

Boron catalysis in Organic Chemistry

Mueller, Tobias

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Boron catalysis in Organic Chemistry

Tobias Müller

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Boron catalysis in Organic Chemistry

Proefschrift

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aan de Technische Universiteit Delft,
op gezag van de Rector Magnificus prof. ir. K. C. A. M. Luyben,
voorzitter van het College voor Promoties,
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door

Tobias MÜLLER
Diplom Chemiker,
Universität Ulm, Duitsland,
geboren te Ulm, Duitsland

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Samenstelling promotiecommissie:

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Ander lid:

dr. K. Djanashvili	Technische Universiteit Delft
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“We cannot change the cards we are dealt, just how we play the hand”

Randy Pausch, The Last Lecture (18 September 2007)

To my German and Serbian family

Für meine Deutsche und Serbische Familie

Mojoj nemačkoj i srpskoj porodici

CONTENTS

Chapter 1	Introduction	1
Chapter 2	Synthesis of tetrahedral boron salts as potential catalysts	21
Chapter 3	Boron catalyzed reactions	41
Chapter 4	Aldol reactions mediated by a tetrahedral boronate	65
Chapter 5	Tetrahedral boronates as basic catalysts in the aldol reaction	87
Chapter 6	Summary	113

List of publications	121
Acknowledgements	123
Curriculum Vitae	127

Introduction

I

1.1. Preface

In 2005 the Pharmaceutical Roundtable launched a paper with the mission to integrate green chemistry and green engineering in the global pharmaceutical industry [1]. They identified OH activation for nucleophilic substitution as one of the target reactions that needs to be “greened”. These reactions would benefit enormously from innovative catalytic methods that would lower the amount of waste in these reactions. Typical synthetic procedures that have been developed over the years to transform OH-groups, and C=O as its oxidized equivalent, into a C-X bond (with X = C, O, N) are the Mitsunobu -, Wittig -, Grignard -, and Horner-Wadsworth-Emmons reactions [2, 3]. These synthetic procedures are non-atom efficient and require copious amounts of often hazardous and expensive chemical reagents.

The importance of alcohols as feedstock is expected to increase considerably the coming years. With depleting fossil feedstocks, biomass becomes an obvious source of carbon compounds. Thermal, chemical or biochemical conversion of its main components will deliver an array of biomass building blocks which in many cases will contain OH or C(O)OH functionalities [4 - 6]. Therefore direct transformation of alcohols and its derivatives into functionalized organic compounds, the subject of this thesis, will be an important synthetic route for the future production of medicines, flavor and fragrance compounds, and polymers.

This project was sponsored by CatchBio (Catalysis for Sustainable Chemicals from Biomass), a public-private partnership of several industrial and academic partners, with the common goal to develop clean and efficient processes for biomass conversion into sustainable chemicals and building blocks for the energy -, chemical-, and pharmaceutical companies. One of the three research areas is to develop sustainable methodologies for the conversion of biomass-derived platform chemicals into pharmaceuticals and fine chemicals. These platform molecules have

a high O/C ratio, and many of them possess alcoholic groups. Selective and direct activation thereof is a pivotal step in achieving sustainable routes for the synthesis of e.g. amides, esters and ethers. These two developments, the direct and sustainable activation of OH-groups, together with the growing importance of alcohols as feedstock, form the background of this thesis. They will be explained in more detail in the following sections.

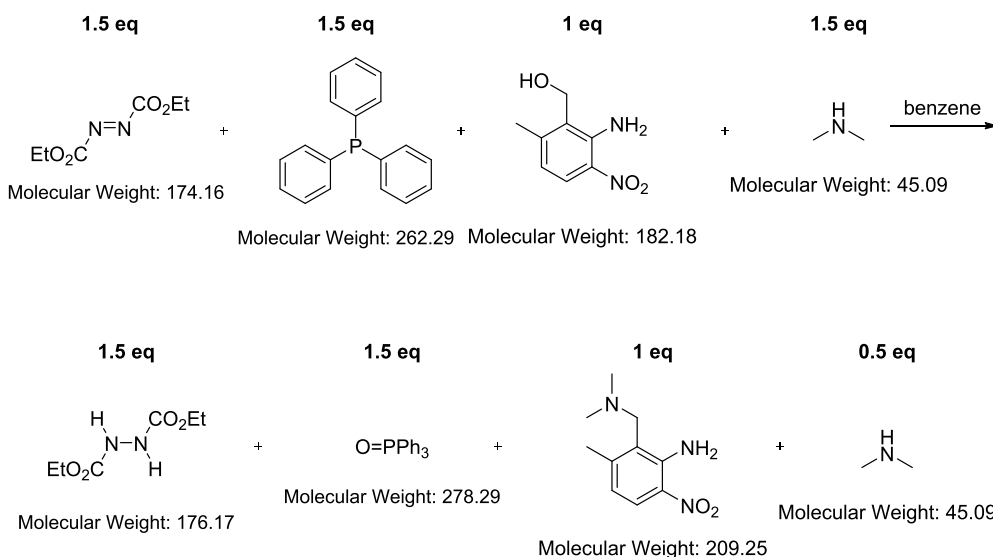
1.2. Green Chemistry

The concept of green chemistry was introduced in the 1990s to address the large environmental burden attached to chemistry. It illustrates problems such as low conversion, stoichiometric additives and waste generation [7, 8]. Following this philosophy will help to introduce economically attractive processes for industry and environmentally friendly products. To realize this target a guideline of the twelve principles of green chemistry can be applied, which were proposed by Anastas [7 – 9]:

1. It is better to **prevent waste** than to treat or clean up waste after it has been created.
2. Synthetic methods should be designed to **maximize the incorporation of all materials** used in the process into the final product.
3. Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no **toxicity** to human health and the environment.
4. Chemical **products should be designed** to preserve effectivity of function while reducing toxicity.
5. The **use of auxiliary substances** (e.g. solvents, separation agents, etc.) should be **made unnecessary** wherever possible or harmless when used.

6. **Energy requirements** of chemical processes should be recognized for their environmental and economic impacts and should be **minimized**. If possible, synthetic methods should be conducted at ambient temperature and pressure.
7. A **raw material or feedstock should be renewable** rather than depleting whenever technically and economically practicable.
8. Unnecessary **derivatisation** (use of blocking groups, protection/deprotection and temporary modification of physical / chemical processes) **should be minimized** or avoided if possible.
9. **Catalytic reagents** (as selective as possible) are superior to stoichiometric reagents.
10. Chemical products should be designed so that at the end of their function they **break down into harmless degradation products** and do not persist in the environment.
11. **Analytic methodologies** need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. Substances and the form of a substance used in a chemical process should be chosen to **minimize the potential for chemical accidents**, including releases, explosions, and fires.

If those principles are applied on reactions for the OH activation (i.e. Mitsunobu) it becomes clear that the first, second, eighth and ninth principle of the guideline, which are related to the problem of waste generation are often violated. As a concept to calculate the ratio between waste produced in a process and product formed an E(nvironmental) - factor was created by Sheldon (equation 1) [10]. Everything that is not defined as desired product is considered as waste for the calculation of the E - factor, including organic solvents. The ideal process is generating no waste but only desired product. Thus an E - factor of zero reflects the ideal process which is attractive both environmentally and economically.



Scheme 1. Nikam *et al* described a Mitsunobu reaction with a substituted benzylalcohol and dimethylamine [11].

As an example, the E - factor (Equation 1) for the Mitsunobu reaction (Scheme 1) with a yield of 86% [11] is calculated below. Silica gel and eluent for the purification were not taken into account since the purification protocol was not described. The general reaction between dimethylamine and the substituted benzylalcohol includes molar ratios as illustrated in Scheme 1.

$$E - factor = \left[\frac{\text{Amount of waste produced without water (kg)}}{\text{Amount of desired product (kg)}} \right]$$

Equation 1. Definition of the E - factor [10].

The E - factor is calculated to be:

$$[261.23\text{g (DEAD)} + 393.44\text{g (tpp)} + 67.64\text{g (amine)} + 182.18\text{g (alcohol)} + 1753\text{g (2 L benzene)}] / [1\text{ mol } 209.25\text{g (product)} * 0.86\text{ (yield)}] = \underline{10.75}$$

This E - factor clearly demonstrates the scale of waste formation during the Mitsunobu reaction; for each kg of product almost 11 kg of waste are formed, not even considering the waste which is produced during purification of the desired product.

The calculation of the E - factor includes chemical yield and auxiliary substances. Water (if not polluted during the process in question) is usually not included in the calculation because of its harmless nature [10]. Considering parameters such as energy, transportation, fuel, toxicity of waste, etc. to get a real picture of a process requires more advanced methodologies such as Life Cycle Analysis [12].

The second concept for the development of a green process is atom economy (AE, also: atom efficiency or atom utilisation) which corresponds to the second principle of green chemistry. Trost developed this method to calculate the amount of waste which will be generated in a chemical process. The advantage is that no experimental data are needed for the estimation of AE [13]. A stoichiometric equation is used for the prediction of the AE, which is defined as the molecular weight of the desired product divided by the sum of the molecular weights of all starting materials (equation 2) [13]. For the Mitsunobu reaction (Scheme 1), the AE can be calculated as follows:

$$AE [\%] = \left[\frac{\text{Molecular weight of desired product}}{\text{Sum of molecular weight of all reagents}} \right] * (100)$$

Equation 2. Definition of Atom Economy [13]

The AE is calculated to be:

$$209.25 / [174.15 + 262.29 + 182.18 + 45.09] = \underline{31.53\%}$$

This atom economy clearly demonstrates that only 32% of the starting material ends up in the final product.

A modern example of atom economy is given by BASF, which introduced ‘the Verbund principle’, also applied in several ‘Verbund sites’ [14]. Waste which is generated in the first process will be used in the second as starting material and heat which is released in one exothermic process or unit operation will be used in another, such as distillation.

In addition to BASF, other organisations have a growing interest in green chemistry. Several leading pharmaceutical companies (GlaxoSmithKline, Pfizer, Merck, Eli Lilly, Schering-Plough and AstraZeneca) and the American Chemical Society Green Chemistry Institute (ACSGCI) formed a Pharmaceutical Roundtable in 2005 (see above) [1]. As already mentioned, they identified important chemical reactions which demanded urgent improvement of reaction conditions. The Mitsunobu reaction together with OH activation for nucleophilic substitution was selected to be part of the top five fields needing improvement (Table 1).

The reason why OH-group transformations are so challenging is because of the poor-leaving ability in nucleophilic substitution reactions. This can be solved by generating a positive charge density δ^+ on the adjacent C atom (C-OH), nucleophilic substitution can take place, following the mechanism of the ‘Walden inversion’ according to S_N2 or according to a S_N1 mechanism [15]. Synthetic protocols therefore always include OH-group activation, with the concomitant production of waste which consists of auxiliary reagents and resulting products thereof [1]. A possible way to generate less waste during OH-activation is the use of catalytic and less harmful reagents.

Table 1. Priority list for chemical reactions, applied in pharmaceutical industry, where improvement of reaction conditions is urgent [1].

Priority:	Research area:
1	Amide formation avoiding poor atom economic (AE) reagents.
2	OH activation for nucleophilic substitution.
3	Reduction of amides without hydride reagents.
4	Oxidation/Epoxidation methods without the use of chlorinated solvents.
5	Safer and more environmentally friendly Mitsunobu reaction.

1.3. Chemicals from biomass

Carbon based molecules are obtained traditionally from coal, gas and oil as fossil feedstocks. Depletion of these resources, the concomitant production of CO₂ coupled to their use for energy production (leading to an ever increasing CO₂ concentration in the atmosphere being one of the main causes of global warming) and political unstable situations of countries providing fossil feedstocks are asking for new, secure and sustainable resources which are available on a global scale.

Biomass is defined as material which is derived from living or recently living organisms including animal and vegetable material [4]. Its positive environmental impact is assigned to the fact that overall a closed netto CO₂ cycle (the ratio absorbed CO₂ to emitted CO₂ is balanced) can be achieved within a relatively short timescale, several months to a few years: CO₂ is absorbed directly by plants while growing. This is in contrast to fossil feedstocks, which absorbed CO₂ billions of years ago [16].

The UK Biomass Energy Centre defined five basic categories as biomass sources [16]:

- 1) **Biomass crops** from fast growing trees, such as poplar or eucalyptus, grasses, sugar crops (beets), starch crops (wheat, corn) or algae (which can be grown in an area unsuitable for conventional crops). This category is the largest in volume, and can be upscaled and integrally processed (see below).
- 2) **Wood waste** which is obtained while processing wood in sawmills or maintaining forests, municipal parks or road verges. This can be waste from pruning (branches), sawmill offcuts, bark or sawdust.
- 3) **Agricultural residue** such as straw from grain which is normally burned or after chopping returned to the soil, corn shell, animal manure and poultry litter.
- 4) **Food waste** which is generated during production (92% of ingredients used for brewing beer or whiskey becomes waste), processing (peel, skin, shell or seeds from fruits or vegetables) or consumption (including food which has gone bad or thrown away because of surplus to requirements) [16].
- 5) **Industrial waste** obtained from the textile industry such as garment cutting waste, material obtained after filtering the processing water such as sewage sludge or the waste stream from the paper industry. During the paper production lignin is separated from cellulose ending in a liquid waste which is called black liquor.

Category 1: The growing biomass crops are a fast and well-known method to bind CO₂ and sunlight and turn it into carbon-containing molecules. Biomass in that respect can be regarded as a reservoir of valuable molecules, including sugars, polysaccharides, lignin and proteins. A lot of applications are already developed to increase the economic value of this source. Traditionally, trees are turned into timber, furniture, paper and sugar beets and starch beets are used as feedstock for living organisms [16]. However in a bio-based economy possibilities are endless.

Recent developments include the integral use of biomass (thus including biomass residues), as well as the wide variety of products that can be produced [4]. This can be facilitated by an increasing production of biomass worldwide. Expert studies show that wisely chosen biomass crops can meet the demands of a growing population [17].

Categories 2 - 5 are normally considered as waste and are commonly burned to generate energy, such as in the case of black liquor [16]. For all categories dedicated sustainable applications can be developed which potentially improve the economic value towards a so-called circular economy. Filtration and recycling of the industrial waste stream or extraction of valuable components from sugar - or starch rich food waste are common examples [16, 18].

In terms of solutions on a global scale, where alternatives for fossil feedstocks need to be developed, category 1, the fast growing biomass crops, is crucial. The US Department of Energy, in 2004, published a strategy to promote the large scale transformation of biomass components into a feedstock for valuable compounds [6].

In conclusion, biomass is an excellent and renewable source of carbons that can replace oil for the production of fuels and chemicals [19]. A successful example of such a development is known as the YXY process by Avantium [20]. In this case HMF, which can ultimately be derived from woody biomass, serves as the starting material. The novel material (plastic) was introduced to the market as a replacement for conventional polyethylene terephthalate (PET) packaging which is entirely based on the biobased material polyethylene furanoate (PEF). According to Avantium the material properties were also upgraded in comparison to traditional materials (lower permeability for oxygen therefore most likely longer shelf life of products and mechanically stronger resulting in reducing amount of packaging needed).

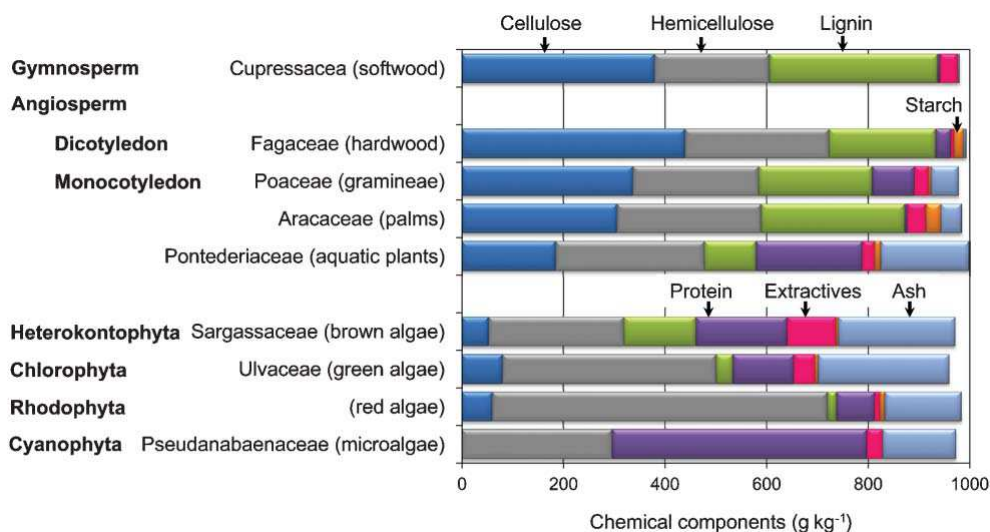


Figure 1. Rabemanolontsoa *et al* described in this Figure the composition of cellulose, hemicellulose and lignin in various fast growing biomass crops [23]. Figure copied with permission from the editor.

CatchBio is a Dutch public-private-partnership combining the interest of both research institutes and companies, to develop clean and efficient processes for biomass conversion into sustainable chemicals and building blocks for energy -, chemical -, and pharmaceutical companies. The idea is to convert the main components which are present in biomass: cellulose, hemicelluloses and lignin, from hardwood, softwood, grasses, palm trees, and algae (Figure 1) [21 - 23] into chemicals and pharmaceuticals.

1.3.1. Cellulose feedstocks and building blocks

Woody biomass typically contains cellulose (35 to 55%), and hemicelluloses (20 to 35%) with lignin as the remainder [22]. Celluloses are polysaccharides (Figure 2), containing hexose units; hemicellulose is a heteropolysaccharide containing a mixture of pentose and hexose monomers; lignin is a complex three-dimensional

polymer containing phenolic units (Figure 3) [22], 20% of the total mass of the Earth's biosphere is lignin. Currently most lignin is burned, as it occurs e.g. in the paper industry. Industrial conversion of lignin into aromatic feedstock for generating benzene, toluene and xylene (BTX) was set as possible route to replace oil as a feedstock [24]. However upgrading towards chemicals is far from straightforward, due to its complex chemical composition.

In contrast, upgrading of cellulosic streams is technologically relatively straightforward [22]. Cellulose, hemicelluloses and starch can be hydrolyzed to generate single sugar units [22]. These sugar units can be transformed into a wide range of valuable compounds (Figure 4) [6].

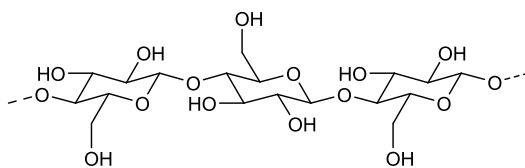


Figure 2. Composition of cellulose described in literature [22].

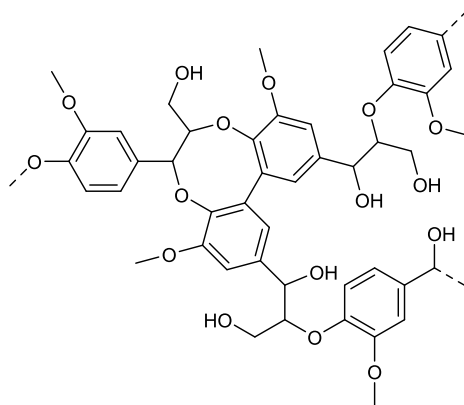


Figure 3. Schematic representation of a part of lignin described in literature [21, 22].

An overview of the chemical transformation of low molecular weight carbohydrates into products with a variety of industrial applications is given in Table 2. As can be seen from the Table, the most common application for carbohydrate derived monomers is the manufacture of polymers.

There are two main routes towards these building blocks: 1) Hydrolysis of (hemi) celluloses, followed by fermentation (Table 2, entries 1,3,4,5,6,13) and 2) Hydrolysis of cellulose and hemi-cellulose, followed by thermolytic or catalytic conversion (furanics, levulinic acid, sorbitol, xylitol).

Glycerol stems from fatty acids (from oils and fats) [6], which can be further converted by selective reduction to 1,3-propanediol. Fermentation of glucose gives access to lactic acid or ethanol [25] and oxidative degradation of starch with hydrogen peroxide [6] could provide access towards 3-hydroxybutyrolactone.

Public attention was given to furanic intermediates such as HMF or FDCA when a Dutch company (Avantium) was developing a process to replace terephthalic acid by a furanic derivative as a building block for the production of polyesters [25]. As an example the polymer cellulose can be hydrolyzed towards its monomeric C6 sugar unit (glucose) and after rearrangement (base catalyzed) fructose can be formed. Dehydration will lead to HMF, with levulinic acid and formic acid as decomposition products. To reduce decomposition, Avantium is modifying the OH group with EtOH in its process (solid catalyst at 175 – 225 °C) to stabilize HMF (formation of ethoxymethylfurfural) [25]. Oxidation with a cobalt catalyst will give access towards FDCA [25]. In the case of HMF, the OH-group is a benzylic analogon and therewith highly reactive. For generic synthetic purposes, it is even more important to convert non-activated alcoholic groups like in e.g. levulinic acid, lactic acid, ethanol, 1,3-propanediol and also sugars in general. Key reactions involved in biomass processing are dehydration - isomerization, aldol reactions, reforming, hydrogenation, and oxidation [22]. A vast amount of work

still needs to be done to develop, improve and optimize routes and catalysts for the conversion of these alcoholic platform chemicals and their derivatives.

Table 2. Suggested application of biobased platform chemicals defined by US Department of Energy and by Bozzell [6, 25]

Entry	Platform Chemical	Application of substrates or derivatives
1	1,4-acids (succinic, fumaric and malic acids)	Solvent, synthetic fibers
2	Furans: 2,5-furan dicarboxylic acid, HMF	Solvent, binder in polymers [20]
3	aspartic acid	Salt for chelating agent, sweetener
4	glucaric acid	Solvent, nylon
5	glutamic acid	Monomer for polyester (PE) and polyamides (PA)
6	itaconic acid	Copolymer
7	levulinic acid	Fuel oxygenates, solvents, copolymer
8	3-hydroxybutyrolactone	Intermediate for high value pharma compounds, solvents
9	lactic acid [25]	Polylactic acid for storage of food and dairy products
10	xylitol/arabinitol	Non nutritive sweeteners, copolymer
11	Sorbitol	PET like polymers, water soluble polymers, antifreeze agent
12	ethanol [25]	Polyethylene (from ethene)
13	3-hydroxypropionic acid	Contact lenses, Super Absorbent Polymers
14	Glycerol	Products for personal care, drugs, pharmaceuticals, foods, beverage, polyether, antifreeze agent [6], C3 plastics [20]

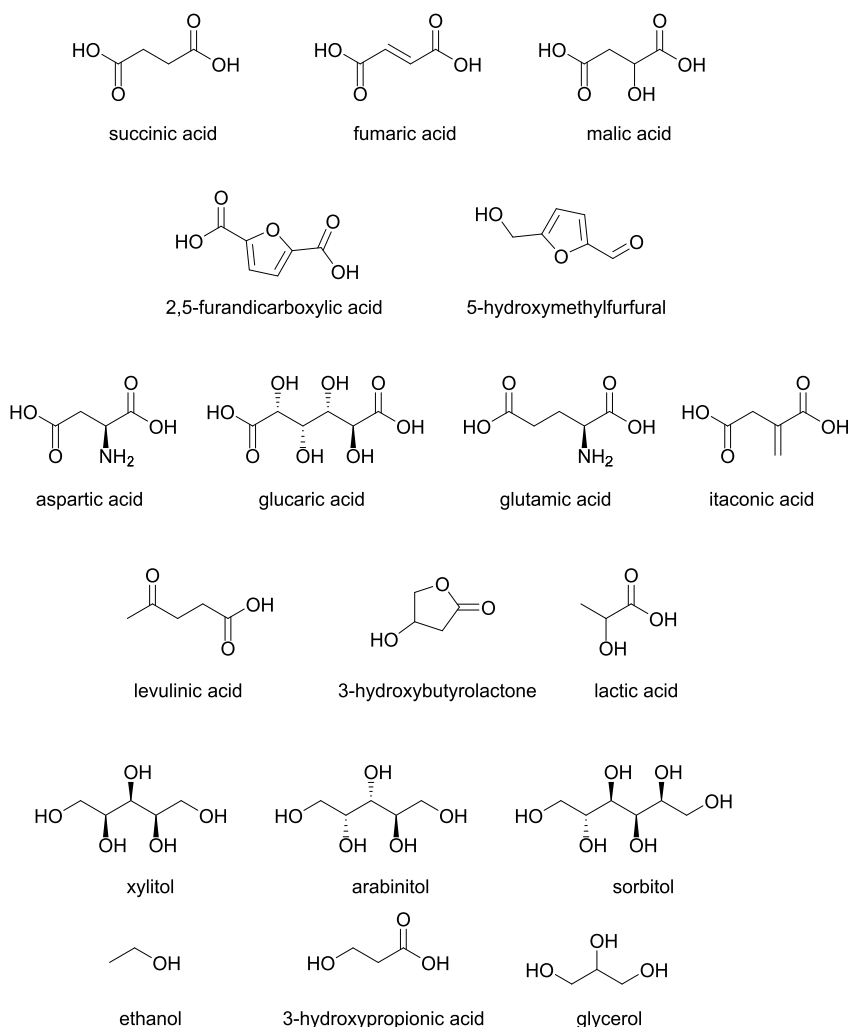


Figure 4. Biobased platform chemicals which are described in literature [6, 25].

