Minimal phase tagging approach with *tert*-butyl groups and its application in Mitsunobu and Wittig reactions

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Theses of PhD dissertation

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1. Introduction

One purpose of synthetic organic chemistry is the efficient preparation of useful molecules to fulfil the needs of mankind. Usually, chemists see this question as the problem of optimization of reaction conditions or reagents; however, it is worth mentioning that the separation of the product from side-products or unreacted reagents determines the efficiency of the reaction as well. Therefore, the development of efficient, simple and cheap separation method is also crucial in the field of synthetic organic chemistry, especially on industrial scale.

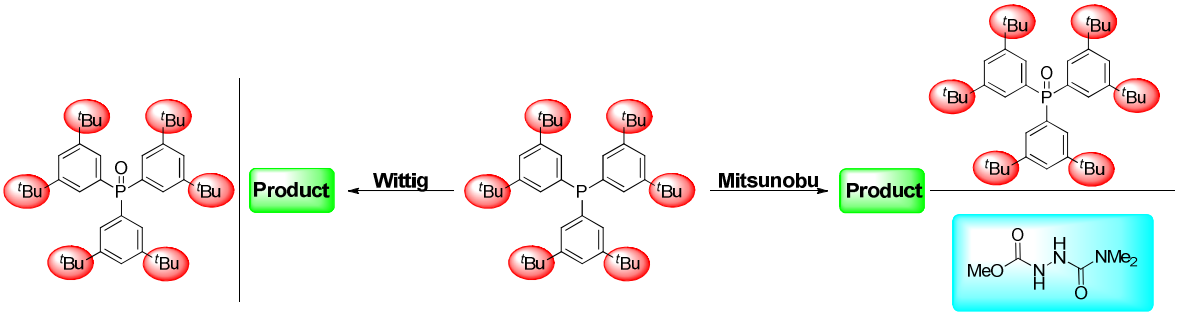
Phase tagging approach is a wide spread approach in organic chemistry. The reagent, catalyst or product is labelled by a phase tag what facilitates the separation of labelled and unlabelled molecules. With this method, the purification is a simple phase separation e.g. filtration, extraction. The significance of phase tagging is further increased when we want to separate not just smaller quantities of catalyst but equivalently formed by-products, for example triphenylphosphine oxide which is formed in the well-known Mitsunobu, Wittig, aza-Wittig, Staudinger of Appel reactions. In these reactions, the separation of the formed phosphine oxide from the product is usually a tedious, time consuming and expensive method, in several cases, chromatographic purification is inevitable. To overcome the problem of purification, several modified reagents have been developed throughout the ages but usually, their availability and price are limiting factors on industrial case. Therefore, the development of a minimalist phase labelling approach what ensures the easy and economic separation of the product from by-products is a key issue in synthetic organic chemistry.

Increasing the efficiency of a reaction is also possible with the use of catalytic systems to decrease the waste formed during the chemical transformation. Organocatalysis has developed to a well-known tool for the synthesis of chiral molecules having even multiple chiral centers. Among these processes, there is a rather rare, but distinct class of strategic approach, the enantioselective stereoablative reactions. These transformations deliver enantioenriched compounds via destroying stereogenic elements. However, this method reduces molecular complexity, it can have several practical advantages that merit further exploration for example in the field of bifunctional thiourea catalysed Michael addition reactions.

2. Aims

During my research, I wished to study the use of a minimally tagged phosphine in Mitsunobu and Wittig reactions. Instead of following the widely explored practice of appending large molecular weight phase labels, we aimed to utilize minimal-size phase tags which still ensure the effective separation of the reagents from a "common organic molecule" without compromising their molecular weight, complexity and reagent cost. To minimize the steric and electronic interference with the nucleophilic site, we envisaged an alkylated triphenylphosphine analogue that has *t*-butyl tags in all meta positions of the phenyl residue.

