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Continuous Processes for the Synthesis and Isolation of Functionalized Biphenyls via Suzuki-Miyaura Cross-Coupling Reactions

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ABSTRACT

The aim of this thesis is the realization of a continuous process for the synthesis and isolation of substituted biphenyls via the Suzuki-Miyaura coupling, a palladium catalyzed cross-coupling reaction.

Although palladium catalyzed cross-coupling reactions are from outstanding importance for the synthesis of fine chemicals, pharmaceuticals and agrochemicals,[1] and despite a general trend in fine chemical and pharmaceutical industry towards continuous manufacturing,[2,3] continuous processes for Pd-catalyzed coupling reactions are not well established. Approaches based on heterogeneous catalysts in packed-bed reactor set-ups commonly suffer from rapid catalyst deactivation and contamination of the final product by leached palladium.[4,5] These issues are today generally attributed to the special mechanism of these reactions, which require dissolved palladium species as catalysts and follow a principally homogeneous mechanism. Nevertheless, recent reports indicate that the use of appropriate supported catalysts in packed bed reactors at carefully chosen reaction conditions and solvent compositions can indeed be a suitable strategy for the continuous or semi-continuous synthesis of biphenyls using Pd-catalyzed cross-coupling reactions.[6]

In this work, highly reactive and leaching resistant novel palladium substituted mixed cerium-tin-oxides as solid catalysts for Suzuki-Miyaura reactions were developed. Such catalysts can be synthesized using the solution combustion method out of non-toxic and cheap precursor materials in a convenient manner. The synthesis and characterization of these novel catalysts, including activity, recyclability, leaching and heterogeneity studies, are presented.

A novel reactor device, the so called “Plug & Play Reactor” designed and engineered in collaboration with OneA engineering, Vöcklabruck, Austria, was used for the continuous experiments employing the novel Pd-Ce-Sn-oxide catalysts in a catalytic fixed-bed. Using this set-up, seven functionalized biphenyls could be synthesized in flow processes, which were stable for up to 30 hours without any catalyst deactivation. Three continuously synthesized biphenyl products were isolated from the reaction solution using a directly coupled continuous crystallization process at overall process yields of up to 96 % on a scale of 151 – 204 mg/h (up to ~5 g/d). The isolated products were highly pure and contained only minimal amounts of palladium (0.28 – 2.1 ppm).

Thus, the described continuous process represents a convenient and reliable synthetic technique for the production of substituted biphenyls on a laboratory scale. Moreover, the main

advantages (especially the ease of preparation of the catalyst and the use of “green solvents” throughout the whole synthesis and crystallization procedure) indicate the potential of this novel process to be used not only in laboratory, but also on a larger scale.

KURZFASSUNG

Das Ziel dieser Arbeit ist die Realisierung eines kontinuierlichen Prozesses zur Synthese und Isolierung substituierter Biphenyle mithilfe der Suzuki-Miyaura Kupplung, einer Palladium-katalysierten Kreuzkupplungsreaktion.

Trotz der außerordentlichen Bedeutung von palladiumkatalysierten Kreuzkupplungs-reaktionen in der Synthese von Feinchemikalien, Pharmazeutika und Agrochemikalien[1] und obwohl ein genereller Trend der chemischen und pharmazeutischen Industrie in Richtung kontinuierliche Chemikalienherstellung feststellbar ist,[2,3] sind kontinuierliche Prozesse für Pd-katalysierte Kupplungsreaktionen in der Industrie nicht etabliert. Mögliche kontinuierliche Prozesse, wie die Anwendung von heterogenen Katalysatoren in Festbettreaktoren scheitern vielfach an einer raschen Deaktivierung der Katalysatoren und der Verunreinigung der Endprodukte mit ausgewaschenem Palladium. [4,5] Nach dem heutigen Wissensstand werden dieses Probleme durch den speziellen Mechanismus dieser Kreuzkupplungsreaktionen verursacht, der gelöstes Palladium und einen prinzipiell homogenen Reaktionsverlauf erfordert. Nichtsdestoweniger haben aktuelle Forschungsarbeiten gezeigt, dass der Einsatz von geeigneten quasi-heterogenen Katalysatoren in Festbettreaktoren bei sorgfältig gewählten Reaktionsbedingungen tatsächlich eine geeignete Synthesestrategie zur kontinuierlichen oder zumindest semi-kontinuierlichen Herstellung von Biphenylen mittels Pd-katalysierten Kreuzkupplungsreaktionen darstellen kann.[6]

Im Zuge dieser Arbeit wurden neuartige, palladium-substituierte gemischte Cer-Zinn-Oxide, die als hoch reaktive und leaching-resistente Katalysatoren für Suzuki-Miyaura Reaktionen eingesetzt wurden, entwickelt. Solche Katalysatoren können mithilfe der sogenannten „solution combustion method“ rasch und unproblematisch aus ungiftigen und preisgünstigen Grundmaterialien hergestellt werden. Die Synthese und Charakterisierung dieser neuartigen Katalysatoren mittels Aktivitäts-, Wiederverwendbarkeits-, Leaching- und Heterogenitätsstudien werden in dieser Arbeit beschrieben.

Eine neue Reaktionsanlage, der sogenannte “Plug % Play Reactor”, die in Zusammenarbeit mit OneA engineering, Vöcklabruck, Oberösterreich, entworfen und hergestellt wurde, wurde zur Durchführung der kontinuierlichen Experimente, in denen die neuen Katalysatoren in einem katalytischen Festbett eingesetzt wurden, durchgeführt. Mithilfe dieser Anlage konnten sieben unterschiedliche funktionalisierte Biphenyle in kontinuierlichen Prozessen hergestellt werden, die bis zu 30 Stunden lang stabil (d.h. ohne erkennbare Katalysatordeaktivierung) gehalten werden konnten. Drei der kontinuierlich hergestellten Biphenyle wurden außerdem in

einer direkt anschließenden Kristallisationsanlage kontinuierlich isoliert. Dabei wurden Gesamtprozessausbeuten von bis zu 96 % in einer Größenordnung von 151 – 204 mg/h (bis zu rund 5 g/d) erreicht. Die isolierten Endprodukte waren außerordentlich rein und enthielten nur minimale Mengen an ausgeschwemmten Palladium (0.28 – 2.1 ppm).

Der in dieser Arbeit beschriebene kontinuierliche Prozess stellt eine praktikable und verlässliche Synthesemethode zur Herstellung von substituierten Biphenylen im Labormaßstab dar. Die großen Vorteile dieser Methode, vor allem die einfache und rasche Herstellung der festen Katalysatoren sowie der Einsatz von „grünen Lösungsmitteln“ über den gesamten Synthese- und Kristallisationsverlauf, legen nahe, dass dieser Prozess auch in einem größeren Maßstab realisiert werden kann.

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A Introduction

Over the last years, continuous flow processes, traditionally applied for the production of petrochemicals, bulk chemicals and polymers at large scales, have gained more and more attention also for the production of fine chemicals, active pharmaceutical ingredients (APIs) and agrochemicals.[7,8] Several examples for continuous multistep API-syntheses or even end-to-end manufacturing plants have been reported[9–15] and reflect the great effort which has been done to establish suitable continuous protocols for the primary and secondary manufacturing of APIs. Although the advantages of continuous processes are well known[2,3] (e.g., increased throughput, reduced waste, simplified scale-up or improved safety, especially when hazardous reagents are used[16]) the application of continuous processes is not yet standard practice in pharmaceutical manufacturing, despite the effort of the FDA (Federal Drug Administration).[17,18] Economic concerns and the lack of adequately educated personnel, technical challenges (insufficient reliability, leaking) and equipment for production at larger scales are hurdles for the implementation of continuous processes in industry.[2] Thus, the development of stable and reliable continuous synthesis and downstream protocols has an extraordinary high potential as pharmaceutical manufacturing is, despite all difficulties, clearly transitioning toward continuous manufacturing. The present work focuses on the development of continuous processes for the synthesis and isolation of functionalized biphenyls via palladium catalyzed Suzuki-Miyaura cross-coupling reactions.

Palladium catalyzed C-C coupling reactions are an important class of reactions prevalent in synthesis protocols adopted for making active pharmaceutical ingredients, natural products and bioinorganic materials on a lab scale as well as in industrial settings.[19] Among the diverse types of Pd-catalyzed coupling reactions, the Suzuki-Miyaura reactions has become the most important one regarding the number of publications and patents over the last decade.[1] Dozens of applications for the large scale synthesis of pharmaceuticals, natural products, agro-chemicals and polymers are known (see Chapter 2.2.4). Based on the premise that the use of heterogeneous palladium catalysts would be advantageous regarding catalyst separation, recycling, process intensification and product purity, numerous immobilized palladium catalysts were developed and tested in batch and continuous mode, especially in packed bed reactors (see Chapter 2.2.2). In practice, the use of immobilized Pd-catalysts in packed bed reactors for cross-coupling reactions is typically highly limited due to rapid catalyst deactivation and considerable palladium leaching into the product stream.[4] In continuous flow processes, catalyst deactivation is today generally attributed to the special reaction mechanism of cross-coupling reactions, which require dissolved Pd-complexes as catalytically active species and therefore follow a principally homogeneous reaction progress (see Chapter 2.2.3., Figure A-5).[20] Thus, the use of immobilized Pd-catalysts in packed bed reactors might appear

inadequate and the development of homogeneous metal catalyst/ligand systems, combined with advanced separation techniques, is currently propagated.[20,5]

Nevertheless, Pandarus *et al*. established a continuous Suzuki-Miyaura reaction process using a single pass packed bed flow reactor, which was stable for up to 40 hours at high product yields and low amounts of palladium leaching.[6] In this work, continuous packed bed flow processes for Suzuki-Miyaura cross-coupling reactions, which are stable for more than 30 hours will be described. Novel, highly leaching resistant Pd-substituted cerium-tin oxides were used for these processes.

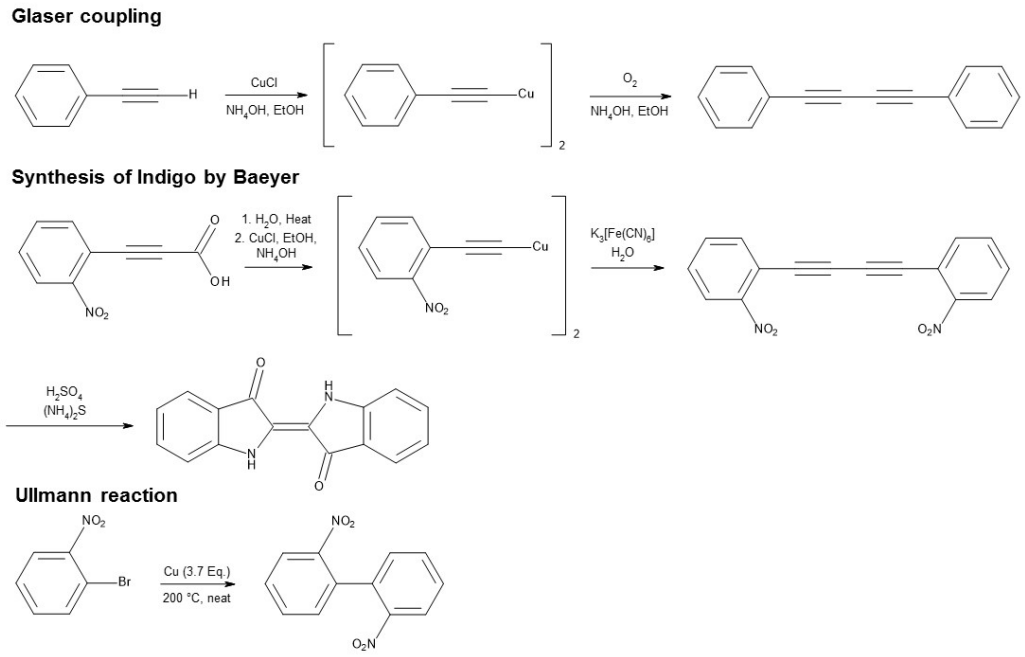
The results published by Pandarus *et al.* and the processes described in this thesis show, that the use of single-pass packed bed reactors employing appropriate quasi-heterogeneous catalysts at carefully chosen reaction conditions are indeed a practicable and attractive strategy for the continuous or semi-continuous synthesis of biphenyls using Pd-catalyzed C-C cross coupling reactions, at least on a laboratory or multigram scale.

1 Coupling Reactions

In organic chemistry, the term coupling reaction denotes diverse transition metal catalyzed reactions, where two hydrocarbons are coupled by the formation of covalent carbon-carbon or carbon-heteroatom bonds.[21] Regarding the coupling partners, one can generally distinguish between homocoupling reactions (the coupling of two identical hydrocarbons yielding symmetric hydrocarbons) and cross-coupling reactions (the coupling of two different hydrocarbon species).

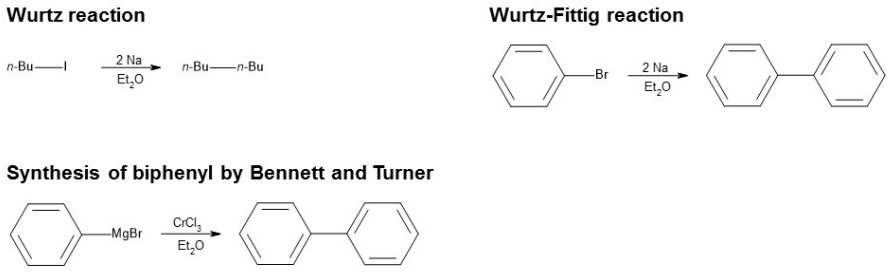
The award of the 2010 nobel price of chemistry to three eminent chemists (Richard F. Heck for his pioneering work on cross couplings involving olefins, Ei-ichi Negishi for the development of a mild cross coupling, and Akira Suzuki for the discovery of a practical process[19]), who worked on the field of Pd-catalyzed cross-coupling reactions, reflects the outstanding importance of these types of reactions in organic chemistry and motivated Seechurn *et al.*[1] to prepare a comprehensive review on historical and recent developments and progresses in coupling chemistry. According to this review, the milestones in the development of cross-coupling chemistry are highlighted and summarized in the following.

From a historical point of view, the development of metal mediated C-C coupling reactions began in the mid-19th and early 20th century with the discovery of metal promoted homocoupling reactions. Several widely known name-reactions were developed in this period. Glaser[22] (1869), Baeyer[23] (1882) and Ullmann[24] (1901) used stoichiometric or superstoichiometric amounts of copper for the formation of C(sp)-C(sp) (Glaser and Baeyer) and C(sp^2)-C(sp^2) bonds (Scheme A-1).



Scheme A-1: Copper mediated stoichiometric and superstoichiometric homocoupling reactions.

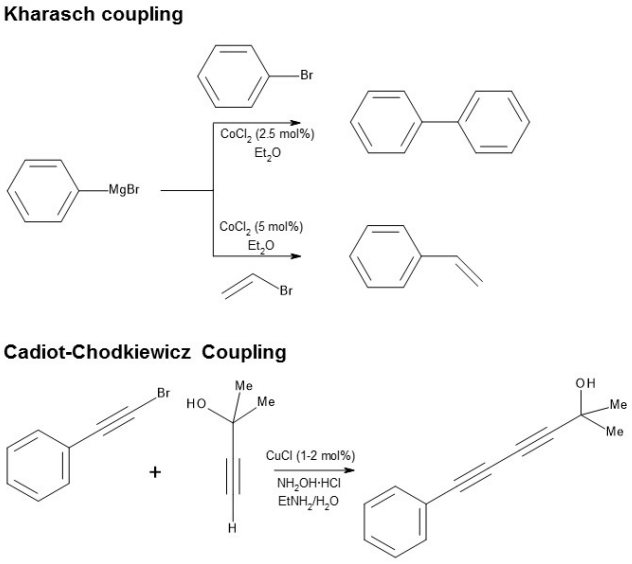
Almost concurrently, Wurtz[25] (1855) and Fittig[26] (1862) reported the homocoupling of alkyl and aryl halides using organosodium chemistry. In the early 20th century, Bennet and Turner[27] (1914) described the synthesis of biphenyl using the chromium mediated dimerization of phenylmagnesium bromide, a Grignard reagent (Scheme A-2).



Scheme A-2: Homocoupling reactions using organosodium and Grignard reagents.

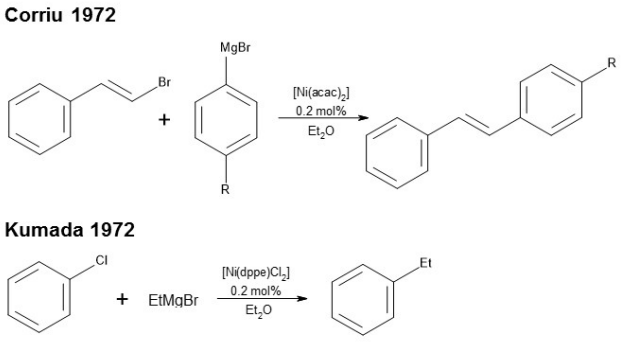
These early coupling reactions often suffered from poor selectivity and were limited to homocoupling reactions. Furthermore, stoichiometric or superstoichiometric amounts of metals had to be used. The capability of copper to promote C-C coupling reactions even if only catalytic amounts of metal are used was recognized by Ullmann already in 1905. However, it took more than 30 years until Meerwein[28] (1939) and Kharasch[29] (1941) systematically investigated copper and cobalt catalyzed homo and cross-coupling reactions. Although these works led to the fundamental premise that transition metals can be used as catalysts for the formation of carbon-carbon bonds, the extreme limitations regarding substrate scope and functional group tolerance hindered their broad application in organic synthesis. More selective

cross-coupling reactions were reported by Cadiot and Chodkiewicz[30] in 1955 and by Castro and Stephens[31] in 1963 (Scheme A-3).



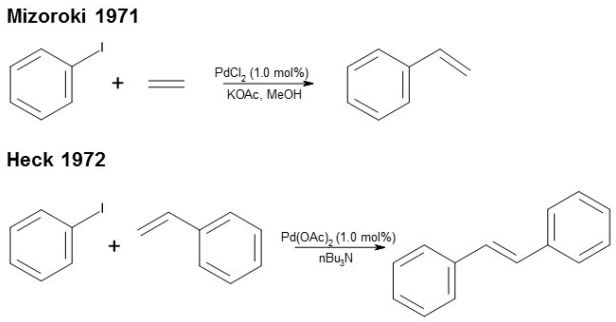
Scheme A-3: Early cobalt and copper catalyzed homo and cross-coupling reactions.

In the following years, the catalytic activity of other transition metals in catalytic cross-coupling reactions were recognized. In 1972, Corriu[32] and Kumada[33] independently demonstrated the cross coupling reaction of Grignard reagents with aryl and alkenyl halides catalyzed by organonickel complexes (Scheme A-4).



Scheme A-4: Coupling of Grignard reagents with organic halides.

Almost concurrently, Mizoroki[34] and Heck[35] independently reported the palladium(II) catalyzed cross-coupling reaction of alkenes with aryl halides (Scheme A-5).



Scheme A-5: Mizoroki-Heck coupling.

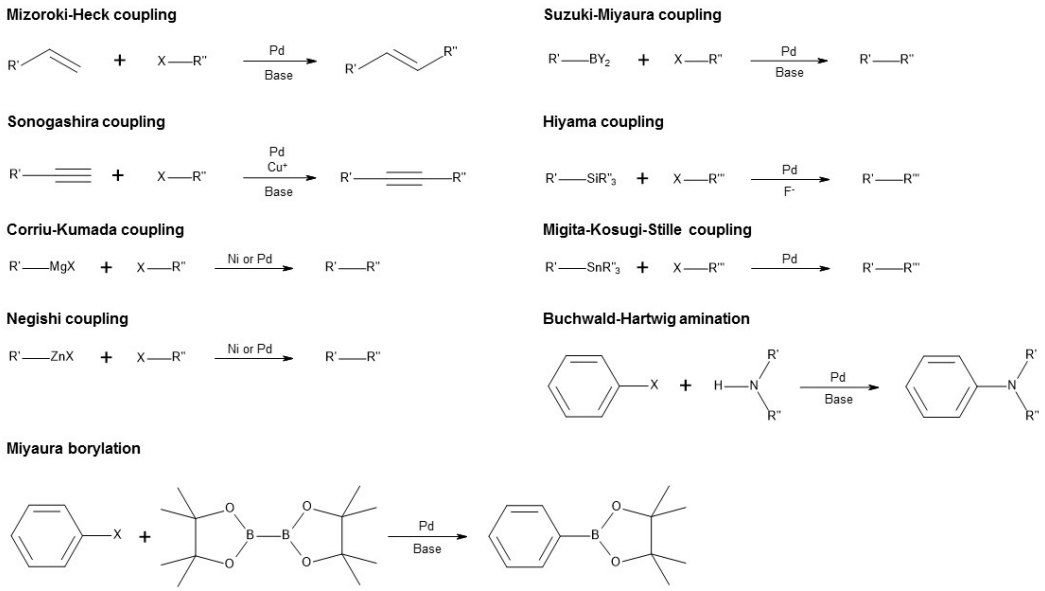
By the mid-1970s, three transition metals dominated organic coupling chemistry: copper for the coupling of acetylene compounds, nickel for Grignard coupling chemistry and palladium for catalyzing the reaction between alkenes and aryl halides, the now called Mizoroki-Heck reaction.

2 Palladium Catalyzed Cross-Coupling Reactions

In the following years, copper and nickel mediated cross-couplings were successively replaced by palladium catalyzed reactions.

In 1975, Sonogashira[36] reported the cross-coupling of acetylenes and aryl halides catalyzed by organopalladium complexes and co-catalyzed by copper iodide. The use of palladium complexed instead of nickel-based catalysts for the coupling of Grignard reagents with aryl and alkyl halides (Corriu-Kumada coupling) proved to be beneficial in terms of stereofidelity and substrate scope. Furthermore, palladium was able to catalyze also the coupling of organolithium species, which was not possible under nickel catalysis.

Due to the intolerance of diverse sensitive functional groups towards the highly reactive organomagnesium and organolithium coupling reagents, other organometallic coupling partners were examined for their reactivity in cross-coupling reactions. In the following years, methods for the cross-coupling of organic halides with organozinc (Negishi coupling[37]), organostannane (Stille coupling[38]), organoborane (Suzuki-Miyaura coupling[39]) and organosilicon (Hiyama reaction[40]) coupling partners. In the 1990s, palladium catalyzed coupling reactions for the formation of carbon-heteroatom bonds were developed by Miyaura[41] (formation of carbon-boron bonds) and by Buchwald and Hartwig[42,43] (formation of carbon nitrogen bonds). The general reaction schemes of today's most relevant palladium catalyzed cross-coupling reactions are depicted in Scheme A-6.



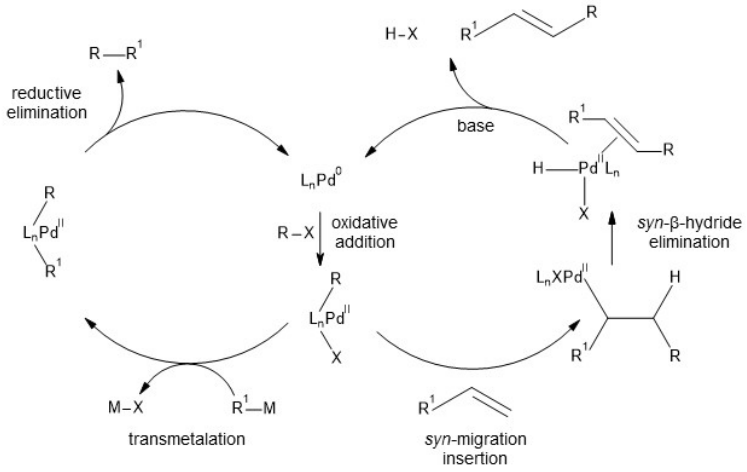
Scheme A-6: Palladium catalyzed cross-coupling reactions.

2.1 Mechanism

From a mechanistic point of view, one has to distinguish between the coupling reactions of organic halides with organometallic species - either preformed (Corriu-Kumada, Negishi, Hiyama, Stille and Suzuki-Miyaura reaction) or generated in situ (Sonogashira coupling) - on the one hand and with alkenes (Heck coupling) on the other hand. The generally accepted mechanisms for both types of reactions are depicted in Figure A-4.[1]

In both types of couplings, the catalytic reactions start with the oxidative addition of the aryl halide (or pseudohalide) to the L_nPd^0 compound (L = organic ligand). The Heck reaction proceeds with the coordination of the alkene to the Pd^{II} species and its *syn*-migration insertion, forming a new organopalladium complex, which undergoes *syn*-β-hydride elimination. The formation of the coupling product is followed by the base-assisted elimination of H-X (X = I, Br, Cl) from the remaining palladium complex to regenerate the L_nPd^0 complex and to close the catalytic cycle.

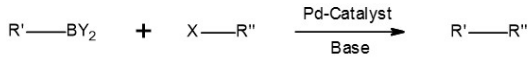
Coupling reactions involving organometallic coupling partners undergo a different reaction procedure. After the common oxidative addition step, a Pd^{II} species bearing two organic fragments is generated by a transmetalation step. Reductive elimination of the reaction partners leads to C-C bond formation, reproduces the Pd^0-complex and closes the catalytic cycle.



Scheme A-7: General Mechanisms of palladium catalyzed cross-coupling reactions (R = organic moiety, L = organic ligand, M = B, Sn, Zn, Mg, Si, X = I, Br, Cl, OTf, OTos).

2.2 The Suzuki-Miyaura Cross-Coupling Reaction

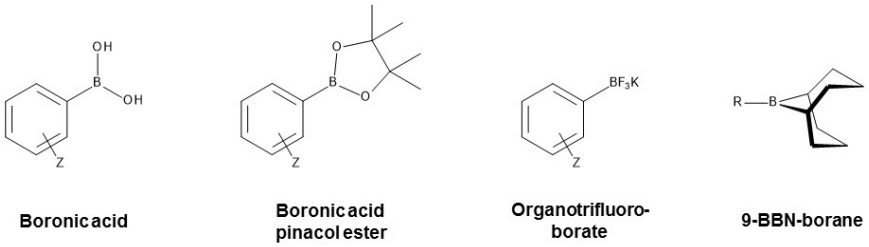
The Suzuki-Miyaura reaction[44] is the palladium catalyzed coupling reaction between organoboron compounds and organic halides or pseudohalides (triflates, tosylates, mesylates or diazonium salts).[45–47]



Scheme A-8: General scheme of the Suzuki-Miyaura cross-coupling reaction.

Among the different types of palladium catalyzed cross coupling reactions, the Suzuki-Miyaura reaction became the most important one in terms of the number of publications and patents over the last decade.[1] Compared to other coupling reactions, the major advantages of the Suzuki-Miyaura coupling are the mild reactions conditions, the high tolerance to diverse functional groups, the commercial availability of various organoboron reagents, which are environmentally safer than other organometallic reagents and which are relatively stable towards heat, air and moisture, as well as the ease of handling and removal of boron containing by-products from the reactions solution.[48,49]

Commonly applied organoboron reagents employed for Suzuki cross coupling reactions include boronic acids, boronic acid derivates, especially boric esters, trifluoroborates and alkenyl boranes (Figure A-1).[50]



Boronic acid | Boronic acid pinacol ester | Organotrifluoro-borate | 9-BBN-borane

Figure A-1: Organoboron coupling partners for Suzuki-Miyaura cross-coupling reactions.

During the initial stages of the reaction development, alkyl borane components (like 9-BBN-boranes) were the most commonly applied organoboron reagents for Suzuki couplings. However, due to several disadvantages, especially their sensibility towards aerobic oxidation as well as their affinity to side reactions (dehydroboration and protodeboronation), boronic acids, boronic esters and trifluoroborates are nowadays more common reagents for Suzuki reactions.

Commonly applied and commercialy available boric esters as reagents in Suzuki coupling reactions are pinacol, neopentyl and catechol boric esters. Possible ways for the synthesis of boronic esters are hydroboration reactions catalyzed by titanium[51], rhodium[52], iron[53] or copper[54] complexes and the Pd-catalyzed Miyaura borylation reaction of aryl[41] and alkenyl[55] halides with diboron reagents (e.g. B_2pin_2) to the corresponding boric ester. The hydrolysis of these boric esters represents also a possible route for the synthesis boronic acids.

Boronic acids can furthermore be synthesized by the reaction of boronic esters (e.g. $B(O\textit{i}Pr)_3$ or $B(OMe)_3$) with suitable nucleophilic organometallic reagents (organolithium compounds[56] or Grignard reagents[57]) and subsequent acidic hydrolysis of the resulting boronic esters.

Analogous to the Miyaura borylation reaction, a direct synthesis of boronic acids via Pd-catalyzed coupling is also know. In this reaction, tetrahydroxydiboron (B_2OH_4) is used instead of B_2pin_2.[58]

Organotrifluoroborates can be prepared by treating boronic acids with potassium bifluoride (KHF_2) or KF/tartaric acid.

Each of these organoboron reagents has advantages and disadvantages in Suzuki-Miyaura cross-coupling reactions. Boronic acids are cheap and atomically economic reagents, however, boronic esters are advantageous for the coupling for the coupling of unstable substrates. Organotrifluoroborates show good activities in the coupling of various organic groups but liberate hazardous HF upon hydrolysis in aqueous media. Also practical aspect, like different solubilities of the various organoboron species in polar or apolar reaction solutions play a role. Hence, the choice of the optimal organoboron reagent is not trivial and has to be adjusted to each particular synthetic problem.[50]

The coupling partners of the nucleophilic organoboron reagents are electrophilic halides or pseudohalides (Figure A-2).

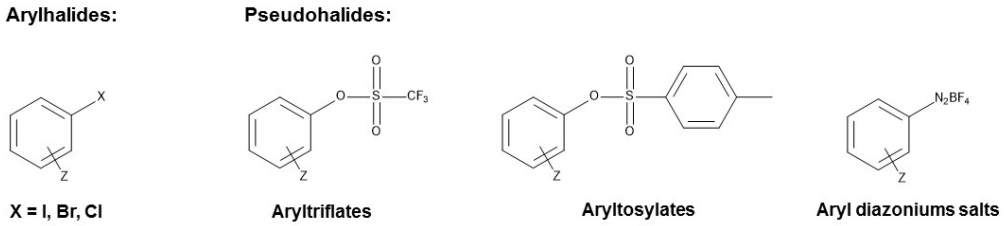


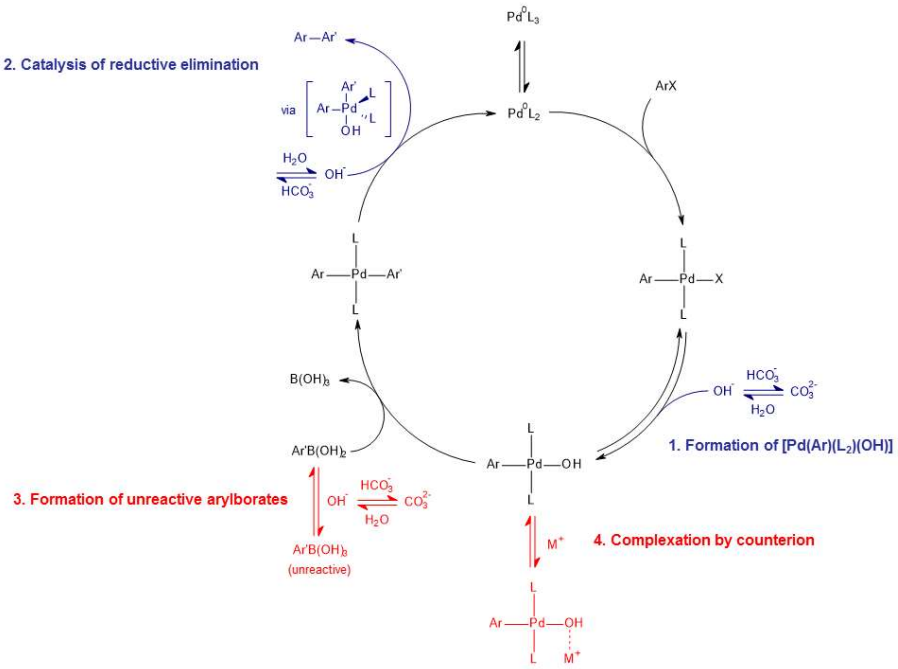
Figure A-2: Electrophilic coupling partners for Suzuki-Miyaura cross-coupling reactions.

Oxidative addition of the organic halide (or pseudohalide) to the catalytically active Pd^0 compound (first step in the catalytic cycle of Suzuki-Miyaura reactions, see Scheme A-7) is often assumed as the rate-determing step for the whole reaction.[59] The reactivity of different arylhalides and pseudohalides follows generally the order I > OTf (triflate) > Br >> Cl. The reactivity is also influenced by the presence or absence of substituents on the aryl ring. Electron-withdrawing substituents (e.g. nitro, nitrile or carbonyl groups) increase the reaction rate (whereby withdrawing groups are more effective on *ortho*- or *para*-positions than on the *meta*-position), whereas electron donating groups (e.g. alkyl, alkoxy or hydroxyl groups) generally decrease the reactivity.[49]

The coupling of the reaction partners in a Suzuki-type cross-coupling reaction has to be facilitated by the addition of a base. A variety of bases (MeO^-, EtO^-, OH^-, CO_3^{2-}, F^-) with different countercations (Na^+, K^+, Cs^+, Li^+, Ag^+, Tl^+, $n Bu_4N^+$) have been applied successfully.[60] Although the addition of a base is obligatory, the exact role of the base in the reaction mechanism has been unclear for a long time.[61] In 2013, Amatore *et al.* published a mechanistic study of Suzuki-Miyaura cross-coupling reactions, in which four roles of the base, two of them positive, two of them negative, in the reaction mechanism were identified:[60]

1. formation of *trans*-$[Pd(Ar)F(L)_2]$ or *trans*-$[Pd(Ar)(L_2)(OH)]$ which react with $Ar'B(OH)_2$ during the transmetallation step (positive)
2. catalysis of the reductive elimination (positive)
3. formation of unreactive arylborates (negative)
4. complexation of the OH group of $[Pd(Ar)(L_2)(OH)]$ by the counteraction (negative)

Scheme A-9 depicts the four different roles of the base in the catalytic cycle exemplarily for a Suzuki reaction using carbonate as base in an aqueous reaction solvent.[62]



Scheme A-9: Positive (blue) and negative (red) roles of the base in the Suzuki-Miyaura catalytic cycle as proposed by Amatore *et al.*[60,62]

2.2.1 Homogeneous Catalysts for Suzuki-Miyaura Cross-Coupling Reactions

According to the reaction mechanism depicted in Scheme A-9, the catalytically active species is a zerovalent L_nPd^0 complex. The active L_nPd^0 is often formed *in situ* by mixing a suitable palladium precursor with a ligand. The *in situ* activation of the catalyst precursors can be problematic. Stable Pd(II) sources (such as $Pd(OAc)_2$ or $PdCl_2$) have to be reduced to Pd(0), a process which can be accompanied by deleterious side reactions. Furthermore, many of the used ligands are highly reactive and thus sensitive to air or even pyrophoric, which is disadvantageous from a practical point of view.[1]

On the other hand, commonly used zerovalent palladium sources are thermally unstable (e.g. $Pd(PPh_3)_4$) or contain ligands, which can impede the coupling reaction (e.g. $Pd_2(dba)_3$). A possibility to circumvent the issues of *in situ* palladium activation and the use of unstable Pd(0) sources is the use of stable palladium precatalysts (isolated L_nPdX complexes, which are prepared in a separate process).[21]

Over the last decades, a plethora of different precursor/ligand or precatalyst systems has been developed, especially to increase catalyst efficiency and to enable cross-coupling reactions of less reactive aryl chlorides.

Many of the reported systems include phosphine containing compounds, nevertheless, in recent years also other types of catalysts have been developed, for example palladacycles, commercially available PEPPSI™-catalysts or carbene containing NHC-complexes (NHC = N-heterocyclic carbine). Figure A-3 shows commonly used palladium sources, a selection[1,63] of phosphine containing ligands and examples for precatalysts developed by Colacot and Shea,[64]

Oberli and Buchwald (palladacycles),[65] Nolan *et al.* (NHC-complexes)[66] as well as the commercially available PEPPSI^{TM}-IPr catalyst.[67]

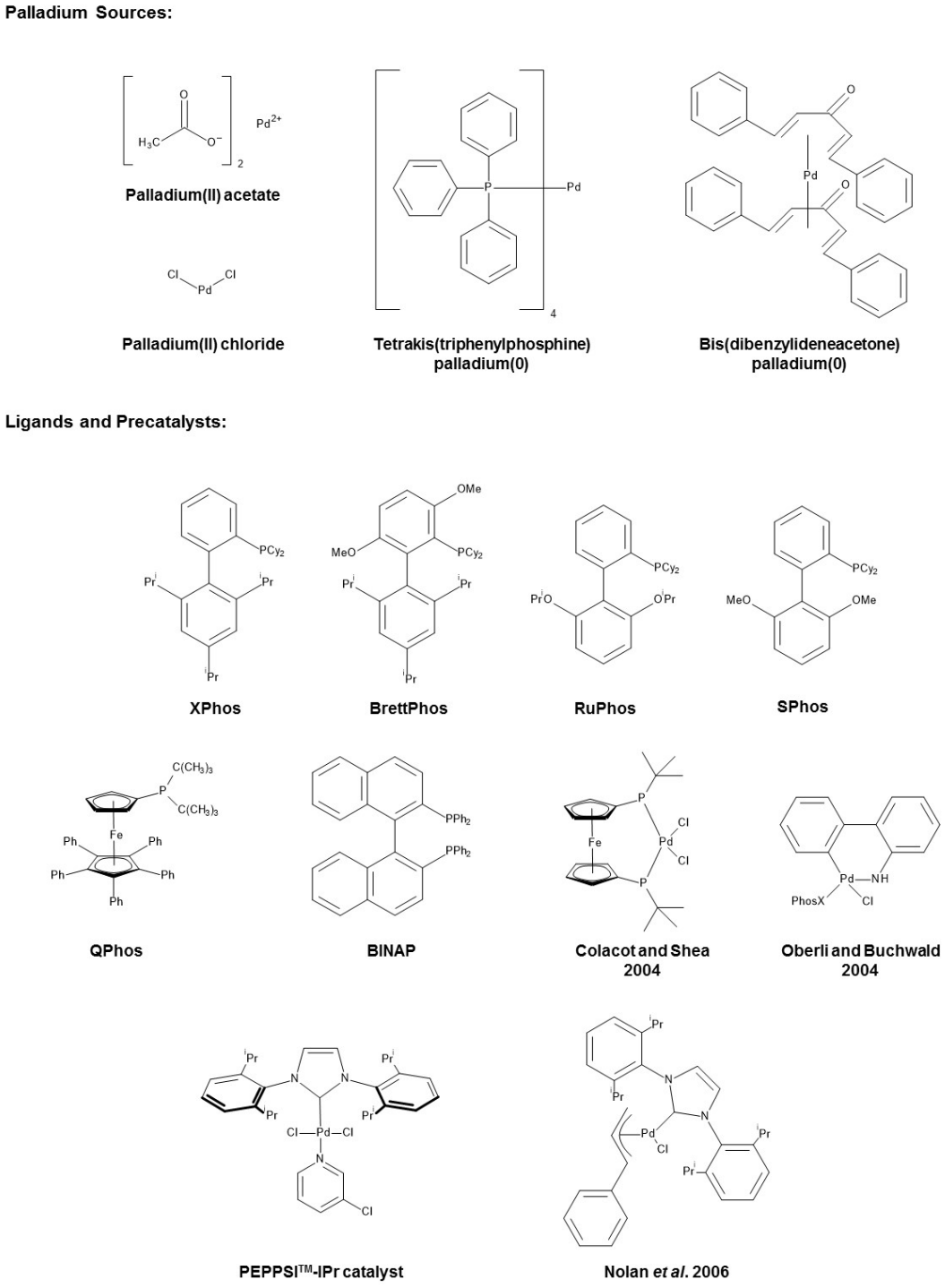


Figure A-3: Commonly used Pd(II) and Pd(0) sources, commercially available ligands and examples for Pd-precatalysts.[1,63]

2.2.2 Heterogeneous Catalysts for Suzuki-Miyaura Cross-Coupling Reactions[1]

Although homogeneous catalysts are very often applied in industrial processes due to their high activity and selectivity, they have one big disadvantage: separation of the catalysts can be difficult, as they are in the same phase as the educts and products (except for phase transfer-catalysts). Although highly potential for metal removal and recycling exist,[5] the complete elimination from the reaction mixture to avoid metal carry-over is intricate and costly, reducing the potential for industrial implementation, especially in the field of pharmaceutical synthesis. Furthermore, many homogeneous systems usually consist of the metal and the ligands in a particular stoichiometric ratio. Thus, the removal of the ligands makes the purification of the product even more expensive.[68]

Immobilization of the catalytic system on solid supports can mitigate these problems, as it allows the straightforward removal of the catalysts from the reaction system. This heterogenization of the catalysts is advantageous, however, the majority of heterogeneous catalysts require harsher conditions than well-tuned homogeneous catalysts, which often results in leaching of the metal from the support. For the synthesis of active pharmaceutical intermediates, this metal contamination of the product is a serious issue.[69,70] Leaching of the catalyst into the product would implicate a time-consuming and costly cleaning step, which would make the whole process more expensive.[71] Furthermore, leaching of the active metal also leads to a decreasing turnover frequency (TOF) of the catalyst.