In our research line, we selected alcohols and aldehydes as starting materials. The challenge is the conversion of alcohol into pharmaceuticals. For that nucleophilic substitution leading to C-C, C-X or C-N bonds is essential. Taking into account the guidelines of green chemistry (see above) non-toxic, sustainable and catalytic reagents need to be developed to activate alcohols in nucleophilic substitution

reactions. In this thesis boron based compounds are chosen as potential catalysts and leaving groups in nucleophilic substitution reactions for the conversion of alcohols towards the desired products, with a minimum of waste as alternative to conventional routes. Boron is a suitable element for a sustainable catalyst since it is environmentally friendly, readily available in large quantities and can be applied in organic and aqueous media, as will be described in the following Chapters.

1.4. Outline of the thesis

As already discussed earlier in this Chapter, the major goal of this project was to deliver a novel and environmentally friendly catalyst able to catalyze the direct C-X (X = C, N, O, S) bond formation from alcohols as feedstocks. The aim is to replace well-established stoichiometric processes. This thesis is subdivided into six chapters, dealing with catalyst development, modification and finally catalyst application in different C-X coupling reactions.

In this first chapter, the background of this thesis is given which illustrates clearly the need to replace the classical Mitsunobu reaction, into a less waste producing more atom efficient methodology, especially in view of the upcoming importance of alcohols as feedstocks.

An overview of the development of different boron based derivatives used in this thesis is given in chapter two. Synthetic procedures, modification strategies and characterization of those catalysts are described in detail. Solubility of the catalyst, which is an important issue in boron catalysis, is addressed as well in this chapter.

In the third chapter of this thesis several boron acids and esters were tested on their catalytic activity for the C-X [X = C, N, O] bond formation. The reactions considered were nucleophilic substitution, amide bond formation, esterification and

aldol reaction. Our approach, proposed reaction mechanism as well as conditions under which reactions were performed are described in detail in this chapter.

Chapter four deals with the application of boronate compounds as catalysts for C-C bond formation. The most promising tetrahedral phenyl boronate developed was tested in aldol reactions. β -hydroxyketones were synthesized from aromatic and aliphatic aldehydes combined with acetone. The chemoselectivity of the reaction is described. Detailed NMR and Raman spectroscopy studies were conducted to elucidate the catalytic reaction mechanism which involves formation of a boron enolate.

Chapter five focuses on the possibility to control product formation. The charge density of the catalyst was manipulated by introducing electron withdrawing groups on the aromatic ring with the aim to suppress undesired elimination reaction of the β -hydroxyketone. Furthermore, different ketones were applied in the process to discuss regio - and stereoselectivity of the reaction.

Chapter six as the final chapter of this thesis summarizes major conclusions and gives an overview and recommendations for future experiments. The most important benefits of novel catalytic processes in terms of yield, selectivity and waste reduction compared to traditional or previously reported processes are discussed. Moreover, process drawbacks are considered as well as the possibilities to overcome those that due to termination of the project are not addressed in this thesis.

1.5. References and Notes

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Synthesis of tetrahedral boron salts as potential catalysts

II

Contents of this chapter related to synthesis and characterisation of fluoro - boron compounds have been published in:

T. Mueller, K. Djanashvili, I.W.C.E. Arends, J. A. Peters, and U. Hanefeld, *Z. Naturforsch. B.* **2015**, *70*, 587 – 595.

2.1. Introduction

Boronic and borinic acids stem from readily available elements in nature [1]. They can be considered as green because their use leads to the production of boric acid, which is a non-toxic, non-corrosive, and biocompatible material [1]. This class of compounds has gained increased scientific interest by the discovery of C-C bond formations using palladium catalyzed cross coupling reactions of aryl and vinylboronic acids [2]. Esters of boronic acid are among the preferred synthetic intermediates of the boron compounds concerned, since they are mild organic Lewis acids and easy to handle [3]. In the past decade great advances have been reported in application of boronic acids and derivatives in molecular recognition, drug development and catalysis [3 - 7].

The research described in this thesis required a series of boronate esters for basic homogeneous catalytic applications. During the initial stages it appeared that the tetrahedral boronic esters are catalytically active in aldol reactions, whereas the corresponding trigonal boronic esters show no activity, since they do not coordinate to the substrates [8]. In literature it has been reported that boronate esters can be accessed from trigonal boronic acid esters and organolithium reagents [9]. However, low thermal stability and low solubility in organic solvents hampers the application of these salts.

This chapter mainly deals with the synthetic strategies used to obtain stable and soluble tetrahedral boronate esters with potential catalytic applications in homogeneous catalysis. The results of an investigation of the effects of substituents on solubility, stability, and pK_a s are described in detail.

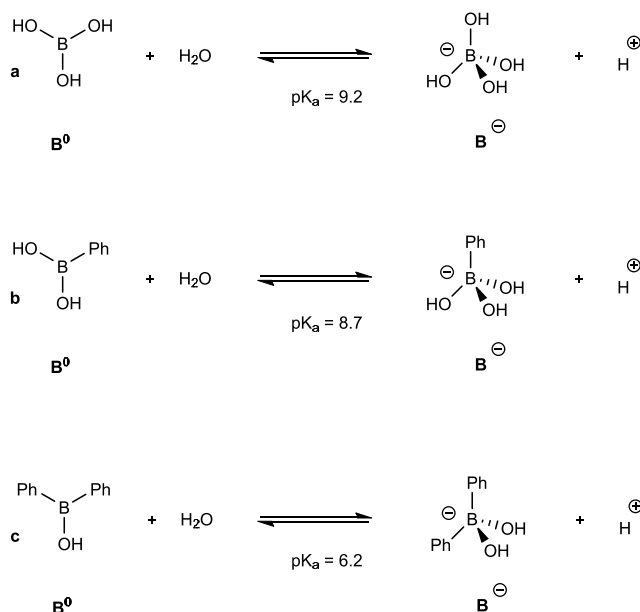
2.1.2. Equilibrium between trigonal and tetrahedral boron esters

Boric acid and its derivatives are sp^2 hybridized [10 - 14]. The trigonal form can

react with water to tetrahedral borate and a proton (Scheme 1) [4]. This equilibrium between the sp^2 and sp^3 hybridized form can be manipulated by changing the pH of the solution. An increase of the pH will result in an increase of the tetrahedral complex [13 - 15]. The equilibrium between the trigonal and the tetrahedral boron structure is described by the pK_a . This value of the acid in water is determined to a large extent by the charge density on the B-atom. For example, the pK_a values of boric acid (**a**) phenylboronic acid (**b**, R = Ph) and diphenylborinic acid (**c**, R = Ph) are 9.2 (Table 1, entry 1), 8.7 (Table 1, entry 3) and 6.2, respectively at 25 °C [4, 16 - 18]. The sp^2 hybridised B-atoms of phenyl boronic and diphenyl borinic acids (Scheme 1, B^0) are electron deficient and therefore electron withdrawing [4]. The electron withdrawing effect is decreased on the sp^3 B-atoms of the corresponding basic form (B^-) [14]. Decrease of the electron density on the B-atom can be achieved by attaching electron withdrawing substituents to the B-atom as is reflected in a decrease of the pK_a [4]. In contrast electron donating substituents increase the pK_a [19, 20].

This phenomenon is confirmed by the Hammett plot of experimentally obtained pK_a values of meta - or para - substituted phenylboronic acids versus the σ -values, which has a positive slope with $\rho = 2.1$ [19]. The ρ value from the Hammett plot can be used to predict the pK_a values of new meta- or para - substituted phenyl boronic acids [19].

Examples of effects of the charge density on the B-atom of a boronate salt (as reflected in the pK_a) on selectivity of an aldol condensation to a β -hydroxyketone are described in chapter 5. By manipulation of the charge density of a boronate salt in the aldol reaction, selectivity towards the desired β -hydroxyketone was controlled. This effect was mainly due to suppression of undesired subsequent elimination reaction of the β -hydroxyketone. The highest selectivity towards the aldol product was obtained with fluoro-substituted Ph-boronic acids with a $pK_a > 7$.



Scheme 1. Equilibrium of boric (a), boronic (b) and borinic acid (c) in trigonal B^0 and tetrahedral form B^- as described in the literature by J. A. Peters [4].

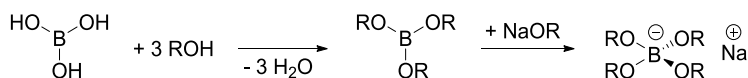
2.2. Results and Discussion

2.2.1. Synthesis of boronate esters

Several methods were described to access trigonal and tetrahedral boron esters [9, 21 - 26]. We have applied an efficient route to obtain the ‘ate’ complex in two steps

(Scheme 2). In the first step, the boronic acid was esterified with an alcohol in a

Dean-Stark apparatus. During the course of esterification, molecular sieve was present in the reaction mixture to remove water and shift the equilibrium towards the desired ester. Subsequently, the ‘ate’ complex was obtained by addition of an equimolar amount of sodium alkoxylate to the reaction mixture containing the corresponding trigonal ester (Scheme 2). Sodium alkoxylates (isopropoxide or 2-pentoxide) were generated *in situ*. After evaporation of the solvent, the pure



Scheme 2. General reaction scheme applied for the synthesis of tetrahedral boron salts.

boronate salt was obtained in high yield, which could be used without further purification (Table 1, entries 7 – 12).

Boronic acid esters can be applied as a catalyst (for example for the amidation reaction) [27], promotor (for the enantioselective generation of cyclopropanes) [28] or templating agent (in the synthesis of Taxol) [29]. A successful application of tetrahedral boronate esters is reported in affinity chromatography (with diols, ribose, to separate RNA from DNA) [3, 30]. Tetrahedral boron structures, with primary catalytic applications, are responsible for improved selectivity in boron promoted processes. Therefore, the interest to develop these salts is growing in recent years [5, 8 and 21]. However, for certain alkyl borates and boronates solubility and stability problems have been described [9].

In order to optimize those two key properties (solubility and stability) several boronate salts were synthesized and characterized (Table 1). Functional groups were introduced with the aim to increase solubility of tetrahedral boronate salts. Electron withdrawing groups, chlorine or fluorine, were introduced either on the isopropoxy side chain or on the aromatic ring in order to decrease electron density on boron and dislocate the negative charge (making it less polar for better solubility in organic solvents) and at the same time stabilize the negative charge on boron.

2.2.2. Stability of boron esters

While triisopropoxyboric ester **1a** was commercially available, the tris-2-pentoxyboric ester **2a** (Figure 3) was obtained by esterification of boric acid with 2-pentanol. The aromatic esters **3a** – **12a** (Figure 3) were also obtained by

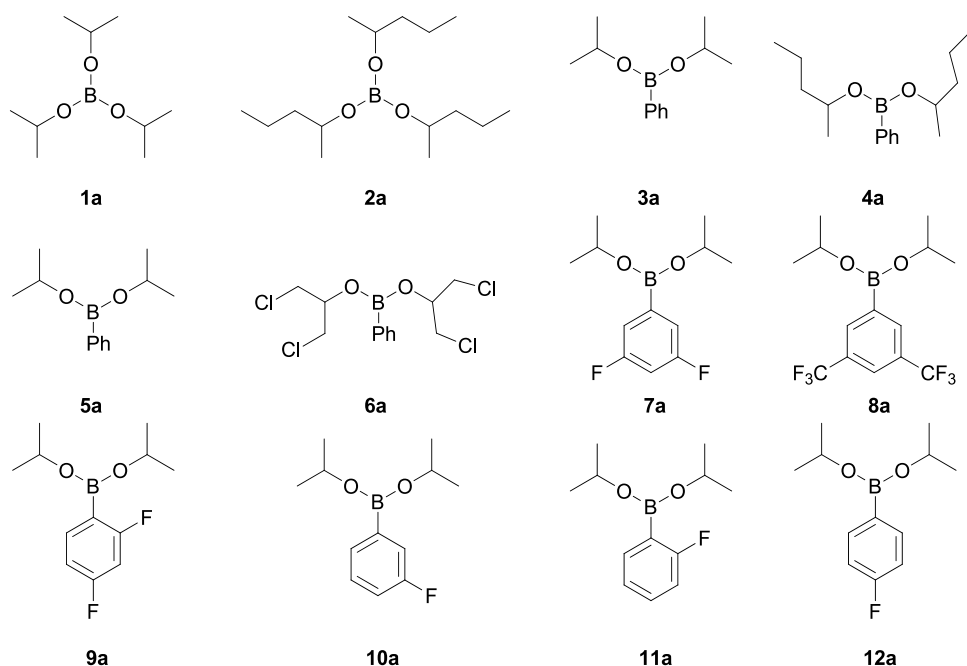


Figure 3. Target molecules for the synthesis of trigonal ester.

esterification with the corresponding alcohol. Purification of the trigonal boroncomplex **1a** - **12a** was performed by distillation (Table 1, entries 1-12). The esters showed a significant thermal stability, distillation between 45 and 140 °C and atmospheric pressure to reduced pressure could be applied (Table 1). However, synthesis of the corresponding tetrahedral esters **1** and **2** (Figure 4) failed due to thermal instability of the ‘ate’ complexes (Table 1, entries 1 and 2).

A similar observation was described for lithium salts by Brown *et al.* who investigated the thermal stability of tetrahedral boric -, boronic - and borinic esters [9]. Tetrahedral boron salts, i.e. lithium tetrakisopropoxyborate, had a low thermal stability and decomposed already at room temperature (RT). It was observed that the most stable esters contained one boron-carbon bond in the structure, i.e. boronic ester derivatives. For example, lithium methyl or phenyl triisopropoxy boronates

were thermally stable until 120 °C. The decomposition product was the corresponding trigonal boronic ester. This is in agreement with the thermal stability which was observed for the tetrahedral phenylboron esters (Table 1).

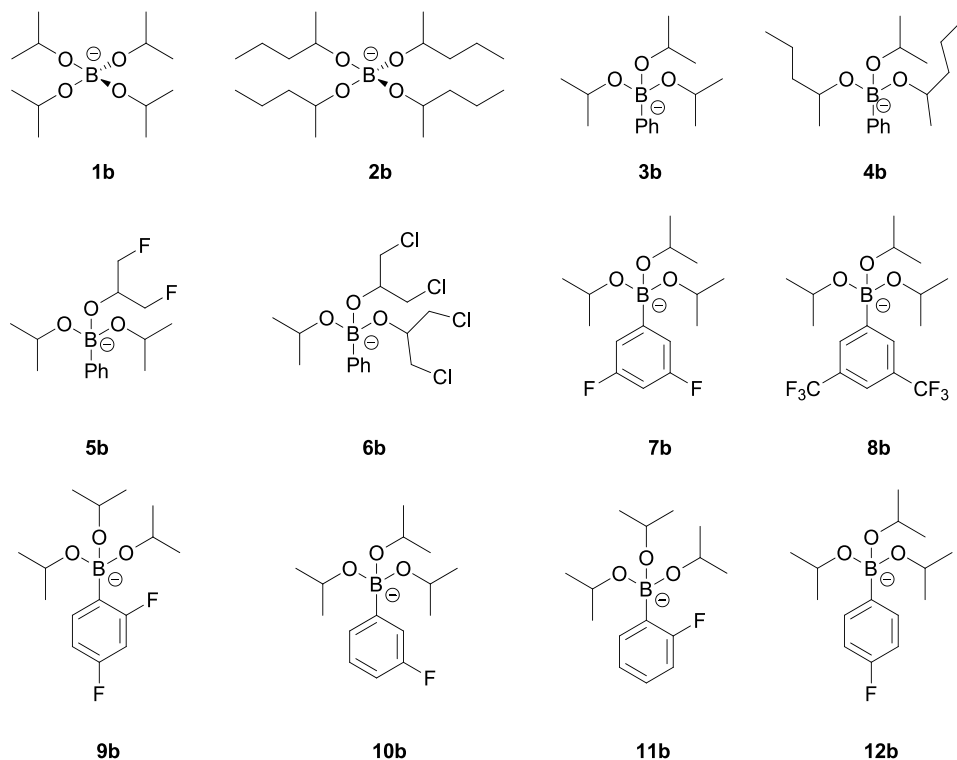


Figure 4. Target molecules for the synthesis of tetrahedral sodium 'ate' complexes.

Table 1. Properties of trigonal (a = sp²) and tetrahedral (b = sp³) esters.

Ester (a/b)	pK _a of B- acid ^f	Bp [°C/mbar]	Stable at least up to	Soluble in:		Yield ^a [%]		Ref.
				sp ² (a)	sp ³ (b)	sp ² (a)	sp ³ (b)	
1	9.2	140/atm [33]	--	Org. solvents ^b	--	--	--	[9] ^{c,d}
2	9.2	47/1.4×10 ⁻¹	--	Org. Solvents	No ^c DMF, DMSO, THF, CH ₃ CN	76	--	--
3	8.7	54/3×10 ⁻²	--	Org. solvents	No CHCl ₃	57	--	[9] ^c
4	8.7	78/2×10 ⁻²	--	Org. solvents	No CHCl ₃	50	--	--
5 (3)	8.7	54/3×10 ⁻²	--	Org. solvents	No CHCl ₃	57	--	--
6	8.7	stable at RT/atm p	--	Org. solvents	No DMF, DMSO, THF, CH ₃ CN, CHCl ₃	62	--	--
7	7.1	50/6.5×10 ⁻²	30 °C	Org. solvents	Org. solvents	56	98	[8]
8	6.6	54/6.8×10 ⁻²	30 °C	Org. solvents	Org. solvents	59	97	[21]
9	7.1	54/5.9×10 ⁻²	30 °C	Org. solvents	Org. solvents	44	96	[21]
10	7.5	63/1.2×10 ⁻¹	30 °C	Org. solvents	Org. solvents	46	99	[21]
11	7.8	45/4.3×10 ⁻²	30 °C	Org. solvents	Org. solvents	44	96	[21]
12	8.6	56/7×10 ⁻²	30 °C	Org. solvents	Org. solvents	44	98	[21]

^aIsolated yield [%] of the corresponding trigonal (sp²) and tetrahedral (sp³) esters; ^bOrg.

solvents = CHCl_3 , alcohols (IPA, 2-pentanol), and toluene; ^conly the trigonal form is characterized in literature not the sodium salt; ^dpurchased from Sigma-Aldrich; ^eNo = not soluble in given solvents; ^f $\text{p}K_a$ values of the boron acid described in literature [19, 20].

2.2.3. Solubility of boron esters

The solubility of trigonal and tetrahedral boron esters was evaluated in solvents with different polarities. The interactions between solvent and compound involve dipole forces and hydrogen bonding. In the ‘handbook of organic solvent properties’ polarity is defined as: ‘Polarity is a widely discussed and quoted property of a solvent but it is used loosely to cover a number of different effects, including those covered by dielectric constant and dipole’ [31]. C. Reichardt determined polarity with a normalized empirical parameter E_T^N . E_T^N is based on the transition energy for the longest wavelength solvatochromic absorption band of a pyridinium *N*-phenolate betaine dye (molecule 36 and 37, Figure 5) which was measured at 25 °C and 1 bar. The scale ranges from TMS, the least polar molecule with a value of 0 to water the most polar molecule with a value of 1 [32]. Polarity

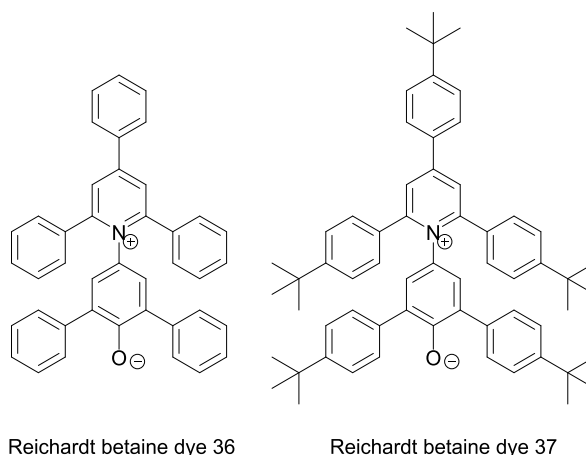


Figure 5. The betaine dyes were used to determine polarity of solvents [32].

values of organic solvents tested, are described in literature and given in Table 2 [32, 34].

All the trigonal esters **1a** - **12a** (Figure 3) were soluble in organic solvents (Table 1). This can be explained by a low electron charge density in the molecule, which made the boron ester less polar, contributing to a good compound - solvent interaction. In contrast, tetrahedral esters **1b** - **6b** (Figure 4) with high electron charge density in the molecule displayed no solubility in organic solvents with lower polarity values, such as THF ($E_T^N = 0.209$) or DMF ($E_T^N = 0.386$, Table 2). An increase of polarity of the solvent to DMSO ($E_T^N = 0.444$) or acetonitrile ($E_T^N = 0.460$) was not sufficient to solubilise the boronate salt (Table 1, entries 1 - 6), due to stability problems or since limited ester - solvent interactions took place. Thus functional groups were introduced in order to address the solubility problem, which as mentioned in the introduction, is crucial for homogeneous catalytic applications.

The prerequisite for homogeneous systems is the solubility of the catalyst in the reaction mixture (solvent). In contrast, if the catalyst is not soluble, the reaction might be facing limitations of typical heterogeneous systems associated with poor mixing and transfer limitations in case of bad solubility.

The best results were obtained by attachment of electron withdrawing groups to the aromatic ring. The location of the substituents, ortho-, meta-, para-, and disubstitution on the aromatic ring has no significant effect on the solubility of boron esters **7b** - **12b** (Figure 4) in organic media. The good solubility of **7b** - **12b** can be explained by decrease of electron density on boron (delocalisation of the negative charge) (Table 1, entries 7 - 12), which improves the intermolecular interaction between ester and solvent. As a result, the tetrahedral boronate salts (**7b** - **12b**) could be synthesized in an excellent yield of at least 96 % (Table 1, entries 7 - 12) which allowed the application of this tetrahedral boronesters as homogeneous catalysts for the aldol reaction [8, 21].

Table 2. Polarity index of solvents. [32, 34]

Solvent	Toluene	THF	CHCl ₃	Acetone	DMF	DMSO	CH ₃ CN	IPA	Water
E_T^N	0.099	0.207	0.259	0.355	0.386	0.444	0.460	0.546	1.000

2.3. Conclusion

An efficient route was described to synthesize tetrahedral sodium boronate salts with good stability and solubility in organic solvents. The equilibrium between trigonal and tetrahedral form in solution is affected by the pH of a solution and dependent on the pK_a value of the boronic ester. The pK_a value can be manipulated by decreasing electron density on the B-atom by addition of electron withdrawing substituents on the phenyl group, which results in a decrease of the pK_a of the substituted acid.

The water removal from the reaction mixture was critical in the synthesis of trigonal boronic compounds. This was achieved by applying a Dean-Stark apparatus and molecular sieves. The corresponding ‘ate’ complex was obtained by reaction of trigonal ester with sodium alkoxylate. The presence of a carbon - boron bond proved to be crucial for the thermal stability of the ‘ate’ complex. Some of the obtained tetrahedral boron esters did show poor solubility in organic media (IPA, toluene, chloroform). The introduction of electron withdrawing groups on the aromatic ring improved their solubility by decreasing the electron density at the B-atom while at the same time stabilizing the negative charge of the boron salt. This led us to conclude that the properties of tetrahedral sodium boronate salts can be tuned to achieve good solubility as well as stability.

