Tandem Catalytic Conversion of Benzaldehyde Dimethyl Acetal in Silica Stabilized Pickering Emulsions

Master Thesis

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Abstract

Compartmentalization is a strategy adapted by nature in order to perform multiple reactions simultaneously. Due to compartmentalization these reactions do not interfere. This strategy can also be used to perform "one-pot" reactions. These are reactions in which sequential steps are performed in the same reaction vessel. In case these steps require different catalytic mechanisms, these reactions are referred to as tandem reactions.

Inspired by nature, we used the compartmentalization effects of emulsion droplets in Pickering emulsions to keep an acid- and a base-catalyst separated. These catalysts were used for acid-base tandem catalytic reactions. The Pickering emulsions were prepared with different silica types as emulsifying particles: hydrophobized Aerosil 200, hydrophobized Stöber silica and hydrophobic HDK® H20. These particles had been studied with TEM, contact angle measurements, IR spectroscopy and nitrogen physisorption. Pickering Emulsions prepared with 6:2 toluene to water volume ratios stabilized by 3 wt-% HDK® H20 were the most stable emulsions of the studied ones. Confocal fluorescence microscopy with Nile red had showed that these emulsions are water-in-oil emulsions which were very polydisperse. Emulsions were also imaged using optical microscopy.

In this study, two showcase tandems were investigated: a deacetalization-Henry and a deacetalization-Knoevenagel tandem reaction of benzaldehyde dimethyl acetal. First, the reactions were studied separately in biphasic systems and Pickering emulsions. Deacetalization of benzaldehyde dimethyl acetal catalyzed by hydrochloric yielded more benzaldehyde in Pickering emulsions than in biphasic systems, also when both hydrochloric acid and piperidine were present in the reaction mixtures. However, when both hydrochloric acid and piperidine were present, conversions and yield were lower, indicating some mutual destruction of acid and base. Separate base-catalyzed Henry reaction of benzaldehyde with nitromethane to yield trans-β-nitrostyrene was neither successful in biphasic systems nor in Pickering emulsions. Deacetalization-Henry reaction did not yield the desired trans-β-nitrostyrene either. Base-catalyzed Knoevenagel condensation of benzaldehyde with malononitrile, however, was successful. Benzylidene malononitrile had even been formed during reaction in 3 hours at room temperature in both Pickering emulsions and biphasic systems. The reaction was more successful in biphasic systems than in Pickering emulsions, probably because the whole reaction takes place in the organic phase and the organic phase is crowded with water droplets in the emulsions. Also when both acid and base were present, Knoevenagel reactions were more successful in biphasic systems. However, benzaldehyde conversions and benzylidene yields decreased compared to the Knoevenagel reactions with only base, which again indicates mutual destruction of acid and base. Furthermore, deacetalization-Knoevenagel reactions of benzaldehyde dimethyl acetal were performed successfully and were studied with varying hydrochloric acid and piperidine concentrations. In this research it was found that deacetalization-Knoevenagel reactions could not be performed in simple toluene-water biphasic systems, but it worked well in Pickering emulsions due to the fact Pickering emulsions are able to partially compartmentalize reagents and keep water soluble hydrochloric acid and oil soluble bases separate, preventing mutual destruction to some extent. Yields of benzylidene malononitrile in these tandem reactions varied between 29 and 59 % after 3 hours at room temperature. If reaction was performed over 24 hours, benzylidene malononitrile yield even reached 76 %.

Contents

1   Introduction

Many chemists are concerned with atom economy and energy efficient processes, and to make chemical synthesis more efficient and sustainable it is important to think of new and innovative ways to perform reactions.[1] A strategy that gained more interest over the last decades is to perform multiple reaction steps in one reaction vessel.[2–4] In fact, this strategy plays a key role in the biosynthesis of compounds in living cells.[4] This is very inspirational to science, which is illustrated by the attempts to mimic the cell.[5–7]

Inspired by the cell, we would like to perform reactions using the "one-pot" strategy. In this work we describe the use of Pickering emulsions to perform tandem catalytic processes. Key aspects of this project are therefore: tandem catalysis, biomimicry of the cell and Pickering emulsions. These will be further explained in the coming subsections. This is followed by a brief description of previous work and the aim of this project.

1.1   "One-Pot" Reactions and Tandem Catalysis

The "one-pot" approach allows us to perform multiple reactions in a single reactor.[2,3] This certainly has benefits over conventional reactions in which one step is performed at a time. Both time and waste are reduced when multiple sequential reaction steps are performed simultaneously. Moreover, loss of materials is prevented, since fewer purification steps are needed.[3,8]

There are several ways to perform "one-pot" reactions. First division in the taxonomy of this type of reactions is made between reactions in which all (pre-)catalysts are present from the beginning of the reactions and those reactions in which they are not. If the latter is the case, the reaction simply consists of isolated catalytic events. However, if all catalysts and reagents are present from the outset, further division is made between cascade catalysis and tandem catalysis, of which the latter is further divided into subcategories.[2,3] These categories are summarized in the flowchart in figure 1.

As can be seen in figure 1, if there is only one catalytic mechanism responsible for the sequential reaction steps taking place in the vessel, it is called cascade catalysis.[2,3] This is often confused with the nearly-synonymous term 'tandem catalysis', which is defined by Fogg and Dos Santos[2] as "coupled catalysis in which sequential transformation of the substrate occurs via two (or more) mechanistically distinct processes". A schematic representation of tandem catalytic processes is depicted in figure 2.
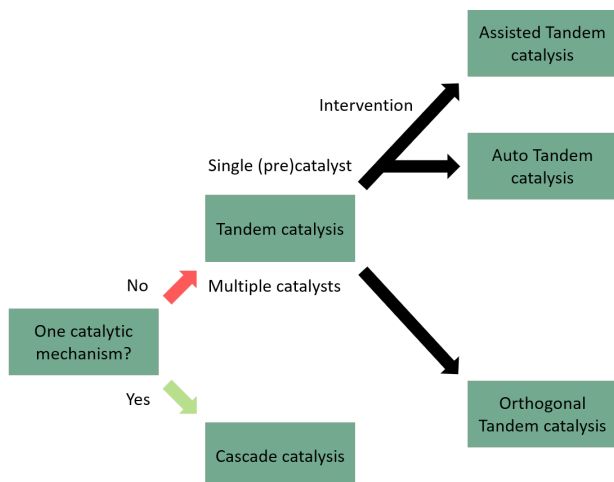
Figure 1: Flowchart of types of "one-pot" reactions in which all catalysts are in the reaction vessel from the outset. Figure adapted from Lohr *et al.*[3]
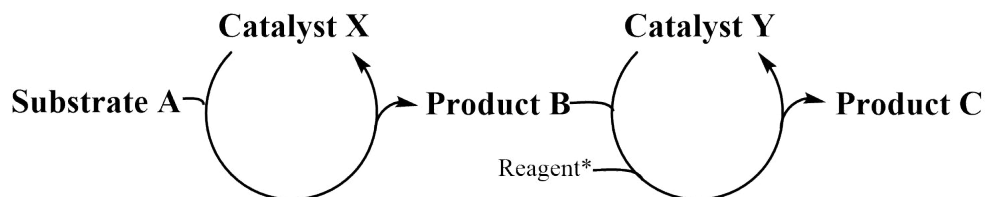

Figure 2: A schematic overview of tandem catalytic conversion of substrate A to product C. Substrate A is converted to Product B via one mechanism using catalyst X. Further conversion of Product B to Product C is achieved using another catalyst (catalyst Y) and via another mechanism for which sometimes an additional reagent is required. Figure adapted from Fogg and Dos Santos.[2]

As already illustrated by figure 1, within the category of tandem catalysis further division is made between auto tandem catalysis, assisted tandem catalysis and orthogonal tandem catalysis. The first two of these types require a single (pre-)catalyst. Auto tandem catalytic processes are processes in which two ore more mechanistically different catalytic reactions promoted by the same catalyst precursor occur.[2,3] The interaction between the different species in the system makes auto-tandem catalysis possible.[3] All reagents are present from the outset of the reaction. In assisted tandem catalysis, on the other hand, a new reagent is added to change the selectivity and performance of a catalyst.[2] Intervention in the system is achieved by the addition of this new reagent resulting in a switch from one catalytic mechanism to the other.[2,3]

Orthogonal tandem catalysis requires multiple catalysts. Much recent interest goes to this type of "one-pot" reactions and it is being applied to challenging synthetic problems lately.[3] In orthogonal tandem catalysis the catalysts for the different steps do preferably not interfere and are functionally different.[2,3] Just as in auto tandem catalysis, all reagents should be in the reaction mixture from the start of the reaction.

When performing "one-pot" reactions in which more than one catalyst is present, i.e. orthogonal tandem catalytic reactions, the catalysts have to be compatible. However, this is often not

the case,[3,4] for example when an acid- and a base-catalyst are used. A way to overcome catalyst incompatibility and prevent mutual destruction of catalysts is to compartmentalize reagents and catalysts, just like cells do.

1.2   Compartmentalization, Mimicking Cells

In living systems many reactions occur at the same time.[6,9] This could be problematic, since reagents inside the system are possibly antagonistic and could thus undergo mutual destruction. However, this is not the case in living cells, since they are capable of compartmentalization. This is one of the strategies a cell adapts to perform multiple chemical processes which are spatially separated. Therefore, it is one of the most important architectural features of the cell.[6] It is the most prominent in eukaryotic cells, since they contain multiple compartments, called organelles,[5] see figure 3. The organelles are enclosed by a biological membrane and fulfill distinct tasks.[5,6,10] Each compartment can perform its function without interference from other parts of the cell. Moreover, due to the localized confinement of reagents (as enzymes and metabolites) their local concentrations can be higher, possibly increasing reaction rates. It is even said that life could not emerge without compartmentalization.[5,6]
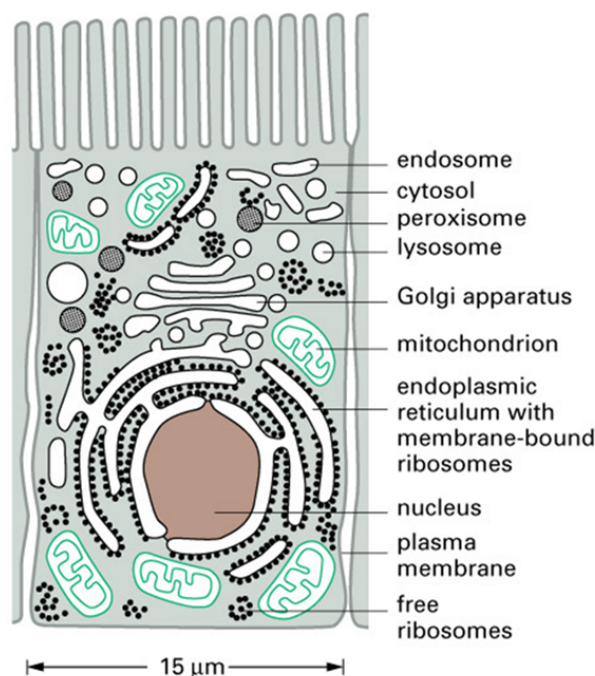

Figure 3: Schematic illustration of an eukaryotic cell with its compartments/organelles. Figure taken from *Molecular Biology of the Cell*.[11]

Thus, it would be very interesting to mimic cell strategies.[5,10] Nano- or microcapsules have to be created in order to mimic these natural compartmentalization phenomena and this can be achieved in several different ways.[5,6] These capsules can be based on inorganic structures as well as on natural systems.[5] One of the examples is capsules based on polymer materials, also known as polymersomes.[5,10,12] These are man-made analogues of natural liposomes. The main difference is the membrane that is made of amphiphilic block copolymers instead of a lipid bilayer. These poly-

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mersomes are easier to chemically modify. Furthermore, they are more stable and less permeable than liposomes.[5] These polymersomes are able to carry enzymes and other reagents and catalysts. Moreover, assemblies with multiple polymersomes have been formed, increasing the number of compartments in these structures, making their architecture increasingly similar to the very complex cell architecture.[10]

Instead of polymers or lipids, capsules can also be prepared using colloids.[10,13] The so-called colloidosomes are prepared by adsorption of the colloids to a water-oil interface. This results in emulsions which are stabilized by solid colloids, which can be used to compartmentalize reagents as well.[9]

1.3 Pickering Emulsions

Apparently, some solid particles (including colloids) can show similar behavior as surfactants and are for instance capable of forming emulsions.[9,13–15] Emulsions which are stabilized by solid particles, with sizes within the nanometric or submicron regime, instead of surfactants are called Pickering emulsions (see figure 4).[9,14–16] They are named after S.U. Pickering, who first described them in 1907.[17,18] While searching for emulsifiers other than soap, he found solid particles which could be used as emulsifying agents.[19]Pickering emulsions have certain benefits compared to classical emulsions. One advantage is the ease with which solid particles can be separated from reaction mixtures in comparison to surfactants.[20] For example, the solid particles can just be filtered or centrifuged.
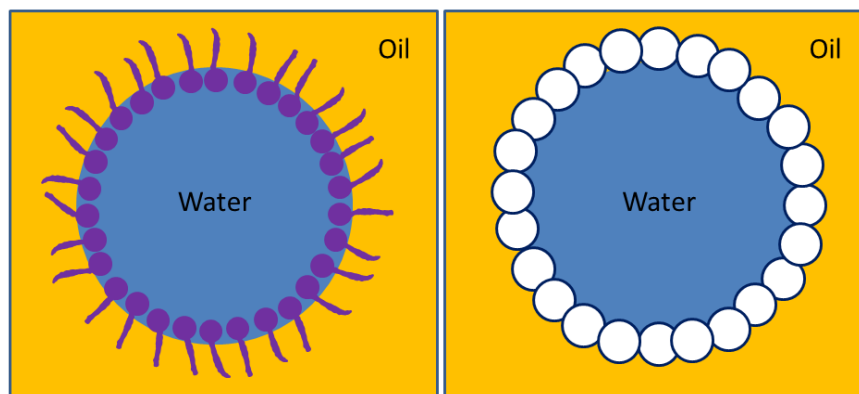

Figure 4: Schematic drawing of a water droplet in oil stabilized by surfactants as in a classical emulsion on the left and the same droplet stabilized by solid particles in a Pickering emulsion on the right.

The particles in Pickering emulsions reside, like surfactants, on the liquid-liquid interface of the emulsion. Therefore these particles have to be wettable by both liquids.[14,21] If particles are too hydrophilic or too hydrophobic and hence not wettable by both liquids, no emulsion will be formed or the emulsion will be very unstable. Wetting properties will be further explained in section 2.2. The wettability of the particle is not the only characteristic affecting emulsion stability; The stability also depends on the size, shape, surface properties and concentration of the particles.[14,15] Also the interactions between particles have shown to be of influence on the emulsions stability.

Although there are many variables affecting Pickering emulsion stability, these emulsions are more stable than classical emulsions.[21] The stabilizing effect of nanoparticles is proven by the fact that emulsion droplets in Pickering emulsions are highly stable against coalescence and Ostwald ripening.[9,17,22] Even bigger droplets, with a sizes within the millimeter regime, have shown to be extremely stable, and this is not observed in emulsions stabilized by surfactants.[14] However, when emulsions are stabilized by either very hydrophilic or hydrophobic particles the droplets are more likely to coalesce.[14] This is presumably caused by the easier removal of those particles from the interface during collisions of droplets. Although Pickering emulsions are known to be very stable, they can still separate.[9,17,22] Oil in water Pickering emulsions have shown to be unstable against shear.[23,24] Moreover, sedimentation or creaming induced by gravity might still occur.[14] Ultracentrifugation of an emulsion, for example, leads to sedimentation and eventual coalescence.[25]

Another advantage of Pickering emulsions is the increased interfacial area compared to simple biphasic systems.[22] By changing the number of emulsifying particles, the droplet size and therefore the interfacial area can be tuned.[16,26] More particles will result in smaller droplets, resulting in a larger oil-water interface. As shown by Zhang et al.[27] the average droplet diameter in the water-toluene Pickering emulsion decreased from 500 μm to 280 μm when the number of bifunctionalized silica particles varied between 0.3 wt-% to 1.2 wt-% with respect to the water phase. The big surface area between a water and oil phase is beneficial, since it allows reactions which occur at the interface to proceed faster.[27]

Furthermore, Pickering emulsions have another interesting feature: the particles that are used to stabilize the emulsion can be tuned and functionalized in a way that the emulsion is responsive to temperature or pH, for example.[20] The particles can even be magnetic, facilitating de-emulsification or they can be functionalized in a way they become catalysts, which opens the doors to so-called Pickering Interfacial Catalysis (PIC).[28,29] After reaction these particles can usually easily be separated from the reaction mixture and they can be re-used, which is an enormous benefit regarding the durability of the particles and Pickering emulsions in general.[29,30] Examples have shown that recovered catalytic emulsion stabilizing particles did not deactivate over several consecutive cycles.[27,29]

In the last decade, researchers have gained more interest in Pickering emulsions as media for chemical transformations[17,31] and for biomedical applications.[15] In this work we present a way to use Pickering emulsions for that first application.