Despite the large number of studies reporting the development of heterogeneous catalytic systems for cross-coupling reactions, the question if a Pd-catalyzed cross-coupling reaction with a truly heterogeneous reaction mechanism could even be possible was a matter of debate for several years. Many of the reported heterogeneous catalysts show good recyclability and low amounts of leached palladium in the reaction solution when tested in batch mode,[72–74] and several heterogeneous reaction mechanisms (with the reaction taking place at the surface of the catalyst) have been hypothesized. However, other authors proposed that dissolved (leached) palladium is responsible for the catalytic activity and that re-adsorbtion on the solid support leads to a quasi-heterogeneous, but mechanistically homogeneous reaction process.

Due to this mechanistic debate, the true catalytically active species (i.e., homogeneous or heterogeneous) has been studied systematically for many catalytic systems over the last decades. Several methods have been developed to distinguish between soluble vs. insoluble catalysts, and detailed reviews have been presented e.g. by Phan *et al*.[75] and Lamblin *et al*.[70] One method that is often applied is the so-called “hot filtration test”. During this test the catalytically active particles are removed from the reaction by filtration after a certain time using

[1] The following subchapters are taken in large parts from a journal article by Lichtenegger *et al*. in Chimica Oggi – Chemistry Today (G.J. Lichtenegger, H. Gruber-Woelfler, Strategies to develop leaching-free heterogeneous catalysts, Chim. Oggi. 33 (2015) 12 – 18)

a hot frit and the filtrate is monitored for continued activity. However, it is known that the hot filtration test alone cannot prove that the reaction occurs heterogeneously, because the leached palladium can re-deposit so quickly that it may not be detected by a filtration test.[76] Furthermore, disruptions, such as hot filtration, may deactivate an existing active dissolved metal, leading to the incorrect conclusion that there are no active homogeneous catalytic species before the filtration. Therefore, other tests were invented to investigate the heterogeneity of supposed heterogeneous catalytic systems. One of these is the "three-phase-test". The test, first developed by Rebek *et al.*[77] is based on covalently immobilizing one of the reaction partners, and examining its reaction with a soluble reagent. The supported catalyst represents the third phase. If the catalyst remains immobilized, it will be incapable of accessing the supported aryl halide. If homogeneous metal is released, the covalently immobilized substrate will be converted into the product. To ensure that an active catalyst is present, a soluble reactant is added. After the reaction, the soluble portion is analyzed after filtration while the immobilized substrate is removed from the support and isolated.

In addition to these methods, Jones *et al.* reported that the most potential method to assess the homogeneity/heterogeneity of a catalytic system is catalyst poisoning.[76] By addition of materials that are known to act as catalyst poisons, soluble reactive metal can be removed from the solution. The poisons that are often used for Pd are 3-mercaptopropyl-functionalized silica gel (MPSG), as thiol-modified surfaces are known to be very effective metal-scavengers.[76,78] In addition, poly(4-vinylpyridine) (PVPy,) is often used because pyridines are known to bind strongly e.g. to Pd(II)[79,80] and several groups applied insoluble PVPy as a Pd trap to confirm the presence of leached, soluble Pd. Furthermore, Quadrapure TU, an organic polymer resin (polystyrene) with a thiourea functionality, and 3-aminopropyl silica gel were studied as poisons. Finally, potential metal leaching can be analysed by quantitative analytical methods, such as ICP/OES analyses.

In addition to the total leaching and overall catalytic activity, reusability is a critical feature for supported catalysts.[81] To test the reuseability, the same catalytic particles are used after filtration from the reaction mixture for several reactions under the same conditions to analyse if the activity (reported as turnover frequency, TOF) of the catalyst is remaining.

If these methods indicate metal leaching, there is a clear need for methods to prevent metal incorporation into organic and pharmaceutical products considering the strict guidelines placed on metal levels in products destined for human consumption. These methods can be broadly divided into scavenging and preventative approaches,[5] the latter being dominated by the development of non-leaching heterogeneous catalysts.

Despite all issues and challenges, a plethora of papers claiming new and highly active heterogeneous catalytic systems for Suzuki-Miyaura couplings have been published.[82] The reported heterogeneous Pd-systems include supported Pd-nanoparticles, unsupported Pd-

nanoparticles and encapsulated Pd-complexes (for examples see Lee *et al.*[83] and references therein) as well as supported Pd-complexes. Figure A-4 depicts just a few examples for reported and commercially available supported palladium catalysts for cross-coupling reactions.

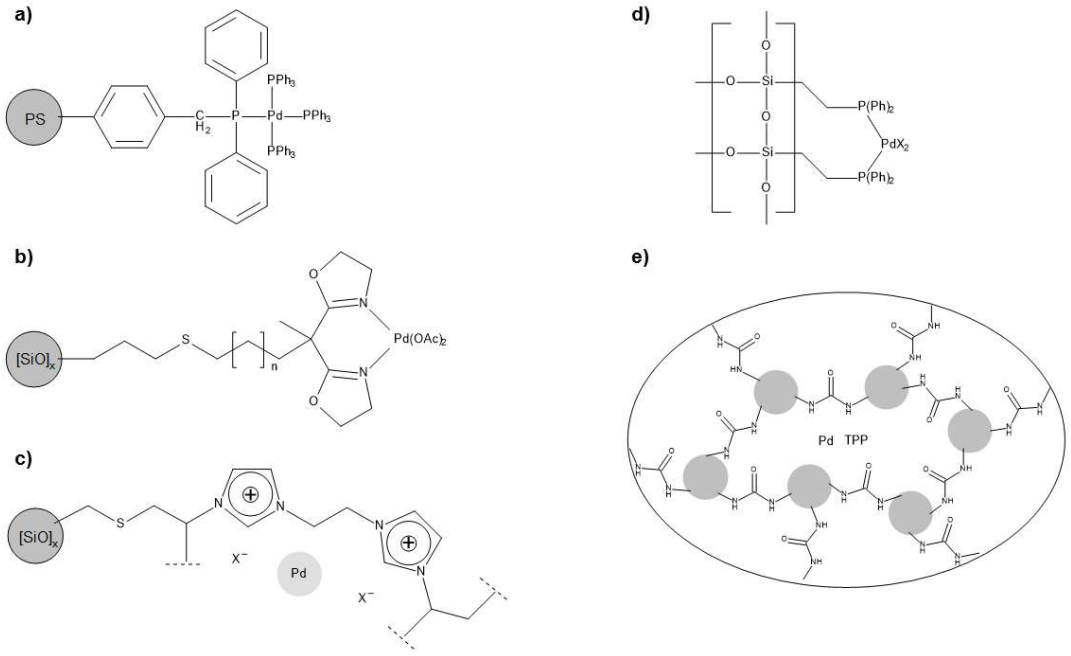


Figure A-4: Examples for heterogeneous Pd-catalysts: a) polystyrene (=PS) bound phosphine complex,[4] b) silica gel bound bisoxazoline complex,[74] c) palladium supported on cross-linked imidazolium network on silica,[84] d) SiliaCat® DPP, e) Pd EnCat® TPP 30.

Modified silica is by far the most utilized support for immobilizing Pd-complexes. For example, unfunctionalized mesoporous silica as support was used by Ying *et al.*[85] Shimizu *et al.*,[86] Bedford *et al.*[87] and Crudden *et al.*[88] have shown that mesoporous silica can be modified with commercially available thiol ligands, resulting in recoverable catalysts for cross-coupling reactions, such as the Suzuki-Miyaura and Heck reactions.

Detailed mechanistic studies have shown that the catalytic reactions using these supports likely occur in solution via leached Pd. For example, the group of Jones *et al.* have reported that catalysis with Pd-SH-SBA-15 is solely associated with leached metal.[76] Also the group of Crudden *et al.* found that small amounts of active Pd leach from the surface when using mesoporous molecular sieves modified by mercaptopropyl trimethoxysilane.

Recently, our group reported a novel Pd-catalyst that is attached to a tethered bis(oxazoline) = (BOX) ligand which is covalently bonded to a functionalized silica gel.[74] In particular, 2,2'-(1-methyl-11-dodecenylidene)bis(4,5-dihydrooxazole) was covalently immobilized on 3-mercaptopropyl functionalized silica gel (MPSG). The metalation of the immobilized BOX ligand with $Pd(OAc)_2$ yielded the stable and active catalyst $Pd(OAc)_2$-BOX-MPSG (Figure A-4 b). Similar immobilized BOX-M complexes (M = Pd, Cu, Zn, Mg, Rh) have been reported for a large variety of enantioselective reactions.[89,90]

The catalyst was tested for Suzuki-Miyaura reactions of different aryl halides with phenylboronic acid. Using several approaches to test the heterogeneity of the catalytic system (hot-filtration test, three-phase-test, recyclability study, ICP/OES analyses), it could be shown that there is virtually no Pd leaching into the reaction solution under the applied reaction conditions. Furthermore, the results indicated that the catalyst is stable and can be reused for at least 10 times. Such stable heterogeneous catalysts would be a key to implement continuous processes in the preparation of pharmaceutical and fine chemical intermediates. However, the addition of certain catalyst poisons led to a quenching of the catalytic activity, which indicates the presence of leached homogeneous Pd. Additionally, TEM pictures of the used catalytic material indicated nanoparticles on the surface. One possible explanation for the behavior of the catalytic system, i.e., poisoning by mercapto-functionalized silica gel and nanoparticle formation, could be that small amounts of Pd leach from the immobilized BOX ligand during the reaction. If a poison is present, this Pd is over-coordinated by the poison. Otherwise, Pd nanoparticles are formed and these particles are trapped by the solid support. Thus, the support would act as the source of the active component and at the same time as sink for Pd, and therefore, constituting a virtually leaching free system.

In addition to organic ligand containing supported catalysts, numerous ligand free supported Pd-catalysts for the use in cross-coupling reactions have been described. A variety of solid supports has been tested, including quite simple inorganic supports (silica, alumina, magnesia, ceria, zirconia and iron oxide), carbon based supports (charcoal, graphite graphene) as well as monolithic materials and polymers.[91] including palladium on palladium on charcoal (Pd/C) and polyurea encapsulated $Pd(OAc)_2$ (Pd EnCat^{TM}, Figure A-4) are the most widely utilized catalysts for cross-coupling reactions.[82] Their usage in continuous flow applications and their leaching behavior is discussed in the review by Cantillo and Kappe.[20] In this work, the application the synthesis of Pd-substituted mixed cerium-tin-oxides by the solution combustion method and their application as catalysts for Suzuki-Miyaura cross-coupling reactions in batch and continuous flow mode will be described.

2.2.3 Pd-Catalyzed Cross-Coupling Reactions in Flow

Today, it's widely accepted, that palladium catalyzed cross-coupling reactions are catalyzed by dissolved palladium species, even if immobilized palladium catalysts are used. The solid support is assumed to act as palladium reservoir that leaches Pd^{II}-species into the reaction solution. The release of Pd typically occurs in the presence of organic halides, which suggest the assumption, that palladium leaching is happening during the oxidative addition step. The leached palladium remains in the reaction solution during the catalytic cycle but can re-deposit on the solid support after completion of the reaction.

Employing supported catalysts in batch reactions, this release-capture mechanism can pretend a heterogeneously catalyzed reaction. However, when supported catalysts are used

under continuous flow conditions, multiple release and capture steps would lead to a migration of the immobilized palladium through the catalytic bed. Like in HPLC-analysis, palladium would be eluted in flow direction, which leads to leaching of palladium out of the packed-bed reactor, contamination of the product and finally to catalyst deactivation (Figure A-5).

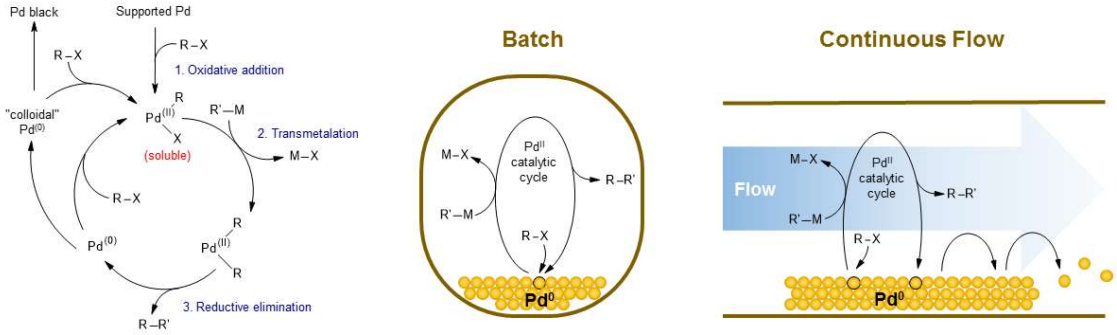


Figure A-5: Mechanistic concept of „ligandless“ palladium catalysis and leaching and re-adsorption behavior under batch and continuous flow conditions as proposed by Cantillo and Kappe.[20]

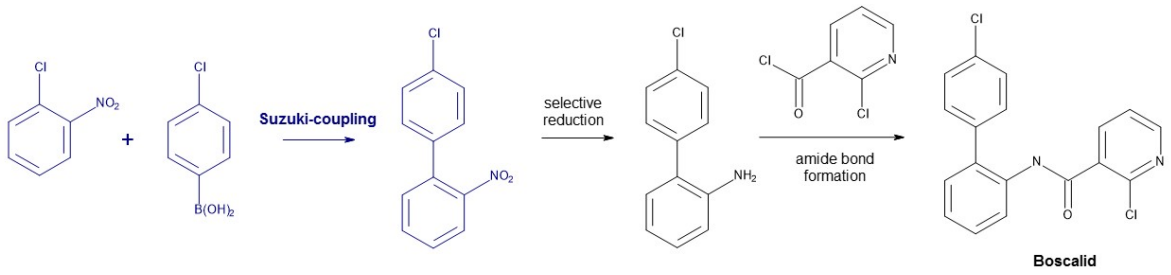
In 2015, the group of Kappe published a benchmarking study,[4] in which the efficiency, durability, and metal leaching resistance of commercially available immobilized phosphine-based palladium catalysts (polymer-bound Pd Tetrakis, FiberCat™ 1001, EnCat™ TPP30 and SiliaCat™ DPP-Pd) in continuous packed bed flow cross-coupling reactions (Mizoroki-Heck and Suzuki-Miyaura coupling) were investigated. Especially when applied for Suzuki-Miyaura reactions, three of the four tested catalysts showed significant catalyst deactivation in relatively short time (120 minutes) and considerable amounts of leached palladium in the reaction solution. Thus, the group of Kappe is convinced that it would be more appropriate to perform continuous Pd-catalyzed cross coupling reactions using suitable homogeneous metal catalyst/ligand systems – combined with advanced separation techniques[80,92,93] - rather than employing supported catalysts in packed bed reactors.[4,20,5]

Nevertheless, one of the tested catalysts, SiliaCat™ DPP Pd, showed superior stability and leaching resistance. Using this catalyst, Pandarus *et al.* were able to establish continuous Suzuki-Miyaura flow reactions using a single pass packed bed reactor, which gave high products yields, low amounts of palladium leaching and were stable (depending on the aryl-halide substrate) for up to 40 hours.[6] These results show that the use of appropriate supported catalysts in packed bed reactors at carefully chosen reaction conditions and solvent compositions can indeed be a suitable strategy for the continuous or semi-continuous synthesis of biphenyls using Pd-catalyzed cross-coupling reactions, at least on a laboratory scale.

2.2.4 Applications of Suzuki-Miyaura Reactions in Organic Synthesis

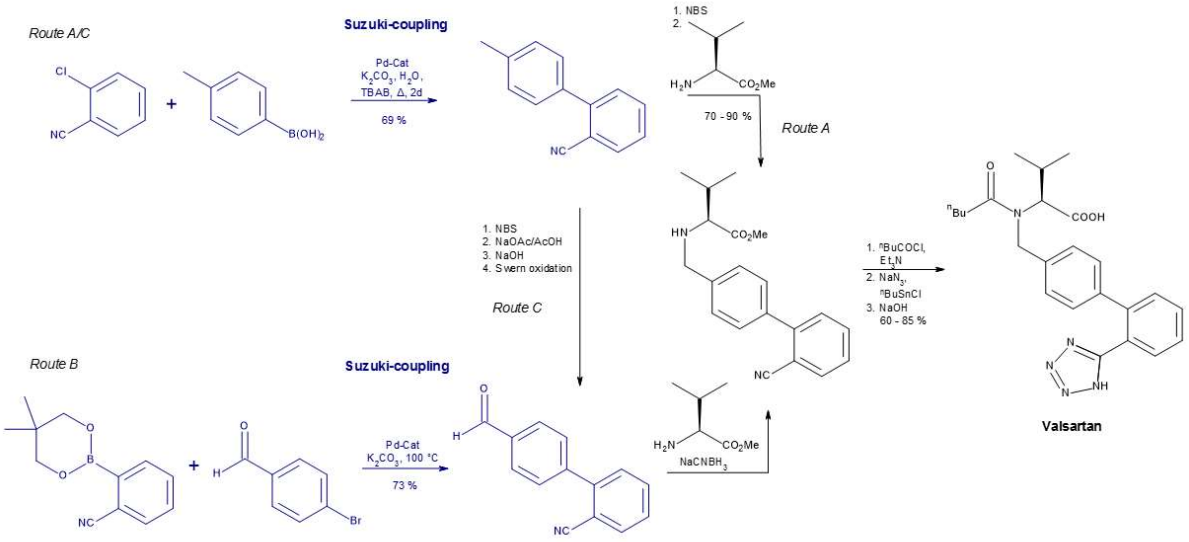
Due to its practicability and versatility, the Suzuki-Miyaura reaction became a widely used method for the formation of carbon-carbon bonds in organic synthesis over the last decades.

Several reviews list dozens of applications for the synthesis of pharmaceuticals, natural products, agro-chemicals and polymers.[1,49,66,94–98] In this chapter, three representative synthetic routes employing the Suzuki-Miyaura reaction for the synthesis of the fungicide Boscalid[99] and the active pharmaceutical ingredients Valsartan[100] and Crizotinib will be briefly described.



Scheme A-10: Total synthesis of Boscalid[99]

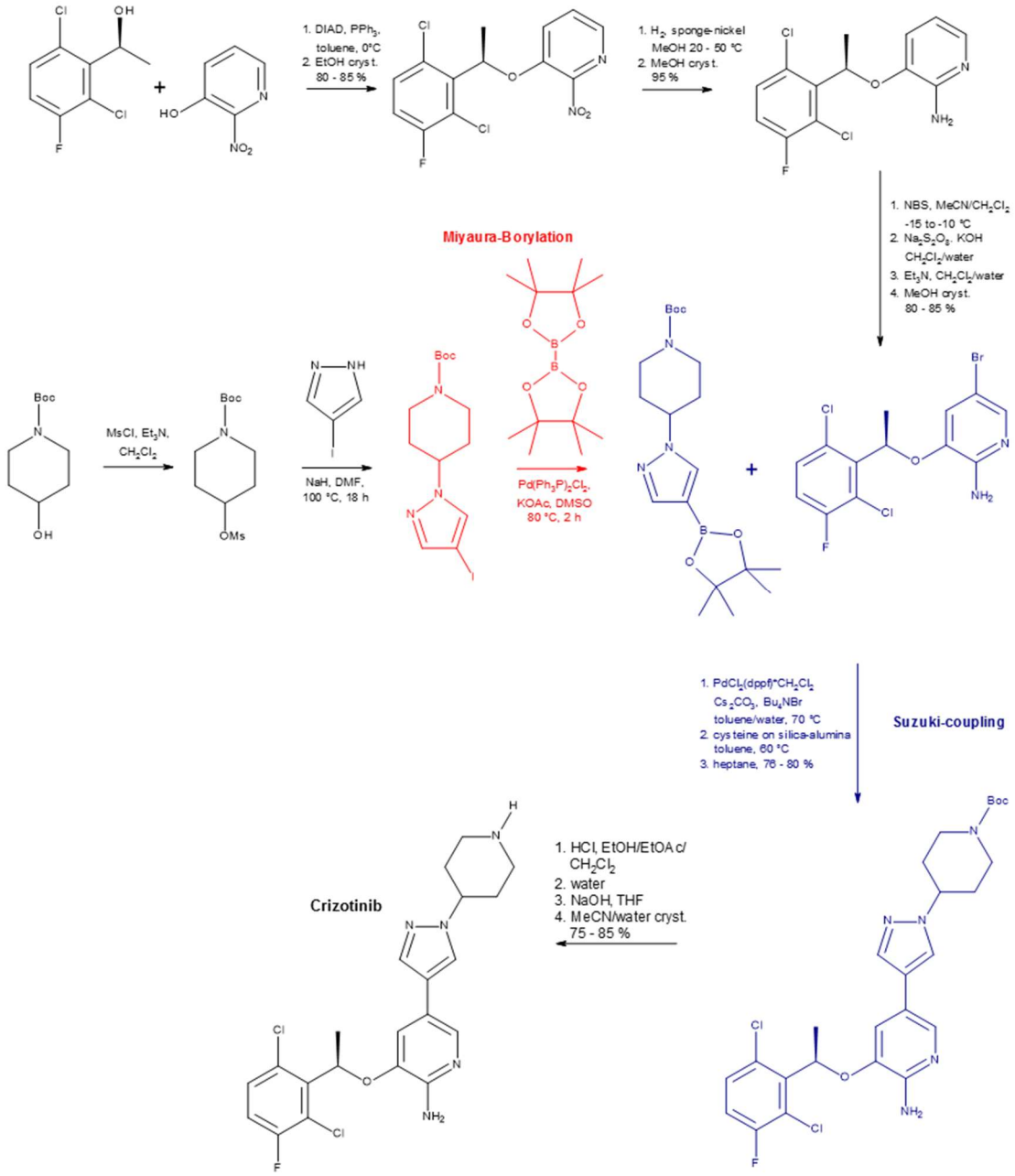
Boscalid, developed and distributed by BASF under the commercial names Cantus®, Bellis®, Signum® or Collis®, is a fungicide belonging to the class of succinate dehydrogenase inhibitors. The industrial total synthesis of Boscalid[99] employs the Suzuki cross-coupling of 1-chloro-2-nitrobenzene and 4-chlorophenylboronic acid in the first step (Scheme A-10) to yield the intermediate 4'-chloro-2-nitrobiphenyl, which is subsequently reduced to the corresponding aniline. The product boscalid is obtained by the final reaction of the aniline with 2-chloronicotinyl chloride.



Scheme A-11: Total synthesis of Valsartan[100]

Valsartan, a nonpeptidic angiotensin-II-receptor antagonist belonging to the therapeutic class of sartans (which are widely used for the treatment of hypertension), is usually

synthesized by one of three principal synthetic pathways (Scheme A-11),[100] each of them employing the Suzuki-Miyaura cross-coupling reaction in the first step to obtain the essential biphenyl structure. The synthesis is completed by the insertion of a secondary amine group (using L-valine methyl ester), its acylation with valeroyl chloride and finally, by conversion of the nitrile group to the tetrazole functionality using tri-*n*-butyltin and sodium azide. Another active ingredient belonging to the group of sartans, Losartan, can also be synthesized employing the Suzuki-Miyaura cross coupling reaction.[101]



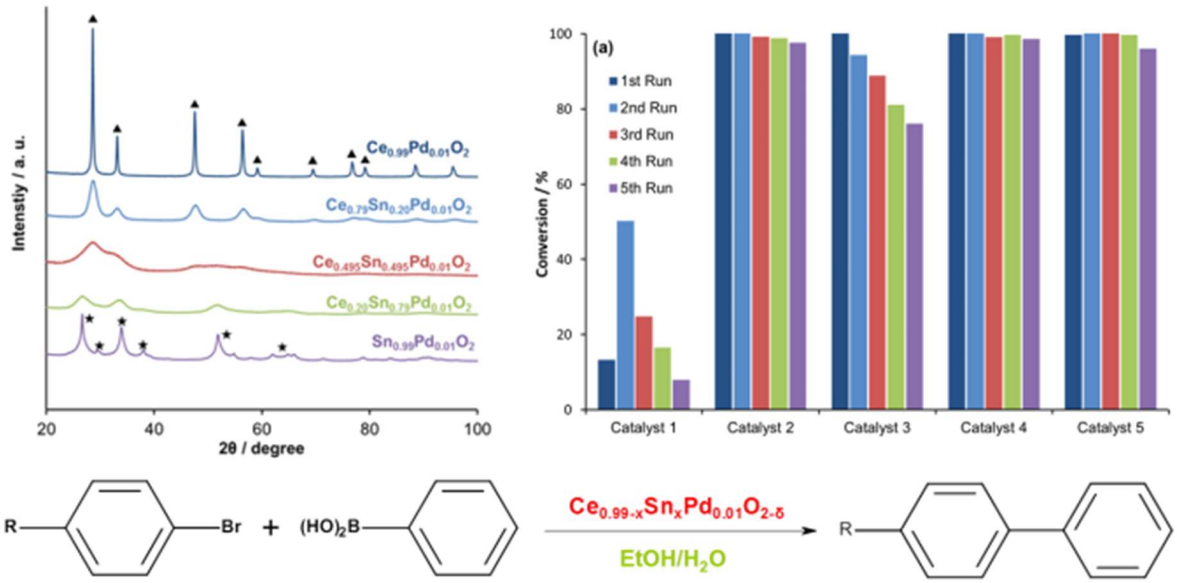
Scheme A-12: Total synthesis of Crizotinib as reported by Koning *et al.*

Crizotinib, distributed by Pfizer under the commercial name Xalkori, is an anti-cancer drug which acts as mesenchymal epithelial transition factor/Anaplastic lymphoma kinase (c-

Met/ALK) inhibitor. It is used for the therapy of non-small cell lung carcinoma.[102] Compared to the syntheses mentioned above, the total synthesis of Crizotinib employs the Suzuki-Miyaura couplirng reaction at a relatively late stage of the synthetic process, directly before the final deprotonation step (Scheme A-12).[103] The total synthesis also involves another palladium catalyzed cross-coupling reaction, the formation of a boronic acid pinacol ester via Miyaura borylation, which is required for the subsequent Suzuki reaction.

The above mentioned substances are among the blockbuster chemicals in agrochemical industry (production of boscalid:[104] >1000 tons year^{-1}) and pharmaceutical industry (worldwide annual revenue of Diovan® (API valsartan) by Novartis:[105] USD 6.1 billion, worldwide annual revenue of Xalkori® (API crizotinib) by Pfizer[106]: USD 488 million) and illustrate the significance of the Suzuki-Miyaura reaction in industry.

B Pd-Substituted Mixed Cerium-Tin-Oxides as Catalysts for Suzuki-Miyaura Cross-Coupling Reactions[2]



Palladium substituted CeO_2, SnO_2 and their mixed oxides have been synthesized in quantitative yields out of nontoxic and inexpensive precursors using a simple and rapid single step solution combustion method. The resulting oxides, especially the mixed oxides $Ce_{0.79}Sn_{0.20}Pd_{0.01}O_{2-\delta}$, $Sn_{0.79}Ce_{0.20}Pd_{0.01}O_{2-\delta}$ and $Sn_{0.99}Pd_{0.01}O_{2-\delta}$ proved to be highly active (TOF > 12,000 h^{-1}) for Suzuki-Miyaura cross-couplings of phenylboronic acid with various bromoarenes. The reactions were carried out in ambient air at moderate temperatures using environmentally friendly aqueous ethanol solutions as reaction solvents. Minimal amounts of palladium in the product solution (<1 mg/L) and the reaction kinetics supported the thesis that the reaction proceeds on metallic palladium via Pd^{2+} ↔ Pd (0) equilibrium. The synthesized catalysts could be reused for at least five times with only minor changes in activity and with no changes concerning the crystal structure, indicating the high potential of the investigated catalysts as heterogeneous C-C coupling catalysts.

[2] The following chapter is taken from a journal article by Lichtenegger *et al.*, submitted to the Journal of Molecular Catalysis A: General (G.J. Lichtenegger, H. Gruber-Woelfler, M. Maier, M. Hackl, J.G. Khinast, W. Gössler, V.S. Phani Kumar, P.A. Deshpande "Suzuki-Miyaura Coupling Reactions Using Novel Metal Oxide Supported Ionic Palladium Catalysts", submitted on Apr 19, 2016)

1 Introduction

Ceria (CeO_2) and ceria based solid solutions containing base metals (Ti, Zr, Sn, etc.) and/or noble metals (Cu, Ag, Au, Pd, Pt, Rh) have gained great importance as active catalysts or catalyst supports in a wide range of applications, especially in environmental catalytic fields such as three way catalysis (TWC), exhaust combustion catalysis or catalytic wet oxidation.[107–109] Over the last decades, a variety of synthetic strategies for the preparation of ceria and its composites, including soft chemical methods (i.e., sol-gel methods,[110] precipitation[111] and co-precipitation[109,112]) as well as high temperature methods (including self-propagation high temperature synthesis (SHS)[113,114] and solution combustion synthesis (SCS)[115–117]), have been developed and intensively studied.

Among the above mentioned techniques, the solution combustion synthesis offers a relatively simple, cheap and rapid method for the synthesis of noble metal substituted ceria and ceria composites. Furthermore, solution combustion methods permit homogeneous mixing of the catalysts precursors on the molecular level (in an aqueous solutions) and ensure high product crystallinity and purity due to the high combustion temperature (>900 °C).[118] These characteristic features allow the production of oxide based catalysts with high specific surface and precise phase composition.[119]

Palladium-containing metal oxides and mixed metal oxides have already been used successfully for Suzuki-Miyaura cross-coupling reactions. Catalysts of this kind, synthesized by sol-gel methods (e.g., $La_1Fe_{0.95}Pd_{0.05}O_x$)[120] or wet impregnation techniques (Pd/Al_2O_3, Pd/TiO_2, Pd/CeO_2) showed extraordinary high reactivity, good recyclability and minimal metal leaching.[121,122]

The synthesis of Pd-doped CeO_2 catalysts by solution combustion methods was developed by Hegde and co-workers. The prepared catalysts proved to be highly active and non-deactivating for gas-phase oxidation reactions.[116] In 2011, Sanjaykumar *et al.* revealed the potential of solution combustion synthesized palladium substituted cerium oxide as a recyclable and ligand free catalyst for Heck coupling reactions.[115] In this report the catalyst was prepared from ammonium cerium(IV) nitrate and palladium chloride using oxalyldihydrazide as fuel. The resulting catalyst was capable of catalyzing heck cross-coupling reactions between bromo- and iodoarenes and different acrylates or styrene.

In this work, a thorough investigation of Pd-ion substituted CeO_2, SnO_2 and their mixed oxides as catalysts for Suzuki-Miyaura cross-coupling reactions was carried out. In particular, the activity of the different catalysts depending on their Ce and Sn amount as well as their tolerance towards different starting materials was studied. Furthermore, the leaching behavior and the recyclability of the catalysts were investigated. All in all, the study demonstrates the high potential of the investigated catalysts as heterogeneous C-C coupling catalysts.

2 Results and Discussion

2.1 Catalyst Synthesis

The synthesis of $Ce_{0.99-x}Sn_xPd_{0.01}O_{2-\delta}$ was done analogously to the method reported by Baidya *et al.*[123] using glycine instead of L-tartaric acid as fuel. The appropriate proportions of catalyst precursors and fuel were calculated using the method described by González-Cortés *et al.*[117] A set of five $Ce_{0.99-x}Sn_xPd_{0.01}O_{2-\delta}$ mixed oxides (with x = 0, 0.2, 0.495, 0.79 and 0.99) was prepared. The synthesis of the five catalysts via combustion of the prepared redox-mixtures yielded the desired compounds in quantitative amounts (> 99 %) within 1 hour. Redox solutions with high amounts of cerium (Ce ≥ 0.8) underwent a highly violent combustion reaction and produced a powdery solid. With increasing amounts of tin (Sn > 0.2), the combustion reactions became more and more gentle, yielding voluminous spongiform solids. After grinding with mortar and pestle and heating to 350 °C for another 5 hours, the solids could be directly used for characterization or reactivity tests.

2.2 Characterization

2.2.1 XRD

The XRD-profiles of the as-synthesized $Ce_xSn_{1-x}Pd_{0.01}O_{2-\delta}$ (x = 0 – 0.99) compounds are shown in Figure B-1**.** The obtained lattice parameters are summarized in Table B-1.

The powder XRD pattern showed broad peaks indicative of nanocrystallinity in the synthesized compounds. Single phase cubic fluorite structures were observed for oxides with tin proportions up to 0.2. The measured cubic lattice constants were in good accordance with the data obtained by Baidya *et al.*[123] for the cerium rich oxides, $Ce_{0.99}Pd_{0.01}O_{2-\delta}$, $Ce_{0.79}Sn_{0.2}Pd_{0.01}O_{2-\delta}$. Due to the smaller ionic radius of Sn^{4+} (0.81 Å) compared to Ce^{4+}, a decrease of the lattice constant from a = 5.412 Å (for x = 99) to a = 5.400 Å (for x = 0.79) indicated a successful incorporation of tin ions at Ce^{4+} sites in the cubic lattice structure.

Table B-1: Lattice constants of the as-synthesized mixed oxides.

Catalyst	Phase	Lattice constants (Å) Cubic a	Tetragonal a	b
$Ce_{0.99}Pd_{0.01}O_{2-\delta}$	cubic	5.412	-	-
$Ce_{0.79}Sn_{0.2}Pd_{0.01}O_{2-\delta}$	cubic	5.400	-	-
$Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$	mixed cubic/tetragonal	5.385	4.562	3.482
$Ce_{0.20}Sn_{0.79}Pd_{0.01}O_{2-\delta}$	mixed cubic/tetragonal	5.260	4.732	3.234
$Sn_{0.99}Pd_{0.01}O_{2-\delta}$	tetragonal	-	7.739	3.186

The XRD patterns in Figure B-1 have been marked with filled triangles (▲) against prominent CeO_2 peaks and good correspondence against pure CeO_2 structure continued for $Ce_{0.79}Sn_{0.2}Pd_{0.01}O_{2-\delta}$, as can be observed from Figure B-1. Contrary to the study of Baidya, a

single phase cubic structure for the mixed oxides with equimolar amounts of cerium and tin ($Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$) could not be observed in our work. Instead, a more amorphous cubic/tetragonal mixed phase structure was observed when high ratios of tin were used ($Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$ and $Ce_{0.20}Sn_{0.79}Pd_{0.01}O_{2-\delta}$). The binary oxide $Sn_{0.99}Pd_{0.01}O_{2-\delta}$ showed a clearly single phase tetragonal structure. The prominent tetragonal peaks of pure SnO_2 have been marked by a filled star (★) in the figure and crystallization of $Sn_{0.99}Pd_{0.01}O_2$ in tetragonal structure can be clearly observed.

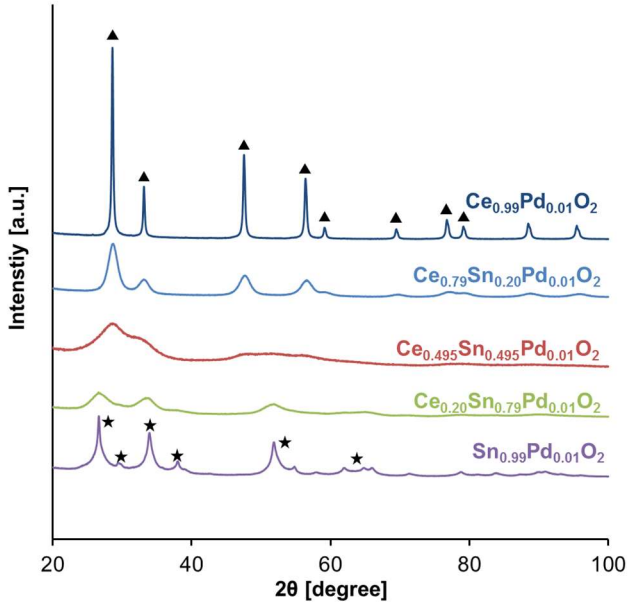


Figure B-1: X-Ray diffraction patterns of as-synthesized $Ce_xSn_{1-x}Pd_{0.01}O_{2-\delta}$ (x = 0 – 0.99), ▲ - Cubic fluorite and ★ - Tetragonal.

In order to confirm substitution of Pd in the lattice, XRD was recorded in a small range of 35-50° as shown in Figure 2. The prominent peak expected for Pd has been marked in the figure. XRD-patterns clearly attributable to PdO or metallic Pd species could not be observed (Figure B-2). This confirmed the absence of PdO or Pd metal particles and indicated a Pd^{2+} ion substitution in the metal oxide lattice.

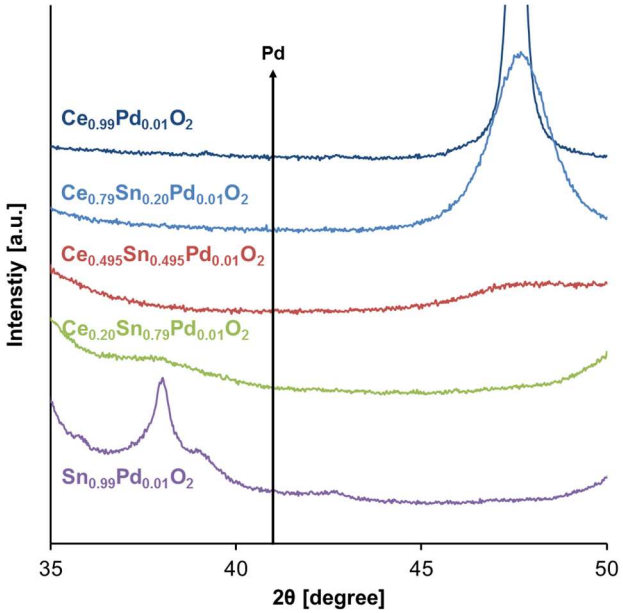


Figure B-2: XRD-pattern of $Ce_xSn_{1-x}Pd_{0.01}O_{2-\delta}$ (x = 0 – 0.99). The arrow shows the peak position for Pd.

2.2.2 Particle size distribution and specific surface area

The particle size distribution and specific surface area are important parameters for catalytic activity, and were therefore included in our studies. The produced oxides appear as fine powders, consisting of agglomerates of the nanocrystalline materials. The analysis of the particle size distribution of these agglomerates revealed particles sizes of ~ 10 – 100 µm with a monomodal size distribution of the cerium-rich catalysts. The catalysts with higher ratios of tin, which originated from more gentle combustion reactions yielding spongiform solids, featured polymodal particle size distributions (Figure B-3).

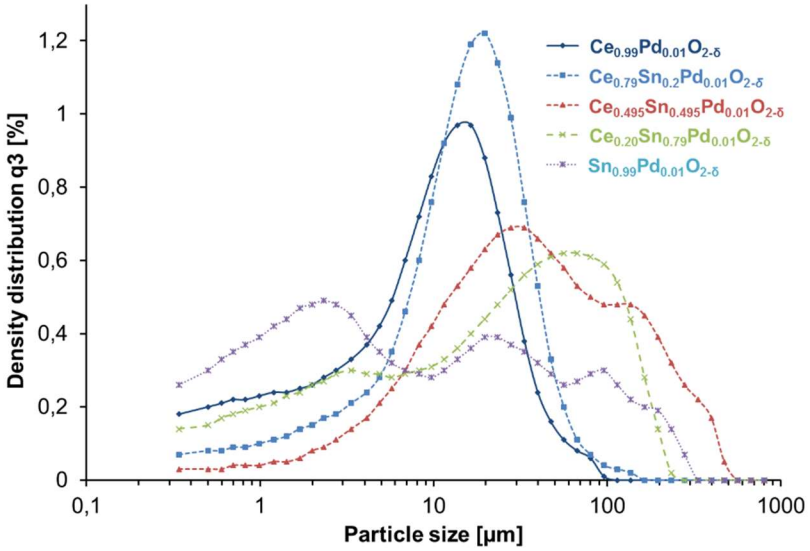


Figure B-3: Particle size distributions of as-synthesized $Ce_xSn_{1-x}Pd_{0.01}O_{2-\delta}$ (x = 0 – 0.99).

$Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$, which contained equimolar amounts of cerium and tin, had the highest mass-median-diameter (x_{50}). Minimum x_{50} were observed for the binary oxides $Ce_{0.99}Pd_{0.01}O_{2-\delta}$ and $Sn_{0.99}Pd_{0.01}O_{2-\delta}$. BET measurements showed specific surface areas at the same order of magnitude for all catalysts with $Ce_{0.99}Pd_{0.01}O_{2-\delta}$ having the lowest (26.9 m²/g) and $Ce_{0.20}Sn_{0.79}Pd_{0.01}O_{2-\delta}$ having the highest surface (97.7 m²/g). Other catalysts had comparable specific surfaces of approximately 50 m²/g (Table B-2).

Table B-2: Characteristic mean diameters x_{10}, x_{50}, x_{90} and specific surface areas of as-synthesized $Ce_xSn_{1-x}Pd_{0.01}O_{2-\delta}$ (x = 0 – 0.99) catalysts.

	x_{10} [µm]	x_{50} [µm]	x_{90} [µm]	BET-Surface [m²/g]
$Ce_{0.99}Pd_{0.01}O_{2-\delta}$	0.8	9.6	28.2	26.9
$Ce_{0.79}Sn_{0.2}Pd_{0.01}O_{2-\delta}$	2.5	15.3	36.6	41.3
$Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$	5.5	33.8	189.4	48.7
$Ce_{0.20}Sn_{0.79}Pd_{0.01}O_{2-\delta}$	1.0	22.4	109.6	97.7
$Sn_{0.99}Pd_{0.01}O_{2-\delta}$	0.6	5.2	92.8	54.8

2.3 Reactivity

The catalytic activity of the as-synthesized catalysts was investigated for the Suzuki-Miyaura cross-coupling reaction of phenylboronic acid with various bromoarenes containing electron donating (methyl-, hydroxyl-), as well as electron withdrawing (acetyl, trifluoromethyl) groups in para position and the electron withdrawing nitrile group in ortho position. The results of the reactivity tests are summarized in Table B-3. In all experiments, the conversions of the bromoarenes and the yields of the products formed out of the bromoarenes were equal within the error limits of the HPLC measurements. The absence of bromoarene-deriving side products (dehalogenation product Ar' and bromoarene homocoupling product Ar' Ar') indicated that the bromoarene substrates were converted to the desired biphenyl compound to the greatest extent in a highly selective manner. However, side products originating from boronic acid homocoupling (biphenyl, ArAr) and boronic acid oxidation (phenol, ArOH) could be found in quantifiable amounts, whereas the formation of the protodeboronation product (benzene, Ar) could not be observed.