2.4. Experimental

2.4.1. Materials and methods

^1H -NMR, ^{13}C -NMR and ^{11}B -NMR spectra were recorded at 400, 100, and 128 MHz respectively with Bruker Avance 400. As reference for the ^{11}B -NMR measurements a 0.1 M boric acid solution in D_2O was used. All other shifts for ^1H and ^{13}C spectra were referenced to the residual solvent peak and are reported in ppm. 2-pentanol (Aldrich), 2-propanol (Aldrich), boric acid (Acros) and the other phenylboronic acids were used without further purification.

2.4.2. Synthesized boron compounds

The trigonal ester **1a** and **3a** is described in literature [9]. Compound **1a** was provided by Sigma-Aldrich. The boronate salts **7b** – **12b** are described in chapter 5 [8, 21]. NMR data are in correspondence with literature. Synthesis and characterisation of the other sodium salts is described below.

Sodium tetra-isopropoxyborate (1b).

The reaction was carried out in a nitrogen atmosphere. 230 mg (10 mmol) sodium was dissolved in 10 mL dry 2-propanol. After stirring for 0.5 h at RT the reaction mixture was heated to 60 °C in an oil bath for 2.5 h. Afterwards 2.1 g (11 mmol) triisopropyl borate was added and the reaction was stirred for 1 h under reflux. Solvent was removed. 2.4 g of a white powder was obtained. Characterisation by NMR failed due to solubility problems of the product.

Tripentan-2-ol boric acid ester (2a).

15.84 g (180 mmol) 2-pentanol and 3.6 g (60 mmol) boric acid were dissolved in 60 mL toluene. The reaction mixture was stirred for 16 h under reflux. Then, the reaction mixture was filtered, solvent was removed and boric ester was distilled. A

clear liquid was obtained (12.4 g yield: 76 %, bp: 47 °C/ 1.4×10^{-1} mbar).

^1H NMR (400 MHz, CDCl_3): δ = 0.91 (t, 9H, CH_3); 1.1 (d, 9H, CH_3); 1.34 – 1.52 (m, 12H, $6 \times \text{CH}_2$); 4.21 (m, 3H, CHOH). ^{11}B NMR (128 MHz, CDCl_3): δ = -4.28. ^{13}C NMR (100 MHz, CDCl_3): δ = 13.7; 18.9; 23.1; 40.8; 67.7.

Sodium tetra-2-pentoxyborate (2b).

The reaction was carried out in a nitrogen atmosphere. 1g (43.5 mmol) Na and 3.84 g (43.5 mmol) 2-pentanol were dissolved in 140 mL THF. The reaction mixture was stirred for 5 h under reflux. 11.84 g (43.5 mmol) tripentan-2-ol borate was dissolved in 40 mL THF and added dropwise to the reaction mixture. The reaction mixture was stirred for 20 h under reflux. Reaction mixture was filtered. The filtrate was washed with (3×40 mL) n-pentane, (3×40 mL) diethyl ether and dried under vacuum (1 mbar). 5.7 g of a yellowish powder was obtained. Characterisation by NMR failed due to solubility problems of the product.

Diisopropyl phenylboronic ester (3a).

a) 2.4 g (20 mmol) phenyl boronic acid and 4.8 g (6 mL; 80 mmol) 2-propanol were dissolved in 6 mL toluene. A Dean-Stark trap was filled with 9 mL 2-propanol and 9 mL toluene was attached to the reaction flask. The reaction mixture was stirred for 20 h under reflux. The solvent was removed and then the residue was distilled (3×10^{-2} mbar, 54 °C). 2 g (9.6 mmol) of **3a** as a colourless liquid was obtained (yield: 48 %).

b) 4.8 g (40 mmol) phenyl boronic acid and 12 g (15 mL; 200 mmol) 2-propanol were dissolved in 15 mL toluene. The Dean-Stark trap was filled with molecular sieve (4Å), 9 mL 2-propanol and 9 mL toluene. The reaction mixture was stirred for 20 h under reflux. The solvent was removed and the residue was distilled (3×10^{-2} mbar, 54 °C). 4.72 g (22.9 mmol) of **3a** as a colourless liquid was obtained (yield:

57 %).

^1H NMR (CDCl_3 , 400 MHz): δ = 1.25 (d, 12H, $4\times\text{CH}_3$); 4.61 (m, 2H, CHOB) 7.34 – 7.79 (m, 5H, CH). ^{11}B NMR (120 MHz, CDCl_3): δ = 6.24. ^{13}C NMR (CDCl_3 , 100 MHz): δ = 24.9; 66.3; 127.8; 129.3; 132.9.

Sodium triisopropoxyphenylboronate (3b).

The reaction was carried out in a nitrogen atmosphere. 173 mg (7.5 mmol) sodium was oxidized with 450 mg (7.5 mmol) 2-propanol in 30 mL THF. The reaction mixture was stirred under reflux for 3 h. Then, 1.55 g (7.5 mmol) diisopropyl phenylboronate dissolved in 10 mL THF was added dropwise to the reaction mixture. The reaction mixture was stirred under reflux for another 43 h. The solvent was removed to give 1.65 g of a yellowish powder. 200 mg of the yellowish powder was washed with 10 ml acetonitrile. A white powder was obtained. Characterisation by NMR failed due to solubility problems.

Dipentan-2-yl phenylboronic ester (4a).

3.05 g (25 mmol) phenyl boronic acid and 4.41 g (50 mmol) 2-pentanol were dissolved in 50 mL toluene. The reaction mixture was heated under reflux for 18 h. The product was distilled (bp: 78 °C/ 2×10^{-2} mbar) to give 3.3 g (12.6 mmol) of a clear liquid (yield 50.3 %).

^1H NMR (CDCl_3 , 400 MHz): δ = 0.92 (t, 6H, $2\times\text{CH}_3$); 1.22 (d, 6H, $2\times\text{CH}_3$); 1.23 – 1.64 (m, 8H, $4\times\text{CH}_2$); 4.47 (m, 2H, CHOB) 7.35 – 8.27 (m, 5H, CH). ^{11}B NMR (120 MHz, CDCl_3): δ = 6.18. ^{13}C NMR (CDCl_3 , 100 MHz): δ = 14.2; 19.0; 23.1; 40.9; 69.5; 127.8; 129.2; 132.9.

Sodium isopropoxybis(pentan-2-yloxy)(phenyl)boronate (4b).

The reaction was carried out in a nitrogen atmosphere. 230 mg (10 mmol) sodium and 600 mg (10 mmol) 2-propanol were dissolved in 35 mL THF. After stirring for

30 min. at RT the reaction mixture was stirred for 3 h under reflux. 2.62 g (10 mmol) dipentan-2-yl phenylboronate was dissolved in 10 mL THF and added dropwise to the reaction mixture. After the reaction mixture was stirred under reflux for another 16 h, the solvent was removed. The yellowish oil obtained was washed with 160 mL n-pentane. N-pentane was removed to give 1 g of a yellowish powder (yield 8.1 %). Characterisation by NMR failed due to solubility problems.

Sodium (1,3-difluoro-2-propanyl) diisopropoxy(phenyl)boronate (5b).

The reaction was carried out in a nitrogen atmosphere. 460 mg (20 mmol) sodium was oxidized with 1.92 g (20 mmol) 1,3-difluoro-2-propanol in 60 mL THF. The mixture was stirred for 10 min. at RT in a waterbath and afterwards for 2 h under reflux. Then, 4.12 g (20 mmol) diisopropyl phenylboronate dissolved in 20 mL THF and added dropwise to the reaction mixture. The mixture was stirred under reflux for another 116 h. After cooling, the precipitate was filtered off to give 460 mg (yield 7 %) of a white powder was obtained. Characterisation by NMR failed due to solubility problems.

Bis(1,3-dichloro-2-propanyl) phenylboronic ester (6a).

2.44 g (20 mmol) phenyl boronic acid and 5.2 g (40 mmol) 1,3-dichloro-2-propanol were dissolved in 10 mL toluene. The reaction mixture was stirred for 18.5 h under reflux. After that, toluene and alcohol was distilled off. The remaining yellowish oil was dissolved in heptane and filtered. After removal of heptane, 4 g (yield: 62 %) of a yellowish oil was obtained.

^1H NMR (400 MHz, CDCl_3): δ = 3.69 – 3.78 (m, 8H, $4 \times \text{CH}_2\text{Cl}$); 4.80 – 4.83 (m, 2H, $2 \times \text{CHOB}$); 7.34 – 7.78 (m, 5H, CH). ^{11}B NMR (120 MHz, CDCl_3): δ = 6.81.

^{13}C NMR (100 MHz, CDCl_3): δ = 45.9; 73.0; 128.3; 130.6; 133.4.

Sodium bis(1,3-dichloropropanyl-2-oxy)(isopropoxy)(phenyl)boronate (6b).

The reaction was carried out in a nitrogen atmosphere. 230 mg (10 mmol) sodium was oxidized with 600 mg (10 mmol) 2-propanol in 35 mL THF. After stirring for 22 h under reflux, 3.4 g (10 mmol) bis(1,3-dichloro-2-propanyl)phenylboronate was dissolved in 10 mL THF and added dropwise to the reaction mixture. The mixture was stirred under reflux for 95 h and filtered. 430 mg of a white powder was obtained which was not soluble in acetonitril, acetone, DMF, DMSO, THF or CDCl_3 . Characterisation by NMR failed due to solubility problems.

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2.6. Appendix: Set-up for the synthesis of the boron ester via a Dean Stark apparatus.



Boron catalyzed reactions

III

3.1. Introduction

Tetrahedral boron esters are weak Lewis bases with a non nucleophilic Brønsted base character and the ligands on the central boron atom can be replaced easily. Those properties make the ester attractive for catalytic applications. In theory, a boron ester can be used for the activation of an alcohol and transform it into a better leaving group due to the stronger B-O bond (oxophilic character) compared to a C-O bond. This chapter deals with an attempt to apply boronic esters as a catalyst for nucleophilic substitution reactions in a sustainable manner.

In addition to nucleophilic substitution, esterification, amide formation and aldol reactions were performed with different substrates. It is expected that the boron catalyst is interacting with the substrate (coordination on aldehyde or bi-coordination on α -hydroxy acid, templating effect), providing new solutions for safer and more environmentally friendly processes. Those processes were identified by ACSGCI and several pharmaceutical companies as crucial, as already mentioned in the first chapter. The results achieved applying a boron catalyst for those processes are described below.

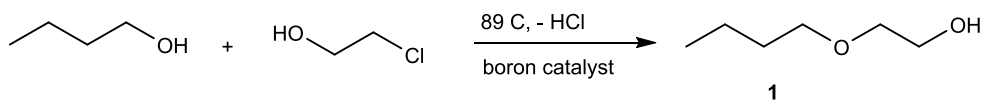
3.2. Nucleophilic substitution of primary and secondary alcohols

Activation of the hydroxy group in primary and secondary alcohols can be done by the Mitsunobu reaction to transform R-OH into a better leaving group. Problems related to AE, E-factor and the 12 principles of green chemistry are described in chapter 1. Therefore, a sustainable and catalytic approach is of great interest.

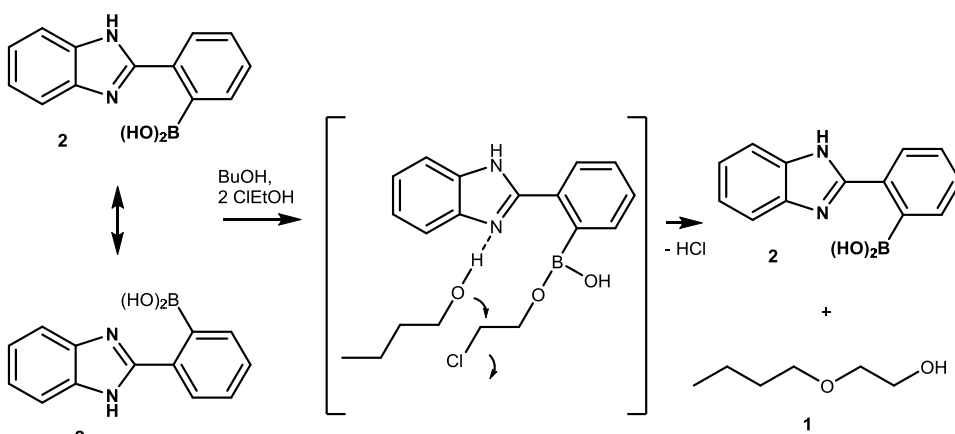
Letsinger et. al. reported a boron promoted nucleophilic substitution, avoiding DEAD/TPP for the activation [1 - 3]. Full conversion of butanol with chloroethanol delivered the desired product (Scheme 1).

Hall suggested that boronic acid **2** is forming a hemiester with 2 - chloroethanol

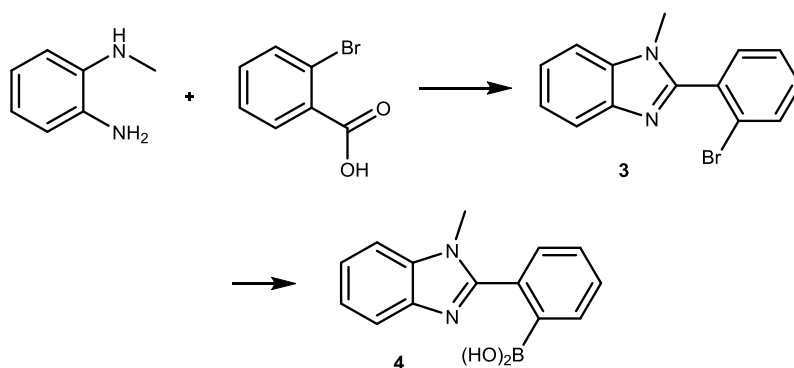
(Scheme 2) while *n*-butanol was coordinating temporarily to one of the two nitrogens to assist chloride substitution (free rotation of the phenyl boronic acid) [4].



Scheme 1. The nucleophilic substitution reaction (S_N2) of *n*-butanol and 2-chloroethanol was catalysed by 2-(2-boronophenyl)benzimidazole (2) [1 - 3].



Scheme 2. Mechanism of the nucleophilic substitution reaction as suggested by Hall [4].

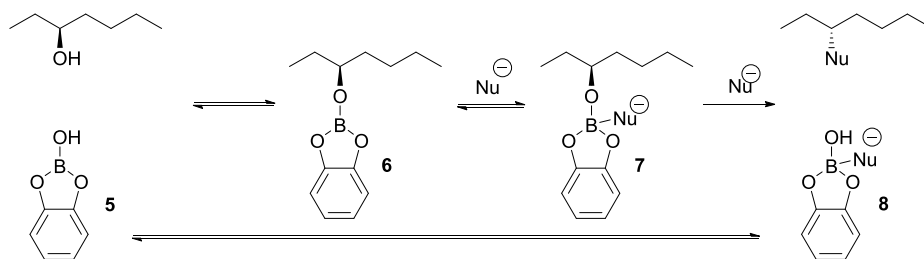


Scheme 3. Two step synthesis for *N*-Methyl-2-(2-boronophenyl)benzimidazole (4) [6].

However, the catalyst, 2-(2-boronophenyl)benzimidazole, was synthesized under harsh reaction conditions (BCl_3 and 300 - 325 °C) [5]. To avoid the addition of a toxic and corrosive gas (BCl_3) and high temperature during the catalyst preparation, our approach was to synthesize *N*-Methyl-2-(2-boronophenyl)-benzimidazole (**4**) according to a milder and greener procedure, which was already described (Scheme 3). By applying **4** as a catalyst, only 2.5 % of 2-butoxy-ethanol was formed. A possible explanation for the disappointing low catalytic activity is that the methyl group on nitrogen is hindering a second nitrogen-boron interaction.

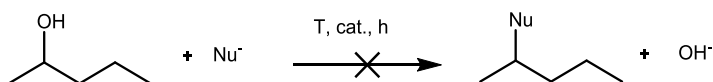
The low yield (2.5%) which was obtained with **4** led us to investigate sterically less hindered catechol boronates **8**, **9**, and **10** as OH activator in nucleophilic substitution reactions with 2-pentanol as model substrate (see Scheme 5).

Several factors are influencing the reaction rate of a nucleophilic substitution reaction: (i) the nucleophilicity of the starting material. A selection of nucleophiles of different strengths was made based on their reported reaction rates in reactions with methyl iodide in DMF and MeOH (see Table 3.1). (ii) It may be expected that the $\text{S}_{\text{N}}2$ mechanism for the nucleophilic substitutions with 2-pentanol is dominating. In this mechanism, some charge separation occurs during the rate determining formation of the transition state. Consequently, solvation may



Scheme 4. Possible activation of the OH function on a chiral alcohol in $\text{S}_{\text{N}}2$ substitution reactions by boronate **8** [9].

influence the reaction rate. Therefore polar DMF and water were selected as solvent with aprotic and protic character, respectively.



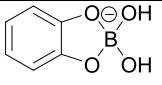
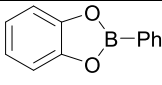
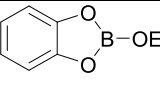
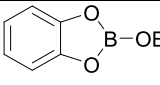
Scheme 5. Proposed reaction scheme for the nucleophilic substitution of 2-pentanol.

Catalyst **8** (tested in aqueous media) was generated *in situ* at pH 11. In contrast to water, in organic media the boron catalyst could not be generated *in situ*. Therefore

Table 1. Reaction rate conditions for different nucleophiles on the S_N2 reaction with methyl iodide. Values are given in $k/(l \times mol^{-1} \times s^{-1})$ [10]

Nu ⁻ / Solvent	CN ⁻	AcO ⁻	N ₃ ⁻	F ⁻	Cl ⁻	I ⁻	SCN ⁻
DMF	30	2.0	0.31	0.1	0.24	--	6.9×10^{-3}
MeOH	3.3×10^{-5}	4.5×10^{-8}	3×10^{-6}	6.3×10^{-8}	1×10^{-7}	1.6×10^{-4}	3×10^{-5}

Table 2. Reaction conditions for the nucleophilic substitution on 2-pentanol. Several boron esters were combined with different nucleophiles.

Solvent	D ₂ O, pH 11	DMSO-d ₆	DMF-d ₇	CD ₃ CN
Nu ⁻	N ₃ ⁻ , CN ⁻ , I ⁻ , SCN ⁻	CH ₃ COO ⁻ , N ₃ ⁻ , CN ⁻ , F ⁻	CH ₃ COO ⁻ , N ₃ ⁻ , CN ⁻ , Cl ⁻	CH ₃ COO ⁻ , N ₃ ⁻ , CN ⁻ , Cl ⁻
Catalyst	 8	 9	 10	 10
T [°C]	RT/50*	60	60	60
time [h]	50/50*	50	50	50

*The reaction was stirred for 50 h at RT, heated to 50 °C and stirred for additional 50 h.

boronester **9** and **10** were synthesized by removing water with a Dean Stark [11]. They were tested in the substitution reaction (Scheme 5, Table 2).

Unfortunately, according to GC and NMR measurements, nucleophilic substitution was not observed with the tested nucleophiles in water at pH 11. This possibly is explained by competition of the nucleophile with OH⁻ present in large amounts in aqueous solution at pH 11. NMR studies also revealed stability problems with the boron ester **9** in organic solvents. The catalyst was cleaved to catechol and phenylboronic acid. In order to overcome this problem, a new boronate salt (Figure 1) was developed, showing good stability and solubility in organic solvents (synthesis described in chapter 2).

Sodium triisopropoxy-(3,5-difluorophenyl)-boronate (**11**) was tested in nucleophilic substitution experiments with isopropanol and also isopulegol, a natural substrate (Scheme 6). The nucleophilicity of the CN⁻ anion was increased by using tetrabutylammonium cyanide as an anion source. Again, no conversion of the alcohol was observed according to GC MS. Most likely the boron catalyst was not activating the alcohol sufficiently for nucleophilic substitution.

The S_N2 substitution of secondary alcohols (2-pentanol, 2-propanol, isopulegol) failed despite the wide range of nucleophiles and solvents (water and organic media) applied. Solvents of different polarity were chosen to ensure proper solvation energy for the nucleophile when combined with boron catalyst **8**, **9**, **10** and **11**.

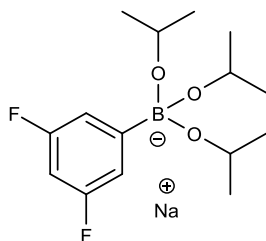
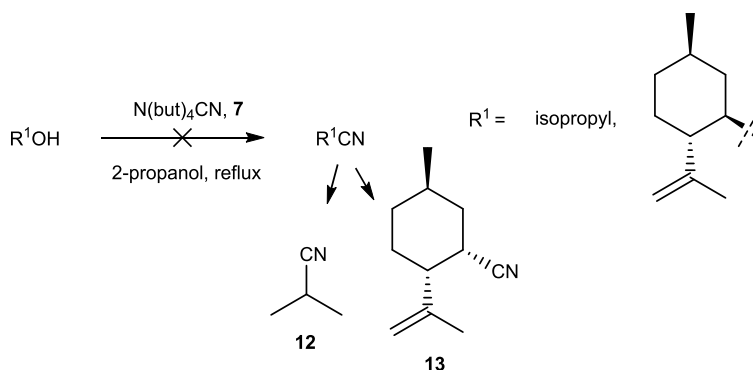


Figure 1. Structure of sodium triisopropoxy-(3,5-difluorophenyl)boronate (**11**).

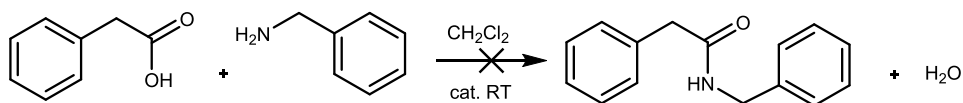


Scheme 6. Proposed scheme for the nucleophilic substitution of isopropanol or isopulegol, catalysed by boronate salt **11**.

3.3. The boron catalyzed amide formation

Amide formation from a carboxylic acid and an amine (nucleophile) is a common tool in synthetic chemistry, particularly in peptide synthesis. The influence of solvent and strength of the nucleophile is less important compared to the nucleophilic substitution reaction. The crucial step is activation of the carboxylic acid group. Activation can be achieved *in situ* with thionylchloride (SOCl_2) to form an acid chloride (Schotten Baumann reaction) followed by dehydration ($-\text{HCl}$) with NaOH to form the desired product (AE: 56%, E - factor: 0.8). Alternative possibilities are formation of an anhydride derivative with 1,1'-Carbonyldiimidazol (CDI) (AE: 59%, E - factor: 0.7) or activation by *N,N'*-Dicyclohexylcarbodiimide (DCC) (AE: 53%, E - factor: 0.9) to form an activated $\text{O}=\text{C}-\text{ODCC}$ intermediate. In all cases a stoichiometric amount of an activation reagent has to be used contributing to a decreased atom economy, compared to a catalytic approach (AE: 93%, E - factor: 0.08). As already described for the nucleophilic substitution reaction, the E - factor is increased by a factor of ten for the non catalytic

approaches and the AE is decreased for 30 - 40%. The calculations were done for the reaction described in Scheme 7.



Scheme 7. The amide reaction was catalysed by electron poor phenyl boronic acids.

Side products from the Schotten Baumann reaction (HCl and SO₂) are released as gas and imidazole from CDI can be removed by liquid-liquid extraction/column chromatography. Depending on the solubility of the desired product, dicyclohexylurea (bad solubility in toluene) can be removed by liquid-liquid extraction or, depending on the properties of the final compound, crystallization might be possible to separate it from the residue. If those methods are not successful for the removal of the activation reagent, column chromatography has to be considered which is again resulting in a higher E - factor.

With regard to the 12 principles of green chemistry, activation by these methods fails according to the first, second, third (especially SO₂ and HCl), fifth (removal of the dicyclohexylurea might be difficult), eighth and ninth principle. In order to avoid stoichiometric activation reagents, catalytic attempts were described in literature to develop a greener process [12].

Hall introduced boron promoted catalytic alternatives reducing the waste generation [12]. Phenyl boronic acids (pba) were applied, containing electron withdrawing groups on the ortho position of the aromatic ring. Phenylacetic acid and benzylamine was converted at RT (Scheme 7). The proposed mechanism of this mild process suggests electrophilic activation of the COOH group by reversible coordination to the boronic acid (Figure 2) [4, 12].