1.4 Previous Work

Due to the highly atom efficient and step saving character of tandem and cascade reactions, systems capable of it have been studied before. Several of these systems even made use of incompatible reagents which were site isolated. Furthermore, Pickering emulsions have been used for several catalytic reactions. In this section some examples will be briefly highlighted, starting with studies focusing on tandem catalysis, followed by applications of Pickering emulsions.

Yang[32] and coworkers developed a type of nanoparticles with a basic core and an acidic shell. These yolk-shell nanoparticles therefore had a well defined morphology. By site isolation basic and acidic functional groups were kept apart, preventing neutralization of acid and base. They tested the catalyst in a deacetalization-Henry reaction (figure 5) at 90 °C in nitromethane for 22 hours and observed excellent conversions (100 %) and yields (>99 % in the first run) when the yolk-shell

catalyst was used with both the acid and base functions. Even during a second and third run the conversions (100 %) and yields (88 and 72 %, respectively) were good. However, the yields of the base-catalyzed reaction seemed to have decreased during these runs.
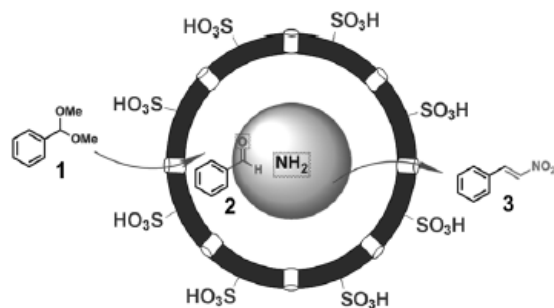

Figure 5: Schematic overview of deacetalization-Henry tandem in a Yolk-Shell Nanoreactor. First benzaldehyde dimethyl acetal (1) is converted to benzaldehyde (2) by the acidic shell. This is followed by Henry reaction in the basic core in which benzaldehyde is converted to trans-β-nitrostyrene (3). Figure from Yang _et al._[32]

Another way to achieve site isolation and perform tandem catalytic conversion is with dendritic systems. Helms and coworkers did this by using star polymers, a type of polymer which is highly branched.[33] Functional and catalytically active groups can be encapsulated within the interior of the polymer molecule. If polymer molecules with different core functionalities are put together the active sites are not able to reach each other because of the dendrites which keep the cores separated. Helms and coworkers demonstrated the approach performing an acid-catalyzed deacetalization of 4-nitrobenzaldehyde dimethyl acetal to 4-nitrobenzaldehyde followed by a base-catalyzed Baylis-Hillman reaction of 4-nitrobenzaldehyde and methyl vinyl ketone as shown in figure 6. This resulted in a final yield of 65% after a 36 hour reaction at 70 °C.
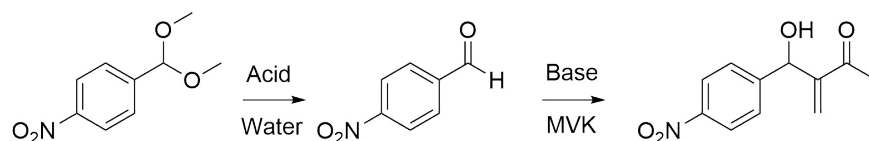

Figure 6: Tandem reaction as performed by Helms and coworkers.[33] First deacetalization of 4-nitrobenzaldehyde dimethyl acetal takes place, which is catalyzed by an acid. This is followed by further conversion of 4-nitrobenzaldehyde under reaction with methyl vinyl ketone (MVK), which is base catalyzed.

Moreover, metal organic frameworks (MOFs) have been widely applied for tandem and cascade reactions as well.[34] MOFs are highly porous crystalline materials which are built up from metal ions which are connected by organic linkers. These metal ions often make MOFs Lewis acid-catalysts. But MOFs can also have other active sites, such as a catalyst encapsulated inside its pores or an active site covalently bound to the organic linker molecules. This results in many possibilities to develop bifunctional MOF catalyst. Therefore, several different tandem reactions have been performed using MOFs, among them oxidation-hydrogenation, oxidation-esterification, nitro reduction-cyclization, deacetalization-Henry and deacetalization Knoevenagel as reviewed by Dhakshinamoorthy _et al._[34]

As stated earlier, Pickering emulsions are capable of compartmentalizing reagents in the emulsion droplets and keeping them separated from the compounds in the continuous phase.[5,9,32] This can make them particularly useful as reaction media. Some groups already did some research on this application. First, Pickering emulsions have been used to perform enzyme catalysis by Wu and coworkers.[35] Enzymes have shown to be very powerful catalysts in organic synthesis. However, to be of practical use to organic reactions, hydrophilic enzymes need to be immobilized or brought into carriers. An easy way to do this is through emulsification. Surfactants, however, can destroy enzymes and therefore it is convenient to use amphiphilic nanoparticles instead of surfactants as emulsifyer in this case.[35] Another advantage is of course the easy separation of particles in comparison to the separation of surfactant molecules.

One of the systems that has been investigated by the group of Yang was a flow Pickering emulsion, in which the water droplets were packed and immobilized in a column, as shown in figure 7.[22] These water droplets confine a water soluble catalyst, for example sulfuric acid or enzymes. The droplets were densely packed in the column. At the bottom of the column a micron-sized filter has been placed. The droplets are too big to go through the filter, but the organic phase is able to flow through. Determination of the concentration of the confined reagent has showed about 95 % of the reagent has still been residing in the column after 120 hours of flowing, confirming the confinement and the immobility of the water droplets. In these flow Pickering emulsions several catalysts and reactions were tested with conversions of 80 % and higher. These systems actually resemble fixed bed reactors.
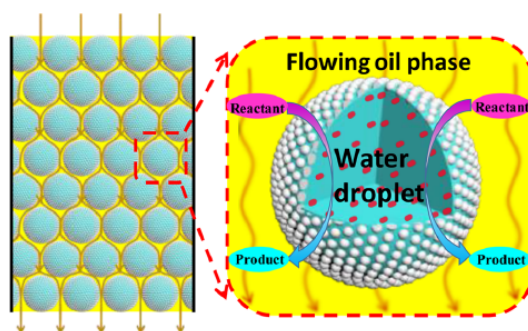

Figure 7: Flow Pickering emulsion. Reactants flow with the organic phase past water droplets containing a catalyst. Inside the droplet or on the interface the reactant is converted in a product that flows further with the organic phase. Figure reproduced from Zhang *et al.*[22]

The group of Yang has also prepared layered Pickering emulsions to perform tandem catalytic conversion reactions.[9] Water in oil emulsions have been used to do so, hence the system has been made of water droplets in an emulsion with oil as continuous phase. Two different emulsions have been prepared, which are stacked on top of each other in several layers. One emulsion contains an acid dissolved in the water droplets, while the other emulsions contains base. This way acid and base are compartmentalized and do not neutralize each other. Oil soluble reagents are able to diffuse through the continuous organic phase and undergo reactions catalyzed by the acid or base in the water droplets. Some of the reactions they have performed this way are the deacetalization-Henry and deacetalization-Knoevenagel tandem reactions, which are both used more frequently to demonstrate tandem catalysis.[9,34]

1.5 Project Aim and Approach

In this project Pickering emulsions will be used to perform tandem catalytic conversion reactions. Incompatible reagents will be dissolved in the two different phases of the emulsion. In order to study reactions in Pickering emulsions, these emulsions should be stable during reaction and therefore first stable emulsions have to be prepared. The aims of the project are therefore:

1.) To prepare silica stabilized Pickering emulsions which are stable, also under reaction conditions.
2.) To determine the efficiency of Pickering emulsions regarding orthogonal tandem reactions with incompatible reagents.

To study Pickering emulsions for tandem catalytic conversion with incompatible reagents, two tandem reactions with an acid- and a base-catalyst are investigated. In this research the focus will be on the deacetalization-Henry tandem reaction and the deacetalization-Knoevenagel tandem reaction of benzaldehyde dimethyl acetal, which are showed in figure 8.
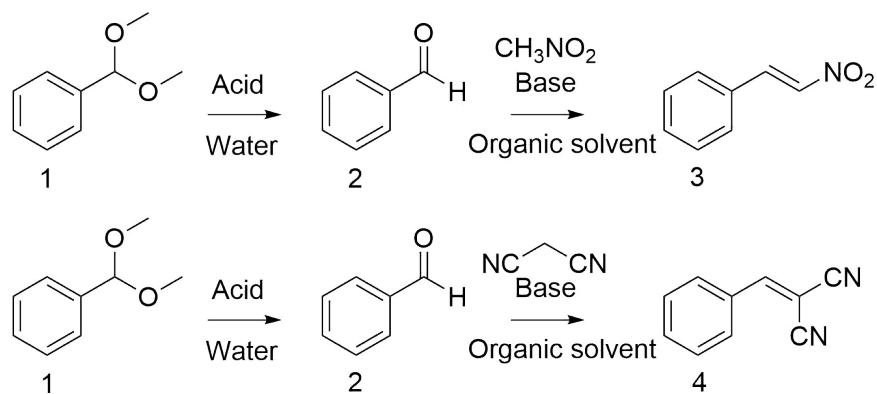

Figure 8: deacetalization-Henry (above) and deacetalization-Knoevenagel tandem reactions with benzaldehyde dimethyl acetal (1) as substrate. Deacetalization yields benzaldehyde (2) which is further converted to either trans-β-nitrostyrene (3) during Henry condensation with nitromethane or benzylidene malononitrile (4) during Knoevenagel condensation with malononitrile

Deacetalization of benzaldehyde dimethyl acetal takes place in both of these tandem reactions. Benzaldehyde dimethyl acetal is converted to benzaldehyde via acid-catalyzed hydrolysis. In the deacetalization-Henry tandem this is followed by the base-catalyzed Henry condensation of benzaldehyde with nitromethane to form trans-β-nitrostyrene. In the deacetalization-Knoevenagel tandem, benzaldehyde is further converted to benzylidene malononitrile using malononitrile and a base-catalyst.

Deacetalization takes place in the water phase, which contains the acid. For this, the benzaldehyde dimethyl acetal needs to diffuse to the interface, since its dissolution in the oil phase is favored over its dissolution in the water phase. The resulting benzaldehyde will diffuse to the organic phase, since it is also quite hydrophobic. Once there, it is expected to react further to yield trans-β-nitrostyrene in the case of Henry condensation and benzylidene malononitrile in case of Knoevenagel condensation. The deacetalization-Knoevenagel tandem reaction is schematically represented for both the biphasic system and Pickering emulsions with piperidine as base-catalyst in figure 9, as is studied most during this project. Deacetalization-Henry reaction is expected to occur in a similar way.
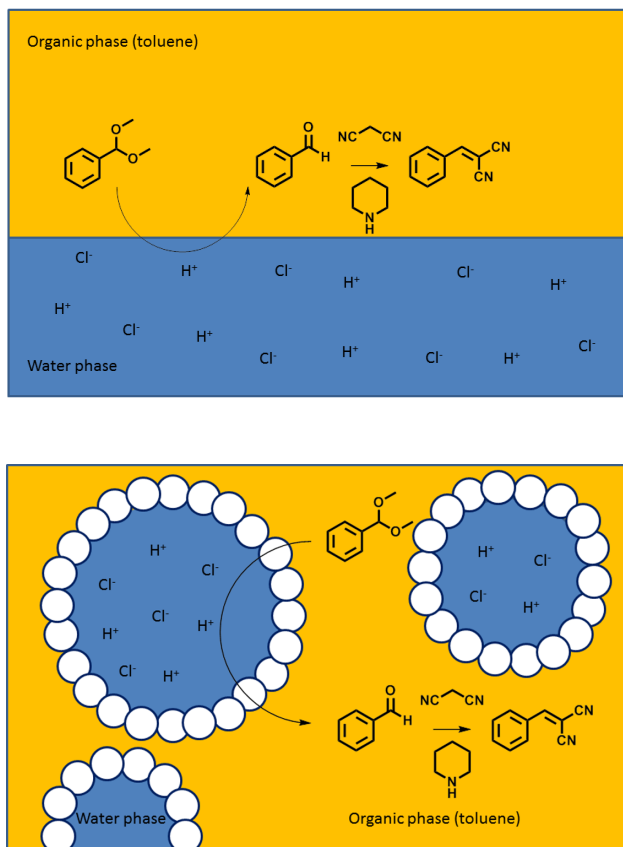

Figure 9: Schematic representation of deacetalization-Knoevenagel tandem reaction in a biphasic system (top) Pickering emulsion (bottom) as also studied in this project: benzaldehyde dimethyl acetal is hydrolyzed using an acid-catalyst (diluted hydrochloric acid), followed by Knoevenagel condensation of benzaldehyde with malononitrile using piperidine as a base-catalyst. Blue depicts water phase, yellow organic phase (toluene) and white silica particles.

2   Theory

In this section the most important theoretical aspects of the project will be addressed. First of all the emulsifying particles will be discussed, followed by a more in-depth discussion of the origins of wetting properties and ways to measure it. Furthermore, reactions at liquid-liquid interfaces and the mechanisms of the reactions studied in this project are highlighted.

2.1   Emulsifying Particles

Several particles capable of being wetted (wetting is further explained in section 2.2) by both an organic and an aqueous phase exist and therefore there are many different particles, either organic or inorganic, which can be used to form Pickering emulsions.[16] These can be for example carbon nanotubes, block copolymers, clays, latex particles or silica colloids.[16,25] These particles assemble at the interface of two different phases to reduce the interfacial area.[15] This is actually the driving force for the particle assembly and emulsion formation.[16]

Interesting types of particles which are particularly capable of stabilizing emulsions are so-called Janus particles and asymmetric patchy particles.[14,36] These particles can be made of many different materials. They are chemically asymmetric, e.g. one side of the particle is hydrophobic, the other is hydrophilic. When these sides have the same size, the particles are called Janus particles. If both sides differ in size they are called asymmetric patchy particles[36] (figure 10). An example of asymmetric particles are the several nanohybrid materials that exist, like carbon-metal oxide nanohybrids[37] and carbon-silica nanohybrids.[38] The chemical asymmetry gives the surfactant-like behavior to the particles which leads to self-assembly at interfaces. These particles can also simultaneously be catalysts and phase-selective catalysis can be performed.[26,39]
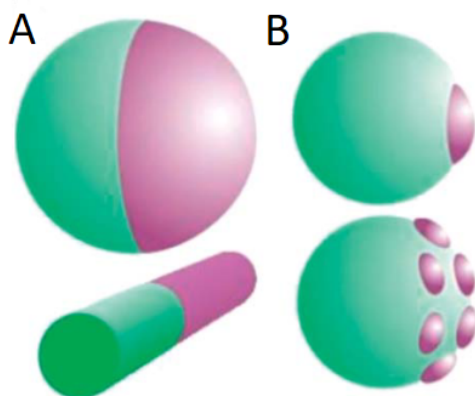

Figure 10: A schematic illustration of Janus particles (A) and asymmetric patchy particles (B). Figure taken from Loget _et al._[36]

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Apart from the wetting properties there are several other variables that have a huge influence on the Pickering emulsions. As mentioned earlier size, shape, surface properties and concentration of the particles have an effect on emulsion properties.[15] As the chemical properties can be modified by chemical grafting, emulsions with some new properties can be prepared. For instance, thermosensitive particles give temperature sensitive emulions, as pH responsive emulsions can be obtained using pH sensitive particles and magnetic field responsive emulsions can be made using magnetic

particles.[16] If one is able to prepare emulsions which respond to stimuli like pH and temperature changes this is of a big advantage. Some groups already made use of this knowledge. They made pH-switched Pickering emulsions that separate upon changing pH, which could be used to help recover catalysts from emulsions.[21, 40]

Silica is often used as emulsifying particle, since it has proven to work very effectively as an emulsifying agent and its surface can easily be modified.[17, 41] However, bare silica is typically not able to stabilize emulsions with oil and water, since it is completely wet by the water phase.[16] Bare silica can only be used when the oil is an organic liquid with chemical functions which are rather polar. To control hydrophilicity of silica particles and increase their emulsifying ability, these particles can be chemically grafted.[42] These particles are usually covered by silanol groups which facilitate chemical anchoring. Several catalytic reactions have been performed with chemically grafted silica on which catalytic active groups, e.g. Brønsted acid and base sides, were anchored.[42, 43]

2.2 Wettability of Solid Particles

Hydrophobicity of the particles is one of the key parameters that has obviously an influence on the type and stability of an emulsion.[14, 25] This is because it influences the wettability of a particle.[14, 18, 25] Wetting describes the way a liquid drop spreads over a surface. Complete wetting or partial wetting might occur depending on the type of liquid and the hydrophilicity of the material of the surface. It is typically measured in terms of the contact angle θ, which the solid particle makes with the oil-water interface, as can be seen in figure 11.[14, 25] Complete wetting occurs when a drop of a certain liquid completely spreads over a surface, partial wetting occurs when a drop does not completely spread and a contact angle between 0 and 180° is found between the droplet and the surface.[18]
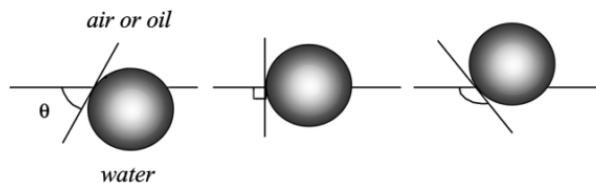

Figure 11: Contact angle θ a solid particle makes with the interface between water and air or oil as measured through the water phase. Left a hydrophilic particle, in the middel a particle of intermediate hydrophilicity and on the right a hydrophobic particle. Figure taken from Binks _et al._[14]

When particles are completely wetted by either the oil or the water phase, the particles will remain dispersed in that phase and no stable emulsion will be formed.[25] If θ, as measured through the water phase, is smaller than 90° the particles are usually hydrophilic and stabilize oil in water (o/w) emulsions. On the other hand if θ is larger than 90°, the particles are hydrophobic and tend to stabilize water in oil (w/o) emulsions.[25] Particles resulting in a contact angle of 90° have the largest possible desorption energy.[15]

The contact angle θ is one of the parameters which determine the strength or energy that holds the particle on the interface. This parameter can be measured as will be explained in the next section. Another parameter is the interfacial tension, γ_{ow}. This tension and the tensions between

the particle and the oil phase γ_{so} and the particle and the water phase γ_{sw} are related to the contact angle and hence to the wettability by Young's law:[25, 44]

$$\gamma_{so} - \gamma_{sw} = \gamma_{ow} \cos \theta$$

This equation holds at constant pressure and temperature.[44]

2.2.1 Contact Angle Measurements

Many techniques have been developed to measure wettability of solids.[41] Scientists aim for direct observation of a nanoparticle on a liquid-liquid interface but the methods typically encounter problems with magnification limits in optical microscopy or moving of particles upon the addition of gelation agents.[41, 45] Grigoriev and Nowak and their coworkers tried to come up with some new, indirect methods involving for example AFM (atomic force microscopy) or an excluded-area technique in which the contact angle is derived from the surface pressure.[44, 45]

In this project wetting of several silica materials is determined using the rather facile sessile drop method.[46, 47] With this method a drop of one liquid is put on a surface of a wafer within the other liquid or air. The profile of the droplet depends on a force balance between the interfacial tensions as well as the contact angle between the drop and the surface it is on.[47] Contact angles can easily be derived from the images of the droplet on the surface. However, these are bulk contact angles and contact angles of individual nanoparticles are still not obtained.