Table B-3 shows the reaction progress expressed as relative yield of the desired Suzuki cross-coupling product based on the concentration of the bromoarene (limiting component). The selectivity is defined as the concentration of the desired product divided by the sum of the concentrations of all formed organic products. All the reactions were carried out using 50 % molar excess of phenylboronic acid and potassium carbonate (K_2CO_3, used as base) at 75 °C, either in pure ethanol or in an aqueous ethanolic solutions (EtOH/H_2O = 7/3 v/v). Due to the low solubility of potassium carbonate in ethanol, reaction mixtures using pure ethanol

appeared as suspensions, whereas the use of aqueous ethanol gave clear and colorless reaction solutions.

Table B-3: Yields and selectivities observed by HPLC-measurements for the Suzuki cross-coupling reactions of phenylboronic acid with various bromoarenes, using $Ce_xSn_{1-x}Pd_{0.01}O_{2-\delta}$ (x = 0 – 0.99) as catalyst.[a]

		Pure Ethanol				EtOH/H_2O = 7/3			
		15 Minutes		120 Minutes		15 Minutes		120 Minutes	
Product	Cat[d]	Yield	Sel.	Yield	Sel.	Yield	Sel.	Yield	Sel.
4-Methylbiphenyl	1	<1	-	<1	-	<1[b]	-	6	98.5
	2	31	92.8	75	90.7	9[b]	98.4	>99	91.4
	3	7	97.9	39	94.9	26	97.3	91	94.4
	4	39	92.7	89	88.0	77[b]	97.3	>99	91.9
	5	48	96.4	85	93.6	82[b]	96.7	98	92.3
4-Phenylphenol	1	<1	-	10	96.0	2[b]	-	45	95.3
	2	41	92.2	77	89.1	50[b]	94.0	>99	84.6
	3	7	97.1	34	92.5	23[b]	96.4	80	93.7
	4	44	94.1	93	90.3	30[b]	95.6	97	91.0
	5	31	97.0	70	93.1	69	95.8	>99	91.9
4-Acetylbiphenyl	1	7	-	85	99.7	55[b]	99.8	>99	88.4
	2	96	-	>99	96.9	>99[b]	97.7	>99	87.1
	3	53	-	98	98.6	38[b]	99.8	>99	93.3
	4	98	99.6	>99	95.9	98[b]	95.9	>99	85.9
	5	96	99.7	>99	98.2	98[b]	94.7	>99	90.0
4-Trifluoromethylbiphenyl	1	<1	-	2	-	<1	-	2	-
	2	20	99.0	88	97.5	95	97.8	>99	87.3
	3	3	-	53	98.3	29	98.8	99	92.7
	4	53	98.2	98	92.1	94	95.3	>99	81.6
	5	61	97.6	97	92.5	>98	92.2	>98	80.3
2-Biphenylcarbonitrile[c]	1	<1	-	<1	-	<1	-	2	-
	2	78	99.6	>99	89.5	38	98.8	>99	98.4
	3	9	-	20	99.6	6	-	29	98.5
	4	68	99.7	>99	83.1	74	99.0	>99	83.3
	5	64	99.8	>99	83.0	66	98.9	>99	88.7

[a] Reaction conditions: aryl bromide (0.7 mmol), phenylboronic acid (1.5. mol eq.), K_2CO_3 (1.5 mol eq.), 5 mg $Ce_xSn_{1-x}Pd_{0.01}O_{2-\delta}$ (corresponding to 0.05 mol% Pd), 20 ml of solvent, 75 °C.
[b] After 10 minutes.
[c] Using 20 mg of catalyst (0.2 mol% Pd).
[d] **Cat 1:** $Ce_{0.99}Pd_{0.01}O_{2-\delta}$, **Cat 2:** $Ce_{0.79}Sn_{0.2}Pd_{0.01}O_{2-\delta}$, **Cat 3:** $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$, **Cat 4:** $Ce_{0.20}Sn_{0.79}Pd_{0.01}O_{2-\delta}$, **Cat 5:** $Sn_{0.99}Pd_{0.01}O_{2-\delta}$.

In general, $Ce_{0.79}Sn_{0.2}Pd_{0.01}O_{2-\delta}$, $Ce_{0.20}Sn_{0.79}Pd_{0.01}O_{2-\delta}$ and $Sn_{0.99}Pd_{0.01}O_{2-\delta}$ (change with tin proportions of 0.2, 0.79 and 0.99, respectively), showed extraordinarily high activities in all investigated Suzuki cross coupling reactions (up to TOF of >12,000 h^{-1} for the coupling of 4-bromoacetophenone with phenylboronic acid). The use of less than 0.05 mol% of active palladium led to a quantitative conversion of all para-substituted bromoarenes in less than two hours with aqueous ethanol as reaction solvent. Full conversion within 2 hours could also be

reached using 2-bromobenzonitrile as aryl halide, however, 4 times more catalyst had to be used to achieve comparable reaction rates. $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$ also showed catalytic activity in all reactions, however significantly lower reaction rates were observed. The binary oxide $Ce_{0.99}Pd_{0.01}O_{2-\delta}$ proved to be the least active catalyst in all investigated reactions. Suzuki reactions of 4-bromotoluene with phenylboronic acid over pure CeO_2 and pure SnO_2 did not show any progress, indicating that Pd is the active species in the investigated catalysts. All in all, at the current stage, our results do not show any direct context between Ce or Sn loading and catalytic activity. However, there might be a relation between the surface area, as well as the particle size and the catalytic activity: our results show that $Ce_{0.99}Pd_{0.01}O_{2-\delta}$ has the lowest surface area and the lowest catalytic activity. The large particle size of $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$ might be the reason for its low activity. But these are just preliminary conclusions and more investigations are needed prove this theory.

In our studies we also investigated the influence of the solvents, bases and starting bromoarenes. As can be seen in Table B-3**,** in all experiments, the use of aqueous ethanolic solvents instead of pure ethanol led to increased reaction rates, which can be attributed to the higher solubility of potassium carbonate in water containing alcoholic solvents. p-bromobenzenes containing electron withdrawing substituents showed, higher reactivity than bromobenzenes containing electron donating groups. Regardless of the reaction solvent, the reactivity follows the order: 4-bromoacetophenone ≥ 4-bromobenzotrifluoride > 4-bromotoluene > 4-bromophenol.

2.3.1 Selectivity

Using HPLC as analytical method, not only the disappearance of the arylbromide and the formation of the biphenyl-product were monitored, also the concentrations of possible side products were determined. Typically observed side products of Suzuki-Miyaura coupling reactions[4,50] are shown in Figure B-4**.**

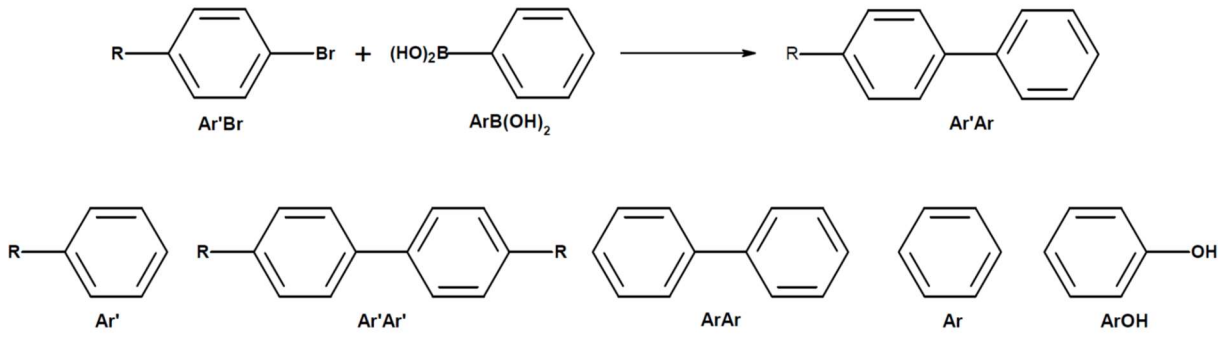


Figure B-4: Main product (Ar'Ar) and typically observed side products in Suzuki-Miyaura cross coupling reactions.

The obtained selectivities are closely related to the catalyst's activity in our calculations. This can be illustrated comparing the concentration profiles and selectivities during the cross-

coupling reactions of phenylboronic acid with 2-biphenylcarbonitrile using $Ce_{0.79}Sn_{0.2}Pd_{0.01}O_{2-\delta}$ and $Ce_{0.20}Sn_{0.79}Pd_{0.01}O_{2-\delta}$, respectively (Figure B-5).

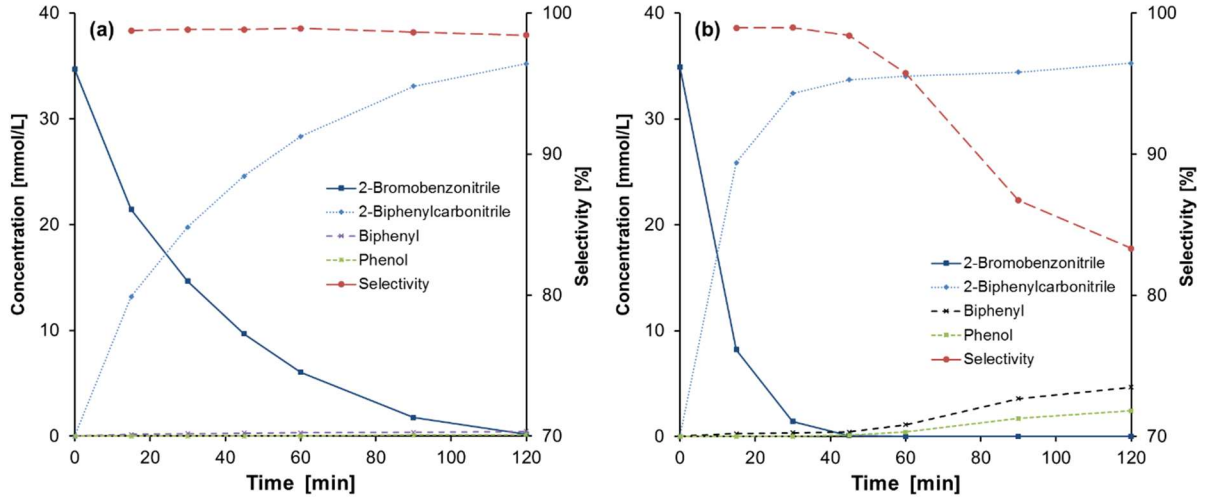


Figure B-5: Concentration profiles for the reaction of 2-bromobenzonitrile and phenylboronic acid catalyzed by (a) $Ce_{0.79}Sn_{0.2}Pd_{0.01}O_{2-\delta}$ and (b) $Ce_{0.20}Sn_{0.79}Pd_{0.01}O_{2-\delta}$.

When full conversion of the starting halide is reached, the values for selectivity are equally high in both reactions (98.4 % after 120 and 45 minutes for $Ce_{0.79}Sn_{0.2}Pd_{0.01}O_{2-\delta}$ and $Ce_{0.20}Sn_{0.79}Pd_{0.01}O_{2-\delta}$ respectively). The side product biphenyl and phenol are formed predominantly at high conversion levels, i.e., in the absence of the already consumed Suzuki reaction partner 2-bromobenzonitrile. Hence, highly selective reactions can be achieved by termination of the reaction just at the moment of full conversion, even when a high excess of phenylboronic acid is used.

The influence of different bases and solvent systems were investigated using the moderately fast reaction of 4-bromotoluene with phenylboronic acid catalyzed by $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$. The results of these tests are summarized in Table B-4.

Although considerable reactivity could be observed using cesium carbonate, potassium hydroxide and sodium hydroxide as base, the often used potassium carbonate proved to be the optimal base when EtOH/H_2O 7/3 (v/v) was used as solvent. The minor activity of the catalyst using sodium carbonate as base may be attributed to the low solubility of Na_2CO_3 in the applied solvent system. Only traces of the product 4-methylbiphenyl could be detected when the weak bases sodium acetate and potassium acetate were used.

A slight increase in catalytic activity with comparable selectivities could be achieved when 2-propanol (at 75 °C) and methanol (at 65°C) were used as alcoholic solvent instead of ethanol. The low product yield when 1-propanol was used can be attributed to the low capability of this system to dissolve highly polar inorganic bases. Taking ecological, toxicological and safety aspects into account 2-propanol/water mixtures may be considered as most practical solvent system for this reaction.

Table B-4: Yields and selectivities after 120 minutes of reaction time observed by HPLC-measurements for the Suzuki cross-coupling reaction of phenylboronic acid with 4-bromotoluene.[a]

Entry	Solvent (v/v ratio)	Base	Temperature [K]	Yield [%]	Selectivity [%]
1	EtOH/H_2O = 7/3	Na_2CO_3	353	32	97.1
2	EtOH/H_2O = 7/3	K_2CO_3	353	92	94.4
3	EtOH/H_2O = 7/3	Cs_2CO_3	353	81	96.2
4	EtOH/H_2O = 7/3	NaOH	353	88	94.6
5	EtOH/H_2O = 7/3	KOH	353	88	95.8
6	EtOH/H_2O = 7/3	NaOAc[b]	353	<1	-
7	EtOH/H_2O = 7/3	KOAc[b]	353	<1	-
8	MeOH/H_2O = 7/3	K_2CO_3	343	96	93.1
9	i-PrOH/H_2O = 7/3	K_2CO_3	353	>99	90.7
10	n-PrOH/H_2O = 7/3	K_2CO_3	353	5	93.5

[a] Reaction conditions: aryl bromide (0.7 mmol), phenylboronic acid (1.5. mol eq.), K_2CO_3 (1.5 mol eq.), 5 mg $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$ (corresponding to 0.05 mol% Pd), 20 ml of solvent.
[b] using 4 mol eq. of base.

2.4 Recyclability and Pd-Leaching

Table B-5 and Figure B-6 show the observed relative conversions of 4-bromotoluene after 30 and 120 minutes reaction time, as well as the recoverability of the used solid catalyst in mass percent. Detailed diagrams of the obtained conversion vs. time are shown in the chapter 5 (Appendix).

Table B-5: Results of the recycling experiments for the Suzuki-Miyaura reaction of 4-bromotoluene with phenylboronic acid.

			Run 1	Run 2	Run 3	Run 4	Run 5
$Ce_{0.99}Pd_{0.01}O_{2-\delta}$	Conversion [%]	30 min	13	50	25	16	8
		120 min	78	91	81	69	49
	Recoverability [%]		84	70	55	43	33
$Ce_{0.79}Sn_{0.2}Pd_{0.01}O_{2-\delta}$	Conversion [%]	30 min	100	100	99	99	98
		120 min	100	100	100	100	100
	Recoverability [%]		88	76	68	68	60
$Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$	Conversion [%]	30 min	100	94	89	81	76
		120 min	100	100	100	98	97
	Recoverability [%]		81	68	58	48	38
$Ce_{0.20}Sn_{0.79}Pd_{0.01}O_{2-\delta}$	Conversion [%]	30 min	100	100	99	100	98
		120 min	100	100	100	100	100
	Recoverability [%]		81	66	50	45	32
$Sn_{0.99}Pd_{0.01}O_{2-\delta}$	Conversion [%]	30 min	100	100	100	100	96
		120 min	100	100	100	100	100
	Recoverability [%]		81	68	54	40	32

Using 0.5 mol% Pd, full conversion after 2 hours could be achieved in five subsequent reactions, when the tin-containing catalysts (x = 0 – 0.99) were used, despite a significant loss of catalysts during the whole recycling procedure (filtration and drying). Using

$Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$, full conversion of 4-bromotoluene within two hours could not be reached in run 4 and 5. However, comparison of the initial reaction rates and the whole reaction progress with the results of the reactivity test shows only minor decrease of the mass specific catalyst activity. A similar recycling behavior could be observed for $Ce_{0.99}Pd_{0.01}O_{2-\delta}$ at a lower activity level.

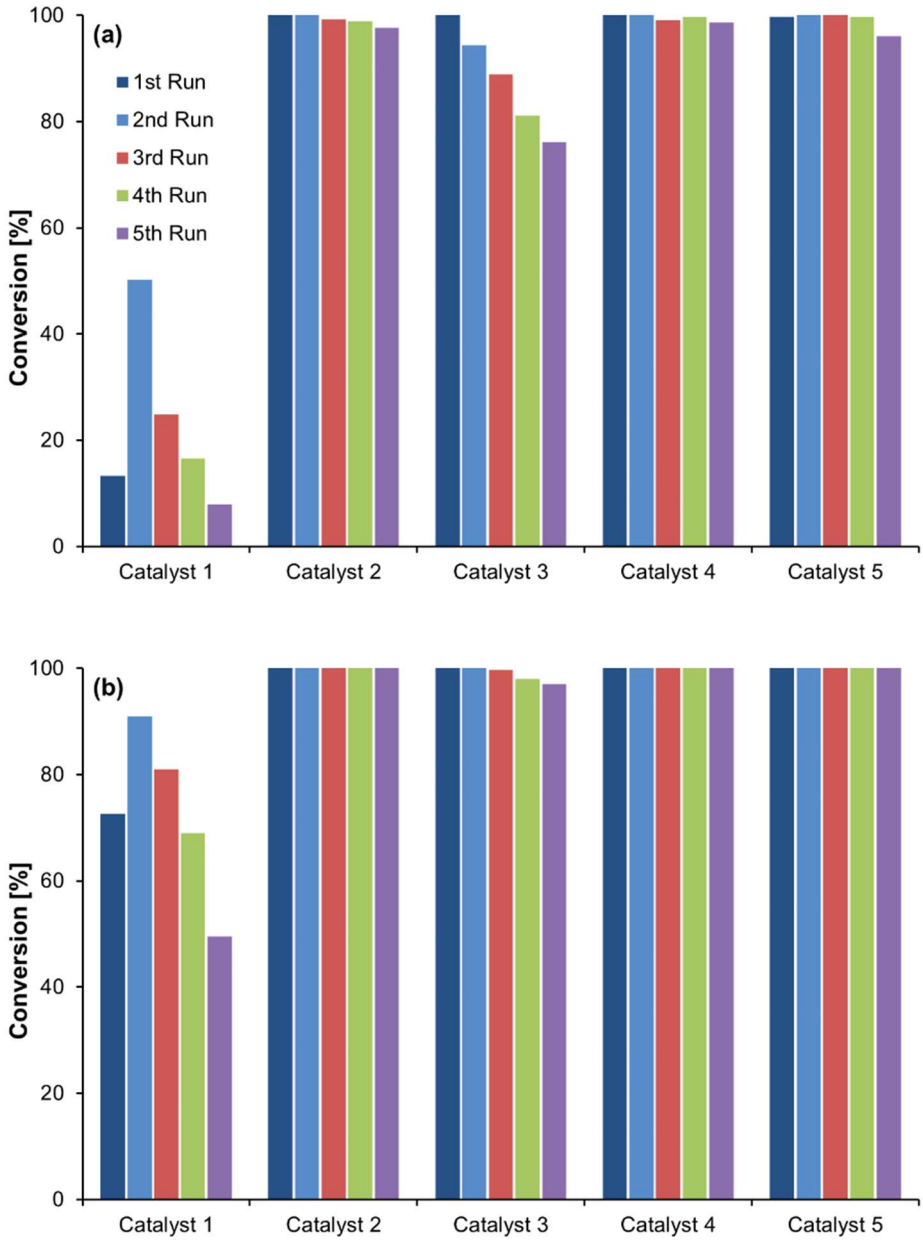


Figure B-6: Observed conversions after 30 (a) and 120 minutes (b) for the Suzuki-coupling of 4-Bromotoluene with phenylboronic acid in 5 subsequent runs using 0.5 mol% Pd. Cat 1: $Ce_{0.99}Pd_{0.01}O_{2-\delta}$, Cat 2: $Ce_{0.79}Sn_{0.2}Pd_{0.01}O_{2-\delta}$, Cat 3: $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$, Cat 4: $Ce_{0.20}Sn_{0.79}Pd_{0.01}O_{2-\delta}$, Cat 5: $Sn_{0.99}Pd_{0.01}O_{2-\delta}$.

To investigate the leaching behaviour of the catalysts, the catalyst was filtered off after each reaction cycle and washed with water and ethanol. The combined reaction and washing solutions were evaporated under reduced pressure and the remaining solids were analyzed for their palladium content by means of ICP-MS. When $Ce_{0.79}Sn_{0.2}Pd_{0.01}O_{2-\delta}$ and

$Ce_{0.20}Sn_{0.79}Pd_{0.01}O_{2-\delta}$ were used as catalysts, the palladium contents were determined after each run. Due to the good reproducibility of the results (0.08 ± 0.01 mg/L and 0.15 ± 0.02 mg/L for $Ce_{0.79}Sn_{0.2}Pd_{0.01}O_{2-\delta}$ and $Ce_{0.20}Sn_{0.79}Pd_{0.01}O_{2-\delta}$, respectively) the Pd content in the reaction solutions was determined representatively for run 3 for all other catalysts. Table B-6 shows the obtained Pd-concentrations in the remaining solids as well as the corresponding palladium concentration in solution, represantively for run 3.

Table B-6: Pd-contents of the residual solids and corresponding Pd-concentrations in solution for the 3rd reaction.

Catalyst	Pd in remaining solids [mg/kg] after 3rd run	Pd in solution [mg/L] after 3rd run
$Ce_{0.99}Pd_{0.01}O_{2-\delta}$	5.0	0.06
$Ce_{0.79}Sn_{0.2}Pd_{0.01}O_{2-\delta}$	6.7	0.09
$Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$	5.3	0.07
$Ce_{0.20}Sn_{0.79}Pd_{0.01}O_{2-\delta}$	10.0	0.13
$Sn_{0.99}Pd_{0.01}O_{2-\delta}$	11.0	0.14

Figure B-7 shows a comparison of the initial reaction rates (expressed as turnover frequencies after 15 minutes reaction time) and the amount of palladium in solution for the third recycling run (catalysts are ordered according to increasing activity). The results demonstrate an apparent correlation between reactivity and amount of leached palladium and support the thesis, that the coupling reaction is actually catalyzed by small amounts of leached palladium via a homogeneous reaction mechanism.

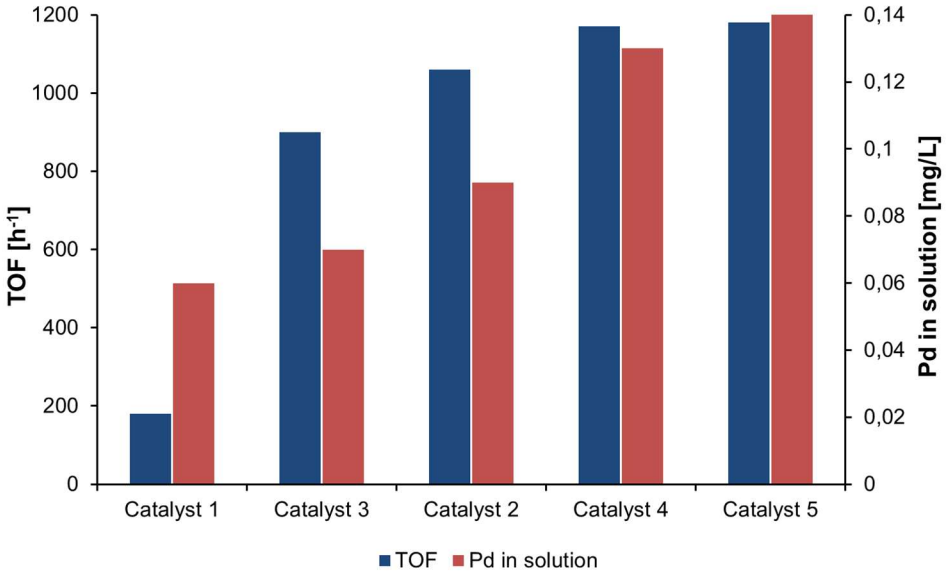


Figure B-7: TOF (after 15 minutes) vs. Pd-concentration in solution (mg/L) for the third recycling experiment.

Amoroso *et al.*[121] described a sigmoidal shape of the temporal conversion profile for Suzuki-couplings using Pd/CeO_2 catalysts and attributed this finding to an induction time period of the reaction due to the formation of dissolved palladium species, acting as true catalytically active

species. Sigmoidal conversion profiles also could be observed in this study in moderately fast reactions, not only for $Ce_{0.99}Pd_{0.01}O_{2-\delta}$ but also for the tin containing catalysts. Figure B-8, illustrates such sigmoidal profiles for the reaction of 4-bromotoluene with phenylboronic acid catalyzed by $Ce_{0.79}Sn_{0.2}Pd_{0.01}O_{2-\delta}$ and $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$, respectively.

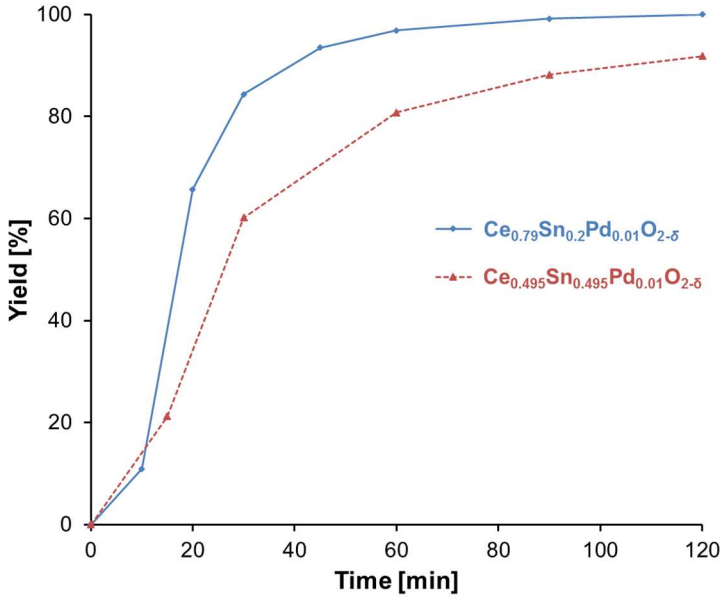


Figure B-8: Sigmoidal profile of the reaction progress for the coupling reaction of 4-bromotoluene with phenylboronic acid using $Ce_{0.79}Sn_{0.2}Pd_{0.01}O_{2-\delta}$ and $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$.

The results of the recycling tests agree very well with the findings of other studies using Pd-doped metal oxides as precatalysts, and substantiate the hypothesis, that the precatalysts act as palladium reservoir, that slowly releases extremely reactive palladium species.[120,121] The successful recycling of the catalysts might be attributed to a Pd release/capture mechanism, which was not only proposed for Pd on metal oxides[120,121] but also for a wide variety of Pd catalysts on different solid supports.[74,76,81,124]

In a second recycling series, the catalysts were used for 3 Suzuki reactions in the same manner and afterwards characterized by means of XRD (Figure B-9). The XRD-patterns of the used catalysts reveal intact fluorite structures of the cerium rich catalysts, $Ce_{0.99}Pd_{0.01}O_{2-\delta}$ and $Ce_{0.79}Sn_{0.2}Pd_{0.01}O_{2-\delta}$ respectively, a crystalline mixed phase structure of the mixed oxides $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$ and $Ce_{0.20}Sn_{0.79}Pd_{0.01}O_{2-\delta}$ and the remaining tetragonal structure of the binary oxide $Sn_{0.99}Pd_{0.01}O_{2-\delta}$. These findings prove the high stability of the produced catalysts at the applied reaction conditions. Also in the used catalysts, patterns attributable to Pd (111) could not be observed, which confirms the absence of PdO or segregated Pd metal species.

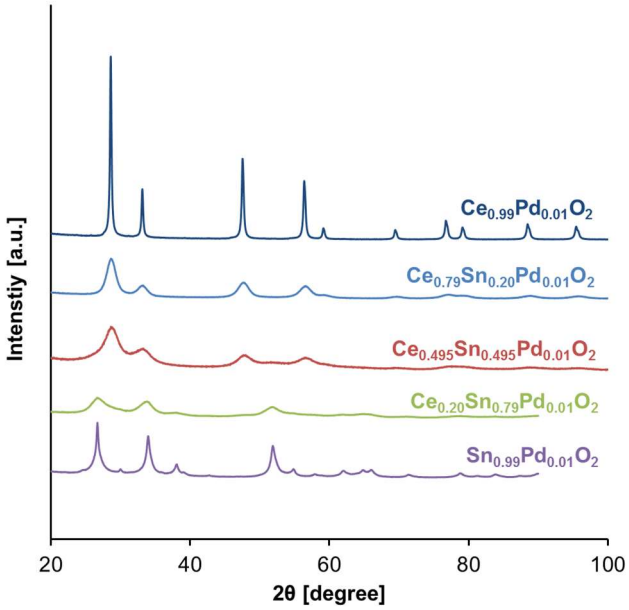


Figure B-9: X-Ray diffraction pattern of three times used $Ce_xSn_{1-x}Pd_{0.01}O_{2-\delta}$ (x = 0 – 0.99).

2.5 Heterogeneity Studies

2.5.1 Hot Filration Test

An often applied test to determine the heterogeneity of a system is the so called hot filtration test. After a certain reaction time, the solid catalyst is removed from the reaction solution by filtration through a hot filter (filter frit or filter crucible). The subsequent reaction progress in the remaining reaction solution without solid catalyst is monitored over time. In our study, this test was performed for all produced catalysts employing the Suzuki cross-coupling reaction of 4-bromotoluene with phenylboronic acid in ethanol/water = 7/3 v/v. Based on the results of the reactivity test, the amount of catalyst and the moment of filtration were chosen in such a way that the obtained conversions of 4-bromotoluene was in the range between 25 and 80 percent. The results of the hot filtration tests are depicted in Figure B-10**.**

In all experiments, the removal of the catalyst by filtration led to a complete stop of the conversion of 4-bromotoluene to 4-methylbiphenyl, although all required reaction participants remained in solution (which was confirmed by HPLC-analysis). This could lead to the assumption, that the reaction is catalyzed by an insoluble catalyst in a heterogeneous manner. However, it is known that hot filtration tests are rather problematic for the precise distinction between homogeneous and heterogeneous catalysis,[125] since catalytically active leached metal can redeposit on the catalyst very quickly during filtration and may not be detected by a filtration test. Furthermore, massive interruptions in the reaction process (such as filtration) can deactivate dissolved metal species. Thus, more reliable methods for the determination of the homogeneous or heterogeneous nature of metal catalyzed reactions, including three-phase-tests[77] and catalyst poisoning tests[76] have been developed.

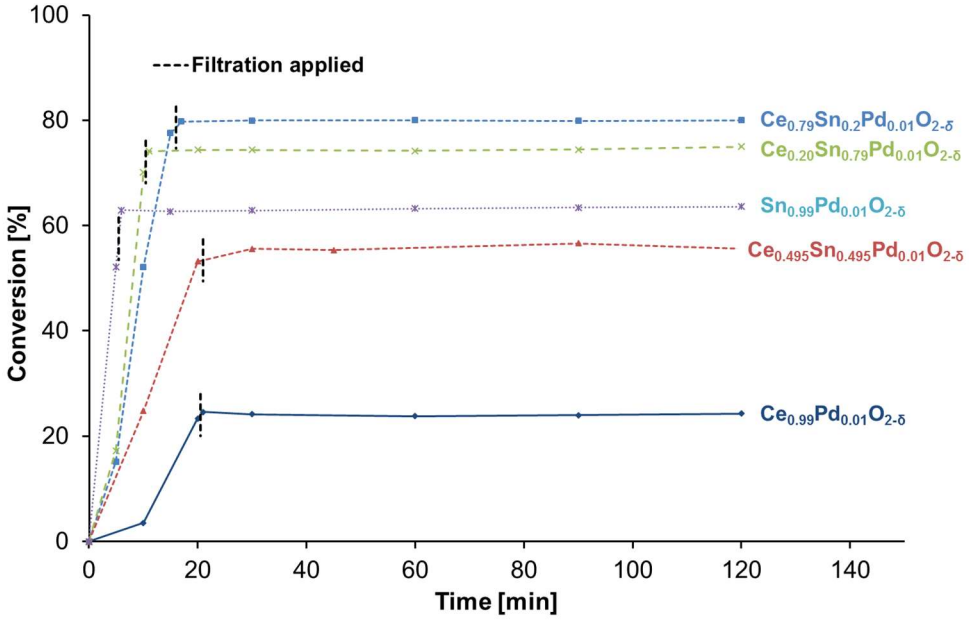


Figure B-10: Hot filtration test employing the Suzuki-Miyaura cross-coupling reaction of 4-bromotoluene and phenylboronic acid.

2.5.2 Catalyst Poisoning

According to Jones *et al.*[76], the catalyst poisoning test represents one of the most potential methods to distinguish between homogeneous and heterogeneous catalytic systems. During this test, materials, which are known to act as selective catalyst poisons for dissolved palladium, are added to the reaction mixtures. Frequently used poisons for palladium catalyzed cross-coupling reactions include Quadrapure TU (polymeric resin), poly(4-vinylpyridine) (PVPy) and 3-mercaptopropyl functionalized silica gel (MPSG).[125] The addition of such materials leads to the removal of soluble reactive metal from the reaction solution and would lead to a suppression of a further reaction progress in a homogeneously catalyzed reaction.

In this work, we used 3-mercaptopropyl functionalized silica gel (100 molecular equivalents of SH-groups with respect to the employed amount of palladium) as selective catalyst poison for the reaction of 4-bromotoluene with phenylboronic acid in ethanol/water = 7/3 v/v (at the same reaction conditions as in the hot filtration test). The complete suppression of the reaction after addition of the catalyst poison (Figure B-11) strongly indicates a homogeneous reaction mechanism via dissolved palladium species. Although the good recyclability of the catalysts and the results of the hot filtration test seemingly suggest a heterogeneous reaction mechanism, the findings of the catalyst poisoning experiments, the sigmoidal profile of the reaction progress and the low but detectable amount of palladium in the filtered reaction solution strongly support the above mentioned thesis, that the produced oxides act as precatalysts and release extremely reactive palladium species, which represent the truly catalytically active species.

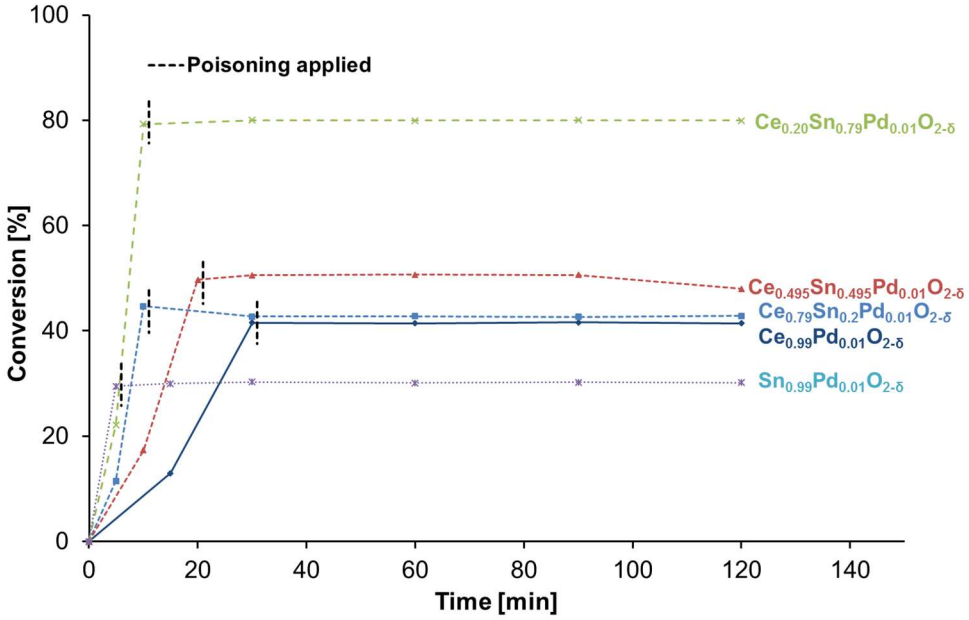


Figure B-11: Catalyst poisoning test employing mercaptopropyl functionalized silica gel in the Suzuki-Miyaura cross-coupling reaction of 4-bromotoluene and phenylboronic acid.

3 Conclusions

Palladium substituted CeO_2, SnO_2 and their mixed oxides proved to be efficient catalysts for Suzuki-Miyaura cross-coupling reactions. The synthesis of the oxides via a one-step solution combustion method represents a further simplification of already rapid and inexpensive preparation strategies, such as sol-gel methods or wet impregnation techniques. In general, tin containing catalysts proved to be clearly more catalytically active than already reported binary cerium-palladium oxides. Especially, the mixed oxides $Ce_{0.79}Sn_{0.2}Pd_{0.01}O_{2-\delta}$, $Ce_{0.20}Sn_{0.79}Pd_{0.01}O_{2-\delta}$ and $Sn_{0.99}Pd_{0.01}O_{2-\delta}$ showed extraordinarily high activities for the coupling of various bromoarenes with phenylboronic acid, although a direct relation between cerium or tin content and activity could not be found. The best performing catalysts could be reused for at least five subsequent Suzuki-Miyaura reaction, yielding full conversion of the bromoarene-substrate within two hours while releasing only minimal amounts of palladium into the reaction solution. Nevertheless, the presence of low amounts of palladium in solution, as well as sigmoidal profiles of the reaction progress substantiate the thesis, that the as prepared mixed oxides act as precatalysts, which release small amounts of dissolved palladium, the truly catalytically active species. The good recyclability of the catalysts can be explained plausibly by a palladium release/capture mechanism proposed for palladium on metal oxides or other solid supports.

The Suzuki-Miyaura reactions were performed in aqueous alcoholic mixtures. Such solvent systems are capable of dissolving a wide variety of Suzuki-Miyaura cross-coupling educts and products and the obligate inorganic bases. The good recyclability and high leaching resistance

in such homogeneous reaction mixtures indicates a high potential of the prepared catalysts for the use in continuous-flow operations, for example in fixed bed reactors.

4 Experimental details

4.1 Synthesis

General principles and methods for the solution combustion synthesis of nanocrystalline materials have been described and reviewed elsewhere.[113,114] The synthesis of $Ce_{0.99-x}Sn_xPd_{0.01}O_{2-\delta}$ was done analogously to the method reported by Baidya *et al.*[123] using glycine instead of L-tartaric acid as fuel. Glycine as the fuel has been used for combustion synthesis by several investigators and has been reported to impart good nanocrystallinity in the product.[116,119,123] A set of five $Ce_{0.99-x}Sn_xPd_{0.01}O_{2-\delta}$ mixed oxides (with x = 0, 0.2, 0.495, 0.79 and 0.99) was prepared. The appropriate proportions of catalyst precursors and fuel were calculated using the method described by González-Cortés *et al.*[117] considering the oxidizing/reducing valencies (Φ_e) of the redox mixture and assuming an ideal and complete combustion without secondary reactions. In this calculation, oxygen was considered as an oxidizer with the valance -2, whereas carbon (+4), hydrogen (+1) and metals (redox valence corresponding to metal valence) were considered as reducing elements. Nitrogen with the redox valence 0 was not considered. Oxidizing/reducing valencies of the reacting species were ammonium cerium (IV) nitrate =-24, tin (IV) nitrate =-20, palladium (II) nitrate = -10 and glycine = +9.

The required amount of fuel for the synthesis of 1 mole $Ce_{0.99-x}Sn_xPd_{0.01}O_{2-\delta}$ can be calculated using the equation:

$$n_{Gly} = (0.99 - x) * \frac{\Phi_{(NH_4)_2Ce(NO_3)_6}}{\Phi_{Gly}} + x * \frac{\Phi_{Sn(NO_3)_4}}{\Phi_{Gly}} + 0.01 * \frac{\Phi_{Pd(NO_3)_2}}{\Phi_{Gly}}$$

For the preparation of 3 g catalyst, appropriate amounts of ammonium cerium(IV) nitrate ($(NH_4)_2Ce(NO_3)_6$, Sigma Aldrich), tin(II) oxalate (SnC_2O_4, Sigma Aldrich), palladium(II) chloride ($PdCl_2$, Aldrich) and glycine ($C_2H_5NO_2$, Sigma Aldrich) were dispersed in 3 ml of water in a borosilicate dish with 600 ml capacity. 2.5 molar equivalent (related to tin (II) oxalate) of nitric acid (HNO_3, 65 %, Merck) were added and the mixture was slightly heated until a viscous but clear solution was obtained. The redox mixture was treated in a muffle furnace at 350 °C. The mixture ignited within 5 minutes, initiating a self-propagating combustion reaction, which yielded a voluminous, porous solid. This solid was ground with mortar and pestle and was heated to 350 °C for another 5 hours. After that procedure, the obtained powders were directly usable as catalyst for the Suzuki-Miyaura cross-coupling reactions.

4.2 Characterization

4.2.1 X-Ray diffraction

The synthesized catalysts were characterized using X-ray diffraction (XRD) with Cukα radiation to analyze the crystal structure. The samples were scanned in a range of 2Θ of 20-100°, a range in which characteristic peaks of CeO_2 and SnO_2 appear.

4.2.2 Specific surface area

Specific surface areas were determined according to the Brunauer–Emmet–Teller (BET) theory on a Tristar II 3020 (Micromeritics, Norcross, Georgia) using nitrogen as analytical gas. Catalyst samples were degassed under vacuum at ambient temperature for 24 h. The volume of nitrogen adsorption was recorded over a relative pressure range between 0.01 and 0.99. 8 points in the relative pressure range of 0.05 to 0.2 were used for the calculation of the BET surface area.

