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Multicomponent Reactions

Multicomponent Cascade Synthesis of Biaryl-Based Chalcones in Pure Water and in an Aqueous Micellar Environment

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Dedicated to Professor Achille Umani-Ronchi in occasion of his 80th birthday.

Abstract: The challenging multicomponent cascade synthesis of biaryl-based chalcones was carried out in pure water and in an aqueous micellar system. The first step of the protocol was a simple Pd-catalysed, ligand-free, and aerobic Suzuki–Miyaura reaction in aqueous medium. This proved to be extremely efficient for the coupling of aryl and heteroaryl bromides with different arylboronic acids. Subsequently, the resulting intermediates underwent an in-situ aldol condensation reaction to give biaryl(hetero)chalcones in good to excellent yields. When the protocol was applied to highly lipophilic or less reactive reagents, micellar catalysis was required for good results. To achieve this, we successfully used a new surfactant obtained from renewable resources that we recently designed. Furthermore, using this additive, the catalytic system can be repeatedly recycled without significant loss of activity.

Introduction

From an environmental point of view, the massive use of solvents is highly concerning, since it gives rise to toxicity, hazard, and pollution issues. Moreover, solvents generally account for the major source of waste mass in chemical processes or synthetic routes.[1] Consequently, much effort has been put into the search for sustainable reaction media.[2] In this context, the use of water as solvent has attracted much interest in recent years. In fact, water offers many advantages because it is a cheap, readily available, nontoxic and nonflammable solvent. This makes it very attractive from both an economical and an environmental point of view.[3]

Of the organic reactions that can be conducted in water, cross-coupling[4] and aldol condensation reactions[5] are particularly significant; moreover, these reactions can be coupled together in one-pot and sequential procedures.

The traditional multistep design of complex molecules generally involves several operations, including extraction and purification processes for each single synthetic step. This leads to synthetic inefficiency, and also generates large amounts of waste.

Multicomponent reactions (MCRs) allow several chemical bonds to be generated in a single synthetic operation, and offer notable advantages such as convergence, operational simplicity, and a decrease of the number of work-up and purification steps, thus minimizing the generation of waste. Generally, one-pot MCRs decrease the overall reaction time, and give higher yields than standard multistep syntheses. MCRs are useful for the development of libraries of potential drugs and lead compounds with high levels of molecular complexity and diversity. Therefore, the design of new MCRs that can be run in water[6] has attracted great attention, especially in the areas of drug discovery and materials science.

In the literature, there are a lot of examples involving a Suzuki–Miyaura cross-coupling reaction followed by an aldol or Knoevenagel condensation as the final steps of longer synthetic routes. These synthetic routes are aimed towards the total synthesis of different classes of natural products, such as alkaloids, fungal metabolites, and hetero-polycyclic compounds that show manifold biological activities.[7]

In particular, the one-pot synthesis of biarylchalcones in aqueous medium, through sequential Suzuki–Miyaura coupling and aldol condensation reactions, is a challenging but attractive synthetic route. Unfortunately, the poor solubility of many substrates in water, the incompatibility of some of these with different catalysts, and the formation of β-arylated ketones as side-products still limit the use of this strategy.[8]

Chalcones are relevant natural products, and they are pivotal intermediates in the synthesis of flavonoids and isoflavonoids. Because of their importance, numerous procedures for their preparation have been developed.[9] Chalcones show a wide range of biological activities; some of them show anti-inflam-

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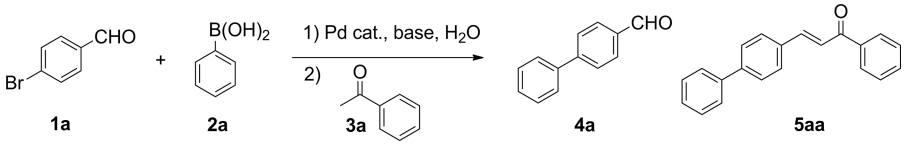
matory, antimicrobial (antibacterial, antifungal), antimalarial, antimitotic, antioxidant, and anticancer properties.

In the chalcone structure, two phenyl rings are linked to a 2-propenone moiety; any alteration of this arrangement is known to result in the loss of their biological activity. Therefore, the two aromatic rings have been extensively modified by appending different hydrophilic or hydrophobic substituents to give a variety of biologically active chalcone-based compounds.[10] As a consequence, biarylchalcones and more complex chalcone derivatives have become important in the field of medicinal chemistry. However, their syntheses are still carried out by two distinct steps using water/organic cosolvents mixtures as reaction media.[11]

Aiming for environmentally sustainable synthetic processes, in this paper we report a highly efficient protocol for the multicomponent cascade synthesis of biaryl(hetero)chalcones and their functionalized derivatives, in pure water or in aqueous micellar system, overcoming the existing drawbacks. The first step of our protocol is a simple Pd-catalysed, ligand-free, aerobic Suzuki–Miyaura reaction in aqueous medium,[12] which proved to be extremely efficient for the coupling of aryl and heteroaryl bromides bearing a carbonyl moiety with different arylboronic acids. In the second step, the third substrate (the appropriate ketone or aldehyde) is added, and this then undergoes an in situ aldol condensation reaction.

