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RESEARCH ARTICLE

Green chemical approaches and tools in the development of environmentally friendly synthetic methods

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Abstract

Addressing the recommendations of the 12 basic lows of green chemistry, the microwave technique was utilized in phospha-Mannich, Diels-Alder and inverse Wittig type reactions, moreover under solventless conditions. In the phase transfer catalysed alkylation of CH-acidic compounds, the quaternary onium salts could be substituted by MW irradiation. The effect of chiral phase transfer catalysts was compared on suitable, potentially enantioselective model reactions. Mono- and bidental P-ligands were developed to make available novel platinum complexes that can be useful as catalysts. Finally, esterifications including diesterifications were studied by in situ Fourier Transform IR spectroscopy.

Keywords

green chemistry · microwave · phase transfer catalysis · P-ligands · transition metal complexes · in situ FTIR

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1 Introduction

These days it is a serious challenge for organic chemists to provide chemical industry including, among others, pharmaceutical industry with environmentally safe synthetic procedures and technologies applying suitable starting materials and atomic-efficient reactions. In the context of the 12 basic lows of green chemistry [1], we aimed at the following points:

- elimination of the use of harmful organic solvents;
- shortening the reaction times by the application of suitable heat transfer;
- development of phase transfer catalytic techniques and application in selective syntheses;
- development of catalysts to promote catalytic transformations;
- monitoring the reactions to find the optimum set of parameters.

In accord with the above purposes, our results are discussed in four subchapters.

2 Results and Discussion

2.1 Microwave-Promoted Solvent-Free Reactions

In the last decade, microwave-assisted accomplishment of organic chemical reactions has become quite widespread. The MW technique is especially preferred to traditional heating when a long period of heating is necessary at a higher temperature. The reaction components may be irradiated in solvents with suitable dielectric constant or without any solvent.

First we studied the phospha-Mannich condensation of secondary amines including N-heterocycles, paraformaldehyde and >P(O)H species, such as diethyl phosphite and diphenylphosphine oxide to afford aminomethylene-phosphonates or aminomethylene-phosphine oxides **1**. The three component mixtures could be best reacted under solventless conditions by irradiation at 80 °C for 30 min (Fig. 1) [2].

Phospha-Michael reactions were also investigated. It was found that simple additions, such as the reaction of dialkyl phosphites with methylvinylketone can be preformed easily under

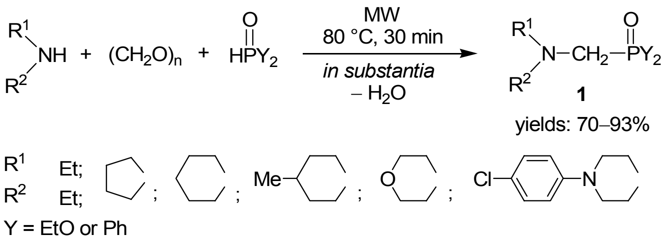
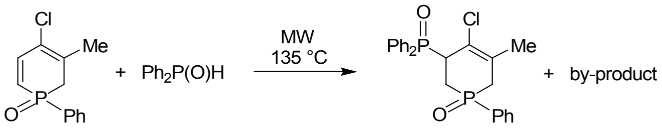


Fig. 1.

traditional conditions, like in the presence of sodium ethylate in ethanol or using diazabicycloundecene (DBU) in chloroform [3]. The application of the MW technique was an attractive alternative in the Michael reaction of diphenylphosphine oxide with 1,2-dihydrophosphinine oxides. The addition of Ph$_2$P(O)H on the α,β-double-bond of **2** at 135 °C giving the desired product (**3**) was, however, accompanied by the inevitable formation of the dimer of the starting material (Fig. 2).



2 **3**

Fig. 2.