2.3 Reactions at the Liquid-Liquid Interface

As mentioned before, in this study Pickering emulsions will be used as reaction media. Performing reactions in Pickering emulsions essentially also means performing reactions in two (or more) otherwise immiscible solvents. This is especially useful if there are any reagents, intermediates or products which normally would not dissolve in the same phase as the other reagents, i.e. if there are immiscible reaction partners.[48] In biomass refinery, for example, oxygen-rich, hydrophilic molecules are converted to species containing less oxygen atoms.[20] These products are typically less hydrophilic and tend to dissolve in the organic phase.[20] This type of reactions is facilitated if the oil and water phase co-exist, enabling formation of hydrophilic molecules which would not easily be formed if there is only a water phase.

In most cases however, mass transfer between these different phases is very low which results in slow reaction rates.[49, 50] This is particularly the case when the interfacial area is small. Therefore, one way to increase the mass transfer is to increase the interfacial area. As we have seen, this can be done by making emulsion droplets, with Pickering emulsions for example.[9] An increased interfacial area is also achieved by making droplets in a microfluidic device as shown by Ji and co-workers.[49]

Besides increasing the interfacial area a Phase Transfer Catalyst (PTC) can also be used to improve mass transfer.[48–51] A PTC facilitates transport of a certain molecule from one phase to the other.[48–51] Liquid-liquid PTC is typically carried out using a quaternary ammonium salt e.g. tetrabutylammonium bromide), phosphonium salts or crown ethers as a catalyst. These catalysts enable transport of anionic reagents from the water phase to the organic phase. Since dissolution of the anionic reagent in the organic phase is weaker than in the water phase, its nucleophilicity is enhanced.

This leads to an increased reaction rate of the anion with a lipophilic reagent in the organic phase.[48]

In this project mass transfer limitations are mainly decreased by increasing the interfacial area, using emulsification. The approach of PTC is left disregarded within this project.

2.4 Catalytic Reactions

The aim of this section is to give some insights into the reaction mechanisms of the reactions that are investigated during this project. First the deacetalization reaction will be described. This is followed by a description of the mechanism of the Henry condensation. The final subsection describes the Knoevenagel condensation mechanism.

2.4.1 Deacetalization Reaction

Acetals and ketals are compounds which are typically formed to protect carbonyl groups during complex synthesis.[52,53] They are stable against bases and basic nucleophiles. Deprotection or deacetalization is carried out to acquire the reactive carbonyl group. Often deprotection is referred to as hydrolysis since water is involved in this reaction.[54] This is achieved by acid catalysis and is facile under aqueous conditions.[52,53] However, it is also claimed that both aliphatic and aromatic dimethyl and diethyl acetals can be deprotected without the use of acid under elevated temperatures (80 °C).[52] In figure 12 the mechanism of acid-catalyzed deacetalization of benzaldehyde dimethyl acetal is depicted.
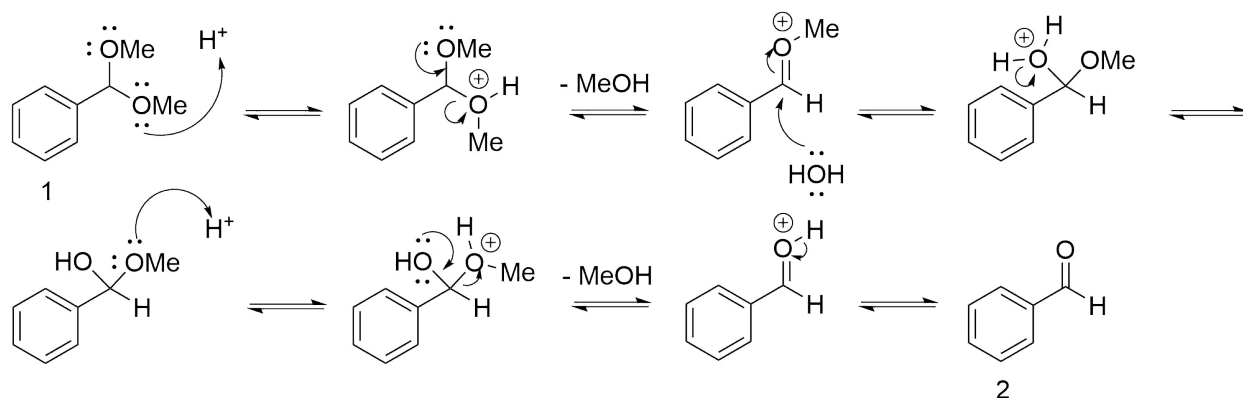
Figure 12: Mechanism of the acid-catalyzed deacetalization of benzaldehyde dimethyl acetal (1) yielding benzaldehyde (2).

First step of the reaction is protonation of one of the methoxy-groups. This is followed by the elimination of methanol yielding an oxonium ion. This ion reacts with water giving a hemiacetal intermediate. This hemiacetal reacts with a proton again, which leads to the protonation of the second methoxy-group. A second methanol molecule has formed yielding a new oxonium ion that is readily converted to yield benzaldehyde and a proton is regenerated.[53]

2.4.2 Henry Condensation

Henry condensation or Henry reaction is the condensation of aldehydes with nitronates.[55] These nitronates are formed under deprotonation of nitroalkanes, which is typically performed by a base. Another name is nitroaldol condensation because of the similarities of reactions of enolates and aldehydes in normal aldol condensation.[53] These reactions are base-catalyzed and yield β-nitroalcohols and, upon further dehydration, β-nitroalkenes.[43,55,56] In figure 13 the mechanism of Henry condensation of benzaldehyde with nitromethane is depicted.
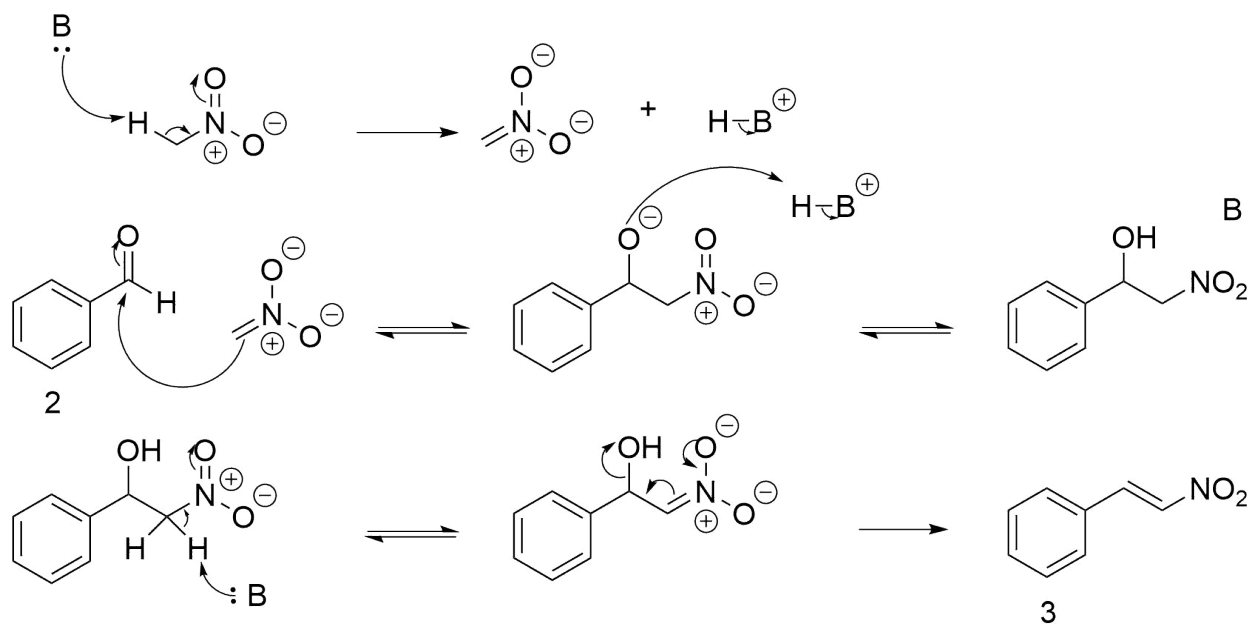
Figure 13: Mechanism of Henry condensation of benzaldehyde (2) with nitromethane yielding trans-β-nitrostyrene (3) upon final dehydration (bottom reaction). Base is depicted by the 'B'.

First step of Henry reaction of benzaldehyde and nitromethane is deprotonation of nitromethane yielding its corresponding nitronate ion. This nitronate ion attacks the benzaldehyde carbonyl carbon atom which eventually yields the β-nitroalcohol (middle reaction). This nitroalcohol undergoes dehydration, which is most often the case for nitroalcohols of aromatic aldehydes.[53]

2.4.3   Knoevenagel Condensation

Aldehydes and ketones may undergo condensation reactions with malononitrile to form aryl- or alkylidenemalononitriles.[57] This reaction is also referred to as Knoevenagel condensation.[9,56,58] According to Li the methylene compound is activated by an amine which functions as a base-catalyst in this reaction.[55] Furthermore, Westheimer and Knoevenagel proposed the formation of an iminium ion in the mechanistic pathway as well.[59] The mechanism of Knoevenagel condensation of benzaldehyde with malononitrile is shown in figure 14.
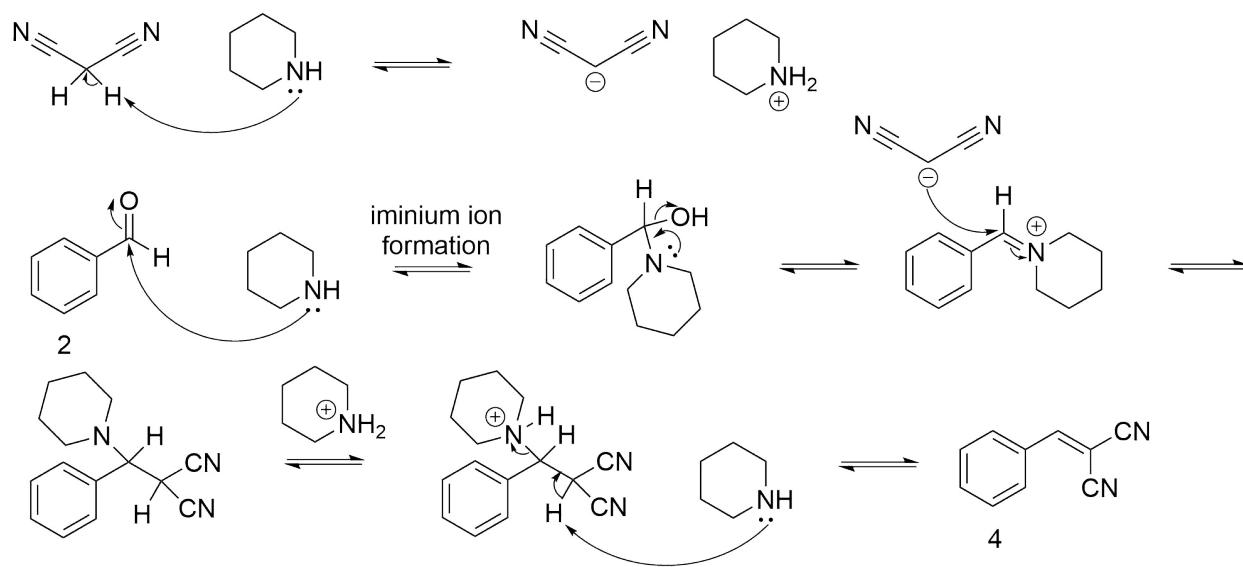
Figure 14: Mechanism of Knoevenagel condensation of benzaldehyde (2) with malononitrile yielding benzylidene malononitrile (4). Base used in reaction mechanism is piperidine.

First malononitrile is activated upon deprotonation with piperidine. Furthermore, piperidine forms an iminium ion with the carbonyl compound (benzaldehyde in this case). This is further converted by a protonated piperidine molecule, the resulting intermediate is deprotonated by another piperidine molecule resulting in simultaneous elimination of a piperidine molecule from the intermediate, which ultimately yields benzylidene malononitrile.

3 Experimental Methods

3.1 Chemicals

Table 1 shows an overview of the chemicals used.

Table 1: Chemicals used in this project.

Chemical	Purity (%) or Grade	Supplier
Acetic acid (glacial)	100	Merck
Aerosil 200, fumed silica		Evonik
Ammonia	28-30	Merck
Anisole	99	Acros Organics
Benzaldehyde	≥ 99	Fluka Analytical
Benzaldehyde dimethyl acetal	≥ 98	Sigma-Aldrich
Benzylidene malononitrile	98	Sigma-Aldrich
Chlorotrimethylsilane	≥ 98	Sigma-Aldrich
Diisopropylamine	≥ 99.5	Sigma-Aldrich
Diisopropylethylamine	≥ 99	Sigma-Aldrich
HDK® H20, fumed silica		Wacker Chemie
Hydrochloric acid		
Malononitrile	99	Acros Organics
Methyl isobutyl ketone	99	Alfa Aesar
2-Methyl tetrahydrofuran	99	Acros Organics
Milli-Q Water		
Nile red	≥ 98	Sigma-Aldrich
Nitromethane	99	Acros Organics
Nitric acid	≥ 65	Merck
Piperidine	99	Acros Organics
4-Propylguaiacol	≥ 99	Sigma-Aldrich
Tetraethoxysilane	≥ 99	Sigma-Aldrich
2,2,6,6-tetramethylpiperidine		Sigma-Aldrich
Toluene	Analytical	Acros Organics
Trans-β-nitrostyrene	99	Sigma-Aldrich
Tributylamine	≥ 99	Sigma-Aldrich

3.2 Synthesis of Colloidal Silica

Colloidal silica was synthesized following an adapted Stöber procedure.[60,61] A 500 mL round bottom flask was filled with 230 mL ethanol and 11.30 g of a 28-30% ammonia solution. The solution was heated to 35 °C and stirred at 250 rpm, after which 17.45 g of tetraethoxysilane (TEOS) was added at once. The reaction mixture was left for 24 hours, after which 8.5 mL of a 65 % solution of nitric acid was added to neutralize the reaction mixture. When neutralized, the silica was dried using rotary evaporation.

The dried silica was calcined in air in an oven at a temperature of 200 °C, which was reached stepwise over 2 hours, after which the temperature was kept this high for an additional 2 hours to remove all remaining water. This was followed by a 2 hour period to heat the oven to 400 °C,

after which again the oven temperature was left another 2 hours to decompose remaining TEOS. Then during 2 hours the oven was further heated to 600 °C. It was kept at 600 °C for an additional 3 hours to decrease the microporosity in the silica colloids. Afterwards it was cooled to room temperature.