A major limitation that is sometimes encountered in this protocol comes from the poor solubility of some substrates, which prevented good results from being obtained. We found an environmentally sustainable solution to this issue by using a new ionic surfactant recently developed by our group.[13] This amphiphilic compound allows the system to undergo micellar catalysis; furthermore, the catalytic system composed of Pd, base, water, and surfactant proved to be highly recyclable without significant loss of activity.

Table 1. Screening of bases and catalysts for the synthesis of biarylchalcone **5aa** in pure water.[a]



1a **2a** **3a** **4a** **5aa**

Entry	Catalyst (amount)	Base	Equiv.	Conv. [%][b]	Yield [%][d]	
					4a	**5aa**
1	$Pd(OAc)_2$ (3 mol-%)	Et_3N	3	100	100	0
2	$Pd(OAc)_2$ (3 mol-%)	nPr_3N	3	100	100	0
3	$Pd(OAc)_2$ (3 mol-%)	nBu_3N	3	100	100	0
4	$Pd(OAc)_2$ (3 mol-%)	DMCHA	3	100	97	3
5	$Pd(OAc)_2$ (3 mol-%)	DMCHA	6	98	98	0
6	$Pd(OAc)_2$ (3 mol-%)	DMAP	3	59[c]	0	0
7	$Pd(OAc)_2$ (3 mol-%)	DBU	3	100[c]	5	4
8	$Pd(OAc)_2$ (3 mol-%)	pyrrolidine	3	99	56	35
9	$Pd(OAc)_2$ (3 mol-%)	K_2CO_3	3	85	82	0
10	$Pd(OAc)_2$ (3 mol-%)	KOH	3	100	96	4
11	$Pd(OAc)_2$ (3 mol-%)	KOH	6	100	4	88 (83)[e]
12	$Pd(OAc)_2$ (3 mol-%)	KOH	9	100	2	81
13	$Pd(OAc)_2$ (1.5 mol-%)	KOH	6	100	15	60
14	Pd/C (3 wt.-%)	KOH	6	100	0	13
15	Pd/C (4 wt.-%)	KOH	6	100	0	25

[a] Reaction conditions: 1) 4-bromobenzaldehyde (**1a**; 0.27 mmol), phenylboronic acid (**2a**; 0.32 mmol), Pd catalyst, base, H_2O (3 mL), 80 °C, 1 h; 2) acetophenone (**3a**; 0.30 mmol), 80 °C, 5 h. [b] Conversion determined by GC–MS [1,3,5-tri(*tert*-butyl)benzene as the internal standard] is referred to **1a**. [c] For characterization of the crude reaction mixtures and identification of the by-products obtained, see the Supporting Information. [d] Yield of product **5aa** determined by GC–MS. [e] Yield of isolated **5aa**.

Results and Discussion

Optimization of Reaction Conditions

The optimal reaction conditions were determined by carrying out a set of experiments. In a model reaction, the Suzuki cross-coupling of 4-bromobenzaldehyde (**1a**; 0.27 mmol) with phenylboronic acid (**2a**; 0.32 mmol), catalysed by $Pd(OAc)_2$ (3 mol-%) was carried out at 80 °C for 1 h in pure water (3 mL) to give biphenyl-4-carbaldehyde (**4a**). This was followed by the addition of acetophenone (**3a**; 0.30 mmol) for an in situ aldol condensation at 80 °C for 5 h, which gave biarylchalcone **5aa** (see Table 1).