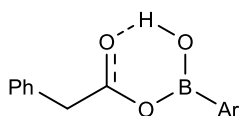


Figure 2. Activation of the carboxylic acid group for the amide formation by coordination of phenylboronic acid [4].

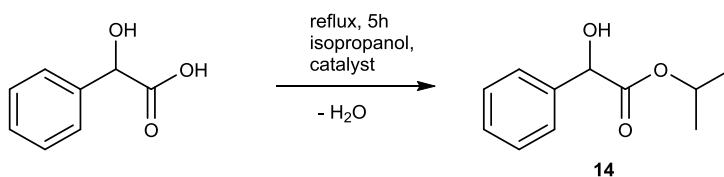
Using this approach, we made an attempt to apply boronate **11** as a catalyst for the amidation reaction. However, no amide formation occurred. Recently a detailed mechanism of this reaction was discussed, providing an explanation for the higher yield of ortho compared to para substituted iodo-phenylboronic acid. Iodine in ortho position could act as an H-bond acceptor to support the elimination of water [4]. Boronate salt **7**, in contrast, cannot provide this activation (no template effect) due to fluoro substituents in meta position, which can explain the absence of activity of **7** for the described amide reaction.

3.4. Boron catalyzed esterification

The esterification reaction is based on a similar activation principle as described for amide formation. Therefore it results in similar problems when evaluating AE, E-factor and green chemistry. Activation of the acid group is the crucial step, strength of the nucleophile and solvent play a minor role. In some cases the nucleophile (i.e. isopropanol) can be also used as solvent (Scheme 8).

Common procedures for the activation of R-COOH involve acid chloride (Thionylchloride, NaOH: AE: 52%, E - factor: 0.9) or anhydride formation (CDI: AE: 49%, E - factor: 1, Scheme 8). Alternatively, activation of the carboxylic acid functionality can be done by addition of catalytic amounts of strong acids such as sulfuric acid or *p*-toluenesulfonic acid (TsOH) which is known as Fischer esterification. Starting material and desired product are in equilibrium, preventing

therefore full conversion towards the desired product. A possibility to increase the yield of this reaction is shifting the equilibrium towards the product by increasing the amount of starting material, azeotropic distillation to remove water, or addition of molecular sieves. Distillation involves an excessive addition of energy to the reaction to increase the temperature to 100 °C, which is in disagreement with the sixth principle of green chemistry. Addition of one starting material or molecular sieve might not lead to complete conversion of the starting material which involves an additional purification step of the desired compound.



Scheme 8. Boronic acid catalysed esterification of α -hydroxyphenylacetic acid [13].

An attempt for a boron catalyzed reaction (AE: 92%, E - factor: 0.09) is described in literature [13 - 15]. As expected, the E - factor is decreased ten times and the atom economy can be increased by 40%, if full conversion towards the desired product is achieved, compared to the noncatalytic approach.

In the group of Yamamoto an α -hydroxy-phenyl acetic acid was esterified with alcohols catalysed by 3,5-bis(trifluoromethyl) phenylboronic acid (Scheme 8). The boronic acid was coordinating on the alpha hydroxy group resulting in electrophilic activation (template effect) of the carboxylic acid group (Figure 3). 22% of Isopropyl 2-hydroxy-2-phenylacetate was obtained (Table 3, entry 1).

When boronate **11** was applied in the esterification reaction, a lower activity was observed (Table 3, entry 3). After 5h 4.2% of the ester was formed. Further addition of molecular sieves, with a purpose of water removal, to the reaction mixture was not successful. It might be possible that coordination (template effect)

of the starting material on the 3,5-bis(fluoro)phenylboronic acid was weaker compared to 3,5-bis(trifluoromethyl) phenylboronic acid due to higher electron density on the boron atom. Electron density on the boron atom on **11** further increased compared to the free boronic acid, resulting in a further decrease of conversion (Table 3, entry 2 and 3).

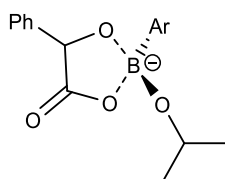


Figure 3. Suggested transition state for the boron catalyzed esterification reaction [13].

Table 3. Overview of several tested boron promoted esterification reactions.

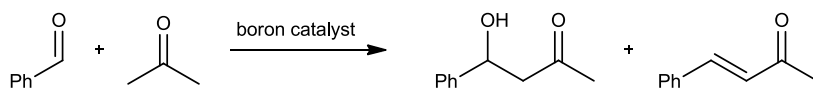
Entry	Catalyst	Conversion [%]
1	3,5-bis(trifluoro methyl)PBA	22a)
2	3,5-di fluoroPBA	7.7
3	11	4.2
4	Mol. Sieves	1.1
5	Mol. Sieves + 11	2.0

a) [ref. 13] b) PBA = phenylboronic acid

3.5. Boron catalyzed aldol reaction

β -Hydroxyketones are versatile building blocks in organic synthesis which can be conveniently synthesized from ketones and aldehydes by the aldol reaction. Activation of the ketone (functional group) is crucial and was done in the past by

functionalizing with trimethylsilylchloride. Compared to the nucleophilic substitution the choice of solvent and strength of the nucleophile are less important. One equivalent of activation reagent (trimethylsilylchloride) was used, resulting in a low atom economy (AE: 52%) of this reaction (Scheme 9). This stoichiometric approach was also generating a significant amount of waste, resulting in an undesired E - factor (0.91). The non catalytic approach is also unsatisfactory in terms of green chemistry as described with the previous reactions.



Scheme 9. High selectivity towards desired product was obtained in the boron catalyzed reaction [16, 17].

An example for 100% atom economy is the catalytic aldol reaction, when one equivalent of benzaldehyde and one equivalent of acetone are converted to one equivalent of 4-hydroxy-4-phenylbutan-2-one, therefore no waste is generated (E - factor: 0). In practice, however, an excess of the ketone is normally used to achieve high conversion of the benzaldehyde, reducing the AE.

An attempt described, using phenylboronate as a catalyst, showed still stoichiometric formation of product. Whiting's catalyst converted ketone and aldehyde within several hours and only a stoichiometric amount (20%) of desired product was obtained (Scheme 9). The main product of this reaction was the undesired elimination product (80%) which is leading to an increased E - factor [18].

Eventhough activation of the acid group failed with boronate **11**, in an additional attempt activation (deprotonation) was tested on ketones. When **11** was applied on the aldol reaction (Scheme 9) full conversion within a few minutes was observed [17]. Also better selectivity towards the desired product was realized, 76

% β -hydroxyketone and 8% of elimination product, compared to other literature known data. Due to the non-nucleophilic basic character of the boronate salt the product formation was promoted, while the undesired elimination reaction was suppressed [16]. The catalyst was dissolved in the substrate and no further co-solvent was needed. Mechanistic details related to the aldol reaction and catalyst **11** are discussed in chapter 4.

This catalytic approach is satisfying the first (besides catalyst only water is present as waste), second (all starting materials are incorporated in the chemical process), fifth (no cosolvent needed), sixth (the reaction was performed at ambient temperature), eighth (no preformation of enol structure via trimethylsilyl group) and ninth principle (catalytic approach) of green chemistry and therefore it represents an improvement/useful addition to existing boron mediated processes.

3.6. Conclusion

An attempt has been made to develop a boron-based catalyst able to catalyze nucleophilic substitution of alcohols. Nucleophilic substitution did not take place on the hydroxy group even though strong nucleophiles were selected for the reaction. It is believed that the carbon oxygen bond was too strong in organic solvents, preventing nucleophilic substitution.

Since only low conversion in the esterification reaction and no conversion in the amide synthesis was observed with sodium triisopropoxy-(3,5-difluorophenyl)boronate as the catalyst, it might be possible that electrophilic activation of the COOH group is not sufficient, therefore conversion of the starting material is limited. With ortho and para – positions still available at the aromatic ring of the catalyst, which can be modulated by electron donating or electron withdrawing groups, enhanced catalysts can be designed to improve the interaction between substrate and catalyst to increase conversion towards the desired product.

The best result was achieved when **11** was applied in the aldol reaction. Already after a few minutes a high conversion was obtained. Also better selectivity towards the desired product was realized, due to the non-nucleophilic basic character of the catalyst, compared to other literature known data. The absence of solvent is an additional advantage for green chemistry, as described in this chapter. Therefore the boron catalyzed aldol reaction is the future topic of investigation.

3.7. Experimental

3.7.1. General methods

Experiments were performed with commercially available chemicals. The phenylboronic esters were synthesized according to procedures reported in the literature. ^1H , ^{11}B and ^{13}C NMR spectra were recorded at 400, 128, 100 MHz with a Bruker Avance 400 spectrometer. As reference for the ^{11}B NMR measurements a 0.1 M boric acid solution in D_2O was used. All other shifts in ^1H and ^{13}C spectra were referenced to the residual solvent peak and are reported in ppm. TLC was performed with Silica gel 60 F254 (Merck) and analyzed at 254 and 365 nm. If needed, the product was visualized with iodine on the TLC-plate. Mass spectroscopy was performed with a Shimadzu GC-MS-QP2010S gas chromatograph mass spectrometer. 3\AA molecular sieves were purchased from Metrohm. Silica-gel (Fluka, particle size 0.06 – 0.2 nm) was used for the isolation of the products. As eluent for column chromatography distilled ethyl acetate and petrol ether 2 / 8 was used. 1-phenyl-2-propanol (Sigma Aldrich), 2-pentanol (Aldrich), benzyl amine (Acros), boric acid (Acros), potassium iodide (Sigma Aldrich), sodium azide (Fluka), sodium cyanide (Sigma Aldrich), sodium thiocyanate (Sigma Aldrich) were used without purification. Catechol (Acros) was crystallised in dry acetone. Acetone was dried with sodium sulfate.

(3.2.) Nucleophilic substitution of alcohols

2-butoxyethanol (1). (Scheme 1)

The reaction was described in literature with catalyst **2**. [1]

2.2 g (27 mmol) 2-chloroethanol, 215 mg (0.9 mmol; 3.3-mol%) *N*-Methyl-2-(2-boronophenyl)benzimidazole **4** and 360 mg (3 mmol) collidine were dissolved in 2 g (27 mmol) butanol and stirred for 20 h at 89 °C. 2-chloroethanol and n-butanol

were removed with low pressure (oil pump). Conversion was determined with an internal standard (Naphthalene) related to ^1H NMR–Signal from the product [$\delta = 0.9$ ppm (CH_3)]. Theoretical yield, based on calculation with the internal standard: 79 mg (0.67 mmol; 2.5 %).

***N*-Methyl-2-(2-bromophenyl)benzimidazole (3). (Scheme 3) [6]**

4.88 g (40 mmol) *N*-methyl phenylene-1,2-diamine, 8.04 g (40 mmol) 2-bromobenzoic acid and 24 g polyphosphoric acid were mixed into a paste and heated to 175 °C for 5 h. The mixture was poured into 160 mL ice-water and the pH was adjusted with ammonium hydroxide solution (33%) to 10 – 11. The solution was filtered and the obtained sticky solid was dissolved in 20 mL ethanol, reprecipitated with ammonium hydroxide solution (pH 11) to yield a black solid (9.8 g). The black solid was filtered and purified by dissolving in ethyl acetate passing through a short dry silica gel column (20 g silica gel, toluene/ethyl acetate, 9 : 1, as eluent) to give a pale cream solid 8.7 g (30.3 mmol, yield: 75.8%; mp : 115 - 118 °C).

^1H NMR (400 MHz, CDCl_3): $\delta = 3.66$ (s, 3H, CH_3N); 7.31 – 7.43 (m, 4H, CH); 7.46 (td, 1H, CH); 7.54 (dd, 1H, CH); 7.71 (dd, 1H, CH); 7.83 (dd, 1H, CH). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 30.9$; 109.7; 120.3; 122.5; 123.1; 124.0; 127.6; 131.5; 132.3; 132.5; 132.9; 135.6; 142.9; 152.7.

***N*-Methyl-2-(2-boronophenyl)benzimidazole (4). (Scheme 3) [6]**

The reaction was carried out in a nitrogen atmosphere. 6.25 mL (10 mmol, 1.6 M in hexane) *n*-butyllithium was dissolved in 30 mL diethyl ether (dry) and cooled to – 78 °C. A solution of 1.43 g (5 mmol) *N*-Methyl-2-(2-bromophenyl) benzimidazole **3** dissolved in 75 mL diethyl ether was added dropwise over 0.5 h. The resulting suspension was stirred for 2 h at – 72 °C. A solution of 3.76 g (20 mmol; 4.59 mL) triisopropylborate dissolved in 50 mL diethyl ether was added

dropwise over 0.5 h. After stirring at $-78\text{ }^{\circ}\text{C}$ for 0.5 h the solution was allowed to warm to room temperature overnight. 60 mL (5%) sodium hydroxide solution was added and the layers separated. The pH of the aqueous phase was adjusted to 1 with concentrated HCl. The aqueous phase was washed with 3×10 mL diethyl ether, was adjusted to pH 7-8 with sodium hydroxide solution (5%), saturated with sodium chloride and the product was extracted with 3×20 mL chloroform. The chloroform layers were collected, solvent was removed and 800 mg (3.2 mmol; yield: 64%) of a cream-coloured solid was obtained.

^1H NMR (400 MHz, CDCl_3): $\delta = 3.58$ (s, 3H, CH_3N); 7.00 – 7.08 (m, 1H, CH); 7.18-7.24 (m, 2H, CH); 7.26 – 7.32 (m, 2H, CH); 7.38 – 7.48 (m, 2H, CH); 7.55 – 7.60 (m, 1H, CH). ^{11}B NMR (128 MHz, CDCl_3): $\delta = -5.01$. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 30.9$; 109.5; 117.4; 122.2; 122.8; 125.0; 125.2; 128.0; 130.1; 132.6; 132.8; 136.1; 137.2; 155.8.

Nucleophilic substitution of 2-pentanol in D_2O (Scheme 5).

The reaction was carried out in a nitrogen atmosphere. 12.5 mg (0.2 mmol) boric acid and 22 mg (0.2 mmol) catechol were dissolved in 2 mL D_2O . The pD was adjusted with NaOD which corresponds to a pH of 11.65. 0.22 mL (2.0 mmol) 2-pentanol was added. The above mixture was divided in four samples. To each sample 1 mmol of a different nucleophile (50 mg sodium cyanide, 166 mg potassium iodide, 66 mg sodium azide or 80 mg sodium thiocyanate) was added. After 50 h at RT the reactions were carried out for further 50 h at $50\text{ }^{\circ}\text{C}$. The reactions were followed via ^1H -NMR. No product was observed.

Nucleophilic substitution of 2-pentanol in organic solvents (Scheme 5).

The reaction was carried out in a nitrogen atmosphere. 176 mg (2 mmol) 2-pentanol and 0.2 mmol boroncatalyst **9** or **10** were dissolved in 2 mL deuterated organic solvent. The reaction solution was divided in four samples. To each sample

1 mmol of a nucleophile was added (Table 2). The samples were heated to 60 °C in an oil bath. The inorganic salts did not dissolve completely. To every sample 13 mg (0.05 mmol) 18-crown-6 ether, dissolved in 0.2 mL corresponding organic solvent, was added. The reactions were followed with $^1\text{H-NMR}$ for (Table 2; $t = h$). No product formation was observed.

General synthesis of the boron derivatives **9** and **10** described in literature [11]:

2-phenylbenzo[*d*][1,3,2]dioxaborole (9).

1.1 g (10 mmol) catechol and 1.2 g (10 mmol) phenyl boronic acid were dissolved in 10 mL toluene. The reaction mixture was stirred for 16 h under reflux. Solvent was removed. Product and 10 % phenyl boronic acid were in the precipitate. Column chromatography of the product failed, decomposition into starting material was observed. For the following nucleophilic substitutions 2-phenylbenzo[*d*][1,3,2]dioxaborole was used without further purification. A white solid was obtained (86 % yield).

$^1\text{H-NMR}$ (C_6D_6 , 400 MHz) $\delta = 6.79 - 8.13$ (several m, 9 H, $\text{H}_{\text{arom.}}$). $^{11}\text{B-NMR}$ (C_6D_6 , 128 MHz): $\delta = 7.1$. $^{13}\text{C-NMR}$ (C_6D_6 , 100 MHz) $\delta = 113.3, 123.5, 129.1, 135.3, 148.9$.

2-ethoxybenzo[*d*][1,3,2]dioxaborol (10).

2.9 g (26 mmol) catechol was dissolved in 6 mL dry toluene. The reaction mixture was heated to 60 °C. Within 5 min. 3.8 g (26 mmol) triethyl borate was added. Subsequently the reaction mixture was heated to 120 °C and distilled via a vigreux column. The ethanol-toluene mixture started to evaporate at 77 °C. After all ethanol was evaporated, the temperature in the column head went to 110 °C. The reaction was stopped. Solvent was removed and the reaction mixture was distilled

(bp.: 2×10^{-2} mbar, 42 °C). 1.6 g of a clear liquid was obtained (9.8 mmol, 38 % isolated yield).

$^1\text{H-NMR}$ (C_6D_6 , 400 MHz) δ = 0.99 (t, 3H, CH_3), 3.80 (q, 2H, OCH_2), 6.75 – 6.92 (m, 4H, H_{arom}). $^{11}\text{B-NMR}$ (C_6D_6 , 128 MHz): δ = 6.83. $^{13}\text{C-NMR}$ (C_6D_6 , 100 MHz) δ = 16.3, 61.8, 112.8, 123.3, 148.5.

Isobutyronitrile (12). (Scheme 6)

The reaction was carried out in a nitrogen atmosphere. 162 mg (0.5 mmol) sodium triisopropoxy-(3,5-difluorophenyl)boronate and 268 mg (1 mmol) tetrabutyl ammonium cyanide were dissolved in 30 mL isopropanol and stirred under reflux for 90 h. Solvent was removed. The reaction mixture was followed with GC-MS and $^1\text{H-NMR}$. No product was observed.

(1S,2R,5R)-5-methyl-2-(prop-1-en-2-yl)cyclohexanecarbonitrile (13). (Scheme 6)

154 mg (170 μL , 1 mmol) isopulegol, 268 mg (1 mmol) tetrabutyl ammonium cyanide and 324 mg (1 mmol) sodium triisopropoxy-(3,5-difluorophenyl)boronate were dissolved in 30 mL 2-propanol. The reaction mixture was stirred under reflux for 21 h. The conversion was followed by GC-MS. One drop of reaction mixture was dissolved in 1 mL ethyl acetate. No conversion was observed.

(3.3.) Boron catalysed amide formation

***N*-benzyl-2-phenylacetamide. (Scheme 7)**

The reaction was carried out in a nitrogen atmosphere. 75 mg (0.55 mmol) phenylacetic acid and 162 mg (0.5 mmol) sodium triisopropoxy-(3,5-difluorophenyl)boronate were dissolved in 7 mL dichloromethane. 1 g molecular sieve (4Å) was added. The mixture was stirred for 10 min. at 29 °C (RT). 54 mg

(0.5 mmol; 55 μ L) benzylamine was added. The reaction mixture was stirred for 48 h at RT. The suspension was filtered and washed with 9 mL of an acidic solution (pH 4, HCl in water), 9 mL of a basic solution (pH 10, NaOH in water) and 12 mL brine (NaCl in water). No product was observed.

(3.4.) Boron catalysed esterification reaction

The yield of this esterification-reactions was determined with an internal standard (Naphthalene) related to ^1H NMR–Signal of desired product [$\delta = 1.11$ ppm (CH_3)]. The reaction is already described in literature and NMR data are provided in the corresponding supporting information [13].

Isopropyl 2-hydroxy-2-phenylacetate (14). (Scheme 8)

913 mg (6 mmol) mandelic acid and 156 mg (0.6 mmol) 3,5-bis(trifluoromethyl)phenylboronic acid were dissolved in 15 mL isopropanol. The reaction mixture was stirred under reflux for 5 h. Solvent was evaporated and a white solid was obtained. Theoretical yield, based on calculation with the internal standard: 254 mg (22%).

Isopropyl 2-hydroxy-2-phenylacetate (14). (Scheme 8)

913 mg (6 mmol) mandelic acid and 95 mg (0.6 mmol) 3,5-difluorophenylboronic acid were dissolved in 15 mL isopropanol. The reaction mixture was stirred under reflux for 5 h. Solvent was evaporated and a white solid was obtained. Theoretical yield, based on calculation with the internal standard: 90 mg (0.464 mmol; 7.7 %).

Isopropyl 2-hydroxy-2-phenylacetate (14). (Scheme 8)

913 mg (6 mmol) mandelic acid and 195 mg (0.6 mmol) sodium triisopropoxy-(3,5-difluorophenyl)boronate were dissolved in 15 mL isopropanol. The reaction

mixture was stirred under reflux for 5 h. Solvent was evaporated and a white solid was obtained. Theoretical yield, based on calculation with the internal standard: 48 mg (0.25 mmol; 4.2 %).

Isopropyl 2-hydroxy-2-phenylacetate (14). (Scheme 8)

913 mg (6 mmol) mandelic acid and 1 g molecular sieve (4Å) were dissolved in 15 mL isopropanol. The reaction mixture was stirred under reflux for 5 h. Solvent was evaporated and an off white solid was obtained. Theoretical yield, based on calculation with the internal standard: 13 mg (1.1 %).

Isopropyl 2-hydroxy-2-phenylacetate (14). (Scheme 8)

913 mg (6 mmol) mandelic acid, 1 g molecular sieve (4Å) and 195 mg (0.6 mmol) sodium triisopropoxy-(3,5-difluorophenyl)boronate were dissolved in 15 mL isopropanol. The reaction mixture was stirred under reflux for 5 h. Solvent was evaporated and a white solid was obtained. Theoretical yield, based on calculation with the internal standard: 24 mg (0.125 mmol; 2 %).

3.8. Reference

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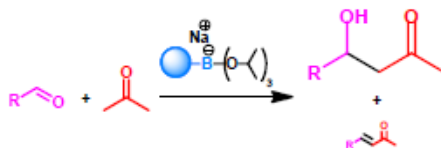
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Aldol reactions mediated by a tetrahedral boronate

IV

Abstract

The base is a key factor in aldol reactions in organic media, determining the selectivity. Here, we describe a tetrahedral phenylboronate salt as a mild non-nucleophilic base that is able to catalyse the aldol reaction and significantly decreases the formation of undesired elimination products.



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4.1. Introduction

The aldol addition is an important C-C bond forming reaction [1]. A key step in the mechanism is nucleophilic attack of a deprotonated ketone (enolate) on an aldehyde to form a β -hydroxyketone. Various inorganic bases, including LiOH, NaOH, Na_2CO_3 and $\text{Ca}(\text{OH})_2$ have been applied for the initial deprotonation of the ketone [2 - 5]. However, the base catalyst is often also active in the elimination reaction, the dehydration of the β -hydroxyketone. Suppression of the aldol elimination is of great interest, as β -hydroxyketones are versatile building blocks in, for instance, the synthesis of diols, amino alcohols, lactones and polyketides [6 - 11].

Boronates are known to mediate aldol reactions by acting both as activator and as template for the reactants, the ketone and the aldehyde [12 - 23]. An interesting modification is the addition of highly reactive trimethyl silyl enol ether to aldehydes in water with sodium dodecyl sulfate as surfactant and diarylborinic acid **1** as the catalyst (Figure 1) [24]. More recently, it was shown that the activation of the ketone as silyl enol ether is unnecessary when salt **2** as the catalyst is applied (Figure 1). In this system, which is limited to aqueous solutions, intramolecular

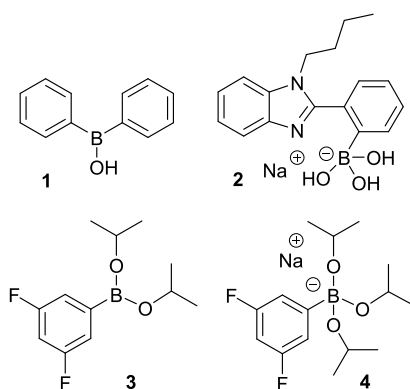
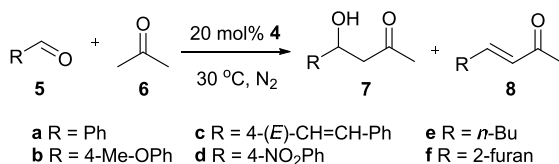


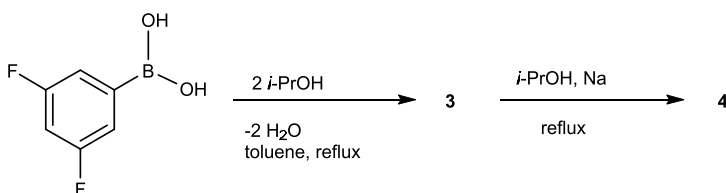
Figure 1. Molecular structures of the boron-based catalysts discussed.