After the comparison of the reactivity of the tagged phosphine to the commercial reagents, the aim of the research was to develop a chromatography-free purification process to isolate Mitsunobu and Wittig products with simple liquid-liquid or solid-liquid extractions.



In the case of Mitsunobu reaction, phosphine oxide and hydrazine by-products are formed in stochiometric amount. Due to the orthogonal phase labeling approach, when the apolar tagged phosphine and a water soluble azo compound are used, we wished to apply liquid-liquid extractions using traditional solvents and solvent mixtures to isolate the formed by-products in immiscible solvent systems.

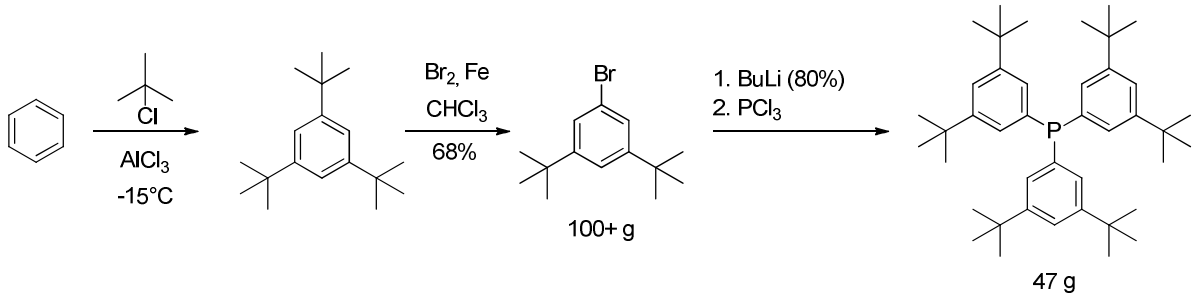
The other aim of my research was to study the organocatalytic Michael addition of dialkylphosphorothioic acid, an odourless H_2S analogue to chalcones. We wished to investigate the possibility of the synthesis of these adducts with high enantioselectivity by stereoablative transformation of the racemic products in a biphasic system, where the organocatalyst is regenerated in the aqueous phase.

3. Results

The main results and conclusions can be summarized as follows:

1. Scaled-up synthesis of the minimally phase tagged phosphine

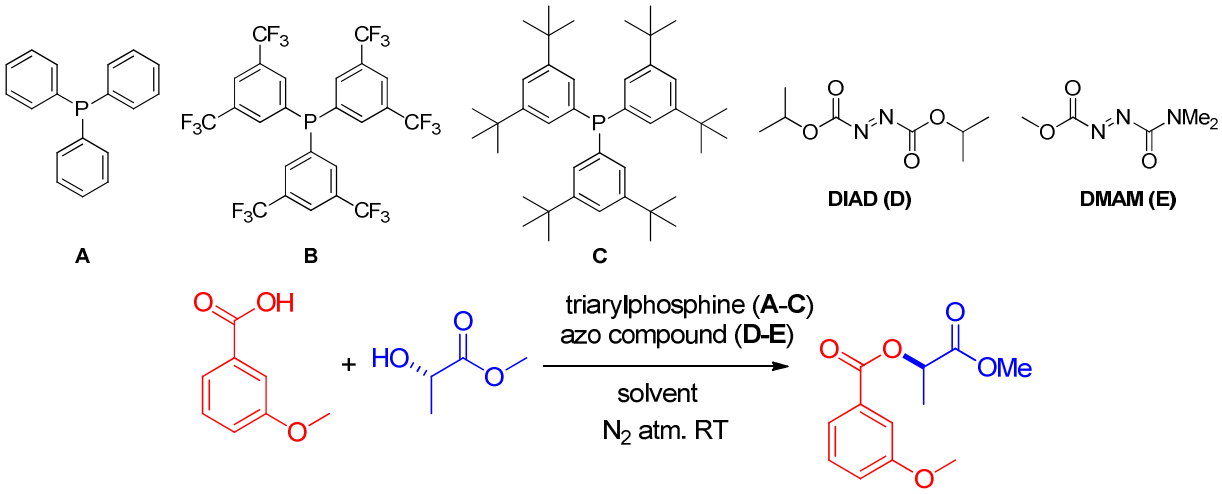
Although this phosphine was earlier described in literature, the development of an efficient and chromatography-free synthesis was needed. From cheap, commercially available starting materials, the tagged phosphine was synthesised on a 50 g scale.