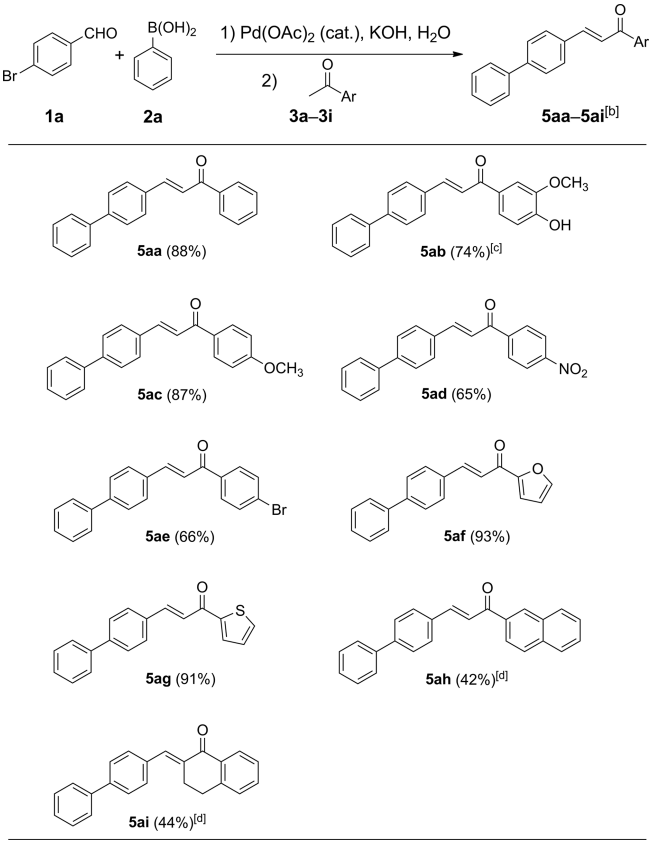
Firstly, we screened different bases: tertiary amines such as Et_3N, nPr_3N, nBu_3N, and *N*,*N*-dimethylcyclohexylamine (DMCHA) promoted the Suzuki coupling reaction very effectively, and resulted in the quantitative formation of intermediate **4a**. However, they were completely ineffective for the aldol condensation, and we did not observe the formation of the desired product (i.e., **5aa**; Table 1, entries 1–4), even when the amount of DMCHA was increased from 3 to 6 equiv. (Table 1, entry 5). When we moved to 4-dimethylaminopyridine (DMAP) and diazabicycloundecene (DBU), only by-products were formed (Table 1, entries 6 and 7).[14] The secondary amine pyrrolidine performed better, and the desired product (i.e., **5aa**) was obtained in 35 % yield (Table 1, entry 8). We realized that strong bases were required at least to promote the aldol condensation, and so we screened some inorganic bases. K_2CO_3 (3 equiv.) was completely ineffective for this reaction (Table 1, entry 9), and when we used 3 equiv. of KOH we obtained only 4 % of **5aa** along with 96 % of intermediate **4a** (Table 1, entry 10). Increasing the amount of KOH to 6 equiv. was, however, successful, and gave 88 % of **5aa** (Table 1, entry 11). Further increasing the amount of KOH did not result in further improvements in the yield (Table 1, entry 12). Although it is still not completely clear why such an excess of base is required to achieve a good yield, we are aware that 2 equiv. of KOH is consumed in the catalytic cycle of the Suzuki cross-coupling reaction.[15] Next, we screened different quantities and types of Pd catalysts: decreasing the amount of $Pd(OAc)_2$ from 3 to 1.5 mol-% gave a lower yield (Table 1, entry 13). Lower yields were also obtained when Pd/C (3 wt.-% and 4 wt.-%) was used (Table 1, entries 14 and 15). Thus, we chose $Pd(OAc)_2$ (3 mol-%) and KOH (6 equiv.) as the optimal conditions for the synthetic protocol.

Later, we focussed on improving the greenness of the work-up procedure. After extracting the crude reaction mixture with ethyl acetate, we isolated pure product **5aa** in very good yield (83 %) by simple recrystallization from methanol, avoiding purification by flash chromatography.

Screening of Different Aromatic Ketones and Additives

After the optimization of the reaction conditions, we explored the scope and limitations of this protocol (Table 2). Therefore, 4-bromobenzaldehyde (**1a**) and phenylboronic acid (**2a**) were coupled in water and subsequently condensed with different aromatic ketones **3a**–**3g** to give biarylchalcones **5aa**–**5ag** in 65–93 % yield. Interestingly, several functional groups were tolerated in the substrates: 4′-hydroxy-3′-methoxyacetophenone (**3b**), 2-acetylfuran (**3f**), and 2-acetylthiophene (**3g**) successfully gave the corresponding hetero-biarylchalcones (i.e., **5ab**, **5af**, and **5ag**, respectively) in good to excellent yields.

Table 2. Cascade Suzuki–aldol reaction of 4-bromobenzaldehyde and phenylboronic acid with different aromatic ketones in water.[a]



[a] Reaction conditions: 1) 4-bromobenzaldehyde (**1a**; 0.27 mmol), phenylboronic acid (**2a**; 0.32 mmol), $Pd(OAc)_2$ (3 mol-%), KOH (6 equiv.), H_2O (3 mL), 80 °C, 1 h; 2) aromatic ketone **3a**–**3i** (0.30 mmol), 80 °C, 5 h. [b] Yield determined by GC–MS (internal standard). [c] KOH (7.1 equiv.) was used. [d] H_2O (2 mL) was used for 15 h in the second step.

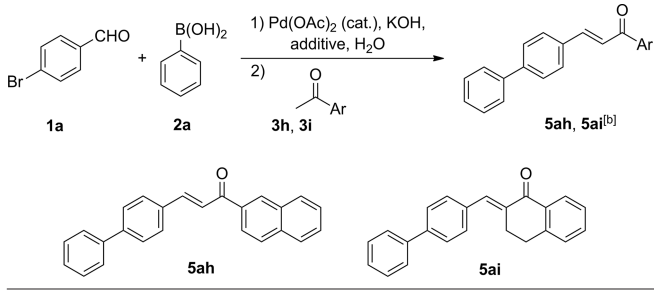
Sharpless et al. used the term "on water" to describe the substantial rate acceleration that is observed when some insoluble organic reactants are stirred in aqueous suspension.[16] McErlean et al. recently proposed a mechanism that explains the phenomenon of on-water catalysis.[17] The protonation of organic substrates at the oil–water interface is driven by the strong adsorption of hydroxide ions to the interface.[18] The protonated species can then undergo acid-catalysed reactions, while the hydroxide ion is sequestered in a deep thermodynamic well. It was also demonstrated that the rate of on-water catalysis was the same in pure water and in water containing NaCl, acid, or NaOH.