3.3 Hydrophobization of Silica

Silica (Aerosil 200 and Stöber) was modified using chlorotrimethylsilane (TMSCl). The silica was weighed and put in a round bottom flask. For each gram of silica, 10 mL of toluene was added to the flask. Furthermore, 10 wt-% of TMSCl with respect to toluene was added dropwise. This mixture was refluxed for 2 hours, after which the silica was filtered under vacuum using a glass filter and washed with toluene. Approximately 50 mL of toluene was used for each gram of silica. The silica was dried on the glass filter over night.

3.4 Silica Characterization

3.4.1 Transmission Electron Microscopy

To get insight into the size and shape of the silica particles that were used, transmission electron microscopy (TEM) was performed on hydrophobized Aerosil 200, hydrophobic HDK® H20 and both hydrophobized and untreated Stöber silica samples. The images were obtained using a FEI Tecnai 20 FEG 200 kV transmission electron microscope. To prepare samples, silica was first crushed, after which it was dispersed in ethanol by ultrasonication over a few minutes using an ultrasonic bath. A drop of each dispersion was put on a formvar/carbon 300 mesh copper grid.

3.4.2 Contact Angle Measurements

Self-supporting wafers of silica had to be made for the contact angle measurements. These wafers were prepared using a pellet press. The wafers were put in a cuvet which was half filled with toluene. An OCA 15EC device from Dataphysics (see figure 28 in section A of the appendix) was used to do the contact angle measurements with. A plastic 1 mL syringe was filled with Milli-Q water. A water droplet was put on each wafer using the automatic syringe pump of the OCA 15EC device. Immediately after the droplet was put on the wafer, after approximately ten minutes and after one hour the water contact angle of the droplet on the silica pellet was measured using the SCA 20 software.

3.4.3 Infrared Spectroscopy

Self-supporting wafers of hydrophobized Aerosil 200 and Wacker HDK® H20 were prepared using a pellet press. All IR measurements were performed using a Perkin Elmer 2000 FT-IR system. The wafers were put in a clean cell and a background spectrum was measured at room temperature and in air. After the measurement the system was put under vacuum and a spectrum was measured before high vacuum was reached and at high vacuum. When high vacuum was reached the temperature increased by 5 °C per minute. At 100, 200, 300 and 400 °C spectra were measured. After the IR measurements pellets were taken out from the cell and weighed to determine silica mass without water.

3.4.4 Nitrogen Physisorption

Nitrogen physisorption experiments were performed on hydrophobized Aerosil 200 and hydrophobic HDK® H20. Measurements were performed using a TriStar 3000 apparatus from Micromeritics.

3.5 Pickering Emulsion Preparation

Preparation of Pickering emulsions was performed following a procedure adapted from Binks and Lumsdon.[25] Emulsions were made in 15 mL Ace pressure tubes or 50 mL centrifuge tubes. First the desired amount of hydrophobic silica was put in the tube. The silica used was hydrophobized Aerosil 200, hydrophobized Stöber silica or hydrophobic HDK® H20. The amount of silica used was 2 to 5 wt-% with respect to the toluene mass (or sometimes another organic solvent). This was followed by adding the desired volume of the organic compound, typically toluene. The silica was dispersed in the organic phase using a Sonics Vibra Cell for 10 W ultrasonication for 2 minutes. During ultrasonication the tubes were kept in an ice bath. Water of Milli-Q quality was added to the tubes after dispersion of silica. Emulsions were formed under vigorous stirring at 15,000 rpm for 2 minutes using the IKA T25 digital Ultra turrax. Emulsions with several oil-to-water phase ratios and a total volume of 8 mL were prepared this way. The ratios ranged from 2:6 to 6:2, toluene to water volume in mL.

3.6 Emulsion Imaging

3.6.1 Confocal Fluorescence Microscopy

To determine the type of the stable emulsions prepared with HDK® H20 and similar emulsions with hydrophobized Aerosil 200, confocal fluorescence microscopy was used. Images were made using a Nikon A1 confocal fluorescence microscope. The 10x and 50x objective lenses were used. The fluorescent dye was excited using a 488 nm laser at a laserpower of 70%. Images were obtained with a pinhole of 1 (21.7 μm) was used, 1/16 frame/s and with 4 times spectral averaging. Gain (SIHV) was set on 140. To obtain higher resolution images, resolution was set on 6 nm/pixel. For this experiment emulsions were prepared with a fluorescent dye, Nile red, which is a hydrophobic dye.

A stock solution of 10^{-5} M Nile red in acetone was prepared. From this stock solution 20 mL was taken and put in a 50 mL round bottom flask. The acetone was evaporated using rotary evaporation. The residual Nile red was dissolved in 20 mL toluene. This Nile red solution was used to prepare two emulsions. The emulsions were prepared with 6 mL of the solution, 2 mL of Milli-Q water and approximately 3 wt-% (relative to toluene mass) HDK® H20 or hydrophobized Aerosil 200. Samples of each emulsion were put on separate microcope slides with a cavity from Agar Scientific. The samples were covered with ⊘ 22 mm cover glasses.

3.6.2 Optical Microscopy

Optical microscopy was used to see differences between Pickering emulsions stabilized by hydrophobized Aerosil 200 and emulsions stabilized by HDK® H20. Two emulsions were prepared, one with hydrophobized Aerosil 200, the other one with HDK® H20. Both emulsions contained 6 mL toluene, 2 mL Milli-Q water and 3 wt-% silica with respect to toluene. Optical microscopy images were obtained using an Axio Zoom.V16 microscope from Zeiss. A PlanNeofluar Z 2.3x/0.25 FWD 56 mm lens was used. Magnification of 410 x was used.

3.7 Catalytic Reactions

3.7.1 GC and GC-MS Measurements

Contents and concentrations of chemicals in the samples were determined using GC and GC-MS. For GC measurements a Varian GC equipped with a VF-5 ms capillary column and an FID detector was used. GC-MS measurements were performed on a Shimadzu GC-2010 using a VF-5 ms column coupled to a Shimadzu GCMS-QP2010 mass spectrometer. After reactions an internal standard of anisole in toluene was added, to give a final concentration of 10 mg/mL of anisole in the organic phase. GC and GC-MS samples were prepared by taking 1 mL of an organic phase, using a syringe, followed by filtering over a 13 mm syringe filter with a 0.45 μm PTFE membrane. These samples were put in 1 mL GC vials. Analysis of sample concentrations was based on calibration curves obtained from calibration series of benzaldehyde dimethyl acetal, benzaldehyde, trans-β-nitrostyrene or benzylidene malononitrile in a solution of anisole in toluene (10 mg/mL).

3.7.2 Emulsion Separation

In case reactions were performed in stable emulsions, as is the case for the reactions in HDK® H20 stabilized emulsions, they needed to be separated before samples for GC and GC-MS could be prepared. Separation was achieved by centrifugation. Emulsions were transferred from Ace pressure tubes to 15 mL centrifuge tubes using a glass pipet. Centrifugation was performed using a Rotina 380R Hettich centrifuge. Centrifugation programme was set on 10 minutes, 11,000 rpm at a temperature of 4 °C. After centrifugation 3 phases could be observed an organic (top) phase, a solid (middle) phase and a water (bottom) phase. Sometimes the water and solid phase were still partially mixed.

3.7.3 Deacetalization Reactions

Deacetalization was first studied kinetically in biphasic systems and Pickering emulsions at 80 °C and stirred at 1000 rpm. Initially, these studied systems contained 1.8 mL toluene, 3.96 mL Milli-Q water and 40 μL 1 M HCl. Furthermore 0.3 mmol (51 μL) of benzaldehyde dimethyl acetal was added to be converted. For the emulsions 2 wt-% hydrophobized Aerosil 200 was used with respect to the the toluene phase. Several reactions were started simultaneously and every few minutes a reaction was stopped. This way the conversion over time could be investigated. There was no need for Pickering emulsion separation, because the emulsions already partially separated. Samples from emulsions were taken from the clear layer that had emerged on top of the emulsions.

Furthermore, Pickering emulsions, using 6:2 toluene to water volume ratios and 3 wt-% Wacker HDK® H20 silica with respect to the toluene phase, were used to perform deacetalization reactions. First deacetalization of benzaldehyde dimethyl acetal in these emulsions was performed at 80 °C for 3 hours. Furthermore, these reactions were performed for 3 hours at room temperature as well. Further deacetalization in biphasic systems and Pickering emulsions (with 3 wt-% HDK®H20 silica relative to toluene mass) at room temperature was performed by using 6 mL toluene and 2 mL water with 0, 10 and 20 mol-% hydrochloric acid (with respect to the substrate) and approximately 1 mmol (150 μL) of benzaldehyde dimethyl acetal was added. Reactions were either stirred at 300 rpm or not stirred to investigate the influence of stirring.

Moreover, deacetalization reactions with hydrochloric acid in the water phase and piperidine in the organic phase had been performed in both simple biphasic systems and Pickering emulsions

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of 6 mL toluene and 2 mL water (and 3 wt-% HDK® H20 in the emulsions). These reactions were performed for 3 hours at room temperature with 1 mmol of benzaldehyde dimethyl acetal. Concentrations of acid and base were varied between 10 and 20 mol-% with respect to the substrate.

3.7.4   Henry Reactions

Henry reaction was performed in both a single toluene phase and biphasic systems of toluene and water. These reactions were performed in 6 mL toluene at 80 °C for approximately a day. In biphasic systems 2 mL Milli-Q water was added. For these reactions 1 or 2 mmol benzaldehyde was used. Furthermore, 1 molar equivalent of nitromethane (with respect to benzaldehyde) and 2, 4 or 8 mol-% of diisopropylethylamine (DIPEA) were used. Moreover, 3:5 toluene to water Pickering emulsions with 3 wt-% hydrophobized Aerosil 200 were used to perform Henry reactions. For these reaction 0.5 mmol benzaldehyde was used. Furthermore, 3 equivalents of nitromethane and approximately 50 mol-% diisopropylamine were added. Reactions were stirred at 600 rpm at a temperature of 80 °C for 1.5 h.

When stable Pickering emulsions were prepared with HDK® H20 silica, piperidine was used as a catalyst for Henry reaction. Henry reactions on 1 mmol benzaldehyde were performed in monophasic, biphasic and Pickering emulsion systems. Biphasic systems and Pickering emulsions were prepared out of 6 mL toluene and 2 mL Milli-Q water. Monophasic reactions were performed in 6 mL toluene. Piperidine was used as base-catalyst and 14, 15 and 30 mol-% piperidine was used. Nitromethane was added to the reaction mixtures in 2.5 benzaldehyde equivalents. All reactions were performed for approximately a day at 80 °C. Pickering emulsions were either stabilized by HDK® H20 silica or hydrophobized Aerosil 200.

3.7.5   Deacetalization-Henry Tandem Reactions

Several attempts were made to perform deacetalization-Henry tandem reactions in Pickering emulsions. Reaction conditions were varied. Emulsions were prepared differently; different toluene to water ratios were used and some emulsions were prepared with 4-propylguaiacol instead of toluene. Emulsions were either stirred or not. Diisopropylamine and DIPEA were used as base-catalysts. Temperature was always 80 °C. A complete overview of reaction conditions can be found in section D of the appendix.

3.7.6   Knoevenagel Reactions

The Knoevenagel reaction had been studied separately as well. Knoevenagel reactions were performed in monophasic, biphasic and Pickering emulsion systems. First, the monophase had been studied to see whether the reaction would work. The monophasic reactions were performed at 80 °C or room temperature with 1 mmol benzaldehyde, 2.5 malononitrile equivalents, 10, 15, 20 or 30 mol-% piperidine or 20 mol-% DIPEA, without stirring. To add malononitrile, it was melted in a lukewarm water bath and 140 μL was added to the reaction mixtures. Reactions were performed for 2, 3, 4, 5 and 24 hours.

The same procedure was followed with simple biphasic systems and Pickering emulsions, but for these systems 2 mL Milli-Q water was added. Furthermore the Pickering emulsions contained 3 wt-% Wacker HDK® H20 silica with respect to the toluene phase. A piperidine concentration of 5, 10 and 20 mol-% with respect to benzaldehyde was used. The reactions were performed at room temperature for 3 hours.

To see whether the reaction was influenced a lot by additional acid in the reaction mixture, Knoevenagel reactions in biphasic systems and Pickering emulsions containing hydrochloric acid and piperidine were performed. Concentrations of acid and base were 10 or 20 mol-% .

3.7.7   Deacetalization-Knoevenagel Tandem Reactions

The deacetalization-Knoevenagel tandem reactions were performed in Pickering emulsions and as a comparison in simple biphasic systems. The emulsions were prepared with 3 wt-% Wacker silica and 5, 10 or 20 mol-% acid. After emulsion preparation 1 mmol (150 μL) of benzaldehyde dimethyl acetal was added. This was followed by the addition of 140 μL melted malononitrile (2.5 equivalents) and 5, 10 or 20 mol-% base. Same amounts of solvents and reagents were used for simple biphasic systems. Reactions were left for 3 hours at room temperature.

4 Results and Discussion

4.1 Silica Characterization

Several silica types were used to prepare Pickering emulsions: hydrophobized Aerosil 200, hydrophobized Stöber silica and commercial hydrophobic HDK®H20. First, differences between commercial HDK® H20 and hydrophobized Aerosil 200 were investigated using TEM. The obtained images can be found in figure 15.
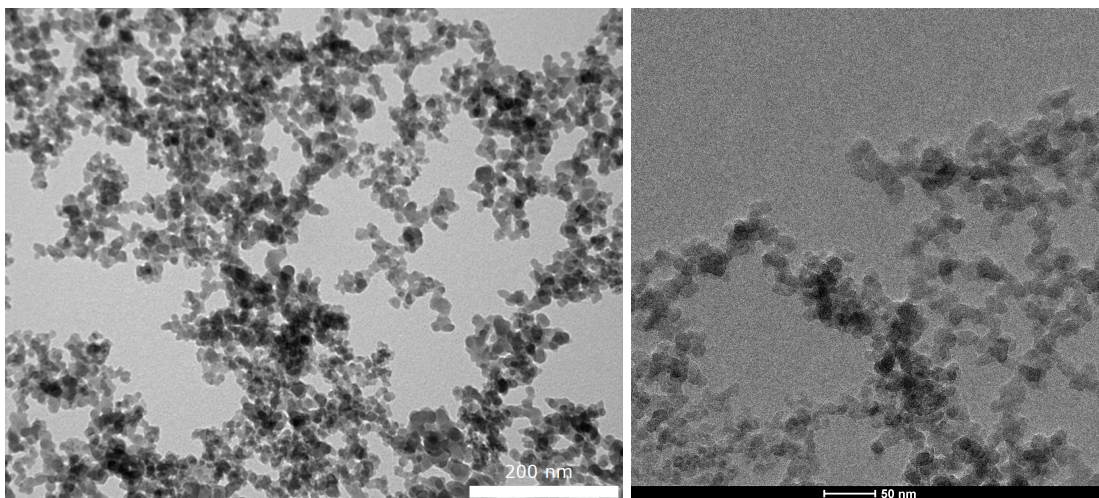
Figure 15: TEM images of hydrophobized Aerosil 200 silica (left, scalebar 200 nm) and commercial HDK® H20 silica (right, scalebar 50 nm)

Both hydrophobized Aerosil 200 and HDK® H20 showed to be constituted of aggregates. Since it is hard to distinguish single particles in these aggregates, it is hardly possible to measure the particle size. Hence, no conclusions about the size influences of these aggregates can be made. Moreover, from these images no clear differences in shape are observed between these particles. The difference in PE stability does not seem to be caused by a shape difference of the particles as observed with TEM.

Furthermore, to confirm whether Stöber silica was successfully synthesized and to determine the particle size images of the Stöber silica were obtained, see figure 16.
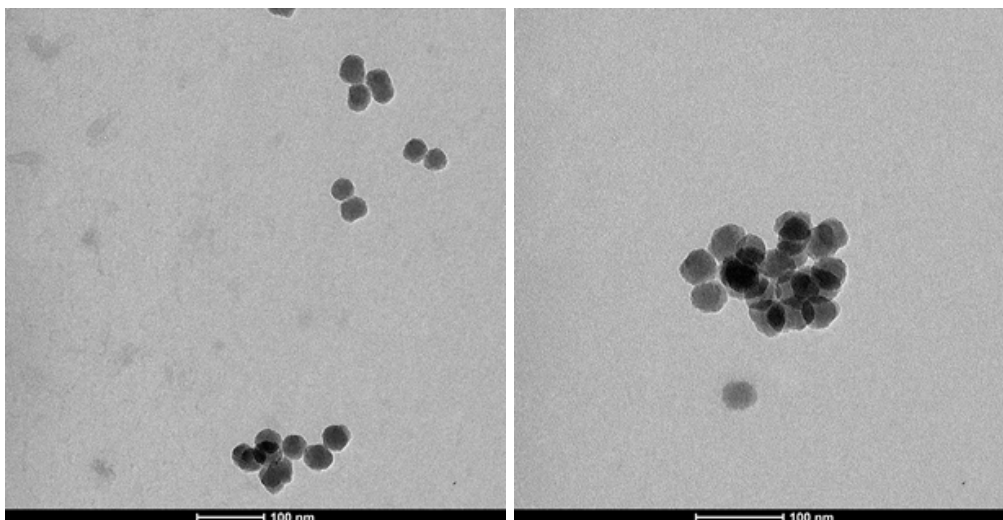
Figure 16: TEM images of Stöber silica particles. Left bare Stöber silica, right hydrophobized Stöber silica. Scalebars are 100 nm.