The synthesis of the tagged phosphine was realised from benzene. Benzene was substituted with *tert*-butyl groups in Friedl-Craft alkylation then one of the *tert*-butyl groups was replaced by bromine to obtain the symmetrical bromobenzene derivative. The triarylphosphine was synthesised via an organolithium compound what reacts with PCl_3. Due to the symmetric substitution pattern and the easy substitution of one of the *tert*-butyl groups, this tagged phosphine can be synthesised from cheap, commercially available starting materials in a scalable manner without chromatography.

2. Reactivity study of the tagged phosphine in Mitsunobu reaction

The reactivity of triphenylphosphine, $-CF_3$ substituted triarylphosphine and the *tert*-butyl substituted phosphine was compared. The $-CF_3$ substituted triarylphosphine, due to its decreased nucleophilic character, furnished the desired product in low yield, however, the *tert*-butyl substituted analogue was almost as efficient as triphenylphosphine. Then this tagged phosphine was combined with the water soluble DIAD analogue DMAM and proved to be efficient in the test reaction.

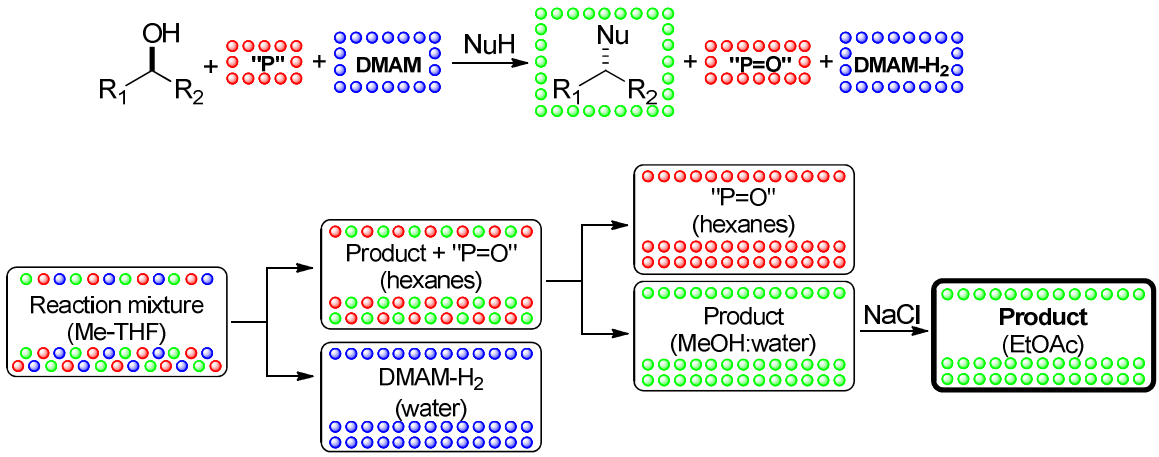


Entry	Phosphine	Azo compound	Solvent	Yield (%)[b]
1	PPh_3(**A**)	DIAD (**D**)	THF	89
2	PPh_3(**A**)	DIAD (**D**)	Me-THF	87
3[c]	B	DIAD (**D**)	Me-THF	46
4	C	DIAD (**D**)	Me-THF	80
5	C	DMAM (**E**)	Me-THF	81

[a]Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol, 1.0 eq), triarylphosphine (1.0 mmol, 1.0 eq), azo compound (1.0 mmol, 1.0 eq), solvent (2.0 ml), 2 h reaction time. [b]Isolated yield after chromatography. [c]24 h reaction time.