4.2.3 Particle size distribution

The particle size measurements were conducted with a HELOS/KR Laser diffraction sensor equipped with an OASISDRY/L dry dispersion system by Sympatec GmbH (injector: 4 mm, dispersing pressure: 2.00 bar, optical concentration 1%-20%, measuring range: combined R2+R5 (0.45 µm - 875 µm), evaluation mode: Fraunhofer approximation, software: WINDOX 5.6.0.0). Each analysis was conducted as a 3-fold determination.

4.3 Catalytic activity

The catalytic activities of the prepared catalysts were tested for the Suzuki-Miyuara cross-coupling reaction of phenylboronic acid with various bromoarenes. In a typical experiment, 0.70 mmol of the aryl bromide, 1.5 molar equivalents of phenylboronic acid and 1.5 molar equivalents of base, respectively, and 1.3 mmol of anisole (internal standard) were dissolved in 20 ml of solvent. 5 mg of the catalyst (corresponding to approximately 0.05 mol.% palladium) were added. The reaction was carried out under stirring at 75 °C. To monitor the reaction progress, samples from the reaction solution (100 µL) were taken after 15, 30, 60, 90 and 120 minutes. HPLC sample solutions were prepared by dissolving 100 µL of the reaction solution in 1 mL of the initial mobile phase. HPLC analysis was done using an Agilent 1100 series HPLC system (Agilent, Waldbronn, Germany), equipped with an online degasser, quaternary pump, autosampler, thermostatted column compartment and UV-visible diode array detector. An Agilent Poroshell 120 EC-C18 reversed-phase column (50x4.6 mm; 2.7 µm) was used as stationary phase. Analysis was carried out under gradient elution conditions using a mobile phase consisting of methanol and aqueous phosphoric acid (water: phosphoric acid = 300:1 v/v). Column temperature was set to 25 °C. UV-detection was performed at wavelengths of 237 and 270 nm over a run time of 15 minutes.

4.4 Recycling tests

The cross-coupling reaction of phenylboronic acid with 4-bromotoluene using potassium carbonate as base was chosen as model reaction for the examination of the recyclability of the different catalysts. The reactions were carried out in 20 ml of the reaction mixture using the same concentrations of 4-bromotoluene, phenylboronic acid, potassium carbonate and internal standard (anisole) for the reactivity tests. Five subsequent reactions with each catalyst were carried out. After a reaction time of 120 minutes, the catalyst was filtered off using a filter crucible and was washed with ethanol and water to remove organic and inorganic impurities. The catalyst was dried in a muffle furnace at 350 °C over night. The filtrate was evaporated under reduced pressure. The solid residue was analyzed for its palladium content by means of ICP-MS. Measurements were performed on an Agilent 7500ce ICP-MS after microwave assisted acidic digestion of the samples. Due to a partial loss of catalyst throughout the recovery procedure, the first experiment was carried out with an initial catalyst loading of 50 mg (corresponding to approximately 0.5 mol % palladium, 10 times more than in the reactivity tests).

5 Appendix

5.1 Catalyst Synthesis

The amounts of catalyst precursors and fuel, which were used for the synthesis of 3 g of each catalyst are listed in Table B-7.

Table B-7: Amounts of catalyst precursors and fuel, which were used for the synthesis of 3 g of each catalyst.

#	x	Molecular formula	$(NH_4)_2Ce(NO_3)_6$	SnC_2O_4	$PdCl_2$	Gly
1	0	$Ce_{0.99}Pd_{0.01}O_{2-\delta}$	9.479 g	-	0.031 g	3.476 g
2	0.2	$Ce_{0.79}Sn_{0.2}Pd_{0.01}O_{2-\delta}$	7.758 g	0.741 g	0.032 g	3.445 g
3	0.495	$Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$	5.051 g	1.905 g	0.033 g	3.397 g
4	0.79	$Ce_{0.20}Sn_{0.79}Pd_{0.01}O_{2-\delta}$	2.124 g	3.164 g	0.034 g	3.345 g
5	0.99	$Sn_{0.99}Pd_{0.01}O_{2-\delta}$	-	4.077 g	0.035 g	3.307 g

5.2 HPLC-Methods

HPLC analysis was done using an Agilent 1100 series HPLC system (Agilent, Waldbronn, Germany), equipped with an online degasser, quaternary pump, autosampler, thermostatted column compartement and UV-visible diode array detector. An Agilent Poroshell 120 EC-C18 reversed phase column (50x4.6 mm; 2.7 µm) was used as stationary phase. Analysis was carried out under gradient elution conditions using a mobile phase consisting of methanol and aqueous phosphoric acid (water:phosphoric acid = 300:1 v/v). Two different methods for the analysis of the reaction solutions were used. The corresponding elution programs are given in Table B-8.

Table B-8: Used HPLC methods applying solvents A (methanol) and B (water:phosphoric acid = 300:1 v/v).

METHOD A Time [min]	% A (v/v)	% B (v/v)	Flow [ml/min]
0	60	40	1
10	80	20	1
12	60	40	1

METHOD B Time [min]	% A (v/v)	% B (v/v)	Flow [ml/min]
0	40	60	1
3	40	60	1
9	80	20	1
11	80	20	1
13	40	60	1

Column temperature was set to 25 °C. An aliquot of 2 µL of sample solution was injected into the HPLC system. UV-detection was performed at 237 and 270 nm over the run time of 15 minutes (Method A) and 16 minutes (Method B), respectively.

The sample solutions were prepared by dissolving 100 µL of the reaction solution in 1 mL of the initial mobile phase. Method A was used for monitoring the synthesis of 4-methylbiphenyl, 4-acetylbiphenyl, 4-trifluoromethylbiphenyl and biphenyl-2-carbonitrile. Method B was used for monitoring the synthesis of 4-phenylphenol.

The wavelengths used for quantification and the retention times of the substrates, products, side products and the internal standard are given in Table B-9.

Table B-9: Wavelengths of quantification and retention times for the used internal standards and substrates and the observed products and side products.

	Retention time t_R [min]		Wavelength of
	Method A	Method B	quantification [nm]
Internal standard			
Anisole	1.56	5.04	270
Substrates			
Phenylboronic acid	0.88	1.70	237
4-Bromotoluene	4.74		237
4-Bromoacetophenone	1.78		237
4-Bromobenzotrifluoride	4.94		237
2-Bromobenzonitrile	1.23		237
4-Bromophenol		5.55	237
Products			
4-Methylbiphenyl	8.18		237
4-Acetylbiphenyl	3.59		237
4-Trifluoromethylbiphenyl	8.44		237
Biphenyl-2-carbonitrile	2.29		237
4-Phenylphenol		8.15	237
Side products			
Biphenyl	5.87	10.34	237
Phenol	0.81	1.53	270
Benzene (not observed)	1.68	4.94	252

5.3 Catalytic Activity

In a typical experiment, 0.70 mmol of the aryl bromide, 1.5 molar equivalents of phenylboronic acid and 1.5 molar equivalents of base, respectively, and 1.3 mmol of anisole (internal standard) were dissolved in 20 ml of solvent. 5 mg of the catalyst (corresponding to approximately 0.05 mol.% palladium) were added. The reaction was carried out under stirring at 75 °C. To monitor the reaction progress, samples from the reaction solution (100 µL) were taken after 15, 30, 60, 90 and 120 minutes.

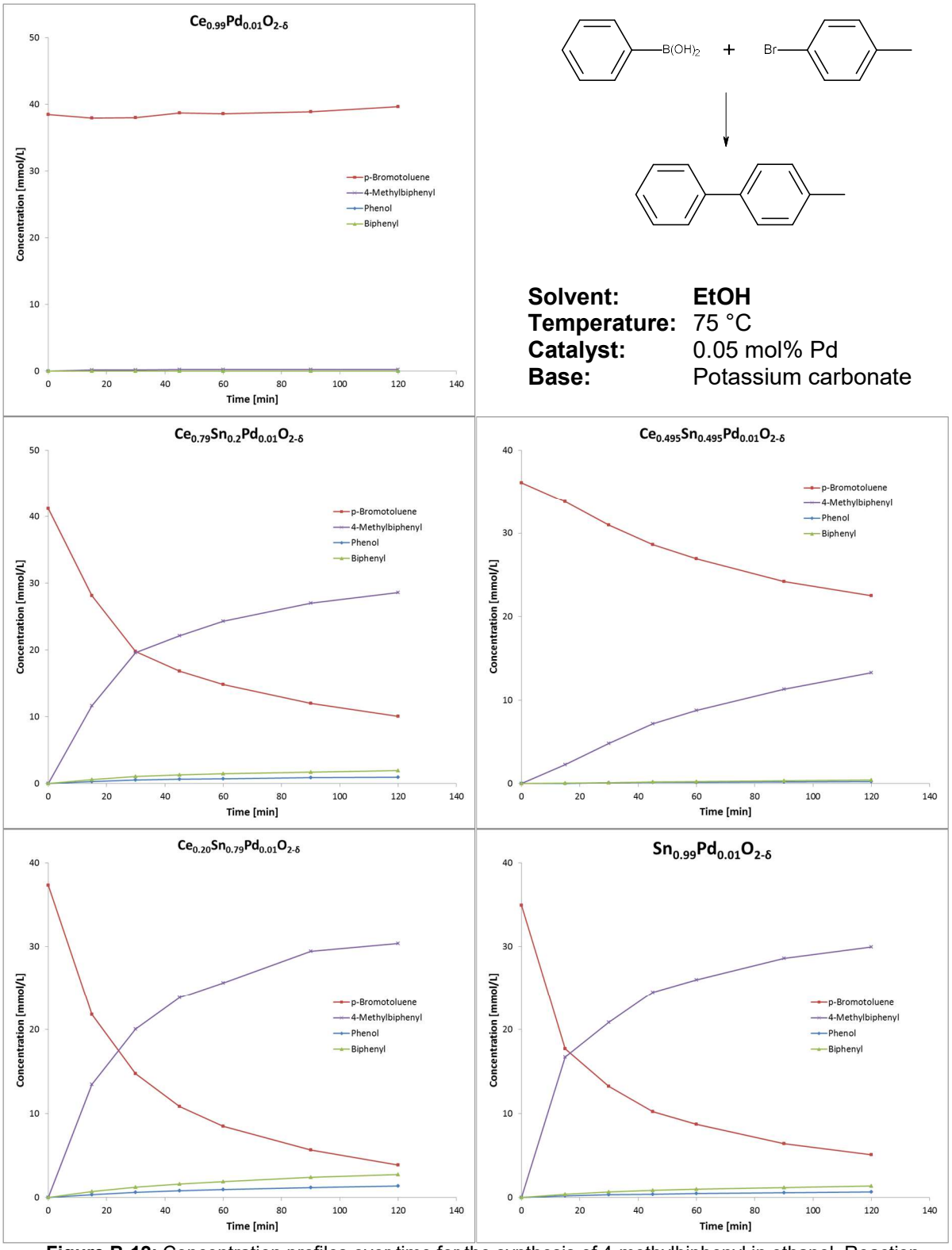


Figure B-12: Concentration profiles over time for the synthesis of 4-methylbiphenyl in ethanol. Reaction conditions: 4-bromotoluene (0.7 mmol), phenylboronic acid (1.5. mol eq.), K_2CO_3 (1.5 mol eq.), 5 mg $Ce_xSn_{1-x}Pd_{0.01}O_{2-\delta}$ (corresponding to 0.05 mol% Pd), 20 ml of solvent, 75 °C.

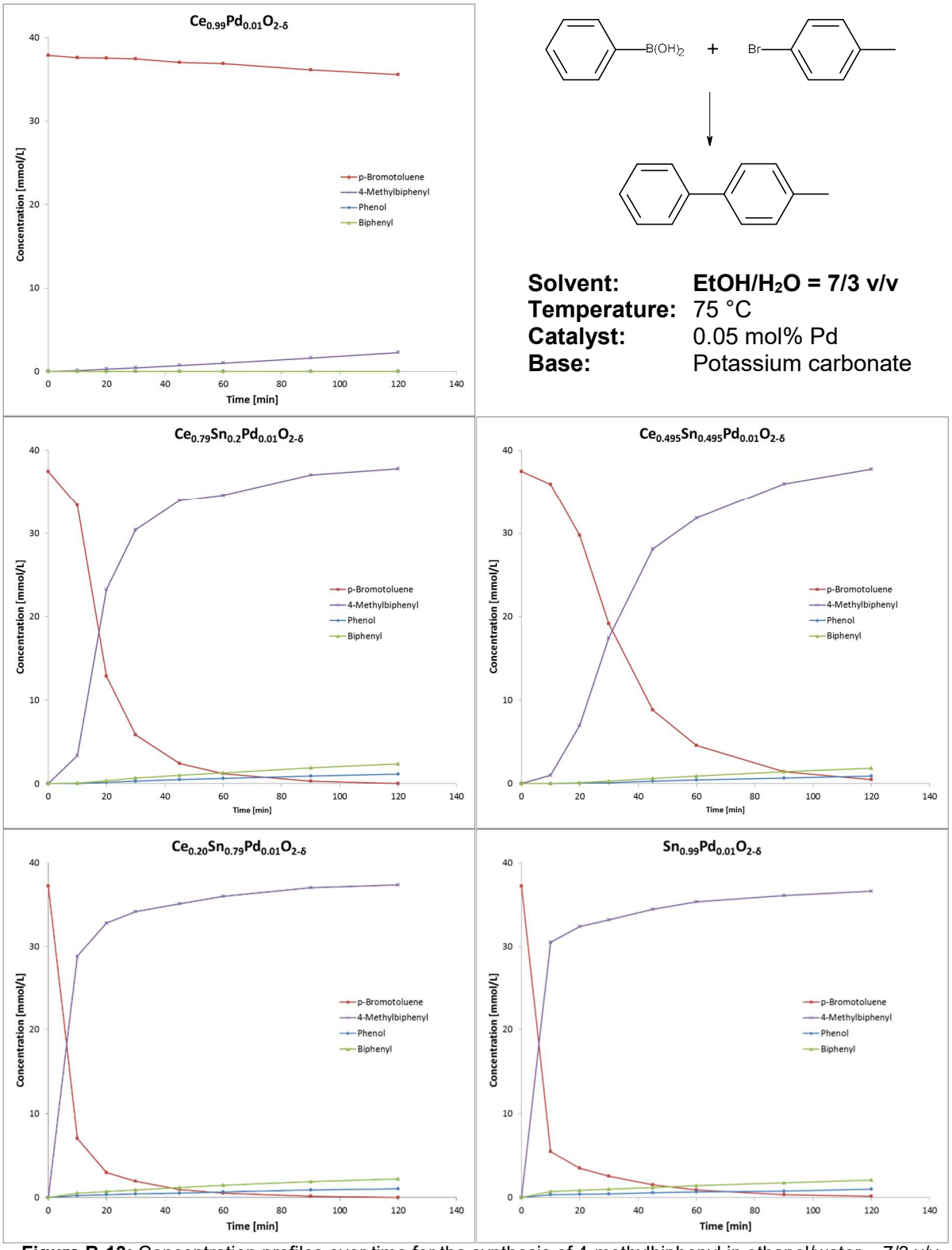


Figure B-13: Concentration profiles over time for the synthesis of 4-methylbiphenyl in ethanol/water = 7/3 v/v. Reaction conditions: 4-bromotoluene (0.7 mmol), phenylboronic acid (1.5. mol eq.), K_2CO_3 (1.5 mol eq.), 5 mg $Ce_xSn_{1-x}Pd_{0.01}O_{2-\delta}$ (corresponding to 0.05 mol% Pd), 20 ml of solvent, 75 °C.

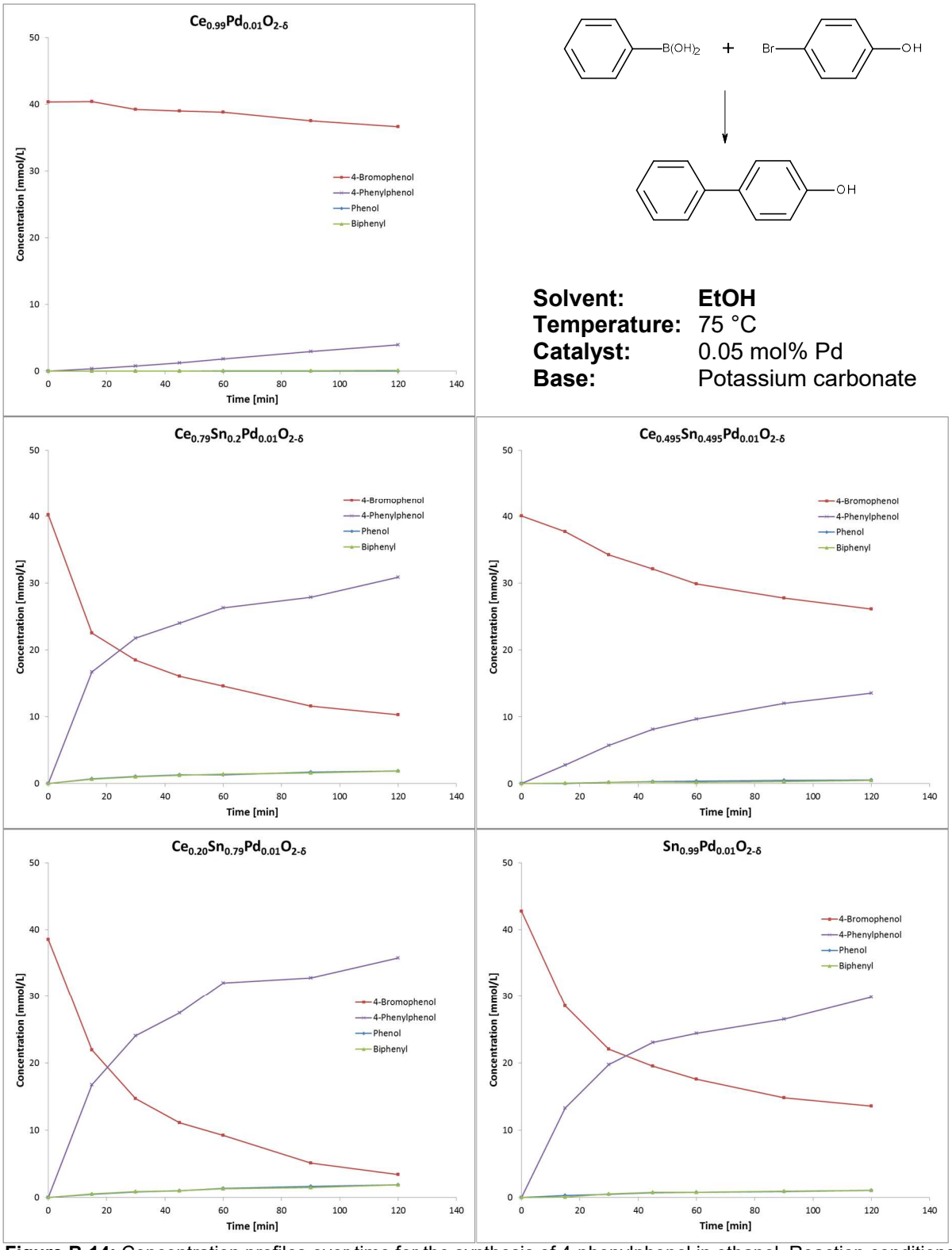


Figure B-14: Concentration profiles over time for the synthesis of 4-phenylphenol in ethanol. Reaction conditions: 4-bromophenol (0.7 mmol), phenylboronic acid (1.5. mol eq.), K_2CO_3 (1.5 mol eq.), 5 mg $Ce_xSn_{1-x}Pd_{0.01}O_{2-\delta}$ (corresponding to 0.05 mol% Pd), 20 ml of solvent, 75 °C.

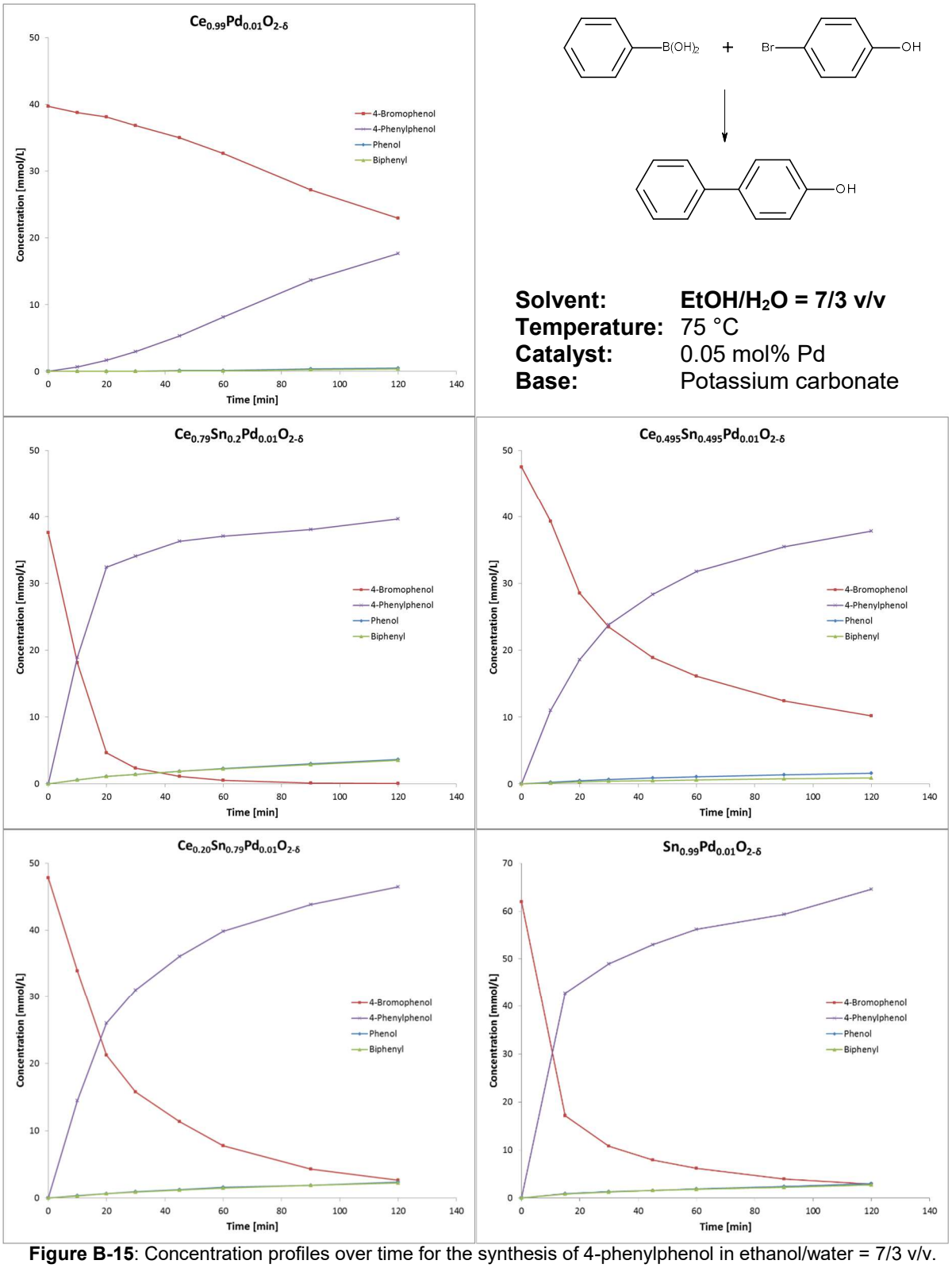


Figure B-15: Concentration profiles over time for the synthesis of 4-phenylphenol in ethanol/water = 7/3 v/v. Reaction conditions: 4-bromophenol (0.7 mmol), phenylboronic acid (1.5. mol eq.), K_2CO_3 (1.5 mol eq.), 5 mg $Ce_xSn_{1-x}Pd_{0.01}O_{2-\delta}$ (corresponding to 0.05 mol% Pd), 20 ml of solvent, 75 °C.

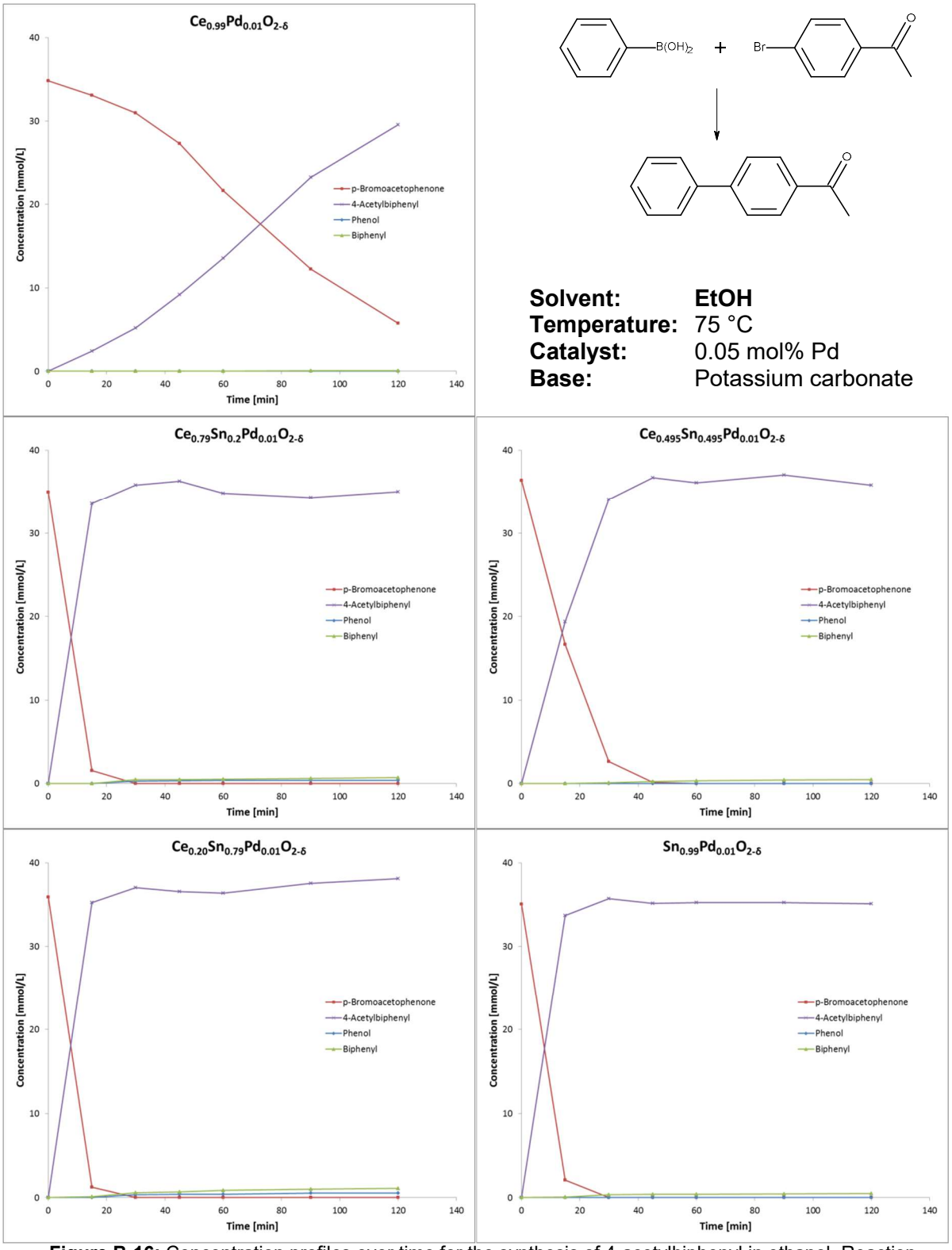


Figure B-16: Concentration profiles over time for the synthesis of 4-acetylbiphenyl in ethanol. Reaction conditions: 4-bromoacetophenone (0.7 mmol), phenylboronic acid (1.5. mol eq.), K_2CO_3 (1.5 mol eq.), 5 mg $Ce_xSn_{1-x}Pd_{0.01}O_{2-\delta}$ (corresponding to 0.05 mol% Pd), 20 ml of solvent, 75 °C.

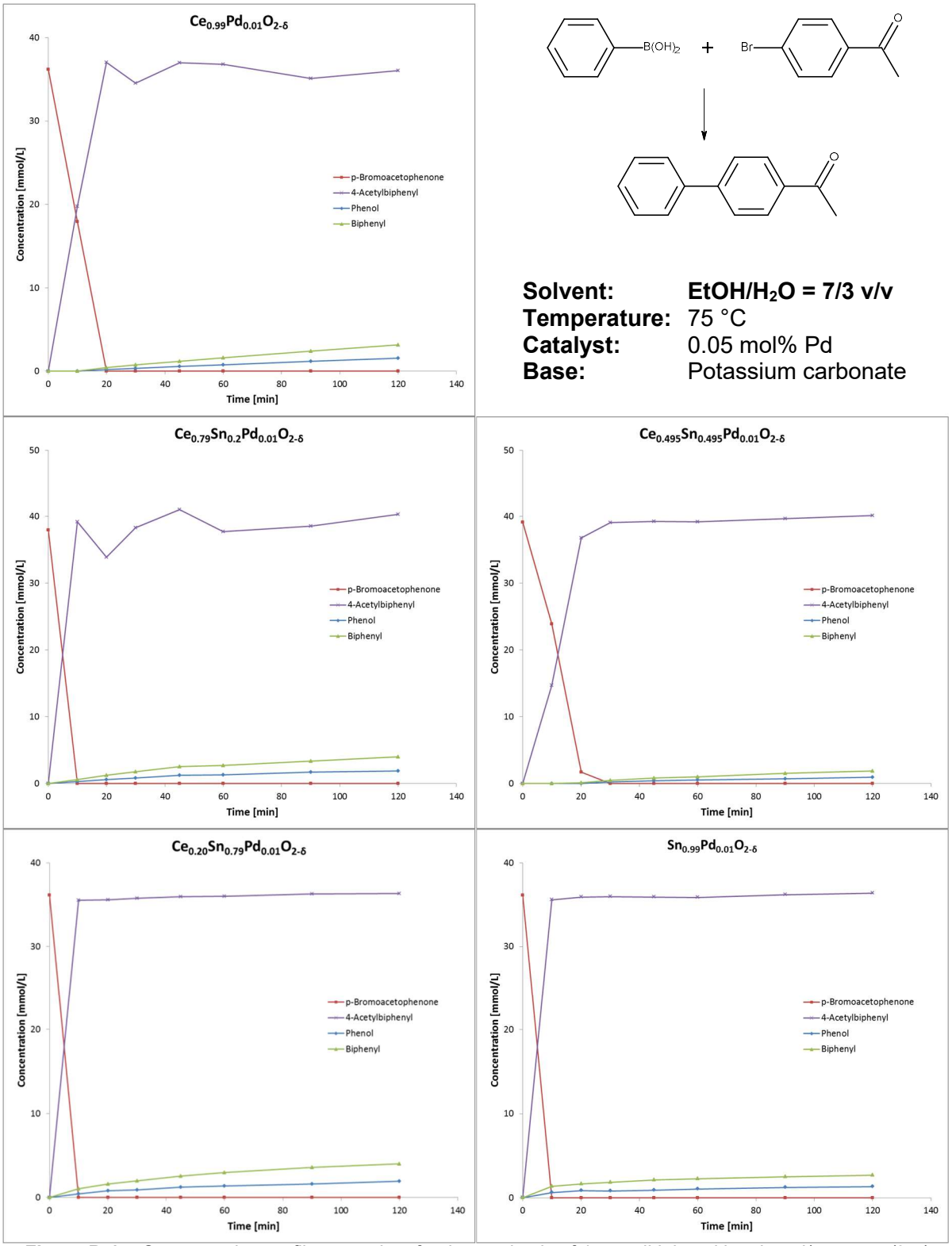


Figure B-17: Concentration profiles over time for the synthesis of 4-acetylbiphenyl in ethanol/water = 7/3 v/v. Reaction conditions: 4-bromoacetophenone (0.7 mmol), phenylboronic acid (1.5. mol eq.), K_2CO_3 (1.5 mol eq.), 5 mg $Ce_xSn_{1-x}Pd_{0.01}O_{2-\delta}$ (corresponding to 0.05 mol% Pd), 20 ml of solvent, 75 °C.

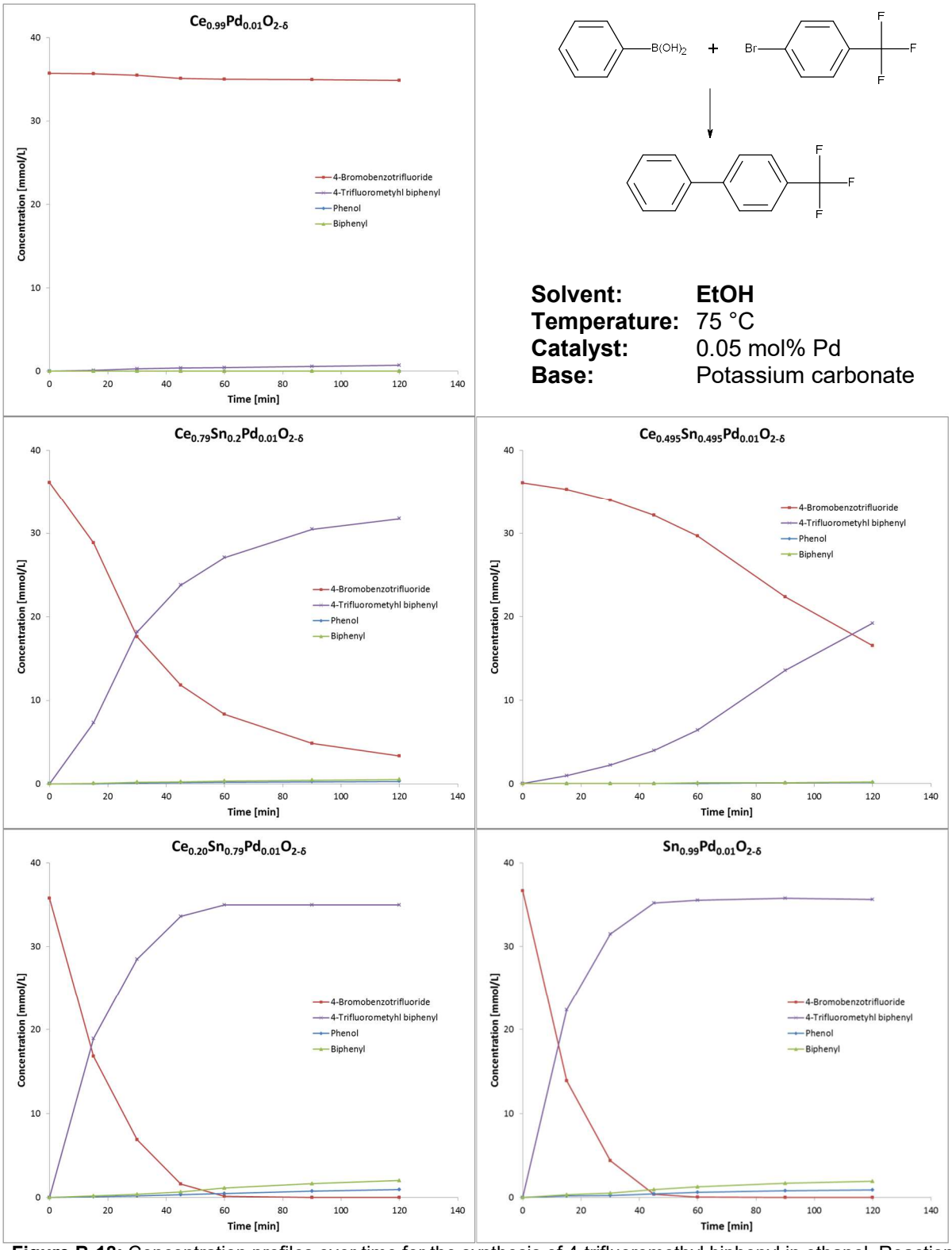


Figure B-18: Concentration profiles over time for the synthesis of 4-trifluoromethyl biphenyl in ethanol. Reaction conditions: 4-bromobenzotrifluoride (0.7 mmol), phenylboronic acid (1.5. mol eq.), K_2CO_3 (1.5 mol eq.), 5 mg $Ce_xSn_{1-x}Pd_{0.01}O_{2-\delta}$ (corresponding to 0.05 mol% Pd), 20 ml of solvent, 75 °C.

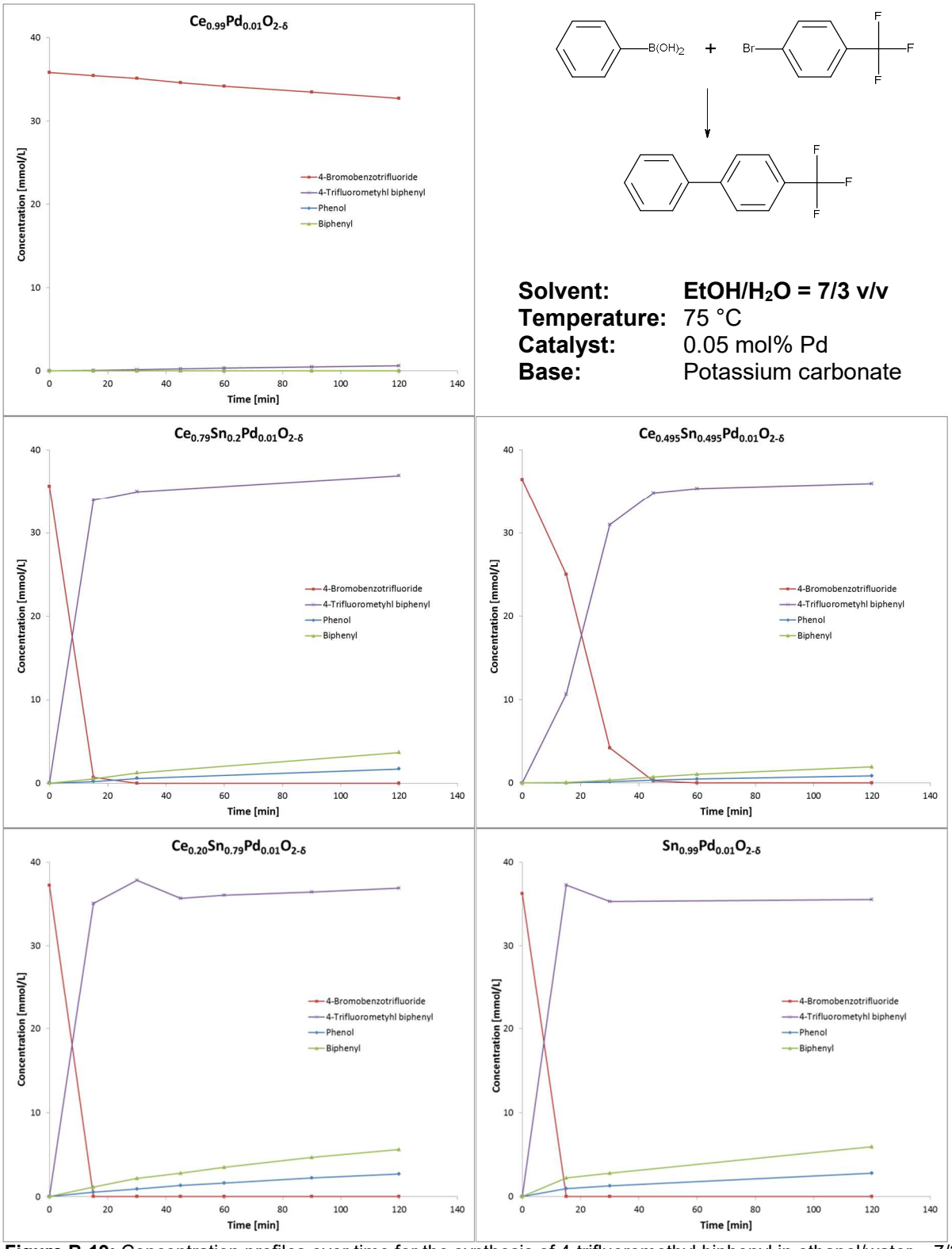


Figure B-19: Concentration profiles over time for the synthesis of 4-trifluoromethyl biphenyl in ethanol/water = 7/3 v/v. Reaction conditions: 4-bromobenzotrifluoride (0.7 mmol), phenylboronic acid (1.5. mol eq.), K_2CO_3 (1.5 mol eq.), 5 mg $Ce_xSn_{1-x}Pd_{0.01}O_{2-\delta}$ (corresponding to 0.05 mol% Pd), 20 ml of solvent, 75 °C.

