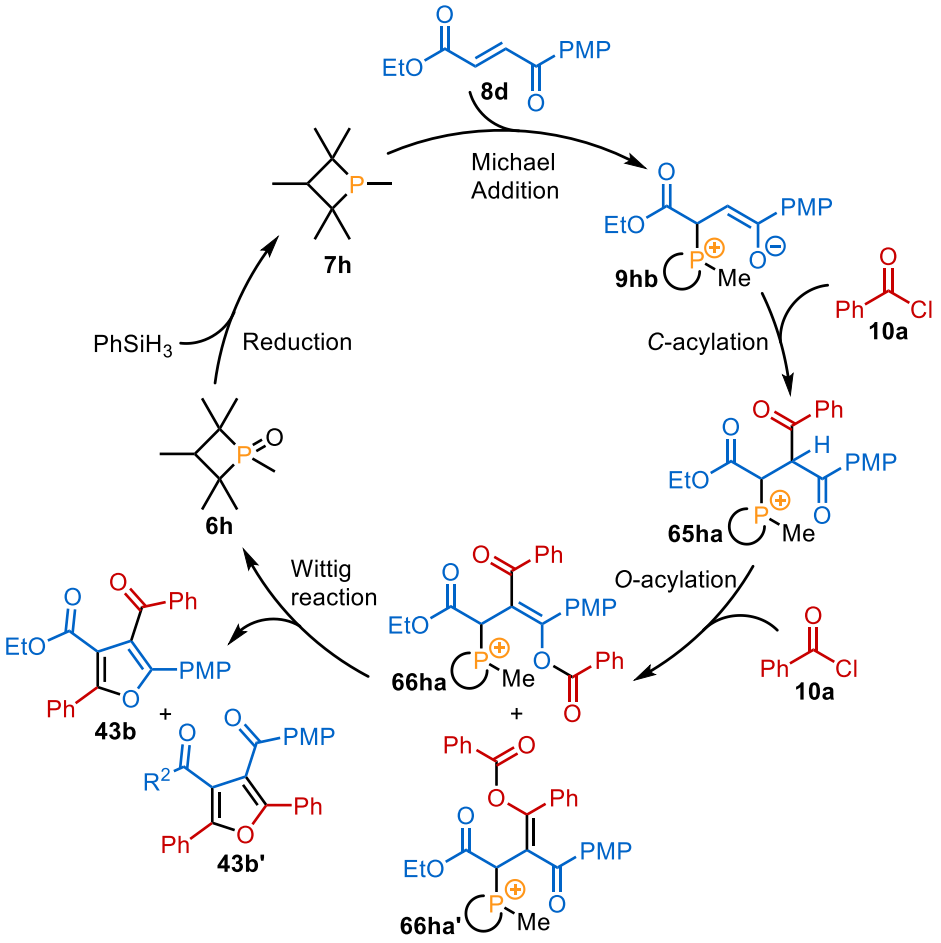
The reaction of the acyl acrylates with acyl chlorides und phosphine redox catalysis proved to be more complex than initially expected due to multiple, possibly competing pathways. Also here, possible intermediates were synthesized and brought to reaction. The formation of the trisubstituted furans **12** also here could be explained by either a *C*-acylation after the Michael addition of the phosphine on the β-carbon in respect to the ester, followed by a ring closure reaction und formation of phosphine oxide, or by a *O*-acylation after addition to the α-carbon, followed by deprotonation and an intramolecular Wittig reaction. While both reaction mechanisms are plausible, the reaction without an added base gave different results in comparison to the reaction of bisacylethenes. Here, product formation was observed, albeit in a lowered yield of 53%. This result would not be expected for the Wittig reaction as the final step of the mechanism. While the reaction containing the Wittig reaction cannot be excluded, the reaction is best explained the Michael addition to the activated double bond, followed by a *C*-acylation and a subsequent ring closure reaction, generating the phosphine oxide, which can be reduced by the terminal reductant (Scheme 31).



Scheme 31: Proposed catalytic cycle for the formation of trisubstituted furans **12h** from acylacrylate **8a**.

The formation of tetrasubstituted furans can also be explained by two plausible reaction mechanisms consisting of a *C*-acylation followed by an *O*-acylation and an intramolecular Wittig olefination (Scheme 32). Only the Michael addition to the α-carbon in respect to the ester can explain the formation of two regioisomers when the substituents of the acylacrylate and the acyl chloride are different. Here, after the Michael addition of the phosphine, a *C*-

acylation leads to the formation of a symmetrized intermediate **65ha**. After deprotonation of the acidic proton, the following *O*-acylation can happen at two different enolates. A subsequent deprotonation, forming the ylid and an intramolecular Wittig reaction leads to the formation of two isomeric furans **43b** and **43b'**.



Scheme 32: Proposed catalytic cycle for the formation of tetrasubstituted furans **43** on the exemplary reaction of acyl acrylate **8d** and benzoyl chloride (**10a**). The deprotonation steps preceding the *O*-acylation and Wittig reaction are not depicted.

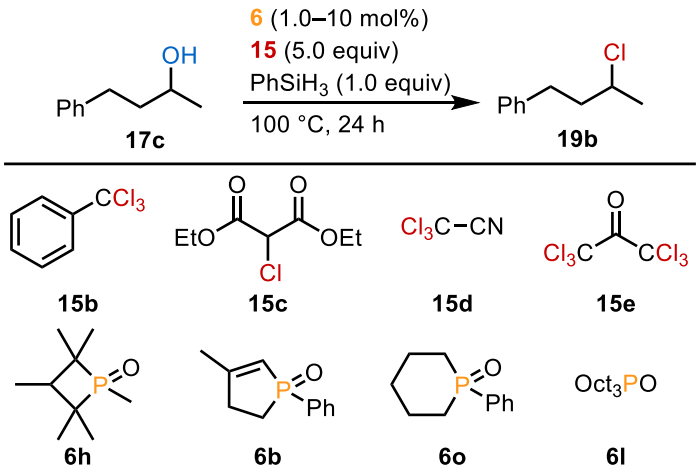
3.3 Organocatalytic Stereospecific Appel Chlorination[88]

The synthesis of halogenated hydrocarbons plays an important role both in formation of (marine) natural products and of active intermediates.[89] The Appel reaction can be used as a mild synthetic method for the halogenation of alcohols and especially their chlorination using triphenylphosphine and carbon tetrachloride.[2a] Disadvantages of this method are the formation of stoichiometric amounts of phosphine oxides and the use of hazardous chlorination agents.

The chlorination of alcohols under catalytic conditions could be shown by Longwitz et al. using a trioctylphosphine catalyst and benzotrichloride as a previously unused chlorine source.[57] While primary chlorides could be obtained in good to excellent yields, secondary chlorides

only formed in moderate yields. Additionally, when using enantiopure reactants, the product could only be obtained with low enantiomeric excess. Reasons for this were inferred to be either the nucleophilic substitution happening by an S_N1 pathway or a subsequent racemization of the product. Thus, our aim was to find a method for the stereospecific chlorination of alcohols using catalytic amounts of more nucleophilic, cyclic phosphine catalysts. A model system was chosen based on our previous work, using the phosphetane catalyst **6h** and phenylsilane as terminal reductant. The secondary alcohol 4-phenyl-2-butanol (**17c**) was first brought to reaction with different chlorine sources (Table 5).

Table 5: Selected chlorine sources and phosphine oxide catalysts in the catalytic Appel reaction

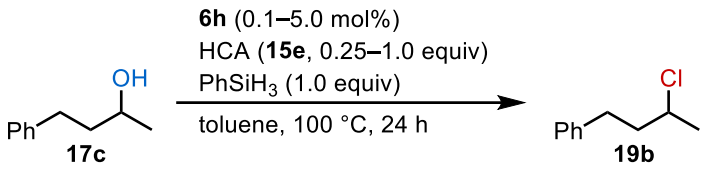


Entry	Cat. (mol%)	Cl-source	Conversion / %	**19b** / %
1	**6h** (10)	**15b**	34	2
2	**6h** (10)	**15c**	>99	35
3	**6h** (10)	**15d**	>99	82
4	**6h** (10)	**15e**	>99	98, (98, 97:3 *er*)[a]
5	**6h** (1)	**15e**	92	87
6	**6b** (10)	**15e**	99	99
7	**6b** (1)	**15e**	95	69
8	**6o** (10)	**15e**	86	39
9	**6l** (10)	**15e**	63	10

Reaction conditions: 1.0 equiv **17c** (0.50 mmol), 5.0 equiv Cl-source **15** (2.5 mmol), 1.0–10 mol% catalyst **6** (5.0–50 µmol), 1.0 equiv $PhSiH_3$ (0.50 mmol) 100 °C, 24 h. Yield and selectivity determined by GC with hexadecane as internal standard. [a] Reaction using (*R*)-**17c**.

While the reaction using benzotrichloride (**15b**) and trioctylphosphine (**7l**) gave a yield of secondary chloride **19b** of 64%, surprisingly, the product could only be obtained in trace amounts using the phosphetane catalyst **6h** (Table 5, entry 1).[57] The classically used tetrachloromethane also resulted in low yields. Diethyl chloromalonate (**15c**) first investigated by van Kalkeren led to the complete conversion of the alcohol **17c**, but only low yield of chloride **19b** of 35% (entry 2). The alcohol **17c** was completely converted both in the reactions with trichloroacetonitrile (**15d**) and hexachloroacetone (**15e**, HCA), while the chloride **19b** was obtained in a good yield of 82% using the nitrile derivative and in near quantitative yield for HCA (entry 3, 4). This reaction was repeated using the enantiopure starting material (*R*)-**17c**, forming the product (*S*)-**19b** in an excellent enantiomeric ratio (*er*) of 97:3. Even at lower catalyst loading of 1 mol% a good yield of 87% was obtained (entry 5). The phospholene catalyst **6b** reacted similarly with near quantitative yield at 10 mol% catalyst loading, but slightly lower yield of 69% at 1 mol% (entry 6, 7). The six-membered phosphinane catalyst **6o** only led to a low yield of 39%, while the trioctylphosphine oxide (**6l**) only reacted slowly, giving a 10% yield of secondary chloride (entry 8, 9).

Table 6: Subset of the optimization reactions for the catalytic Appel reaction.



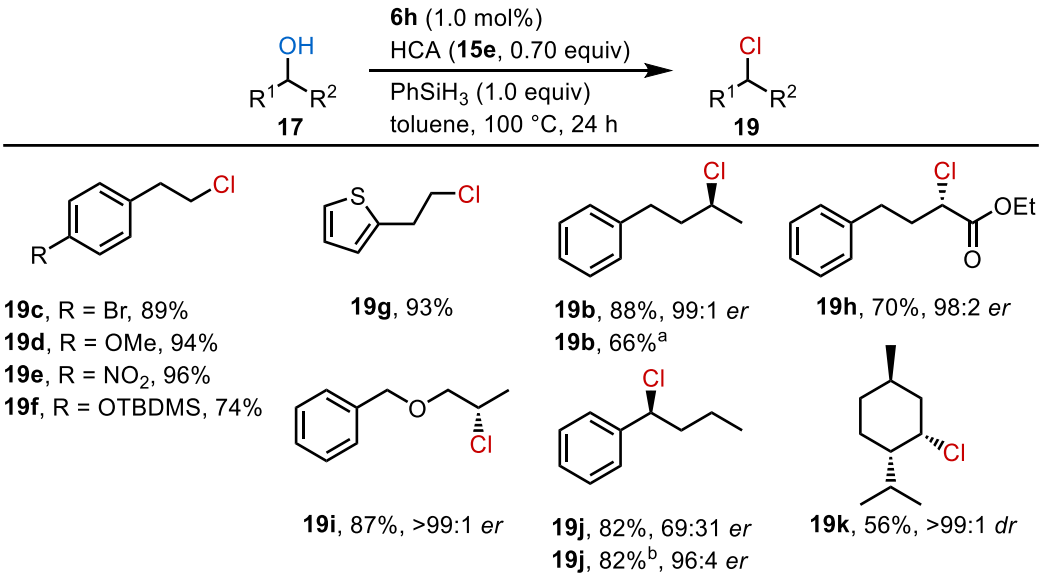
Entry	**6h** / mol%	**15e** / equiv	**19b** / %
1	5.0	1.0	95
2	5.0	0.5	80
3	5.0	0.25	41
4	1.0	0.7	88
5	0.1	0.7	66
6[a]	0.1	0.7	73
7[b]	1.0	0.7	71

Reaction conditions: 1.0 equiv **17c** (0.50 mmol), 0.25–1.0 equiv HCA (**15e**, 0.13–0.5 mmol), 0.1–10 mol% catalyst **6h** (0.5–50 µmol), 1.0 equiv $PhSiH_3$ (0.50 mmol) 100 °C, 24 h. Yield and selectivity determined by GC with hexadecane as internal standard. [a] Reaction time: 48 h. [b] 5.0 equiv PMHS (2.5 mmol [Si]-H).

For further optimization of the reaction the amount of HCA was lowered to 1.0 equivalents at 5 mol% catalyst loading, which gave a good yield of secondary chloride **19b** of 95% (Table 6, entry 1). Lower equivalents of HCA could show that two chlorine atoms per molecule were

available for the reaction. At 0.5 equivalents a good yield of 80% of chlorinated product could be obtained, while with 0.25 equivalents only 41% yield could be observed (entry 2, 3). For further investigations 0.7 equivalents of HCA (**15e**) were used, which in a reaction with 1 mol% of phosphetane catalyst **6h** led to the formation of the secondary butyl chloride **19b** in a good yield of 88% (entry 4). These conditions were used for the substrate scope. Interestingly, even a lowering of the catalyst loading to 0.1 mol% led to an acceptable yield of 66% after 24 h and 73% after 48 h (entry 5, 6). This shows an unusually high activity of the phosphetane catalyst under reaction conditions, which is rarely seen in organocatalysis. Additionally, the reaction could also be conducted using 5.0 equivalents PMHS as the terminal reductant, giving an acceptable yield of 71% (entry 7).

As a test for the functional group tolerance a set of primary alcohols was brought to reaction under optimized conditions. 14 primary chlorides **19** were isolated in generally good to excellent yields. As such, the bromo-substituted chloride **19c** was isolated in a yield of 89% and the methoxy-derivative **19d** in an excellent yield of 94% (Scheme 33). Interestingly, the nitrophenyl derivative **19e** also gave excellent yields of 96%, although under similar reaction conditions but higher catalyst loading Nykaza et al. reported the reduction of this functional group.[72b, 73] Since no reduced side products were observed, the reduced phosphetane catalyst appears to be unavailable for this reaction. The reaction of phenol derivatives led to a mediocre yield, but protection of the free hydroxy group improved this. The acid labile TBDMS-protected phenol thus formed the respective chloride **19f** in a yield of 74%.

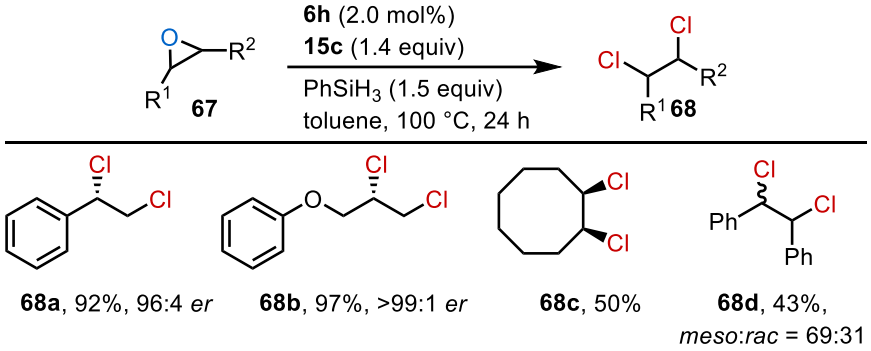


Scheme 33: Selected alcohols converted in the organocatalytic, stereospecific Appel reaction. Reaction conditions: 1.0 equiv **17** (1.0 mmol), 0.70 equiv HCA (0.70 mmol), 1.0 mol% **6h** (10 µmol), 1.0 equiv $PhSiH_3$ (1.0 mmol), toluene (0.5 ml), 100 °C, 24 h. Isolated yields are given. [a] catalyst loading: 0.1 mol% (1 µmol) [b] modified reaction conditions: 5.0 mol% **6h** (50 µmol), 40 °C, 48 h.

Also, the thiophene derivative was well compatible with the reaction conditions and formed the respective chloride **19g** in a yield of 93%. In a second step the reactivity and compatibility of secondary and tertiary alcohols were investigated. The model substrate **17c** was converted to the respective chloride **19b** in a good yield of 88% and an excellent *er* of 99:1. Similar enantiomeric ratios were achieved forming the α-chloroester **19h** and the benzoxypropyl chloride **19i** at yields of 70% and 87%, respectively. While the benzylic chloride **19j** was isolated in a good yield of 82%, a reduced *er* was observed, which can be explained by a higher share of an S_N1-type mechanism in the final nucleophilic substitution of the reaction. At milder conditions using an increased catalyst loading (5 mol%), lower temperature (40 °C) and longer reaction times (48 h) a similar yield of **19j** was achieved, but with improved enantiomeric ratio (96:4 *er*). Notably, also menthol could be chlorinated forming neomenthyl chloride (**19k**). This challenging reaction product easily eliminates HCl under harsher reaction conditions, forming menthenes.

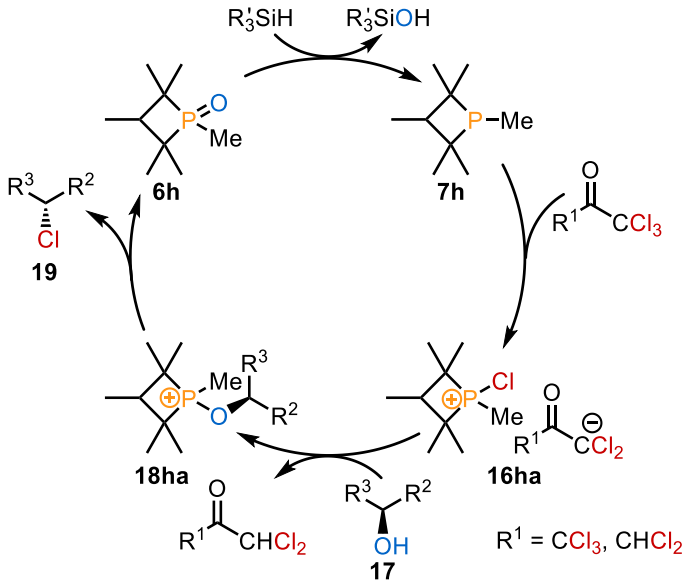
Additional reactions showed the limitations of this method. Triphenylmethanol could not be chlorinated, possibly due to its large steric bulk. Also, amine-substituted substrates could not be converted successfully since a partial decomposition of hexachloroacetone occurred, hampering the reaction.