Based on this new understanding of acid catalysis on water, we expected that in all cases, the rate of the aldol condensation of intermediate **4a** with aromatic ketones could be accelerated by carrying out the reaction as a heterogeneous suspension of organic droplets in water (the reaction conditions described by Sharpless et al. as "on water"). On the other hand, two highly

lipophilic ketones, 2-acetonaphthone (**3h**) and α-tetralone (**3i**), were poorly reactive under the optimized reaction conditions, and gave low yields of the expected products [i.e., **5ah** (42 %) and **5ai** (44 %)] only at higher concentrations and after longer reaction times.

Therefore, we tested different additives to improve the performance of lipophilic ketones in the reaction (Table 3). The addition of 0.5 equiv. of each selected additive gave different results: we observed lower yields of **5ah**, along with increased amounts of by-products in the presence of tetra-*n*-butylammonium bromide (TBAB) or sodium dodecyl sulfate (SDS) (Table 3, entries 1 and 3). In contrast, we obtained the desired product (i.e., **5ah**) in 87 % yield in the presence of Triton X-100 (Table 3, entry 2). Next, we tested the new surfactant C18-OPC (Figure 1), developed by our research group, and synthesized from itaconic acid.[19] Given that the carboxylic acid moiety of this surfactant is converted into a carboxylate anion under the basic reaction conditions, we slightly increased the amount of KOH, and pleasingly we obtained **5ah** in a comparably high yield (89 %; Table 3, entry 4).

Table 3. Cascade Suzuki–aldol reaction of 4-bromobenzaldehyde and phenylboronic acid with lipophilic aromatic ketones in water, in the presence of different additives.[a]



Entry	Additive	Yield [%][b]	
		5ah	**5ai**
1	TBAB	21	–
2	Triton X-100[c]	87	54
3	SDS	73	–
4	C18-OPC[c]	89	67
5	C18-OPC[c,d]	86	–

[a] Reaction conditions: 1) 4-bromobenzaldehyde (**1a**; 0.27 mmol), phenylboronic acid (**2a**; 0.32 mmol), $Pd(OAc)_2$ (3 mol-%), KOH (6 equiv.), additive (0.5 equiv.), H_2O (3 mL), 80 °C, 1 h; 2) aromatic ketone **3h** or **3i** (0.30 mmol), 80 °C, 5 h. [b] Yield determined by GC–MS (internal standard). [c] KOH (6.5 equiv.) was used. [d] C18-OPC (0.5 equiv.) was added during the second step.

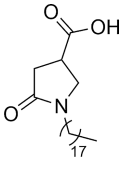


Figure 1. 1-Octadecyl-5-oxopyrrolidine-3-carboxylic acid (C18-OPC).

Moreover, we studied the effect of adding C18-OPC only during the second synthetic step, and we obtained a comparable result; compound **5ah** was obtained in 86 % yield (Table 3, entry 5). This means that in the specific case of the Suzuki coupling reaction of **1a** with **2a**, the addition of C18-OPC had only a minor beneficial effect on the cross-coupling step, in which smaller and less lipophilic molecules are involved. In contrast, C18-OPC was found to be crucial for providing a suitable reaction medium for the subsequent aldol condensation with bulky ketone **3h**.

Encouraged by this result, we compared our surfactant with Triton X-100 also in the presence of α-tetralone (**3i**). By using C18-OPC, we obtained **5ai** in higher yield (67 %; Table 3, entry 4).

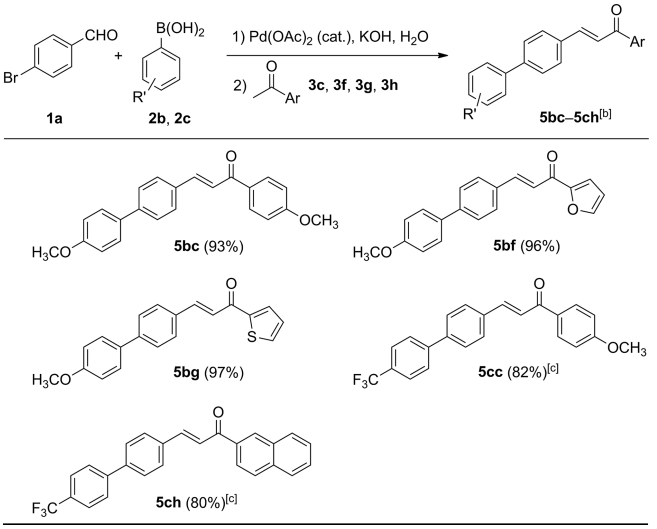
Subsequently, we tested the generality of the previously optimized work-up procedure. Pleasingly, after extracting the crude reaction mixtures with ethyl acetate, we were able to isolate pure products **5ab**–**5ai** by simple recrystallization from methanol without appreciable loss of yield, which confirms the robustness of our work-up procedure.