Diels-Alder reactions form a well-studied group of MW-assisted reactions. The cycloaddition of 1,2-dihydrophosphinine oxides (**4**) and dimethyl acetylenedicarboxylate (DMAD) or N-phenylmaleimide (NPMI) results in the formation of 2-phosphabicyclo[2.2.2]octadiene (**5**) and bicyclooctene (**6**), respectively (Fig. 3). Under traditional heating in boiling toluene, the reaction was rather slow. On MW irradiation at 110 °C in the absence of any solvent, the cycloaddition became 30-times faster and the side-reactions deriving mainly from the polymerization of the starting materials were suppressed. Hence, the yields were excellent [4].

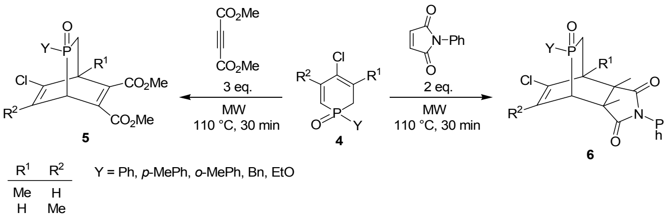


Fig. 3.

Interestingly, the above reaction of the 1-(2,4,6-triisopropylphenyl) starting material (**4**, Y = 2,4,6-tri^{i}PrPh) took another route at 150 °C and furnished the corresponding β-oxophosphorane. Moreover, this type of inverse Wittig reaction was general and proceeded also with other 1-trialkylphenyl P-heterocycles (**7**). The reactions were, however, rather sluggish under traditional heating, since completion at 150 °C required ca 10 days. Application of the MW brought a real breakthrough resulting in a complete conversion already after a 3 h irradiation at 150 °C. In the lack of polymerization, the purification was simpler and the yields of the β-oxophosphoranes (**8**) were much better (Fig. 4) [5].

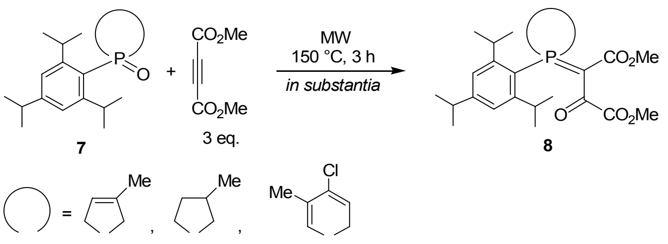
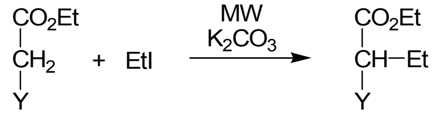


Fig. 4.

Application of the MW technique made possible the reaction of trimethylphenyl derivatives, otherwise unable to enter into interaction with DMAD. On the other hand, there was no double-bond rearrangement under MW irradiation. The organophosphorus compounds prepared are potentially of biological activity.

2.2 Phase Transfer Catalytic Reactions

Alkylation of CH-acidic substrates, that is a basic reaction in pharmaceutical industry, received much attention. An elegant way of accomplishment involves the application of phase transfer catalytic technique. We wished to explore if the reaction under discussion could be realized under solvent-free conditions and if MW irradiation had a beneficial effect on the course of the reaction. The solid-liquid phase alkylation of diethyl malonate (**9**, Y = CO$_2$Et) with ethyl iodide in the presence of potassium carbonate and an onium salt was chosen as the model reaction. It was found that the heterogeneous reaction took place smoothly in the absence of any solvent and the MW irradiation was stimulating. It was a surprising experience that not only the reaction time could be shortened under MW, but the phase transfer catalyst could also be omitted from the reaction mixture. Hence, MW irradiation may substitute onium salts. Moreover, this kind of novel monoalkylation could be extended to other model compounds and alkyl halides. A few examples are shown in Fig. 5 [6].



9 **10**

Y	T [°C]/p [bar]	t [min]	Yield
CO$_2$Et	120/13	40	94%
CO$_2$Me	100/11	30	86%
CN	80/9	30	78%

Fig. 5.

The above method for selective monoalkylation is a real breakthrough from the point of view of green chemistry, as the phase transfer catalyst, that generally is not recovered in the industry, can be eliminated from the system. Not even mentioning the solvent-free accomplishment.