Also, the dichlorination of epoxides was optimized, using styrene epoxide (**67a**) as the model substrate. By doubling the catalyst loading (2 mol%), chlorine source (1.4 equiv) and solvent (1 M) and an increase of phenylsilane (1.5 equiv), the dichlorinated product **68a** could be obtained in a yield of 94% as determined GC-FID. Finally, 9 epoxides **67** were converted to the respective dichlorides. Under the optimized reaction conditions, the dichloride **68a** was formed in very good yield of 92% and an *er* of 96:4, while an ever better yield of 97% of dichloropropan **68b** with an *er* of >99:1 was achieved in the reaction of phenyl glycidyl ether (Scheme 34).



Scheme 34: Selected epoxide converted in the organocatalytic, stereospecific Appel reaction. Reaction conditions: 1.0 equiv **67** (1.0 mmol), 1.4 equiv HCA (**15e**, 1.4 mmol), 2.0 mol% **6h** (20 µmol), 1.5 equiv $PhSiH_3$ (1.5 mmol), toluene (1.0 ml), 100 °C, 24 h. Isolated yields are given.

The *cis*-1,2-dichlorocyclooctane (**68c**) was isolated as the only isomer in a yield of 50%, whereas the reaction of *trans*-stilbene oxide formed dichloride **68d** as both the *meso*-isomer as well as the racemic mixture in a ratio of 69:31. The stereospecificity of the reaction of styrene oxide and stilbene oxide in the formation of dichlorides **68a** and **68d** can be explained when looking at the ring opening step of the reaction. Thakore et al. showed that the ring opening in a dichlorination of epoxides occurs at the more substituted carbon.[90] In case of the styrene oxide this leads to the selective chlorination of the benzylic position, leaving the oxygen moiety in the primary position for the second chlorination step. In case of the stilbene oxide the oxygen moiety is left in a benzylic position, leading to similar selectivity problems as seen in benzylic chloride **19j**.



Scheme 35: Proposed, simplified mechanism for the organocatalytic, stereospecific Appel reaction.

The mechanism of the reaction proved to be difficult to investigate by NMR, due to a multitude of observed phosphorous species that were not isolable. A stepwise reaction showed the formation of an insoluble intermediate in the reaction of reduced phosphetane and hexachloroacetone, which was isolated and used in the subsequent chlorination of secondary alcohol **17c**. This led to the position of following simplified reaction mechanism: The phosphine oxide **6h** is reduced by the terminal reductant to the phosphine **7h**, which reacts with either hexachloroacetone (**15e**) or pentachloroacetone to form the chlorophosphonium salt **16ha**. The substrate **17** reacts with this activated phosphine **16ha**, forming the alkoxyphosphonium salt **18ha**. The chloride counter ion reacts with the alcohol in an S_N2 reaction, forming the chloride **19** and regenerating the phosphine chloride **6h**.

4 Summary

In this work, new methods in the field of P(III)/P(V) redox catalysis were developed. In the first part, a new method for the synthesis of highly substituted olefins using a phosphetane catalyst was developed, which opened the possibility to use poly(methylhydrosiloxane) (PMHS) as the terminal reductant. PMHS is an environmentally friendly, non-toxic, and inexpensive terminal reductant, which is formed as a waste product of the silicone industry.[82] While previous methods largely used fossil-based toluene as the solvent, butyl acetate and other polar-aprotic solvents were shown to be renewable alternatives. The wide functional group tolerance of this method was shown in the synthesis of 26 highly substituted alkenes in yields up to 96% and excellent *E*/*Z*-selectivities. As part of the investigation, the formation of water by condensation of silanols under reaction conditions was observed. In this reaction water leads to the formation of succinates as a persistent side product. While this condensation reaction of silanols is so far only reported in few select circumstances, the general reaction principle is of importance not just for P(III)/P(V) redox cycling catalysis, but also for reactions which are more susceptible for hydrolysis.

Using this method for the base-free Wittig reaction, a library of overall 22 exocyclic maleimides was synthesized and transferred to the University Medical Center Rostock, where these substances were evaluated on their cytotoxic and anti-proliferative activity on different cancer cell lines, as well as their activity on the growth rate of different bacteria strains was investigated.[86] Multiple endocyclic maleimides had previously shown good activity in this regard, while the shift of the double bond was thought to stabilize an intermediate in the probable mechanism of action of these compounds. Despite this, the analyzed maleimides showed no significant activity.

While activated alkenes react with phosphines in the catalytic base-free Wittig reaction in a Michael addition, followed by a protonation/deprotonation sequence, forming an ylid, the enolate formed in the first reaction step can also react with a sufficiently active electrophile, such as an acyl chloride. Subsequent Wittig or ring closure reaction leads to the formation of substituted furans. Here, the reaction of bisacylethenes and acyl acrylates with acyl chlorides was investigated, forming an underexplored subset of substituted furans. Bisacylethenes were brought to reaction using a phosphetane catalyst, amine base and phenylsilane as terminal reductant, leading to the formation of 12 trisubstituted furans. Unexpectedly, the reaction of acyl acrylates not just formed trisubstituted furans, but also tetrasubstituted derivatives, the ratio of which was dependent on the employed catalyst. This led to the formation of 14 trisubstituted furans using a phospholene catalyst, and an additional 6 tetrasubstituted furan using a phosphetane catalyst. Problematic was the formation of substrate dependent tetrasubstituted isomers due to a symmetrization step in the reaction mechanism.

Also, a method for the catalytic Appel chlorination was developed using hexachloroacetone as the chlorination source in substoichiometric amounts with a phosphetane catalyst at very low catalyst loadings of 1 mol% and phenylsilane as terminal reductant. With this, a wide functional group tolerance was shown in the reaction of 14 primary alcohols with yields up to 96%, while examples for the excellent stereospecificity were shown in the reaction of 12 secondary and tertiary alcohols with enantiomeric ratios of up to >99:1. Also, 9 epoxides could be dichlorinated stereospecifically with yields up to 97% and *er* up to >99:1.

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6 Appendix

My contributions to publications are given

Publication 1 J. Tönjes, L. Longwitz, T. Werner, *Green Chem.* **2021**, *23*, 4852–4857.

"Poly(methylhydrosiloxane) as a reductant in the catalytic base-free Wittig reaction"

A major part of experiments was conducted by me. Lars Longwitz synthesized parts of the substrate scope. The manuscript and supporting information were written by me and corrected by Lars Longwitz and Thomas Werner. My overall contribution to this work is 70%.

Publication 2 J. Tönjes, V. Medvarić, T. Werner, *manuscript submitted*

"Synthesis of Trisubstituted Furans from Activated Alkenes by P(III)/P(V) Redox Cycling Catalysis"

A major part of experiments was conducted by me. Viktorija Medvarić synthesized parts of the substrate scope. The manuscript was written by me and supporting information were written by me and Viktorija Medvarić. Corrections were done by Viktorija Medvarić and Thomas Werner. My overall contribution to this work is 75%.

Publication 3 J. Tönjes, L. Kell, T. Werner, *Org. Lett.* **2023**, *25*, 9114–9118.

"*Organocatalytic Stereospecific Appel Reaction"*
A major part of experiments was conducted by me. Lukas Kell conducted parts of the reaction optimization. The manuscript and supporting information were written by me and corrected by Lukas Kell and Thomas Werner. My overall contribution to this work is 80%.

6.1 Poly(methylhydrosiloxane) as a reductant in the catalytic base-free Wittig reaction

J. Tönjes, L. Longwitz, T. Werner, *Green Chem.* **2021**, *23*, 4852–4857.

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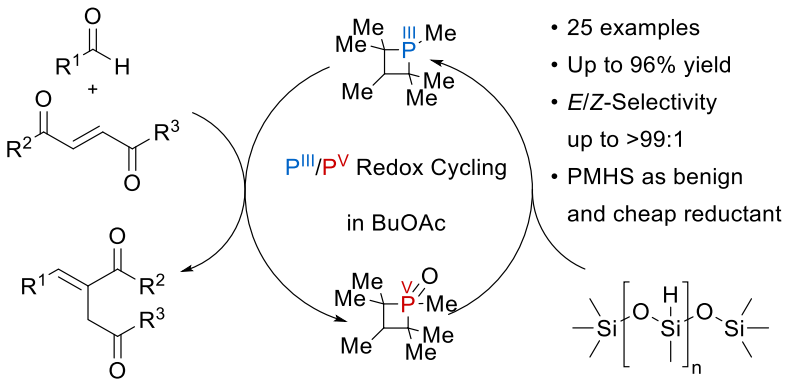

Abstract:

Herein, we report a catalytic, base-free Wittig reaction forming highly functionalized alkenes with PMHS as a terminal reductant and butyl acetate as a green solvent. Poly(methylhydrosiloxane) (PMHS) is a non-toxic, environmentally friendly, inexpensive and easy to handle reductant. However, the inherent low reactivity hampers its applicability in catalytic reactions, such as P(III)/P(V) redox cycling reactions. Most of these catalytic systems include highly active aryl silanes to facilitate phosphine oxide reduction and are not compatible with PMHS or similar more sustainable terminal reductants. The herein reported catalyst system which is based on a methyl-substituted phosphetane operates at low catalyst loadings without additional co-catalysts and allows the use of PMHS as terminal reductant. A wide variety of functional groups was tolerated and 25 different alkenes were synthesized in yields up to 96% with excellent stereoselectivity. Mechanistic studies revealed the formation of water from silanol condensation as the main pathway of siloxane formation.

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Poly(methylhydrosiloxane) as a reductant in the catalytic base-free Wittig reaction†

Jan Tönjes, [a] Lars Longwitz [a] and Thomas Werner *[a,b]

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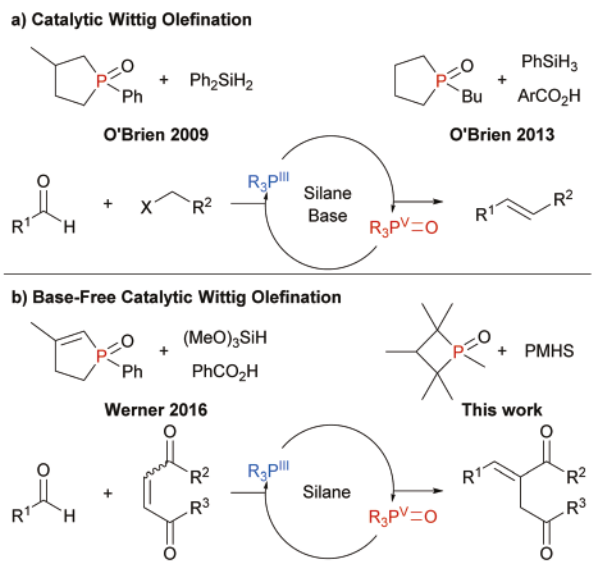
Herein, we report a catalytic, base-free Wittig reaction forming highly functionalized alkenes with PMHS as a terminal reductant and butylacetate as a green solvent. Poly(methylhydrosiloxane) (PMHS) is a non-toxic, enviromentally friendly, inexpensive and easy to handle reductant. However, the inherent low reactivity hampers its applicability in catalytic reactions, such as P(III)/P(V) redox cycling reactions. Most of these catalytic systems include highly active aryl silanes to facilitate phosphane oxide reduction and are not compatible with PMHS or similar more sustainable terminal reductants. The herein reported catalyst system which is based on a methyl-substituted phosphetane operates at low catalyst loadings without additional co-catalysts and allowes the use of PMHS as terminal reductant. A wide variety of functional groups was tolerated and 25 different alkenes were synthesized in yields up to 96% with excellent stereoselectivity. Mechanistic studies revealed the formation of water from silanol condensation as the main pathway of siloxane formation.

Introduction

After its discovery in 1953, the Wittig reaction quickly became one of the most important olefination methods in organic synthesis both in lab scale and industrial applications.[1–3] Over the years numerous modifications were implemented that improved the *E*/Z selectivity or added to the number of usable reagents.[4–9] Still, the formation of stoichiometric amounts of phosphane oxide remained a disadvantage due to the amount of waste generated, as well as challenges associated with the separation of phosphane oxides from the product. Considerable amount of work was performed to improve the work-up by developing water-soluble phosphane oxides, immobilized phosphane reagents or separation techniques by complexation.[10–12] In industrial settings triphenylphosphane oxide has been recycled by reaction with hazardous phosgene, followed by the reduction with elemental phosphorus or aluminium, forming the respective chlorides as coupling products.[2,13,14] As an alternative strategy to avoid stoichiometric phosphane oxide waste, a catalytic Wittig reaction was developed by O'Brien *et al.* in 2009 and subsequently further elaborated (Scheme 1a).[15–17] Here the active phosphane reagent is regenerated *in situ* by reduction of the formed phosphane oxides using organosilanes. Subsequently, catalytic methods based on P(III)/P(V) redox cycling have been employed in Staudinger,[18–20] Appel,[21] reductive C–N coupling,[22,23] olefin reduction[24] or base-free Wittig reactions.[25–29] Besides facilitating the work-up of the reaction, these catalytic processes also show advantages in terms of sustainability. In a life cycle assessment classical and catalytic Wittig reactions were evaluated in terms of their cumulative energy demand (CED) and



Scheme 1 General concept of catalytic Wittig olefination and its base-free variant.

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greenhouse gas emissions (GHG). Thus, by using phenylsilane as terminal reductant in the catalytic Wittig reaction CED and GHG were reduced by 20% and 33% respectively in a model study.[30] However, the use of polymethylhydrosiloxane (PMHS) reduced the CED and GHG by as much as 62% and 66% respectively, showing the impact of the terminal reductant. As a by-product of silicone industry PMHS is inexpensive and readily available.[31] While it is also non-toxic and stable to air and moisture, the low reactivity of PMHS without the use of a separate catalyst hampers its application. For these reasons, only limited number of catalyst systems in phosphorus redox cycling can use PMHS or related siloxanes as terminal reductants. A phosphorus-catalyzed Staudinger reduction was reported by Mecinović *et al.* in which the formed aza-ylide reacted with PMHS at 106 °C.[19] While the reduction of acyclic phosphane oxides with PMHS can only take place at highly elevated temperatures of 175 °C or by using an additional catalysts, phospholene derivatives can be reduced in refluxing toluene.[32–34] Still, the reduction proceeds too slowly to be viable for a catalytic process. The reduction of phosphetane oxide **4a** by PMHS could be shown under basic or acidic conditions at 100 °C and 120 °C respectively.[22–24,35]

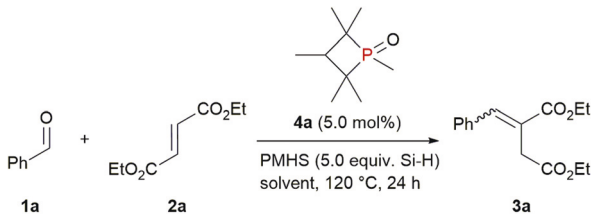
The base-free Wittig reaction is a method to efficiently synthesize highly functionalized olefins (Scheme 1b). In this case, the ylide is formed not by deprotonation of a phosphonium salt but by addition of phosphane to an activated alkene.[36] Our previous work investigated the use of catalytic amounts of tributylphosphane with phenylsilane and phospholene derivatives with trimethoxysilane as terminal reductants in this reaction.[25,26] While good yields could be achieved, highly active silanes had to be employed and the addition of benzoic acid was necessary to accelerate the reduction of the phosphane oxides. Furthermore, the problematic solvent toluene was used and the *E*/*Z*-selectivity showed room for improvement.[37] Thus, we aimed to improve the catalyst system for the base-free catalytic Wittig reaction based on a highly efficient phosphetane catalyst in green solvents using sustainable PMHS as a terminal reductant.

Results and discussion

Parameter optimization and catalyst screening

We started our investigation with the model reaction of benzaldehyde (**1a**) with diethyl fumarate (**2a**) forming the trisubstituted alkene **3a** by using 5.0 mol% of the phosphetane oxide **4a** as a catalyst and PMHS as a terminal reductant. While in previous methods for catalytic Wittig reactions toluene has been established as the solvent, it is of general interest to use more sustainable alternatives.[37,38] The non-polar solvents cymene (Table 1, entry 1)[39] and limonene (entry 2)[39] led to acceptable yields of 67% and 69%, respectively. *n*-Butyl acetate (entry 3),[37] *tert*-butyl acetate (entry 4),[40] 2-methyl tetrahydrofuran (2-MeTHF, entry 5)[41] and cyclopentyl methyl ether (CPME, entry 6)[42] led to improved yields up to 88%. Under solvent free conditions a good yield of 77% was obtained

Table 1 Optimization of the reaction parameters in the model reaction of benzaldehyde (**1a**) and diethyl fumarate (**2a**)



1a **2a** **3a**

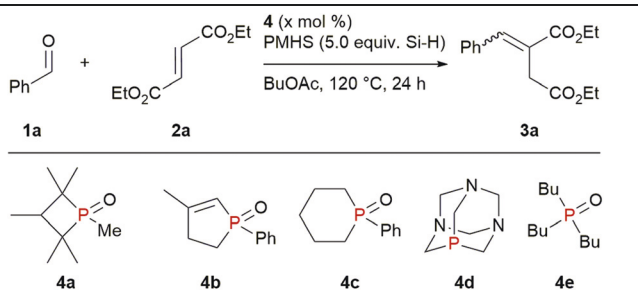
Entry	Solvent	Yield **3a**/%[a]	*E*/*Z*[a]
1	Cymene	67	98 : 2
2	Limonene	69	97 : 3
3	BuOAc	86	97 : 3
4	*t*BuOAc	84	97 : 3
5	2-MeTHF	86	98 : 2
6	CPME	88	98 : 2
7[b]	Solvent free	77	98 : 2
8	GVL	71	97 : 3
9	Propylene carbonate	18	97 : 3

Reaction conditions: 1.0 equiv. **1a** (0.5 mmol), 1.5 equiv. **2a** (0.75 mmol), 5.0 mol% catalyst **4a** (25 μmol), 5.0 equiv. Si–H of PMHS (2.5 mmol), 1.5 ml solvent, 120 °C, 24 h. [a] Yield and selectivity determined by GC-FID with hexadecane as internal standard. [b] 3.0 equiv. PMHS, 2 mmol reaction scale.