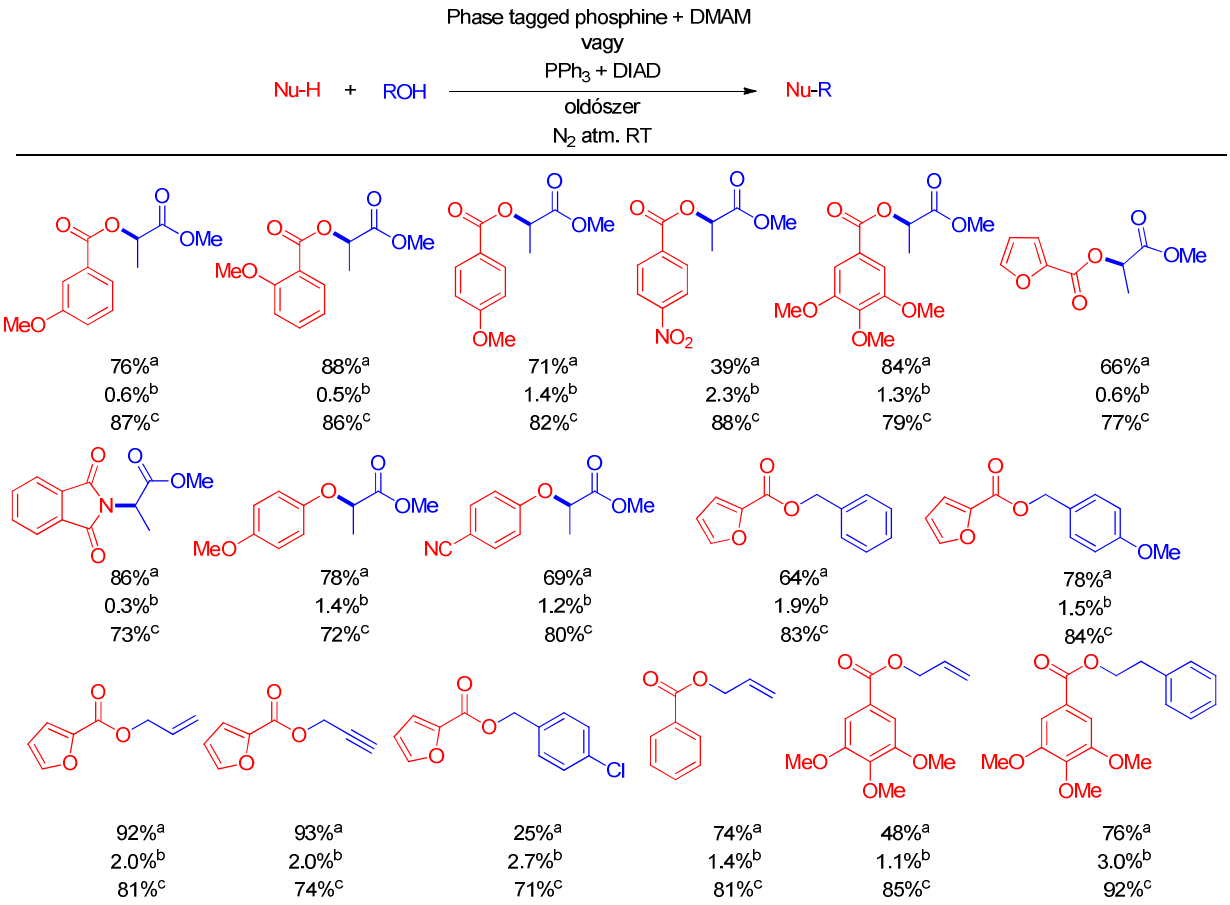
3. Orthogonal phase tagging approach

The combination of the apolar phosphine and the water soluble DMAM enables the use of orthogonal phase tagging approach: the product and by-products can be isolated in immiscible solvents or solvent mixtures. The phosphine oxide is soluble in hexanes, the hydrazine by-product in water and the product is soluble in aqueous methanol.