On the other hand, the effect of traditional cinkonidin alkaloids (**11**/**12**) and glucose-based lariat ethers (**13**/**14**) with a P-functionalized side chain was compared as phase transfer catalysts in typical prochiral reaction models. Two representative examples are discussed.

In the first example that is a Darzens condensation moderate enantioselectivities were attained using cinkonin alkaloids **11** and **12**, while a poor ee value was detected when lariat ether **13** was the catalyst (Fig. 6/1). In the other reaction model that is Michael addition, a record ee value was, however, detected in the presence of a lariat ether with a one carbon atom longer chain (**14**) (Fig. 6/2) [7].

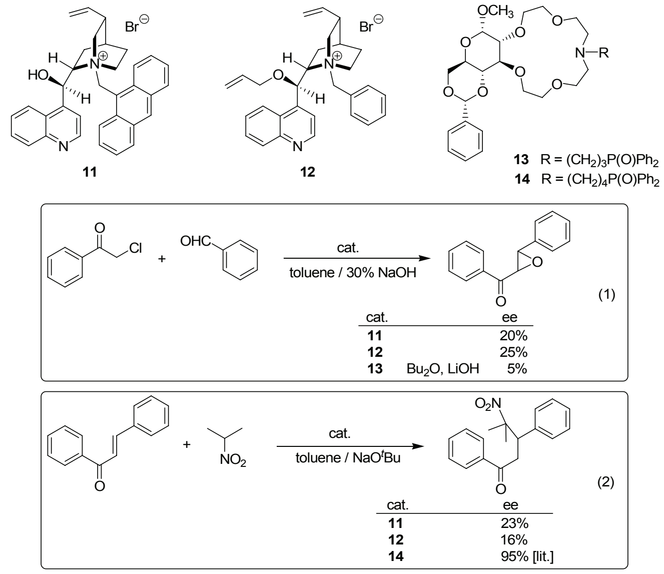


Fig. 6.

2.3 Mono- and Bidentate P-Ligands and their Platinum Complexes

The use of transition metal complexes including P-ligands in a variety of heterogeneous and homogeneous catalytic systems became a common approach. We aimed at the development of special P-ligands. In one part of our project, achiral and chiral dibenzo[*c*.*e*][1,2]oxaphosphorins with different P-functions (**16**) were synthesized that were converted to the corresponding platinum (II) complexes (**17**) (Fig. 7) [8,9].

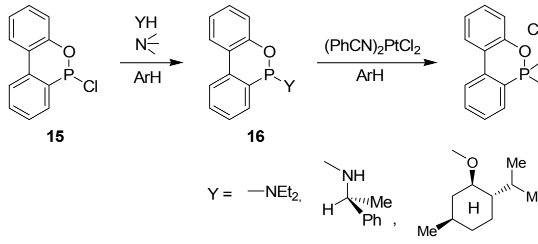


Fig. 7.

Ring opening of a dibenzooxaphosphorin (**18**) afforded 1-hydroxy-1'-diphenylphosphino-biphenyl (**19**) that was used immediately, or in the phosphorylated form (**20**) in complexation with $(PhCN)_2PtCl_2$ to furnish complexes **21** and **22**, respectively. The latter one (**22**) was derived from bidental P-ligand **20** (Fig. 8) [10].

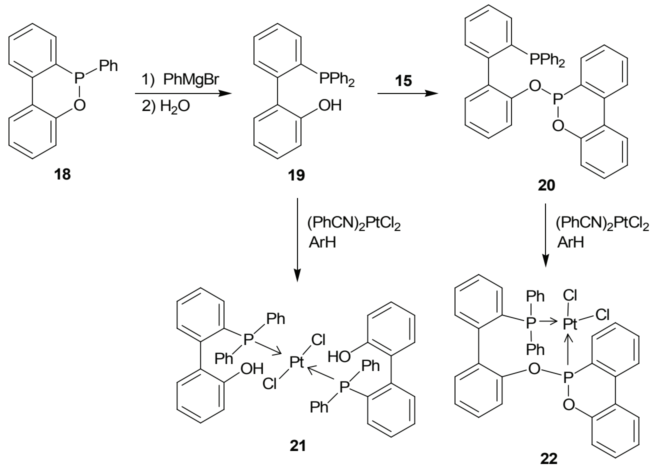


Fig. 8.