(entry 7). However, the formation of a silicone-like polymer made work-up of the reaction mixture more demanding and also led to a poor reproducibility.[38] A similar polymer formation was observed when using γ-valerolactone (GVL, entry 8)[41] and propylene carbonate (entry 9)[39] with yields of 71% and 18%, respectively. Independent of the solvent, the reaction afforded the product **3a** in excellent *E*/*Z*-selectivity. For further investigations *n*-butyl acetate was chosen due to the good yield, as well as its good evaluation for sustainability.[37]

We further investigated other catalytic systems and different reaction parameters in the reaction. The reduction of catalyst loading to 2.5 mol% (Table 2, entry 1) and 1.0 mol% (entry 2) afforded a lower yield of 71% and 31%, respectively. A lower reaction temperature of 100 °C also led to a lower yield of 53% (entry 3). O'Brien *et al.* reported an improved yield by addition of benzoic acid derivatives to a catalytic Wittig reaction using a phospholane oxide as a catalyst.[16] A similar increase in yields was observed in catalyst systems for the base-free variant of the catalytic Wittig reaction.[26] Besides the effect on the phosphane oxide reduction, the mechanistic investigation of the intramolecular base-free Wittig reaction also showed the involvement of the acid in the formation of the ylide.[27] Notably, in case of the phosphetane catalyzed reaction by addition of benzoic acid (5.0 mol%) a decrease in the yield from 86% to 69% was observed. Previously reported catalysts for catalytic Wittig reactions have been investigated under the optimized conditions with catalyst loading of 2.5 mol%. The phospholene oxide catalyst **4b** afforded a yield of 11% with a reduced *E*/*Z*-selectivity of 90 : 10 (entry 5). Due to the low reactivity of PMHS, the phosphinane **4c**, as well as the triazaphosphaadamantane **4d** led to only traces of product, whereas for tributylphosphane oxide (**4e**) no

Table 2 Comparison of previously employed catalysts to the phosphetane oxide **4a**



Entry	Catalyst (mol%)	Yield **3a**/% [a]	*E*/*Z*[a]
1	**4a** (2.5)	71	97 : 3
2	**4a** (1.0)	31	97 : 3
3[b]	**4a** (5.0)	53	97 : 3
4[c]	**4a** (5.0)	69	97 : 3
5	**4b** (2.5)	11	90 : 10
6	**4c** (2.5)	1	n.d.
7	**4d** (2.5)	1	n.d.
8	**4e** (2.5)	0	n.d.

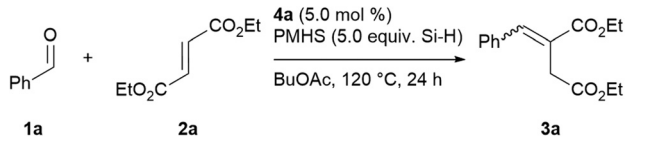
[a] Reaction conditions: 1.0 equiv. **1a** (0.5 mmol), 1.5 equiv. **2a** (0.75 mmol), 2.5 mol% catalyst **4** (13 μmol), 5.0 equiv. Si–H of PMHS (2.5 mmol), 1.5 ml solvent, 120 °C, 24 h. Yield and selectivity determined by GC with hexadecane as internal standard. [b] 100 °C. [c] Additional 5 mol% $PhCO_2H$.

product was observed (entries 6 and 7). This demonstrates the importance of the choice of phosphane catalyst, when using PMHS as the terminal reductant.

Water formation under the reaction conditions

During our investigation we found reduction of alkene **2** to the respective alkane to be a persistent side reaction, so that a decrease in alkene loading to 1.1 equiv. led to a noticeable reduction in yield. Our previous findings showed that the reduction to the corresponding alkane can take place in the presence of water under similar conditions with the same catalyst.[24] Although no significant amount of water could be found in the starting materials, the reaction was repeated using water scavengers. While the addition of molecular sieves (MS) afforded a small decrease in yield from 72% to 58% (Table 3, entries 1 and 2), the addition of Na_2SO_4 or triethyl orthoformate led to good yields of 78% and 80% respectively (entries 3 and 4). Thus, we postulated that water is formed during the reaction by condensation of two silanol groups. Whether water or hydrogen is formed in the reduction of phosphane oxides by silanes seems to be highly dependent on the reaction conditions. While Petit *et al.* reported the formation of water in the titanium-catalyzed reduction of triphenylphosphane oxide with tetramethyldisiloxane,[43,44] the majority of proposed mechanisms include the generation of hydrogen by reaction of the formed silanol with a second silane or do not lay focus on the fate of the silanol.[32,45–47] The reactions were repeated without the addition of aldehyde and with different amounts of catalyst. We proposed that the formation of silanol by

Table 3 Evaluation of common water scavengers



Entry	Water scavenger	Yield **3a**/% [a]	*E*/*Z*[a]
1	—	72	96 : 4
2	30 wt% molecular sieves (3 Å)	58	96 : 4
3	30 wt% Na_2SO_4	78	97 : 3
4	2.5 equiv. triethyl orthoformate	80	97 : 3

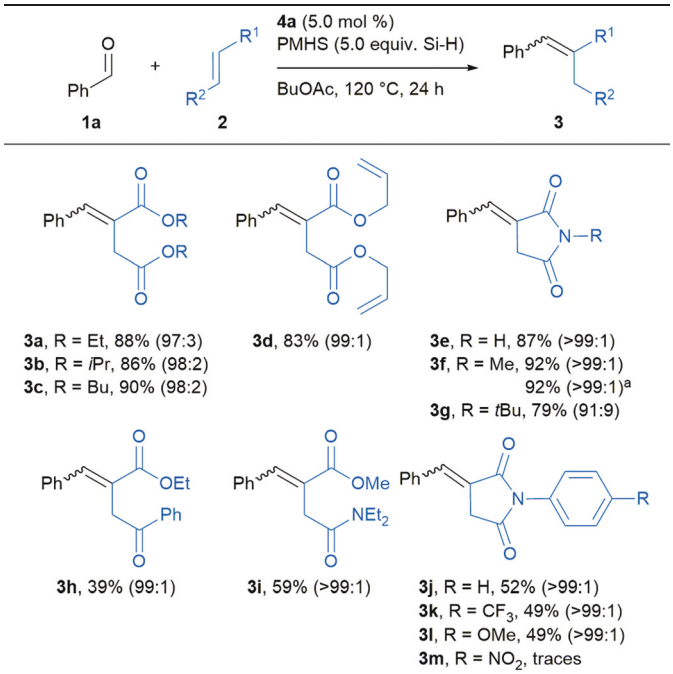
[a] Reaction conditions: 1.0 equiv. **1a** (0.5 mmol), 1.1 equiv. **2a** (0.55 mmol), 5.0 mol% catalyst **4a** (25 μmol), 5.0 equiv. Si–H of PMHS (2.5 mmol), 1.5 ml solvent, 120 °C, 24 h. Yield and selectivity determined by GC with hexadecane as internal standard.

reduction of the catalyst (1.0 equiv.) and its condensation leads to the formation of water (0.5 equiv.) and consequently to 0.5 equiv. of alkane by reduction of the corresponding alkene and regeneration of the phosphane oxide (0.5 equiv.). Thus, the reduction of 1.0 equiv. of the oxide in presence of fumarate **2a** led to the quantitative formation of the corresponding succinate.[38] The use of less phosphane oxide decreases the yield of succinate. The formation of water from silanol condensation under the reaction conditions was further investigated using NMR spectroscopy. The reduction of the catalyst in the presence of triethyl orthoformate showed the formation of ethyl formate (0.5 equiv.) in ^{1}H NMR spectrum.[38] The formed water can be helpful in facilitating hydrogen shifts or stabilizing ionic intermediates, as well as detrimental in conducting side reactions or deactivation of catalysts. Thus, this finding is of interest for the design of better catalytic systems not just in phosphorus redox catalysis.

Substrate scope

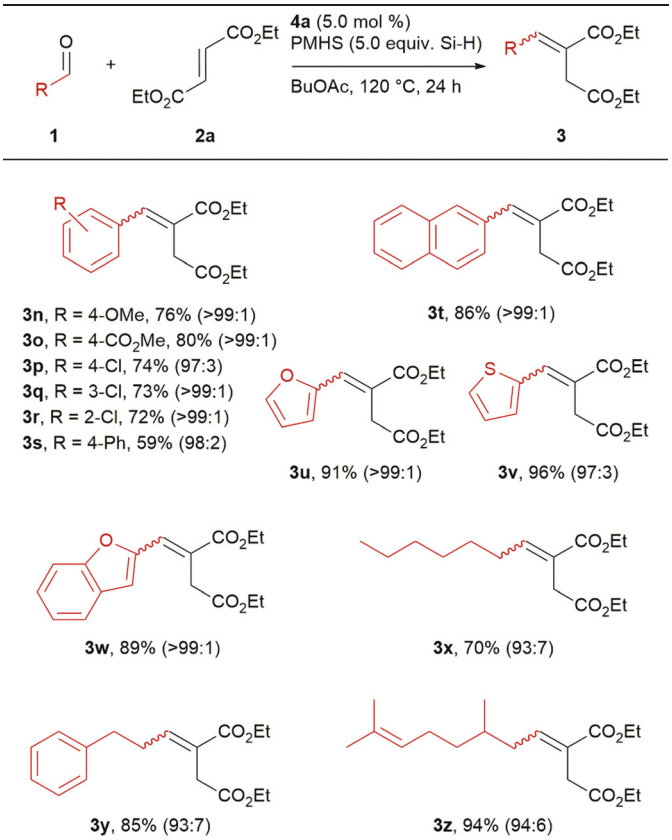
Next, we turned our attention to the substrate scope. Based on the previously determined optimized conditions the model substrate **3a** afforded an isolated yield of 88% with an *E*/*Z* selectivity of 97 : 3 (Table 4). Other activated alkenes, like the isopropyl, butyl and allyl derivatives **3b–3d** could be isolated in 86%, 90% and 83% respectively. The Wittig reaction with alkyl substituted as well as unsubstituted maleimides **3e–3g** worked well with yields of 79% to 92%, although in part with slightly lower stereoselectivity. The conversion of **2f** was also performed on a 10 mmol scale. In this case the product was purified by recrystallization leading to the desired product **3f** in 92% yield. Aryl substituted maleimides **3j–3l** however only gave moderate yields of 49% to 51%. The nitro derivative **3m** afforded no product at all, likely due to the reduction of nitro moiety which can occur under the reaction conditions.[22,23] As expected, less activated alkenes gave lower yields with the keto-ester derivative **3h** and the amide **3i** producing yields of 39% and 59% respectively. Weaker Michael acceptors, such as diketones or acrylates, could not be converted.[38] Independent of the electronic situation of the ring system, the derivatives of

Table 4 Substrate scope of activated alkenes



Reaction conditions: 1.0 equiv. **1a** (0.5 mmol), 1.5 equiv. **2** (0.75 mmol), 5.0 mol% catalyst **4a**, 5.0 equiv. Si–H of PMHS, 1.5 ml solvent, 120 °C, 24 h. Isolated yields are given. [a] Reaction scaled to 10 mmol and purified by recrystallization.

Table 5 Substrate scope of different aldehydes

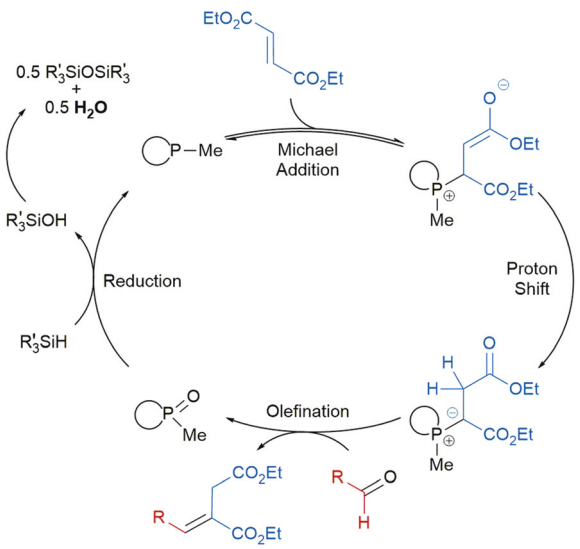


Reaction conditions: 1.0 equiv. **1** (0.5 mmol), 1.5 equiv. **2a** (0.75 mmol), 5.0 mol% catalyst **4a**, 5.0 equiv. Si–H of PMHS, 1.5 ml solvent, 120 °C, 24 h. Isolated yields are given.

benzaldehyde **3n–3r** led to good isolated yields of 72%–80% (Table 5), whereas the biphenyl derivative **3s** afforded a slightly lower yield of 59%. Naphthyl derivative **3t** also gave a good yield of 86%. Conversion of heteroaromatic carbaldehydes **1u–1w** led to excellent yields of up to 96%. Finally, the substrate scope in respect to alkyl aldehydes was studied. Heptanal (**1x**) was converted to the corresponding alkene **3x** in a yield of 70%. The reaction of phenylpropane aldehyde (**1y**) and citronellal (**1z**) afforded the product in yields of 85% and 94% respectively.

Mechanism

We set out to investigate the mechanism of the reaction using deuterium labelling experiments. For this, the model reaction was repeated using ethyl fumarate-2,3-d_2 (**2a-d_2**), which led to a product with an H/D ratio of 32 : 68.[38] Since an internal H-shift in the formation of the ylide would lead to the retention of the incorporated deuterium, the loss of deuterium supports a protonation/deprotonation step for the formation of the ylide. The water formed by condensation of the silanol could be involved in this proton shuttling, although the product formed by reaction of ethyl fumarate-2,3-d_2 (**2a-d_2**) in the presence of triethyl orthoformate showed little difference in the H/D ratio. Based on this observation, the results of the water scavenging experiments and our previous findings, we proposed the following mechanism (Scheme 2).[24] Firstly, the phosphetane oxide is reduced by the silane in the first step of the catalytic cycle. The formed silanols can condensate



Scheme 2 Proposed mechanism for the catalytic base-free Wittig reaction.

forming siloxanes and water. Subsequently, the phosphetane reacts with the alkene in a reversible Michael addition and an intermolecular protonation/deprotonation step follows which

forms the respective ylide. The ylide now reacts with the aldehyde to liberate the olefination product and regenerating the phosphane oxide. As a side reaction the ylide can also hydrolyse, forming the corresponding succinate.

Conclusions

In conclusion, a method for the base-free catalytic Wittig reaction using the green and renewable solvent BuOAc was developed. The use of a phosphetane based catalyst facilitates the P(III)/P(V) redox cycling. This allows the use of the inexpensive and environmentally friendly PMHS as a terminal reductant. A broad scope of substrates could be converted to give highly functionalized alkenes in excellent and improved stereoselectivity. Various functional groups were tolerated under the reaction conditions. The dimerization of silanols forming water under reaction conditions and the mechanism were investigated by *in situ* NMR experiments, deuterium labelling and control experiments.

Experimentals

General procedure (GPB)

Under an argon atmosphere polymethylhydrosiloxane (173 mg, 173 μL, 5.00 equiv. Si–H) was added to a mixture of aldehyde (**1**, 0.50 mmol, 1.00 equiv.) and alkene (**2**, 0.75 mmol, 1.50 equiv.). Subsequently, the catalyst (**4a**, 4.4 mg, 0.025 mmol, 5.0 mol%) was added as a solution in BuOAc (0.017 M, total volume of BuOAc is 1.5 ml). The reaction mixture was heated to 120 °C in an oil bath for 24 h. The solution was cooled to room temperature, diluted with EtOAc and SiO_2 (40–63 μm) was added. All volatiles were removed and the adsorbed crude product was purified by column chromatography (eluent cyclohexane : EtOAc).

Conflicts of interest

The authors declare no conflict of interest.