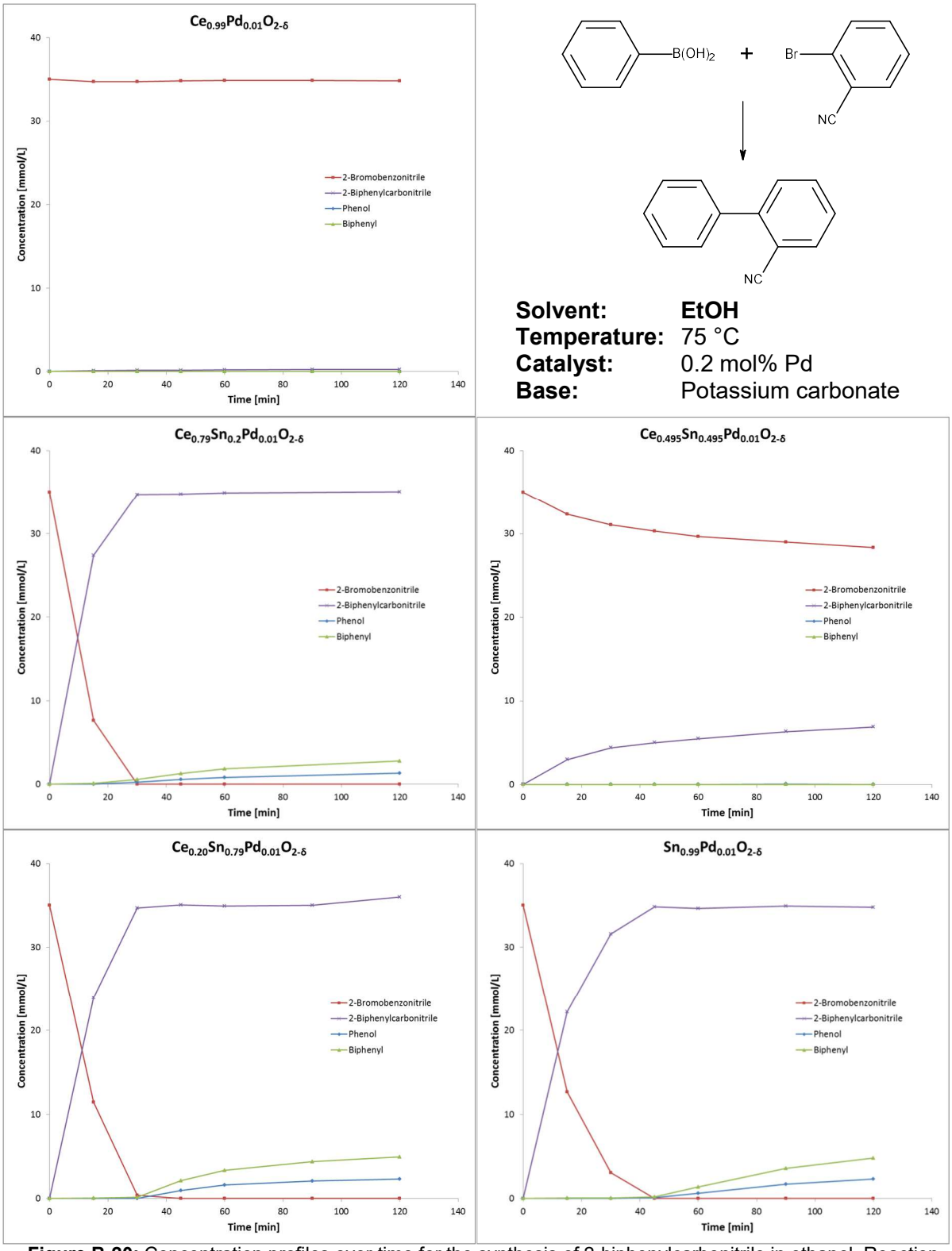


Figure B-20: Concentration profiles over time for the synthesis of 2-biphenylcarbonitrile in ethanol. Reaction conditions: 2-bromobenzonitrile (0.7 mmol), phenylboronic acid (1.5. mol eq.), K_2CO_3 (1.5 mol eq.), 20 mg $Ce_xSn_{1-x}Pd_{0.01}O_{2-\delta}$ (corresponding to 0.2 mol% Pd), 20 ml of solvent, 75 °C.

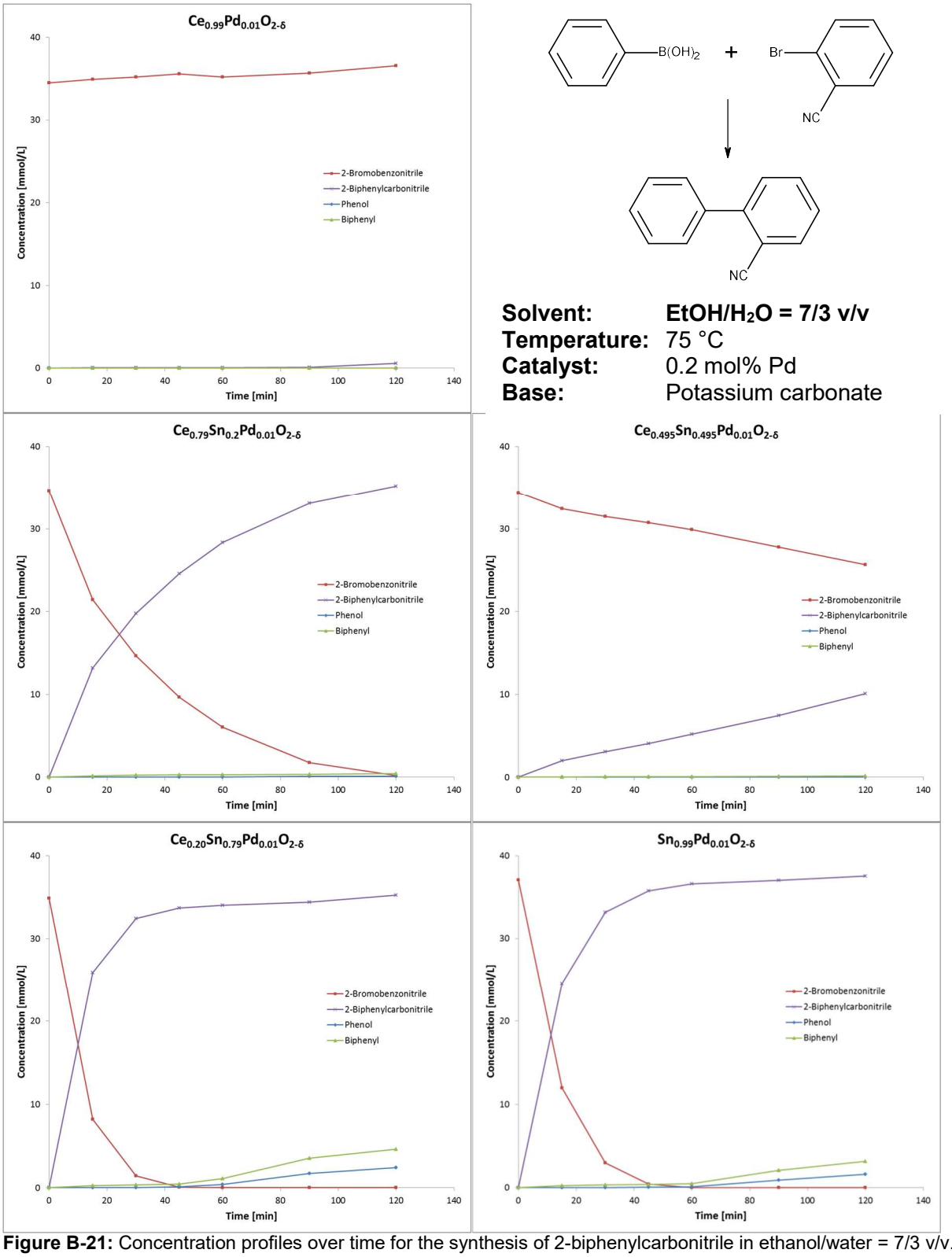


Figure B-21: Concentration profiles over time for the synthesis of 2-biphenylcarbonitrile in ethanol/water = 7/3 v/v. Reaction conditions: 2-bromobenzonitrile (0.7 mmol), phenylboronic acid (1.5. mol eq.), K_2CO_3 (1.5 mol eq.), 20 mg $Ce_xSn_{1-x}Pd_{0.01}O_{2-\delta}$ (corresponding to 0.2 mol% Pd), 20 ml of solvent, 75 °C.

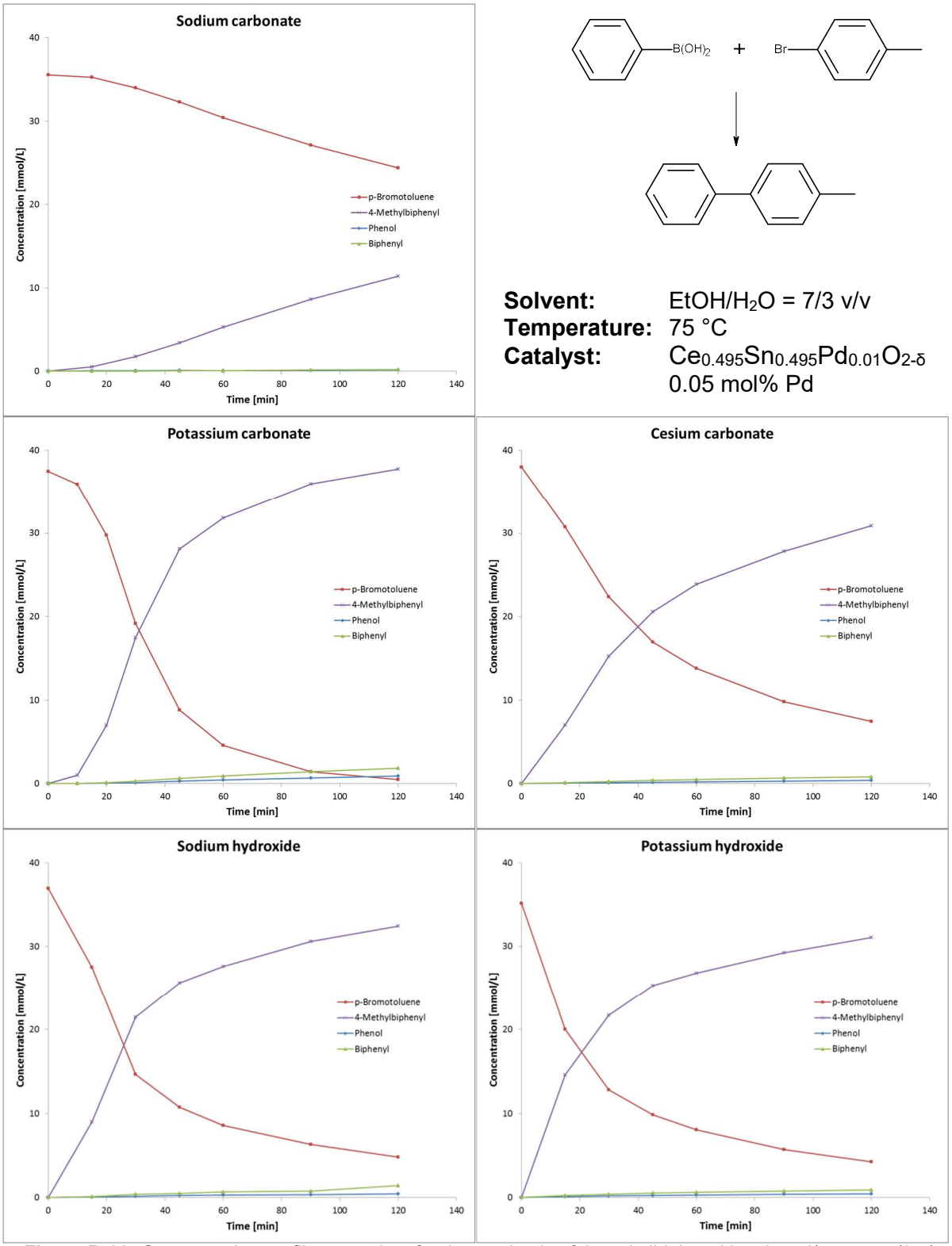
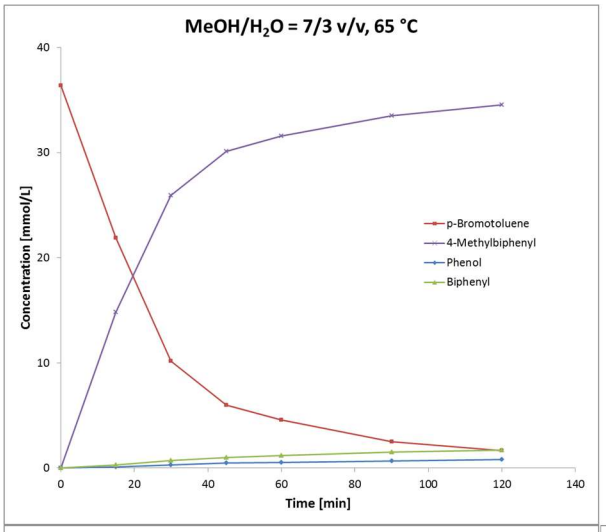
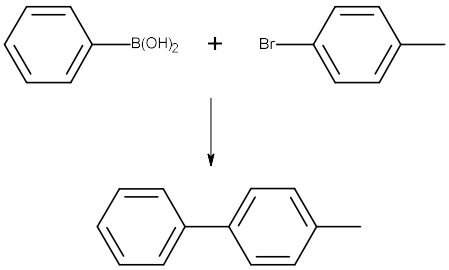


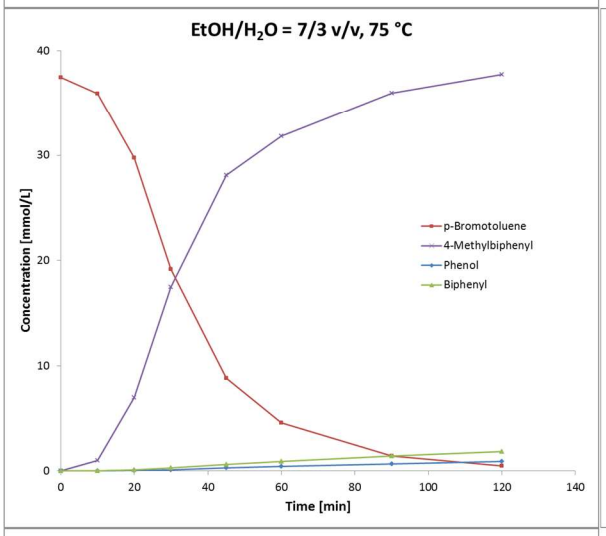
Figure B-22: Concentration profiles over time for the synthesis of 4-methylbiphenyl in ethanol/water = 7/3 v/v using various bases. Reaction conditions: 4-bromotoluene (0.7 mmol), phenylboronic acid (1.5. mol eq.), base (1.5 mol eq.), 5 mg $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$ (corresponding to 0.05 mol% Pd), 20 ml of solvent, 75 °C.

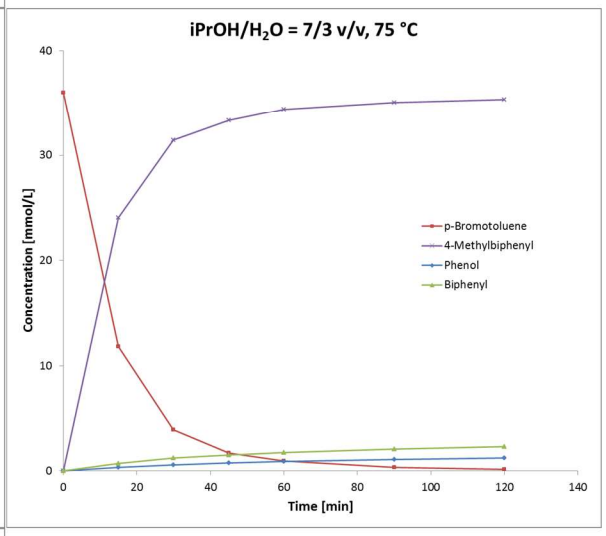




Catalyst: $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$ 0.05 mol% Pd

Base: Potassium carbonate





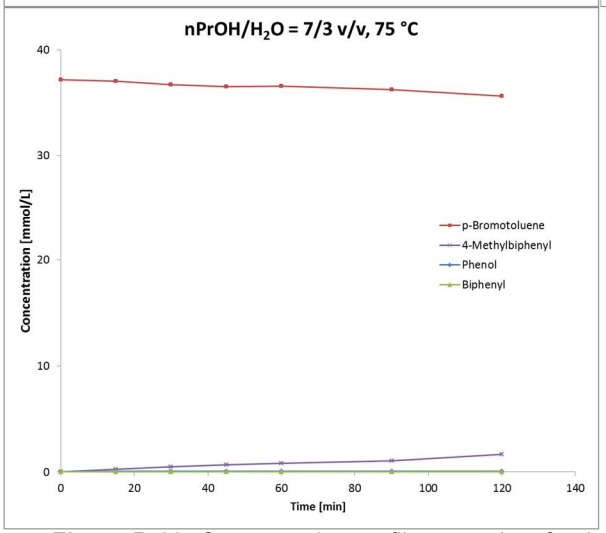


Figure B-23: Concentration profiles over time for the synthesis of 4-methylbiphenyl using various solvent mixtures. Reaction conditions: 4-bromotoluene (0.7 mmol), phenylboronic acid (1.5. mol eq.), K_2CO_3 (1.5 mol eq.), 5 mg $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$ (corresponding to 0.05 mol% Pd), 20 ml of solvent.

5.4 Recyclability

The cross-coupling reaction of phenylboronic acid with 4-bromotoluene using potassium carbonate as base was chosen as model reaction for the examination of the recyclability of the different catalysts. The reactions were carried out in 20 ml of the reaction mixture using the same concentrations of 4-bromotoluene, phenylboronic acid, potassium carbonate and internal standard (anisole) for the reactivity tests. Five subsequent reactions with each catalyst were carried out. After a reaction time of 120 minutes, the catalyst was filtered off using a filter crucible and was washed with ethanol and water to remove organic and inorganic impurities. The catalyst was dried in a muffle furnace at 350 °C over night. The filtrate was evaporated under reduced pressure. Due to a partial loss of catalyst throughout the recovery procedure, the first experiment was carried out with an initial catalyst loading of 50 mg (corresponding to approximately 0.5 mol .% palladium, 10 times more than in the reactivity tests).

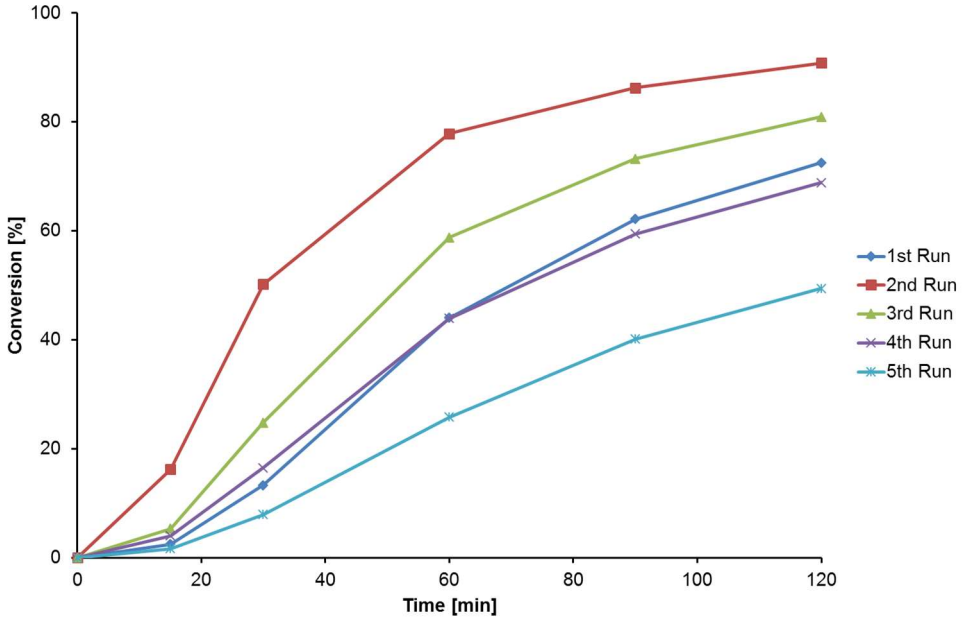


Figure B-24: Conversion vs. time for the synthesis of 4-methylbiphenyl using $Ce_{0.99}Pd_{0.01}O_{2-\delta}$ in five subsequent runs. Reaction conditions: 4-bromotoluene (0.7 mmol), phenylboronic acid (1.5. mol eq.), K_2CO_3 (1.5 mol eq.), 50 mg $Ce_{0.99}Pd_{0.01}O_{2-\delta}$ (corresponding to 0.5 mol% Pd in the first run), 20 ml of ethanol/water = 7/3 v/v.

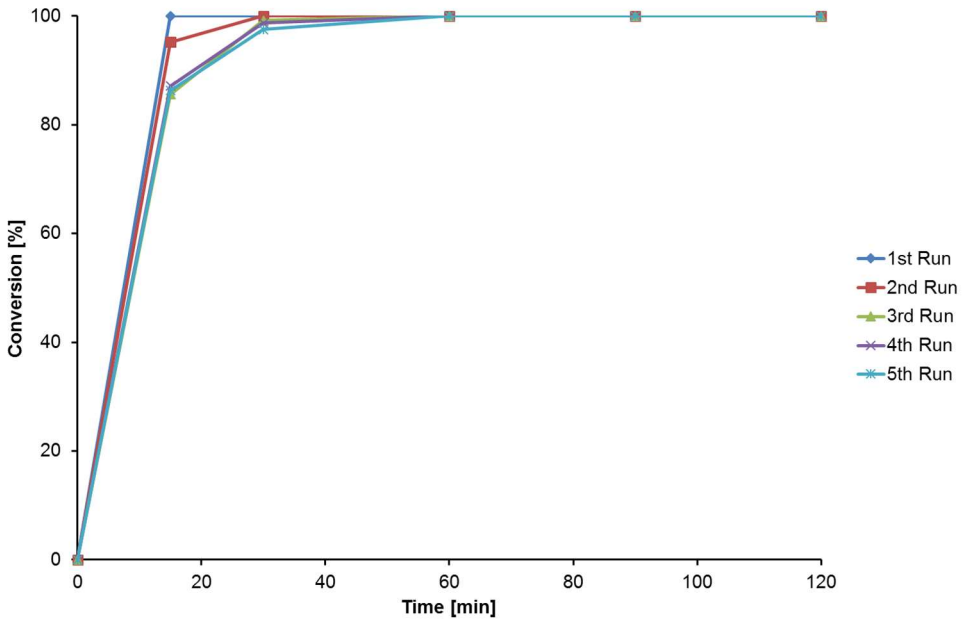


Figure B-25: Conversion vs. time for the synthesis of 4-methylbiphenyl using $Ce_{0.79}Sn_{0.2}Pd_{0.01}O_{2-\delta}$ in five subsequent runs. Reaction conditions: 4-bromotoluene (0.7 mmol), phenylboronic acid (1.5. mol eq.), K_2CO_3 (1.5 mol eq.), 50 mg $Ce_{0.79}Sn_{0.2}Pd_{0.01}O_{2-\delta}$ (corresponding to 0.5 mol% Pd in the first run), 20 ml of ethanol/water = 7/3 v/v.

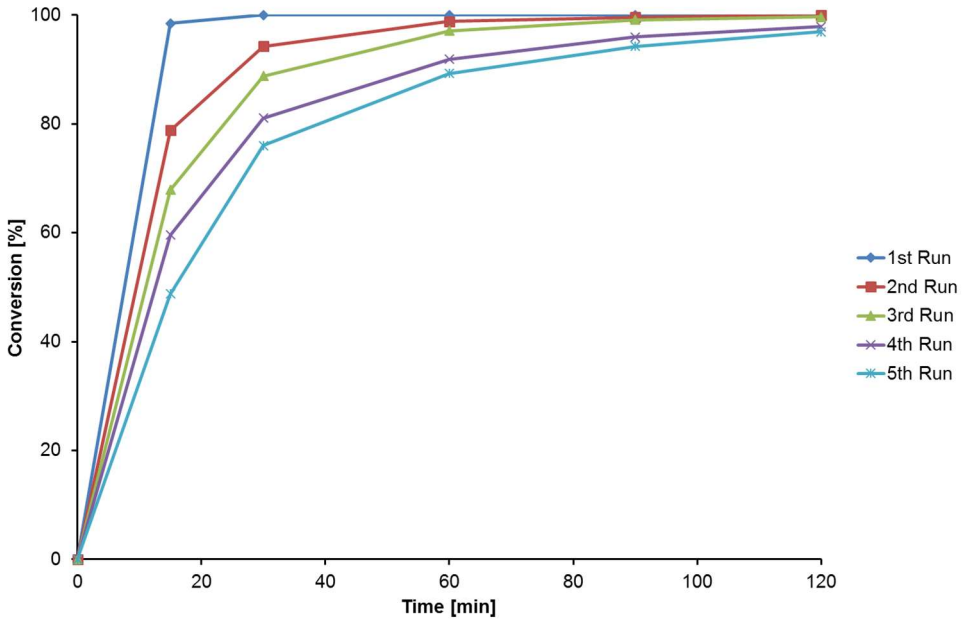


Figure B-26: Conversion vs. time for the synthesis of 4-methylbiphenyl using $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$ in five subsequent runs. Reaction conditions: 4-bromotoluene (0.7 mmol), phenylboronic acid (1.5. mol eq.), K_2CO_3 (1.5 mol eq.), 50 mg $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$ (corresponding to 0.5 mol% Pd in the first run), 20 ml of ethanol/water = 7/3 v/v.

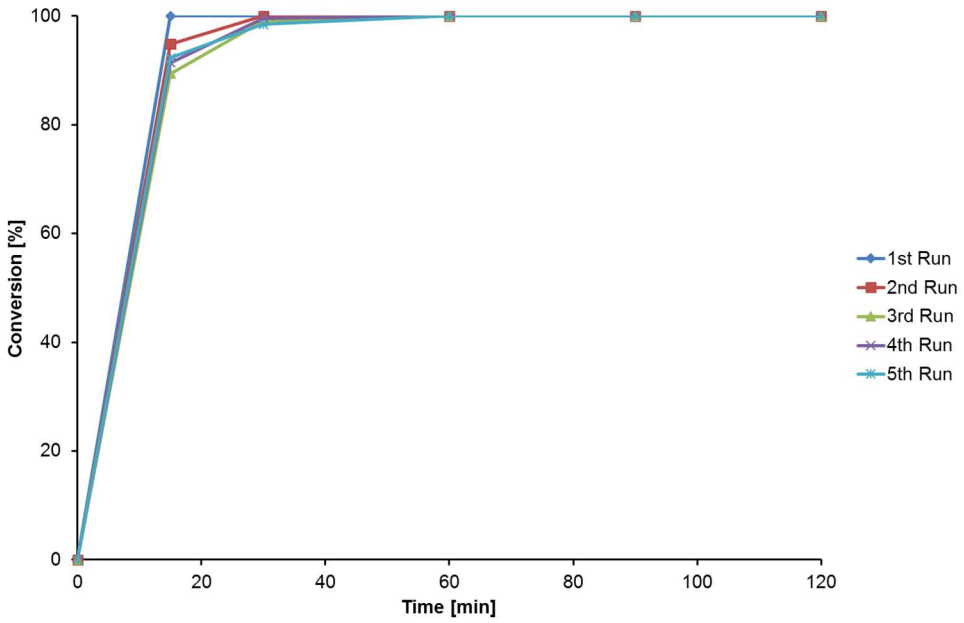


Figure B-27: Conversion vs. time for the synthesis of 4-methylbiphenyl using $Ce_{0.20}Sn_{0.79}Pd_{0.01}O_{2-\delta}$ in five subsequent runs. Reaction conditions: 4-bromotoluene (0.7 mmol), phenylboronic acid (1.5. mol eq.), K_2CO_3 (1.5 mol eq.), 50 mg $Ce_{0.20}Sn_{0.79}Pd_{0.01}O_{2-\delta}$ (corresponding to 0.5 mol% Pd in the first run), 20 ml of ethanol/water = 7/3 v/v.

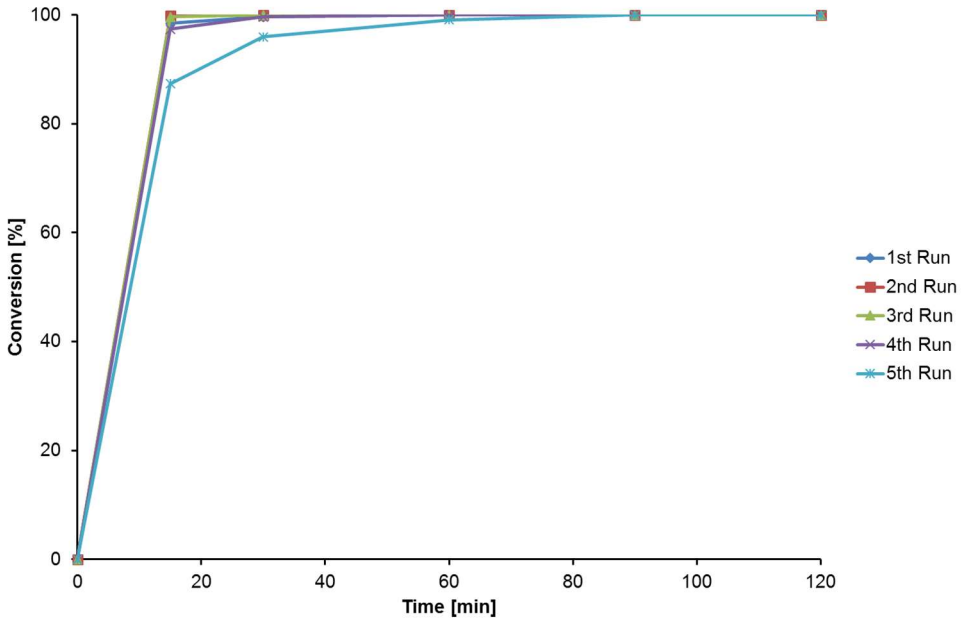
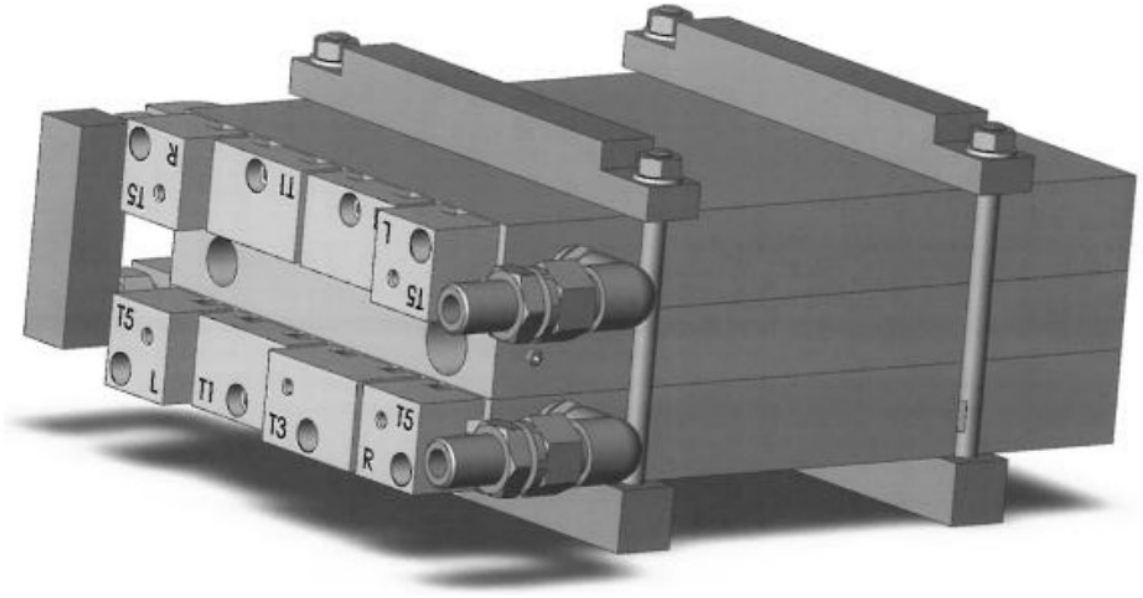


Figure B-28: Conversion vs. time for the synthesis of 4-methylbiphenyl using $Sn_{0.99}Pd_{0.01}O_{2-\delta}$ in five subsequent runs. Reaction conditions: 4-bromotoluene (0.7 mmol), phenylboronic acid (1.5. mol eq.), K_2CO_3 (1.5 mol eq.), 50 mg $Sn_{0.99}Pd_{0.01}O_{2-\delta}$ (corresponding to 0.5 mol% Pd in the first run), 20 ml of ethanol/water = 7/3 v/v.

C The Plug & Play Reactor[3]



The so-called "Plug & Play Reactor" is a novel reaction device with exchangeable reaction segments as well as modules for heating/cooling and mixing. The performance of the reactor is demonstrated with two model processes: the production of acetylsalicylic acid with a fixed-bed of commercial ion-exchange particles, and a Suzuki-Miyaura cross-coupling with a solid Pd-catalyst developed by us. The reaction progress was monitored by inline UV/Vis spectroscopy and compared with offline HPLC. The novel set-up leads to quantitative yields and selectivity as well as to an improved practicability of the processes. Thus, the Plug & Play reactor is an attractive alternative to existing batch processes.

[3] This chapter is taken in large parts from a journal article by Lichtenegger *et al*. in Chemie Ingenieur Technik (G.J. Lichtenegger, V. Tursic, H. Kitzler, K. Obermaier, J.G. Khinast, H. Gruber-Wölfler, "The Plug & Play Reactor: A Highly Flexible Device for Heterogeneous Reactions in Continuous Flow", accepted on Jul 1, 2016)

1 Introduction

Chemistry in flow has gained a lot of interest during the last two decades.[126] While continuous synthesis is standard in petrochemistry and food industry, the pharmaceutical industry still uses mainly batch processes. However, pharmaceutical manufacturing is currently transitioning towards continuous manufacturing in several areas,[2,16,127,128] also driven by the "PAT"[18] and several other initiatives of the FDA (Federal Drug Administration).[17] An interesting example in this context is the development of a continuous end-to-end manufacturing plant for the preparation of Aliskiren by the Novartis-MIT Center for Continuous Manufacturing.[13,14] All intermediate synthetic steps, separations, crystallizations, drying and formulation of the final pharmaceutical product are performed in a single integrated, fully continuous process.

In addition to numerous scientific publications claiming new and efficient systems for continuous flow chemistry,[129] many commercial set-ups have been developed.[16,130,131]

Although these systems have many advantages, we desired a reactor that (i) allows the straightforward testing of the heterogeneous catalysts prepared in our lab with particle sizes of 10 - 1000 µm, (ii) can be easily implemented in existing (industrial) pharmaceutical and fine chemical reaction and purification processes, (iii) is very compact and small but still able to produce enough amount for at least clinical trials and (iv) allows a flexible and modular setup that can be easily modified to react within a short time to the changing demands of the market.

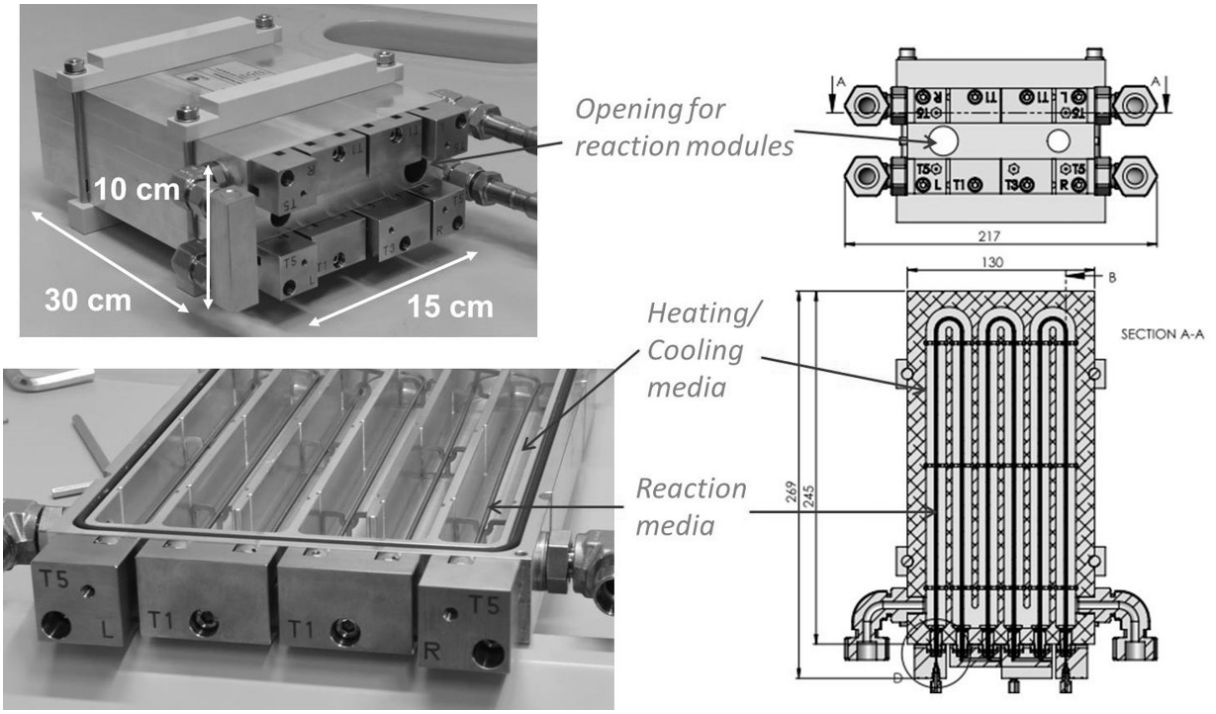


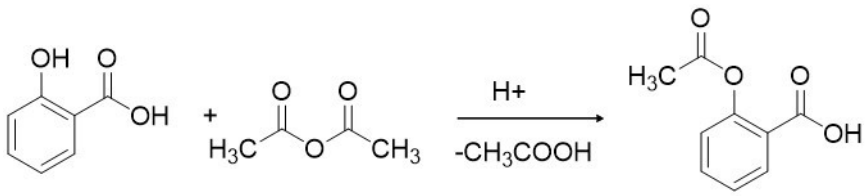
Figure C-1: Picture and scheme of the plug & play reactor.

Therefore, we developed the so called "plug & play" reactor (Figure C-1). This device includes commercially available HPLC columns as the reaction modules. The HPLC columns

are filled with catalyst particles to act as fixed bed reactors. With this approach, the packing of the catalysts is as simple and straightforward as possible and no extra catalyst cartridge systems are necessary. Additionally, it is possible to increase the catalyst amount and thus the residence time by connecting several filled HPLC columns within the reaction module. The HPLC columns and thus the catalyst can also be simply removed and exchanged as a whole. The regeneration of the catalyst or the setup of a new reaction is possible without any contamination of the new reaction components. Additionally, HPLC columns are safe to use for high temperature and high pressure applications. Similar set-ups using HPLC columns packed with catalyst material were used for heterogeneous continuous flow reactions by several other researchers. Examples include biocatalysis[132] and organocatalysis[133,134] in flow, heterogeneous catalysis in microreactor technology[135] and cross-coupling reactions,[136,137] just to name a few.

The upper performance limits of the plug & play" reactor are 200°C and 40 bar, however, this is mainly due to the sealing material. Nevertheless, gas/solid, liquid/solid, as well as gas/liquid/solid reactions are possible in the reactor. The tubes for the reaction media (1 mm inner diameter) are embedded in the channels that are filled with the heating/cooling media in order to allow rapid heat transfer. In these pipes, the mixing of the reaction media takes place and can be intensified by using tubes with periodic arranged narrowings to increase turbulence.[138] Thus, no external mixing device is needed, which leads to a high compactness of the "plug & play" reactor. We present here results obtained with two heating modules and one reaction module. With this set-up the dimensions of the plug & play reactor are 10 cm x 15 cm x 30 cm. However, it can be easily extended just by numbering up the reaction modules and the heating/cooling modules.

The flexibility and applicability of the plug & play reactor was tested using two different reactions. A typical reaction set-up used for these reactions is shown in Figure C-2. The first reaction involves the esterification of salicylic acid with acetic anhydride to produce acetylsalicylic acid (Scheme C-1).



Scheme C-1: Reaction of salicylic acid with acetic anhydride to produce acetylsalicylic acid.

While the common esterification protocol includes the use of H_2SO_4 or H_3PO_4 as catalysts,[139] we used a bed of commercially available ion exchange gels (Amberlite 120 IR and Amberlyst 15, both in hydrogen form) for the catalytic conversion. These gels are strongly acidic cation exchange polystyrene/styrene-divinylbenzene resins with sulfonic acid

functionality and a particle size of 620-830 µm (Amberlite 120 IR) and ~ 300 µm (Amberlyst 15).

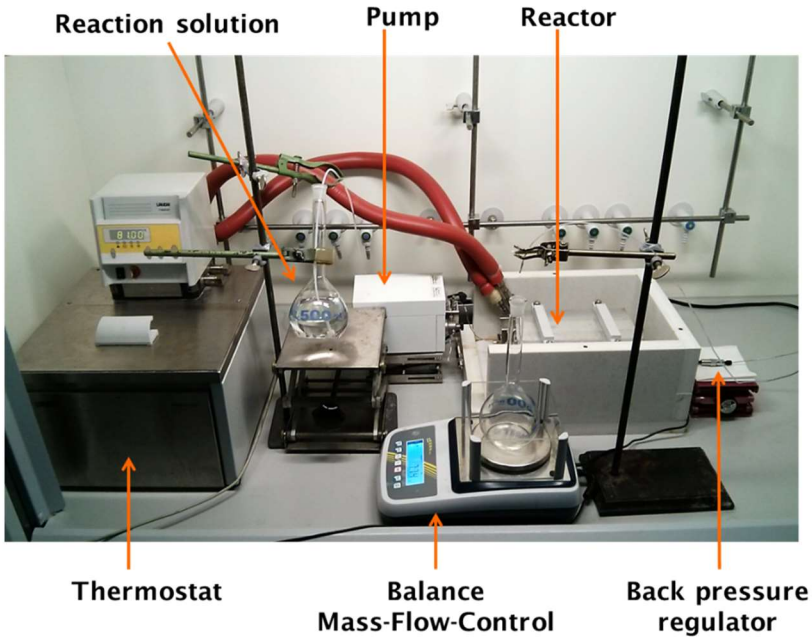
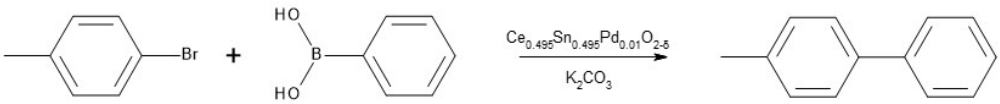


Figure C-2: Picture of the typical reaction set-up.