To the best of our knowledge, there are no reports of the isolation of biaryl-based chalcone derivatives by similar procedures, in which tedious and solvent-consuming chromatographic purifications are avoided.

Screening of Different Arylboronic Acids

Next, the influence of the electronic properties of the arylboronic acid derivatives on the reaction with 4-bromobenzaldehyde was investigated, by carrying out the Suzuki coupling reaction of **1a** with different arylboronic acids (Table 4). (4-Methoxyphenyl)boronic acid (**2b**), bearing a *para* electron-donating group, gave the desired products (i.e., **5bc**–**5bg**) in pure water in excellent yields. On the other hand, [4-(trifluoromethyl)phenyl]boronic acid (**2c**) showed a much lower reactivity in the Suzuki coupling reaction with **1a** in pure water, but

Table 4. Cascade Suzuki–aldol reaction of 4-bromobenzaldehyde and arylboronic acids with different aromatic ketones in water.[a]



[a] Reaction conditions: 1) 4-bromobenzaldehyde (**1a**; 0.27 mmol), arylboronic acid **2b** or **2c** (0.32 mmol), $Pd(OAc)_2$ (3 mol-%), KOH (6 equiv.), H_2O (3 mL), 80 °C, 1 h; 2) aromatic ketone **3c**, **3f**, **3g**, or **3h** (0.30 mmol), 80 °C, 5 h. [b] Yield determined by GC–MS (internal standard). [c] C18-OPC (0.5 equiv.) and KOH (6.5 equiv.) were used for 2 h in the first step.

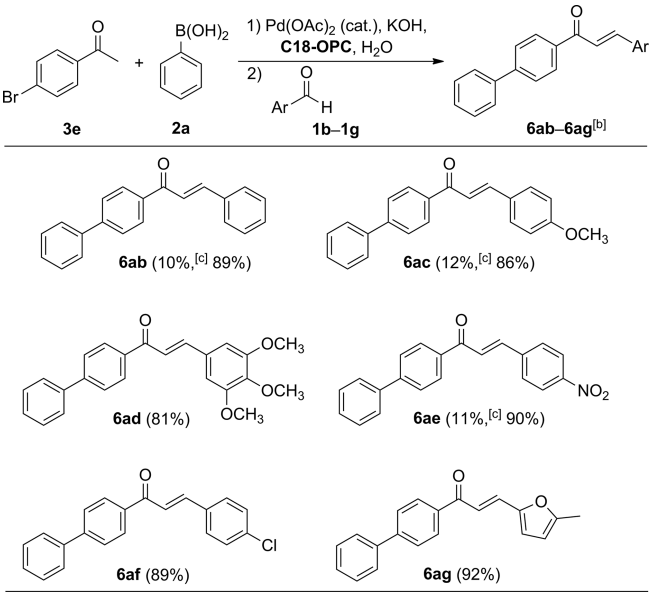
we obtained the expected products (i.e., **5cc** and **5ch**) in high yields under the micellar catalysis conditions (C18-OPC, 0.5 equiv.).

Suzuki Coupling Reaction on the Ketone Moiety Followed by Aldol Condensation

To further extend the flexibility of our synthetic protocol, and to synthesize new biaryl-based chalcones, we changed the halogenated partner in the Suzuki coupling reaction from 4-bromobenzaldehyde (**1a**) to 4-bromoacetophenone (**3e**). The resulting 4-biphenyl methyl ketone can then react with various aromatic aldehydes (Table 5).

In this case, we found that pure water was an unsuitable reaction medium both for the synthesis and for the further aldol condensation of such a nonpolar intermediate ketone (the final yields of **6ab**, **6ac**, and **6ae** in pure water were about 10 %). Therefore, micellar catalysis conditions were used by adding C18-OPC (0.5 equiv.), and this gave the desired products (i.e., **6ab**–**6ag**) in very high to excellent yields. To the best of our knowledge, no deep studies have been published on micellar catalysis (mediated by an environmentally sustainable surfactant) for the synthesis of new biaryl-based chalcone derivatives with such promising results. We also observed that when the micellar catalysis conditions were required, we were able to use the previously optimized work-up procedure and isolate pure products **6ab**–**6ag** without appreciable loss of yield.

Table 5. Cascade Suzuki–aldol reaction of 4-bromoacetophenone and phenylboronic acid with different aromatic aldehydes in water.[a]