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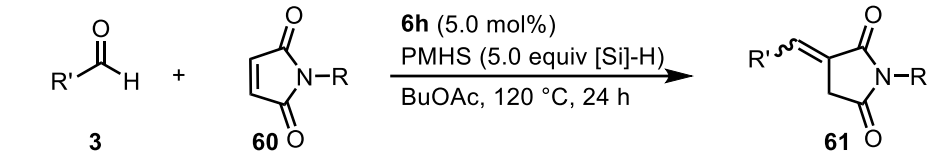
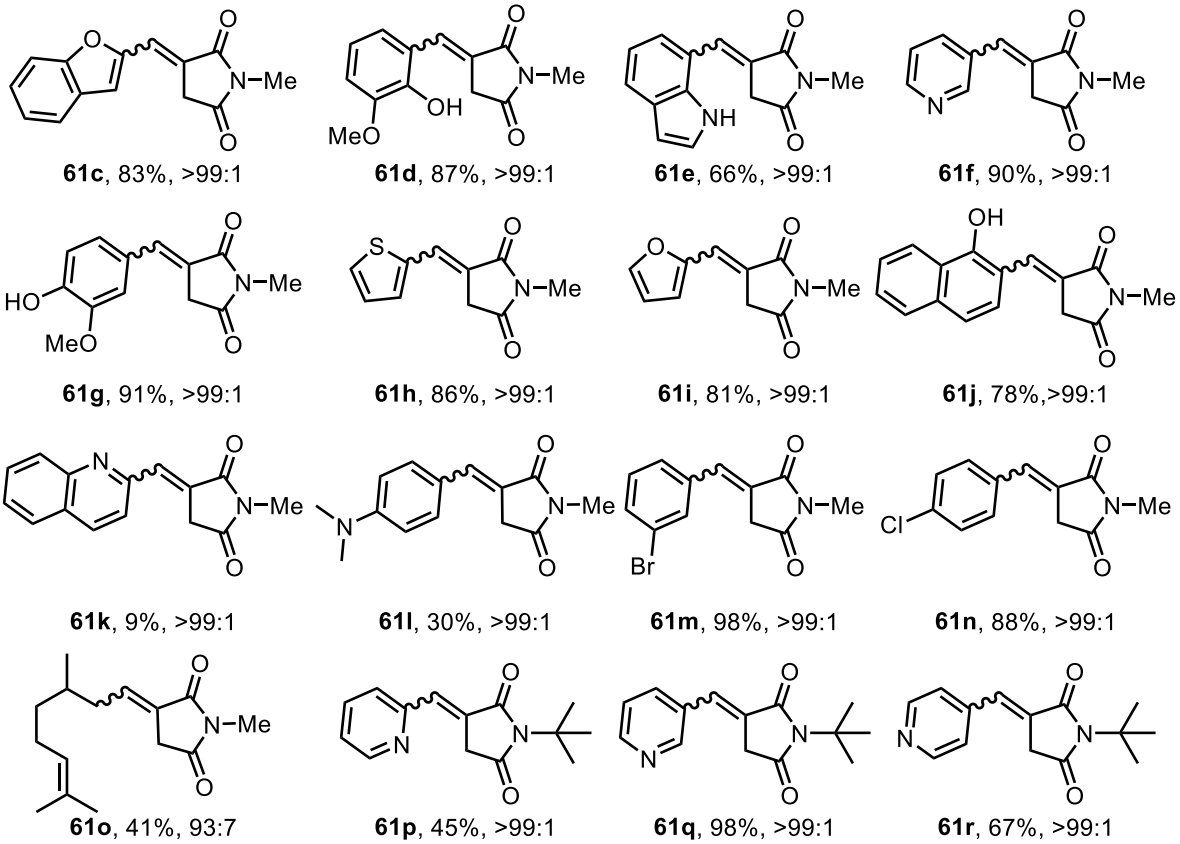
6.1.1 Experimental section for chapter 3.1.1





General Procedure

A 50 ml Schlenk flask is put under vacuum and flushed with argon. The aldehyde (**3**, 1.00 mmol, 1.00 equiv), alkene (**3**, 1.50 mmol, 1.50 equiv) and poly(methylhydrosiloxane) (345 mg, 142 µL, 5.00 equiv [Si]-H) were added. Subsequently, the catalyst (**6h**, 0.050 mmol, 0.050 equiv) was added as a solution in BuOAc (0.017 M, total volume of BuOAc is 3.0 ml). The reaction mixture was heated to 120 °C in an oil bath for 24 h. The solution was cooled to room temperature, diluted with EtOAc and SiO_2 (40–63 µm) was added. All volatiles were removed and the product **61** was obtained after purification with column chromatography (eluent cyclohexane:EtOAc).

3-(Benzofuran-2-ylmethylene)-1-methylpyrrolidine-2,5-dione (61c)

According to the GP, benzofuran-2-carbaldehyde (146 mg, 1.00 mmol, 1.00 equiv) was converted with 1-methylpyrrolidine-2,5-dione (166 mg, 1.50 mmol, 1.50 equiv) and PMHS in the presence of 1,2,2,3,4,4-hexamethylphosphetane 1-oxide (**6h**, 8.7 mg, 0.050 mmol, 0.050 equiv) in BuOAc (3.0 ml). Purification (SiO_2, cyclohexane:EtOAc = 3:1) gave alkene **61c** (199 mg, 0.826 mmol, 83%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65–7.60 (m, 1H), 7.51–7.48 (m, 1H), 7.47 (t, *J* = 2.4 Hz, 1H), 7.42–7.36 (m, 1H), 7.31–7.27 (m, 1H), 7.05–7.02 (m, 1H), 3.79 (d, *J* = 2.3 Hz, 2H), 3.13 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.6, 170.7, 156.1, 152.4, 128.1, 126.9, 124.2, 123.8, 122.2, 120.8, 113.2, 111.7, 34.7, 25.1 ppm. IR (ATR): 3432 (w), 2951 (w), 2163 (w), 1759 (s), 1694 (s), 1652 (s), 1474 (s), 1447 (s), 1431 (s), 1382 (w), 1270 (s), 1169 (s), 1122 (w), 1106 (w), 1077 (s), 1018 (s), 908 (w), 880 (w), 855 (w), 830 (s), 752 (s), 737 (s) cm^{-1}. MS (EI, 70 eV): *m/z* (%): 241 (52) [M$^+$], 157 (12), 156 (100), 155 (28), 128 (55), 127 (27), 126 (16), 102 (35). HRMS(ESI+): *m/z* calcd for $C_{14}H_{12}NO_3$ [M+H]$^+$ 241.0817, found: 242.0820.

3-(2-Hydroxy-3-methoxybenzylidene)-methylpyrrolidine-2,5-dione (61d)

According to the GP, o-vanillin (152 mg, 1.00 mmol, 1.00 equiv) was converted with 1-methyl-pyrrolidine-2,5-dione (166 mg, 1.50 mmol, 1.50 equiv) and PMHS in the presence of 1,2,2,3,4,4-hexamethylphosphetane 1-oxide (**6h**, 8.7 mg, 0.050 mmol, 0.050 equiv) in BuOAc (3.0 ml). Purification (SiO_2, cyclohexane:EtOAc = 2:1+ 5% MeOH) gave alkene **61d** (215 mg, 0.870 mmol, 87%) as a colorless solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.01 (t, *J* = 2.4 Hz, 1H), 7.04–6.94 (m, 1H), 6.94–6.84 (m, 2H), 6.16 (s, 1H), 3.93 (s, 3H), 3.53 (d, *J* = 2.4 Hz, 2H), 3.12 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 174.7, 171.3, 147.0, 145.8, 128.9, 123.8, 121.1, 120.7, 119.9, 112.0, 56.3, 34.4, 25.0 ppm. IR (ATR): 3246 (w), 2162 (w), 1760 (s), 1687 (s), 1683 (s), 1600 (w), 1580 (w), 1477 (w), 1456 (w), 1436 (s), 1383 (s), 1348 (w), 1268 (s), 1249 (w), 1237 (w), 1154 (w), 1076 (w), 1024 (s), 884 (w), 777 (s), 719 (w), 684 (s) cm^{-1}. MS (EI, 70 eV): *m/z* (%): 248 (15), 247 (100) [M$^+$], 230 (15), 216 (18), 190 (26), 162 (20), 161 (39), 147 (31), 144 (12), 119 (17), 118 (10). HRMS (EI): *m/z* calcd for $C_{13}H_{13}NO_4$ [M]$^+$ 247.0839, found: 247.0840.

3-((1H-Indol-7-yl)methylene)-1-methylpyrrolidine-2,5-dione (61e)

According to the GP , 1H-indole-7-carbaldehyde (145 mg, 1.00 mmol, 1.00 equiv) was converted with 1-methylpyrrolidine-2,5-dione (166 mg, 1.50 mmol, 1.50 equiv) and PMHS in the presence of 1,2,2,3,4,4-hexamethylphosphetane 1-oxide (**6h**, 8.7 mg, 0.050 mmol, 0.050 equiv) in BuOAc (3.0 mL). Purification (SiO2, cyclohexane:EtOAc = 2:1) gave alkene **61e** (158 mg, 0.657 mmol, 66%) as a colorless solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ = 11.76 (s, 1H), 8.08 (t, *J* = 2.3 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.44–7.35 (m, 2H), 7.11 (t, *J* = 7.7 Hz, 1H), 6.52 (dd, *J* = 3.1, 1.8 Hz, 1H), 3.72 (d, *J* = 2.3 Hz, 2H), 2.98 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ = 174.6, 170.9, 135.6, 128.6, 127.2, 126.1, 124.8, 122.4, 121.3, 119.4, 118.1, 101.9, 34.3, 24.5 ppm. IR (ATR): 3307 (m), 2942 (w), 1752 (m), 1677 (m), 1637 (m), 1431 (m), 1380 (w), 1270 (m), 1089 (m), 1034 (m), 995 (m), 793 (m), 722 (s), 664 (m) cm^{-1}. MS (EI, 70 eV): *m/z* (%): 240 (38) [M$^+$], 223 (21), 183 (10), 154 (100), 126 (18), 77 (13), 63(12). HRMS (ESI+): *m/z* calcd for $C_{14}H_{13}N_2O_2$ [M+H]$^+$ 241.0977, found: 241.0969.

1-Methyl-3-(pyridine-3-ylmethylene)pyrrolidine-2,5-dione (61f)

According to the GP, nicotinaldehyde (107 mg, 1.00 mmol, 1.00 equiv) was converted with 1-methylpyrrolidine-2,5-dione (166 mg, 1.50 mmol, 1.50 equiv) and PMHS in the presence of 1,2,2,3,4,4-hexamethylphosphetane 1-oxide (**6h**, 8.7 mg, 0.050 mmol, 0.050 equiv) in BuOAc (3.0 ml). Purification (SiO_2, cyclohexane:EtOAc = 3:1) gave alkene **61f** (181 mg, 0.896 mmol, 90%) as a brown solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.77 (d, *J* = 2.3 Hz, 1H), 8.63 (dd, *J* = 4.9, 1.6 Hz, 1H), 7.83–7.73 (m, 1H), 7.61 (t, *J* = 2.4 Hz, 1H), 7.45–7.35 (m, 1H), 3.58 (d, *J* = 2.4 Hz, 2H), 3.13 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.6, 170.6, 151.3, 150.8, 136.5, 130.7, 130.2, 126.1, 124.0, 34.0, 25.2 ppm. IR (ATR): 2902 (w), 1775 (s), 1694 (s), 1659 (s), 1539 (w), 1563 (w), 1482 (w), 1453 (w), 1432 (s), 1401 (w), 1382 (s), 1269 (s), 1199 (w), 1156 (w), 1082 (w), 1019 (w), 960 (w), 920 (w), 820 (s), 735 (w), 701 (s) cm^{-1}. MS (EI, 70 eV): *m/z* (%): 202 (22) [M^+], 201 (34), 117 (100), 116 (15), 90 (45), 89 (71). HRMS (ESI+): *m/z* calcd for $C_{11}H_{11}N_2O_2$ $[M+H]^+$ 203.0820, found: 203.0820.

3-Methyl-3-(4-hydroxy-3-methoxybenzylidene)-1-methylpyrrolidine-2,5-dione (61g)

According to the GP, vanillin (152 mg, 1.00 mmol, 1.00 equiv) was converted with 1-methyl-pyrrolidine-2,5-dione (166 mg, 1.50 mmol, 1.50 equiv) and PMHS in the presence of 1,2,2,3,4,4-hexamethylphosphetane 1-oxide (**6h**, 8.7 mg, 0.050 mmol, 0.050 equiv) in BuOAc (3.0 ml). Purification (SiO_2, cyclohexane:EtOAc = 2:1 + 5% NEt_3) gave alkene **61g** (225 mg, 0.910 mmol, (91%) as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.54 (t, *J* = 2.3 Hz, 1H), 7.12–7.03 (m, 1H), 7.00 (s, 1H), 6.98–6.96 (m, 1H), 3.94 (s, 3H), 3.55 (d, *J* = 2.3 Hz, 2H), 3.11 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 174.5, 171.5, 148.0, 146.9, 134.5, 126.8, 124.8, 120.7, 115.3, 112.4, 56.1, 34.2, 25.0 ppm. IR (ATR): 3456 (w), 2942 (w), 2166 (w), 1760 (w), 1679 (s), 1645 (s), 1584 (s), 1520 (s), 1432 (s), 1383 (w), 1271 (s), 1212 (w), 1160 (w), 1123 (w), 1087 (w), 1029 (s), 943 (w), 872 (w), 797 (w),686 (s), 622 (s) cm^{-1}. MS (EI, 70 eV): *m/z* (%): 248 (15), 247 (100) $[M]^+$, 162 (75), 147 (24). HRMS (EI): *m/z* calcd for $C_{13}H_{13}NO_4$ $[M]^+$ 247.0839, found: 247.0836.

1-Methyl-3-(thiophen-2-ylmethylene)pyrrolidine-2,5-dione (61h)

According to the GP, thiophene-2-carbaldehyde (113 mg, 1.00 mmol, 1.00 equiv) was converted with 1-methylpyrrolidine-2,5-dione (166 mg, 1.50 mmol, 1.50 equiv) and PMHS in the presence of 1,2,2,3,4,4-hexamethylphosphetane 1-oxide (**6h**, 8.7 mg, 0.050 mmol, 0.050 equiv) in BuOAc (3.0 ml). Purification (SiO_2, cyclohexane:EtOAc = 3:1) gave alkene **61h** (177 mg, 0.856 mmol, 86%) as a light-brown solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.81 (t, *J* = 2.3 Hz, 1H), 7.59 (d, *J* = 5.1 Hz, 1H), 7.38–7.34 (m, 1H), 7.16 (dd, *J* = 5.1, 3.7 Hz, 1H), 3.48 (d, *J* = 2.3 Hz, 2H), 3.11 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.9, 170.9, 138.5, 133.2, 131.0, 128.4, 127.0, 121.2, 34.1, 25.1 ppm. IR (ATR): 3083 (w),

2931 (w), 2584 (w), 2163 (w), 1839 (w), 1752 (s), 1686 (s), 1640 (s), 1417 (w), 1386 (w), 1273 (s), 1234 (w), 1218 (w), 1081 (s), 1046 (w), 1012 (w), 934 (w), 850 (w), 724 (s), 696 (s), 661 (w) cm^{-1}. MS (EI, 70 eV): *m/z* (%): 207 (28) $[M]^+$, 122 (100), 121 (78), 96 (21), 95 (22). HRMS (ESI+): *m/z* calcd for $C_{10}H_{10}NO_2S$ $[M+H]^+$ 208.0432, found: 208.0437.

3-(Furan-2ylmethylene)-1-methylpyrrolidine-2,5-dione (61i)

According to the GP, furan-2-carbaldehyde (96 mg, 1.0 mmol, 1.0 equiv) was converted with 1-methylpyrrolidine-2,5-dione (166 mg, 0.75 mmol, 1.50 equiv) and PMHS in the presence of 1,2,2,3,4,4-hexamethylphosphetane 1-oxide (**6h**, 8.7 mg, 0.050 mmol, 0.050 equiv) in BuOAc (3.0 ml). Purification (SiO_2, cyclohexane:EtOAc = 2:1) gave alkene **61i** (156 mg, 0.813 mmol, 81%) as a colorless solid.

^1H NMR (300 MHz, $CDCl_3$) δ = 7.60–7.58 (m, 1H), 7.35 (t, *J* = 2.3 Hz, 1H), 6.73–6.68 (m, 1H), 6.53 (dd, *J* = 3.5, 1.8 Hz, 1H), 3.60 (d, *J* = 2.3 Hz, CH_2, 2H), 3.09 (s, CH_3, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ= 174.7, 171.0, 151.0, 145.9, 121.1, 120.4, 116.9 112.7, 34.3, 25.0 ppm. IR (ATR): 3121 (w), 2951 (w), 1754 (s), 1685 (s), 1647 (s), 1556 (w), 1477 (w), 1432 (s), 1382 (s), 1342 (s), 1313 (s), 1278 (s), 1266 (s), 1225 (w), 1151 (s), 1085 (s), 1012 (s), 931 (s), 880 (w), 838 (w), 770 (s), 740 (s), 721 (w) cm^1. MS (EI, 70 eV): *m/z* (%): 191 (73.4) $[M^+]$, 134 (17.6), 106 (100), 78 (43.5), 77 (11.2). HRMS (EI): *m/z* calcd for $C_{10}H_9O_3N$ $[M]^+$ 191.0577, found: 191.0578.

3-((1-Hydroxynapthalen-2-yl)methylene-1-methylpyrrolidine-2,5-dione (61j)

According to the GP, 1-hydroxy-2-napthaldehyde (172 mg, 1.00 mmol, 1.00 equiv) was converted with 1-methylpyrrolidine-2,5-dione (166 mg, 1.50 mmol, 1.50 equiv) and PMHS in the presence of 1,2,2,3,4,4-hexamethylphosphetane 1-oxide (**6h**, 8.7 mg, 0.050 mmol, 0.050 equiv) in BuOAc (3.0 ml). Purification (SiO_2, cyclohexane:EtOAc = 2:1 + 5% MeOH) gave alkene **61j** (209 mg, 0.782 mmol, 78%) as a yellow solid.

^1H NMR (400 MHz, DMSO-d_6) δ= 10.29 (s, 1H), 8.35–8.30 (m, 1H), 8.10 (t, *J* = 2.3 Hz, 1H), 7.90–7.84 (m, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.59–7.50 (m, 2H), 7.47 (d, *J* = 8.8 Hz, 1H), 3.73 (d, *J* = 2.3 Hz, 2H), 2.97 (s, 3H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ= 174.6, 171.2, 153.5, 134.8, 127.8, 127.6, 127.4, 125.7, 125.3, 125.2, 123.3, 122.9, 119.9, 116.6, 33.8, 24.5 ppm. IR (ATR): 3246 (w), 2449 (w), 1749 (w), 1670 (s), 1630 (s), 1616 (s), 1568 (s), 1510 (w), 1431 (s), 1386 (s), 1347 (s), 1281 (w), 1263 (s), 1219 (w), 1155 (w), 1141 (w), 1082 (w), 1023 (w), 797 (s), 734 (s), 715 (s), 667 (s) cm^{-1}. MS (EI, 70 eV): *m/z* (%): 268 (16), 267 (88) $[M]^+$, 236 (29), 211 (11), 210 (64), 209 (10), 182 (60), 181 (100), 180 (36), 153 (18), 152 (43), 151 (13), 128 (14), 97 (11). HRMS (ESI+): *m/z* calcd for $C_{16}H_{14}NO_3$ $[M+H]^+$ 268.0974, found: 268.0976.