The second reaction involved the Suzuki-Miyaura coupling[44,59] of 4-bromotoluene with phenylboronic acid (Scheme C-2). This type of reaction was chosen as it is one of the most successful strategies for C-C bond formation.



Scheme C-2: Suzuki-Miyaura reaction of 4-bromotoluene with phenylboronic acid.

Furthermore, due to the high stability of the organoboron reagents, the ease of preparation, the low toxicity and the importance of the produced biaryls for pharmaceuticals and liquid crystals, this reaction has become part of the standard toolbox of organic chemists. The importance of the reaction is also reflected by the fact that one of the inventors, Akira Suzuki, was awarded with the Nobel Prize in chemistry in 2010. Although these reactions are that important, they have been carried out mostly in batch processes. However, with the upcoming microfluidic technology, more and more examples were published presenting continuous flow techniques for these important organic syntheses.[21,140]

A large number of heterogeneous catalysts for cross-coupling reactions was published and investigated concerning their leaching behaviour and heterogeneity.[20,5,74,76,82,125] We used palladium-substituted mixed cerium-tin-oxides (general formula $Ce_{0.99-x}Sn_xPd_{0.01}O_{2-\delta}$ with x = 0, 0.2, 0.495, 0.79 and 0.99) as inorganic, heterogeneous ligand free catalysts for the Suzuki-Miyaura cross coupling reactions (Scheme C-2).[125]

The reaction progress of both reactions was monitored using inline UV/Vis spectroscopy. UV/Vis spectroscopy was chosen because it has a high sensitivity and a high applicability with relatively low investment costs compared to NIR and Raman. Furthermore, the inline analysis allows fully automated monitoring of the continuous process with real-time data to facilitate the process understanding and to increase product quality. To validate the UV/Vis results the data was compared with offline HPLC analyses. For this purpose, the UV/Vis data was processed using the Classical Least Square (CLS) method as well as the method of simultaneous equation. The comparison of these data with offline HPLC analyses is also shown in the following (Figure C-3 and Figure C-6).

2 Results and Discussion

2.1 Heterogeneous Esterification – Synthesis of Acetylsalicylic Acid in Continuous Flow

The obtained yield of acetylsalicylic acid (ASA) using the catalyst Amberlyst 15 hydrogen form is shown in Figure C-3. A stable process with a yield of ~ 98% was obtained for at least 24 h after 30 min. With the used setup an ASA production of ~ 80g/d would be possible.

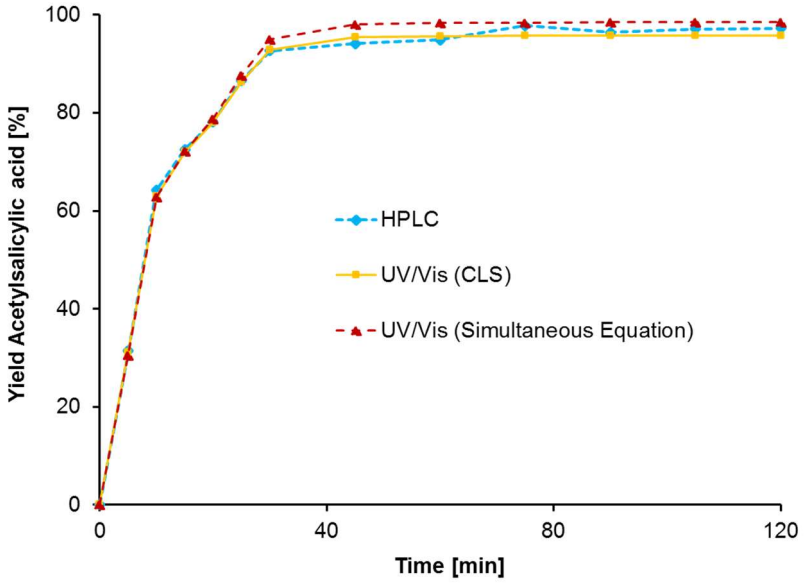


Figure C-3: Yield of acetylsalicylic acid and comparison of the data obtained with the inline UV/Vis measurement and with offline HPLC. The reaction was carried out with 0.4 mol/L salicylic acid and 0.55 mol/L acetic anhydride in ethyl acetate at 60°C with a flow rate of 1 mL/min using 1 g of Amberlyst 15 as catalyst.

The first experiments were carried out using the cation exchange gel Amberlite IR120 in hydrogen form. However, high back pressures with up to 40 bar (which is the limit of the plug & play reactor) and low yields were obtained with this catalyst. The reason for that might be particle swelling due to the organic solvents, which was also investigated theoretically.[141] Therefore, we used the catalyst Amberlyst 15 hydrogen form for further experiments.

In addition to analyzing the reaction solution offline using HPLC, we also succeeded in the implementation of a UV/Vis system to monitor the reaction progress inline. The comparison of the data obtained by CLS fitting in the wavelength range λ = 269-296 nm with HPLC measurements yielded a mean deviation of only 1.03% and maximum deviation of 2% (Figure C-3). The comparison of UV/Vis-data obtained using the simultaneous equation method with HPLC measurements led to a slightly higher deviation of ~ 4%. Nevertheless, the results clearly indicate that the inline UV/Vis spectroscopy is a powerful method to monitor this kind of reactions in real-time.

2.2 Continuous Suzuki-Miyaura Reaction

For the continuous Suzuki-Miyaura reactions the reaction modules were filled with the catalyst $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-x,}$ which was prepared using the solution-combustion method.[125] Similar catalysts were proven to be highly active in batch Mizoroki-Heck cross-coupling reactions.[115]

The reactants were added as a mixture in a solution of ethanol and water. After an inductive phase of ~ 30 min a stable process with > 99% yield for up to 36 h was obtained with this system (Figure C-4). Although it is well known that Suzuki-Miyaura reactions tend to form also byproducts by homocouplings,[4,50] we were able to receive a selectivity of > 99.5 % over the complete reaction time (Figure C-4). The yield of the usual byproduct biphenyl is lower than 1 % and the amount of 4,4'-dimethylbiphenyl is below the quantitation limit (< 0.2 % yield) of the HPLC analysis.

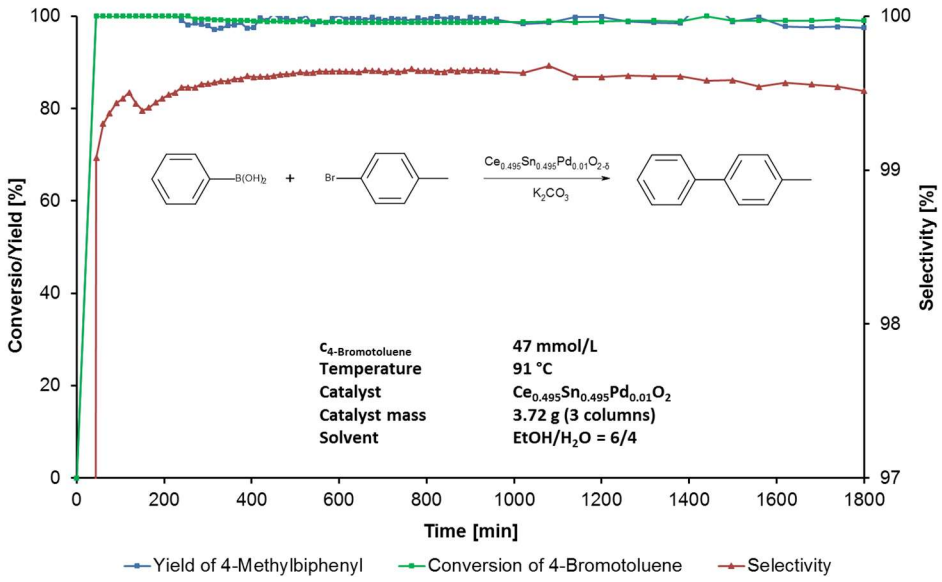


Figure C-4: Typical results for the Suzuki-Miyaura reaction of 4-bromotoluene with phenylboronic acid in EtOH/H_2O 6/4 with 3.7 g catalyst $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$ (= 25 mg; 1.1 mol% Pd). Volume flow: 0.25 ml/min, Temp.: 91°C.

The influence of the mass flow and temperature on the yield of 4-methylbiphenyl is shown in Figure C-5. It can be seen that the reaction system responds within minutes to the change of the parameters. As expected, an increasing flow rate, as well as a decreasing temperature, leads to decreasing reaction yields.

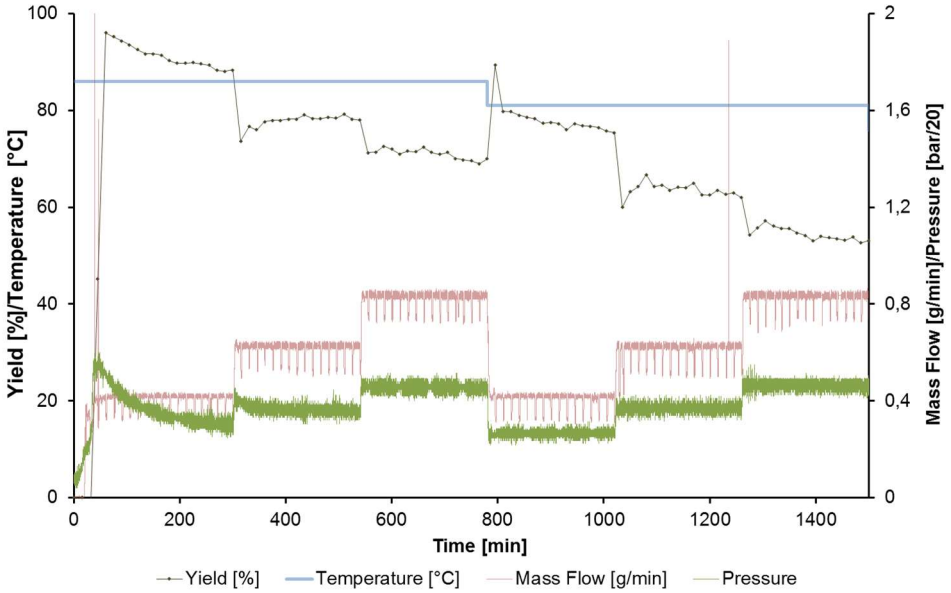


Figure C-5: Influence of the reaction parameters on the yield of the Suzuki-Miyaura reaction of 4-bromotoluene with phenylboronic acid in EtOH/H_2O 7/3, with 2.4 g catalyst $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$ (= 16 mg; 0.35 mol% Pd). The fluctuations in the mass flow are due to the sampling for HPLC analysis.

The particle size of the catalyst is 34 µm (x_{10} = 5.5 µm, x_{50} = 33.8 µm, x_{90} = 189.4 µm). Although this particle size is relatively small, the back pressure in the fixed bed was no issue. Depending on the reaction parameters, the pressure was below 15 bar (Figure C-5 and Figure C-6). The increase of the catalyst amount, which also includes an increase of retention time, is straightforward and leads to the expected increase of productivity: With one filled column (= 1.25 g ± 0.05 g catalyst including 8.3 mg Pd) an average yield of ~51 % could be obtained, with two filled columns (= 2.4 g catalyst including 24.9 mg Pd) ~ 72% yield. Three filled columns (= 3.75 g catalyst including 37 mg Pd) led to a conversion of > 90%. The residence time in each column was 4 min.

In addition to a high productivity and selectivity, the contamination of the product with leached metal is an important parameter.[74] We carried out ICP/MS measurements to analyze the metal content in the crystalline product over time and found that the Pd content is 3 ppm.

Finally, we also succeeded in the inline monitoring of the reaction progress by the UV/Vis set-up. Comparison of the data, obtained by CLS fitting in the wavelength range λ=239-279 nm, with HPLC measurements yielded mean deviation of 1.91 % and maximum deviation of 5.6 %. Furthermore, it can be seen in Figure C-6 that the UV/Vis system reacts very fast to the reaction parameter variations. Thus, this system is also highly applicable for the inline measurement of continuous Suzuki-Miyaura reactions.

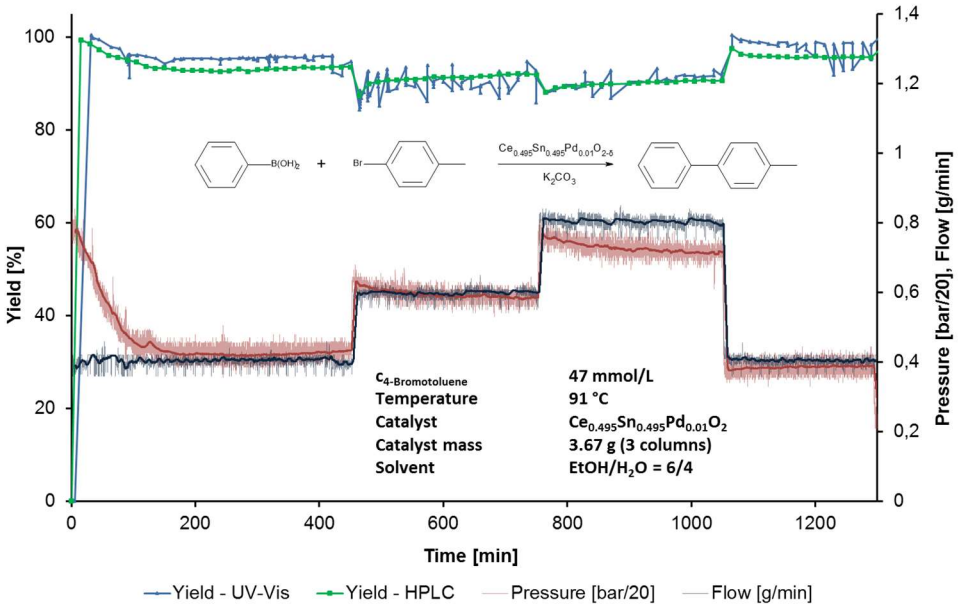


Figure C-6: Comparison of UV/Vis data with HPLC results. Suzuki-Miyaura reaction of 4-bromotoluene with phenylboronic acid in EtOH/H_2O 6/4, with 3.7 g catalyst $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$ (= 25 mg; 0.65 mol% Pd), T = 91°C. The fluctuations in the mass flow are due to the sampling for HPLC analysis.

3 Conclusion

The so-called “plug & play reactor” was tested to be a flexible and versatile tool for different reactions involving heterogeneous catalysts. The flexibility of the novel reaction set-up was tested for the continuous synthesis of (i) acetylsalicylic acid via a heterogeneous esterification and (ii) 4-methylbiphenyl via a heterogeneous Suzuki-Miyaura reaction. Both reactions proved to give stable processes over > 24 h and produced 80 g/d ASA and ~ 10 g/d 4-methylbiphenyl, respectively. For the Suzuki-Miyaura reaction the obtained selectivity was >99% and the Pd amount in the product was only 3 mg/kg, which is below the critical amount for Pd in oral pharmaceuticals.[69,76] It could be shown that the reaction set-up responds within minutes to changes of the process parameters. All in all, such stable and successful processes would be a key to implement continuous processes in the preparation of pharmaceutical and fine chemical intermediates.

Future research will concentrate on the implementation of other interesting reactions in the plug & play set-up as well as on the coupling of the reaction device with integrated continuous work-up processes, such as crystallization.

4 Experimental

Figure C-1 shows the plug & play reactor with two modules for the heating/cooling media at the top and the bottom of the reactor. The reactor includes the opening for the exchangeable reactions modules. In these openings commercially available HPLC columns filled with

heterogeneous catalysts are inserted. The volume and size of the HPLC columns (L x D: 40 mm x 8.0 mm) was calculated using kinetic data obtained via batch experiments.

A typical reaction set-up is shown in Figure C-2. The reactions mixtures were pumped through the plug & play reactor with a HPLC pump (Knauer, Azura P4.1 S) using different mass flows. With this pump the system pressure was monitored. The mass flow was observed using a Kern balance (EWJ 600 -2M) connected via a RS-232 to a PC. The data for the mass flow and the system pressure was acquired using the software Labview. The reactor was heated with a Lauda P18 Proline thermostat. Temperature was monitored using a K-type thermocouple attached to the outside of the HPLC column.

Offline HPLC analysis was carried out with an Agilent 1100 Series HPLC with a Poroshell 120 EC-C18 column. The mobile phase for HPLC analyses was ultrapure water, methanol (>99.9%, Roth) and orthophosphoric acid (>85%) 300:200:1 (v:v:v) for the esterification reaction and 200:300:1 (v:v:v) for the Suzuki-Miyaura cross coupling reaction, respectively. Detection was carried out with a UV/Vis spectrometer. Anisole (99%, Aldrich) was used as internal standard.

ICP-MS measurements were performed with an Agilent 7500ce ICP-MS after microwave assisted acidic digestion of the samples.

4.1 UV/Vis Measurements[4]

Inline UV/Vis spectroscopy was carried out using a STARNA flow cell (584.4.-Q-0.01) with 0.01 mm light path, two fiber optic cables with 400 µm (PC-UV400) and a cuvette holder CUV-UV/Vis. The spectrometer used was an AvaSpec-ULS2048, an AvaLight-DS was used as the light source. The data was collected with the AvaSoft-Full software. A picture of the set-up is shown in Figure C-7.

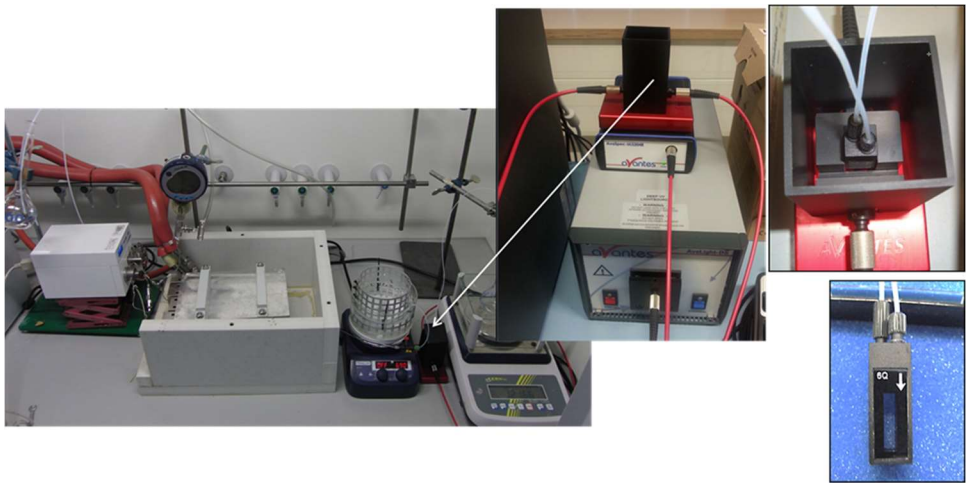


Figure C-7: Picture of the UV/Vis Flow cell coupled to the reactor set-up.

[4] UV-Vis measurements were developed by Mr. Vitan Tursic, B.Sc., within the Plug & Play project in the course of his diploma thesis.

The calibration set-up was designed similar to the set-up for reaction monitoring in order to provide uniform conditions of analysis for both set-ups. Calibration mixtures were pumped through the UV/Vis flow cell with a HPLC pump (Knauer, Azura P4.1 S) at a constant flow rate of 1 ml/min. To guarantee isothermal measurement conditions, a PTFE tube (for lower temperatures) or a stainless steel tube was assembled between the pump (and the reactor outlet for the reactions) and the flow cell. The tube was fitted into a water bath that was kept to the appropriate temperature (25°C or 84°C)

4.1.1 Esterification

4.1.1.1 Calibration

For the calibration 24 acetylsalicylic acid (ASA) and salicylic acid (SA) single component mixtures were prepared in ethyl acetate (EtOAc) in concentration range from 0.0052 - 0.4 M ASA and from 0.0089 - 1.3028 M SA. To obtain a constant signal for each acquisition, we removed previous sample residuals by pumping 15 ml of single component mixture through the calibration set-up. Acquisition was performed against pure EtOAc. The integration time was optimized to 1s, in average 2000 spectra were recorded. Typical spectra of ASA and SA are shown in Figure C-8.

To determine extinction coefficients 18 single component mixtures were selected. This was done to reach best linear relationship between absorbance and concentration.

For the simultaneous equation method wavelengths at the SA maximum (λ=306.103 nm) and ASA maximum (λ=276.218 nm) and for the CLS method wavelength range 257 - 312 nm were selected. The range for the CLS method was than further optimized by comparison of the analyses in flow with HPLC analyses. For validation purposes 6 multicomponent synthetic mixtures of SA and ASA were used.

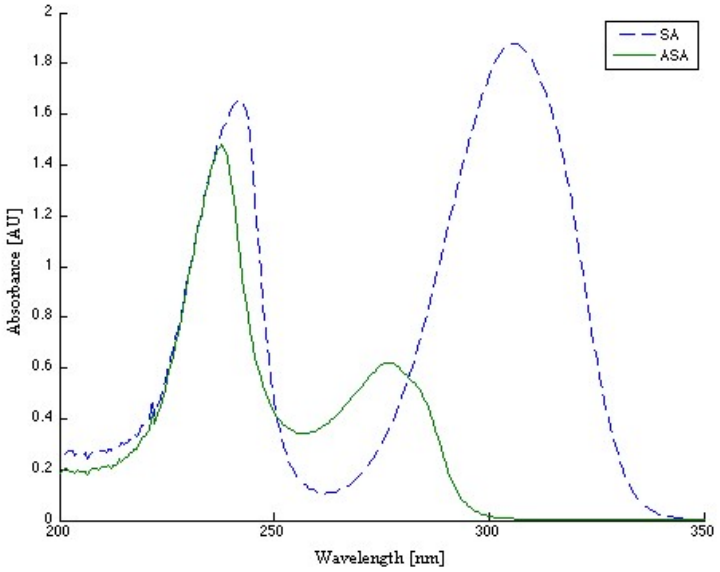


Figure C-8: UV spectra of acetylsalicylic acid (ASA) and salicylic acid (SA).

4.1.1.2 Analyses in Flow

For the inline analysis in flow the same parameters as for the calibration experiments were used (integration time 1s, in average 2000 spectra were recorded). The wavelength range of λ = 269-296 nm was used for the comparison of the data with HPLC measurements. The obtained data is shown in Figure C-9.

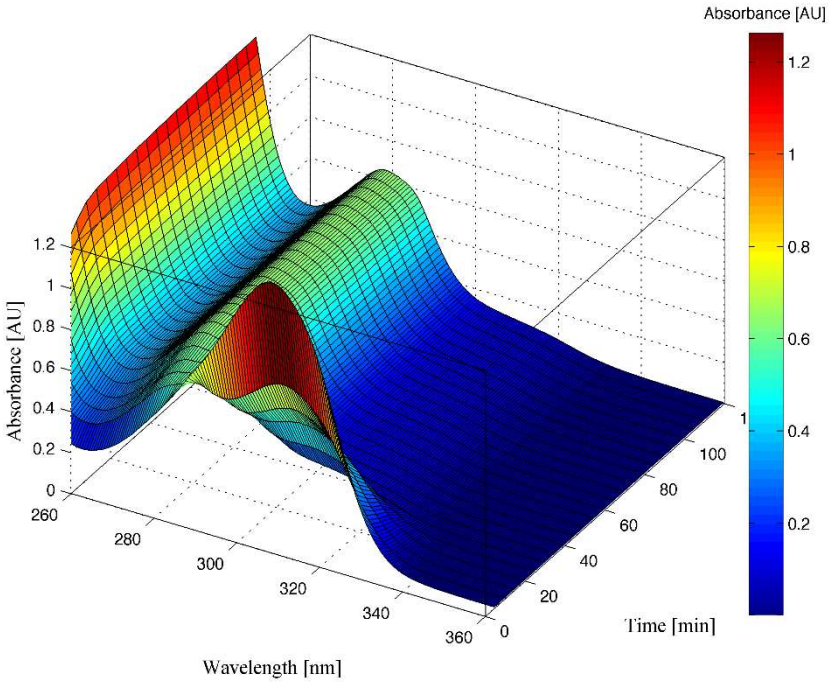


Figure C-9: Data acquired during the continuous synthesis of ASA by in-line UV-Vis spectroscopy. The reaction was carried out with 0.4 mol/L salicylic acid and 0.55 mol/L acetic anhydride in ethyl acetate at 60°C with a flow rate of 1 mL/min using 1 g of Amberlyst 15 as catalyst.

4.1.2 Suzuki-Miyaura Reaction

4.1.2.1 Calibration

For the calibration 27 calibration single component solutions were prepared. Typical spectra are shown in Figure C-10. The components were dissolved in EtOH/H_2O 60/40 (v/v) solutions and the single component measurements were carried out at water bath temperature kept at 84°C to determine extinction coefficients (Figure C-11). The integration time was 1.7s, in average 2000 spectra were recorded. Analyses in flow at 30°C showed that the components tend to crystallize in the flow cell at lower temperatures. Thus, to ensure constant temperature inside the cuvette holder in the range of 65°C-70°C while water bath was kept at 84°C.

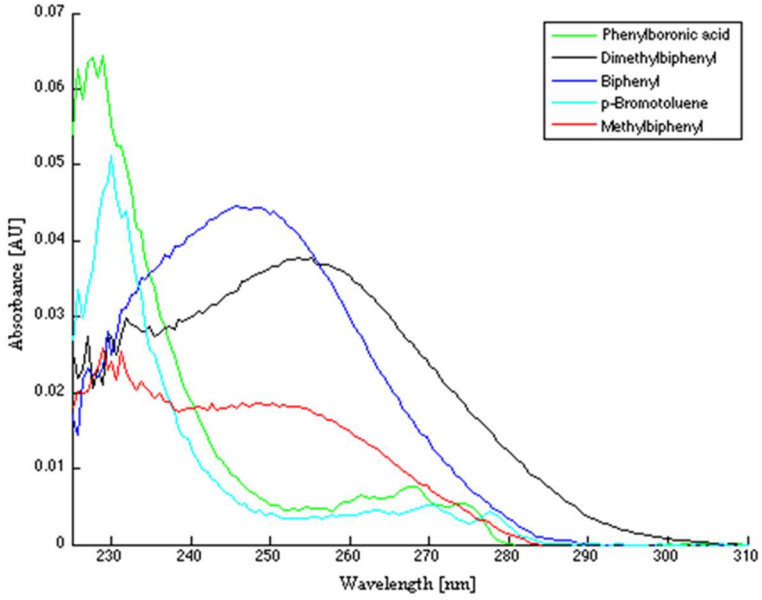


Figure C-10: Spectra of the components of the Suzuki-Miyaura reaction.

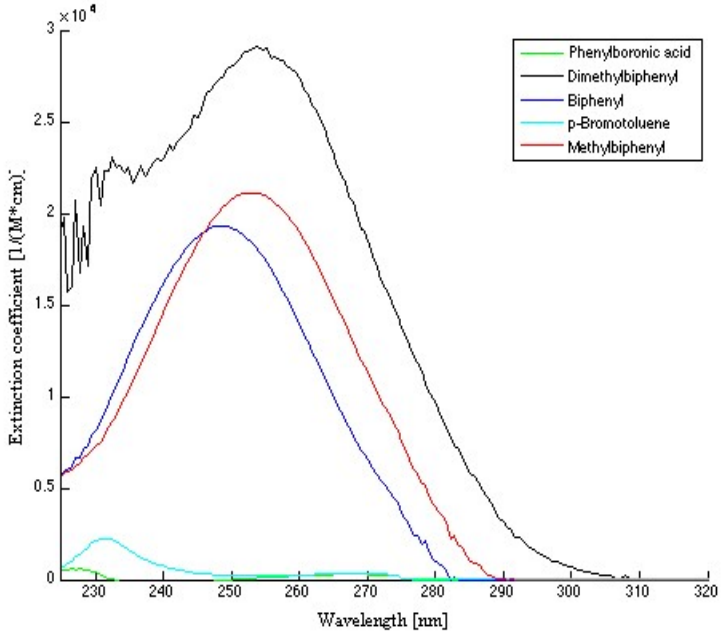


Figure C-11: Extinction coefficient [1/(M*cm)] vs. wavelength [nm].

4.1.2.2 Analyses in Flow

For the inline analysis in flow the same parameters as for the calibration experiments were used (integration time 1.7s, in average 2000 spectra were recorded). To compare the UV/Vis data with the HPLC data the wavelength range 239-279 nm was used. Due to significant baseline drift of measured spectra, we used a one-point (325.78 nm) baseline correction (Figure C-12).

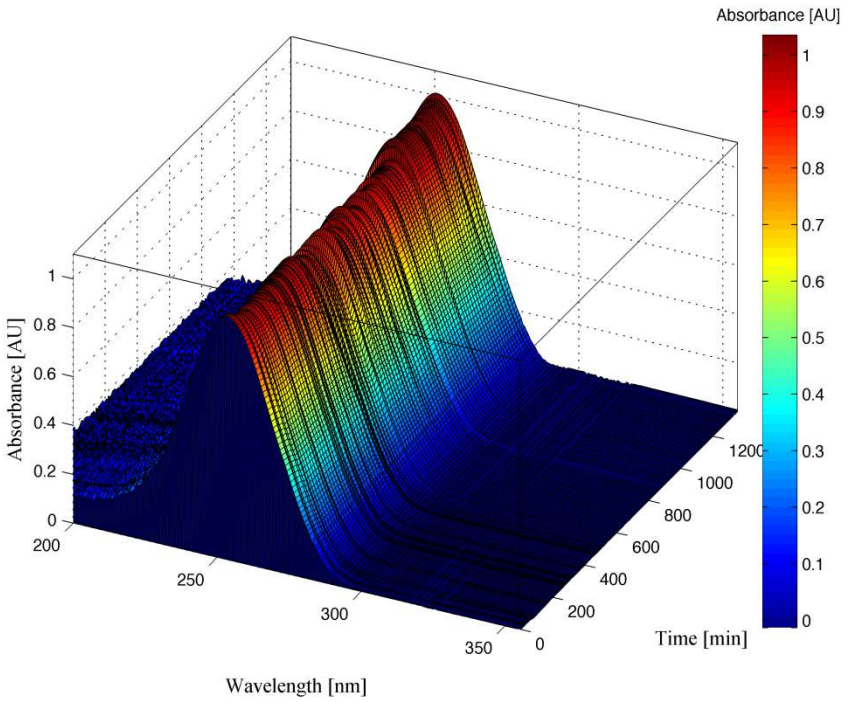


Figure C-12: UV/Vis data including baseline correction acquired for the continuous Suzuki-Miyaura reaction of 4-bromotoluene with phenylboronic acid in EtOH/H2O 6/4, with 3.7 g catalyst Ce0.495Sn0.495Pd0.01O2- δ (= 36 mg; 0.93 mol% Pd), reaction temperature = 91°C.

4.2 Heterogeneous Esterification – The Synthesis of Acetylsalicylic Acid in Continuous Flow

A solution of 0.06 mol (8.287 g) salicylic acid (≥99 %, Sigma-Aldrich) and 1.5 mol-equivalent (8.50 ml; regarding to salicylic acid) of acetic anhydride (≥99 % Roth) in 200 ml ethyl acetate (>99.5 % Roth) were used. The reaction solution was pumped through the preheated tube at 70 ºC and was then pumped through the reactor, with the HPLC column filled with 1.116 g of the catalyst Amberlyst 15 (hydrogen form, Aldrich).

4.3 Continuous Suzuki-Miyaura Reaction

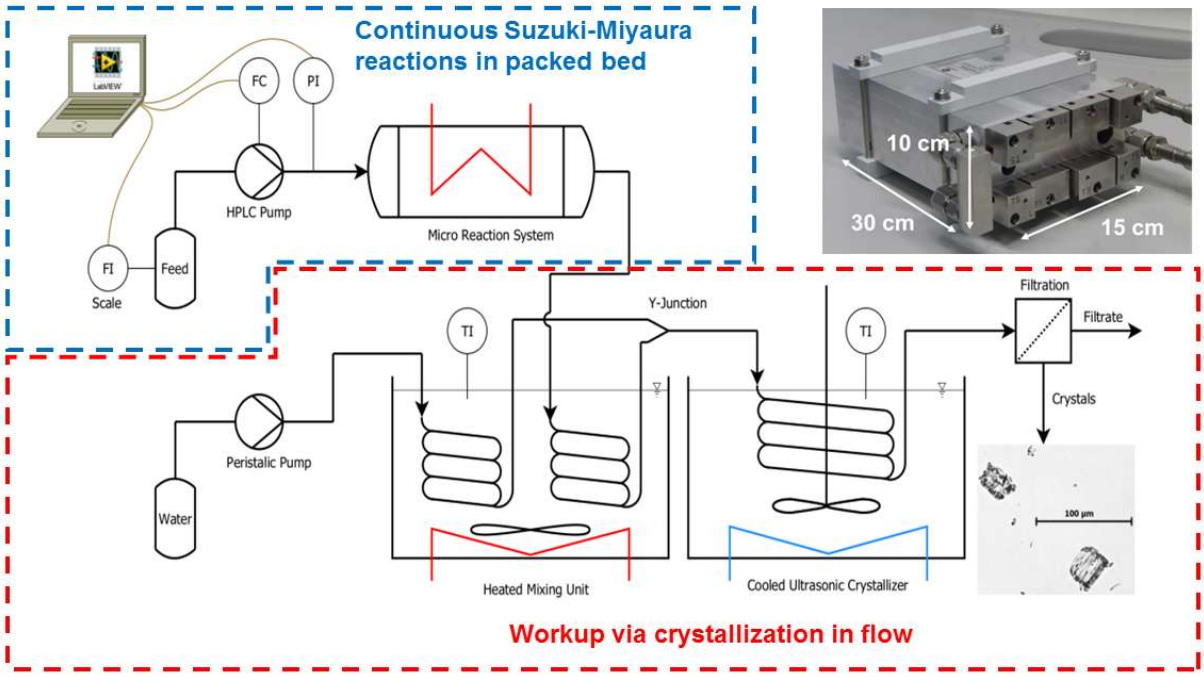
For a typical Suzuki-Miyaura reaction 8 g/L (= 0.035 mol/L) 4-bromotoluene (98%, Aldrich) were mixed with 1.5 mol equiv. phenylboronic acid (>97%, Fluka) and 1.5 mol equiv. potassium carbonate (99.9%, Roth) in EtOH/H_2O 6/4 or 7/3 (v/v). Absolute EtOH (ACS, Reag. Ph. Eur.) was purchased from VWR.

For the preparation of 3 g $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$, 5.051 g ammonium cerium(IV) nitrate ($(NH_4)_2Ce(NO_3)_6$, Sigma Aldrich), 1.905 g tin(II) oxalate (SnC_2O_4, Aldrich), 0.033 g palladium(II) chloride ($PdCl_2$, Aldrich) and 3.397 glycine (fuel, $C_2H_5NO_2$, Sigma) were dispersed in 2 ml of water in a borosilicate dish with 600 ml capacity.

The redox mixture was heated in a muffle furnace at 350°C. The mixture ignited within less than 5 minutes, initiating a self-propagating combustion reaction, which yielded a voluminous, porous solid. This solid was grinded with mortar and pestle and was heated to 350 °C for

another 5 hours. After that procedure, the solid was directly usable as catalyst for the Suzuki-Miyaura cross-coupling reactions.

D Continuous Suzuki-Miyaura Reactions with Novel Ce-Sn-Pd-Oxides and Integrated Crystallization as Continuous Downstream Protocol[5]



An integrated process including continuous flow syntheses directly coupled to product isolation via continuous crystallization is presented. For the synthesis part, $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$ was used as heterogeneous catalyst in a custom-made packed-bed reactor (the so called "Plug-and-Play Reactor") for continuous Suzuki-Miyaura cross-couplings of various para- and ortho-substituted bromoarenes with phenylboronic acid using environmentally friendly aqueous ethanolic mixtures as reaction solvents. The reactions were stable for up to 30 hours without any detectable catalyst deactivation. The desired biaryl-products were obtained in gram scale with good to excellent yields and high selectivity. For three methyl-, ketyl- and nitrile-functionalized biphenyls product isolation was done using water as anti-solvent in an integrated crystallization process as continuous downstream protocol. The desired products could be isolated with high purity and with yields of up to 95 % for the overall process.

[5] This chapter is taken in large parts from a journal article by Lichtenegger *et al*. in Journal of Flow Chemistry (G.J. Lichtenegger, M.Maier, J.G. Khinast, H. Gruber-Wölfler, "Continuous Suzuki-Miyaura Reactions with Novel Ce-Sn-Pd-Oxides and Integrated Crystallization as Continuous Downstream Protocol", accepted on Jun 17, 2016)

1 Introduction

We present here a novel continuous set-up for an integrated synthesis-crystallization process in flow. In particular, continuous Suzuki-Miyaura reactions were carried out in a packed bed reactor and the product isolation was done by continuous anti-solvent crystallization. Continuous crystallization is a common unit operation for the purification of organic compounds because of its high efficiency, and the low capital and operational costs.[142] In addition to large-scale batch and continuous crystallizers, numerous small scale semi-batch and continuous set-ups with high-intensity mixers and impeller jets have been reported in literature.[143] Furthermore, particle formation in flow-through devices with inner diameters of few centimeters, have been published. Our group published several studies focusing on the controlled growth of crystals by selecting precise cooling trajectories in continuous flow crystallizers.[142–145]

The coupling of a chemical reaction in flow with a continuous purification is a step further in the development of completely continuous end-to-end manufacturing and has become more and more popular in recent years.[15,146] Probably the most well-known example is the work by the MIT-Novartis Center for the end-to-end manufacturing of the API aliskiren hemifumarate.[14]

In our work, $Ce_{0.495}Sn0_{.495}Pd_{0.01}O_{2-\delta}$ was used as heterogeneous catalyst in a custom-made packed-bed reactor (the so-called “Plug & Play Reactor”) for continuous Suzuki-Miyaura cross-couplings of various *para* and *ortho*-subsituted bromoarenes with phenylboronic acids. The synthesis set-up was directly coupled to a continuous crystallization process to obtain the crystalline products with high purity.

Palladium substituted cerium and mixed cerium-tin oxides can be prepared by the solution combustion technique.[123] Using this method, palladium substituted ceria and ceria composites can be synthesized at the gram scale, out of inexpensive precursors, in an easy and rapid manner (within a few hours) with standard laboratory equipment and without specialized working techniques. Furthermore, due to the homogeneous mixing of the catalyst precursors at the molecular level and the high combustion temperature (>900 °C)[118] this method guarantees high crystallinity, high purity, large specific surface areas and precise elemental and phase composition of the resulting mixed oxides.[119] Initially developed as catalysts for gas-phase oxidation reactions,[116] catalysts of this type also proved to be highly active and reusable ligand-free catalysts for Heck-type C-C coupling reactions.[115]

Palladium catalyzed cross-coupling reactions, used for the formation of carbon-carbon and carbon-heteroatom bonds, are an indispensable synthetic tool for organic chemists and are widely used in the production of fine chemicals, APIs and agrochemicals.[97,147,148] Among the different types of cross-coupling reactions, the Suzuki-Miyaura reaction is by far the most popular reaction in terms of publications and patents.[1] Initially published by Miyaura and Suzuki in 1979,[39] this reaction involves the coupling of organoborons with organic halides, catalyzed

by palladium and with the aid of an adequate base. To benefit from the numerous advantages of heterogeneously catalyzed processes, especially the easy separation of the palladium containing catalyst from the reaction solution, a high number of heterogeneous catalysts has been developed and applied in Suzuki-Miyaura cross coupling reactions.[91] Commonly used solid supports for the immobilization of palladium on organically modified and ligand-free systems include silica, polymers beads, monolithic supports and PdEnCatTM.[140] Although many of these systems show good activity and recyclability when used in batch processes, such heterogeneous catalysts often suffer from rapid deactivation and significant palladium leaching into the solution when used in continuous flow packed bed reactors.[20] This phenomenon is attributed to a homogeneous mechanism of the cross-coupling reaction, involving soluble PdII-species during the oxidative addition step. The good recyclability in batch reactions is assigned to a re-adsorption of palladium on the solid support upon completion of the reaction (assuming the solid support as reservoir for catalytically active palladium).[74,120,121,76] Using continuous flow packed bed reactors, soluble palladium will migrate through the packed catalyst bed (as in chromatography), which leads to elution of palladium into the reaction solution, contamination of the product and finally to catalyst deactivation.[4,5] Hence, some authors propagate the use of homogeneous catalytic systems in continuous flow, combined with appropriate catalyst recycling strategies[149] or recirculating reactors[84] rather than packed bed flow reactors.[4,20,5] Nevertheless, Pandarus *et al*.[6] reported the use of Sol-Gel Entrapped SiliaCat DPP-Pd as suitable heterogeneous catalyst for Suzuki-Miyaura cross coupling reactions in a continuous packed bed reactor. In this study, continuous processes for the synthesis of unsymmetrical biaryls with moderate to high yields and low palladium-contents in the isolated product, which were stable for up to 40 hours, could be established. Thus, the realization of stable continuous processes using packed-bed reactors with heterogeneous palladium catalysts appears to be principally possible when the appropriate catalyst/solvent/base systems are used.

2 Results and Disussion

2.1 Continuous Flow Process Design

The continuous Suzuki-Miyaura reactions were carried out in the so-called “Plug & Play reactor” which was developed by us together with the company OneA engineering.[125,150] This novel reaction device (Figure D-1) includes all in all three modules arranged in a sandwich approach: at the bottom and the top two heating modules and in the middle the reaction module. The reaction module includes two openings in which commercial HPLC columns (L x D: 40 mm x 8.0 mm) filled with the catalyst particles were introduced.