Clearly, single colloidal silica particles can be observed in the images of figure 16. The sizes of these particles can be measured as well. It can be concluded that colloidal Stöber silica was succesfully synthesized. Both hydrophobic and hydrophilic Stöber silica have an average particle size of 37.6 nm. This size lies within the size range of Stöber silica particles as found by van den Berg *et al.*,[61] where the synthesis method in 3.2 is based on. Just as the size, the shape does not seem to have changed much upon modification of the particle surface with TMSCl.

To determine any differences in hydrophobicity of the used silica types, contact angles of water droplets on wafers made of the commercial Wacker HDK® H20 silica and of hydrophobized Aerosil 200 were measured using the sessile drop method. Resulting pictures can be found in figure 17.
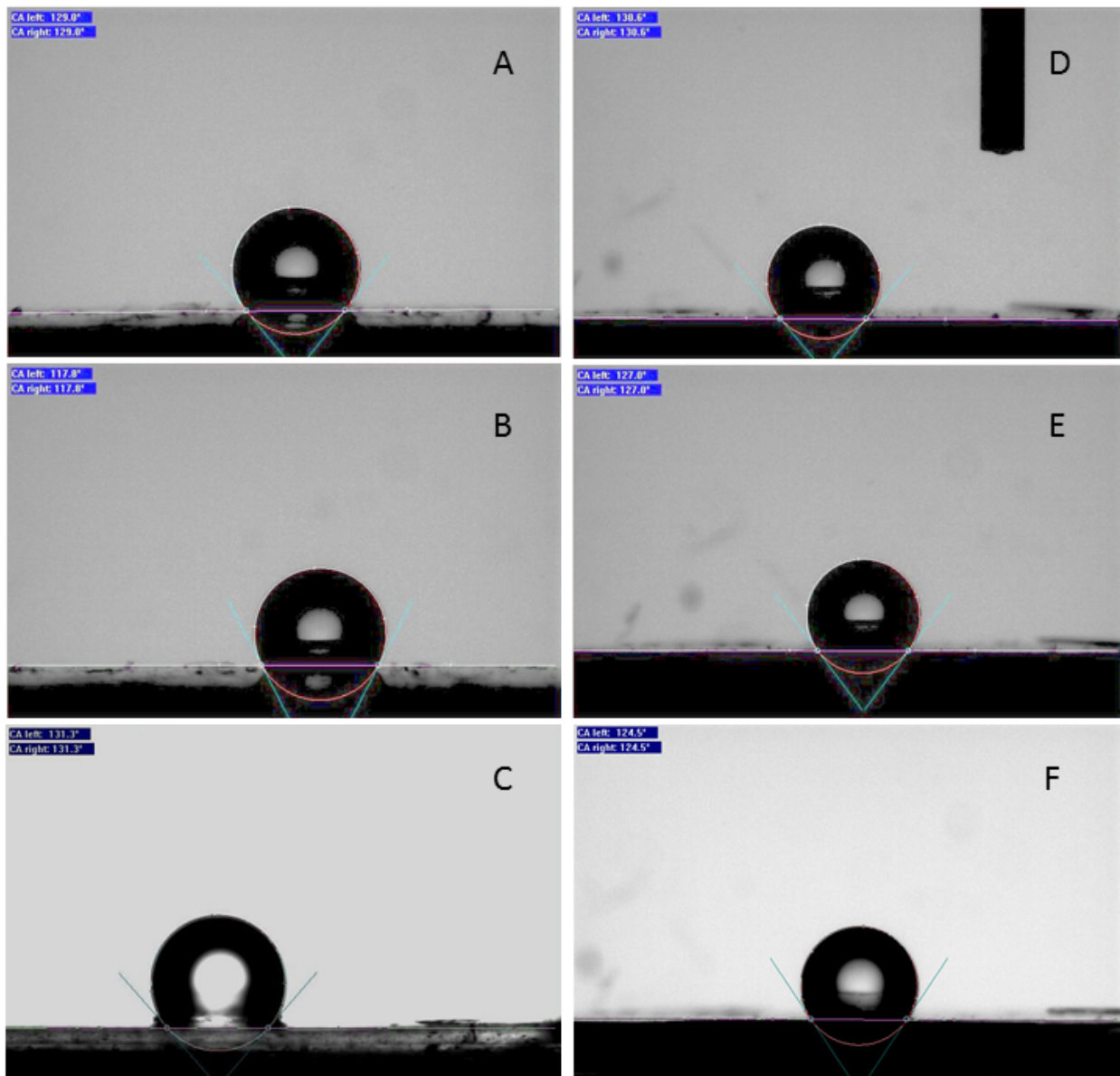
Figure 17: Results of contact angle measurements on a water droplet on the surface of a silica wafer in toluene. A, B and C are pictures of a water droplet on a wafer of hydrophobic HDK® H20 initially after landing of the droplet, after 10 minutes and after 1 h, respectively. D, E and F are pictures of a water droplet on hydrophobized Aerosil 200 silica after the same time intervals. Contact angle is 129.0° in A, 117.8° in B, 131.3° in C, 130.6° in D, 127.0 ° in E and 124.5° in F.

When A, B and C in figure 17 are compared, the contact angle seems to vary over time. Same holds when D, E and F are compared. The contact angle of the water droplet makes with the silica surface is approximately between 115°and 130°, meaning the surface is very hydrophobic. The observed change of the contact angle over time can be caused by experimental errors, because of encircling of the water droplet is performed by people. The way it is encircled can vary a bit, causing an error. Since the contact angles of the water droplets on both pellets are quite similar, it is concluded from these contact angle measurements that these silica samples were almost equally hydrophobic.

To confirm that bare Aerosil 200 was indeed not hydrophobic contact angle measurements were performed on pellets from this silica as well. The result can be seen in figure 18.
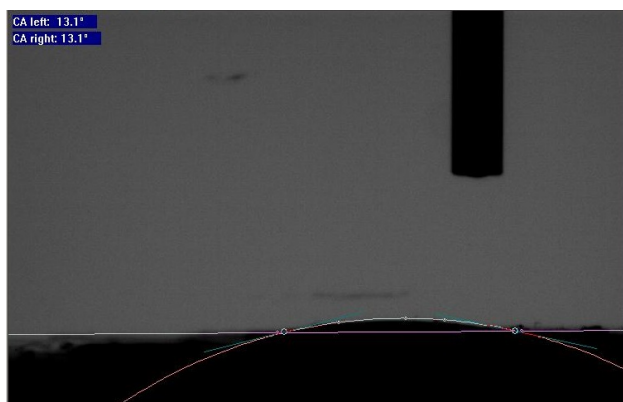
Figure 18: Water droplet on Aerosil 200 wafer in toluene, almost immediately after landing on the pellet. Contact angle is 13.1°.

As figure 18 shows, the wafer was almost completely wetted by the water droplet within a few seconds. Therefore, it can be concluded that untreated Aerosil 200 is hydrophilic. Silylation with TMSCl results in silica of which hydrophobicity increased much.

Stöber silica pellets have also been prepared for contact angle measurements. Contact angles of both bare and hydrophobized Stöber silica have been measured. This can be seen in figure 19.
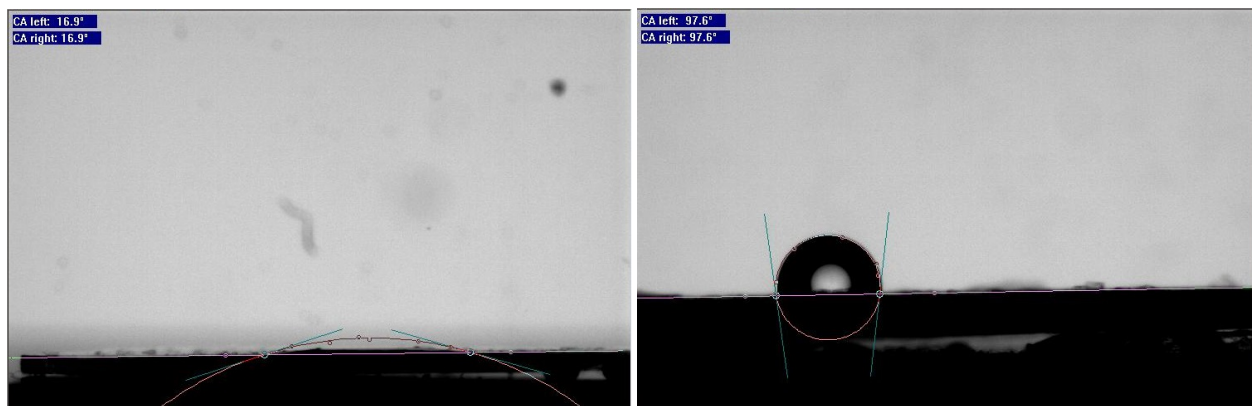
Figure 19: Water droplet on bare (left) and hydrophobized (right) Stöber silica. As can be seen the water droplet had already disappeared on the left image. Water droplet on the right image was 97.6°.

As figure 19 shows, bare Stöber silica was completely wetted by a water droplet, whereas a wafer of hydrophobized Stöber silica clearly was partially wetted by a water droplet. A contact angle of 97.6° is observed for a water droplet on a pellet of hydrophobized Stöber silica. Obviously, hydrophobization of Stöber silica was performed successfully, however the resulting contact angle is smaller than in case of hydrophobized Aerosil 200 and commercial HDK® H20 silica. This might be caused by the available surface area of the colloidal silica is bigger than that of the aggregates of the fumed silica. This is because parts of the surface of the particles in aggregates is covered by other particles. Therefore, perhaps more TMSCl is needed to silylate a bigger part of the surface of Stöber silica.

Measuring contact angles with this sessile drop method gave a clear indication of the hydrophobicity of the particles compared to each other. However, the contact angles obtained via this method may differ from the actual contact angles single particles would give, because of the assumptions which have to be made performing these experiments. One of these assumptions is that the surface is smooth and does not contain any pores.[41] Another assumption is that there is no change in surface chemistry when the pellets are made. This is already contradicted by some studies, which showed that increased compaction pressure resulted in decreased contact angles.[41] Furthermore, hydrophobization procedures can lead to silylation of parts of the surface, whereas other parts are not modified, resulting in non-homogeneous surface functionalization.[62] Therefore, the contact angle may be highly dependent on the site of the surface the drop is placed. Nevertheless, it is an easy and quick method to determine the hydrophobicity of a material which suffices for this project.

Because the contact angle measurements might be less reliable due to some experimental errors, the hydrophobicity of the hydrophobized Aerosil 200 and hydrophobic HDK® H20 was further studied using IR spectroscopy. The spectra were normalized to the pellet mass as determined after IR measurements, when all water was removed from the wafers. A table with peak wavenumbers and their corresponding vibration modes was obtained by studying literature on silica materials and IR characterization of these materials, see table 2.[63–66]

Table 2: IR absorbance wavenumbers and their corresponding vibration modes in silica materials.

Peak wavenumber (cm^{-1})	Corresponding vibration
3750	OH stretching in isolated silanol groups
3600 (shoulder)	OH stretching in geminal silanol groups
3750-3000 (general)	OH stretching vibrations
2900	CH asymmetric stretch vibrations
2850	CH symmetric stretch vibrations
1800 and 1600	Si-O vibration modes in Si-O-Si-O... network
1250-1000	O-Si-O asymmetric stretch vibrations
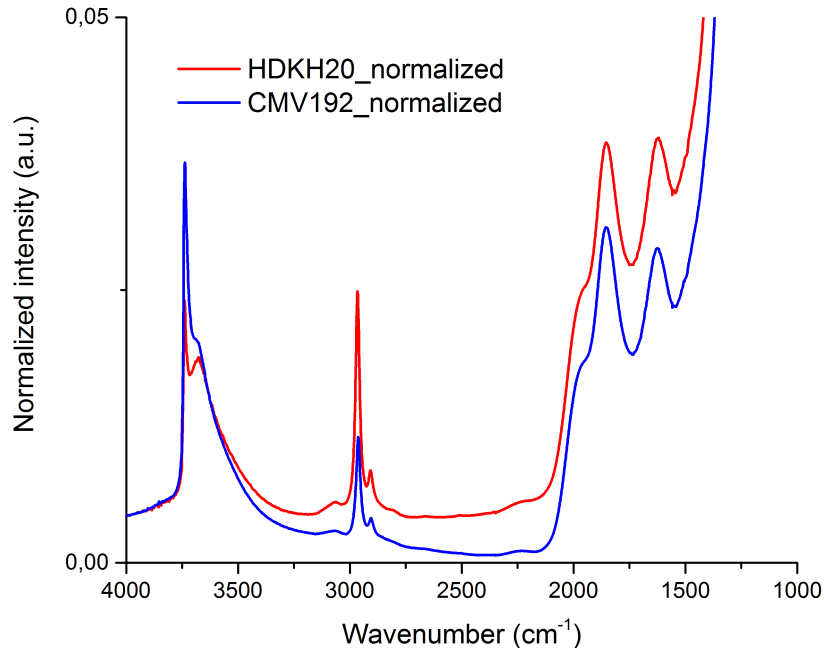
Figure 20: IR spectra of hydrophobized Aerosil 200 (CMV192, blue) and commercial hydrophobic silica from Wacker, HDK® H20 (red) at 400 °C under vacuum. The spectra were normalized to the pellet mass after measurements.

The spectra depicted in figure 20 show peaks at the same wavenumbers, as was expected. However, the relative intensity of the peaks at 3750 cm^{-1} and 2920 cm^{-1} differ much. In case of the hydrophobized Aerosil 200 the first peak, originating from OH stretch vibrations, is way more intense than the peaks coming from CH$_3$ stretch vibrations at 2920 and 2850 cm^{-1}. Whereas in case of the HDK® H20 these peaks are equally intense. This is due to the fact the hydrophobized silica still has more surface OH groups, while the HDK® H20 has more methyl groups on its surface. Therefore, the HDK® H20 silica seems to be more hydrophobic, explaining better dispersion of the silica in toluene and hence the formation of more stable emulsions.

However, comparing this to the data obtained by contact angle measurements, the results seem to contradict each other. From the contact angle measurements only, it was concluded that the silica samples were equally hydrophobic. As stated before, the contact angle is site-dependent. Since IR spectroscopy of a wafer includes a bigger part of the surface, it says more about the overall hydrophobicity and therefore it is a more reliable method.

To obtain more information on the differences between hydrophobized Aerosil 200 and hydrophobic HDK® H20, nitrogen physisorption measurements were performed. During these physisorption measurements data for physisorption isotherms was obtained. The obtained isotherms are depicted in figure 21.
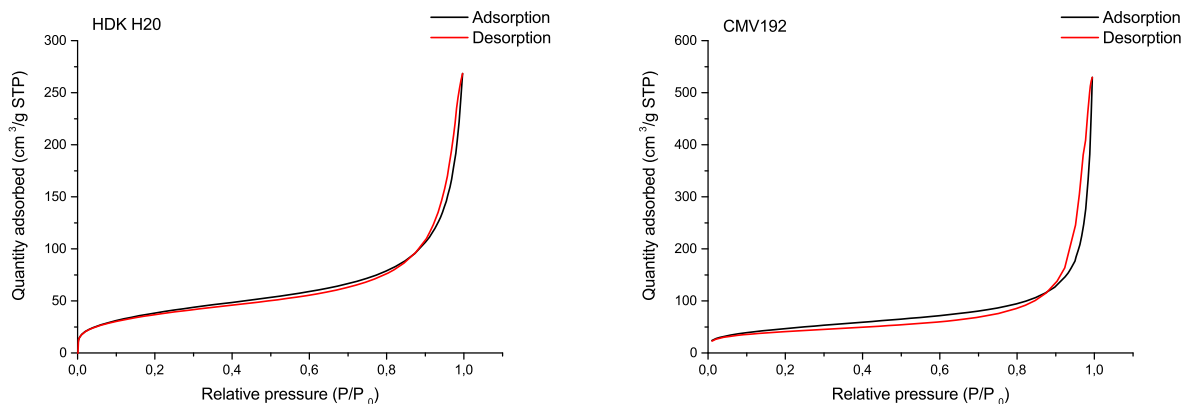
Figure 21: Physisorption isotherms of adsorption (black) and desorption (red) as obtained during physisorption experiments on samples of HDK® H20 (left) and hydrophobized Aerosil 200 (right).

The isotherms in figure 21 resemble isotherms of type II as defined by IUPAC.[67] Which means that the materials investigated with nitrogen physisorption do not have any pores or are macroporous. It is known that fumed silica is a nonporous material which explains the shape of these isotherms since both silica samples are made of fumed silica.