Scheme 1. The aldol reaction with a series of aldehydes and acetone.

interaction of the neighbouring nitrogen and boron atoms stabilizes the tetrahedral boronate. Side reactions, such as dehydration remain a problem; particularly when the reaction is favoured by stabilization of the elimination product as a result of mesomerism.

Here, we report on the results of an investigation on the feasibility of the application of phenylboronate **4** applied as catalyst in aldol reactions in organic media (Scheme 1). For comparison, the corresponding boronic acid **3** and the classic base sodium isopropoxide were included in this study. Compounds **3** and **4** were synthesized from 3,5-difluorophenylboronic acid by reaction with the appropriate amount of isopropanol and sodium isopropoxide (Scheme 2) and were isolated as stable solids with a purity greater than 99%. Both new compounds show good solubility and thermal stability in organic solvents; they did not show any dissociation as demonstrated by their characteristic ¹¹B NMR chemical shifts for trigonal and tetragonal B-atoms, respectively (Figure Appendix A1C and A2C; related to H₃BO₃ (0.1M) at 0 ppm). The high stability of these B-compounds may be ascribed to the electron-withdrawing fluoro-substituents in the aromatic ring.



Scheme 2. Synthesis of the trigonal (**3**) and tetrahedral (**4**) phenyl boronic acid ester.

4.2. Results and Discussion

These substituents also contribute to the high solubility of these complexes in organic solvents, which allows to perform the aldol reaction with one of the reactants acting as solvent. In the present investigation, acetone was used as the solvent and the reactions were monitored by NMR and GC-MS. To rule out the possible deactivation of the catalyst (**4**) by water, the reaction was performed in the presence of equimolar amounts of it (relative to **4**). Neither product formation nor selectivity was influenced by water.

In the presence of NaOiPr as the catalyst and at 30 °C, benzaldehyde (**5a**) and an excess of acetone (**6**) reacted very fast to aldol **7**, which was subsequently dehydrated to α,β -unsaturated ketone **8** with a lower reaction rate (Figure 2B). The rates of both the aldol reaction and the elimination reaction appeared to be strongly dependent on the concentration of the catalyst (Table 1, entries 1-4).

Table 1. The aldol reactions of 2 mmol **5a** and 20 mmol **6** (see Scheme 2) for 20 min at 30 °C. Conversions and yields are determined by ¹H NMR.

Ent.	4 (mol%)	NaOiPr (mol%)	Conv. ^[a] (%)	Yield 7 (%)	Yield 8 (%)
1	-	20	>99	18	57
2	-	10	>99	23	55
3	-	5	97	40	40
4	-	2	13	13	<1
5	20	-	96	76	8
6	10	-	90	80	10
7	5	-	39	35	4
8	10	10	>99	11	45

^[a] dimerization side-product, PhC=C(C=O)C=CPh (**9**) was detected by GC-MS.

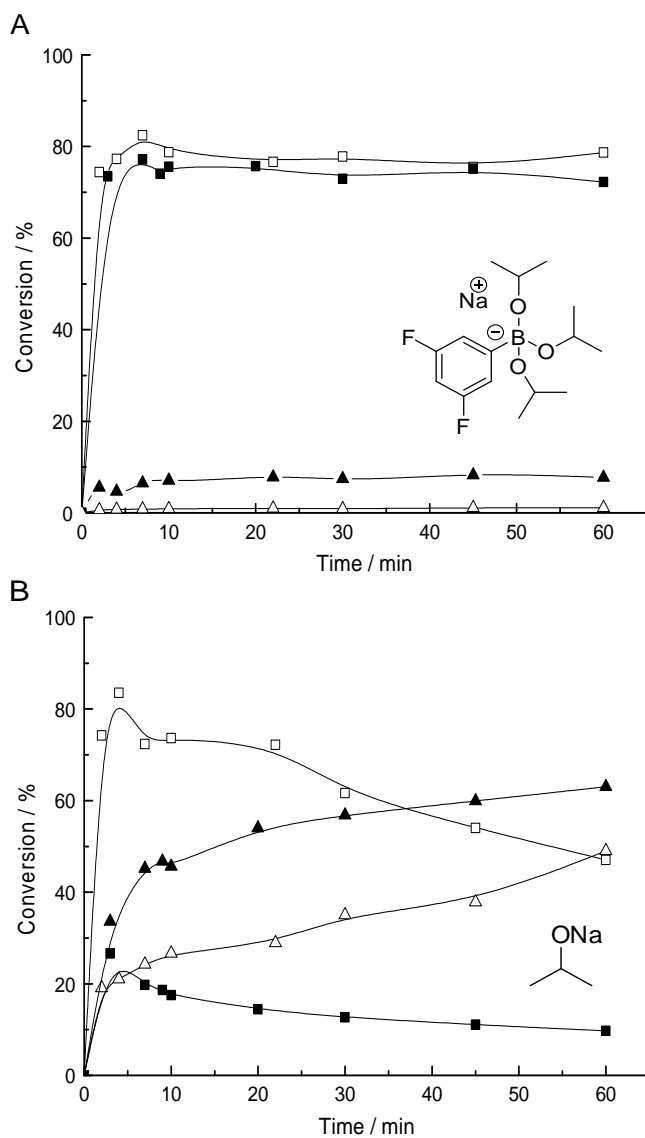


Figure 2. Reaction between benzaldehyde and acetone, catalysed by 20 mol% of boronate salt **4** (A) and sodium 2-propanolate (B), monitored by ¹H NMR at 30 °C (solid data points) and 5 °C (empty data points). The aldol and the elimination product formation is presented by squares and triangles, respectively.

In addition to the elimination side product, higher molecular weight side product **9** resulting from dimerization was observed as well. Decreasing the temperature to 5 °C, did not improve the selectivity towards the desired aldol product (Figure 2B). Decreasing temperature and catalyst concentration at the same time was not inhibiting the elimination reaction either (Figure 3).

Trigonal B-compound **3** (up to 20 mol%) was completely inactive in the aldol reaction of **5a** and **6**, which suggests that a base is essential for the reaction to proceed. By contrast, application of tetragonal boronate **4** resulted in high conversion to the aldol within a few minutes (Table 1, entries 5 - 7), the reaction rate towards the aldol was about the same as that with NaOiPr as the catalyst, but

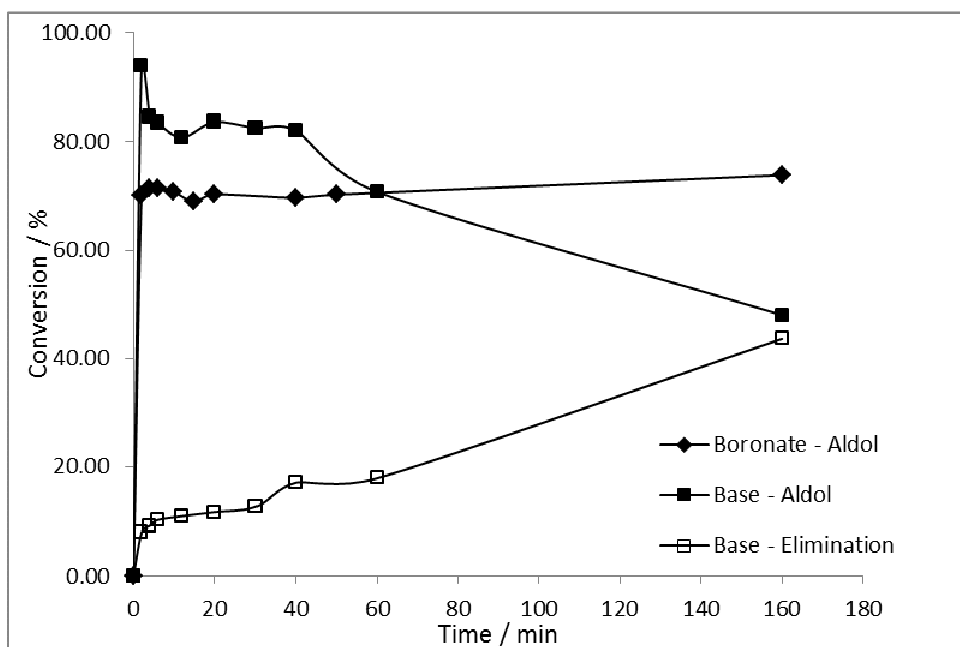


Figure 3. Conversion of benzaldehyde in the presence of 10 mol% of boronate salt **4** or 10 mol% of NaOiPr at 5 °C monitored by ^1H NMR. Formation of dimerization side-products during boronate catalysed reaction was detected by the MS, which explains the lower yield of the aldol; no elimination product was detected.

now the subsequent elimination reaction was much slower. With 20 mol% **4**, only 8% elimination product was obtained. By decreasing the reaction temperature to 5 °C, similar results were obtained (Figure 2A). Combining 10 mol% **4** and 10 mol% of NaOiPr resulted in full conversion of the benzaldehyde. Aldol product was formed which was dehydrated by NaOiPr to the condensation product and some higher molecular weight products resulting from dimerization (Table 1, entry 8).

A series of aldehydes was tested in the aldol reaction in the presence of catalyst **4** (Scheme 1, Table 2). The reactions proceeded within a few minutes with high conversions. Aromatic aldehydes and furfural, a bio-based platform chemical, all gave rise to both aldol adduct **7** and the corresponding dehydration product **8** with a high selectivity towards **7**, compared to the results obtained with the reported boron catalysts **1** and **2** [24 - 25].

The highest selectivity was obtained with aliphatic aldehyde **5e**: 66% of the β -hydroxyketone **7e** and less than 1% of the dehydration product **8e** were formed (Table 2, entry 5). For the aromatic aldehydes conversion and selectivity to the β -hydroxyketone seems to be related to the nature of substituents and the bond delocalization. Similar lower yields and selectivities for **5b** and **c** were observed earlier [24 - 25].

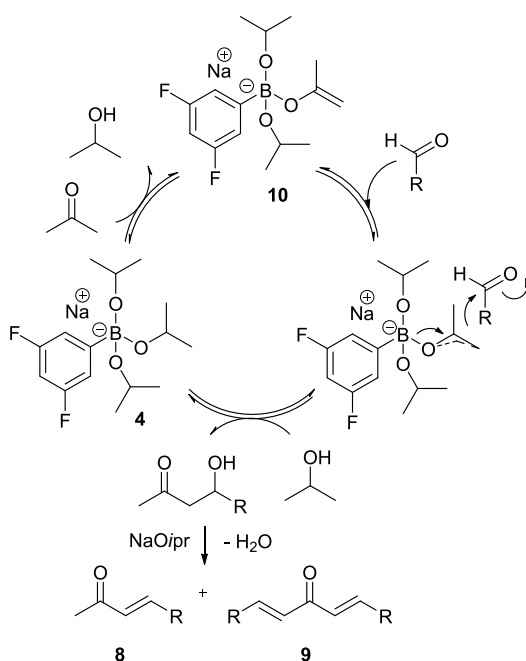
We suggest a reaction mechanism as depicted schematically in Scheme 3. Under the reaction conditions applied, the dissociation of compound **4** towards O^- and corresponding **3** is negligible in acetone. This is confirmed by its ^{11}B NMR spectrum which shows exclusively a resonance for tetrahedral boron at around -15.49 ppm (Figure 4; as a standard 0.1 M boric acid solution in D_2O at 0 ppm was used). No resonance related to compound **3** was observed. Since the reaction rate of the aldol reaction, in the presence of 2 mol% NaOiPr, is much lower than with 20 mol% **4**, it is likely that undissociated **4** rather than isopropoxide is the actual catalyst in this system (Table 1, entries 4 and 5).

Table 2. The aldol reactions of 2 mmol **5** and 20 mmol **6** (Scheme 1), catalysed by 20 mol% of **4** at 30°C. Conversions and yields are determined by $^1\text{H NMR}$.

Entry	R	t (min)	Conversion ^[a] (%)	Yield 7 (%)	Yield 8 (%)
1	A	20	96	76	8
2	B	20	80	38	24
3	C	10	88	47	41
4	D	5	95	52	<5
5	E	30	95	66	<1
6	F	15	99	40	21

^[a] dimerization side-product, $\text{PhC}=\text{C}(\text{C}=\text{O})\text{C}=\text{CPh}$ (**9**) was detected by GC-MS.

After deprotonation of acetone by **4**, the resulting enolate exchanges with *i*PrOH.



Scheme 3. Proposed mechanism for the aldol reaction catalysed by tetrahedral boronate salt **4**, including the elimination reaction in the presence of a strong nucleophilic base, NaOiPr.

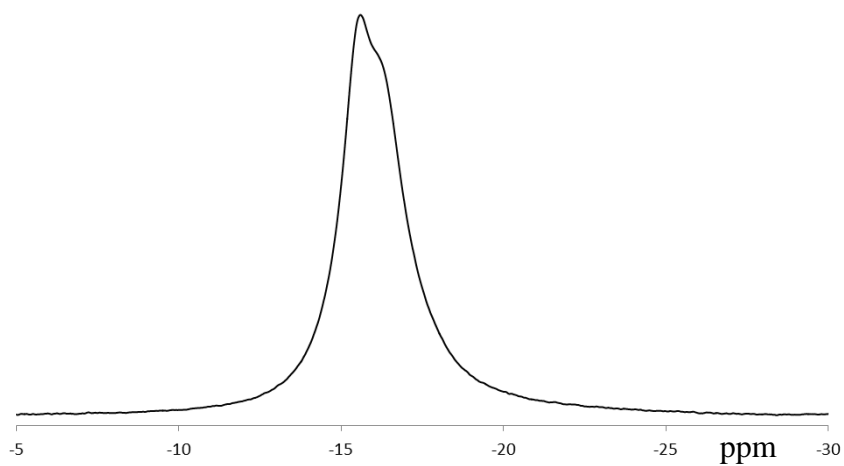


Figure 4. ^{11}B NMR spectrum of boronate salt **4** and benzaldehyde in acetone.

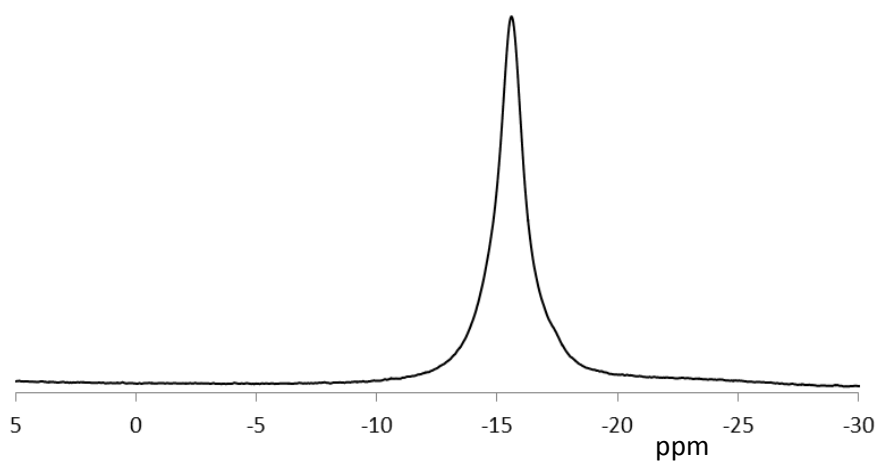


Figure 5. ^{11}B NMR spectrum of boronate salt **4** and benzaldehyde in CD_2Cl_2 .

The resulting tetrahedral boron-enolate **10** reacts with the aldehyde to form the aldol product. In presence of *i*PrOH the aldol product **7** is released and the tetrahedral boronate **4** returns into the catalytic cycle.

The occurrence of an intermediate tetrahedral boronate with both, aldehyde and acetone coordinated to the B-atom, as suggested by Evans for other B-activated aldol reactions [12] is unlikely in the present case. ^{11}B NMR spectra of a sample of **4** and benzaldehyde showed a single resonance at -16 ppm, thus no coordination of benzaldehyde to **4** (Figure 5; related to 0.1 M boric acid solution in D_2O at 0 ppm). This also rules out the mechanism, similar to Evans, suggested by Shibasaki [12, 14 - 16].

On the contrary, acetone is coordinating to tetrahedral boronate **4**, which could be confirmed by both ^{11}B NMR and Raman spectroscopy (Figure 6).

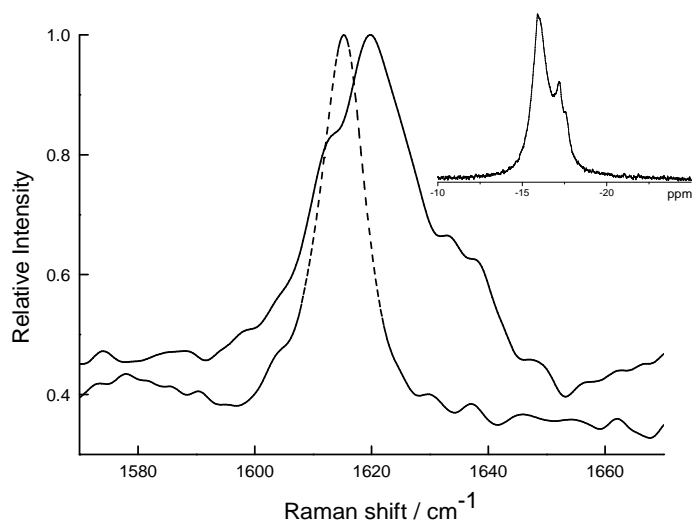


Figure 6. Raman spectra of tetrahedral boronate salt **4** as a solid (dashed line) and as a solution in acetone (solid line). An additional boron ester peak corresponds to the conjugate of **4** with acetone through formation of enolate. The inset represents the ^{11}B NMR spectra of **4** interacting with acetone (related to H_3BO_3 (0.1M) at 0 ppm).

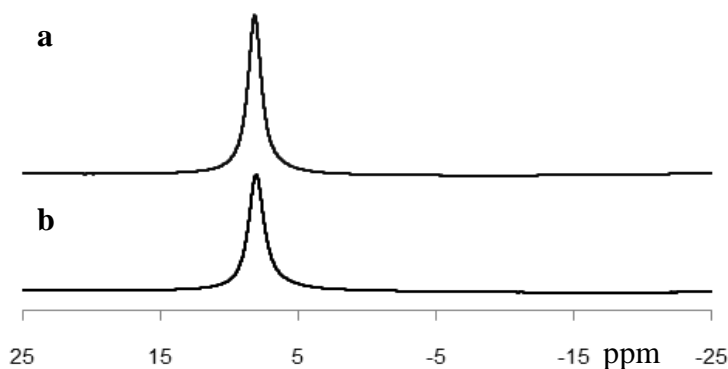


Figure 7. ^{11}B NMR spectra of boron ester **3** mixed with a) acetone (**6**), b) acetone and benzaldehyde (**5a**). Neither acetone nor benzaldehyde was coordinating to boron ester **3**. No tetrahedral boronate salt was formed, which excludes a six membered transition state as a possible mechanism. As a standard 0.1 M boric acid solution in D_2O at 0 ppm was used. No other solvent was added.

The latter spectra demonstrate the appearance of an additional boron ester peak as result of the interaction between **4** and acetone (solid line) compared to the spectra of **4** measured in its solid form (dashed line). Furthermore, the ^{11}B NMR spectra (inset) shows an additional resonance at around -17.1 ppm, confirming the interaction of **4** with acetone.

In contrast ^{11}B NMR experiments with **3** showing, no tetrahedral boronate was formed due to coordination of acetone (**6**) or benzaldehyde (**5a**) to phenyl boronic ester **3** (Figure 7). In both cases, the only observable resonance was at 8 ppm (related to H_3BO_3 (0.1M) at 0 ppm) corresponding to the trigonal boronic acid ester **3**. This is in agreement with its catalytic inertness in the aldol reaction. The advantage of the designed catalytic tetrahedral boronate **4**, is its steric bulkiness, which results in a reduced rate of water elimination reaction in the aldol formation compared to that when isopropoxide is applied as the base catalyst.

4.3. Conclusion

In conclusion, we present tetrahedral sodium triisopropoxy-(3,5-difluorophenyl)boronate (**4**) as a base, that can catalyse the aldol reaction. It is soluble in organic media, allowing the use of a substrate, acetone, as solvent. The reaction proceeds rapidly, with high conversion, and good selectivity towards β -hydroxyketone. The tetrahedral boronate acts as a base, suitable to form boron-enolate with acetone, but is not able to dehydrate the formed aldol.

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4.4. Experimental

Experiments were performed with commercially available chemicals. Dry toluene and 2-propanol were used to synthesize the catalyst. 3Å molecular sieves were purchased from Metrohm and was used for the isolation of the products. The aldehydes were freshly distilled or crystallized prior use in the reaction. Aldol reactions were performed at two temperatures, 30 and 5 °C, under N₂-atmosphere. Separation of **7e** and **8e** was done by column chromatography, using silica-gel (Fluka, particle size 0.06 – 0.2 nm) and dichloromethane with 1% methanol and 1% triethyl amine as eluent. TLC was performed with Silica gel 60 F254 (Merck) and analysed at 254 and 365 nm. When required, the product was visualized with Iodine on the TLC-plate. NMR spectra were recorded with either Bruker Avance-400 or Varian-Inova-300 spectrometer operating at 400, 128, and 100 MHz (¹H, ¹¹B and ¹³C NMR) or 300, 96, 75 MHz respectively. The NMR chemical shifts are reported in ppm, referencing either to 0.1M solution of boric acid (¹¹B NMR) or to the residual solvent peak. A Hololab series 5000 Raman spectroscopy (Kaiser Optical System, Inc.) facilitated the recording of Raman spectra of solids and solutions. The Raman spectra were recorded by excitation radiation at 785 nm using a NIR probe.

4.4.1. Synthesis of boron-based mediators

Diisopropyl 3,5-difluorophenylboronic acid ester (3).

4.74 g (30 mmol) 3,5-difluorophenylboronic acid and 12 g (15 mL, 200 mmol) 2-propanol were dissolved in 15 mL toluene. The Dean-Stark trap was filled with 11 g molecular sieves (3Å), 5 mL 2-propanol and 5 mL toluene. The reaction mixture was stirred for 24 h under reflux. Solvent was removed and the product was

distilled (6.5×10^{-2} mbar, 50 °C). 4.1 g (16.9 mmol) of a colourless liquid was obtained (isolated yield: 56 %).

^1H NMR (400 MHz, CDCl_3): δ = 1.25 (d, 12H, $4 \times \text{CH}_3$, J = 6.4 Hz); 4.58 (sept, 2H, $2 \times \text{CHOB}$, J = 6.6 Hz); 6.81 (m, 1H, HAr); 7.06 (m, 2H, $2 \times \text{HAr}$). ^{11}B NMR (128 MHz, CDCl_3): δ = 7.6. ^{13}C NMR (100 MHz, CDCl_3): δ = 24.6; 66.7; 104.7 (t, J = 25.2 Hz); 115.1 (m); 138.5 (s); 163.0 (dd, J = 11.2 Hz; J = 249.7 Hz).

Sodium triisopropoxy-(3,5-difluorophenyl)boronate (4).

The reaction was carried out in a N_2 -atmosphere. 345 mg (15 mmol) sodium was dissolved in 60 mL 2-propanol. The solution was stirred for 1 h under reflux and then cooled to 30 °C. 3.63 g (15 mmol) diisopropyl 3,5-difluorophenylboronic acid ester (**3**) was dissolved in 8 mL 2-propanol and added dropwise over 30 min. The mixture was stirred for 16 h at 30 °C. The solvent was removed under vacuum. 5.12 g of a white powder was obtained (3.828 g boronate; 11.8 mmol; Yield: 79 %).