The reaction mixtures were premixed and pumped through the reactor using a HPLC pump. First, the media was preheated in the heating modules. They include U-shaped tubes (1mm

inner diameter) that are embedded in six channels (Figure D-1, right) filled with thermostatic oil in order to allow a fast heat transfer. The reaction media enters then the catalyst bed in the HPLC columns via an isolated capillary that connects the heating module with the reaction modules (not shown in Figure D-1).

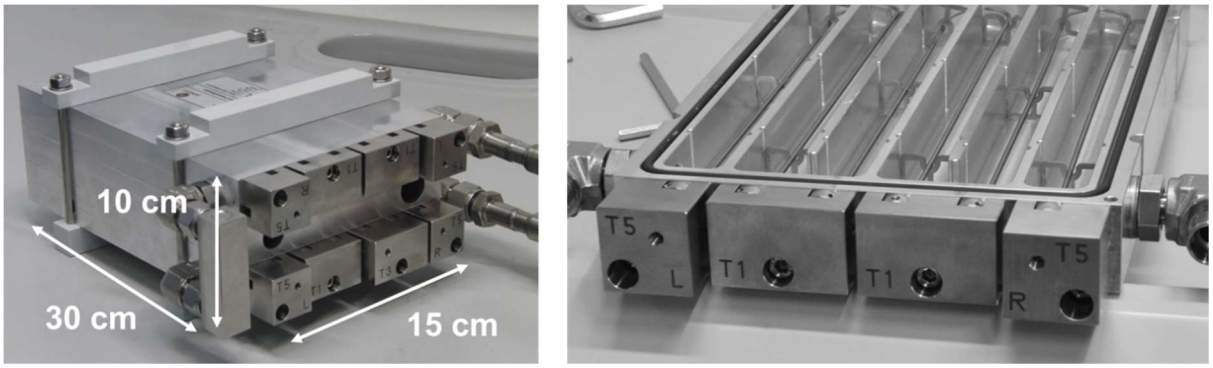


Figure D-1: Pictures of the "Plug & Play" reactor. Left: The reactor with the heating modules (top and bottom) and the reaction module in the middle. Right: Inner view of the heating modules that include U-shaped tubes in which the reaction media is preheated.

The use of the above described reaction setup allows a wide variation of reaction parameters. The HLPC pump allows flow rates of the reaction solution between 0.1 ml/min and (theoretically) 50 ml/min. The amount of catalyst can be adjusted to the desired synthesis by using larger HPLC-columns or by employment of multiple reaction modules in line. The reactor itself allows reaction temperatures of up to 200 °C and a pressure of up to 40 bar. Flow rates, temperature and the pressure inside the system were continuously monitored using the software LabView.

2.2 Continuous Suzuki-Miyaura Reaction

The continuous Suzuki-Miyaura reactions were carried out using a bed of the $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$ particles in the HPLC columns.

Figure D-2 (a) shows the reaction progress of 4-bromotoluene vs. time for the continuous synthesis of 4-methylbiphenyl using one reaction module (1.10 g catalyst) at a flow rate of 0.45 ml/min and a temperature of 86 °C. The conversion profiles using $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$ as catalyst in continuous flow generally show an initial phase, which is characterized by a rapid decrease of substrate conversion. After this initial phase, the process enters a phase of constant substrate conversion and product yield (with an average conversion of 50.6 % of 4-bromotoluene during the period between 120 – 930 minutes). The initial phase is also characterized by a visually recognizable, significant loss of palladium by leaching into the reaction solution. This was confirmed using ICP-OES analysis. As expected, the first fraction, deriving from the initial phase (120 minutes), showed a very high content of palladium (13.5 g/kg dried solid). However, the Pd-content of the fractions taken from the period of constant

conversion (120 – 930 minutes) was below the limit of quantitation of the applied analytic method (<10 mg/kg dried solid) in any sample.

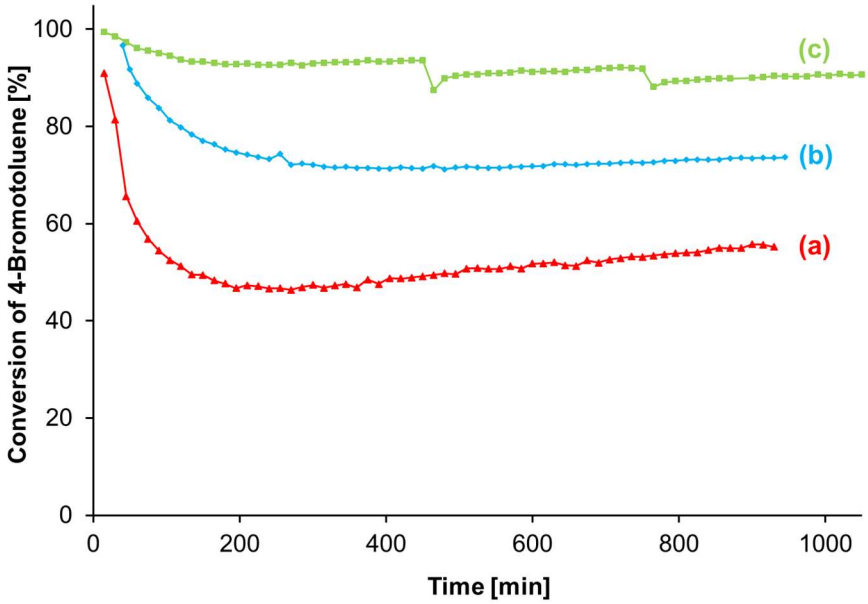


Figure D-2: Continuous synthesis of 4-methylbiphenyl from 4-bromotoluene and phenylboronic acid using one (a), two (b) and three (c) reaction modules at different flow-rates, substrate concentrations and temperatures.

Figure D-2 (b) shows the same reaction, using two reaction modules (2.41 g catalyst) at the same flow rate (0.45 ml/min). Due to the limited solubility of the product 4-methylbiphenyl in the applied reaction solvent (EtOH/H_2O = 6/4 v/v), the concentration of the substrate 4-bromotoluene had to be reduced from 58 mmol/L to 47 mmol/L to prevent precipitation of the product and subsequent blocking of the system at the reactor outlet at higher conversion rates. The use of a third reaction module (3.67 g catalyst) and an increase of temperature to 91 °C led to an almost complete conversion of 4-bromotoluene (93.2 % average conversion in the period between 120 and 450 minutes, Figure D-2 (c)). In this experiment, also higher flow rates were applied (450 – 750 minutes: 0.675 ml/min, average conversion: 91.1 %, 750 – 1050 minutes: 0.9 ml/min, average conversion: 90.0 %). Due to the higher temperature of 91 °C, product solubility in the outlet stream could be enhanced and system blocking did not occur even at high conversion rates. In each experiment depicted in Figure D-2, a stable process without observable catalyst deactivation could be established for at least 15 hours using various substrate concentrations, flow rates and temperatures.

In order to test the performance of the catalyst at high conversion levels for a longer period of time, a long-time-experiment using three reaction modules at 91 °C was performed (Figure D-3).

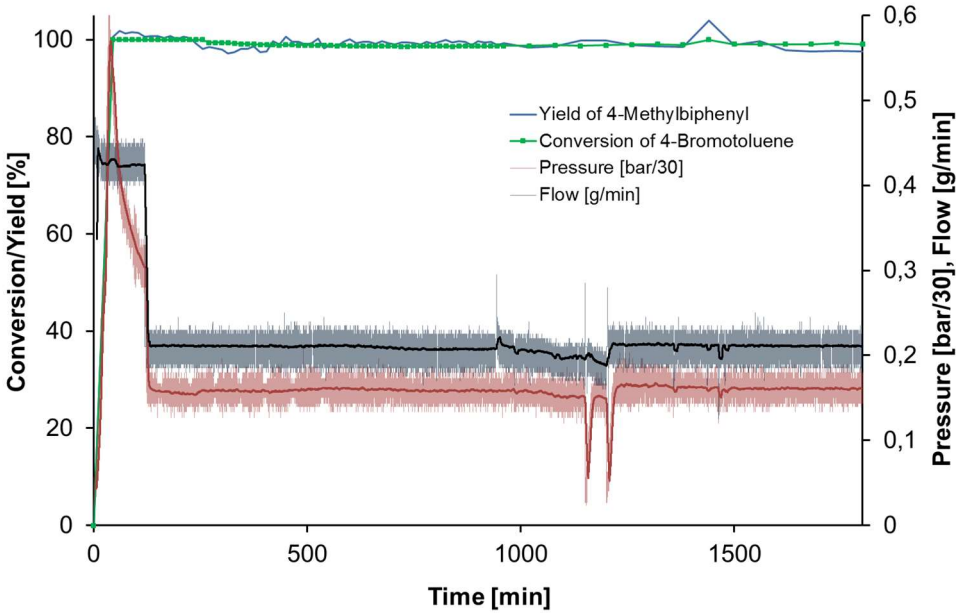


Figure D-3: Continuous synthesis of 4-methylbiphenyl from 4-bromotoluene and phenylboronic acid: long time experiment (30 hours) using three reaction modules, flow rate 0.225 ml/min.

In this case, the flow rate was reduced after 120 minutes from 0.45 ml/min to 0.225 ml/min. Using these reaction conditions, an average conversion of 99 % could be reached for more than 30 hours. The time scale of the performed continuous reaction experiments was oriented on other studies, which performed continuous Pd-catalyzed C-C coupling reactions (Suzuki, Heck and Negishi couplings) in single pass packed bed flow reactors on a time frame between 2 and 40 hours.[6,137,151–153] To the best of our knowledge, Pandarus *et al*.[6] set the benchmark for a stable single-pass packed-bed flow process with 30 hours for practically complete conversion for the synthesis of 4-methoxybiphenyl. In order to reach this benchmark in terms of stability over time, our longtime experiments were also performed for a period of 30 hours also in our study. Since rapidly deactivating catalysts for Suzuki- and Heck reactions can undergo dramatic loss of reactivity in less than 2 hours[4], the experiments using other substrates than 4-bromotoluene were performed with reaction times of 15 and 9 hours, respectively. Within all these time frames, no deactivation of the catalyst could be realized. Future work will concentrate on further investigation of the overall life time of the catalytic material.

Figure D-3shows in addition to the substrate conversion vs. time also the measured mass-flow, the obtained system pressure, as well as the product yield over time. As can be seen, the yield of 4-methylbiphenyl, also determined by HPLC-analysis, equaled the measured conversion of 4-bromotoluene to the greatest extent within the error limits of the HPLC-method. Together with the low amounts of homo-coupling side products biphenyl (originating from the homo-coupling of phenylboronic acid, average concentration 0.17 mmol/L) and 4,4'-dimethylbiphenyl (homocoupling product of 4-bromotoluene, average concentration 0.024

mmol/L) and the complete absence of other side products (protodeboronation product benzene, boronic acid oxidation product phenol and dehalogenation product toluene) in the chromatograms, this proves the extraordinarily high selectivity of the process (99.6 % in the period between 120 and 1800 minutes).

Another important feature, which illustrates the high robustness of the process, is the constant system pressure over time, which indicates the absence of precipitating products or side-products inside the catalyst bed. During the experiment depicted in Figure D-3, flushing of the HPLC with pure reaction solvent was necessary twice due to decreasing mass flow rates (indicated by the sudden drop of system pressure after 1150 and 1200 minutes). However, these short interruptions of the process did not lead to any observable change of the catalyst performance regarding substrate conversion, product yield or pressure in the subsequent process period.

In further experiments, the catalyst performance for the reaction of different 2- and 4-substituted bromoarenes with phenylboronic acid was tested for the synthesis of 4-methylbiphenyl, biphenyl-4-carbonitrile, biphenyl-4-methanol and 4-phenylphenol, using approximately 1.25 g of catalyst (1 reaction module) at a flow rate of 0.45 ml/min and a temperature of 90 °C.

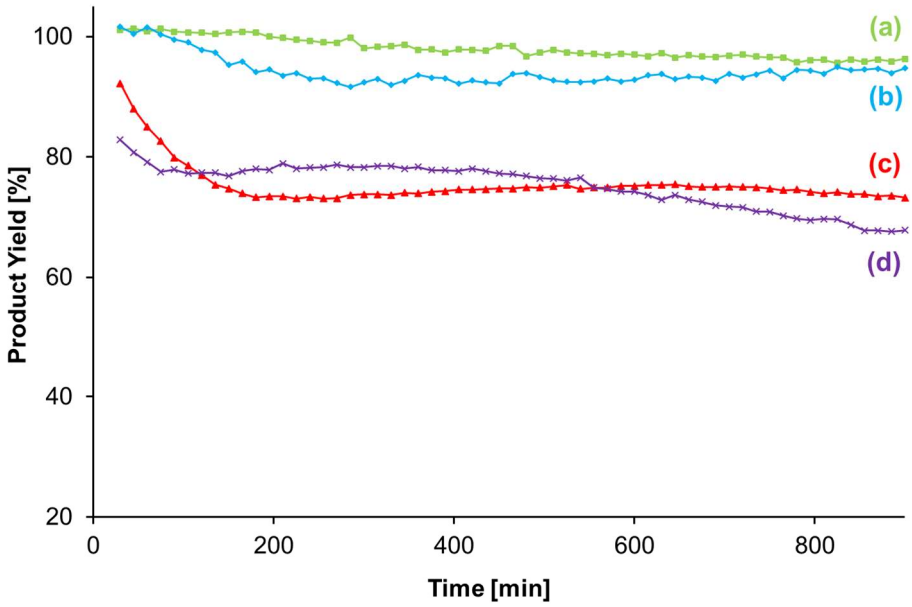


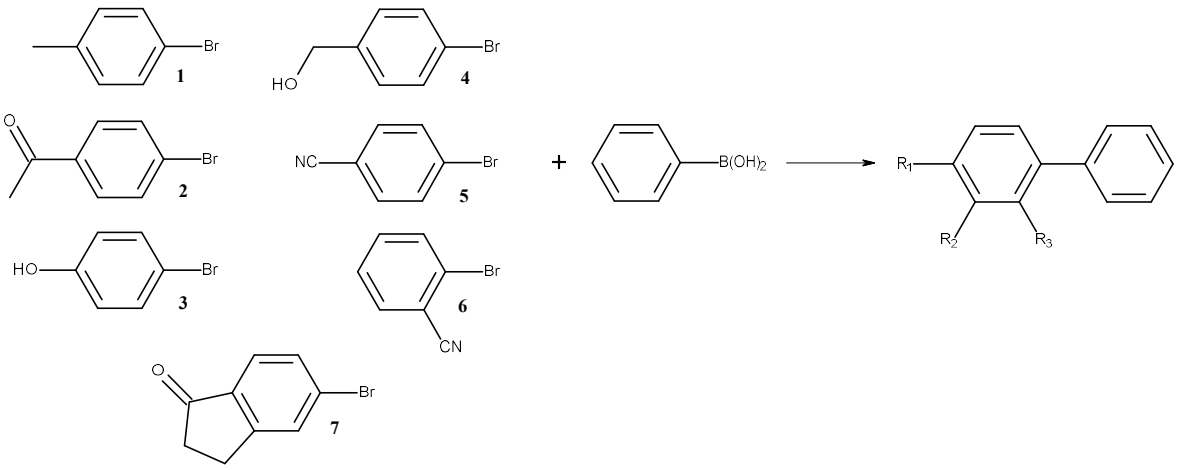
Figure D-4: Continuous synthesis of 4-acetylbiphenyl (a), biphenyl-4-carbonitrile (b), biphenyl-4-methanol (c) and 4-phenylphenol (d). Product yields were determined by HPLC-analysis.

The initial concentration of the aryl-bromide varied between 40 and 50 mmol/L, dependent on the solubility of the reaction educts and products in the applied reaction solvent. Furthermore, 2-bromobenzonitrile and 5-bromo-1-indanone were reacted with phenylboronic acid in shorter experiments (9 hours). The applied reaction parameters and the observed

product yields, selectivities and turnover-frequencies for each reaction are summarized in Table D-1. Detailed illustrations including conversions, yields, system pressure and flow rates of each reaction are given in the Figure D-5 to Figure D-14.

In all experiment, except for the synthesis of 4-phenylphenol, stable processes without any observable deactivation of the catalyst after the initial phase could be established (Figure D-4).

Table D-1: Continuous Suzuki-Miyaura cross-coupling reaction of phenylboronic acid with various bromoarenes, using $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$ as catalyst and K_2CO_3 as base: reaction parameters and summarized results.



Entry	Bromide	Conc. [mmol/L]	Solvent H_2O/EtOH[a]	Cat. [g][b]	T [°C]	Flow [ml/min]	t^R [min][c]	Yield [%][d]	Sel. [%][e]	Prod. [mg/h]	TOF [h^{-1}][f]
1	1	58.5	6/4	1.09	86	0.45	4	51.8	99.6	138	12.1
2		46.8	6/4	2.41	86	0.45	8	73.1	99.8	155	6.2
3		46.8	6/4	3.72	91	0.225	24	99.1	99.5	105	2.7
4		46.8	6/4	3.67	91	0.45	12	93.2	99.8	198	5.2
5						0.675	9	91.1	99.8	290	7.6
6						0.90	6	90.1	99.8	383	10.0
7	2	40	6/4	1.22	90	0.45	4	97.7	99.7	207	13.9
8	3	50	1/1	1.28	90	0.45	4	74.8	98.7	172	12.7
9	4	45	6/4	1.27	90	0.45	4	74.3	99.8	166	11.5
10	5	45	6/4	1.26	90	0.45	4	93.6	99.6	204	14.6
11	6	40	6/4	4.06	90	0.225	24	80.9[g]	99.2	78	1.7
12	7	35	6/4	1.28	90	0.45	4	93.4	99.6	184	11.1

[a] Solvent ratios in v/v

[b] 1 g of catalyst corresponds to 6.6 mg or 0.062 mmol palladium

[c] Residence time in the reaction modules

[d] Average Yields, determined by HPLC-analysis after the initial process phase (120 min) or at constant process yield (Entry 5 and 6)

[e] Calculated as $c_{Heterocoupling\ Product}/(c_{Heterocoupling\ Product} + c_{Homocoupling\ Products})$, averages after the initial process phase (120 min) or at constant process yield (Entry 5 and 6)

[f] Turnover frequencies were calculated from the volumetric flow rate u_V [L/h], the product yield Y [%], the concentration of arylbromide substrate c_{ArX} [mol/L], the catalyst mass m_{Cat} [g] and the palladium content of the catalyst $c_{Pd,Cat}$ [mol/g] using the equation: $TOF = \frac{u_V * Y * c_{ArX}}{m_{Cat} * c_{Pd,Ca}}$

[g] Initial phase: 180 minutes

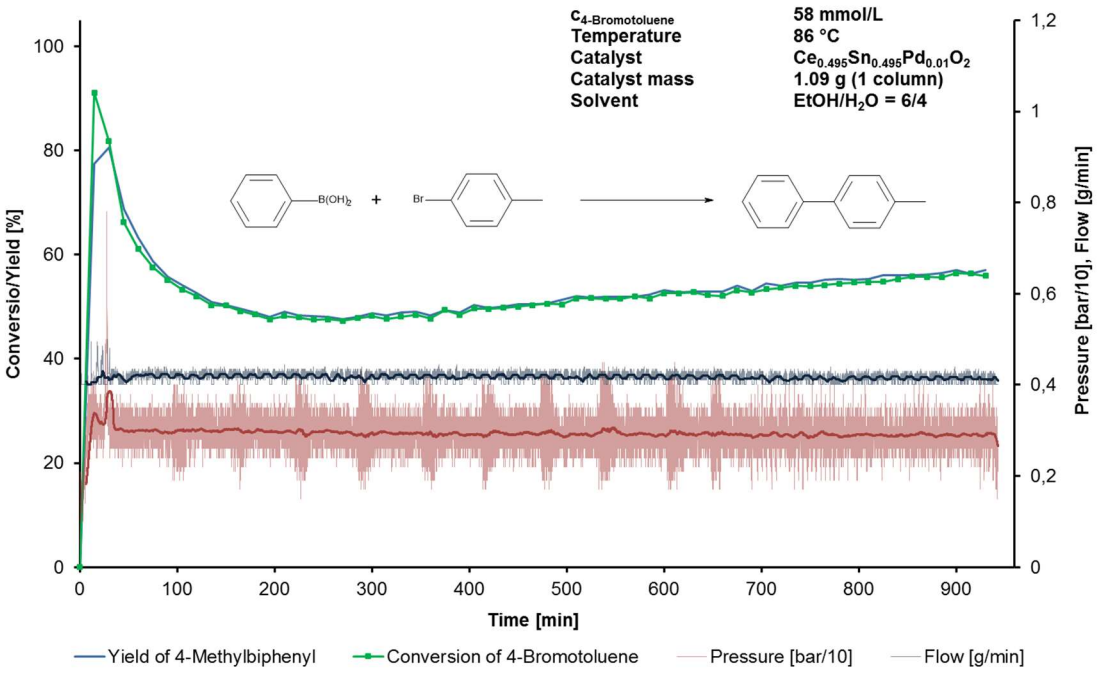


Figure D-5: Synthesis of 4-Methylbiphenyl using one reaction module (Table D-1, Entry 1).

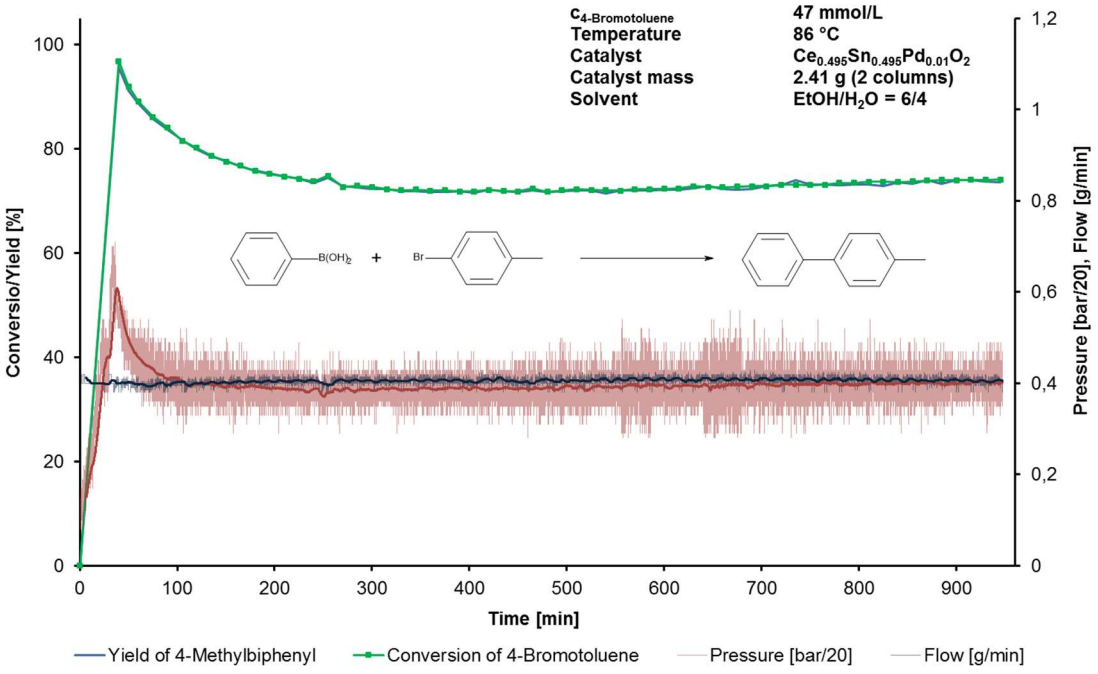


Figure D-6: Synthesis of 4-Methylbiphenyl using two reaction modules (Table D-1, Entry 2).

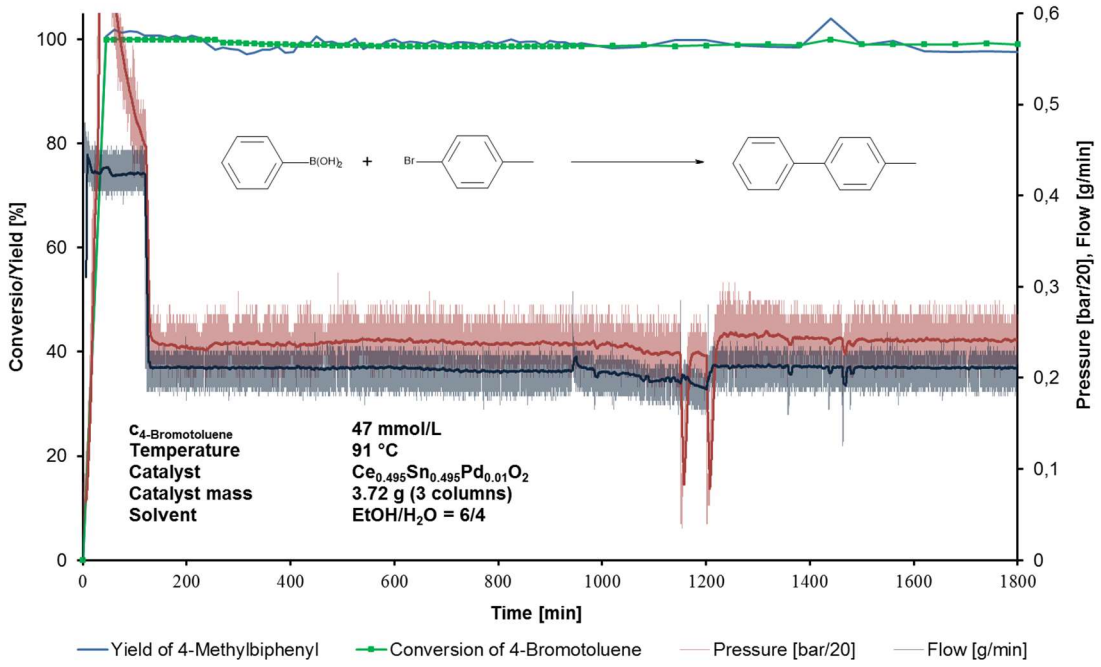


Figure D-7: Synthesis of 4-Methylbiphenyl, longtime experiment using three reaction modules (Table D-1, Entry 3).

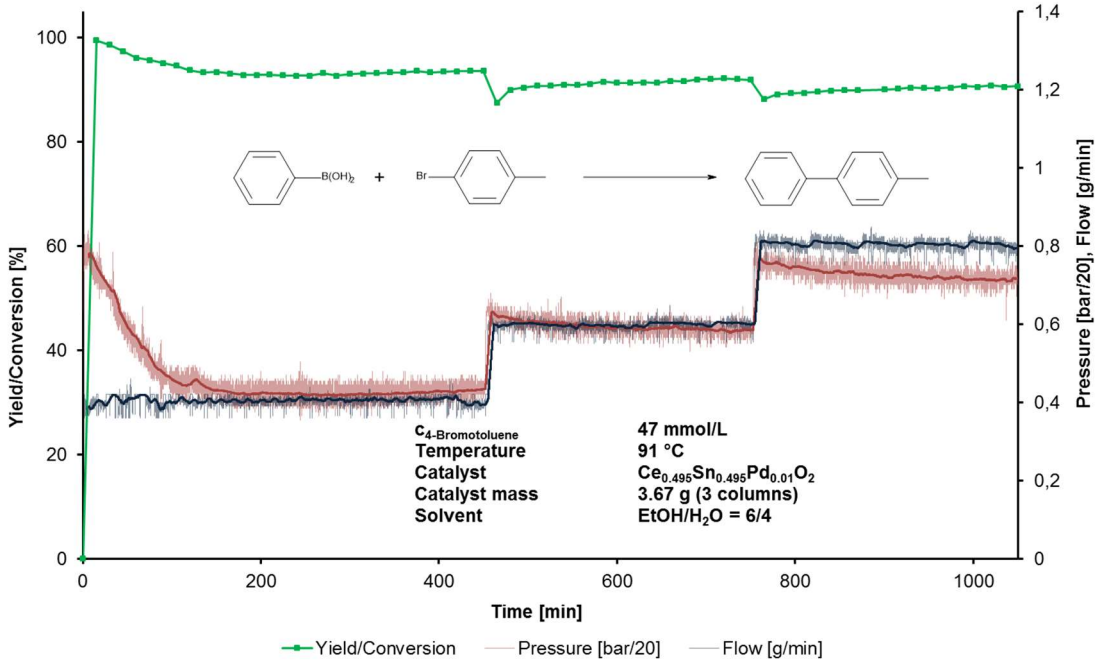


Figure D-8: Synthesis of 4-Methylbiphenyl, without internal standard, assuming yield = conversion (Table D-1, Entry 4 – 6).

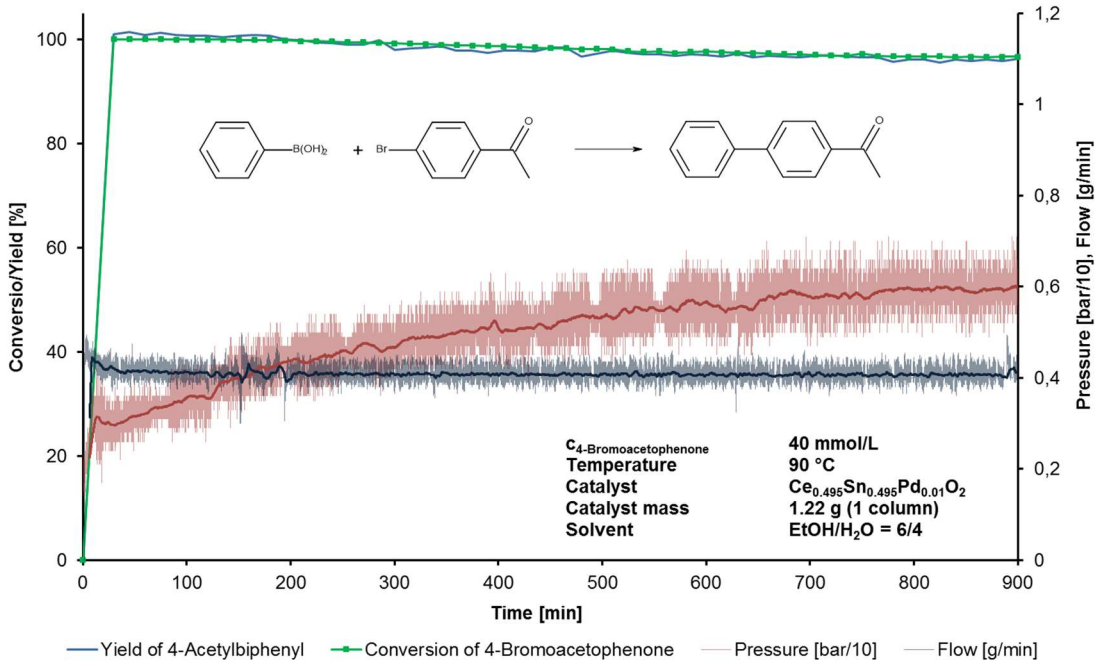


Figure D-9: Synthesis of 4-Acetylbiphenyl (Table D-1, Entry 7).

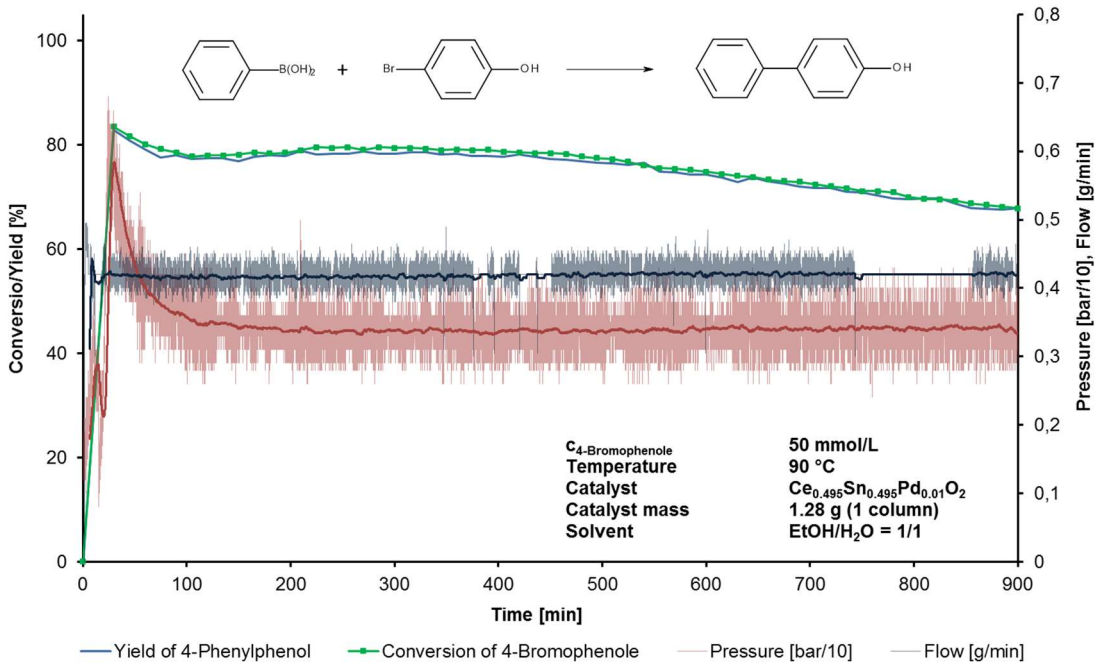


Figure D-10: Synthesis of 4-Phenylphenol (Table D-1, Entry 8).

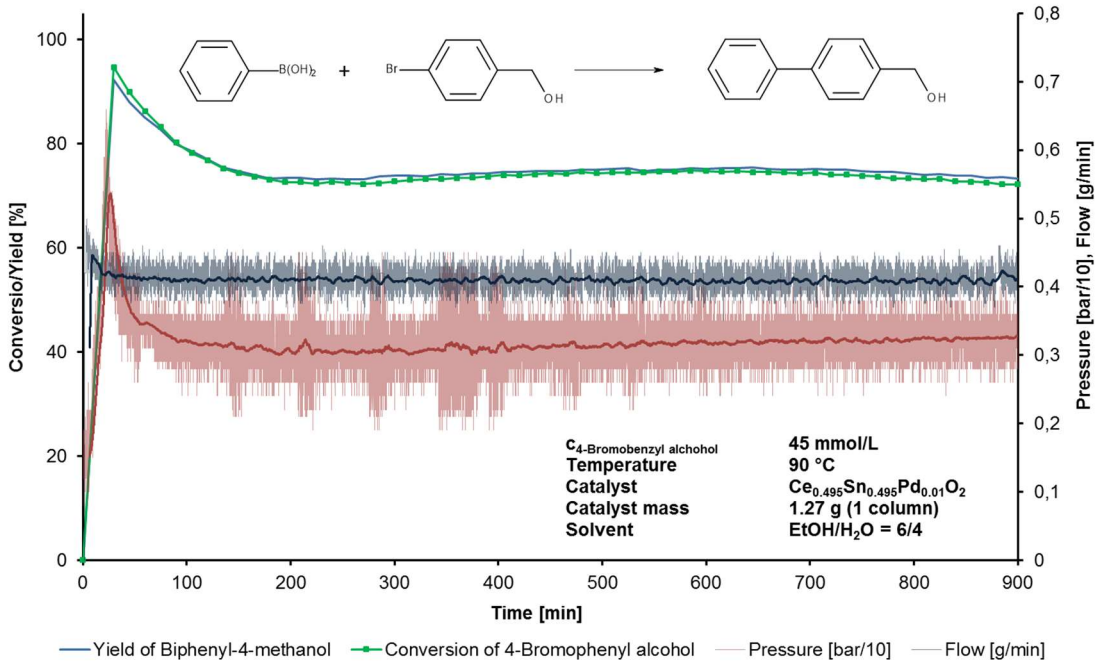


Figure D-11: Synthesis of Biphenyl-4-methanol (Table D-1, Entry 9).

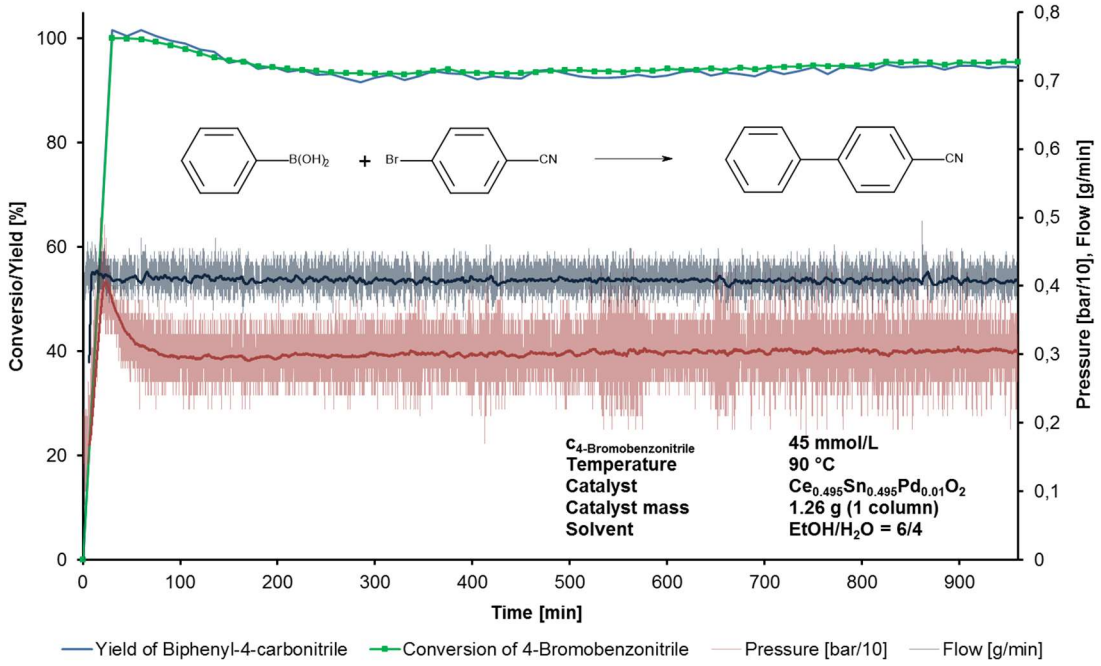


Figure D-12: Synthesis of Biphenyl-4-carbonitrile (Table D-1, Entry 10).

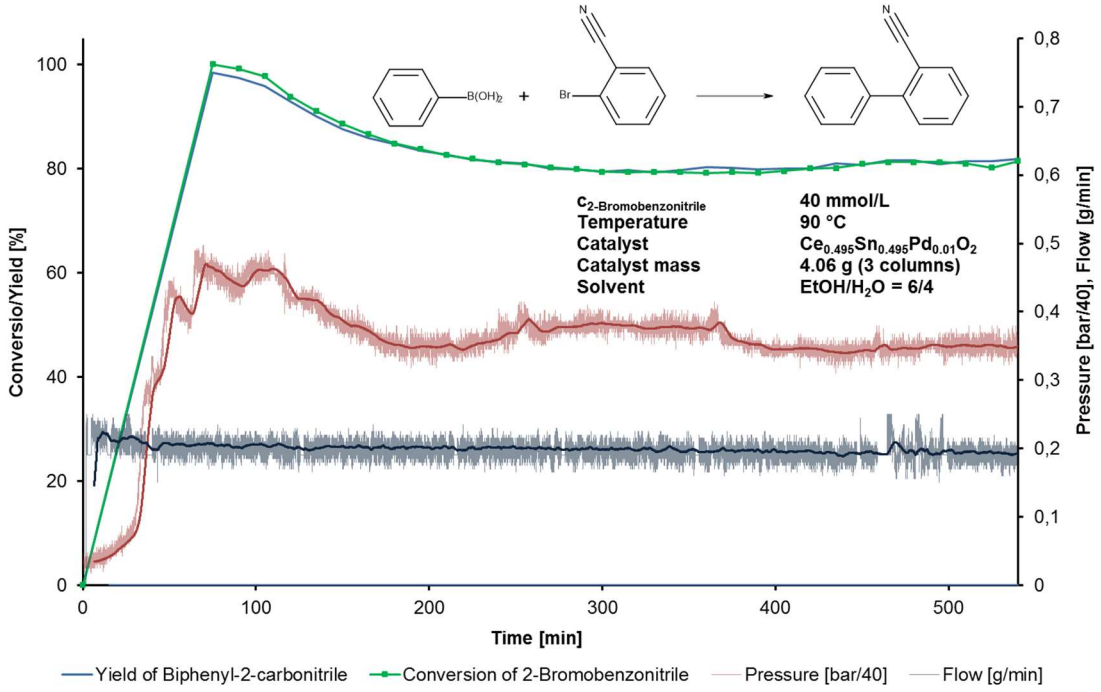


Figure D-13: Synthesis of Biphenyl-2-carbonitrile (Table D-1, Entry 11).