Furthermore, these isotherms can be used to calculate the so-called BET surface area of the material. This resulted in the surface areas in table 3:

Table 3: BET surface areas and standard deviations of HDK®H20 and CMV192

Silica sample	BET surface area (m^2/g)	Standard deviation (m^2/g)
HDK® H20	143.0165	0.8089
Hydrophobized Aerosil 200	170.8326	0.6473

The values of the surface area do not differ that much. Therefore, it be concluded that the surface area does not influence the Pickering emulsion stability in this case.

To conclude this section, the hydrophobic HDK® H20 silica is more hydrophobic than hydrophobized Aerosil 200 as is found using IR spectroscopy. This is probably also why the HDK® H20 silica is more capable of stabilizing toluene-water Pickering emulsions (see section 4.2). Hydrophobized Stöber silica was even less hydrophobic than hydrophobized Aerosil 200,

4.2   Pickering Emulsion Preparation

Several silica types were tried for Pickering emulsions. Most reproducible stable emulsions were made of 6:2 toluene to water emulsions stabilized by 3 wt-% HDK® H20 silica, similar toluene-water emulsions were prepared by Skale *et al.*[17] Preparation of stable emulsions with hydrophobized Stöber silica and hydrophobized Aerosil 200 was not always reproducible. An overview of all the organic phase-water ratios that were tried to prepare emulsions is given in section B of the appendix.

4.3 Emulsion Imaging

4.3.1 Confocal Fluorescence Microscopy

Images of 6:2 emulsions stabilized by 3 wt-% of hydrophobized Aerosil 200 or HDK® H20 silica were obtained using confocal fluorescence microscopy with Nile red dissolved in the organic phase. The images are shown in figure 22.
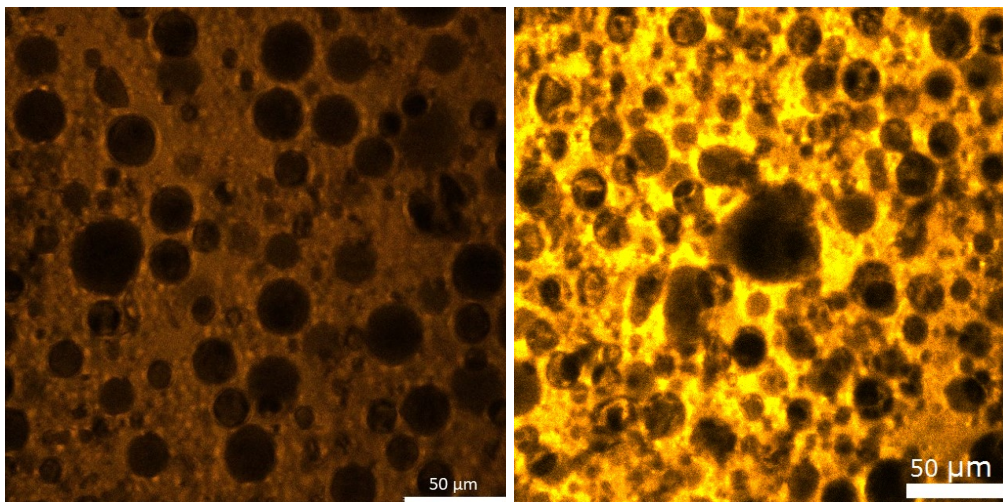
Figure 22: Confocal fluorescence microscopy images of 6:2 toluene to water emulsions stabilized by 3 wt-% silica with 10^{-5} M Nile red in toluene. Left image is of an emulsion prepared with HDK® H20 silica, right image is of an emulsion with hydrophobized Aerosil 200. Scalebars indicate 50 μm.

Since Nile red only dissolves in the oil phase, that is in toluene for these emulsions, and the continuous phase is colored, it is concluded that both emulsions were water in oil emulsions, as can also be expected from the contact angle. This contact angle was between 115° and 130° and therefore larger than 90°. Particles having a water contact angle larger than 90° tend to stabilize water in oil emulsions.[25] The droplet size was polydisperse and both emulsions showed an average droplet diameter of approximately 17 μm as measured with iTEM with 70 counts for the HDK® H20 stabilized emulsions and 61 counts for the hydrophized Aerosil 200 stabilized emulsions. The latter type had a maximum droplet size of 27 μm and a minium of 7 μm). As can be seen in the right image, some drops already deformed a bit after a few minutes in the emulsions stabilized by hydrophobized Aerosil 200, while the droplets in the left image are still round. This may be caused by the fact that the emulsions stabilized by hydrophobized Aerosil 200 are less stable. Using confocal fluorescence microscopy only the droplets on the surface can be seen well. Droplets lying deeper in the sample can not easily be observed because of the fluorescence of the dye molecules that lie above them.

4.3.2 Optical Microscopy

Optical microscopy on both types of emulsions is performed as well. Images are depicted in figure 23.
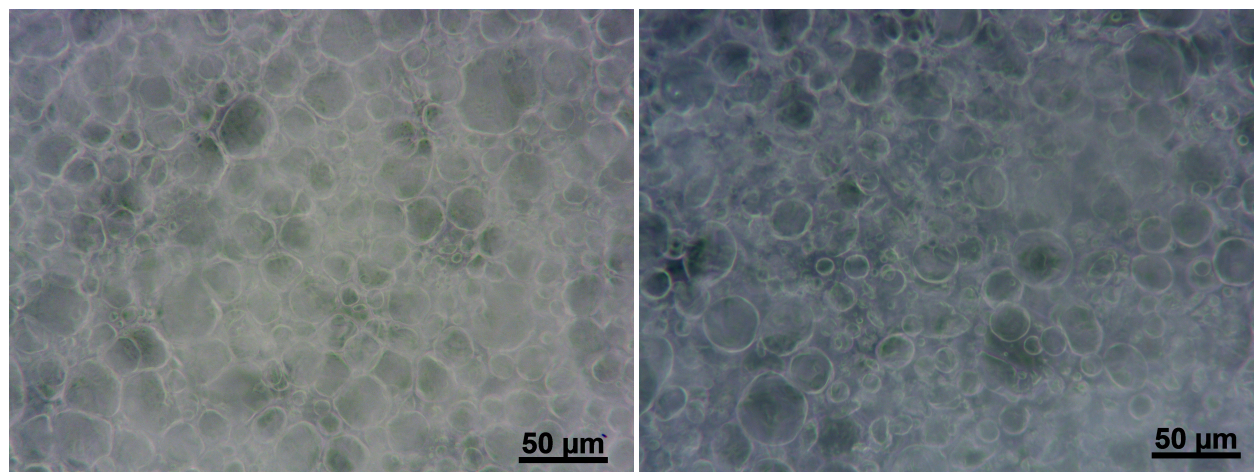
Figure 23: Optical microscopy images of 6:2 toluene to water emulsions stabilized by 3 wt-% silica, magnification 410 times. Emulsion in left image is stabilized by HDK® H20 silica, right image by hydrophobized Aerosil 200. Scalebars indicate 50 μm.

These images confirm the polydispersity in drop size of the Pickering emulsions. Optical microscopy also allows to see drops in deeper parts of the emulsion sample and droplets lying on top of each other can be observed. Drops in both emulsions seem to have slightly deformed, which is probably caused by drying of part of the emulsions. After microscopy images were taken, most of the emulsion samples seemed to have partially dried out. This could also be the cause for the deforming of the droplets in the right image of figure 22.

4.4 Catalytic Reactions

4.4.1 Deacetalization Reactions

The first deacetalization experiments were the kinetic experiments, performed with 12 mol-% hydrochloric acid. The emulsions used for these experiments were not stable. Both emulsions and biphasic systems for this reaction were rapidly stirred (1000 rpm), which could have caused the emulsions to separate, since Pickering emulsions had shown earlier to be unstable against shear.[23] Because the Pickering emulsions were not stable, it could not be said that the whole reaction occurred in the emulsion. However, these first results already showed deacetalization to proceed faster in Pickering emulsions than in simple biphasic systems. A diagram showing the conversion over time in both Pickering emulsions and simple biphasic systems can be found in section C of the appendix.

Further deacetalization reactions had been performed in stable Pickering emulsions over 3 hours at 80 °C without stirring. This resulted in 100 % conversion of benzaldehyde dimethyl acetal and 86 % benzaldehyde yield. Furthermore, deacetalization reactions at room temperature in these stable Pickering emulsions were compared to deacetalization in biphasic systems and the influence of stirring was investigated. The efficiency of the reactions in these systems is compared in terms of benzaldehyde dimethyl acetal conversions and benzaldehyde yields. Results of these can be found in figure 24.
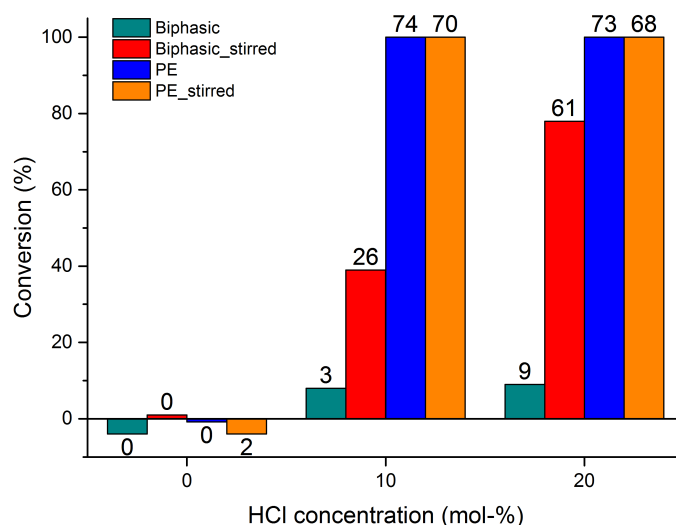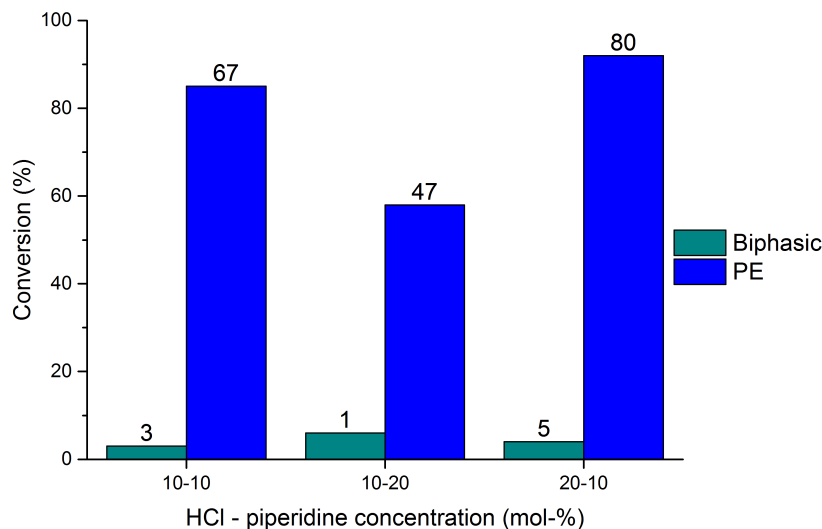
Figure 24: Conversions and yields of deacetalization of benzaldehyde dimethyl acetal in Pickering emulsions and simple biphasic systems. Reactions were performed for 3 hours at room temperature. Bar height indicates benzaldehyde dimethyl acetal conversion in %. Bar labels indicate benzaldehyde yields in %. Concentrations of hydrochloric acid are shown horizontally.

From figure 24 it can be concluded that hydrolysis of benzaldehyde dimethyl acetal worked more efficiently in Pickering emulsions in comparison to simple biphasic systems. This is probably because benzaldehyde dimethyl acetal resides mainly in the organic phase and contacts water more easily in the emulsions because of the increased interfacial area. Furthermore, stirring seems to have influenced the conversions and yields in simple biphasic systems. These increased upon stirring at 300 rpm. Probably also because stirring increases the interfacial area between the water and the oil phase, increasing contact between benzaldehyde dimethyl acetal and acidic water.

Williams and coworkers showed that 4-methoxybenzaldehyde dimethyl acetal was already hydrolyzed during 1 hour reaction at 25 °C in water.[52] However, as can be seen in figure 24 no conversion was observed if no acid was used. Therefore, the use of acid for the hydrolysis was continued.

Although acid-catalyzed deacetalization showed to work properly, benzaldehyde yields and benzaldehyde dimethyl acetal conversions did not match. This might be due to a slight solubility of benzaldehyde and benzaldehyde dimethyl acetal in water, which is not very likely since these compounds are hydrophobic and did not seem to dissolve in water in pilots which were carried out earlier. A study into partitioning of these compounds would maybe help clarifying this. Moreover part of the error was caused by an error in the measurements and methods, occurring during weighing and GC measurements. In a pilot the error of the concentration of certain compounds was found to be 5 to 10 %. This also holds for the results which are discussed in the next sections. Another fact that needs to be considered is that these were single measurements. To obtain hard data these experiments should be carried out in duplicates. However, these data show clear trends which can also be explained very well.

Deacetalization with both acid and base in the system was investigated as well. This led to the results of figure 25.

Figure 25: Conversions and yields of deacetalization of benzaldehyde dimethyl acetal in Pickering emulsions and simple biphasic systems. Reactions were performed for 3 hours at room temperature. Bar height indicates benzaldehyde dimethyl acetal conversion in %. Bar labels indicate benzaldehyde yields in %. Concentrations of hydrochloric acid and piperidine are shown horizontally.

Similar to the deacetalization with only acid in the system in figure 24, deacetalization with both acid and base showed higher benzaldehyde dimethyl acetal conversions and benzaldehyde yields in Pickering emulsions than in biphasic systems. However, benzaldehyde dimethyl acetal conversions were lower, when piperidine was also in the system, especially when there was more piperidine than hydrochloric acid. This was probably caused by neutralization of the acid by the base, resulting in less acid available for catalysis. This means compartmentalization in Pickering emulsions is not perfect.

4.4.2 Henry Reactions

Henry reactions in monophasic and biphasic systems catalyzed by diisopropylethylamine (DIPEA) did not show any significant benzaldehyde conversion or trans-β-nitrostyrene yield. Even while the reactions were left for 24 h at 80 °C. This could partially be explained with the fact that only 1 equivalent of nitromethane was present in the reaction mixtures. However, some conversion was expected, since similar conditions had led to successful Henry reactions before.[9,56] These reactions were guanidine- or ethyldiamine-catalyzed. But, since these bases are very water-soluble, they could not be used, because they would react with the acid in the water droplets. Also the Henry reactions in Pickering emulsions catalyzed by diisopropylamine were not successful. The emulsions were not stable and no trans-β-nitrostyrene was observed. Henry reactions in monophasic, biphasic and Pickering emulsion system catalyzed by piperidine were also investigated. These experiments gave the results in table 4. The Pickering emulsions stabilized by Aerosil 200 separated within an hour.

Table 4: Results of piperidine-catalyzed Henry reactions of 1 mmol benzaldehyde and 2.5 nitromethane equivalent in monophasic, biphasic and Pickering emulsion (PE) systems with 6 mL toluene at 80 °C. Conversion of benzaldehyde (2) and yield of trans-β-nitrostyrene (3) are given in this table. All experiments were performed once, except last one (entry 7), that was performed twofold and an average is given.

Entry	Reaction time (h)	System	Silica type	Base concentration (mol-%)	Conversion of 2 (%)	Yield of 3 (%)
1	22	monophase	-	15	33	41
2	22	monophase	-	30	56	41
3	22	biphasic	-	15	15	trace
4	22	biphasic	-	30	27	trace
5	22	PE	Aerosil 200	15	21	trace
6	22	PE	Aerosil 200	30	25	trace
7	24	PE	HDK® H20	14	35	trace

As can be seen in table 4, only monophasic reactions showed some yields, in samples from systems with two phases (either biphasic or PE) only trace amounts of trans-β-nitrostyrene were found and low conversions were observed, even after reaction for 22 or 24 h. This could be caused by adsorption of trans-β-nitrostyrene onto silica particles. Another explanation would be dissolution of trans-β-nitrostyrene in the water phase, however pilots with solid trans-β-nitrostyrene showed that it did not dissolve in water, so it would not explain the fact that only trace amounts of it were found in the organic phase.

Another remarkable observation is done in entry 1 in table 4. In this reaction a benzaldehyde conversion of 33 % was observed, whereas a yield of 41 % was found. Since 1 mol of benzaldehyde would result in 1 mol of trans-β-nitrostyrene this would not be possible. This is caused by an error in measurements of both benzaldehyde and trans-β-nitrostyrene concentrations after reaction and benzaldehyde concentration at the start of the reaction.

4.4.3   Deacetalization-Henry Tandem Reactions

Deacetalization-Henry tandem reactions were not performed with success, whereas it had been done before in layered Pickering emulsions with ethyldiamine.[9] In almost all cases the emulsion (partially) separated. Furthermore, only trace amounts of trans-β-nitrostyrene were found using GC-MS, just as in studies involving the separate Henry reaction (section 4.4.2). An interesting fact is that benzaldehyde dimethyl acetal was converted to benzaldehyde in many of the emulsions, implying that the acid-catalyst is still active. Together with the fact that some trans-β-nitrostyrene had been formed, this means that in at least some cases the acid and the base did not completely neutralize each other. An overview of the reaction conditions that were tried, together with an example of a chromatogram, can be found in section D of the appendix.