4. The use of orthogonal phase tagging approach: product purification in Mitsonobu reaction

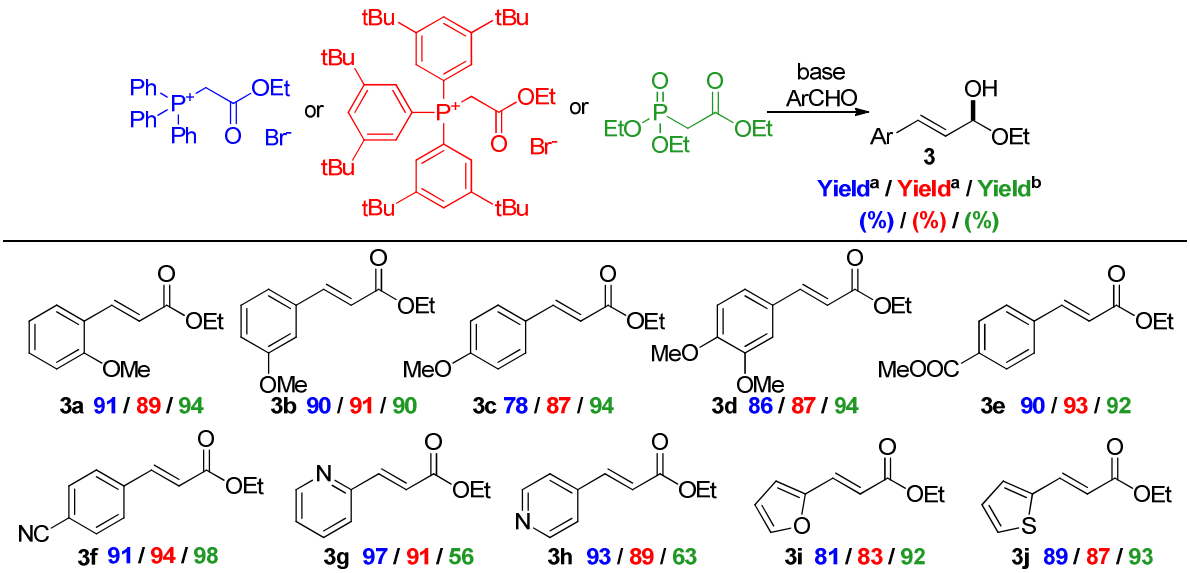
The liquid-liquid extraction process was used to purify several Mitsunobu products. The isolated yields obtained in this process were compared to the ones obtained in the classical Mitsunobu reactions (PPh_3/DIAD reagents, chromatography). The orthogonal phase tagging approach was as efficient as the classical one in several cases, although the solubility of the product in aqueous methanol limits the applicability of this process. In every case, the phosphine oxide contamination was less than 3% and the residual hydrazine was not detectable.



[a]Reaction conditions: nucleophile (1.0 mmol), alcohol (1.0 mmol, 1.0 eq), phase tagged phosphine (**C**) (1.0 mmol, 1.0 eq), DMAM (**E**) (1.0 mmol, 1.0 eq), Me-THF (2.0 ml), 2 h reaction time. Purification: liquid-liquid extraction. [b]Determination of residual phosphine oxide by ^{1}H NMR. [c]Reaction conditions: nucleophile (1.0 mmol), alcohol (1.0 mmol, 1.0 eq), triphenylphosphine (**A**) (1.0 mmol, 1.0 eq), DIAD (**D**) (1.0 mmol, 1.0 eq), Me-THF (2.0 ml), 2 h reaction time. Purification: chromatography.