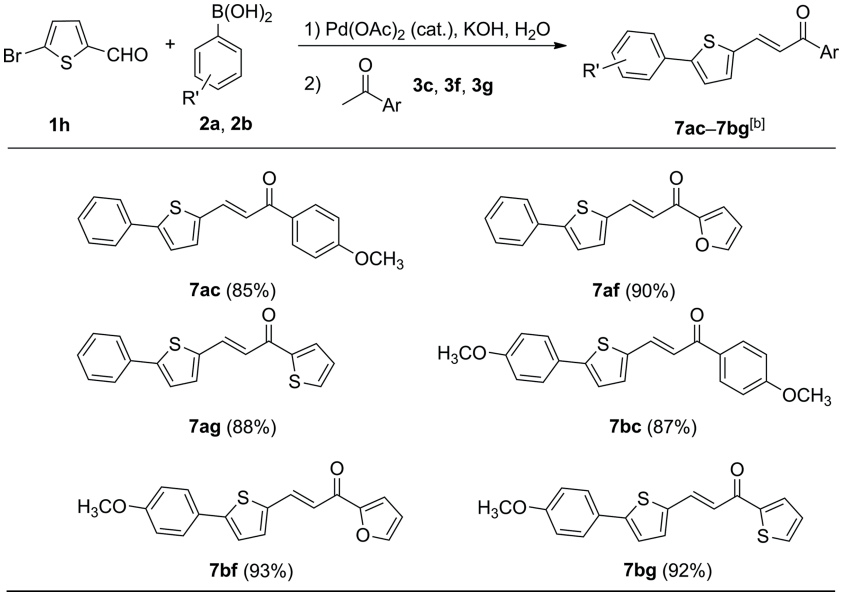
[a] Reaction conditions: 1) 4-bromoacetophenone (**3e**; 0.25 mmol), phenylboronic acid (**2a**; 0.30 mmol), $Pd(OAc)_2$ (3 mol-%), KOH (6.5 equiv.), C18-OPC (0.5 equiv.), H_2O (3 mL), 80 °C, 1 h; 2) aromatic aldehyde **1b**–**1g** (0.28 mmol), 80 °C, 5 h. [b] Yield determined by GC–MS (internal standard). [c] KOH (6 equiv.) and pure water (3 mL) were used.

Synthesis of Thiophene-Centred Biarylchalcones

Thiophene-containing biarylchalcones are intriguing structures for medicinal chemistry, because thiophene nuclei are found in many natural products with promising anticancer, antibacterial, and antifungal activities.[20,21] In particular, a biarylchalcone containing a thiophene nucleus flanked by a phenyl ring on one side and a phenylpropenone on the other side is a scaffold that is found in specific classes of DNA-binding anticancer drugs.[21b]

There are many reports dealing with the synthesis of thiophene-containing biarylchalcones[22] through Suzuki-coupling–

Table 6. Cascade Suzuki–aldol reaction of 5-bromo-2-thiophenecarbaldehyde and arylboronic acids with different aromatic ketones in water.[a]



[a] Reaction conditions: 1) 5-bromo-2-thiophenecarbaldehyde (**1h**; 0.26 mmol), arylboronic acid **2a** or **2b** (0.31 mmol), $Pd(OAc)_2$ (3 mol-%), KOH (6 equiv.), H_2O (3 mL), 80 °C, 1 h; 2) aromatic ketone **3c**, **3f**, or **3g** (0.29 mmol), 80 °C, 5 h. [b] Yield determined by GC–MS (internal standard).

Wittig-olefination reactions,[22a] Vilsmeier–Haack chloroformylation–cyclization reactions,[22b] direct arylation of thiophene-containing alkenes,[22c] and Pd-catalysed C–H olefination of (hetero)arenes with (hetero)aryl ethyl ketones[22e] in the literature. However, some of these methods have drawbacks, such as a requirement for harsh reaction conditions (phosphine reagents, hazardous organic solvents, high temperatures, etc.), and very long reaction times. In particular, (hetero)biarylcarbaldehydes,[23] the key intermediates for the synthesis of (hetero)aryl-centred biarylchalcones, are commonly obtained through cross-coupling reactions that exploit various Pd catalysts containing expensive ligands, such as dialkylbiphenylphosphinyl[23a,23b] or 1,1′-bis(diphenylphosphanyl)ferrocene.[23d]

Bearing in mind the importance of these scaffolds, we tested whether our new protocol could be used for the synthesis of thiophene-centred biarylchalcones (Table 6). 5-Bromo-2-thiophenecarbaldehyde (**1h**) was successfully coupled with phenylboronic acid (**2a**), and a subsequent condensation with selected aromatic ketones (**3c**, **3f**, or **3g**) gave (hetero)biarylchalcones **7ac**–**7ag** in very high yields. We then examined (4-methoxyphenyl)boronic acid (**2b**) as a Suzuki coupling partner for **1h**; the resulting (hetero)biarylcarbaldehyde intermediate condensed with selected aromatic ketones to give the desired products (i.e., **7bc**–**7bg**) in very high to excellent yields.

To the best of our knowledge, there are no reports of Suzuki coupling and aldol condensation reactions being carried out in a cascade manner, using pure water as the reaction medium, for the synthesis of bisthiophene-substituted enone derivatives.