1-Methyl-3-(quinoline-2-ylmethylene)pyrrolidine-2,5-dione (61k)

According to the GP, quinoline-2-carbaldehyde (157 mg, 1.00 mmol, 1.00 equiv) was converted with 1-methylpyrrolidine-2,5-dione (166 mg, 1.50 mmol, 1.50 equiv) and PMHS in the presence of 1,2,2,3,4,4-hexamethylphosphetane 1-oxide (**6h**, 8.7 mg, 0.050 mmol,

0.050 equiv) in BuOAc (3.0 ml). Purification (SiO_2, cyclohexane:EtOAc = 4:1 + 5% NEt_3) gave alkene **61k** (22 mg, 0.087 mmol, 9%) as an off-white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.20 (dd, *J* = 8.5, 0.8 Hz, 1H), 8.11 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.86–7.80 (m, 1H), 7.79–7.72 (m, 1H), 7.70 (t, *J* = 2.5 Hz, 1H), 7.61–7.52 (m, 2H), 4.09 (d, *J* = 2.5 Hz, 2H), 3.16 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 175.7, 171.2, 153.4, 148.4, 136.9, 131.0, 130.3, 130.0, 130.0, 127.7, 127.7, 127.4, 124.1, 35.8, 25.0 ppm. IR (ATR): 2923 (w), 1763 (s), 1698 (s), 1651 (s), 1592 (w), 1503 (w), 1431 (s), 1385 (w), 1272 (s), 1234 (w), 1218 (w), 1149 (w), 1084 (w); 1031 (s); 931 (w), 830 (s), 782 (w), 753 (w), 731 (s), 683 (s) cm^{-1}. MS (EI, 70 eV): *m/z* (%): 253 (17), 252 (100) [M^+], 194 (25), 168 (14), 167 (88), 166 (25), 140 (12), 139 (16). HRMS (ESI+): *m/z* calcd for $C_{15}H_{13}N_2O_2$ $[M+H]^+$ 253.0977, found: 253.0972.

3-(4-(Dimethylamino)benzylidene)-1-methylpyrrolidine-2,5-dione (61l)

According to the GP, 4-(dimethylamino)benzaldehyde (149 mg, 1.00 mmol, 1.00 equiv) was converted with 1-methylpyrrolidine-2,5-dione (166 mg, 1.50 mmol, 1.5 equiv) and PMHS in the presence of 1,2,2,3,4,4-hexamethylphosphetane 1-oxide (**6h**, 8.7 mg, 0.05 mmol, 0.050 equiv) in BuOAc (3.0 ml). Purification (SiO_2, cyclohexane:EtOAc = 3:1+5% NEt_3) gave alkene **61l** (71 mg, 0.29 mmol, 30%) as a yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.52 (t, *J* = 2.2 Hz, 1H), 7.42–7.35 (m, 2H), 6.77–6.66 (m, 2H), 3.51 (d, *J* = 2.2 Hz, 2H), 3.09 (s, 3H), 3.04 (s, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 175.0, 172.0, 151.5, 134.9, 132.3, 121.9, 117.5, 112.0, 40.2, 34.4, 24.9 ppm. IR (ATR): 2913 (w), 2859 (w), 2803 (w), 1755 (s), 1687 (s), 1635 (w), 1592 (s), 1521 (s), 1426 (w), 1380 (s), 1359 (s), 1311 (w), 1270 (s), 1224 (w), 1199 (s), 1154 (s), 1124 (s), 1084 (s), 1012 (s), 1000 (s), 970 (w), 941 (w), 929 (w), 816 (s), 745 (w), 719 (w) cm^{-1}. MS (EI, 70 eV): *m/z* (%): 245 (16), 244 (100) [M^+], 243 (31), 159 (40), 158 (33). HRMS (ESI+): *m/z* calcd for $C_{14}H_{17}N_2O_2$ $[M+H]^+$ 245.1290, found: 245.1286.

3-(3-Bromobenzylidene)-1-methylpyrrolidine-2,5-dione (61m)

According to the GP, 3-bromobenzaldehyde (185 mg, 1.00 mmol, 1.00 equiv) was converted with 1-methylpyrrolidine-2,5-dione (166 mg, 1.50 mmol, 1.50 equiv) and PMHS in the presence of 1,2,2,3,4,4-hexamethylphosphetane 1-oxide (**6h**, 8.7 mg, 0.050 mmol, 0.050 equiv) in BuOAc (3.0 ml). Purification (SiO_2, cyclohexane:EtOAc = 2:1) gave alkene **61m** (275 mg, 0.983 mmol, 98%) as a colorless solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.62 (t, *J* = 1.8 Hz, 1H), 7.57–7.53 (m, 2H), 7.42 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 3.57 (d, *J* = 2.3 Hz, 2H), 3.14 (s, 3H). ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.8, 170.8, 136.2, 133.1, 132.8, 132.6, 130.7, 128.7, 125.1, 123.3, 34.0, 25.1 ppm. IR (ATR): 2944 (w), 1763 (m), 1694 (s), 1650 (s), 1555 (m), 1479 (m), 1429 (m), 1382 (m), 1271 (s), 1160 (m), 1075 (m), 1024 (m), 786 (s), 683 (s), 659 (s) cm^{-1}. MS (EI, 70 eV): *m/z* (%): 279

(47) [M$^+$], 222 (12), 194 (65), 115 (100), 89 (12). HRMS (EI): *m/z* calcd for $C_{12}H_{10}BrNO_2$ [M]$^+$ 278.9889, found: 278.9892.

3-(4-Chlorobenzylidene)-1-methylpyrrolidine-2,5-dione (61n)

According to the GP, 4-chlorobenzaldehyde (141 mg, 1.00 mmol, 1.00 equiv) was converted with 1-methylpyrrolidine-2,5-dione (166 mg, 1.50 mmol, 1.50 equiv) and PMHS in the presence of 1,2,2,3,4,4-hexamethylphosphetane 1-oxide (**6h**, 8.8 mg, 0.050 mmol, 0.050 equiv) in BuOAc (3.0 ml). Purification (SiO_2, cyclohexane:EtOAc = 3:1) gave alkene **61n** (209 mg, 0.89 mmol, 88%) as a colorless solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.56 (t, *J* = 2.4 Hz, 1H), 7.42 (m, 4H), 3.53 (d, *J* = 2.4 Hz, 2H), 3.12 (s, 3H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 173.9, 171.0, 136.4, 133.0, 132.6, 131.4, 129.6, 124.2, 34.1, 25.1 ppm. IR (ATR): 3068 (w), 2943 (w), 2163 (w), 1981 (w), 1813 (w), 1756 (s), 1692 (s), 1648 (s), 1583 (s), 1526 (w), 1487 (s), 1431 (s), 1409 (s), 1382 (s), 1309 (w), 1273 (s), 1181 (s), 1155 (w), 1080 (s), 1013 (s), 972 (w), 955 (w), 935 (w), 905 (w), 841 (s), 811 (s), 742 (s), 706 (s), 657 (s) cm^{-1}. MS (EI, 70 eV): *m/z* (%): 237 (21), 236 (11), 235 (63) [M$^+$], 152 (33), 151 (14), 150 (100), 149 (11), 115 (91), 114 (11). HRMS (EI): *m/z* calcd for $C_{12}H_{10}ClNO_2$ [M]$^+$ 235.0395, found: 235.0399.

3-(3,7-Dimethyloct-6-en-1-ylidene)-1-methylpyrrolidine-2,5-dione (61o)

According to the GP, citronellal (154 mg, 1.00 mmol, 1.00 equiv) was converted with 1-methyl-pyrrolidine-2,5-dione (166 mg, 1.50 mmol, 1.50 equiv) and PMHS in the presence of 1,2,2,3,4,4-hexamethylphosphetane 1-oxide (**6h**, 8.7 mg, 0.050 mmol, 0.050 equiv) in BuOAc (3.0 ml). Purification (SiO_2, cyclohexane:EtOAc = 2:1) gave alkene **61o** (103 mg, 0.412 mmol, 41%) as a light-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.83 (tt, *J* = 7.7, 2.3 Hz, 1H), 5.12–4.99 (m, 1H), 3.18 (s, 2H), 3.04 (s, 3H), 2.28–2.11 (m, 1H), 2.09–1.88 (m, 3H), 1.75–1.62 (m, 1H), 1.67 (s, 3H), 1.58 (s, 3H), 1.44–1.29 (m, 1H), 1.28–1.12 (m, 1H), 0.91 (d, *J* = 6.7 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 174.4, 170.1, 137.9, 131.8, 126.4, 124.2, 37.3, 36.8, 32.6, 32.2, 25.8, 25.7, 24.8, 19.7, 17.9 ppm. IR (ATR): 2961 (m), 2915 (m), 1770 (m), 1704 (s), 1677 (s), 1431 (m), 1380 (m), 1272 (m), 1085 (w), 993 (m), 723 (m), 67(m) cm^{-1}. MS (EI, 70 eV): *m/z* (%): 249 (17) [M$^+$], 206 (32), 166 (69), 139 (48), 126 (55), 109 (66), 81 (47), 69 (100). HRMS (ESI+): *m/z* calcd for $C_{15}H_{24}NO_2$ [M+H]$^+$ 250.1807, found: 250.1813.

1-(*tert*-Butyl)-3-(pyridin-2-ylmethylene)pyrrolidine-2,5-dione (61p)

According to the GP, 2-pyridinaldehyde (54 mg, 0.50 mmol, 1.00 equiv) was converted with 1-(*tert*-butyl)-pyrrolidine-2,5-dione (137 mg, 0.75 mmol, 1.50 equiv) and PMHS (173 mg, 2.50 mmol, 5.00 equiv)in the presence of 1,2,2,3,4,4-hexamethylphosphetane 1-oxide (**6h**, 4.4 mg, 0.025 mmol, 0.050 equiv) in BuOAc (1.5 ml). Purification (SiO_2, cyclohexane:EtOAc = 7:1) gave alkene **61p** (55 mg, 0.22 mmol, 45%) as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ = ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (dddd, *J* = 4.7, 1.9, 0.9, 0.5 Hz, 1H), 7.76–7.66 (m, 1H), 7.45–7.38 (m, 2H), 7.22 (ddd, *J* = 7.7, 4.7, 1.2 Hz, 1H), 3.76 (d, *J* = 2.5 Hz, 2H), 1.65 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 176.4, 172.3, 154.0, 150.1, 136.7, 129.9, 129.4, 126.9, 123.3, 58.7, 36.1, 28.7 ppm. IR (ATR): 2971 (w), 2928 (w), 1759 (m), 1698 (s), 1659 (s), 1580 (m), 1468 (m), 1329 (s), 1149 (m), 928 (m), 783 (m), 721 (m) cm^{-1}. MS (EI, 70 eV): *m/z* (%): 244 (26) [M^+], 188 (35),172 (42), 160 (21), 144 (27), 117 (100), 89 (49). HRMS (ESI+): *m/z* calcd for $C_{14}H_{17}N_2O_2$ $[M+H]^+$ 245.1290, found: 245.1290.

1-(*tert*-Butyl)-3-(pyridin-3-ylmethylene)pyrrolidine-2,5-dione (61q)

According to the GP, 3-pyridinaldehyde (54 mg, 0.50 mmol, 1.00 equiv) was converted with 1-(*tert*-butyl)-pyrrolidine-2,5-dione (137 mg, 0.75 mmol, 1.50 equiv) and PMHS (173 mg, 2.50 mmol, 5.00 equiv)in the presence of 1,2,2,3,4,4-hexamethylphosphetane 1-oxide (**6h**, 4.4 mg, 0.025 mmol, 0.050 equiv) in BuOAc (1.5 ml). Purification (SiO_2, cyclohexane:EtOAc = 1:1 + 5 mol% MeOH) gave alkene **61q** (119 mg, 0.488 mmol, 98%) as a colorless solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.75–8.69 (m, 1H), 8.63–8.56 (m, 1H), 7.78–7.70 (m, 1H), 7.51–7.46 (m, 1H), 7.43–7.33 (m, 1H), 3.51–3.44 (m, 2H), 1.68–1.58 (m, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 174.5, 171.5, 151.1, 150.3, 136.3, 130.5, 129.3, 126.7, 124.0, 59.0, 34.8, 28.7. IR (ATR): 2976 (w), 2902 (w), 1755 (w), 1696 (s), 1651 (m), 1479 (m), 1337 (m), 1161 (s), 1109 (m), 1028 (w), 810 (m), 701 (s), 671 (s) cm^{-1}. MS (EI, 70 eV): *m/z* (%): 244 (13) [M^+], 229 (16), 201 (5), 198 (100), 144 (18), 117 (48), 89 (35). HRMS (ESI+): *m/z* calcd for $C_{14}H_{17}N_2O_2$ $[M+H]^+$ 245.1290, found: 245.1290.

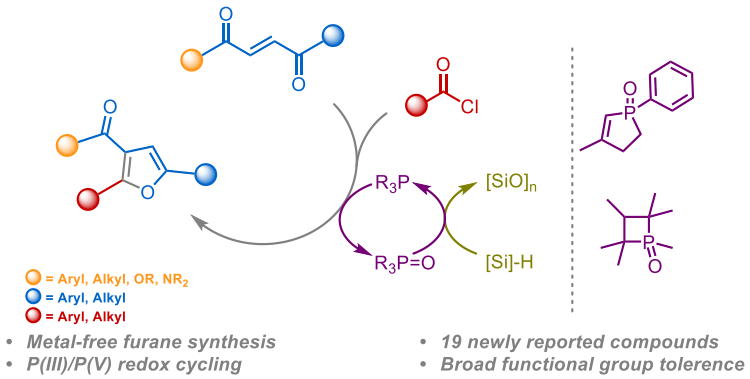
1-(*tert*-Butyl)-3-(pyridin-4-ylmethylene)pyrrolidine-2,5-dione (61r)

According to the GP, 4-pyridinaldehyde (54 mg, 0.50 mmol, 1.00 equiv) was converted with 1-(tert-butyl)-pyrrolidine-2,5-dione (137 mg, 0.75 mmol, 1.50 equiv) and PMHS (173 mg, 2.50 mmol, 5.00 equiv)in the presence of 1,2,2,3,4,4-hexamethylphosphetane 1-oxide (**6h**, 4.4 mg, 0.025 mmol, 0.050 equiv) in BuOAc (1.5 ml). Purification (SiO_2, cyclohexane:EtOAc = 1:1 + 5 mol% NEt_3) gave alkene **61r** (82 mg, 0.33 mmol, 67%) as a colorless solid.

^{1}H NMR (300 MHz, CDCl3) δ = 8.72–8.67 (m, 2H), 7.43 (t, *J* = 2.6 Hz, 1H), 7.32–7.28 (m, 2H), 3.49 (d, *J* = 2.6 Hz, 2H), 1.65 (s, 9H). ^{13}C NMR (75 MHz, CDCl3) δ = 174.3, 171.2, 150.6, 141.7, 130.0, 129.4, 123.6, 59.2, 34.7, 28.6 ppm. IR (ATR): 2970 (w), 2938 (w), 1760 (m), 1698 (s), 1654 (m), 1594 (m), 1420 (m), 1327 (s), 1262 (m), 1161 (m), 935 (w), 818 (m), 720 (w) cm^{-1}. MS (EI, 70 eV): m/z (%): 244 (14) [M+], 229 (11), 201 (10), 198 (100), 144 (19), 118 (31), 89 (34). HRMS (ESI+): m/z calcd for $C_{14}H_{17}N_2O_2$ $[M+H]^+$ 245.1290, found: 245.1292.

6.2 Synthesis of Trisubstituted Furans from Activated Alkenes by P(III)/P(V) Redox Cycling Catalysis

J. Tönjes, V. Medvarić, T. Werner, *manuscript submitted.*



Abstract:

The organocatalytic formation of an underrepresented family of tri- and tetrasubstituted furans from activated alkenes and acyl chlorides is reported. In a reaction sequence based on P(III)/P(V) redox cycling catalysis, the cyclic phosphine catalysts react with bisacylethenes or acylacrylates in a Michael addition, followed by an acylation and either an intramolecular Wittig reaction or a ring closure reaction, liberating the furans. The formed phosphine oxides are reduced in situ by phenylsilane as terminal reductant. In a first step, 12 diacylethenes were converted to the respective trisubstituted furans. The reaction of acylacrylates showed a surprising, catalyst dependent alternate reaction forming tetrasubstituted furans. Two additional methods were developed, giving 14 trisubstituted furans using a phospholene catalyst and an additional 6 tetrasubstituted furans using a phosphetane catalyst. This encompassed 19 newly described compounds.

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Synthesis of Trisubstituted Furans from Activated Alkenes by P(III)/P(V) Redox Cycling Catalysis

Jan Tönjes, Viktorija Medvarić, and Thomas Werner*

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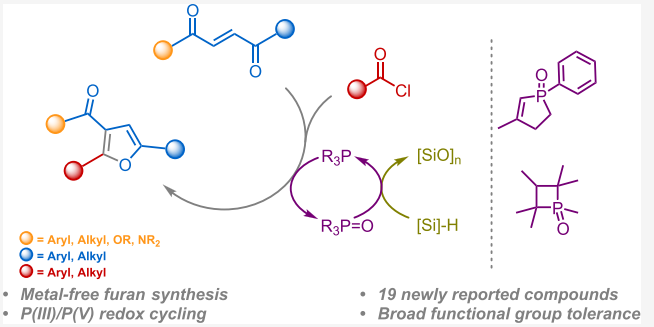
ABSTRACT: The organocatalytic formation of an underrepresented family of trisubstituted and tetrasubstituted furans from activated alkenes and acyl chlorides is reported. In a reaction sequence based on P(III)/P(V) redox cycling catalysis, the cyclic phosphine catalysts react with diacylethenes or acyl acrylates in Michael addition, followed by acylation and either an intramolecular Wittig reaction or a ring closure reaction, liberating the furans. The formed phosphine oxides are reduced in situ by phenylsilane as a terminal reductant. In the first step, 12 diacylethenes were converted to the respective trisubstituted furans. The reaction of acyl acrylates showed a surprising, catalyst-dependent alternate reaction forming tetrasubstituted furans. Two additional methods were developed, giving 14 trisubstituted furans using a phospholene catalyst and an additional 6 tetrasubstituted furans using a phosphetane catalyst. This encompassed 19 newly described compounds.