In another line of this research, 1,2,3,6-tetrahydrophopshinine oxides with an exocyclic P-function in position 3 (**24**) were prepared by the trimethylaluminum-mediated addition of >P(O)H species on the electronpoor double-bond of 1,2-dihydrophosphinine oxides **23**. (See also Fig. 2) The Michael addition took place in a diastereoselective manner [11]. The 3-P-tetrahydrophosphinine oxides (**24**) were then subjected to catalytic hydrogenation to give the corresponding 1,2,3,4,5,6-hexahydrophosphinine oxides (**25**) again diastereoselectively [12] (Fig. 9).

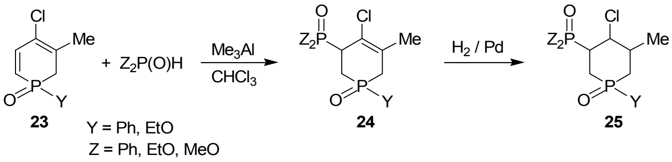


Fig. 9.

The stereostructure and conformation of P-heterocycles **24** and **25** was evaluated on the basis of theoretical calculations and stereospecific NMR couplings. Double deoxygenation of 3-diphenylphosphinoxido-1-phenyl derivatives **24** and **25** (Y = Z = Ph) resulted in diphosphines (**26** and **27**, respectively) that were suitable bidental P-ligands to form chelate complexes **28** and **29**, respectively, in reaction with $(PhCN)_2PtCl_2$ (Fig. 10) [13,14].

Platinum complexes **21**, **22**, **28** and **29** are to be tested in catalytic hydrogenations and hydroformylations.

2.4 Monitoring Organic Reactions by *in situ* Fourier transform Infra Red Spectroscopy

It is also a green chemical requirement to run a reaction at the optimum conditions for the necessary time. An up to date tool

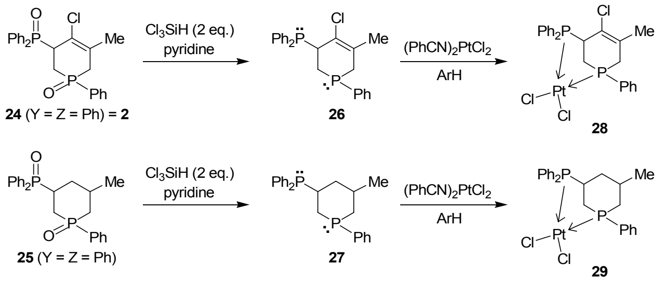


Fig. 10.

for monitoring organic chemical reactions is the use of *in situ* Fourier transform IR spectroscopy becoming shortly a routine method in pharmaceutical industry.

We used *in situ* Fourier transform IR spectroscopy to follow and optimize esterifications. On the one hand, the acylation of n-butanol with benzoic acid (Fig. 11/1), while on the other hand the two step esterification of phthalic acid anhydride with n-butanol (Fig. 11/2) investigated. In the first case, the equilibrium constant was determined on the basis of the equilibrium concentrations. Equilibrium step of the model reactions studied was shifted by azeotropic distillation. It was possible to point out the intermediate of the two-step esterification, formed by the addition of butanol to the anhydride.

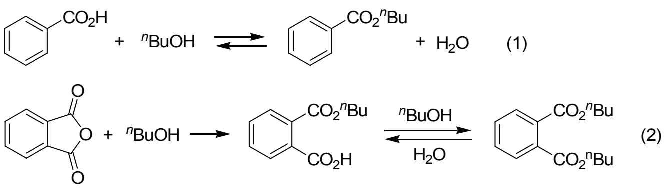


Fig. 11.

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