5. Application of phase tagged phosphine in Wittig reactions

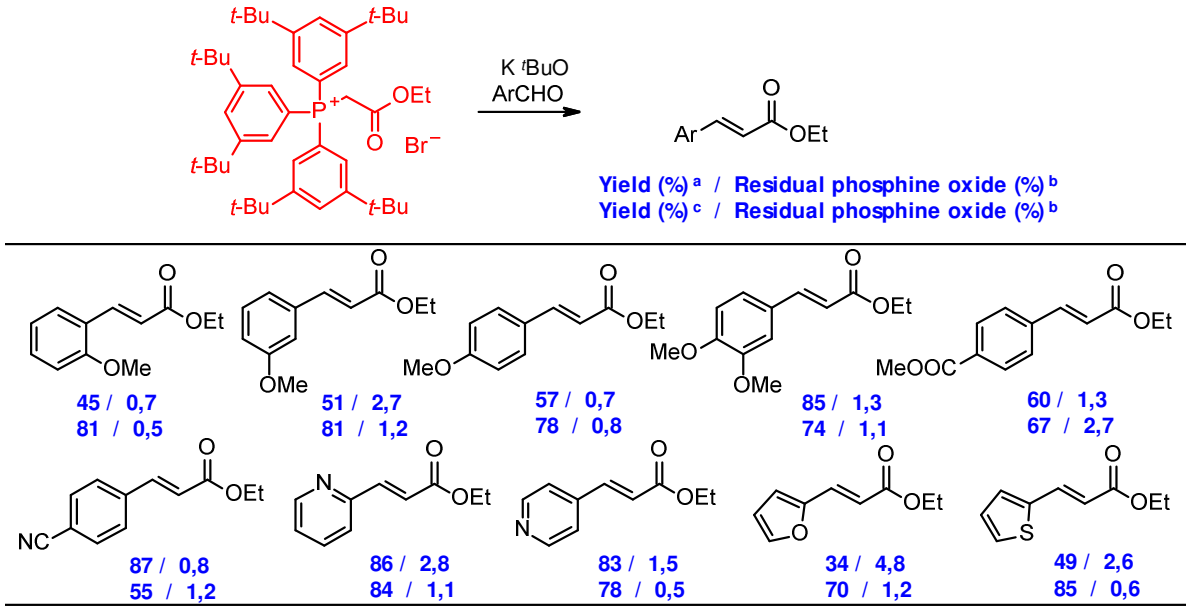
The reactivity of the Wittig salts derived from triphenylphosphine and the tagged phosphine was compared to the reactivity of Horner-Wadsworth-Emmons reagent. In the studied reactions, the isolated yields of the reactions with Wittig salts synthesised from the tagged phosphine were comparable to the classical reagents'. In the case of polar substrates, HWE reaction furnished the appropriate product in a lower yield.



Reaction conditions: Wittig reagent (1.0 mmol), base (1.0 mmol, 1.0 eq), THF (5.0 ml), aldehyde (1.0 mmol, 1.0 eq). [a]Purification: chromatography. [b]Purification: extraction

6. Purification of Wittig products with liquid-liquid and solid-liquid extraction

Due to the phase labelling, the tagged phosphine oxide can be removed from the mixture with simple extraction. In the case of polar substrates, the liquid-liquid extraction firnished the products in good yields, however, in the case of apolar products, the yields are lower, because of the disadvantageous partition between hexanes and aqueous methanol. To overcome the problem of partition between liquid phases, a solid-liquid extraction was developed to isolate Wittig products. With this method, the isolated yields were comparable to the ones obtained after chromatography, however, it is worth mentioning, that in this case, the solubility of the product in aqueous methanol is the limitation of this method. In the case of polar substrates, the solid-liquid extraction procedure was inferior to the HWE reactions.