INTRODUCTION

Substituted furans are a valuable synthetic target, not only due to their wide occurrence in natural products and active compounds, including approved pharmaceuticals, despite their propensity to lead to toxic metabolites.[1,2] They can also serve as an interesting synthon for the synthesis of natural or complex products due to their versatile reactivity.[3,4] This can be exemplified by their ability to react in Diels−Alder type cycloadditions by the formation of synthetically useful products with different oxidants or exchange of oxygen with different heteroatoms.[5−7]

While furan derivatives for technical applications are mostly derived from biomass, classical reactions for the formation of substituted furans include the Paal−Knorr synthesis for disubstituted products or the Feist−Benary synthesis for tetrasubstituted furans.[8−10] Following this, a multitude of methods have been developed to form furans with diverse substitution patterns and to employ various starting materials.[11−16] A large number of methods employ transition metal catalysts, especially on the basis of silver and gold using alkynes or ketenes as substrates, although catalysts on the basis of palladium, copper, and others have also been reported.

Phosphines can be used for the synthesis of substituted furans under transition metal-free conditions. Some substrates can be activated by catalytic amounts of phosphine, forming substituted furans by rearrangement.[17] In a more general method, the phosphine can react in Michael addition with an activated alkene, which, in turn, can be acylated with acid anhydrides or acid chlorides. Deprotonation of this intermediate leads to the formation of a substituted furan via an intramolecular Wittig reaction.[18−21] Here, stoichiometric amounts of phosphine have to be employed to form phosphine oxide as a byproduct, which can lead to separation problems and an enlarged waste stream.

First steps to alleviate this general issue were done by O'Brien et al. in 2009 with the development of P(III)/P(V) redox cycling catalysis.[22] In this reaction principle, the phosphine oxide formed in a reaction of this type is reduced in situ using silanes as terminal reductants. Thus, catalytic amounts of phosphines are sufficient, reducing the phosphine oxide waste stream, simplifying the purification of the products and making the use of specialized phosphines more economically viable. This methodology was adapted for different reactions, including reductive C−N coupling reactions, Morita−Baylis−Hilman/Wittig cascade, Vilsmeier−Haack reaction, Staudinger/Aza-Wittig reaction, base-free Wittig reaction, and the reduction of activated alkenes.[23−28] P(III)/P(V) redox cycling catalysis has also been employed for the formation of substituted furans. Lin and co-workers reworked their method for the synthesis of tetrasubstituted furans from trisubstituted activated alkenes using stoichiometric amounts of tributylphosphine toward the use of

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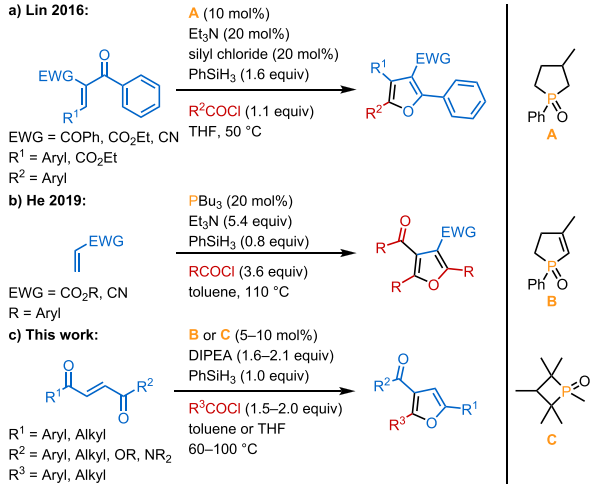
catalytic amounts of a phospholane catalyst with silyl chlorides as promoters and phenylsilane as a terminal reductant (Scheme 1a).[21,29] He and co-workers updated their synthesis of

Scheme 1. Different Approaches toward Substituted Furans by P(III)/P(V) Redox Cycling Catalysis



tetrasubstituted furans starting from acrylates toward the use of catalytic amounts of tributylphosphine at elevated temperatures with the same terminal reductant (Scheme 1b).[20,30] Recently, Lin and co-workers also revised their method toward the synthesis of furo[2,3-*f*]dibenzotropones.[31]

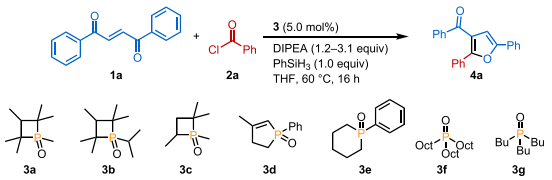
In the field of activated alkenes, neither the use of 1,2-diacylethenes nor 3-acyl acrylates has been explored for the metal-free, catalytic synthesis of substituted furans, and only few examples can be found in the literature under stoichiometric conditions.[32] Thus, our aim was to explore these activated alkenes in a Michael-addition/acylation/Wittig sequence under phosphine redox cycling catalysis and develop methods for the synthesis of new products in the valuable field of substituted furans (Scheme 1c).

RESULTS AND DISCUSSION

We started our investigation with the reaction of 1,2-dibenzoylethene (**1a**) with benzoyl chloride (**2a**) in THF as the solvent, diisopropylethylamine (DIPEA) as the base, and phenylsilane as the terminal reductant. In the first step, the reactivity of various phosphine catalysts was evaluated. The use of hexamethylphosphetane oxide **3a** afforded the desired trisubstituted furan **4a** in a satisfactory yield of 71% (Table 1, entry 1). This highly active catalyst was used in various transformations in recent years.[28,33−35] In the presence of the more sterically demanding phosphine oxide **3b**, no product formation was observed (entry 2). Surprisingly, the less sterically demanding tetramethylphospetane oxide **3c**, which was recently introduced by the group of Radosevich, gave the product **4a** in only 24% yield (entry 3).[23,36] Several other phosphine oxides **3d**−**3g** were employed as catalysts. However, **4a** was obtained in low yields <10% in all cases (entries 4−7). This is especially unexpected for phospholene **3d**, which is widely used in P(III)/P(V) redox cycling catalysis.

The exchange of THF with cyclopentyl methyl ether (CPME), butyl acetate, or MeTHF gave all similar but lower yields of furan **4a** between 43 and 55%, while the use of toluene and MeCN led to significantly lower yields of 34% and

Table 1. Catalyst Screening and Optimization of the Reaction Conditions for the Formation of Triphenylfuran 4a from Dibenzoylethene 1a[b]



entry	3	2a/equiv	DIPEA/equiv	modification	4a yield[a]/%
1	**3a**	1.1	1.2		71
2	**3b**	1.1	1.2		0
3	**3c**	1.1	1.2		24
4	**3d**	1.1	1.2		7
5	**3e**	1.1	1.2		3
6	**3f**	1.1	1.2		3
7	**3g**	1.1	1.2		2
8	**3a**	1.1	1.2	40 °C	13
9	**3a**	1.1	1.2	80 °C	66
10	**3a**	1.5	1.6		87
11	**3a**	2.0	2.1		99
12	**3a**	2.0	2.1	4 h	99
13	**3a**	2.0	2.1	2 h	82

[a]Yield determined by GC-FID with hexadecane as the internal standard. [b]Reaction conditions: 1.0 equiv of **1a** (0.50 mmol), 1.1−2.0 equiv of BzCl (**2a**, 0.55−1.0 mmol), 1.2−2.1 equiv of DIPEA (0.60−1.05 mmol), 5.0 mol % catalyst **3** (25 μmol), 1.0 equiv of $PhSiH_3$ (0.50 mmol), 1.5 mL of solvent, 60 °C, 16 h.

2%, respectively.[37] Different amine bases, sodium carbonate and butylene oxide, as a capped base were also tested.[37] Butylene oxide proved to be an alternative to DIPEA, affording the furan **4a** in a yield of 69%, whereas the other tested bases only gave **4a** in yields <10%. A reduction in the reaction temperature to 40 °C led to a significantly lower yield of 13% (entry 8), whereas at 80 °C, **4a** was obtained in 66% yield (entry 9). An increase in the amounts of base and benzoyl chloride (**2a**) led to improved yields. In the presence of 1.5 equiv of **2a**, the desired product was obtained in 87% yield, while 99% yield was achieved when 2.0 equiv of **2a** was used (entries 10 and 11). Notably, the reaction time could be shortened to 4 h without a reduction in the amount of product **4a**, while even 2 h led to a good yield of 82% (entries 12 and 13). In the absence of phenylsilane or catalyst **3a**, no product was formed, while in the absence of DIPEA, traces of furan **4a** were obtained.[37]

When the optimized conditions were employed, dibenzoylethene **1a** yielded the product **4a** in an isolated yield of 93% after a reaction time of 4 h. However, test reactions for other substrates led to unsatisfactory yields (Figure 1). For the further evaluation of the substrate scope, the reaction time was extended to 16 h. Under these conditions, the electron-rich dimethoxyderivative **1b** was converted to the trisubstituted furan **4b** in a yield of 81%, while the dichlorocompound **1c** afforded the respective furan **4c** in a moderate yield of 58%. Both the more challenging dithiophene compound **1d** and more sterically hindered dinaphthyl compound **1e** gave comparable yields of 50 and 54% of the respective furans **4d** and **4e**, respectively. The hexenedione **1f** could be converted to the methylsubstituted furan **4f** in a yield of 40%, whereas the phenylpentenedione **1g** afforded 3-acetyl-2,5-diphenylfuran (**4g**) in a yield of 74%. Only less than 7% of the isomer was

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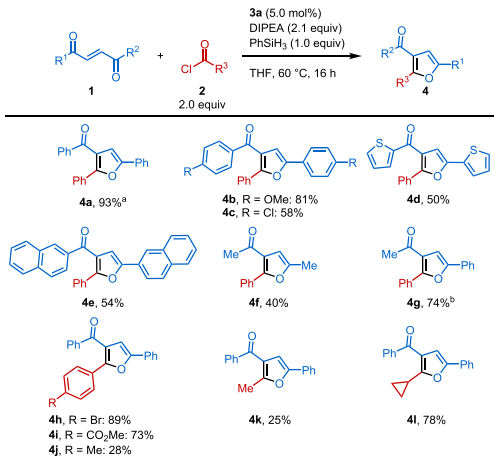

Figure 1. Substrate scope for the conversion of diacylalkenes **1**. Reaction conditions: 1.0 equiv of **1** (1.0 mmol), 2.0 equiv of **2** (2.0 mmol), 2.1 equiv of DIPEA (2.1 mmol), 5.0 mol % catalyst **3a** (50 μmol), 1.0 equiv of $PhSiH_3$ (1.0 mmol), 3.0 mL of solvent, 60 °C, 16 h. [a]Reaction time, 4 h. [b]<7% of isomeric 3-benzoyl-5-methyl-2-phenylfuran was formed. Isolated yields are given.

formed. With less distinctly different acyl groups, a less favorable isomeric mixture is to be expected. By exchanging the acid chloride for derivative **2b**, the bromophenyl substituted furan **4h** was isolated in a good yield of 89%. The electron-poor methoxycarbonylbenzoyl chloride (**2c**) led to a slightly lower yield of 73% of furan **4i**, whereas the more electron-rich methylbenzoyl chloride **2d** led to a reduced yield of 28% of furan **4j**. Similarly, the reaction of model compound **1a** with acetyl chloride (**2e**) led to the expected trisubstituted furan **4k** in a yield of 25%, whereas a surprisingly good yield of 78% of furan **4l** was obtained in the reaction of cyclopropylcarbonyl chloride **2f**.

Based on the work of He and co-workers, two reaction pathways are plausible for the reaction of diketone **1** with acyl chloride **2** using the phosphetane catalyst **3a** and phenylsilane as the terminal reductant.[30] In the first reaction pathway, after Michael addition of reduced phosphine **5** to activated alkene **1**, formed enolate **I-1** reacts with acyl chloride under *C*-acylation and subsequent deprotonation to form enolate **I-2** (Figure 2, reaction pathway **I**). A nucleophilic attack of the enolate leads to a ring closure reaction, and the subsequent deoxygenation results in the formation of trisubstituted furan **4** and phosphine oxide **3**, which can be reduced by the terminal reductant. In the second reaction pathway, the formed enolate **II-1** reacts under *O*-acylation to form the enolester **II-2** (Figure 2, reaction pathway **II**). Deprotonation of the phosphonium salt forms an ylide, which reacts in an intramolecular Wittig reaction, forming the trisubstituted furan **4** and the phosphine oxide **3**.

The triketone **6** was synthesized and converted to the trisubstituted furan **4a** using phosphetane catalyst **3a** and phenylsilane under 60 °C in THF, demonstrating the general viability of the ring closure reaction. Upon the addition of benzoyl chloride (**2a**) and DIPEA to the reaction mixture, only a little trisubstituted furan **4a** was formed, while the tetrasubstituted furan **7** was isolated as the main product in a yield of 64%. The formation of this product was not previously observed in the reaction of diketone **1** with acyl chloride **2**. Additionally, without an added base, only traces of trisubstituted furan **4a** were formed in the reaction of diketone

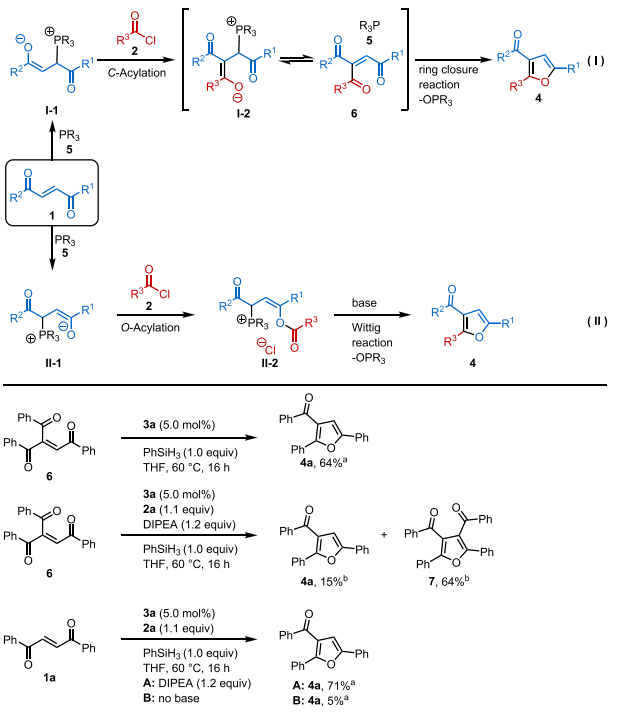

Figure 2. Plausible reaction pathways and test reactions for the synthesis of trisubstituted furan **4** from diacylethene **1**. The reduction of phosphine oxide **3** using phenylsilane as the terminal reductant was omitted from the scheme. [a]Yield determined by GC-FID with hexadecane as an internal standard. [b]Isolated yields are given.

1a with acyl chloride **2a**, while an insoluble salt was formed. Thus, reaction path **II**, which includes the intramolecular Wittig reaction, depicts a more plausible reaction mechanism.

Furthermore, the reaction of ethyl benzoyl acrylate (**8a**) with benzoyl chloride **2a** using phosphetane catalyst **3a** was conducted (Table 2). Surprisingly, in addition to the expected trisubstituted furan **9a**, also the tetrasubstituted furan **10a** was formed. The ratio of the formed furans **9a** and **10a** was found to be dependent on phosphine catalyst **3** used. The hexamethylphosphetane **3a** was the only catalyst tested, which led to an excess in the formation of the tetrasubstituted furan **10a** (entry 1). The isopropyl-substituted furan **3b** achieved only a low yield, while the less sterically demanding tetramethylphosphetane **3c** led to a good overall yield of 49% but with a nearly equal product distribution (entries 2 and 3). The formation of trisubstituted furan **9a** was clearly favored when using the phospholene catalyst **3d** with a 48% yield of trisubstituted furan **9a** and a 6% yield of tetrasubstituted furan **10a** (entry 4). While also clearly preferring the formation of trisubstituted furan **9a**, the phosphinane catalyst **3e**, as well as trioctylphosphine oxide (**3f**) and tributylphosphine oxide (**3g**), only led to yields in the single digit range (entry 5−7). The trialkyl catalysts **3f** and **3g** were also brought to reaction at higher temperatures, but only slight improvements in yield were observed, while the product ratio remained similar.[37] Higher reaction temperatures were shown to be advantageous for the formation of trisubstituted furan **9a**. Thus, an increased temperature of 100 °C in CPME and toluene improved the yields to 69% and 74%, respectively (entries 8 and 9). Even higher temperatures of 120 and 140 °C yielded nearly identical results.[37]

Increasing the amounts of benzoyl chloride (**2a**) and DIPEA to 1.5 and 1.6 equiv led to an increased yield of furan **9a**

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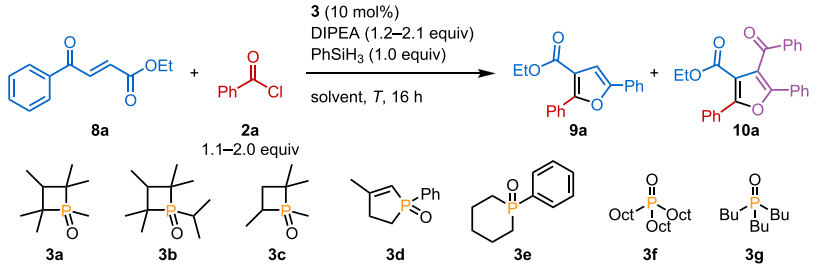
Table 2. Catalyst Screening and Reaction Optimization for the Formation of Trisubstituted Furan 9a and Tetrasubstituted Furan 10a from Acylacrylate 5a[d]



entry	3	2a/equiv	DIPEA/equiv	solvent	T/°C	9a yield[a]/%	10a yield[a]/%	9a:10a
1	**3a**	1.1	1.2	THF	60	11	25	31:69
2	**3b**	1.1	1.2	THF	60	5	3	68:33
3	**3c**	1.1	1.2	THF	60	27	22	55:45
4	**3d**	1.1	1.2	THF	60	48	6	89:11
5	**3e**	1.1	1.2	THF	60	4	<2	98:3
6	**3f**	1.1	1.2	THF	60	2	<2	91:9
7	**3g**	1.1	1.2	THF	60	2	<2	95:5
8	**3d**	1.1	1.2	CPME	100	69	6	92:8
9	**3d**	1.1	1.2	toluene	100	74	8	90:10
10	**3d**	1.5	1.6	toluene	100	80	10	89:11
11	**3d**	2.0	2.1	toluene	100	81	12	87:13
12[b]	**3d**	1.5	1.6	toluene	100	82	10	89:11
13[c]	**3d**	1.5	1.6	toluene	100	67	9	88:12
14	**3a**	5.0	5.0	toluene	60	14	71	16:84

[a]Yield determined by GC-FID with hexadecane as the internal standard. [b]Reaction time: 4 h. [c]Reaction time: 2 h. [d]Reaction conditions: 1.0 equiv of **8a** (0.50 mmol), 1.1–5.0 equiv of BzCl (**2a**, 0.55–2.5 mmol), 1.2–5.0 equiv of DIPEA (0.60–2.5 mmol), 10 mol % catalyst **3** (50 μmol), 1.0 equiv of $PhSiH_3$ (0.50 mmol), 1.5 mL of solvent, 60–100 °C, 2–16 h.