4.4.4   Knoevenagel Reactions

First Knoevenagel reactions were performed in toluene. One was DIPEA (20 mol-%) catalyzed the other was piperidine (15 mol-%) catalyzed. Both reactions showed to be working as was concluded from GC-MS results. Benzaldehyde was not observed with GC-MS, benzylidene malononitrile was present in the mixture. Further monophasic reactions were performed, all showing 100 % conversions after 2, 4, 5 and 24 hours at 80 °C. Results of these reactions in toluene only can be found in table 12 in section E of the appendix. Benzylidene malononitrile yields could not be determined for these reactions, since benzylidene malononitrile was not yet available at the time and therefore calibration of this compound on the GC was not carried out yet.

More Knoevenagel reactions in monophasic systems were performed and temperature, base and base concentration were varied. Results can be found in table 5.

Table 5: Results for Knoevenagel condensation in a toluene monophase with several reaction conditions. Reaction was performed with 1 mmol benzaldehyde (2) and 2.5 equivalents malononitrile. Conversion of benzaldehyde (2) and yield of benzylidene malononitrile (4) are given in this table. Every number gives an average of an experiment performed in duplo.

Entry	Time (h)	Temperature (°C)	Base	Base concentration (mol-%)	Conversion of 2 (%)	Yield of 4 (%)
1	3	RT	Piperidine	10	100	71
2	3	RT	Piperidine	20	100	61
3	1h40	80	Piperidine	20	100	68
4	3	80	DIPEA	20	100	74

First Knoevenagel reactions at room temperature (entry 1 and 2) showed excellent conversions as well. These were both performed in duplo, one duplo was performed with 10 mol-% piperidine whereas the other was performed with 20 mol-% piperidine. The first had a yield of 71 % and the latter gave a yield of 61 %. Probably because more side product is formed when too much catalyst is present in the monophasic system. In these monophasic reactions some solid remained, which could be explained by the fact that malononitrile is a solid at room temperature. However, it can be concluded that Knoevenagel condensation of benzaldehyde with malononitrile catalyzed by piperidine occurs at room temperature. This may mean that the reaction should be quenched, otherwise further reaction takes place during sample preparation and measurements. Quenching was tried in samples with acetic acid, since that is an organic molecule and has more affinity with toluene. Results of quenching experiments can be found in table 13 in section E of the appendix. However, yields after quenching were not very different from the yields obtained without quenching. Furthermore, acetic acid is not that strong and therefore an equilibrium is set up. Since quenching is also not possible in the tandem reactions, because acid would catalyze further deacetalization, it was not further investigated. Reactions of entry 3 were followed over time and therefore stopped when conversion was 100 %.

From entry 3 and 4 it can be concluded that catalysis by piperidine and DIPEA resulted in similar yields and both catalysts were further studied in tandem reactions (see section 4.4.5). However, this finding is rather interesting, since DIPEA is not able to form an iminium ion as is necessary according to the mechanism of the Knoevenagel condensation in figure 14. This means that the reaction possibly also occurs via another mechanism. A proposed mechanism can be found in figure

32 in section F of the appendix. Another explanation would be some impurity in the DIPEA stock, which would be surprising, since the bottle is new and purity is very high.

Moreover, Knoevenagel condensation was carried out in both simple biphasic systems and Pickering emulsions. This reaction was performed over 3 hours at room temperature. The biphasic systems were made of 6 mL toluene and 2 mL Milli-Q water. The Pickering emulsions used were 6:2 toluene to water emulsions with 3 wt-% HDK® H20 silica. Results are depicted in figure 26.
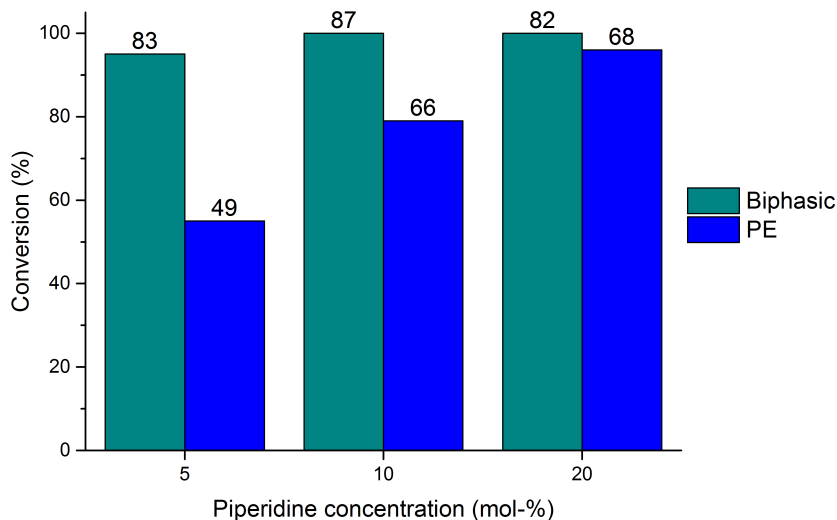
Figure 26: Conversions and yields of the Knoevenagel reaction of benzaldehyde with malononitrile in Pickering emulsions and simple biphasic systems. Reactions were performed for 3 hours at room temperature. Height of the bars indicates conversion of benzaldehyde in %, bar labels indicate benzylidene malononitrile yields in %. Piperidine concentrations are shown horizontally.

Apparently, Knoevenagel condensation of benzaldehyde with malononitirle to form benzylidene malononitrile gives higher conversions and yields over 3 hours at RT in biphasic systems in comparison to Pickering emulsions. Therefore, the Knoevenagel reaction seems to proceed faster in biphasic systems. This is probably because it is a reaction that takes place in the organic phase only. When it is performed in a Pickering emulsion the continuous oil phase gets crowded with water droplets, decreasing probability of collision between reacting molecules, in this case benzaldehyde, malononitrile and piperidine.

The difference between the conversions and yields between Pickering emulsions and biphasic systems seems to decrease with increasing piperidine concentrations. Another explanation for the efficiency difference might be a partial dissolving of piperidine into the water phase, which goes faster in Pickering emulsions because of the increased interfacial area. Therefore, less piperidine is available for the reaction to occur in the organic phase. When there is more piperidine available, more of it will still be in the organic phase. It will then still be available for catalyzing the Knoevenagel condensation. A partitioning study of piperidine might help to confirm this explanation.

These Knoevenagel reactions were also studied in simple biphasic systems with both acid and base. Results of these reactions are depicted in figure 27.
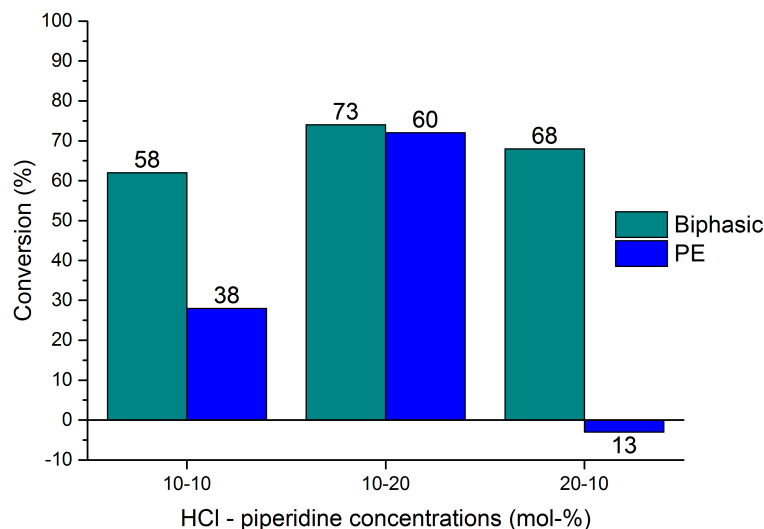
Figure 27: Conversions and yields of the Knoevenagel reaction of benzaldehyde with malononitrile in Pickering emulsions and simple biphasic systems with both acid and base in the system. Reactions were performed for 3 hours at room temperature. Height of the bars indicates conversion of benzaldehyde in %, bar labels indicate benzylidene malononitrile yields in %. Hydrochloric acid and piperidine concentrations are shown horizontally.

As figure 27 shows, if both acid and base were in the system, still more benzaldehyde conversion was observed in biphasic systems than in Pickering emulsions. Furthermore, conversions and yields in systems with acid and base were lower than in systems with base only as depicted in figure 26. This was again caused by mutual destruction of acid and base, leading to less active piperidine catalysts.

4.4.5 Deacetalization-Knoevenagel Tandem Reactions

The deacetalization-Knoevenagel tandem was studied in both simple biphasic systems of 6 mL toluene and 2 mL water and in Pickering emulsions of 6:2 toluene to water stabilized by 3 wt-% HDK® H20. First, the tandem reactions in simple biphasic systems will be discussed. This tandem reaction was first performed at elevated temperature (80 °C) for 3 hours and both piperidine and DIPEA were tried as base-catalyst. Hydrochloric acid was used as acid-catalyst. Table 6 shows the results of these experiments.

Table 6: Results for deacetalization-Knoevenagel tandem in simple biphasic systems at 80 °C over 3 hours. Reaction was performed on 1 mmol of benzaldehyde dimethyl acetal and 2.5 equivalent of malononitrile was used. Piperidine or DIPEA was used as base-catalyst and hydrochloric acid was used as acid-catalyst. Averages of benzaldehyde dimethyl acetal (1) conversion, benzaldehyde (2) conversion and benzylidene malononitrile (4) yield are given for experiments performed in fourfold (entry 1) or in duplo (entry 2).

Entry	Acid conc. (mol-%)	Base	Base conc. (mol-%)	Conversion of 1 (%)	Conversion of 2 (%)	Yield of 4 (%)
1	20	Piperidine	20	55	57	21
2	20	DIPEA	20	57	58	10

Piperidine and DIPEA were both successful as base-catalyst. However, the yield when DIPEA was used is slightly lower. Therefore, further deacetalization-Knoevenagel tandem reactions in biphasic systems were performed at room temperature using piperidine as base-catalyst. Hydrochloric acid as acid-catalyst. Acid and base concentrations were varied. Reactions were left for 3 hours. Table 7 shows the results of these reactions.

Table 7: Results for deacetalization-Knoevenagel tandem in simple biphasic systems in 3 hours at RT with varying acid and base concentrations. Reaction was performed on 1 mmol of benzaldehyde dimethyl acetal and 2.5 equivalent of malononitrile was used. Piperidine was used as base-catalyst and hydrochloric acid was use as acid-catalyst. Averages of benzaldehyde dimethyl acetal (1) conversion, benzaldehyde (2) conversion and benzylidene malononitrile (4) yield are given.

Entry	Acid conc. (mol-%)	Base conc. (mol-%)	Conversion of 1 (%)	Conversion of 2 (%)	Yield of 4 (%)
1	5	10	6	0	0
2	10	10	-3	0	3
3	10	20	4	0	0
4	20	20	5	0	0

It can be concluded from table 7 that no reaction took place in a simple biphasic system at room temperature. However, from table 6 it can be seen that some reaction takes place at 80 °C. Probably heating increases partitioning of benzaldehyde dimethyl acetal in the water phase. Furthermore, these low conversions and yields at elevated temperature and no conversion and yield at RT may be caused by mutual destruction of acid and base, since both reactions normally give reasonable conversions and yields if performed separately.

Moreover, these deacetalization-Knoevenagel tandem reactions were studied in Pickering emulsions. Deacetalization-Knoevenagel tandems showed better conversions and yields in Pickering emulsions at room temperature. Again, different acid and base concentrations had been studied to find trends in possible interactions between both. Results are depicted in table 8. In this table the mass balance is shown as well. This was calculated to see whether there had been some loss of reagents, intermediates or products to the water phase or to adsorption to silica particles. This was convenient, since with the focus on 3 compounds mass balances can not immediately be seen from the abundancy of these compounds. The mass balance is calculated by dividing the sum of concentrations of benzaldehyde dimethyl acetal, benzaldehyde and benzylidene malononitrile by the initial concentration of benzaldehyde dimethyl acetal and multiplying this quotient with 100 to get a percentage.

Table 8: Results for deacetalization-Knoevenagel tandem in Pickering emulsions over 3 hours at RT. *Deacetalization-Knoevenagel tandem in Pickering emulsions over 24 hours. Reaction was performed on 1 mmol of benzaldehyde dimethyl acetal and 2.5 equivalent of malononitrile was used. Piperidine was used as base-catalyst and hydrochloric acid was used as acid-catalyst. Averages of benzaldehyde dimethyl acetal (1) conversion, benzaldehyde (2) conversion and benzylidene malononitrile (4) yield are given.

Entry	Acid conc. (mol-%)	Base conc. (mol-%)	Conversion of 1 (%)	Conversion of 2 (%)	Yield of 4 (%)	Mass balance (%)
1	5	5	45	100	42	97
2	5	10	41	100	29	88
3	5	20	51	95	36	90
4	10	10	100	36	36	100
5	10	20	42	100	39	98
6	20	10	100	31	37	106
7	20	20	55	100	59	101
8*	10	10	82	95	76	101

The mass balances are quite reasonable. From these mass balances it can be concluded that few to none of the investigated molecules dissolve in the water phase. Deviations from 100 % can be explained with experimental errors which occur during weighing of the substrate and determination of the concentrations of every compound with GC.

Tandem catalytic conversion in the Pickering emulsion showed to have worked and conversions of both benzaldehyde dimethyl acetal and benzaldehyde are observed in all emulsions containing acid and base. Yields of benzylidene malononitrile after 3 hour reaction at room temperature were between 29 and 59 %. Yang and coworkers also described Knoevenagel condensation at room temperature over 10 hours, which yielded 84 % of 4-methoxybenzylidene malononitrile.[9] Maybe if reactions were performed for 10 hours, similar yields would be found, as for instance is seen in entry 8 (76 % yield after 24 hours). During their other deacetalization-Knoevenagel tandem reactions they obtained similar yields, however they used elevated temperatures (60 °C) and longer reaction times.

As can be seen in table 8 conversions of acetal and benzaldehyde were highly dependent on the acid and base concentrations. For example, in entries 1 to 3 only 5 mol-% of acid is used. Conversion of benzaldehyde dimethyl acetal in these entries was only between 41 and 51 %. When

acid concentrations were higher, benzaldehyde dimethyl acetal conversion were 80 to 100 % as can be seen in entries 4, 6 and 8. The acid concentration of 5 mol-% seemed to be too low for full benzaldehyde dimethyl acetal conversion in 3 hours at room temperature. Lower acetal conversions were also observed when 20 mol-% base was used, as in entries 5 and 7. This 20 mol-% probably resulted in faster diffusion of piperidine to the water droplets, resulting in faster mutual destruction of acid and base. Since probably enough base was available for the conversion of benzaldehyde after partial neutralization, still high conversions of benzaldehyde were observed. Mutual destruction can probably be prevented by using a base that is more hydrophobic than piperidine.

A closer look to entries 4, 5 and 6 shows high conversions of benzaldehyde dimethyl acetal if there is 10 mol-% acid and 10 mol-% base and if there is 20 mol-% acid and 10 mol-% base. Conversion of benzaldehyde dimethyl acetal is lower when the base concentration is higher than acid concentration in entry 5. This trend is also seen in figure 25. Entries 4, 5 and 6 show a similar in benzaldehyde conversion as in figure 27 as well. However, this tandem can not directly be compared to separate reactions, since the reaction mixtures have different components, which might influence reaction rates.

Benzaldehyde conversions are lower in entries 4 and 6 than in the other entries in table 8. This was first attributed to partial destruction of acid and base as well. However, deacetalization still was successful in these tandem reactions. In reaction 6 this can be explained by the higher acid concentration compared to the base concentration. Maybe a small excess of acid enables deacetalization in entry 4. Another possible explanation for low benzaldehyde conversions is the short reaction time. This was tested by performing a deacetalization-Knoevenagel tandem over 24 hours. This experiment was performed in duplo. Acid and base concentrations were 10 mol-%. This resulted in an average benzaldehyde dimethyl acetal conversion of 82 % an average conversion of benzaldehyde of 95 % and a benzylidene malononitrile yield of 76 % as can be seen in entry 8 of table 8. Apparently, the reaction is not fully quenched due to neutralization of acid and base and still goes on after 3 hours giving higher yields. Striking is that benzaldehyde dimethyl acetal conversion over 24 hours (entry 8) is lower than in the same reaction (entry 4) in 3 hours. Maybe less acid is added due to some experimental error. Anyway, it would be interesting to do more runs over longer time periods than 3 hours and compare these to the results of Yang *et al.*[9]

5   Conclusions

In this project Pickering emulsions with different organic solvents and silica particles were prepared by dispersion of silica in the organic compound using ultrasonication followed by adding water and vigorous stirring. Emulsions prepared with 6:2 toluene to water and 3 wt-% HDK® H20 silica with respect to the toluene mass showed to be the most stable. Confocal fluorescence microscopy on emulsions prepared with Nile red showed that these emulsions were w/o emulsions.