^1H NMR (300 MHz, 2-propanol- d_8): δ = 1.11 (d, 18H, $6 \times \text{CH}_3$, J = 6 Hz); 3.9 (sept, 3H, CHOB, J = 6 Hz); 6.54 – 7.04 (m, 3H, $3 \times \text{HAr}$). ^{11}B NMR (128 MHz, 2-propanol- d_8): δ = -15.5. ^{13}C NMR (75 MHz, 2-propanol- d_8): δ = 25.3; 63.6; 99.3 (m); 115.3 (m); 162.6 (dd, J = 10.3 Hz; J = 245.8 Hz); 162.9 (dd, J = 10.4 Hz; J = 246.5 Hz).

4.4.2. General procedures for the aldol reactions with **4**

Aldol reaction in the flask:

130 mg (0.4 mmol) sodium triisopropoxy-(3,5-difluorophenyl)boronate (**4**) and 2 mmol of an aldehyde were dissolved in 1.161 g (20 mmol) acetone. The reaction mixture was stirred at 30 °C for a given amount of time. Acetone was removed and the residue was dissolved in 3 mL water. The product was extracted with 3×5 mL

ethyl acetate. The organic layers were combined, dried with MgSO_4 , filtered and solvent was removed. The crude product was purified with column chromatography.

Aldol reaction in the NMR tube:

66 mg (0.2 mmol) sodium triisopropoxy-(3,5-difluorophenyl)boronate (**4**), 1 mmol of an aldehyde 68 mg (0.4 mmol) 1,3,5-trimethoxybenzene were dissolved in 640 mg (10 mmol) acetone. 50 μL of benzene- d_6 was added to lock the signal. The conversion was followed by ^1H -NMR at 30 or 5 $^\circ\text{C}$. The ^1H NMR peak of the latter (6.1 ppm) was integrated and used to calculate the amount of formed aldol (i.e. aldol product of benzaldehyde at $\delta = 5.16$ ppm).

Aldol reaction with sodium 2-propanolate (Table 1, entries 1 - 4):

Benzaldehyde (**5a**) 213 mg (2 mmol) was dissolved in 1.161 g (20 mmol) acetone and a given amount of sodium 2-propanolate (2 mol% up to 20 mol%) was added to the solution. The reaction mixture was stirred at 30 $^\circ\text{C}$ for 20 min. Small samples (25 μl) were dissolved in CDCl_3 and conversion was determined by ^1H NMR.

4.4.3. NMR data of isolated products **7** and **8**

4-hydroxy-4-phenylbutan-2-one (7a).

^1H NMR (400 MHz, CDCl_3): $\delta = 2.18$ (s, 3H, CH_3); 2.77 – 2.92 (m, 2H, CH_2); 3.30 (s, 1H, OH); 5.16 (m, 1H, CHCOH); 7.28 – 7.36 (m, 5H, HAr). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 30.8$; 52.1; 69.9; 125.7; 127.7; 128.6; 142.9; 209.1. (isolated yield: 34%).

(E)-4-phenylbut-3-en-2-one (8a).

^1H NMR (400 MHz, CDCl_3): $\delta = 2.39$ (s, 3H, CH_3); 6.72 (d, 1H, CHCO , $J = 16.4$ Hz); 7.33 – 7.56 (m, 6H, $5 \times \text{HAr} + \text{CHCAr}$). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 27.6$; 127.3; 128.4; 129.1; 130.6; 134.5; 143.6; 198.6. (11%).

4-hydroxy-4-(4-methoxyphenyl)butan-2-one (7b).

^1H NMR (400 MHz, CDCl_3): $\delta = 2.17$ (s, 3H, CH_3); 2.74 – 2.91 (m, 2H, CH_2); 3.37 (s, 1H, OH); 3.79 (s, 3H, OCH_3); 5.08 (d, 1H, CHOH); 6.87 (d, 2H, $2 \times \text{HAr}$); 7.26 (d, 2H, $2 \times \text{HAr}$). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 30.8$; 52.0; 55.3; 69.5; 113.9; 127.0; 135.1; 159.1; 209.3. (27%).

(E)-4-(4-methoxyphenyl)but-3-en-2-one (8b).

^1H NMR (400 MHz, CDCl_3): $\delta = 2.36$ (s, 3H, CH_3); 3.84 (s, 3H, OCH_3); 6.60 (d, 1H, CHCO , $J = 16.2$ Hz); 6.91 – 7.51 (m, 5H, $4 \times \text{HAr} + \text{CHCAr}$). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 27.4$; 55.4; 114.5; 127.1; 130.1; 132.0; 143.4; 161.7; 198.6. (7%).

(E)-4-hydroxy-6-phenylhex-5-en-2-one (7c).

^1H NMR (300 MHz, CDCl_3): $\delta = 2.19$ (s, 3H, CH_3); 2.75 (d, 2H, CH_2 , $J = 6.0$ Hz); 3.23 (s, 1H, OH); 4.74 (dd, 1H, CHOH , $J = 6.0$ Hz and 6.0 Hz); 6.19 (dd, 1H, CArCH=CH , $J = 6.0$ Hz and 16.0 Hz); 6.63 (d, 1H, CArCH=CH , $J = 16.0$ Hz); 7.21 – 7.39 (m, 5H, $5 \times \text{HAr}$). ^{13}C NMR (75 MHz, CDCl_3): $\delta = 30.9$; 50.1; 68.5; 126.6; 127.8; 128.7; 130.3; 130.5; 136.6; 209.0. (28%).

(3E,5E)-6-phenylhexa-3,5-dien-2-one (8c).

^1H NMR (300 MHz, CDCl_3): $\delta = 2.31$ (s, 3H, CH_3); 6.25 (d, 1H, CHCO , $J = 15.6$ Hz); 6.88 – 6.93 (m, 2H, CArCH=CH); 7.24 – 7.48 (m, 6H, $5 \times \text{HAr} + \text{CH=CHCO}$).

^{13}C NMR (75 MHz, CDCl_3): δ = 27.4; 126.7; 127.3; 128.9; 129.3; 130.6; 136.0; 141.4; 143.5; 198.5. (22%).

4-hydroxy-4-(4-nitrophenyl)butan-2-one (7d)*.

^1H NMR (400 MHz, CDCl_3): δ = 2.21 (s, 3H, CH_3); 2.83 – 2.89 (m, 2H, CH_2); 3.66 (s, 1H, OH); 5.23 – 5.26 (m, 1H, CHO); 7.52 (d, 2H, HAr, J = 8.64 Hz); 8.18 (d, 2H, HAr, J = 8.76 Hz). ^{13}C NMR (100 MHz, CDCl_3): δ = 30.8; 51.6; 69.0; 123.9; 126.5; 147.4; 150.1; 208.7. (29%).

*52% aldol, 5% aldehyde was determined by internal standard and other by-products (42%) were obtained.

4-hydroxyoctan-2-one (7e).

^1H NMR (300 MHz, CDCl_3): δ = 0.94 (t, 3H, CH_3 , J = 6.9 Hz); 1.30 – 1.64 (m, 6H, $\text{CH}_2\text{CH}_2\text{CH}_2$); 2.17 (s, 3H, CH_3); 2.48 – 2.63 (m, 2H, CH_2CO); 4.03 (m, 1H, CHO). ^{13}C NMR (75 MHz, CDCl_3): δ = 14.1; 22.8; 27.8; 30.9; 36.2; 50.1; 67.7; 210.2. (49%).

4-(furan-2-yl)-4-hydroxybutan-2-one (7f).

^1H NMR (400 MHz, CDCl_3): δ = 2.20 (s, 3H, CH_3); 2.90 (dd, 1H, CHH, J = 3.5 Hz and 17.4 Hz); 3.04 (dd, 1H, CHH, J = 8.9 Hz and 17.4 Hz); 3.61 (s, 1H, OH); 5.19 (m, 1H, CHO); 6.26 – 6.32 (m, 2H, $2\times\text{H}_{\text{Furan}}$); 7.36 (m, 1H, H_{Furan}). ^{13}C NMR (100 MHz, CDCl_3): δ = 30.6; 48.2; 63.6; 106.2; 110.3; 142.1; 155.1; 208.3. (24%).

(E)-4-(furan-2-yl)but-3-en-2-one (8f).

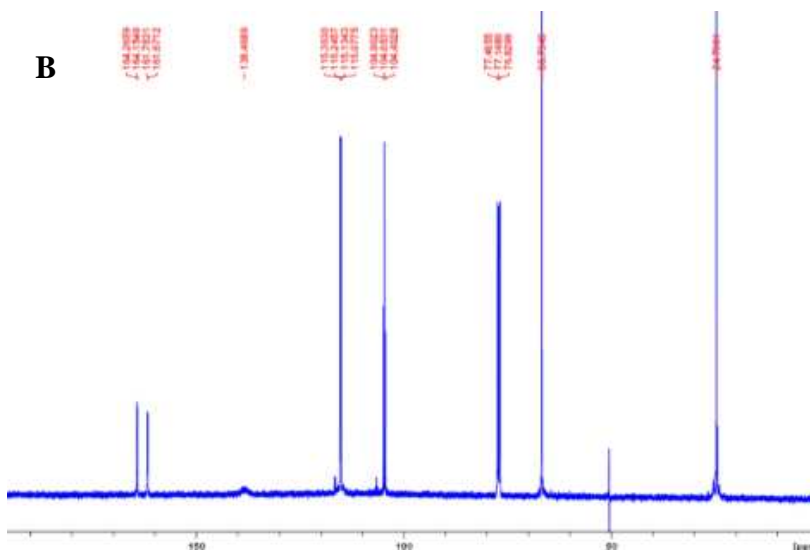
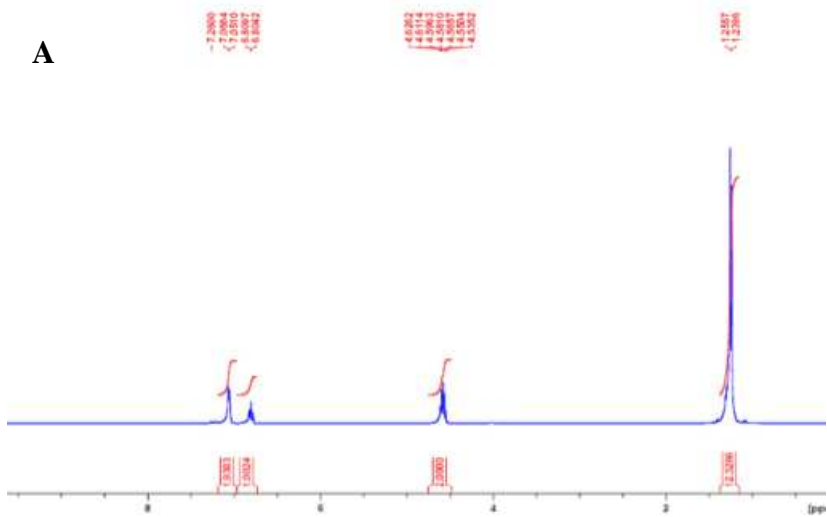
^1H NMR (400 MHz, CDCl_3): δ = 2.32 (s, 3H, CH_3); 6.49 (m, 1H, H_{Furan}); 6.61 (d, 1H, $\text{CH}=\text{CHCO}$, J = 16.0 Hz), 6.66 (m, 1H, H_{Furan}); 7.27 (d, 1H, $\text{CH}=\text{CHCO}$, J = 16.0 Hz); 7.50 (m, 1H, H_{Furan}). ^{13}C NMR (100 MHz, CDCl_3): δ = 28.0; 112.6; 115.7; 124.4; 129.5; 145.1; 151.0; 197.9. (16%).

4.5. Notes and references

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4.6. Appendix



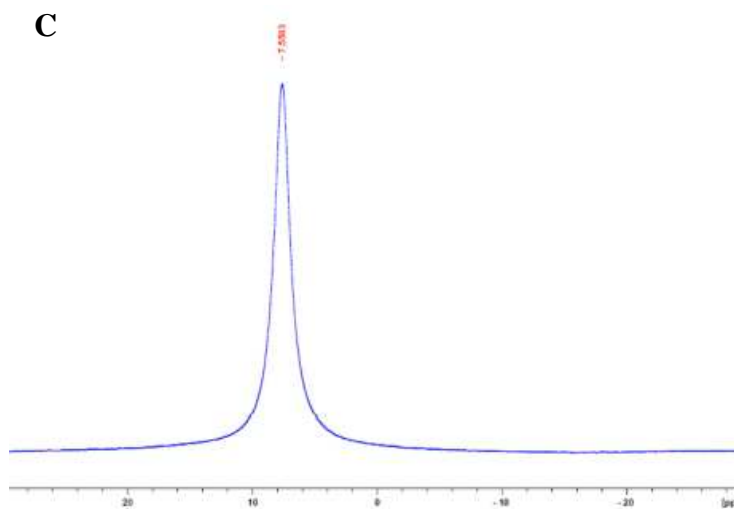
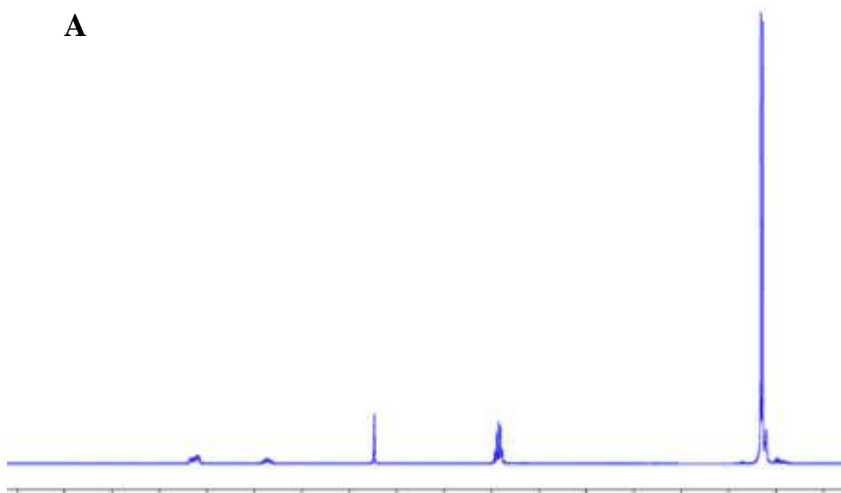


Figure. A1 NMR spectra of Diisopropyl 3,5-difluorophenylboronic acid ester (**3**): ^1H NMR (A) and ^{13}C NMR (B), and ^{11}B NMR (C).



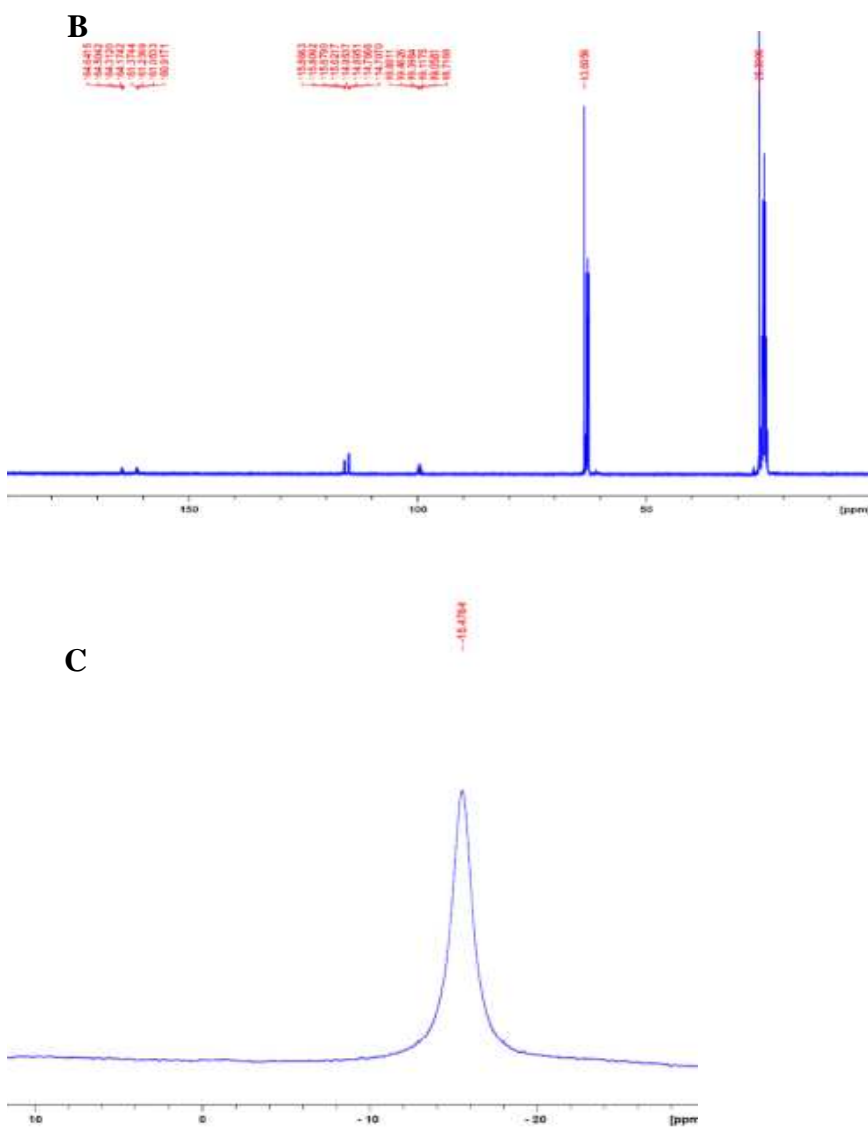


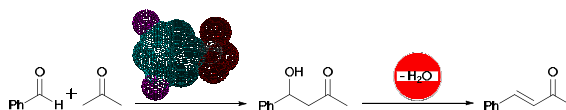
Figure. A2 NMR spectra of sodium triisopropoxy-(3,5-difluorophenyl) boronate (**4**): ^1H NMR (A) and ^{13}C NMR (B), and ^{11}B NMR (C).

Tetrahedral boronates as basic catalysts in the aldol reaction



Abstract

β -Hydroxyketones are versatile building blocks in organic synthesis, which can be conveniently synthesized from ketones and aldehydes by aldol reactions. Unfortunately, these reactions often suffer from dehydration of the initially formed β -hydroxyketones. Previously, tetrahedral 3,5-difluorophenylboronate was shown to be an efficient and selective catalyst for this reaction. The present investigation concerns the catalytic performance of phenyl boronates with different substitution patterns in the aldol reaction. It appears that the dehydration reaction can be suppressed by selecting substituents and substituent positions with reduced electron withdrawing effects on the boronate function. Optimal suppression of the dehydration of β -hydroxyketones was obtained for compounds corresponding to phenylboronic acids with a $pK_a > 7$. The reactions between benzaldehyde and butanone or 3-pentanone did not show diastereoselectivity, which suggest that the catalysts merely act as bases rather than as templates for the transition state of the aldol reaction. Sterically more demanding ketones were not converted.



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T. Mueller, K. Djanashvili, I.W.C.E. Arends, J. A. Peters and U. Hanefeld, *Z. Naturforsch. B.* **2015**, *70*, 587 – 595.

5.1. Introduction

The aldol reaction was discovered 150 years ago and originally was performed with stoichiometric amounts of sodium to deprotonate the enol in the activation step of the reaction [1]. Later, other inorganic bases such as LiOH, NaOH, Na₂CO₃ and Ca(OH)₂ have been applied in stoichiometric amounts for this purpose [2 - 5]. Unfortunately, the base used for the initial deprotonation of the ketone is often also active in an undesired consecutive reaction, dehydration of the formed β -hydroxyketone. Suppression of this elimination reaction is highly desired as β -hydroxyketones can be used as building blocks for diols, amino alcohols and polyketides [6 - 11].

A way to increase the chemo-selectivity towards the β -hydroxyketone was introduced by Mukaiyama *et al*, applying stoichiometric amounts of a silyl enol ether as donor in the aldol reaction to form β -hydroxyketone [12 - 14]. A further improvement was introduced by Mori *et al*, who applied diarylborinic acid in the Mukaiyama reaction [15]. The advantage is a higher stereoselectivity of the reaction than that obtained before. This can be explained by a shorter bond length of the Boron - Oxygen bond as compared to metal oxygen bonds, resulting in a tighter six-membered ring transition state of the addition reaction [16, 17]. The boron mediated reaction by Mori with silyl enol ethers was performed in water at 30 °C.

More recently, activation of the ketone by the highly reactive trimethylsilyl chloride was avoided by generating the boron-enolate *in situ* [18]. However, with this procedure, high selectivities towards aldols could only be obtained when the ketone had an α -hydroxygroup.

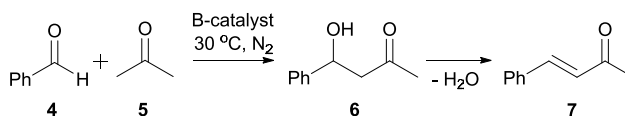
In a recent communication, we presented a boronate salt, as a basic catalyst for the aldol reaction, which showed high selectivity towards the aldol product with a wide range of aldehydes. This catalyst was soluble in organic solvents, which

An attempt to prepare the 2,6-difluoro and 2,4,6-trifluoro substituted boronate salts failed due to cleavage of the B-C bond during the reaction with sodium isopropanolate. This is most likely caused by an increase of steric strain and electrostatic repulsion during the conversion of the boron atom from planar trigonal to tetrahedral [20, 21].

5.2.2. Performance of the catalysts in the aldol reaction

The catalysts were tested in the aldol reaction of benzaldehyde (**4**) and acetone (**5**) at 30 °C (Scheme 2). High conversions were obtained rapidly after mixing the reactants. With 10 mol% of catalyst, a maximum conversion to the desired β -hydroxyketone (**6**) was obtained within 10 min. In addition, small amounts of side products (mainly **7**) were obtained due to elimination and oligomerisation reactions.

Figures 1A and 1B display the course of the reaction as a function of time (0-90 min) for the reaction using 10 or 20 mol% catalyst **3**, respectively. After fast conversion of benzaldehyde to the aldol product during the first few minutes, a relatively slow decrease of the concentration of **6** occurs. Analysis of the reaction mixture showed that this is caused by elimination of water from **6** to give **7** and minor amounts of its oligomerisation products. The large difference in reaction rates between the aldol reaction and the subsequent elimination allows termination of the reaction when the yield of aldol is maximal (Table 1).



Scheme 2. The aldol reaction catalysed by boronate salts **3a-f**.

The final slopes of the curves in Figure 1 suggest that the relative rates of the elimination reaction for the various catalysts increase in the order $3a < 3b < 3c < 3d < 3e < 3f$. This order is the same as that of the pK_a values of the corresponding phenylboronic acids **1** in water, which are 6.62, 7.08, 7.12, 7.50, 7.83 and 8.66, respectively (Scheme 1) [22 - 23].

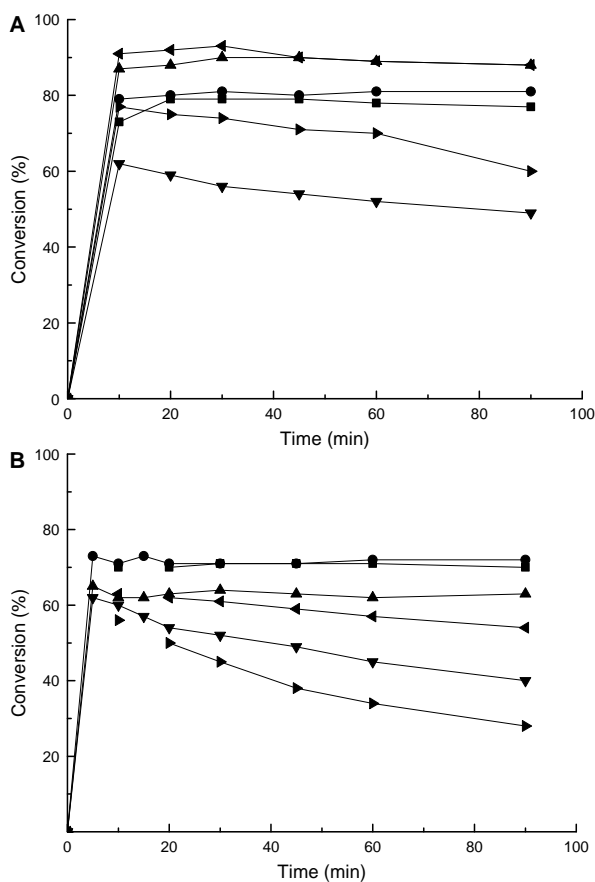


Figure 1. Amount of aldol **6** (in % of initial benzaldehyde **4** concentration) as a function of time during the reaction of 2 mmol of **4** in 20 mmol of acetone at 30 °C in the presence of (A) 10 mol% **3** and (B) 20 mol% **3**; **3a**▲ **3b** ●, **3c**■, **3d**◄, **3e** ▼, and **3f** ►.