(80%), while a further increased loading to 2.0 and 2.1 equiv only resulted in an increased formation of side product **10a** (entries 10 and 11). The reaction time could be shortened to 4 h without large changes in yield and selectivity, while shorter reaction times led to reduced yields (entries 12 and 13). Test reactions without a catalyst or phenylsilane did not lead to product formation, while in the absence of a base, still 53% of the trisubstituted furan **9a** was formed.[37] The tetrasubstituted furan **10a** was best formed utilizing phosphetane catalyst **3a**, an excess of benzoyl chloride **2a**, and DIPEA at a reaction temperature of 60 °C (entry 14). Under these conditions, tetrasubstituted furan **10a** was formed in a yield of 71%.

Under these reaction conditions, the model substrate was converted to diphenylfuran **9a** in an isolated yield of 74% (Figure 3). Additionally, tetrasubstituted furan **10a** was isolated in a yield of 13%. The electron-rich methoxy derivative **8b** led to the formation of the trisubstituted furan **9b** in a yield of 70%. Attempts to isolate the tetrasubstituted side product revealed a property of the reaction that was concealed during the optimization due to the choice of reactants. If R^1 and R^3 are distinct, two isomers of tetrasubstituted furan **10** are formed in a substrate-specific ratio, which happens due to the formation of a symmetric diacyl-intermediate (see discussion of the mechanism). The more sterically hindered 1-naphthyl derivative **8c** led to furan **9c** in a good yield of 78%. Similarly, the furan derivative **8d** gave the furanylphenylfuran **9d** in a good yield of 71%, while chloro derivative **8e** and piperonyl derivative **8f** formed their respective trisubstituted furans **9e** and **9f** in slightly lower yields of 59% and 57%, respectively. Also, the conversion of ethyl oxopentenoate **8g** was possible, resulting in the respective methyl-substituted furan **9g** in a yield of 60%.

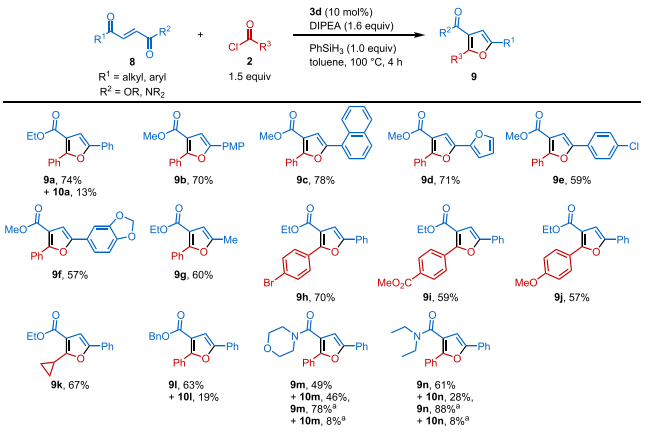


Figure 3. Substrate scope for the conversion of acyl acrylates **8**. Reaction conditions: 1.0 equiv of **8** (1.0 mmol), 1.5 equiv of **2** (1.5 mmol), 1.6 equiv of DIPEA (1.6 mmol), 10 mol % catalyst **3d** (0.10 mmol), 1.0 equiv of $PhSiH_3$ (1.0 mmol), 3.0 mL of toluene, 100 °C, 4 h. Isolated yields are given. PMP: *p*-methoxyphenyl.[a]Reaction conditions: 1.0 equiv of **8** (1.0 mmol), 5.0 equiv of **2** (5.0 mmol), 5.0 equiv of DIPEA (5.0 mmol), 10 mol % catalyst **3a** (0.10 mmol), 1.0 equiv of $PhSiH_3$ (1.0 mmol), 3.0 mL of toluene, 60 °C, 16 h.

Next, the acyl chloride was varied. The bromobenzoyl chloride **2b** gave the respective furan **9h** in a yield of 70%. Both electron-rich and electron-poor acid chlorides performed similarly. Methoxycarbonylbenzoyl chloride **2c** and methoxybenzoyl chloride **2g** formed furans **9i** and **9j** in yields of 59% and 57%, respectively. The reaction of cyclopropylcarbonyl chloride (**2f**) with ethyl benzoyl acrylate yielded the trisubstituted furan **9k** with 67% yield.

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Additionally, R^2 could be modified. While the benzyl derivative reacted as expected, forming trisubstituted furan **9l** in a slightly lower yield of 63%, with 19% tetrasubstituted furan **10l** as the side product, the altered electronic properties on the double bond when employing an amide derivative led to changed selectivities. Presumably, the diminished mesomeric effect of the amide group in comparison to the ester drastically changes the preferred reaction path. The less electron-deficient morpholine amide **8m** reacted to the trisubstituted furan **9m** in a moderate yield of 49%, but at the same time, a considerable amount of tetrasubstituted furan **10m** was formed with a yield of 46%. In contrast to the formation of tetrasubstituted furan **10a** from acyl acrylate **8a** (Table 2, entry 14) when utilizing the phosphetane catalyst **3a**, unexpectedly high selectivities toward the trisubstituted furan **9m** were observed in a good yield of 78% with only 8% of tetrasubstituted furan **10m** as the side product. A similar effect could be seen in the reaction of diethylamide **8n** under standard reaction conditions, forming the trisubstituted furan **9n** and tetrasubstituted furan **10n** in yields of 61% and 28%, respectively. However, the modified conditions led to yields of 88% and 8%, respectively.

The reaction of acyl acrylates **8** with acyl chlorides **2** and phosphine catalysts **3** also shows multiple plausible reaction pathways (Figure 4). Analogous to the formation of furan **4** from diacylethene **1**, the trisubstituted furan **9** can be either formed by a reaction sequence of Michael addition to the more electron-deficient β-position in relation to the ester group, *C*-acylation, and a ring-closure reaction (reaction path **I-a**) or by a reaction sequence of Michael addition to the less electron-poor α-position, *O*-acylation, deprotonation, and intramolecular Wittig reaction (reaction path **II-a**). The viability of the ring-closure reaction (reaction path **I-a**) was demonstrated in the conversion of diacyl acrylate **11** using phospholene catalyst **3d** in the presence of benzoyl chloride (**2a**) and DIPEA. Both trisubstituted furan **9a** and tetrasubstituted furan **10a** were formed, albeit in lowered selectivity (Figure 5, reaction **1**). Also, the optimization of this reaction demonstrated that the lack of an added base leads to a moderate yield of trisubstituted furan **9a** (53%), indicating that the primary reaction pathway is **I-a**.[37] A lack of base in the intramolecular Wittig reaction of reaction pathway **II-a** is not expected to lead to product formation.

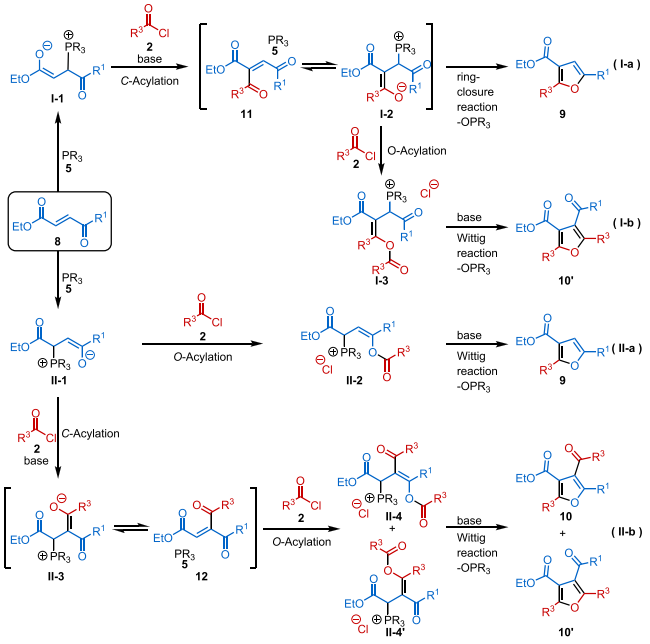

Figure 4. Plausible reaction pathways for the synthesis of tri- and tetrasubstituted furans **9** and **10** from acyl acrylates **8**. The reduction of phosphine oxide **3** using phenylsilane as the terminal reductant was omitted from the scheme.

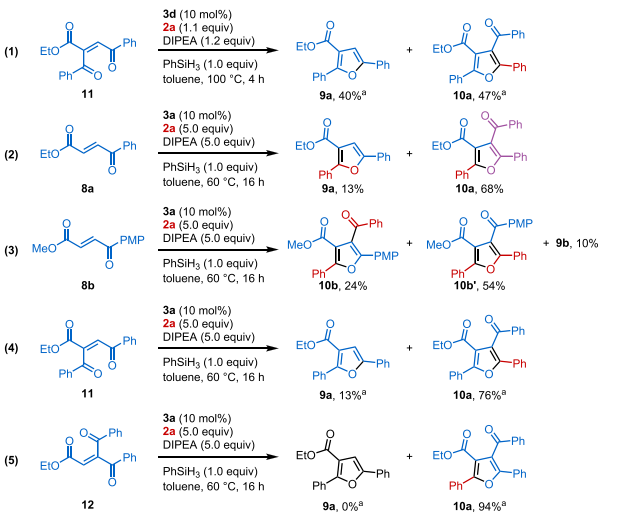

Figure 5. Test reactions for the synthesis of tri- and tetrasubstituted furans **9** and **10** from acyl acrylates **8**. Isolated yields are given. PMP: *p*-methoxyphenyl. [a]Yield determined by GC-FID with hexadecane as the internal standard.

Ethyl benzoyl acrylate (**8a**) was converted with an excess of benzoyl chloride **2a** and DIPEA utilizing phosphetane catalyst **3a**. Here, the tetrasubstituted furan **10a** was isolated in a yield of 68% and the side product **9a** was isolated in a yield of 13% (reaction **2**). When the substituents of acyl acrylate **8** and acyl chloride **2** are distinct, two regioisomers of tetrasubstituted furan **10** are formed. The conversion of methoxy-derivative **8b** led to the formation of the trisubstituted furan **9b** as a side product in 10% yield, while two regioisomers of the tetrasubstituted furans **10b** and **10b′** were isolated in yields of 24% and 54%, respectively (reaction **3**). Also, the formation of tetrasubstituted furan **10** can be described by two viable reaction pathways. In reaction pathway **I-b**, intermediate **I-2** can undergo *O*-acylation, followed by a deprotonation and an intramolecular Wittig reaction to form tetrasubstituted furan **10′**. The viability of this sequence was demonstrated in reaction **4**, although here, the formation of only one regioisomer of furan **10** is expected. The formation of two isomers **10** can be described by the reaction of intermediate **II-1** in *C*-acylation, followed by *O*-acylation, forming two isomers of intermediate **II-3** (reaction path **II-b**). Subsequent deprotonation and intramolecular Wittig reaction led to the formation of two regioisomers of tetrasubstituted furan **10**. Reaction **5** demonstrates the viability of this reaction sequence via the intramolecular Wittig reaction.

An alternate reaction mechanism can be proposed based on the work of Lin and co-workers.[38,39] Here, the diacyl acrylate **11** could be formed in a β-acylation reaction from the intermediates **II-2**, while diacyl acrylate **12** could be formed by *O*-acylation and β-acylation of intermediate **I-1**. This would avoid the proposal of a *C*-acylation reaction. However, diacyl

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acrylates **11** and **12** were never observed in the reaction mixture.

CONCLUSIONS

The reactivity of activated alkenes with acyl chlorides under the P(III)/P(V) redox cycling conditions was investigated. We developed a reaction sequence of Michael addition of the phosphine catalyst and acylation, followed by either an intramolecular Wittig reaction or a ring closure reaction, resulting in the formation of tri- and tetrasubstituted furans. A phosphetane catalyst enabled the synthesis of 12 trisubstituted furans from diacylethenes. The reaction of acyl acrylates resulted in the unexpected formation of not just trisubstituted furans but also tetrasubstituted derivatives, while the product ratio depended on the employed catalyst. Two methods using a phospholene or phosphetane catalyst allowed the synthesis of 14 trisubstituted furans and an additional 6 tetrasubstituted furans. These include 19 novel compounds in this underexplored field of substituted furans.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c00985.

Additional information on reaction optimization, experimental procedures, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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6.3 Organocatalytic Stereospecific Appel Reaction

J. Tönjes, L. Kell, T. Werner, *Org. Lett.* **2023**, *25*, 9114–9118.

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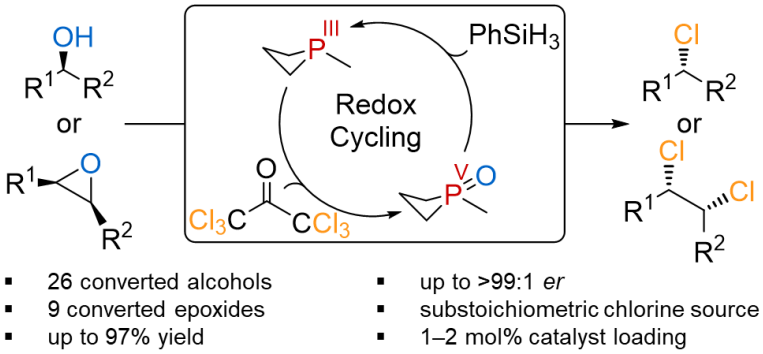

Abstract:

Herein we report a new method for the catalytic Appel reaction by P(III)/P(V) redox cycling at very low catalyst loadings of 1–2 mol % using low amounts of hexachloroacetone as the halogen source and phenylsilane as the terminal reductant. Twenty-six alcohols and nine epoxides containing a wide variety of functional groups were converted to the respective chlorides and dichlorides in yields of up to 97%, enantiospecificities of up to >99%, and enantiomeric ratios of up to >99:1.

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Organocatalytic Stereospecific Appel Reaction

Jan Tönjes, Lukas Kell, and Thomas Werner*

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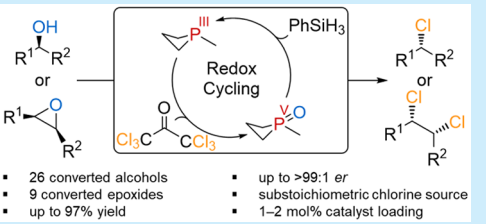
ABSTRACT: Herein we report a new method for the catalytic Appel reaction by P(III)/P(V) redox cycling at very low catalyst loadings of 1−2 mol % using low amounts of hexachloroacetone as the halogen source and phenylsilane as the terminal reductant. Twenty-six alcohols and nine epoxides containing a wide variety of functional groups were converted to the respective chlorides and dichlorides in yields of up to 97%, enantiospecificities of up to >99%, and enantiomeric ratios of up to >99:1.



The nucleophilic substitution of alcohols by halides plays an important role in both natural product synthesis and the formation of reactive intermediates. Although more than 5000 naturally occurring organohalogen compounds are known, mainly from marine organisms, chiral alkyl halides have still been described as valuable, underexplored motifs for medicine.[1−3]

Classical halogenations of alcohols often employ highly reactive reagents such as thionyl chloride or phosphorus trichloride, which can lead to low functional group compatibility and low stereospecificity or require prior activation of the alcohol, which leads to increased waste streams. The reaction of triphenylphosphine with carbon tetrachloride and their reaction with alcohols was thoroughly investigated by Appel.[4] The formed chlorophosphonium salts react with the alcohol, yielding the respective alkyl halides in a largely stereospecific reaction. A similar system using *N*-chlorosuccinimide enabled the dichlorination of internal asymmetric epoxides in the total synthesis of natural chlorosulfolipids.[5] A drawback of these reactions is the stoichiometric amounts of phosphine oxide that arise as a byproduct.

A first catalytic Appel reaction was developed by Denton in 2010 and further developed for the conversion of epoxides.[6−9] Here, catalytic amounts of triphenylphosphine oxide react with oxalyl chloride to form chlorophosphonium chloride *in situ*, which reacts with the substrate while regenerating the phosphine oxide. In this P(V)/P(V) catalytic cycle, alkyl alcohols and epoxides can be converted at room temperature with release of CO_2, toxic CO, and HCl. However, the use of highly reactive oxalyl chloride hampers functional group tolerance.

In recent years, P(III)/P(V) redox cycle catalysis has shown wide applicability in many phosphine-mediated reactions, leading to simplified purifications and less waste.[10,11] Here, an *in situ* reduction of the formed phosphine oxides to the active phosphine species is accomplished by organosilanes. This catalysis technique of phosphorus redox cycling was further developed and applied to multiple reactions, among others the (base-free) Wittig and Staudinger reactions, reductive C−N and N−N couplings, olefin reduction, and the synthesis of (hetero)cycles by Michael/Wittig tandem reaction.[12−19]

Phosphorus redox cycling was first applied to the Appel reaction by van Kalkeren et al. in the bromination of alcohols using diethyl bromomalonate, a dibenzophosphole, and diphenylsilane (Figure 1a).[20,21] In contrast to bromination, the corresponding chlorination largely failed. The authors concluded that for a successful catalytic Appel chlorination, a more nucleophilic catalyst is needed to activate the less electrophilic halogen donor, which in turn is less likely to react with the terminal reductant.