Aerosil 200 was successfully hydrophobized by silylation with TMSCl and emulsions were stabilized with this silica compound. However, most of the emulsions prepared with this silica were not stable and separated soon over time. TEM images, nitrogen physisorption, contact angle measurements and IR spectroscopy were used to see what differences this silica showed with respect to commercial HDK® H20 silica from Wacker Chemie AG. The only difference explaining the other behavior in Pickering emulsions was found in IR spectroscopy. According to the IR spectra hydrophobized Aerosil 200 still contained more silanol groups in comparison to hydrophobic methylsilyl groups. However, both silica types were aggregated fumed silica, had a similar BET surface area and similar contact angles of a water droplet on a silica surface were found.

Stöber silica was prepared and particles with an average diameter of approximately 38 nm were obtained. These particles were also hydrophobized. The contact angles showed these particles were less hydrophobic than hydrophobized Aerosil 200 and hydrophobic HDK® H20. This could explain the instability of emulsions prepared with it, even with 10 wt-% silica. Preparation of stable emulsions with this type of silica showed to be irreproducible and therefore no further experiments were performed with it.

The applicability of Pickering emulsions for tandem catalytic conversion was explored using the deacetalization-Henry and deacetalization-Knoevenagel tandems with benzaldehyde dimethyl acetal as substrate. Therefore first the separate reactions were investigated:

Deacetalization of benzaldehyde dimethyl acetal catalyzed by hydrochloric acid showed to be very efficient. Deacetalization of 1 mmol benzaldehyde dimethyl acetal over 3 hours at room temperature gave higher conversions and yields in Pickering emulsions than in simple biphasic systems, which could be explained by the increased interfacial area in emulsions. Conversions of benzaldehyde dimethyl acetal and yields of benzaldehyde were also higher in Pickering emulsions compared to simple biphasic systems when both acid and base were in the system. However, conversions and yields were somewhat lower, probably because of mutual destruction of acid and base.

Henry reactions of benzaldehyde with nitromethane did not show significant conversions and yields in most attempts. Even not after several days at 80 °C. Piperidine-catalyzed Henry reaction in toluene had a trans-β-nitrostyrene yield of 41 % when performed over 22 hours at 80 °C. However, same reactions in biphasic systems and Pikcering emulsions only yielded trace amounts of trans-β-nitrostyrene. Deacetalization-Henry tandem reactions were not performed successfully either.

Knoevenagel reaction was studied in monophasic and biphasic systems and in Pickering emulsions, catalyzed by piperidine most of the times. This reaction went well even at room temperature over 3 hours. Therefore, further study of deacetalization-Knoevenagel reactions was performed using different acid- and base-catalyst concentrations. This tandem was performed in both biphasic systems and Pickering emulsions at 80 °C and room temperature over 3 hours. Tandem catalytic

conversion in simple biphasic systems did not result in any conversion of benzaldehyde dimethyl acetal at room temperature. It did, however, give rather low conversions and yields at 80 °C. At room temperature these tandem reactions were performed in Pickering emulsions with benzylidene malononitrile yields between 29 and 59 %. These yields are lower than for the separate Knoevenagel condensation, which might be due to mutual neutralization of catalysts. Conversions and yields were also lower in the separate Knoevenagel condensation with both acid and base in the system, which was probably also caused by mutual destruction of catalysts. Furthermore, an extra reaction step (deacetalization) is needed for the tandem reactions, which of course increases the over all reaction time.

In conclusion, Pickering emulsions are applicable for the tandem catalytic conversion of benzaldehyde dimethyl acetal in a deacetalization-Knoevenagel tandem to yield benzylidene malononitrile.

6 Outlook

As this project showed Pickering emulsions were used to perform a deacetalization-Knoevenagel tandem reaction with hydrochloric acid and piperidine as catalysts and benzaldehyde dimethyl acetal as substrate. It would be very interesting to see whether other reagents can be used. One possibility is to use acetals of aliphatic aldehydes.

If these other substrates are fluorescent the tandem reaction can be followed *in situ* with confocal fluorescence microscopy. A major challenge is to find a reaction in which the substrate, intermediate product and final product have another fluorescence wavelength.

It would also be interesting to use other bases for the deacetalization-Knoevenagel tandem. When a base is used that is more hydrophobic than piperidine, probably mutual destruction of acid and base takes place.

Another idea for future research is to synthesize particles which are both emulsifying agents and catalysts. These could possibly be Janus particles with acid sites in the water phase and base sites in the organic phase of the Pickering emulsion. This way acid-base phase isolated tandem catalysis can be performed and no neutralization of acid and base will occur. Also other bifunctional catalysts could be prepared this way. A nice merit of using emulsifying particles as catalysts is the fact that the catalysts can simply be recovered by separation of the emulsion.

Since apparently emulsions are not certainly stable and the way emulsions are prepared is energy consuming with ultrasonication and stirring steps, industrial application seems to be far away. However, if smart emulsions will be designed, this rather elegant approach can be of great help to synthetic chemistry, even for the synthesis of complex molecules.

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Appendix

A. Contact Angle Measurement Instrument
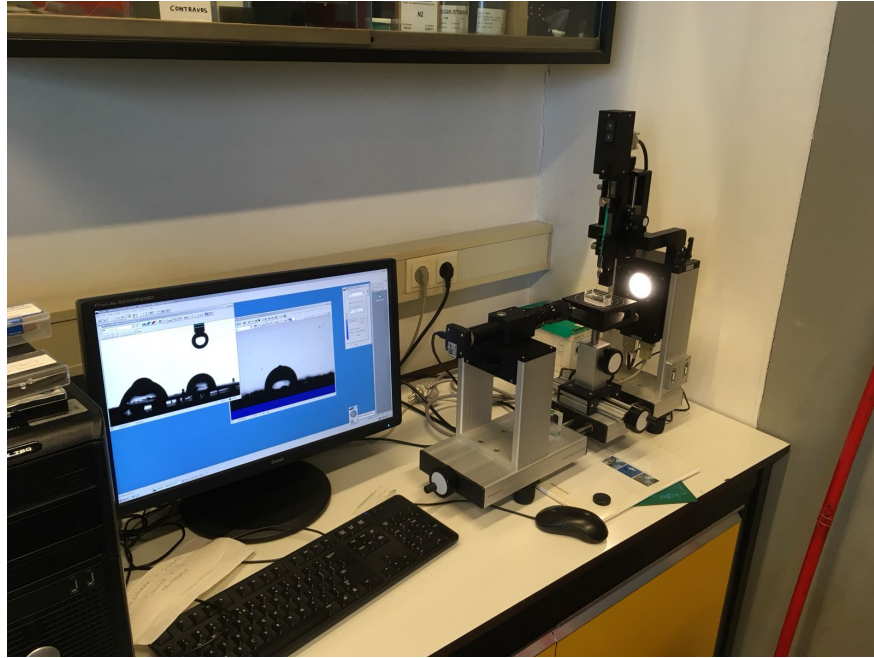
Figure 28: A picture of the setup used for contact angle measurements. On the right is the OCA 15EC device from Dataphysics. A cuvet is placed between the lamp and a camera. On top is an automatic syringe pump. Data is obtained using special SCA 20 software to encircle droplets on wafer surfaces and the contact angle is calculated based on this circle and the baseline (left screen).

B. Pickering Emulsion Preparation
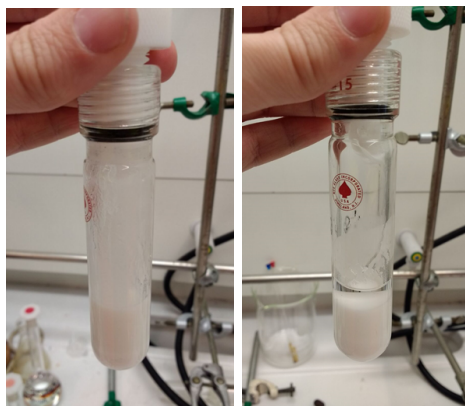
Figure 29: Pictures of a stable Pickering emulsion (left) and an unstable one (right). Stable Pickering emulsions stabilized by silica are homogeneous white dispersion. When an emulsion is unstable, a clear layer can be found on top or on the bottom.

Table 9: Overview of Pickering emulsions prepared with hydrophobized Aerosil 200 silica with differen toluene to water volume ratios. Silica wt-% is relative to toluene mass. Stability of the Pickering emulsions was determined initially, after 1 h and after 1 night.

Toluene volume (mL)	Water volume (mL)	Silica wt-%	Initially stable?	Stable after 1h?	Stable after 1 night?
2	6	2	no	no	no
2	6	3	no	no	no
2	6	5	yes	no	no
3	5	2	no	no	no
3	5	3	yes	yes	no
3	5	5	yes	no	no
4	4	2	yes	no	no
4	4	3	yes	yes	no
4	4	5	yes	no	no
5	3	2	yes	yes	very thick
5	3	3	yes	yes	very thick
5	3	5	yes	yes	very thick
6	2	2	yes	no	yes
6	2	3	yes	no	yes
6	2	5	yes (very thick)	yes (very thick)	very thick

Table 10: **Hydrophobized Stöber silica and Wacker HDK®H20 were tried as a Pickering emulsion stabilizing agents. A silica wt-% of 10 and 20 was used as adapted from Yang *et al.*[9] for the colloidal Stöber silica and 1, 2 and 3 wt-% of Wacker silica.**

Toluene volume (mL)	Water volume (mL)	Silica type	Silica wt-%	Stable?
6	2	Stöber	10	no
6	2	Stöber	20	no
6	2	Wacker	1	no
6	2	Wacker	2	mostly
6	2	Wacker	3	yes

C. Deacetalization, Kinetic Experiments

In figure 30 results of the first deacetalization experiments in Pickering emulsions and biphasic systems are depicted. These are performed in
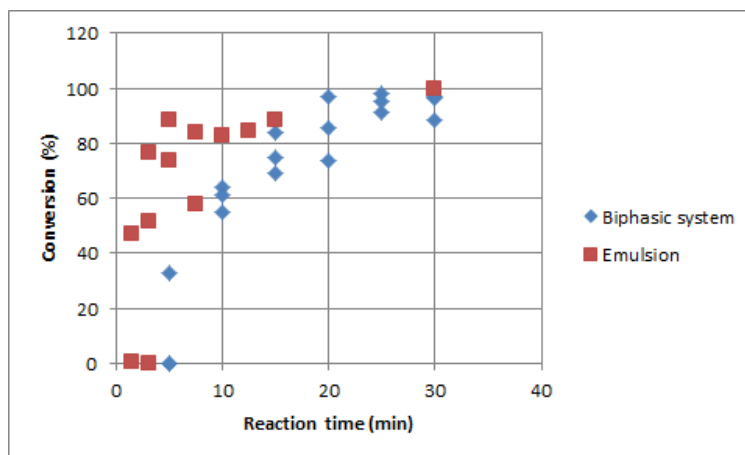
Figure 30: **Conversion of benzaldehyde dimethyl acetal during deacetalization over time. Conversion (%) is depicted on the vertical axis and reaction time (min) on the horizontal axis. Red squares are from an emulsion, blue diamonds are from simple biphasic systems.**

D. Deacetalization-Henry Tandem

Table 11: Overview of deacetalization-Henry tandems that were tried in Pickering emulsions. All emulsions were prepared with hydrophobized Aerosil 200. T29-T31 were Pickering emulsions with 4-propylguaiacol as organic solvent, organic solvent in other entries was toluene. B32-B37 were not performed in Pickering emulsions but in simple biphasic systems. T1-T16 were also stirred at 600 rpm, rest was not stirred.

Code	Organic phase volume (mL)	Water volume (mL)	Acid conc. (mol-%)	Base	Base conc. (mol-%)	T (°C)	Reaction time (h)
T1, T2	3	5	14	diisopropylamine	86	80	1.5
T3-T8	3	5	8	diisopropylamine	11	100	20
T9, T10	3	5	8	diisopropylamine	11	80	6
T11, T12	3	5	8	diisopropylamine	11	80	20
T13, T14	3	5	8	diisopropylamine	5	80	4.5
T15, T16	3	5	8	diisopropylamine	11	40	24
T17	6	2	8	DIPEA	3.5	80	5
T18	6	2	8	DIPEA	3.5	80	22
T19	6	2	8	DIPEA	3.5	80	24
T20	6	2	8	DIPEA	3.5	80	26
T21, T22	6	2	8	DIPEA	3.5	80	48
T23	4	4	8	DIPEA	7	60	48
T24	4	4	8	DIPEA	7	60	96
T25	6	2	8	DIPEA	3.5	60	48
T26	6	2	8	DIPEA	7	60	96
T27, T28	6	2	8	DIPEA	3.5	60	24
T29-T31	6	2	5	DIPEA	3	80	1
T32-T37	6	2	5	DIPEA	3	80	1
B32-B37	6	2	5	DIPEA	3	80	1
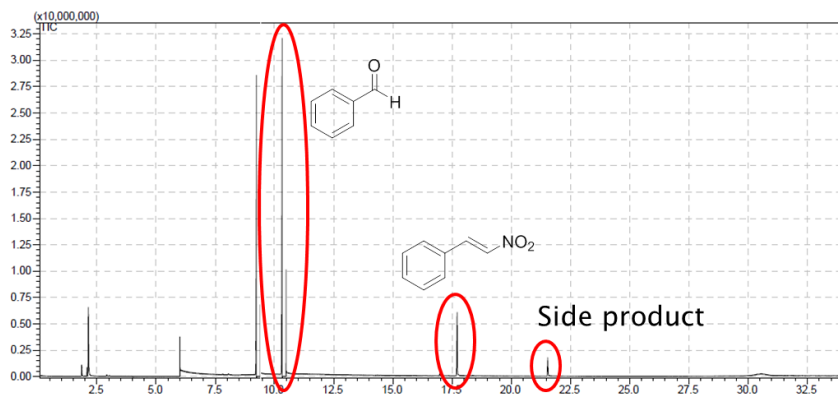
Figure 31: Chromatogram obtained with GC-MS of T8. The peaks of intermediates and products are assigned. The peak just after 10 minutes is from benzaldehyde. Around 17.5 minutes a peak originating from trans-β-nitrostyrene is found. The peak of the side product is likely to come from trans-β-nitrostyrene with an extra methyl-group attached, as was found with MS.

E. Knoevenagel Condensation in Monophasic Systems

Table 12: Results of Knoevenagel condensation of 1 mmol (in 6 mL toluene) or 2 mmol (in 12 mL toluene) benzaldehyde with 2.5 equivalent malononitrile at 80 °C. Piperidine or DIPEA was used as base-catalyst and reaction times were varied.

Entry	Time (h)	Organic phase Volume (mL)	Base	Base concentration (mol-%)	Benzaldehyde Conversion (%)
1	24	6	Piperidine	15	100
2	24	6	Piperidine	30	100
3	5	6	DIPEA	20	100
4	5	6	Piperidine	15	100
5	4	12	Piperidine	15	100
6	2	12	Piperidine	15	100
7	2	12	DIPEA	20	100

Table 13: Results of Knoevenagel condensation of **2 mmol benzaldehyde with 2.5 equivalent malononitrile in 12 mL toluene at 80 °C. Piperidine (20 mol-%) was used as base-catalyst and two samples were taken after every 20 minutes, after which one sample was acidified with glacial acetic acid.**

Reaction	Time (min)	Benzylidene malnononitrile yield (%)	Benzylidene malnononitrile when acidified yield (%)
1	20	84	83
2	20	76	75
1	40	71	72
2	40	67	72
1	60	87	92
2	60	83	69
1	80	80	82
2	80	76	80
1	100	76	66
2	100	77	67

F. Knoevenagel Condensation, Alternative Mechanism
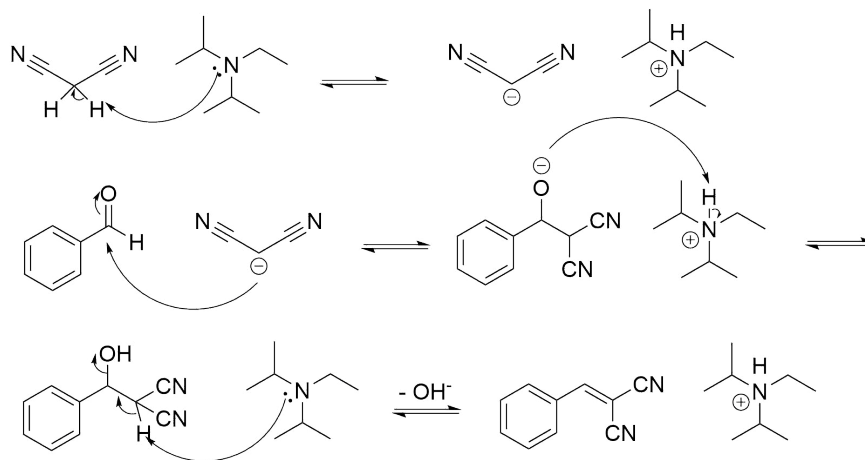
Figure 32: Knoevenagel condensation of benzaldehyde with malononitrile, when catalyzed by DIPEA. This mechanism works differently from the mechanism in figure 14, since DIPEA is not able to form an iminium ion.

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