The pK_a values of the boronic acids are determined by the charge density at the boron atom and hence it can be concluded that the activities in the elimination reaction with catalysts **3a-f** depend on the charge density of the boron atoms. Those with the highest positive charge density (the catalysts derived from the boronic acids with the lowest pK_a) show the lowest elimination rates, whereas the rates of the aldol reaction are very high for all catalysts investigated.

Table 1. Conversion and selectivity for the boron catalysed aldol reactions between benzaldehyde (2 mmol) and acetone (20 mmol), at 30 °C after 10 min.^[a]

Entry	Catalyst	Amount of catalyst [mol%]	Conversion [%]	Aldol 6 ^[b] [%]
1	3a	10	93	87
2	3b	10	90	80
3	3c	10	94	73
4	3d	10	93	91
5	3e	10	95	62
6	3f	10	94	77
7	3a	20	96	62
8	3b	20	95	77
9	3c	20	95	72
10	3d	20	96	64
11	3e	20	97	60
12	3f	20	96	56
13	3f	5	42	40
14	3f	2	25	23

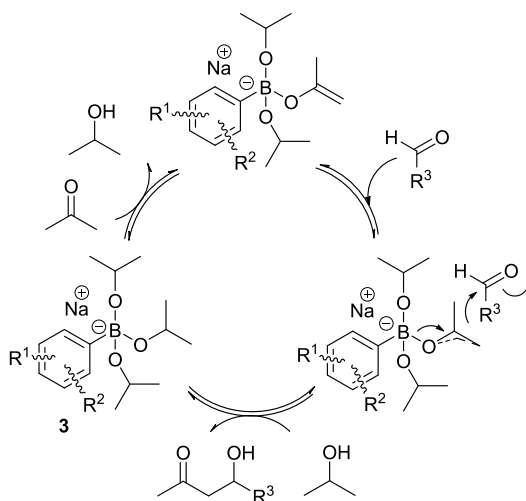
[a] As determined by NMR. [b] The remainder is mainly elimination product **7** in addition to minor amounts of products derived from sequential oligomerisation and elimination reactions.

The initial rates of the reactions with 10 or 20 mol% of catalyst were too high to enable accurate kinetics. Neither reducing the catalyst concentration (Table 1, entries 13, 14) nor cooling the reaction mixture enabled evaluation of accurate kinetics [19]. Comparison of the benzaldehyde (**4**) conversion at various catalyst concentrations (see Table 1) and of the final slopes of the aldol concentration as a function of time (Figure 1) suggest that both the rates of the aldol reaction and the subsequent elimination reaction are approximately first order in catalyst, which underlines the importance of the catalyst in the rate determining step of these reactions.

The effect of variation of the ratio **4** : **5** was investigated in reactions with 10 mol % of **3b** under the conditions given in Table 1. Increase of this ratio from 1:5, 1:10 to 1:20 led to an increase of the aldol reaction rate as reflected in an increase of the conversion from 55 to 95%, while the selectivity for aldol **6** remained about 80 %. All phenomena observed are consistent with the previously suggested mechanism (Scheme 3) [19].

Catalyst **3** deprotonates acetone to form the boron - bound enolate. Then reaction with the aldehyde results in β -hydroxyketone (**6**). The subsequent dehydration is not catalysed by any of the catalysts **3** due to their steric bulk. This is in contrast to sterically less demanding bases such as NaOiPr [19].

Increasing the positive charge density on the boron - atoms through the substituents at the phenyl groups of the catalysts will make them more electron withdrawing and hence the neighbouring oxygen - atoms will have higher negative charge densities. Consequently, these catalysts will be stronger Brønsted bases leading to enhancement of the reaction rate of the deprotonation of acetone. Accordingly, catalysts **3** corresponding to boronic acids (**1**) with the lowest pK_a values show the slowest elimination reactions.



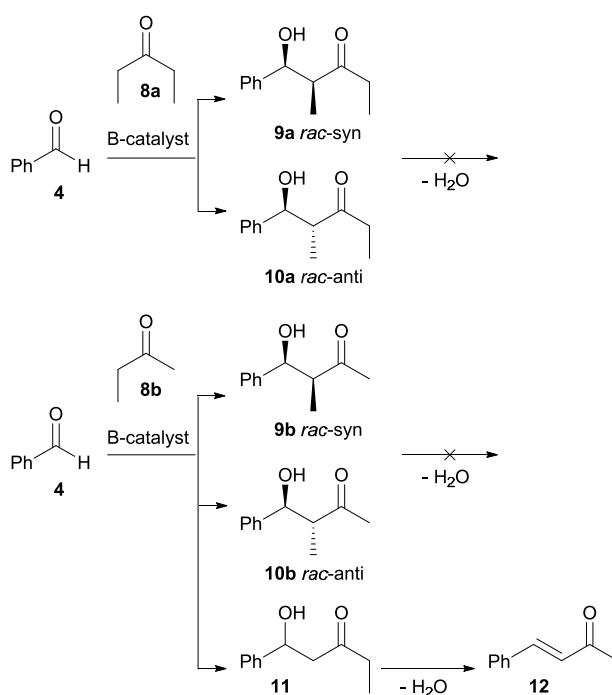
Scheme 3. The mechanism of the aldol reaction catalysed by the synthesised boronate salts **3 a-f**.

5.3. Regio - and stereoselectivity

To evaluate the regio- and stereoselectivity, catalysts **3a-c** and **3e** were also applied in the aldol reactions between benzaldehyde (**4**) and 3-pentanone (**8a**) or butanone (**8b**) at 30 °C (Scheme 4). In this study 20 mol% of the boron catalyst was used and again very fast conversion of benzaldehyde was observed during the first few minutes of the reaction, after which the reaction slowed down dramatically. The maximum amount of β-hydroxyketone was obtained already after 10 min (Table 2).

For 3-pentanone (**8a**), the selectivity towards the *rac*-syn- and *rac*-anti-β-hydroxyketones (**9a**, **10a**) was high, no dehydration was observed. In contrast, one of the aldols formed from reaction of butanone (**11**) dehydrated to give **12** (Scheme 4).

Probably steric hindrance by the methyl group is preventing the elimination reaction of **9** and **10**. With NaOiPr as the basic catalyst, the behaviour was similar. These reactions appeared to be prone to oligomerization of the aldol product after 90 min, as observed by GC-MS analysis. This oligomerisation could be suppressed by decreasing the reaction temperature to 0 °C. However, under those conditions, the reaction stopped after 30 min at 26 % conversion of benzaldehyde (Table 2, entry 6). Probably at low temperatures, the aldol reaction products are coordinating relatively strongly to the catalyst and thereby blocking it for further reaction [24].



Scheme 4. The boron catalyzed aldol reaction with benzaldehyde and 3-pentanone (**8a**) or butanone (**8b**).

All reactions with butanone and 3-pentanone showed no diastereoselectivity, neither with NaOiPr nor with **3a**, **b**, **c**, and **3e** as the catalyst (Table 2, entries 1 - 6 and 7 - 11). The ratio of **9** and **10** is in all cases about the same. If the aldol products were coordinated to the boronate salt, a different diastereoselectivity would be expected.

Therefore, it is not very likely that catalysts **3** are acting as a template for a six-membered transition state in the reaction between the enolate of the ketone (**5**, **8a/b**) and benzaldehyde (**4**) [25 - 27].

Table 2. Conversion and selectivity for the boron catalysed aldol reactions between benzaldehyde (2 mmol) and 3-pentanone (**8a**) or butanone (**8b**, 20 mmol) in the presence of 20 mol% of catalyst, at 30 °C after 10 min.^[a]

Entry	Catalyst	Conversion (%)	9 (%)	10 (%)	11 (%)	12 (%)
8a						
1	NaOiPr	91	33	56	— ^b	— ^b
2	3a	92	25	41	—	—
3	3b	91	26	47	—	—
4	3c	94	29	57	—	—
5	3e	94	24	48	—	—
6	3e^c	26	10	15	—	—
8b						
7	NaOiPr	93	10	16	25	41
8	3a	92	13	17	32	7
9	3b	75	12	12	36	— ^b
10	3c	97	7	8	21	37
11	3e	95	7	10	22	37

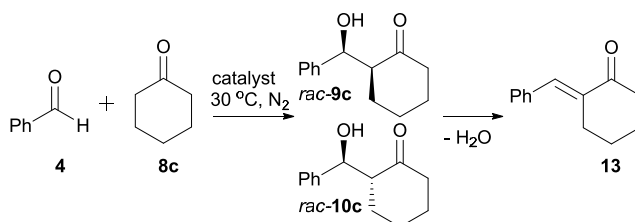
[a] As determined by NMR; GC-MS suggests that the remainder consists probably of oligomerization products, [b] Not observed. [c] after 30 min at 0 °C.

Compounds **3** rather are basic catalysts for the deprotonation of the ketone in this case. When more rigid cyclohexanone (**8c**) was employed instead of 3-pentanone **8a** only traces of the aldol products were observed (Scheme 5). While **3a** displayed sufficient activity to catalyse the conversion of acetone, **8a** and **8b**, the boron catalyst is too weak as a base to deprotonate the cyclic ketone **8c**. This might be due to an increased ring strain when deprotonating **8c**. Also no dehydration occurred and product **13** was not detected. NaOiPr as a much stronger base catalysed the reaction; formation of aldol product and subsequent dehydration took place (Table 3). As expected for NaOiPr no diastereoselectivity was observed, **9c** and **10c** were formed in equal amounts. Due to the higher activation energy for the deprotonation this catalyst displayed slightly better selectivity and only 4% of elimination product **13c** was detected.

Table 3. Conversion and selectivity for the boron catalysed aldol reaction between benzaldehyde and cyclohexanone (**8c**) in the presence of 20 mol% of catalyst, at 30 °C after 10 min.

Entry	Catalyst	Conversion (%)	9c+10c (%)	13 (%)
8c				
1 ^a	NaOiPr	72	34+34	4
2 ^b	3a	~2	Traces	--

^a 2 mmol benzaldehyde in 20 mmol cyclohexanone with 20 mol% NaOiPr. Conversion determined by ¹H NMR. ^b 1 mmol benzaldehyde in 10 mmol perdeuterated cyclohexanone with 20 mol% **3a**; reaction was followed *in situ* by ¹H-NMR.



Scheme 5. The boron catalyzed aldol reaction of benzaldehyde and cyclohexanone (**8c**).

5.4. Conclusions

Triisopropyl esters of fluoro-substituted phenylboronic acids are efficient basic catalysts for the aldol reactions of unhindered starting materials. They are highly stable in the substrate, which can also function as solvent. Manipulation of the charge density of the boronate group through the fluoro-substituents can be used to optimise the selectivity towards the desired β -hydroxyketone. This effect is mainly due to suppression of the undesired subsequent elimination reaction of the β -hydroxyketone. The highest selectivity towards the aldol product was obtained with boronates corresponding to fluoro-substituted phenylboronic acids with a $pK_a > 7$. As the catalyst acts as a mild base rather than as template, no diastereoselectivity is observed, also more demanding ketones were not converted due to this weak basicity.

5.5. Experimental

5.5.1. Materials

Experiments were performed with commercially available chemicals. Dry toluene and dry 2-propanol were used to synthesize the catalysts. All phenylboronic esters were synthesized by following the procedure of diisopropyl 3,5-difluorophenylboronic ester or sodium triisopropoxy 3,5-difluorophenylboronate (see below). 3Å molecular sieves were purchased from Metrohm. Silica-gel (Fluka, particle size 0.06 – 0.2 nm) was used for the isolation of the products. For the separation of the products ethyl acetate/petroleum ether (gradient) were used as eluent. Benzaldehyde was freshly distilled.

5.5.2. Analytical techniques

^1H , ^{11}B and ^{13}C NMR spectra were recorded at 400, 128, and 100 MHz, respectively, with a Bruker Avance-400 spectrometer, and at 300 (^1H) or 75 MHz (^{13}C) with a Varian Inova-300 spectrometer. The chemical shifts in ^{11}B NMR spectra were referenced to a 0.1 M boric acid solution in D_2O at 0 ppm. All other resonances in the ^1H and ^{13}C spectra were referenced to the residual solvent peak and are reported in ppm with respect to TMS. Boron substituted aromatic carbon nuclei were not observed in some cases due to severe line broadening. NMR data of aldol products were compared with literature to assign structures. TLC was performed with Silica gel 60 F254 (Merck) and analyzed at 254 and 365 nm. If needed, the product was visualized with iodine on the TLC plate. Mass spectrometry was performed with a Shimadzu QP-2010S GCMS spectrometer using GCMS solution software for data processing. Satisfactory elemental analyses or high-resolution mass spectra could not be obtained probably due to the boron and fluorine content of the compounds. Similar problems have been reported

previously [28-30].

5.5.3. Synthesis of the catalyst

All the catalysts were prepared according to procedure described for **2b** and **3b**.

Diisopropyl 3,5-difluorophenylboronate (2b).

3,5-Difluorophenylboronic acid (4.74 g, 30 mmol) and 2-propanol (12 g, 15 mL, 200 mmol) were dissolved in 15 mL of toluene. The reaction mixture was stirred for 24 h under reflux under a Dean-Stark trap filled with molecular sieve 3Å (11 g), 2-propanol (5 mL) and toluene (5 mL). After that the solvent was evaporated under reduced pressure and the product was distilled under reduced pressure. Pure **2b** (4.1 g) was obtained as a colourless liquid (16.9 mmol, 56 %). B.p 50 °C/6.5×10⁻² mbar. ¹H NMR (400 MHz, CDCl₃): δ = 1.25 (d, 12H, 4×CH₃, *J* = 6.5 Hz), 4.58 (sept, 2H, 2×CHOB, *J* = 6.5 Hz), 6.81 (m, 1H, H_{Ar}), 7.06 (m, 2H, 2×H_{Ar}). ¹¹B NMR (128 MHz, CDCl₃): δ = 7.6. ¹³C NMR (100 MHz, CDCl₃): δ = 24.6, 66.7, 104.7 (t, *J* = 25.2 Hz), 115.1 (m), 138.5 (C-B), 163.0 (dd, *J*₁ = 249.7 Hz, *J*₂ = 11.2 Hz).

Sodium triisopropoxy-(3,5-difluorophenyl)boronate (3b).

The reaction was carried out under a nitrogen atmosphere. Sodium (345 mg, 15 mmol) was dissolved in 60 mL of 2-propanol. The solution was stirred for 1 h under reflux and then cooled to 30 °C. Then a solution of 3.63 g (15 mmol) of diisopropyl 3,5-difluorophenylboronate (**2b**) in 8 mL of 2-propanol was added dropwise over 30 min. The mixture was stirred for 16 h at 30 °C, after which the solvent was removed under vacuum to give 4.78 g of a white powder (14.8 mmol; yield: 98 %). ¹H NMR (300 MHz, 2-propanol-*d*₈): δ = 1.11 (d, 18H, 6×CH₃, *J* = 6 Hz), 3.9 (sept, 3H, CHOB, *J* = 6 Hz), 6.54-7.04 (m, 3H, 3×H_{Ar}). ¹¹B NMR (128 MHz, 2-propanol-*d*₈): δ = -15.5. ¹³C NMR (75 MHz, 2-propanol-*d*₈): δ = 25.3, 63.6, 99.3 (m), 115.3 (m), 162.6 (dd, *J* = 10.3 Hz; *J* = 245.8 Hz), 162.9 (dd, *J*₁ = 246.5

Hz; $J_2 = 10.4$ Hz).

NMR data of the other phenylboronic esters:

Diisopropyl 3,5-bis-(trifluoromethyl)phenylboronate (2a).

^1H NMR (400 MHz, CDCl_3): $\delta = 1.27$ (d, 12H, $4 \times \text{CH}_3$, $J = 6.1$ Hz), 4.59 (sept, 2H, $2 \times \text{CHOB}$, $J = 6.1$ Hz), 7.89 (m, 1H, H_{Ar}), 8.00 (m, 2H, $2 \times \text{H}_{\text{Ar}}$). ^{11}B NMR (128 MHz, CDCl_3): $\delta = 7.5$. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 24.70$, 67.10, 123.19 (quin, $J = 3.8$ Hz), 123.2 (q, $J = 274.0$ Hz), 130.90 (q, $J = 33.0$ Hz), 133.0, 137.3 (C-B).

Sodium triisopropoxy 3,5-bis-(trifluoromethyl)phenyl-boronate (3a).

^1H NMR (300 MHz, CD_3OD): $\delta = 1.15$ (d, 18H, $6 \times \text{CH}_3$, $J = 6.2$ Hz), 3.92 (sept, 3H, CHOB , $J = 6.2$ Hz), 7.56 (s, 1H, H_{Ar}), 8.03 (s, 2H, $2 \times \text{H}_{\text{Ar}}$). ^{11}B NMR (128 MHz, 2-prop- d_8): $\delta = -15.51$. ^{13}C NMR (75 MHz, CD_3OD): $\delta = 25.3$, 64.7, 119.3 (quin, $J = 3.89$ Hz), 124.3, 127.9, 130.0 (q, $J = 117.68$ Hz), 131.54, 134.1.

Diisopropyl 2,4-difluorophenylboronate (2c).

^1H NMR (300 MHz, CDCl_3): $\delta = 1.22$ (d, 12H, $4 \times \text{CH}_3$, $J = 6.0$ Hz), 4.44 (sep, 2H, $2 \times \text{CHOB}$, $J = 6.0$ Hz), 6.70-6.80 (m, 1H, H_{Ar}), 6.84 – 6.94 (m, 1H, H_{Ar}), 7.30-7.42 (m, 1H, H_{Ar}). ^{11}B NMR (128 MHz, CDCl_3): $\delta = 8.0$. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 24.6$, 67.2, 103.51 (dd, $J_1 = 12.2$ Hz; $J_2 = 28.8$ Hz), 111.5 (dd, $J_1 = 20.3$ Hz; $J_2 = 3.2$ Hz), 134.9 (dd, $J_1 = 7.6$ Hz; $J_2 = 9.5$ Hz), 162.9 (dd, $J_1 = 67.34$ Hz; $J_2 = 11.7$ Hz), 166.2 (dd, $J_1 = 11.6$ Hz; $J_2 = 11.5$ Hz).

Sodium triisopropoxy-(2,4-difluorophenyl)boronate (3c).

^1H NMR (300 MHz, CD_3OD): $\delta = 1.15$ (d, 18H, $6 \times \text{CH}_3$, $J = 6.2$ Hz), 3.93 (sept, 3H, CHOB , $J = 6.2$ Hz), 6.51 – 6.59 (m, 1H, H_{Ar}), 6.65- 6.72 (m, 1H, H_{Ar}), 7.44-

7.51 (m, 1H, H_{Ar}). ¹¹B NMR (128 MHz, 2-prop.-d₈): $\delta = -15.8$. ¹³C NMR (75 MHz, MeOH-d₄): $\delta = 25.3, 64.7, 102.5$ (dd, $J_1 = 16.9$ Hz; $J_2 = 33.0$ Hz), 110.0 (dd, $J_1 = 18.3$ Hz; $J_2 = 2.9$ Hz), 131.7 (C-B), 138.0 (dd, $J_1 = 15.8$ Hz; $J_2 = 8.6$ Hz), 163.1 (dd, $J_1 = 241.5$, Hz; $J_2 = 13.7$ Hz), 165.8 (dd, $J_1 = 238.6$ Hz; $J_2 = 10.5$ Hz).

Diisopropyl 3-fluorophenylboronate (2d).

¹H NMR (300 MHz, CDCl₃): $\delta = 1.29$ (d, 12H, 4×CH₃, $J = 6.1$ Hz), 4.64 (sept, 2H, 2×CHOB, $J = 6.1$ Hz), 7.06-7.14 (m, 1H, H_{Ar}), 7.29-7.38 (m, 3H, H_{Ar}). ¹¹B NMR (128 MHz, CDCl₃): $\delta = 7.3$. ¹³C NMR (75 MHz, CDCl₃): $\delta = 24.7, 66.5; 116.2$ (d, $J = 21.0$ Hz), 119.5 (d, $J = 19.1$ Hz), 128.4 (d, $J = 3.0$ Hz), 129.6 (d, $J = 7.2$ Hz), 136.4 (C-B), 162.7 (d, $J = 244.9$ Hz).

Sodium triisopropoxy (3-fluorophenyl)boronate (3d).

¹H NMR (300 MHz, CD₃OD): $\delta = 1.15$ (d, 18H, 6×CH₃, $J = 6.2$ Hz), 3.93 (sept, 3H, CHOB, $J = 6.2$ Hz), 6.67-6.73 (m, 1H, H_{Ar}), 7.08- 7.19 (m, 2H, H_{Ar}), 7.27 (d, 1H, H_{Ar}, $J = 7.1$ Hz). ¹¹B NMR (128 MHz, 2-propanol-d₈): $\delta = -15.1$. ¹³C NMR (75 MHz, CD₃OD): $\delta = 25.3, 64.7; 112.1$ (d, $J = 21.2$ Hz), 119.8 (d, $J = 16.2$ Hz), 128.6 (d, $J = 7.5$ Hz), 129.6 (d, $J = 2.3$ Hz), 155.9 (C-B), 164.1 (d, $J = 240.7$ Hz).

Diisopropyl 2-fluorophenylboronate (2e).

¹H NMR (400 MHz, CDCl₃): $\delta = 1.22$ (d, 12H, 4×CH₃, $J = 6.1$ Hz), 4.44 (sept, 2H, 2×CHOB, $J = 6.1$ Hz), 7.01 (t, 1H, H_{Ar}, $J = 7.3$ Hz), 7.14 (t, 1H, H_{Ar}, $J = 8.5$ Hz), 7.35 (m, 2H, 2×H_{Ar}). ¹¹B NMR (128 MHz, CDCl₃): $\delta = 8.3$. ¹³C NMR (100 MHz, CDCl₃): $\delta = 24.6, 67.1, 114.9$ (d, $J = 24.1$ Hz), 121.9 (C-B), 124.6 (d, $J = 2.8$ Hz), 130.8 (d, $J = 8.2$ Hz), 133.7 (d, $J = 10.0$ Hz), 164.4 (d, $J = 239.7$ Hz).

Sodium triisopropoxy (2-fluorophenyl)boronate (3e).

¹H NMR (400 MHz, 2-propanol-d₈): $\delta = 1.16$ (d, 18H, 6×CH₃, $J = 6.2$ Hz), 3.94

(sept, 3H, CHOB, $J = 6.2$ Hz), 6.62 – 6.78 (m, 1H, H_{Ar}), 6.88 – 7.06 (m, 2H, H_{Ar}); 7.61 – 7.82 (m, 1H, H_{Ar}). ^{11}B NMR (128 MHz, 2-propanol- d_8): $\delta = -15.7$. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 25.2, 64.7; 112.0$ (d, $J = 28.3$ Hz), 119.77 (d, $J = 21.6$ Hz), 128.6 (d, $J = 9.0$ Hz), 129.6 (d, $J = 3.1$ Hz), 155.9, 164.1 (d, $J = 320.9$ Hz).

Diisopropyl 4-fluorophenylboronate (2f).

^1H NMR (300 MHz, CDCl_3): $\delta = 1.25$ (d, 12H, $4\times\text{CH}_3$, $J = 6.1$ Hz), 4.60 (sept, 2H, $2\times\text{CHOB}$, $J = 6.1$ Hz), 7.05 (t, 2H, H_{Ar} , $J = 9.1$ Hz), 7.58 (t, 2H, H_{Ar} , $J = 7.29$ Hz). ^{11}B NMR (128 MHz, CDCl_3): $\delta = 8.2$. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 24.8, 66.4, 114.9$ (d, $J = 19.8$ Hz), 129.3 (C-B), 135.2 (d, $J = 7.5$ Hz), 163.9 (d, $J = 246.6$ Hz).

Sodium triisopropoxy (4-fluorophenyl)boronate (3f).