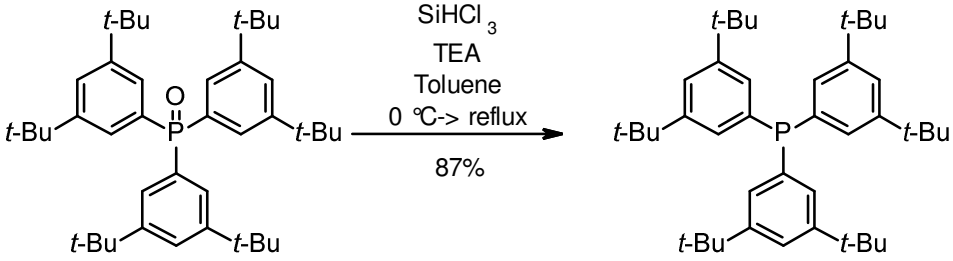


[a]Purification: liquid-liquid extraction. [b]Residual phosphine oxide was determined by ^{1}H NMR.

[c]Purification: solid-liquid extraction.

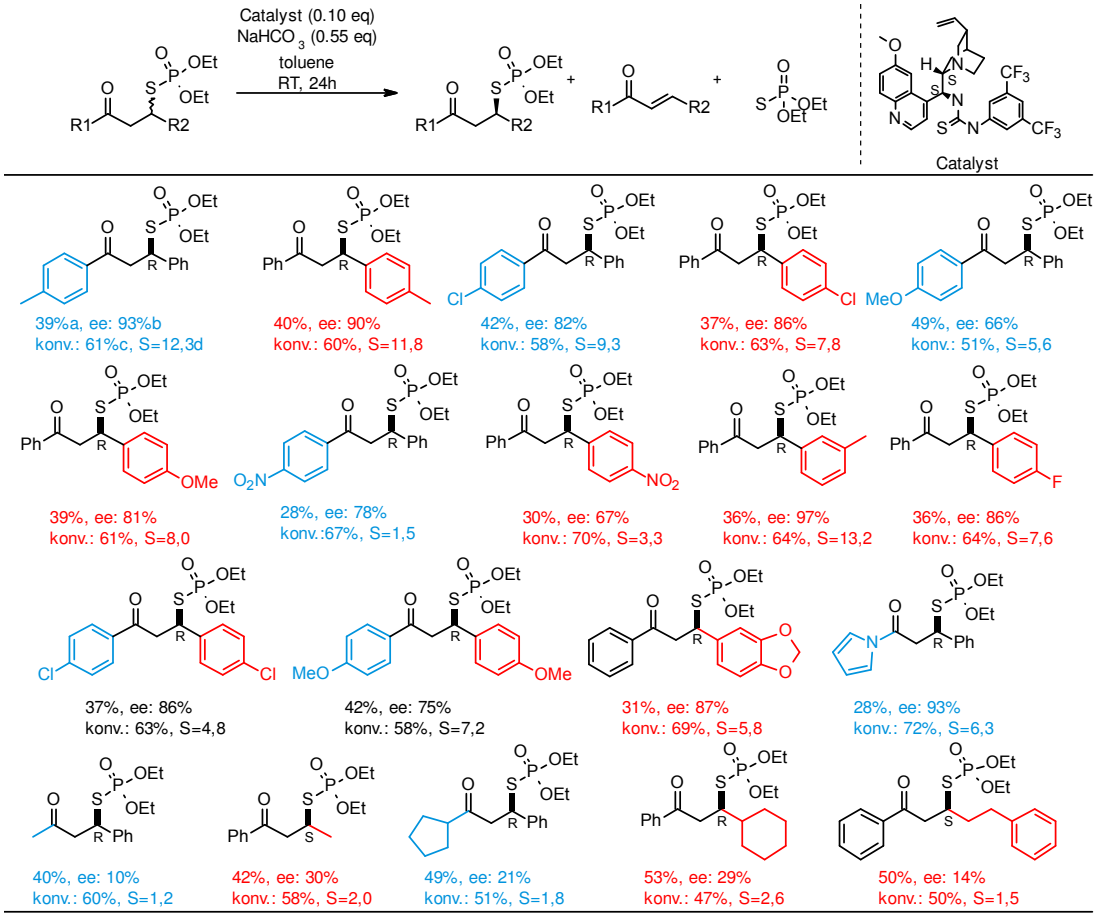
7. The recovery of the phase tagged phosphine

Due to the phase labelling, at the end of the applied extractions, phosphine oxide is dissolved in hexanes. The tagged phosphine is obtained after reduction of the oxide with trichlorosilane in the presence of TEA.