Our previous work investigated the use of catalytic amounts of trioctylphosphine with phenylsilane for the chlorination of alcohols (Figure 1b).[22] With this system, benzotrichloride could be used under solvent-free conditions as a halide source. While primary alcohols were converted in good to excellent yields, secondary and tertiary halides could be synthesized in moderate yields with little stereospecificity.

Kirk et al. rationalized the large influence of the structure of phosphine oxides on their reducibility through a reaction energy comparison of acyclic and cyclic phosphine oxides via DFT calculations.[23] The ring strain of cyclic phosphines facilitates the formation of the transition state needed for hydride transfer from silane to phosphine oxide. The strained phosphetane oxide first employed in redox cycling reactions by Radosevich and co-workers showed high activity in multiple reactions, including the Wittig reaction and reductive C−N

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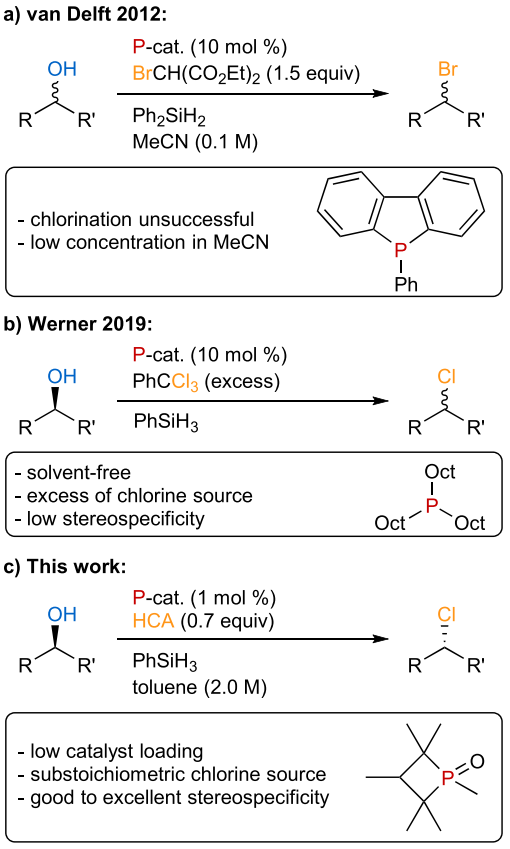


Figure 1. Overview of approaches toward the catalytic Appel reaction. HCA: hexachloroacetone.

coupling.[24−26] Herein we report the use of cyclic phosphine oxides as catalysts in the Appel chlorination of chiral and achiral alcohols and epoxides (Figure 1c).

We started our investigation based on our previous work with methyl phosphetane oxide **1a** as the catalyst and phenylsilane as the terminal reductant. The secondary alcohol 4-phenylbutan-2-ol (**2a**) was chosen as the model substrate since the stereospecificity of the reaction should also be investigated. Initially, the influence of different chlorine sources was tested (Figure 2). Surprisingly, the solvent-free reaction of the previously used benzotrichloride (**3a**) and 10 mol % catalyst **1a** gave a conversion of 34% but only a 2% yield of the chlorinated product **4a**, whereas with the previous trioctylphosphine catalyst a yield of 64% could be obtained.[22] The classically used tetrachloromethane (**3b**) and ethyl trichloroacetate (**3c**) led to increased conversions but still low yields of 17% and 18%, respectively. The more electrophilic chlorine source diethyl chloromalonate (**3d**) led to full conversion and a yield of 35%, whereas trichloroacetonitrile (**3e**) afforded a yield of 82%. Cheap and readily available hexachloroacetone (**3f**, HCA) gave the best yield of 98%. The alcohol (*R*)-**2a** was converted to (*S*)-**4a** with an enantiospecifity (*es*) of 95% and obtained in an enantiomeric ratio (*er*) of 97:3 under inversion of configuration.[27] Additionally, the influence of different phosphine oxide catalysts was investigated.[28]

Subsequently, we investigated the amount of hexachloroacetone needed. The use of lower amounts of HCA made the addition of solvent necessary as well as an optimization of concentrations and conditions (Table 1). In toluene (2 M reactant **2a**), chloride **4a** was obtained in 95% yield (Table 1, entry 1). Further reduction of HCA to 0.5 equiv and

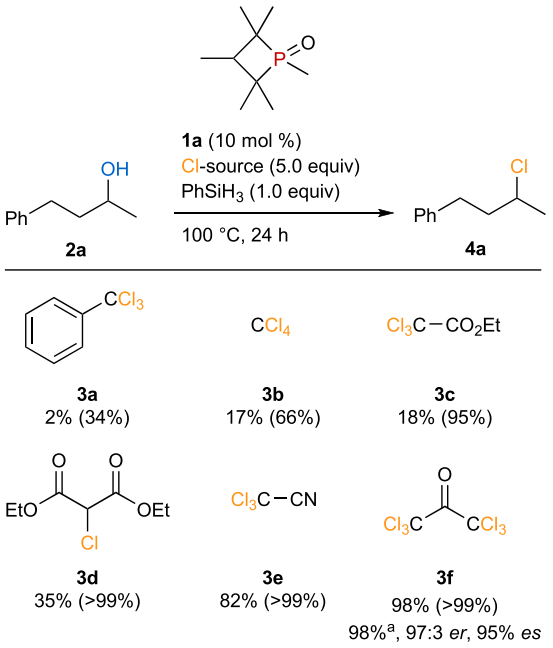
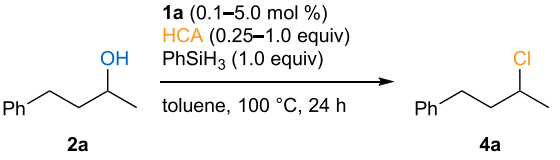


Figure 2. Screening of different chlorine sources. Reaction scale: 0.5 mmol. Yields and conversions (given in parentheses) were determined by GC with hexadecane as the internal standard. The *er* and *es* values were determined by GC on a chiral stationary phase. [a]Reaction using (*R*)-**2a**.

Table 1. Optimization of the Reaction Conditions[a]



entry	equiv of HCA	**1a** (mol %)	yield of **4a** (%)
1	1.0	5.0	95
2	0.5	5.0	80
3	0.25	5.0	41
4	0.7	1.0	88
5	0.7	0.1	66
6	0.55	–	0
7[b]	0.7	5.0	82

[a]Reaction scale: 0.5 mmol. Yields were determined by GC with hexadecane as an internal standard. [b]Modified conditions: 5.0 mol % **1a** (25 μmol), 40 °C, 48 h.

0.25 equiv resulted in decreases in yield to 80% and 41%, respectively, which showed that two chlorine atoms of hexachloroacetone reacted readily under the given conditions (entries 2 and 3). Therefore, 0.7 equiv of HCA was chosen as the amount for further reactions. Reduction of the catalyst loading to 1 mol % in toluene afforded chloride **4a** in a yield of 88% (entry 4). Remarkably, even a low catalyst loading of 0.1 mol % in toluene led to a good yield of 66% for the desired product **4a** (entry 5), showing an exceptional activity of the phosphetane organocatalyst **1a** rarely seen in organocatalysis.[29−31] A longer reaction time of 48 h gave another increase in yield to 73%, whereas in the absence of either catalyst (entry 6) or silane no product formation was observed.[28] A reaction at a lower reaction temperature of 40 °C at a higher catalyst loading of 5.0 mol % was conducted. While phosphine oxide

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1a was shown to be reducible by phenylsilane even at room temperature, a longer reaction time of 48 h was necessary for a good yield of 83% (entry 7).[25]

Under the optimized conditions, the substrate scope of the reaction was examined. Initially, different 2-phenylethanol derivatives **2b**−**2g** bearing various functional groups were investigated (Figure 3). The desired products were obtained in

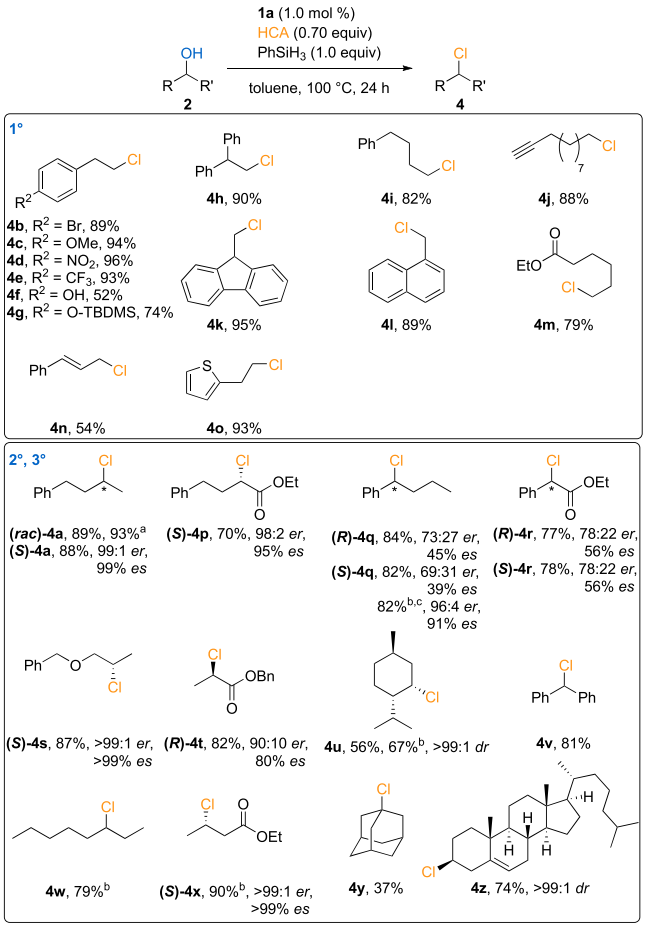

Figure 3. Substrate scope of the catalytic Appel reaction. Reaction scale: 1.0 mmol. Isolated yields are given. The *er* and *es* values were determined by GC on a chiral stationary phase. [a]Reaction scale: 5.0 mmol. [b]Yield was determined by NMR with mesitylene as the internal standard. [c]Modified conditions: 5.0 mol % **1a** (50 μmol), 40 °C, 48 h.

yields of up to 96%. Interestingly, nitrophenylethanol **2d** was chlorinated, leading to **4b** in a yield of 96%. In contrast to the reduction of the nitro moiety previously reported under comparable conditions but higher catalyst loading, no corresponding reduced products were observed.[24,26] By protecting the phenol group of **2f** with a silyl group, the yield of the respective chloride **4g** could be increased from 52% to 74%. Various alcohols **2h**−**2m** bearing different functional groups were converted in good to excellent yields of 79−95%. Although the allyl chloride **4n** could only be obtained in a moderate yield of 54%, no trace of the corresponding branched allyl chloride was detected as shown by Allen and co-workers.[32]

In the next step, the reactivity of secondary and tertiary alcohols and the stereospecificity of the reaction were investigated. The model compound **4a** could be isolated in 89% yield from *rac*-**2a**. The conversion of (*R*)-**2a** led to (*S*)-**4a** in 88% yield with an excellent enantiomeric ratio of 99:1 and an enantiospecifity of 99%. The benzylic alcohols (*S*)-**2q** and (*R*)-**2q** were converted to the respective chlorides (*R*)-**4q** and (*S*)-**4q** in 84% and 82% yield, respectively. The enantiospecifity was lower, and the products were obtained in moderate *er* of 73:27 and 69:31, respectively. This indicates an increased contribution of a nonspecific S_N1-type background reaction facilitated by the stabilization of the carbocation in the benzylic position. However, lower reaction temperatures of 40 °C and increased catalyst loading (5 mol %) led to excellent *er* for (*R*)-**2q** to (*S*)-**4q** of 96:4 after 48 h. Similarly, the mandelates (*S*)-**2r** and (*R*)-**2r** could be converted in good yields of 77% and 78%, respectively, but with a lower *er* of 78:22 for each. Benzyloxypropanol (*R*)-**2s** could be converted to the chloride (*S*)-**4s** with an excellent *er* of >99:1 in a good yield of 87%. Notably, (−)-menthol (**2u**) was converted to neomenthyl chloride (**4u**) in 56% yield. Chlorination of this challenging substrate usually leads to the elimination of HCl and formation of menthenes.

Additionally, 3-octanol (**2w**) and ethyl (*S*)-3-hydroxybutanoate (*S*)-**2x** were converted to **4w** and **4x** in yields of 79% and 90%, respectively. (*S*)-**4x** showed an excellent *er* of >99:1. The tertiary adamantanol **2y** could be chlorinated to form **4y** in a yield of only 37%, probably due to the restrictions for an S_N2 backside attack. Interestingly, cholesterol (**2z**) could be chlorinated to form 3β-cholesteryl chloride (**4z**) in 74% yield under retention of the configuration, which has been observed in other previous studies.[6]

Furthermore, the reactivity of the epoxides was investigated (Figure 4). The optimization of reaction parameters showed the need to double the catalyst loading, the amount of HCA, and the amount of solvent used as well as to increase the phenylsilane by 50%.[28] Under these conditions, (*R*)-styrene oxide ((*R*)-**5a**) could be converted to the respective dichloride (*S*)-**6a** in a good yield of 92% with an excellent *er* of 96:4.

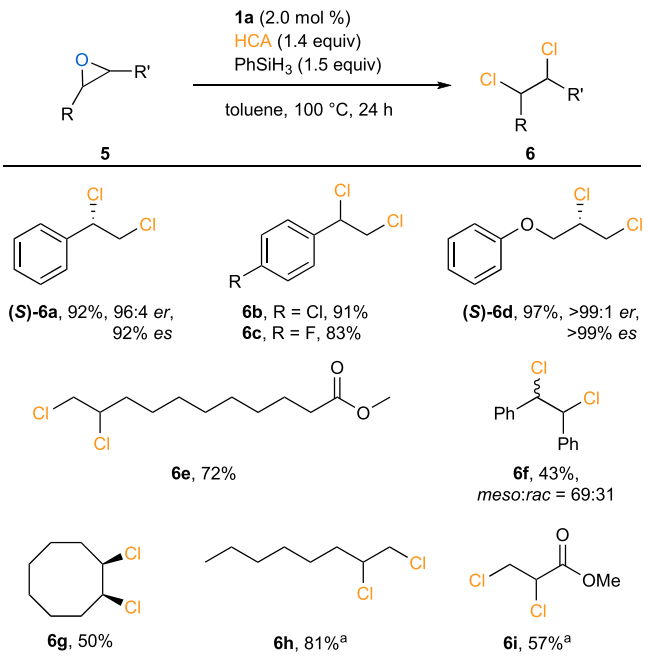

Figure 4. Substrate scope of terminal and internal epoxides. Reaction scale: 1.0 mmol. Isolated yields are given. The *er* and *es* values were determined by GC or HPLC on a chiral stationary phase. [a]Yield was determined by NMR with mesitylene as the internal standard.

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Thakore et al. showed that the initial ring opening of epoxides in a dichlorination occurs on the most substituted carbon.[33] This might be the reason for the excellent *er* achieved in the chlorination of styrene oxide (*R*)-**5a**, whereas the substitution of benzylic alcohol (*R*)- and (*S*)-**2q** led to lower enantiomeric ratios. Similarly, chlorine- and fluorine-substituted dichlorides **6b** and **6c** were formed in yields of 91% and 83%, respectively. The dichloride (*S*)-**6d** was afforded by the reaction of (*S*)-glycidyl phenyl ether ((*S*)-**5d**) under inversion in excellent yield (97%) and *er* (>99:1), while the fatty acid-derived dichloride **6e** was obtained in a yield of 72%. The reaction of *trans*-stilbene oxide (**5f**) in the dichlorination afforded dichloride **6f** in a yield of 43%. The diastereomeric ratio of 69:31 *meso* to racemic compound indicates the higher share of the S_N1 mechanism. Cyclooctene oxide (**5g**), on the other hand, could be converted to the respective *cis*-dichloride **6g** as the only stereoisomer in a yield of 50%. Additional substrates showing little or no product formation are depicted in the Supporting Information.[28]

The previous investigations of the Appel reaction showed the complexity of the reaction mechanism due to a multitude of reactive intermediates.[4] Similarly, initial NMR studies of the catalytic Appel reaction also proved to be challenging. Therefore, the mechanism was investigated in a stepwise reaction, leading to the proposed simplified mechanism (Figure 5).[28] Following the reduction of phosphine oxide **1**

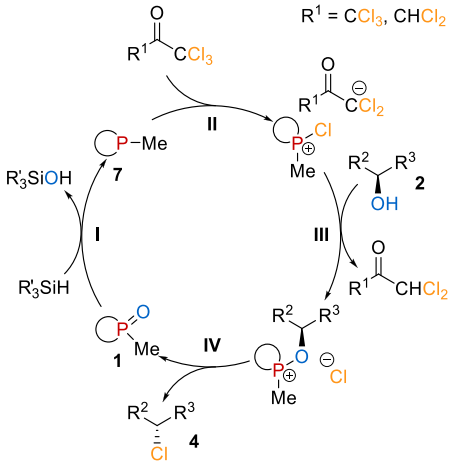

Figure 5. Proposed mechanism for the stereospecific catalytic Appel reaction.

(step **I**), which is not considered to be the rate-determining step, the phosphine **7** reacts with penta- or hexachloroacetone, forming a chlorophosphonium salt (step **II**).[25] The following reaction with **2** leads to the formation of an alkoxyphosphonium species and protonated chloroacetone (step **III**). Finally, a nucleophilic substitution, generally following an S_N2 reaction pathway, leads to the formation of alkyl chloride **4** and the regeneration of phosphine oxide **7**.

A new method for the stereospecific catalytic Appel reaction for the chlorination of alcohols and the dichlorination of epoxides was developed. At very low catalyst loadings of 1−2 mol %, a series of 26 alcohols and nine epoxides were converted to the respective products in generally good to excellent yields, enantiomeric ratios, and stereospecificities. This method gives general and facile access to mono- and dichlorides from alcohols and epoxides.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c03463.

General methods, synthetic procedures and spectra, additional data on reaction optimization, and additional information on the substrate scope (PDF)

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Notes

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