^1H NMR (400 MHz, CD_3OD): $\delta = 1.15$ (d, 18H, $6\times\text{CH}_3$, $J = 6.2$ Hz), 3.92 (sept, 3H, CHOB, $J = 6.2$ Hz), 7.05 (m, 2H, H_{Ar} , $J = 9.0$ Hz), 7.46 (dd, 2H, H_{Ar} , $J_1 = 6.15$, $J_2 = 8.5$ Hz). ^{11}B NMR (128 MHz, 2-propanol- d_8): $\delta = -14.9$. ^{13}C NMR (100 MHz, MeOD): $\delta = 25.3, 64.7, 113.5$ (d, $J = 18.4$ Hz), 135.5 (d, $J = 6.3$ Hz), 162.9 (d, $J = 237.7$ Hz).

Diisopropyl 2,6-difluorophenylboronate.

^1H NMR (300 MHz, CDCl_3): $\delta = 1.21$ (d, 12H, $4\times\text{CH}_3$, $J = 6.0$ Hz), 4.38 (sept, 2H, $2\times\text{CHOB}$, $J = 6.0$ Hz), 6.82 (m, 2H, $2\times H_{Ar}$), 7.28 (m, 1H, H_{Ar}). ^{11}B NMR (128 MHz, CDCl_3): $\delta = 5.0$. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 24.6, 67.7, 111.0$ (dd, $J_1 = 25.7$ Hz; $J_2 = 1.7$ Hz), 131.2 (t, $J = 9.8$ Hz), 164.5 (dd, $J_1 = 243.2$ Hz; $J = 14.7$ Hz).

Diisopropyl 2,4,6-trifluorophenylboronate.

^1H NMR (300 MHz, CDCl_3): $\delta = 1.21$ (d, 12H, $4\times\text{CH}_3$, $J = 6.2$ Hz), 4.38 (sept, 2H, $2\times\text{CHOB}$, $J = 6.2$ Hz), 6.60 (dd, 2H, H_{Ar} , $J = 6.8$ Hz, $J = 9.0$ Hz). ^{11}B NMR (96

MHz, CDCl₃): δ = 7.0. ¹³C NMR (75 MHz, CDCl₃): δ = 24.5, 67.8, 100.0 (ddd, J = 3.2 Hz; J = 25.1 Hz; J = 28.6 Hz), 106.6 (C-B), 163.9 (td, ; J_1 = 249.6 Hz, J_2 = 15.7 Hz), 164.7 (ddd, J_1 = 243.3 Hz; J_2 = 18.0 Hz; J_3 = 16.9 Hz).

5.5.4. General procedure for the aldol reaction (with acetone)

Aldol reactions were performed in a NMR tube with 5 mm diameter at 30 °C. The reaction was monitored by ¹H NMR spectroscopy. The amount of sodium boronate (**3a-f**) desired for the particular experiment, 1 mmol of benzaldehyde and 68 mg (0.4 mmol) of 1,3,5-trimethoxy benzene, which was used as an internal standard, were dissolved in 640 mg (10 mmol) of [D₆]acetone.

5.5.5. General procedure for the aldol reaction (with butanone, 3-pentanone)

The aldol reactions were performed in a 10 mL onenecked flask (dried in the oven overnight, flushed with nitrogen). Benzaldehyde (212 mg, 2 mmol, 1 eq) and 1,3,5-trimethoxybenzene (100 mg, 0.6 mmol, 0.3 eq, internal standard for quantitative measurements by integration of signals) were dissolved in butanone or 3-pentanone (20 mmol, 10 eq). An aliquot of 25 μ L was taken from the reaction mixture to prepare the NMR samples in CDCl₃. A catalyst (boronate salt, 0.4 mmol, 20 mol%) was added to the reaction mixture and the conversion was followed by ¹H NMR spectroscopy at 30 °C.

5.5.6. General procedure for the aldol reaction (with cyclohexanone)

5.5.6.1. With sodium isopropoxide

The aldol reaction was performed in a 10 mL onenecked flask (dried in the oven

overnight, flushed with nitrogen). Benzaldehyde (212 mg, 2 mmol, 1 eq) and 1,3,5-trimethoxybenzene (67 mg, 0.4 mmol, 0.2 eq, internal standard for quantitative measurements by integration of signals) were dissolved in cyclohexanone (20 mmol, 10 eq). A 25 μ L sample was taken from the reaction mixture to prepare the ^1H NMR samples in CDCl_3 . NaOiPr (33 mg, 0.4 mmol, 20 mol%) was added to the reaction mixture and the conversion was followed by ^1H NMR spectroscopy at 30 $^\circ\text{C}$. The products were compared with literature known compounds [31].

5.5.6.2. With sodium boronate **3a**

The aldol reaction was performed in a 5 mm \varnothing NMR tube at 30 $^\circ\text{C}$. The reaction was monitored by ^1H NMR spectroscopy. 85 mg (0.2 mmol) of sodium boronate (**3a**), 106 mg (1 mmol) of benzaldehyde and 68 mg (0.4 mmol) of 1,3,5-trimethoxybenzene, which was used as an internal standard, were dissolved in 1.08 g (10 mmol) of $[\text{D}_{10}]$ cyclohexanone.

5.5.7. Isolation of aldol product **6**

Boronate salt (0.4 mmol **3b**) and 2 mmol of benzaldehyde were dissolved in 1.16 g (20 mmol) of acetone. The reaction mixture was stirred for 20 min at 30 $^\circ\text{C}$. The excess of acetone was evaporated and the residue was dissolved in 3 mL of water. The product was extracted with 3 \times 5 mL of ethyl acetate. The organic layers were combined, dried with MgSO_4 , filtered and the solvent was evaporated. The crude product was purified by column chromatography to yield 34% of 4-hydroxy-4-phenylbutan-2-one (**6**).

^1H NMR (400 MHz, CDCl_3): δ = 2.18 (s, 3H, CH_3), 2.77-2.92 (m, 2H, CH_2), 3.30 (s, 1H, OH), 5.16 (m, 1H, CHCOH), 7.28 – 7.36 (m, 5H, H_{Ar}). ^{13}C NMR (100 MHz, CDCl_3): δ = 30.8, 52.1, 69.9, 125.7, 127.7, 128.6, 142.9, 209.1.

5.5.8. Isolation of the aldol products **9a** and **10a**

Boronate salt (0.2 mmol **3b**) and 212 mg (2 mmol) benzaldehyde were dissolved in 1.72 g (20 mmol) of 3-pentanone (**8a**). The reaction mixture was stirred for 20 min at 30 °C. The excess of 3-pentanone was evaporated and the residue was dissolved in 3 mL of water. The product was extracted with 3×5 mL of ethyl acetate. The organic layers were combined, dried over MgSO₄, filtered and the solvent was evaporated to give 489 mg of crude product, which was purified by column chromatography using a column of 10 g silica gel (0.060 – 0.200 mm, pore diameter: 6 nm) The column was eluted subsequently with 9:1 petroleum ether : ethyl acetate 9:1, 8:2, and 7:3. The fractions containing the aldol products were combined and the solvents were evaporated to give 50 mg of a colourless oil consisting of a *syn*-1-hydroxy-2-methyl-1-phenylpentan-3-one (0.26 mmol, 13 % yield) and *anti*-1-hydroxy-2-methyl-1-phenylpentan-3-one (0.52 mmol, 26 % yield).

***Syn*-1-hydroxy-2-methyl-1-phenyl-pentan-3-one (9a).**

¹H NMR (300 MHz, CDCl₃): δ = 0.97 (t, *J* = 7.2 Hz, 3H, CH₃), 1.01 (d, *J* = 7.3 Hz, 3H, CH₃), 2.28 – 2.52 (m, 2H, CH₂), 2.93 (dq, *J*₁ = 7.2 Hz, *J*₂ = 4.2 Hz, 1H, CHCH₃), 5.05 (*J* = 4.2 Hz, 1H, CHOH), 7.27 – 7.37 (m, 5H, H_{Ar}). ¹³C NMR (100 MHz, CDCl₃): δ = 7.61, 10.7, 35.5, 52.4, 73.4, 126.0, 127.5, 128.0, 142.0, 216.4.

***Anti*-1-hydroxy-2-methyl-1-phenyl-pentan-3-one (10a).**

¹H NMR (300 MHz, CDCl₃): δ = 0.93 (d, *J* = 7.2 Hz, 3H, CH₃), 1.01 (t, *J* = 7.3 Hz, 3H, CH₃), 2.28 – 2.52 (m, 2H, CH₂), 2.93 (dq, *J*₁ = 7.2 Hz, *J*₂ = 8.3 Hz, 1H, CHCH₃), 4.75 (*J* = 8.2 Hz, 1H, CHOH), 7.27 – 7.37 (m, 5H, H_{Ar}). ¹³C NMR (100 MHz, CDCl₃): δ = 7.55, 14.6, 36.6, 52.8, 76.8, 126.1, 128.4, 128.6, 142.3, 216.2.

5.5.9. Isolation of aldol products **9b**, **10b** and **11**

Boronate salt (0.2 mmol) and 212 mg (2 mmol) of benzaldehyde were dissolved in 1.44 g (20 mmol) of butanone (**8b**). The reaction mixture was stirred for 20 min at 30 °C. Butanone was evaporated and the residue was dissolved in 3 mL of water. The product was extracted with 3×5 mL of ethyl acetate. The organic layers were combined, dried with MgSO₄, filtered and the solvent was evaporated to give 320 mg of the crude product. For purification by column chromatography, 20 g of silica gel (0.060 – 0.200 mm, pore diameter: 6 nm) was used, along with a 8:2 petroleum ether: ethyl acetate eluent. From two combined fractions containing the aldol products, the solvents were evaporated. The residues were two colourless oils, one of these being *anti*-4-hydroxy-3-methyl-4-phenylbutan-2-one in a yield of 28.6 mg (0.16 mmol, 8.0%) and the other being a mixture of 1-hydroxy-1-phenylpentan-3-one (34.7 mg, 0.20 mmol, 9.7%) and *syn*-4-hydroxy-3-methyl-4-phenylbutan-2-one (11.6 mg, 0.07 mmol, 3.2%).

***Syn*-4-hydroxy-3-methyl-4-phenylbutan-2-one (9b).**

¹H NMR (400 MHz, CDCl₃): δ = 1.02 – 1.06 (d, *J* = 7.4 Hz, 3H, CH₃), 2.14 (s, 3H, CH₃), 2.82 (dd, *J*₁ = 3.8 Hz, *J*₂ = 7.4 Hz, 1H, CH), 3.08 (s, br, 1H, OH), 5.12 (d, *J* = 4.2 Hz, 1H, CHOH), 7.30 – 7.36 (m, 5H, H_{Ar}). ¹³C NMR (100 MHz, CDCl₃): δ = 10.2, 29.4, 53.2, 73.0, 125.6, 125.9, 128.5, 141.8, 213.5.

***Anti*-4-hydroxy-3-methyl-4-phenylbutan-2-one (10b).**

¹H NMR (400 MHz, CDCl₃): δ = 0.93 (d, 3H, CH₃), 2.21 (s, 3H, CH₃), 2.84 (s, br, 1H, OH), 2.92 (dd, 1H, CHCH₃), 4.74 (d, 1H, CHOH), 7.31 – 7.35 (m, 5H, H_{Ar}). ¹³C NMR (100 MHz, CDCl₃): δ = 14.1, 30.0, 53.7, 76.5, 126.6, 128.0, 128.5, 141.9, 213.4.

1-hydroxy-1-phenylpentan-3-one (11).

^1H NMR (400 MHz, CDCl_3): δ = 1.06 (t, J = 7.4 Hz, 3H, CH_3), 2.45 (q, J = 7.3 Hz, 2H, CH_2), 2.82 (dd, J_1 = 3.7 Hz, J_2 = 8.7 Hz, 2H, CH_2), 3.36 (s, br, 1H, OH), 5.16 (dd, J_1 = 8.8 Hz, J_2 = 4.0 Hz, 1H, CHOH), 7.30 – 7.36 (m, 5H, H_{Ar}). ^{13}C NMR (100 MHz, CDCl_3): δ = 7.50, 36.8, 50.7, 70.0, 125.9, 128.5, 142.9, 211.9.

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Summary

VI

The C-X bond formation is an important tool to access new routes for molecules in organic chemistry. However, in many processes based on stoichiometric reactions a huge amount of waste is generated (Mitsunobu-, Wittig-, Grignard reaction). Our aim was to develop a novel and economical friendly catalytic system which would lead to, diminishing waste generation and improving selectivity of the reaction. Boron based compounds have been chosen as potential catalyst candidates considering that transformation of the primary and secondary alcohol into a boron ester would decrease electron density on the α -C atom, allowing nucleophilic substitution on the C-O bond for C-X bond formation (X= O, N, S). An additional argument for the application of a boron acid is the vast availability and easier regeneration of the catalyst, compared to phosphorus compounds.

Chapter 1 is giving the background of this thesis which illustrates clearly the need to replace the classical Mitsunobu reaction, into a less waste producing more atom efficient methodology, especially in view of the upcoming importance of alcohols as feedstocks.

In chapter 2 a route to synthesize tetrahedral sodium boronate salts with improved solubility and stability properties was described. Tetrahedral structures in contrast to trigonal boron esters exert significant catalytic activities due to facilitated coordination of the substrate. The equilibrium between trigonal and tetrahedral form in solution can be influenced by varying the pH value of a solution and manipulating the pK_a value of the given boron ester itself. An increase in pH shifts the equilibrium towards the desired tetrahedral structure. The pK_a value of the boron ester can be manipulated by decreasing electron density on the B-atom by adding electron withdrawing substituents in the phenyl group which results in a decrease of the pK_a of the substituted acid. In contrast, electron donating substituents increase the pK_a .

Water was removed from the reaction mixture in the synthesis of trigonal boron compounds to avoid hydrolysis. To further obtain the 'ate' complex, conversion of trigonal ester with sodium alkoxylate was performed. However, the stability of some of the synthesized 'ate' complexes under synthetic conditions (high T) turned out to be a problem. The presence of a carbon-boron bond proved to be essential to improve the thermal stability of the 'ate' complex.

In addition, some of the obtained tetrahedral boron esters exerted poor solubility in organic media (IPA, toluene, chloroform). By introducing electron withdrawing groups into the aromatic ring to stabilize the negative charge of the boron salt, the solubility in organic solvents could be improved significantly. The tetrahedral boron compounds with satisfactory stability and solubility in organic media were applied as catalysts in the aldol formation (Chapter 4 and 5).

Chapter 3 deals with the development of a potential boron-based catalyst, being able to catalyze nucleophilic substitution of primary and secondary alcohols. The experiments performed showed that nucleophilic substitution did not take place on the hydroxyl group as expected even though strong nucleophiles were selected for the reaction. This lack of reactivity was ascribed to the strength of the carbon-oxygen bond. Potentially, a boron catalyzed nucleophilic substitution could be achieved if primary and secondary alcohols would be replaced by their allylic analogues (weaker carbon – oxygen bond).

The low catalytic activity which was observed with sodium triisopropoxy-(3,5-difluorophenyl)-boronate as a catalyst in the esterification reaction and absence of conversion of the starting material in the amide reaction was ascribed to weak coordination of the substrate on the boronate salt. Nevertheless, by modulating the ortho and para – positions still available at the aromatic ring of the catalyst with electron donating or electron withdrawing groups, enhanced catalysts could be

designed to improve coordination of the substrate and increase conversion towards the desired product.

Application of sodium triisopropoxy-(3,5-difluorophenyl)-boronate in the aldol reaction resulted in a remarkable catalytic activity. Only after a few minutes of reaction time conversion of the aldehyde as high as 96% was observed. In addition to the high catalytic activity, there was improved selectivity towards the desired product when compared to other literature known data. An additional benefit with respect to environmental impact of the aldol reaction is the absence of solvent as described in the second chapter.

Chapter 4 describes the application of sodium triisopropoxy-(3,5-difluorophenyl)-boronate in the aldol process. Already after a short reaction time, high conversion and good selectivity towards the desired product was obtained, which indicated that this is an excellent catalyst candidate for the aldol reaction. Furthermore, NMR and Raman spectroscopy studies were used to elucidate the reaction mechanism and formation of the boron enolate.

Chapter 5 describes the catalytic performance of phenyl boronates with different substitution patterns in the aldol reaction. It appears that the dehydration reaction can be suppressed by selecting substituents and substituent positions with reduced electron withdrawing effects on the boronate function. Optimal suppression of the dehydration of β -hydroxyketones was obtained for compounds corresponding to phenylboronic acids with a $pK_a > 7$. The reactions between benzaldehyde and butanone or 3-pentanone did not show diastereoselectivity, which suggest that the catalysts merely act as bases rather than as templates for the transition state of the aldol reaction. Sterically more demanding ketones were not converted.

Samenvatting

De vorming van C - X bindingen is een belangrijke manier om toegang te krijgen tot nieuwe routes naar moleculen in de organische chemie. Echter, in veel processen op basis van stoichiometrische reacties wordt een enorme hoeveelheid afval geproduceerd (Mitsunobu-, Wittig-, Grignard reactie). Ons doel was om een nieuw en economisch vriendelijk katalytisch systeem te ontwikkelen dat zou leiden tot minder productie van afval en verbetering van de selectiviteit van de reactie. Op boor gebaseerde verbindingen werden als mogelijke katalysator kandidaten gekozen, aangezien de transformatie van de primaire en secundaire alcohol in een boorester zou leiden tot een afname van de elektronendichtheid op het α -C-atoom, waardoor nucleofiele substitutie op de C=O groep onder vorming van een CX binding (X = O, N, S) mogelijk zou worden. Een ander argument voor de toepassing van een boorzuur is de ruime beschikbaarheid en gemakkelijkere regeneratie van de katalysator, in vergelijking tot fosforverbindingen.

Hoofdstuk 1 beschrijft de achtergrond van dit proefschrift en illustreert duidelijk de noodzaak om de klassieke Mitsunobu reactie te vervangen door een minder afval producerende en atoom efficiëntere methode, in het bijzonder vanwege het opkomende belang van alcoholen als grondstof.

In hoofdstuk 2 wordt een route beschreven naar tetraëdrische natrium boronaatzouten met verbeterde oplosbaarheids- en stabiliteitseigenschappen. Tengevolge van sterkere coordinatie van het substraat, vertonen de tetraëdrische structuren, anders dan trigonale booresters, significante katalytische activiteit. Het evenwicht tussen de trigonale en tetraëdrische vorm kan worden beïnvloed door variatie van de pH van de oplossing en het manipuleren van de pK_a waarde van de boorester zelf. Een verhoging van de pH verschuift het evenwicht naar de gewenste

tetraëdrische structuur. De pK_a waarde van de boorester kan worden gemanipuleerd door het verlagen van elektronendichtheid op het B-atoom, door middel van het aanbrengen van elektronenzuigende substituenten op de fenylgroep, hetgeen resulteert in een verlaging van de pK_a van het gesubstitueerde zuur. Daarentegen verhogen elektronen donerende substituenten de pK_a .

Tijdens de synthese van trigonale boorverbindingen werd water uit het reactiemengsel verwijderd om hydrolyse te voorkomen. Het "aat" complex werd gevormd via reactie van de trigonale ester met natrium alkoxylaat. De stabiliteit van enkele gesynthetiseerde "aat" complexen bleek echter een probleem (bij hoge temperaturen). De aanwezigheid van een koolstof-binding bij borium bleek essentieel om de thermische stabiliteit van het "aat" complex te verbeteren.

Sommige van de verkregen tetraëdrische booresters zijn slecht oplosbaar in organische media (IPA, toluen, chloroform). Om de negatieve lading van boorzouten te stabiliseren werden elektronen-zuigende groepen op de aromatische ring aangebracht, waardoor de oplosbaarheid in organische oplosmiddelen aanzienlijk verbeterd werd. De tetraëdrische boorverbindingen, met voldoende stabiliteit en oplosbaarheid in organische media, werden toegepast als katalysatoren in de aldolformatie (hoofdstuk 4 en 5).

Hoofdstuk 3 gaat over de bereiding van een op boor gebaseerde potentiële katalysator voor nucleofiele substitutie van primaire en secundaire alcoholen. De uitgevoerde experimenten toonden aan dat de verwachte nucleofiele substitutie op de hydroxylgroep niet heeft plaatsgevonden, alhoewel sterke nucleofielen werden geselecteerd voor de reactie. Dit gebrek aan reactiviteit werd toegeschreven aan de sterkte van de koolstof-zuurstofbinding. Mogelijk kan een boor gekatalyseerde nucleofiele substitutie worden verkregen als primaire en secundaire alcoholen zouden worden vervangen door hun allylisch analogen (zwakkere koolstof - zuurstof binding).

De lage katalytische activiteit die bij de veresteringsreactie met natrium triisopropoxy-(3,5-difluorfenyl)boronaat als katalysator werd waargenomen en het falen van de omzetting van het uitgangsmateriaal in het amide werd toegeschreven aan zwakke coördinatie van het substraat aan het boronaatzout. Niettemin, kunnen door moduleren van ortho- en para- functies, welke nog steeds beschikbaar zijn op de aromatische ring van de katalysator, met elektronen donerende of elektronen zuigende groepen, verbeterde katalysatoren ontworpen worden met een sterkere coördinatie van het substraat en dientengevolge snellere omzetting naar het gewenste product.

Toepassing van natrium triisopropoxy-(3,5-difluorfenyl)boronaat in de aldol reactie resulteerde in een opmerkelijke katalytische activiteit. Al na enkele minuten reactietijd werd 96% conversie van het aldehyde waargenomen. Naast de hoge katalytische activiteit was er een verhoogde selectiviteit naar het gewenste product in vergelijking met andere uit de literatuur bekende gegevens. Een bijkomend voordeel ten aanzien van het milieu-effect van de aldolreactie is de afwezigheid van oplosmiddel, zoals beschreven in het tweede hoofdstuk.

Hoofdstuk 4 beschrijft de toepassing van natrium triisopropoxy-(3,5-difluorfenyl)-boronaat in het aldol proces. Reeds na korte reactietijd werd hoge omzetting en goede selectiviteit naar het gewenste produkt verkregen, waaruit bleek dat dit een uitstekende katalysator-kandidaat voor de aldolreactie is. Verder werden NMR en Raman spectroscopie studies gebruikt om het reactiemechanisme en de vorming van het boriumenolaat op te helderen.

Hoofdstuk 5 beschrijft de katalytische prestaties van fenylboronaten met verschillende substitutiepatronen in de aldolreactie. Het blijkt dat de dehydratatiereactie onderdrukt kan worden door de aard en de posities van de substituenten zodanig te kiezen dat het electronenzuigende effect op boor

verminderd wordt. Optimale onderdrukking van de dehydratatie van β -hydroxyketonen werd verkregen voor verbindingen corresponderend met fenylboronzuren met een $pK_a > 7$. De reacties tussen benzaldehyde en butanon of 3-pentanon vertoonden geen diastereoselectiviteit hetgeen suggereert dat de katalysator uitsluitend als base fungeert en niet als template voor de aldolreactie. Sterisch omvangrijkere ketonen werden niet omgezet.

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Public release

T. Mueller, K. Djanashvili, I.W.C.E. Arends, J. A. Peters and U. Hanefeld, *Z. Naturforsch. B.* **2015**, *70*, 587 – 595: Tetrahedral boronates as basic catalysts in the aldol reaction.

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T. Mueller, I.W.C.E. Arends, K. Djanashvili, U. Hanefeld, *Boron catalysed C-C bond formation*, Lecture, NCCC (11 - 13/03/2013), Noordwijkerhout, The Netherlands.

T. Mueller, I.W.C.E. Arends, K. Djanashvili, U. Hanefeld, *A catalytic S_N2 reaction of alcohols*, Lecture, CatchBio (22 - 24/01/2013), Nunspeet, The Netherlands.

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T. Mueller, I.W.C.E. Arends, K. Djanashvili, U. Hanefeld, *Solvent free aldol reactions*, Poster, Gordon Research Conference on Organic Reactions and Processes, (15 - 20/07/2012), Smithfield, RI, America.

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Curriculum Vitae

Tobias Müller was born on 04.June.1983 in Ulm, Germany. After finishing high school in 2002 at Technisches Gymnasium Biberach, he pursued his Diploma degree, with studies in Organic-, Inorganic-, Polymer and Physical Chemistry at the Faculty of Science in the University of Ulm. In 2008 he graduated within the Organic Chemistry Group at the University of Ulm on the subject of Transition Metal Catalysed Decomposition of Diazomalonic Ester Amides in Ionic Liquids under the supervision of Prof. Dr. Gerhard Maas. He moved to the Netherlands in 2009 and started a PhD project at the Technical University of Delft of which the results are presented in this dissertation.