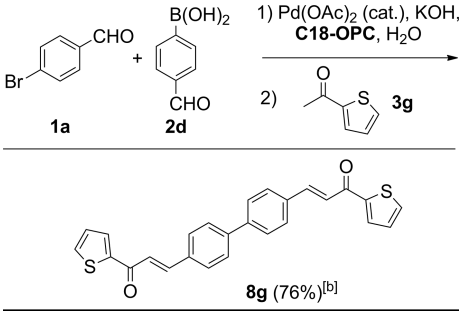
Synthesis of Bischalcones and (Bis)Biarylated-Chalcones

As a final implementation of the synthetic strategy described above, we investigated aldol–Suzuki–aldol and Suzuki–aldol–Suzuki cascade reactions in water, in order to obtain more complex biaryl-based chalcone derivatives. Bischalcones show a wide range of pharmacological properties,[24] including antibacterial activity,[24b,24d] cytotoxic activity against a number of human cancer cell lines,[24a,24e,24f] and anti-inflammatory activity by inhibiting the production of NO.[24c]

We synthesized bischalcone **8g** through an aldol–Suzuki–aldol cascade approach under micellar catalysis conditions achieved by the addition of C18-OPC (0.75 equiv.). We carried out the Suzuki coupling reaction of 4-bromobenzaldehyde (**1a**) with (4-formylphenyl)boronic acid (**2d**), and then a double aldol condensation between the (1,1′-biphenyl)-4,4′-dicarbaldehyde intermediate and aromatic ketone **3g** to give bischalcone **8g** in good yield (Table 7).

We went on to develop a strategy for the synthesis of (bis)biarylated-chalcones.[25] These interesting scaffolds not only have wide-ranging pharmacological properties, including anticancer, antimicrobial, analgesic, and DPPH (2,2-diphenyl-1-picrylhydrazyl) scavenging activities,[25a,25c] but also some of their derivatives are essential components of organic-based electroluminescent devices.[25b] However, an attempted one-pot Suzuki–aldol–Suzuki reaction gave **9b** in only 18 % yield (Table 8). In contrast, when the aldol condensation was carried out first between 4-bromobenzaldehyde (**1a**) and 4-bromoacetophenone

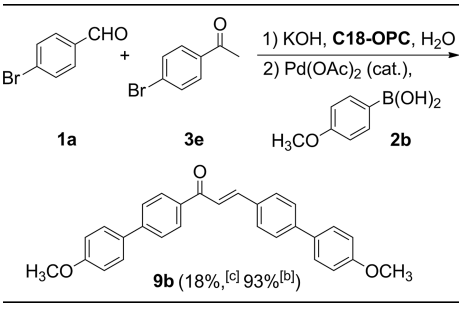
Table 7. Synthesis of bischalcone **8g** by cascade aldol–Suzuki–aldol reaction in water.[a]



[a] Reaction conditions: 1) 4-bromobenzaldehyde (**1a**; 0.27 mmol), (4-formylphenyl)boronic acid (**2d**; 0.32 mmol), $Pd(OAc)_2$ (3 mol-%), KOH (10.75 equiv.), C18-OPC (0.75 equiv.), H_2O (4 mL), 80 °C, 2 h; 2) 2-acetylthiophene (**3g**; 0.59 mmol), 80 °C, 5 h. [b] Yield determined by GC–MS (internal standard).

(**3e**), followed by a double Suzuki coupling reaction between the intermediate 4,4′-dibromochalcone and (4-methoxyphenyl)boronic acid (**2b**), we obtained the expected product (i.e., **9b**) in 93 % yield.

Table 8. Synthesis of (bis)biarylated chalcone **9b** by cascade Suzuki–aldol–Suzuki reaction in water.[a]



[a] Reaction conditions: 1) 4-bromobenzaldehyde (**1a**; 0.27 mmol), 4-bromoacetophenone (**3e**; 0.30 mmol), KOH (8.75 equiv.), C18-OPC (0.75 equiv.), H_2O (5 mL), 80 °C, 2 h; 2) (4-methoxyphenyl)boronic acid (**2b**; 0.65 mmol), $Pd(OAc)_2$ (6 mol-%), 80 °C, 2 h. [b] Yield determined by GC–MS (internal standard). [c] One-pot, 80 °C, 4 h.

We were pleased to obtain the desired products (i.e., **8g** and **9b**) in good to excellent yields, confirming the versatility of our new surfactant C18-OPC in promoting both Suzuki coupling and aldol condensation reactions directed towards the synthesis of highly functionalized biaryl-based chalcone derivatives.

Recycling Tests of Catalytic Systems

The recycling of solvents, additives, and catalysts is one of the main goals of sustainable chemistry. It not only reduces the overall cost of the synthetic process, but it also avoids the generation of waste and potentially polluting materials.

To evaluate the lifetime and reusability of the Pd catalyst, recycling experiments were carried out. First of all, we carried out recycling tests using as a model reaction the synthesis of **5aa** under the best conditions found. When the reaction was complete (i.e., complete consumption of starting material), the product was extracted with ethyl acetate. Further 4-bromo-

benzaldehyde (**1a**), phenylboronic acid (**2a**), KOH, and acetophenone (**3a**) were then added to the remaining aqueous phase. The yields of **5aa** for the first three cycles were 88, 46, and 35 %, respectively, clearly indicating a worsening of the catalyst performance. Next, we investigated whether micellar catalysis conditions (water/C18-OPC) would give better results in the synthesis of **6af**. After the first cycle, the catalytic system composed of Pd, C18-OPC, and H_2O was used in the next run by adding 4-bromoacetophenone (**3e**), phenylboronic acid (**2a**), KOH, and 4-chlorobenzaldehyde (**1f**). In this case, we ran five cycles without any significant loss in activity; the yield of each cycle is shown in Figure 2.