8. The investigation of stereoablative retro-sulfa-Michael reactions

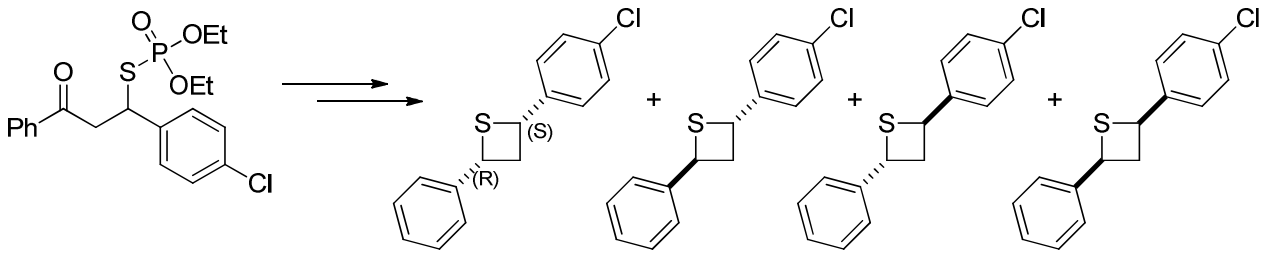
The racemic Michael adducts of dialkylphosphorothioic acids and chalcones in the presence of organocatalysts can be transformed to enantioenriched products in a stereoablative retro-sulfa-Michael reaction. The chiral catalyst selectively reacts with one of the enantiomers and the starting materials are formed, meanwhile the residual Michael product has high ee. The dialkylphosphorothioic acid forms a salt with the catalyst, therefore it is deactivated. To overcome this problem and maintain the system catalytic, the catalyst is regenerated in a biphasic system with the aid of aqueous base.



[a]Isolated yields for the enantioenriched Michael adducts. [b]Enantioselectivity was determined by chiral HPLC measurements. [c]Conversion % for the starting racemic compound.[d]Selectivity factor

9. Further transformation of the products of sulfa-Michael addition: the synthesis of 2,4-Diarylthietanes

In order to further demonstrate the utility of chiral sulfa-Michael adducts and the stereoablative procedure that deliver them, the diastereoselective synthesis of all possible stereoisomers of 2,4 diaryl-substituted thietanes was attempted. This one-pot synthesis starts with the stereoselective CBS (Corey–Bakshi–Shibata) reduction of the carbonyl moiety followed by the ring closing reaction. With this method, all four diastereomers of the product can be synthesised.



Papers Forming the Basis of the Dissertation

„The Goldilocks Principle in Phase Labeling. Minimalist and Orthogonal Phase Tagging for Chromatography-free Mitsunobu Reaction"
Szigeti, M; Dobi, Z; Soós, T.; *J. Org. Chem.* **2018**, *accepted*
DOI: 10.1021/acs.joc.8b00014

„Bifunctional Thiourea-Catalyzed Stereoablative Retro-Sulfa-Michael Reaction: Concise and Diastereoselective Access to Chiral 2,4-Diarylthietanes"
Bacsó, A.; Szigeti, M.; Varga, Sz.; Soós, T.; *Synthesis***2017**, *49*, 429-439.

Other publications

„Lipase-catalyzed kinetic resolution of 4-aryl- and 4-heteroarylbut-3-en-2-ols,,
Szigeti, M., Tőke, E. R.; Turóczi, M. C.; Nagy, V.; Szakács, G.; Poppe, L.; *Arkivoc*, **2008**, 54-65.