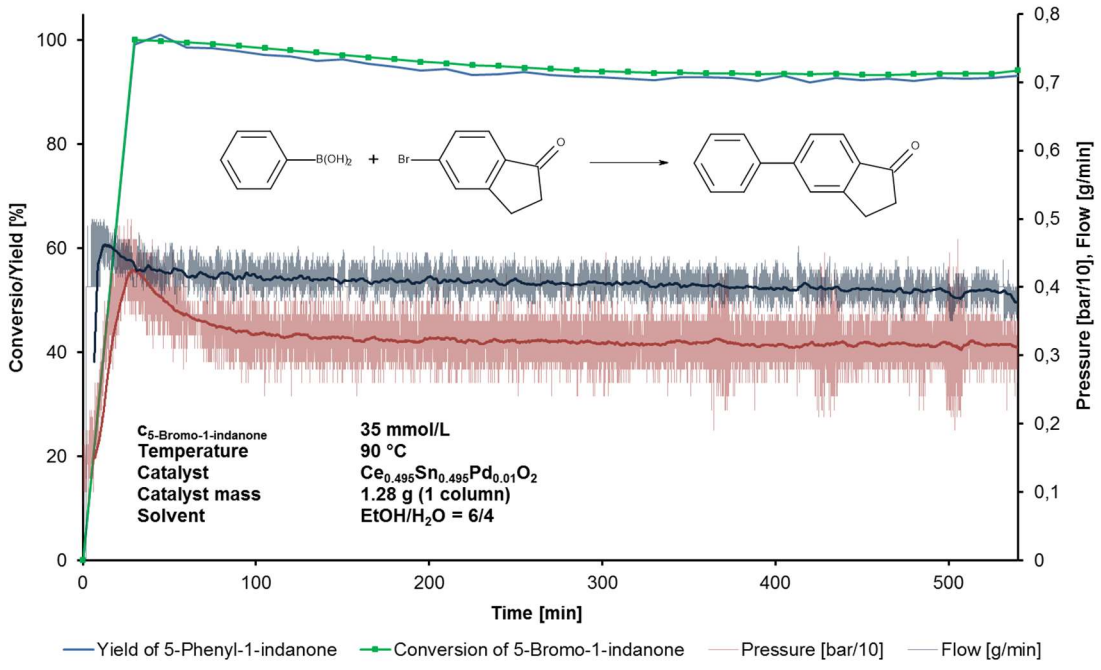


Figure D-14: Synthesis of 5-Phenyl-1-indanone (Table D-1, Entry 12).

Preliminary experiments have shown that the catalyst lifetime is massively influenced by the choice of the reaction solvent, i.e. in this study especially the ratio of ethanol and water in

the solvent mixture. In general, higher ratios of water lead to improved catalyst stability, but lower the achievable concentration of arylbromide as well as the solubility of the biphenyl products. When 4-bromophenol was used a substrate, a slight, but continuous decrease of product yield could be observed (from 77% after 120 minutes to 68 % after 900 minutes, although a higher ration of water in the reaction solvent was used for the synthesis of 4-phenylphenol (EtOH/H_2O = 1/1 v/v, compared to EtOH/H_2O = 6/4 in all other experiments). Nevertheless, we assume that a further optimization of the reaction solvent could be a suitable strategy to enhance catalyst stability also in this reaction.

As expected, bromoarene substrates bearing electron withdrawing groups in *para*-position (4-bromoacetophenone, 4-bromobenzonitrile, 5-bromo-1-indanone) showed higher reactivity than substrates with more electron releasing substituents (4-bromotoluene, 4-bromophenol, 4 bromobenzyl alcohol). The lowest reaction rates were observed for the coupling reaction of the sterically more demanding 2-bromobenzonitrile with phenylboronic acid. Nevertheless, also biphenyl-2-benzonitrile could be synthesized at a scale of 78 mg/h and with yields above 80 %.

In general, the described method using $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$ as heterogeneous catalyst in a fixed bed reactor proved to be a convenient, uncomplicated and reliable procedure for the synthesis of substituted biphenyls at good to excellent yields and extraordinarily high selectivities on a scale of up to 10 g per day.

2.3 Continuous Crystallization

In order to continuously separate the reaction product from the reaction solvent, a continuous crystallization unit was attached to the reactor outlet. The integrated synthesis and crystallization process is illustrated in a flow sheet in Figure D-15, the experimental set-up for the continuous synthesis and the subsequent continuous crystallization of 4-acetylbiphenyl is shown in Figure D-16. To show the flexibility of the set-up, continuous crystallization was carried out for three reaction products: 4-methylbiphenyl, 4-acetylbiphenyl and biphenyl-4-carbonitrile.

Crystallization of the product was achieved by addition of water as anti-solvent and subsequent cooling of the reaction mixture. In preliminary experiments, the biphenyl products bearing hydroxyl groups (4-phenylphenol and biphenyl-4-methanol) showed considerable solubility in the applied ethanol/water mixtures, indicating that the used approach employing water as anti-solvent is not the ideal separation strategy for hydroxy-functionalized biphenyls. On the other hand, methyl-, ketyl- and nitrile-functionalized biphenyls proved to be more suitable substances for crystallization using water as anti-solvent. In this study, three products, which represent examples for each of these functional groups (4-methylbiphenyl, 4-acetylbiphenyl and biphenyl-4-carbonitrile representatively for methyl-, ketyl- and nitrile-functionalized biphenyls) were isolated in an integrated continuous crystallization process

directly after synthesis. The amount of added anti-solvent as well as the temperature during crystallization was adapted for each product in order to maximize the yield of the crystallized product but, at the same time, to minimize the product agglomeration in the crystallization tube and to prevent system clogging.

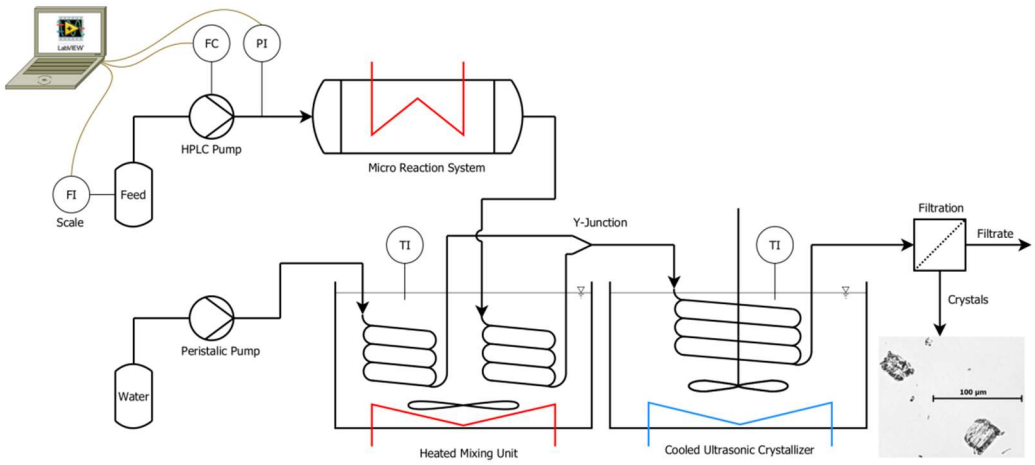


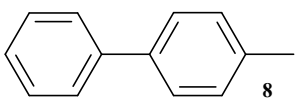
Figure D-15: Integrated process for the continuous synthesis and subsequent continuous crystallization of 4-acetylbiphenyl, biphenyl-4-carbonitrile and 4-methylbiphenyl.

Figure D-16: Experimental set-up for the continuous synthesis and subsequent continuous crystallization of 4-acetylbiphenyl.

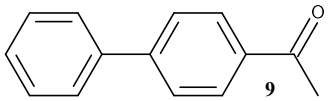
The crystallization was carried out under ultrasonic irradiation at temperatures between 8 and 20 °C. The addition of the anti-solvent was done via a Y-junction, which was placed directly in the cooled ultrasonic bath for the crystallization of 4-acetylbiphenyl. For the crystallization of biphenyl-4-benzonitrile and 4-methylbiphenyl, the reaction solvent as well as the anti-solvent was preheated before mixing. Both, preheating and crystallization under ultrasonic irradiation was done to prevent precipitation of the product inside the Y-junction and product

agglomeration in the crystallization tube which would decrease product yields and/or to clogging of the crystallization system. The crystallized product was finally separated from the reaction solvent by filtration using a glass frit. A summary of all reaction and crystallization conditions is given in Table D-2.

Table D-2: Process parameters and summarized results for the integrated continuous synthesis and crystallization of 4-methylbiphenyl (8), 4-acetlybiphenyl (9) and biphenyl-4-carbonitrile (10)



8



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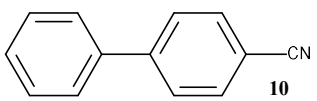

10

Entry	Bromide	$c_{Bromide}$ [mmol/L]	Product	T_R[a] [°C]	m_{Cat} [g]	Flow RS[b] [ml/min]	Flow AS[c] [ml/min]	T_{Mix}[d] [°C]	T_{Cry}[e] [°C]	$Y_{Syn.}$[f] [%]	Y[g] [%]	Prod. [mg/h]
1	**1**	50	**8**	90	3.59	0.45	0.3	70	20	>99	67	151
2	**2**	40	**9**	90	2.70	0.45	0.1	RT	8	>99	89	189
3							0.3	RT	8	>99	92	194
4							0.5	RT	8	>99	96	204
5	**5**	45	**10**	90	2.40	0.45	0.3	80	8	>99	91	198

[a] Temperature for the continuous synthesis reaction
[b] Flow rate of the reaction solvent during biphenyl synthesis
[c] Flow rate of the anti-solvent (water)
[d] Temperature at the mixing point (Y-junction)
[e] Crystallization temperature in the cooled ultrasonic bath
[f] Yield of the continuous synthesis process, determined by HPLC-Analysis
[g] Yield of the overall process, determined gravimetrically after drying of the product in a desiccator at reduced pressure

To guarantee practically full conversion of the substrates, two reaction modules filled with catalyst were used for the synthesis of 4-acetylbiphenyl and biphenyl-4-carbonitrile. After the above mentioned initial phase (120 minutes) of considerable palladium leaching, the continuous synthesis unit was connected with the crystallization unit.

During crystallization of 4-acetylbiphenyl (Table D-2, Entry 2-4 and Figure D-17), three different operating points, characterized by three different flow rates of the anti-solvent (0.1, 0.3 and 0.5 ml/min) were examined successively in a single experiment. For each operating point, the flow rate of anti-solvent was kept constant for three hours. After increasing the flow rate, the system was allowed to equilibrate for half an hour. Product collection was started after the equilibration time again and was continued for another three hours. Thus, the overall process was run for 13 hours (crystallization process: 11 hours) at excellent yields of the isolated product (89 – 96 %). During this time, no considerable pressure increase or visually recognizable clogging could be observed.

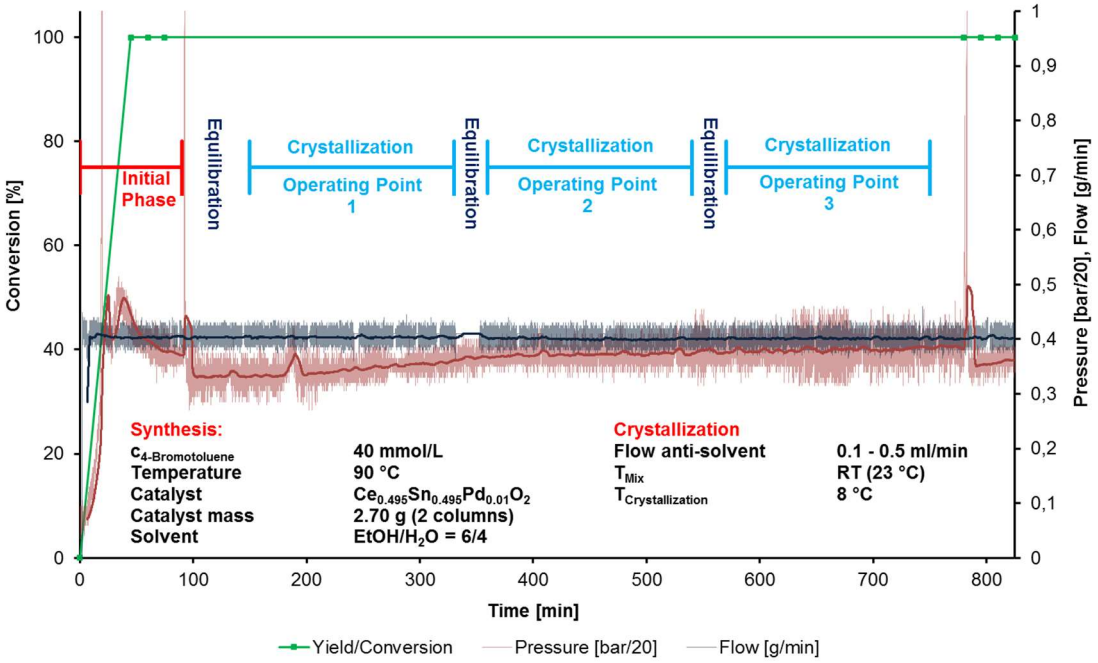

Figure D-17: Synthesis and crystallization of 4-Acetylbiphenyl (Table D-2, Entry 2 - 4).

Biphenyl-4-carbonitrile was continuously crystallized using one operating point (flow of anti-solvent: 0.3 ml/min) for a period of 5 hours (Figure D-18). Due to product precipitation at the mixing point (Y-junction), when water was added at room temperature, the reaction solution as well as the anti-solvent had to be preheated before mixing. Using preheated solvents, clogging of the Y-junction and pressure increase could be avoided and biphenyl-4-carbonitrile could be isolated with high yield (91 %).

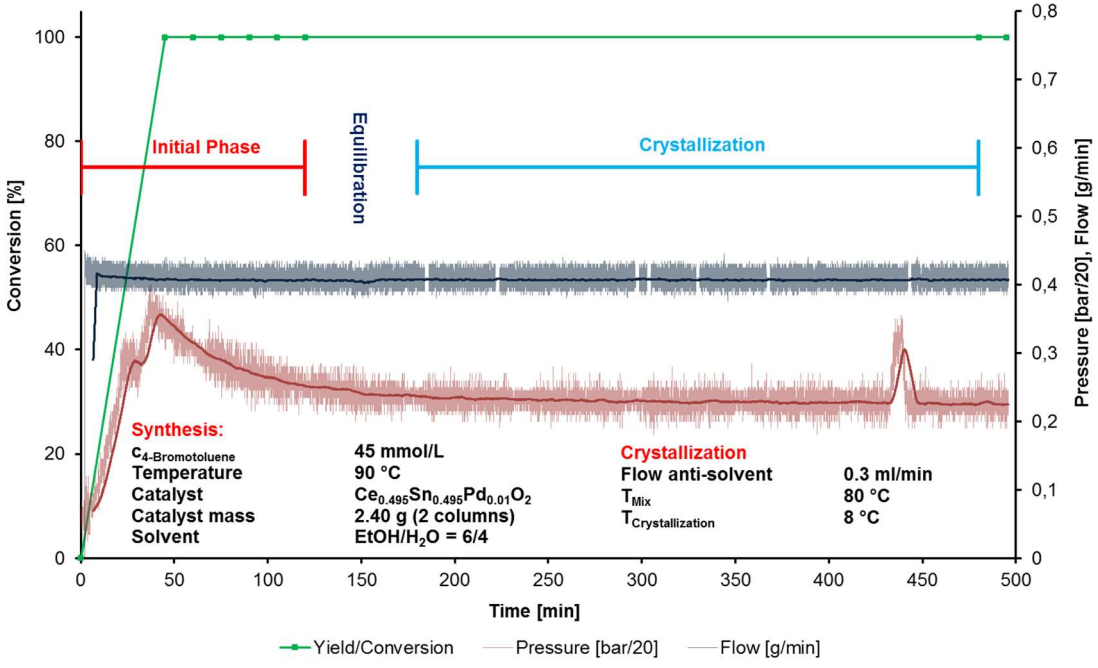

Figure D-18: Synthesis and crystallization of Biphenyl-4-carbonitrile (Table D-2, Entry 5).

The lowest overall product yields were obtained for the crystallization of 4-methylbiphenyl. At low temperatures, product deposition at the walls of the crystallization tube was observed despite ultrasonic irradiation. Hence, the crystallization temperature had to be increased to 20 °C at an anti-solvent flow rate of 0.3 ml/min. Under these conditions, the product could not be quantitatively crystallized from the reaction mixture. However, an overall process yield of 67 % could be achieved.

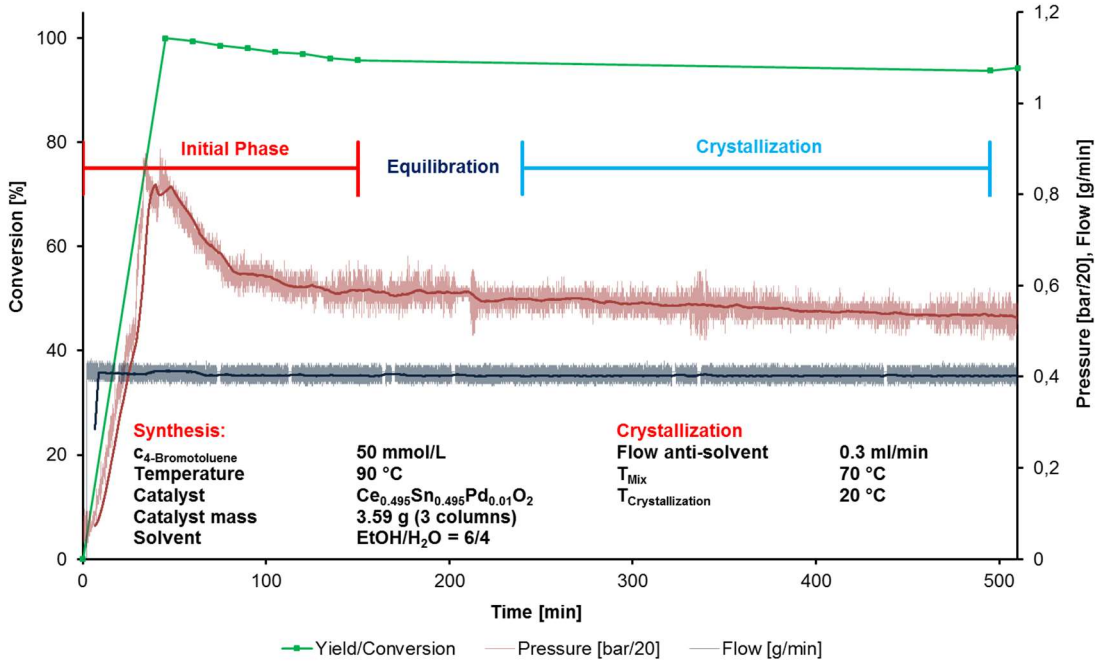

Figure D-19: Synthesis and crystallization of 4-Methylbiphenyl (Table D-2, Entry 1).

The amount of side products in the crystallized products was determined by means of HPLC-measurements. Besides the desired product-peak, only one peak, which was assigned to the boronic acid homocoupling product biphenyl, could be observed in the chromatograms of all tested final products. Phenylboronic acid, arylbromide substrates or other side products could not be detected. Hence, the crystallization process acts not only as separation process for the organic compounds, but also represents a purification process, especially for reactions, where a complete conversion of the bromide-substrate cannot be achieved (as it was the case for the synthesis of 4-methylbiphenyl). The degree of contamination of the final products with the catalyst-metals cerium, tin and palladium was analyzed by means of ICP-MS. The amounts of residual metal in the low ppm range prove the high stability and leaching resistance of the employed catalyst. The results of these analyses are summarized in Table D-3.

Table D-3: Amounts of the side-product biphenyl and the catalyst metals cerium, tin and palladium in the final product

Entry	Product	Biphenyl [g/kg][a]	Ce [mg/kg][b]	Sn [mg/kg][b]	Pd [mg/kg][b]
1	**8**	2.0	1.9 ± 1.1	0.39.± 0.25	1.1 ± 0.1
2	**9.1**	0.4	0.12 ±0.01	0.20 ±0.05	0.28 ±0.01
3	**9.2**	0.7	0.83 ±0.03	0.19 ±0.04	0.96 ±0.1
4	**9.3**	0.4	0.17 ± 0.08	0.21 ± 0.05	0.59 ± 0.04
5	**10**	3.6	0.54 ± 0.07	0.26 ± 0.06	2.1 ± 0.1

[a] Determined by HPLC-analysis
[b] Determined by ICP-MS-analysis

The particle size distribution of the crystallized products was analyzed using laser diffraction (HELOS Sympatec). All obtained crystals are plate shaped (see Figure D-15 for an example of a 4-methylbiphenyl crystal). For 4-methylbiphenyl the largest particles were obtained (x_{10}: 14 µm, x_{90}: 100 µm), the other products have a particle size in the range of ~3 µm (x_{10}) to ~ 30 – 46 µm (x_{90}) (Table D-4) and a monomodal q_3 density distribution (Figure D-20). As described above, 4-acetylbiphenyl (**9**) was crystallized using three different operation parameters (anti-solvent flow rates from 0.1 – 0.5 ml/min), however, these parameters did not notably influence the particle size of the crystals.

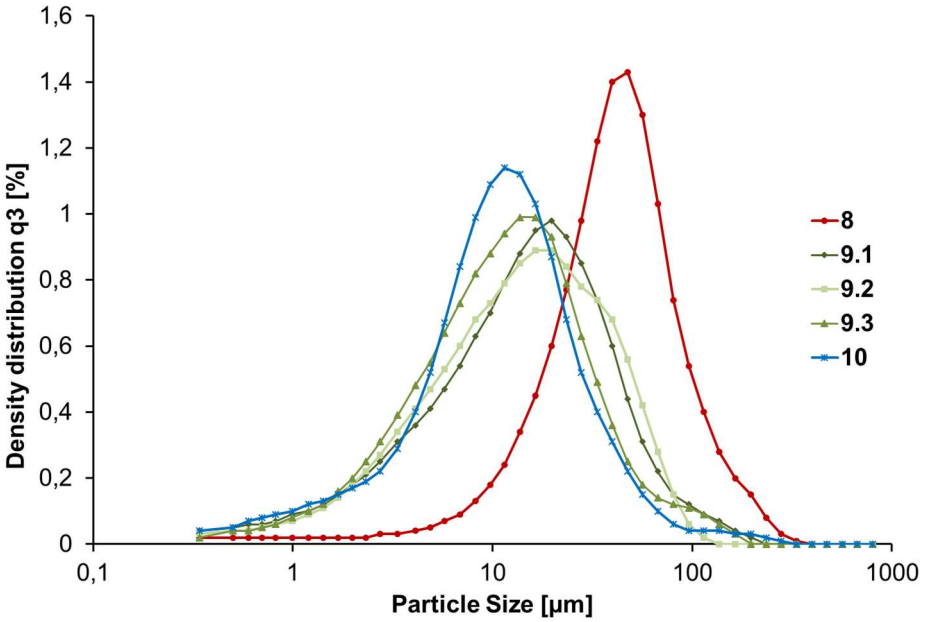

Figure D-20: Particle size distribution of the obtained crystals.

Table D-4: Characteristic mean diameters x_{10}, x_{50}, x_{90} of the obtained crystals

Entry	Product	x_{10} [µm]	x_{50} [µm]	x_{90} [µm]
1	**8**	13.9	41.7	100.3
2	**9.1**[a]	3.0	14.5	46.5
3	**9.2**[b]	2.8	11.8	37.0
4	**9.3**[c]	2.7	15	46.4
5	**10**	2.7	11.1	32.6

[a] Flow rate of anti-solvent: 0.1 ml/min (operating point 1)
[b] Flow rate of anti-solvent: 0.3 ml/min (operating point 2)
[c] Flow rate of anti-solvent: 0.5 ml/min (operating point 3)

3 Conclusions

In this study, seven different substituted arylbromides were coupled with phenylboronic acid in a continuous-flow packed bed reactor using the Suzuki-Miyaura cross-coupling reaction. The palladium substituted mixed cerium-tin oxide $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$ catalyst did not show any deactivation over 30 h. The desired biphenyls could be synthesized in good to high yields and very high selectivties on a scale of 78 – 383 mg/h, depending on the reaction partners and the applied reaction conditions. Three continuously synthesized biphenyls (4-methylbiphenyl, 4-acetylbipheny and biphenyl-4-carbonitrile) were isolated out of the reaction solution using a directly coupled continuous crystallization process. Continuous crystallization of the products was achieved by addition of water as anti-solvent and subsequent cooling of the mother liquor in an ultrasonic bath. Using the integrated continuous synthesis/crystallization process, overall process yields of up to 96 % on a scale of 151 – 204 mg/h (up to ~5 g/d) were achieved.

All in all, the described process allows the easy and reliable continuous production and isolation of various substituted biphenyls at excellent yields and high purities. Minimal amounts of metals, especially palladium in the final product at the low ppm level indicate the high stability and good leaching resistance of the employed inorganic catalyst. Furthermore, the use of the "green solvents" ethanol and water throughout the whole synthesis and crystallization procedure can be seen as main advantage of the described process and indicates the potential for an application on a larger scale.

4 Experimental

All chemicals were purchased from commercial suppliers and used as received, except for phenylboronic acid, which was recrystallized from water prior to use.

4.1 Catalyst Synthesis

$Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta}$ was synthesized using a modification of the solution combustion method reported by Baidya *et al.*[123] For the production of 3 g of $Ce_{0.495}Sn_{0.495}Pd_{0.01}O_{2-\delta,}$ 5.000 g ammonium cerium(IV) nitrate, 1.861 g tin(II) oxalate, 0.033 g palladium(II) chloride and 3.294

g glycine (fuel) were thoroughly mixed by grinding the components using mortar and pestle. The solid mixture was suspended in 2 ml of water in a borosilicate dish with 600 ml capacity. The suspension was treated in an ultrasonic bath, until a viscous but clear solution was formed. The mixture was placed in a muffle furnace at 350 °C, which led to an ignition of the redox mixture within less than 5 minutes. The resulting spongiform, voluminous and porous solid was ground with mortar and pestle and was heated for another 5 hours at 350 °C. After that procedure, the synthesized oxide was directly usable as catalyst. The catalyst itself appears as porous, light brown and powderly solid with a particle size of ~ 190 µm (x_{10} = 5.5 µm, x_{50} = 33.8 µm, x_{90} = 189.4 µm). The XRD spectra of the particles clearly show that PdO or metallic Pd species could not be observed and a cubic/tetragonal mixed phase structure was observed.

4.2 Continuous Suzuki-Miyaura Reactions

For continuous Suzuki-Miyaura reactions, the arylbromide (35 – 50 mmol/L, depending on the solubility of the arylbromide and the corresponding biphenyl product), 1.5 molecular equivalents of phenylboronic acid, 1.5 molecular equivalents of base (potassium carbonate) and anisole (internal standard for the HPLC-analysis, 1 g/L) were dissolved in the reaction solvent (EtOH/Water = 6/4 v/v, except for the synthesis of 4-phenylphenol, where a reaction solvent of EtOH/Water = 1/1 v/v was used) and degassed in an ultrasonic bath for 30 minutes. Pumping of the reaction mixture through the Plug & Play reactor was done using a HPLC pump (Knauer, Azura P4.1 S) at flow rates between 0.225 and 0.9 ml/min. The pressure inside the system was monitored via the internal pressure sensor of the HPLC-pump. The mass flow was observed using a balance (Kern EWJ600-2M), which was connected via a serial RS-232 to a PC. The acquisition of the observed data (pressure, system pressure) was done using the software LabView. The reactor was externally heated using a Lauda P10 Proline thermostat and Lauda Ultra 350 as heating medium. The temperature was monitored using a K-type thermocouple attached to the outside of the HPLC column.

To monitor the reaction progress, HPLC-samples were drawn at an interval of 15 minutes from the outlet of the reactor.

In this study, the amount of catalyst was generally adjusted to the synthetic problem by employing one, two or three standard HPLC columns (L x D: 40 mm x 8.0 mm), each filled with approximately 1.25 g of catalyst (corresponding to 6.7 mg or 0.08 mmol palladium), as reaction modules.

4.3 Continuous Crystallization

Continuous crystallization of the synthesized product was done by addition of anti-solvent (water) and a subsequent cooling of the mother liquor. The crystallization was done in a polyfluorethylenpropylene (FEP) tube (length: 4 m, I.D.: 2 mm, O.D.: 4 mm), which was immersed in an ultrasonic bath (Elma Transsonic 780). A Lauda Alpha RA 12 was used as

external cryostat to cool the ultrasonic bath. The addition of water (anti-solvent) via a polypropylene Y-junction was done using an Ismatec Regio Digital MS-4/6-100 peristaltic pump. For the crystallization of 4-methylbiphenyl and biphenyl-4-carbonitrile, the anti-solvent as well as the reaction solvent had to be preheated before mixing to avoid product precipitation in the Y-junction. This was done in a water bath which was heated by a Heidolph MR 3001 K magnetic stirrer. At the outlet of the crystallization unit, the solid product was separated from the mother liquor by filtration using a glass frit connected to a water aspirator. After separation, the solid product was dried in a desiccator at room temperature under reduced pressure for several days.

ICP-MS measurements were performed on an Agilent 7500ce ICP-MS after microwave assisted acidic digestion of the samples.

The particle size measurements were conducted with a HELOS/KR (Sympatec) Laser diffraction sensor. For the measurements the particles were suspended in a water solution containing Tween 20 as tenside.

4.4 HPLC-Analysis

HPLC analysis was done using an Agilent 1100 series HPLC system (Agilent, Waldbronn, Germany), equipped with an online degasser, quaternary pump, autosampler, thermostatted column compartement and UV-visible diode array detector. An Agilent Poroshell 120 EC-C18 reversed phase column (50x4.6 mm; 2.7 µm) was used as stationary phase. Analysis was carried out under gradient elution conditions using a mobile phase consisting of methanol and aqueous phosphoric acid (water:phosphoric acid = 300:1 v/v). Two different methods for the analysis of the reaction solutions were used. The corresponding elution programs are given in Table D-5.

Column temperature was set to 25 °C. An aliquot of 2 µL of sample solution was injected into the HPLC system. UV-detection was performed at 237 and 270 nm over the run time of 15 minutes (Method A) and 16 minutes (Method B), respectively.

The sample solutions were prepared by dissolving 100 µL of the reaction solution in 1 mL of the initial mobile phase. Method A was used for monitoring the synthesis of 4-methylbiphenyl, 4-acetylbiphenyl, biphenyl-4-methanol and biphenyl-2-carbonitrile. Method B was used for monitoring the synthesis of 4-phenylphenol, Biphenyl-4-carbonitrile and 5-phenyl-1-indanone.

Table D-5: HPLC methods applying solvents A (methanol) and B (water:phosphoric acid = 300:1 v/v)

METHOD A			
Time [min]	% A (v/v)	% B (v/v)	Flow [ml/min]
0	60	40	1
10	80	20	1
12	60	40	1

METHOD B			
Time [min]	% A (v/v)	% B (v/v)	Flow [ml/min]
0	40	60	1
3	40	60	1
9	80	20	1
11	80	20	1
13	40	60	1

The wavelengths used for quantification and the retention times of the substrates, products, side products and the internal standard are given in Table D-6.

Table D-6: Wavelengths of quantification and retention times for the used internal standards and substrates and the observed products and side products

	Retention time t_R [min]		Wavelength of
	Method A	Method B	quantification [nm]
Internal standard			
Anisole	1.56	5.04	270
Substrates			
Phenylboronic acid	0.88	1.70	237
4-Bromotoluene	4.74		237
4-Bromoacetophenone	1.78		237
4-Bromobenzoic acid	1.29		237
2-Bromobenzonitrile	1.23		237
4-Bromophenol		5.55	237
4-Bromobenzonitrile		5.57	237
5-Bromo-1-indanone		6.64	237
Products			
4-Methylbiphenyl	8.18		237
4-Acetylbiphenyl	3.59		237
Biphenyl-4-methanol	2.32		237
Biphenyl-2-carbonitrile	2.29		237
4-Phenylphenol		8.15	237
Biphenyl-4-carbonitrile		9.01	237
5-Phenyl-1-indanone		9.09	237
Side products			
Biphenyl	5.87	10.34	237
Phenol	0.81	1.53	270
Benzene	1.68	4.94	252

E Summary and Outlook

1 Summary

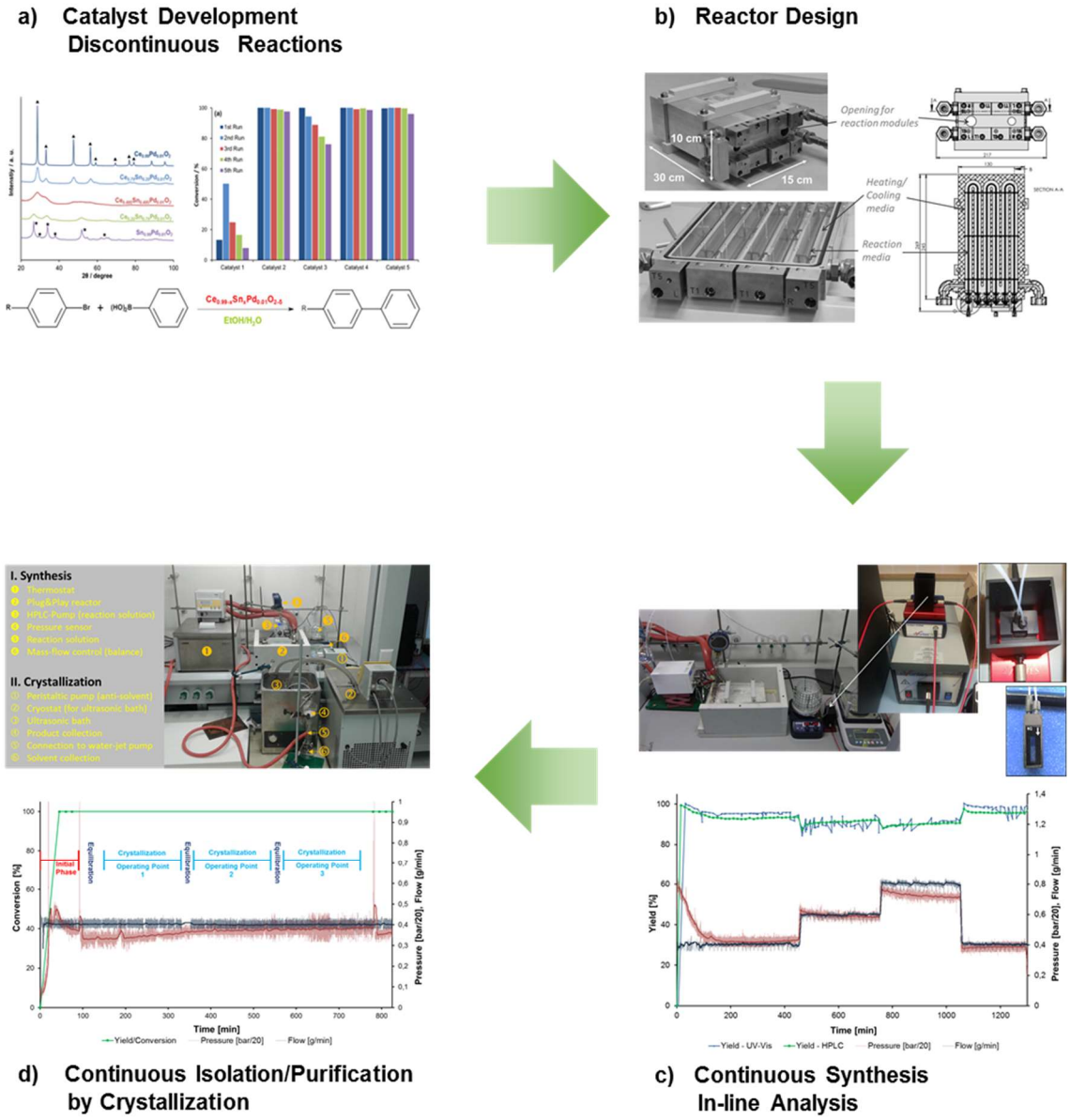

Figure E-1: Graphical Summary.

In this work, novel palladium substituted mixed cerium-tin-oxides were developed and investigated for their activity as solid catalysts in discontinuous and continuous Suzuki-Miyaura cross-coupling reactions.

Five different mixed oxides ($Ce_{0.99-x}Sn_xPd_{0.01}O_{2-\delta}$ with x = 0, 0.2, 0.495, 0.79 and 0.99) were prepared using the solution combustion method, a synthetic technique, which allows the rapid

preparation of the desired oxides out of non-toxic precursor substances. The reactivity of the obtained catalysts in Suzuki-Miyaura reactions of different arylbromides with phenylboronic acid was tested in batch mode.

Especially the mixed oxides $Ce_{0.79}Sn_{0.2}Pd_{0.01}O_{2-\delta}$, $Ce_{0.20}Sn_{0.79}Pd_{0.01}O_{2-\delta}$ and $Sn_{0.99}Pd_{0.01}O_{2-\delta}$ showed extraordinarily high catalytic activity with turnover frequencies above 12,000 h^{-1}. Catalysts with equimolar amounts of cerium and tin ($Ce_{0.49}Sn_{0.49}Pd_{0.01}O_{2-\delta}$) showed good, but relatively lower catalytic activity. Palladium substituted cerium oxides without any tin content ($Ce_{0.99}Pd_{0.01}O_{2-\delta}$) proved to be the least active materials.

All tested catalysts showed good recyclability and could be reused for at least five times with only minor loss of activity. XRD-analyses of as prepared and used catalysts proved the high chemical and mechanical stability of the oxides. Nevertheless, low, but detectable amounts of leached Pd in the reaction solution, the reaction kinetics (sigmoidal profiles of the reaction progress) and heterogeneity studies (catalyst poisoning tests) substantiate the thesis, that the as prepared mixed oxides act as precatalysts, which release small amounts of dissolved palladium, the truly catalytically active species.

However, the high leaching resistance and the recyclability even in rather polar solvents (aqueous ethanolic mixtures) revealed the high potential of the prepared catalysts for the use in continuous-flow operations.

Continuous Suzuki-Miyaura reactions were performed using a novel reaction device, the so called “Plug & Play Reactor”, which was designed by the Institute of Process and Particle Engineering in collaboration with OneA Enginneering, Vöcklaburck, Austria. The Plug & Play Reactor uses exchangeable reaction devices (commercially available HPLC columns) which are filled with solid catalysts and act as packed bed reactors. Reaction temperatures of up to 200 °C and a pressure of 40 bar can be realized. Furthermore, the modular design of the reaction device allows a straightforward implementation of analytical tools (temperature and pressures sensors, mass-flow control, UV-VIS-spectroscopy) and on-line process monitoring.

Although not being the most reactive catalyst in batch experiments, oxides with equimolar amounts of cerium and tin ($Ce_{0.49}Sn_{0.49}Pd_{0.01}O_{2-\delta}$) exhibited superior stability and leaching resistance when used in continuous packed-bed flow reactions. Using these catalysts, continuous syntheses of seven different functionalized biphenyls could be realized. The desired biphenyls could be synthesized in good to high yields and very high selectivties on a scale of 78 – 383 mg/h, depending on the reaction partners and the applied reaction conditions. Long time experiments for the synthesis of 4-methylbiphenyl did not show any catalyst deactivation after a reaction time of 30 hours. All reactions were carried out in environmentally friendly aqueous ethanolic solvents.

Three continuously synthesized biphenyls (4-methylbiphenyl, 4-acetylbipheny and biphenyl-4-carbonitrile) were isolated out of the reaction solution using a directly coupled continuous crystallization process. Using the integrated continuous synthesis/crystallization process, overall process yields of up to 96 % on a scale of 151 – 204 mg/h (up to ~5 g/d) were achieved. Crystallization was done in a using water as anti-solvent and cooling of the mother liquor in an ultrasonic bath. Thus, only non-toxic and environmentally friendly solvents (water and ethanol) were used throughout the whole synthesis/crystallization process. The isolated products were highly pure (>99 % according to HPLC-analysis) and contained only minimal amounts of palladium (0.28 – 2.1 ppm), cerium (0.12 – 1.9 ppm) and tin (0.19 – 0.39 ppm).

Using the novel palladium substituted cerium-tin-oxide $Ce_{0.49}Sn_{0.49}Pd_{0.01}O_{2-\delta}$, easy and reliable processes for the continuous synthesis and isolation of various functionalized biphenyls at excellent yields and high purities could be realized on a laboratory scale. The employed catalyst can be prepared rapidly out of commercially available, cheap and non-toxic precursor substances without the need for special laboratory equipment. “Green solvents” (water and ethanol) were used throughout the whole synthesis/crystallization procedure. These major advantages indicate the potential of the described process to be used not only in laboratory, but also on a larger scale.

2 Outlook

Although the use of ethanol/water mixtures as green solvents can be seen as advantage of the process, such solvents have one major drawback: a limited solubility of the reaction partners in these solvent systems. The described continuous reactions were carried out at rather low concentrations (35 – 60 mmol/L, depending especially on the solubility of the arylbromide substrate and the biphenyl product). Pandarus *et al.*[6] could intensify a similar process (using SiliaCat DPP-Pd as catalyst) using trinary mixtures of DMF/MeOH/H_2O as reaction solvents (achieving concentrations of 0.5 – 1 mol/L). However, the choice of the reaction solvent proved to be the most critical parameter regarding the catalytic stability of the novel $Ce_{0.49}Sn_{0.49}Pd_{0.01}O_{2-\delta}$-catalyst. Thus, a change of the reaction solvents for the described process is not straightforward, but must be carefully investigated.

In this work, the catalysts were used “as prepared”, that means, as fine powders with characteristic mean mass diameters (x_{50}) of around 30 µm. When used in larger packed bed reactors, the use of such small catalysts particles can lead to a massive pressure drop. In order to produce larger catalyst particles, a further processing of the original catalyst powder (granulation, pelletizing) could be advantageous.

The reactivity of palladium substituted cerium oxide in Heck-type cross-coupling reactions was already reported.[115] In preliminary experiments during this work, a significant reactivity of the used catalysts could also be observed for Miyaura borylation reactions. Such reactions can be used to synthesize rather expensive organoborons, which can be coupled with arylhalides in a subsequent Suzuki-Miyaura cross-coupling reaction. The use of the developed reaction system for continuous Heck cross-coupling reactions or Miyaura borylations could be a possible continuation of the present work.

As described in Capter A2.2.4 (Application of Suzuki-Miyaura Reactions in Organic Synthesis), Suzuki-Miyaura reactions are often only one step in a multi-step synthesis of a desired product. The combination of the developed process with foregoing synthetic processes or subsequent reaction steps and the establishing of a totally continuous full synthesis of a relevant chemical should of course be the final goal of ongoing work.

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