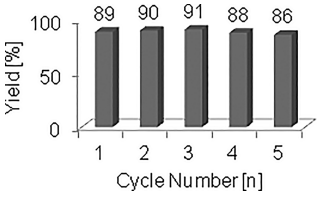


Figure 2. Recycling of the Pd/C18-OPC/H_2O system in the synthesis of biarylchalcone **6af**.

As extensively described in the literature, $Pd(OAc)_2$ in the aqueous phase acts as a catalyst precursor. In fact, it is reduced in situ to give catalytically active Pd^0 species in molecular, colloidal, and nanoparticle forms. Further aggregation of these species occurs in pure water to form larger and less reactive particles, eventually leading to the deposition of Pd black.[26] The addition of additives/stabilizers can prevent this aggregation, significantly prolonging the catalyst's lifespan and making recycling more successful.[27]

Our new surfactant C18-OPC proved to be highly effective for this purpose, probably interacting with the in-situ-generated Pd nanoparticles through its carboxylic moiety. Careful analysis of the extraction medium allowed us to exclude the possibility of any appreciable loss of C18-OPC during the work-up of the reaction; as a result, the whole micellar catalytic system can be used for different cycles, as reported below (Figure 2).

The loss of the Pd catalyst was determined by atomic absorption measurements (GFAAS), and it was found that at the end of each synthetic cycle, the extraction solvent contained approximately 3–7 ppm of Pd (see Table S3 in the Supporting Information). This means that a significant amount of Pd catalyst remained in the aqueous micellar environment, so it could be reused in the next cycle maintaining its high activity.

Conclusions

We have developed a highly efficient synthetic protocol for multicomponent cascade Suzuki–aldol reactions aimed at the synthesis of (hetero)biarylchalcone derivatives in water. In some cases, micellar catalysis gave much better results, when carried out using the new surfactant C18-OPC, developed by our research group and accessible through manipulation of itaconic acid (industrially produced from renewable resources).

A wide range of functional groups were tolerated in the reactants, and good to excellent yields were obtained under the optimized conditions. Furthermore, this synthetic protocol was extended to allow the multiple construction of carbon–carbon bonds through aldol–Suzuki–aldol and Suzuki–aldol–Suzuki cascade reactions carried out in a micellar environment, to obtain more complex biarylchalcones derivatives. This demonstrates the generality and robustness of the developed synthetic routes.

Besides the green reaction medium, our catalytic system showed other sustainable features such as the fact that a Pd catalyst without phosphine ligands was used, and the fact that no significant amount of metal or additive was found in the final product. The most important feature is that the $Pd(OAc)_2$/C18-OPC/H_2O catalytic system could be recycled at least five times without significant loss in activity. Finally, due to the high yields and the fact that few by-products were formed, the pure products could be isolated without a significant loss of material by simple recrystallization from methanol, avoiding chromatographic separation.

The design of similar new catalytic systems and the development of multicomponent tandem/cascade cross-coupling reactions are in progress at our laboratory.

Experimental Section

General Procedures for the Synthesis of Compounds 5aa–9b

Synthesis of Compounds 5aa–5ag: 4-Bromobenzaldehyde (**1a**; 0.27 mmol), phenylboronic acid (**2a**; 0.32 mmol), $Pd(OAc)_2$ (3 mol-%), and KOH (6 equiv.) were dissolved in H_2O (3 mL), and the mixture was stirred at 80 °C for 1 h (until complete conversion of **1a**). Then aromatic ketone **3a**–**3g** (0.30 mmol) was added, and the mixture was stirred at 80 °C for 5 h. The progress of reaction was monitored by TLC and GC–MS. When the reaction was complete, the mixture was cooled to room temp., diluted with water (2 mL), and extracted with ethyl acetate (3 × 5 mL).[28] The combined organic phases were washed with brine, and dried with Na_2SO_4. The solvent was removed under reduced pressure, and the solid residue was purified by recrystallization from methanol to give pure **5aa**–**5ag**.

Synthesis of Compounds 5ah and 5ai: 4-Bromobenzaldehyde (**1a**; 0.27 mmol), phenylboronic acid (**2a**; 0.32 mmol), $Pd(OAc)_2$ (3 mol-%), KOH (6.5 equiv.), and C18-OPC (0.5 equiv.) were dissolved in H_2O (3 mL), and the mixture was stirred at 80 °C for 1 h (until complete conversion of **1a**). Then aromatic ketone **3h** or **3i** (0.30 mmol) was added, and the mixture was stirred at 80 °C for 5 h. The progress of reaction was monitored by TLC and GC–MS. When the reaction was complete, the same work-up procedure described above was adopted to give pure **5ah** and **5ai**.

Synthesis of Compounds 5bc–5bg: 4-Bromobenzaldehyde (**1a**; 0.27 mmol), (4-methoxyphenyl)boronic acid (**2b**; 0.32 mmol), $Pd(OAc)_2$ (3 mol-%), and KOH (6 equiv.) were dissolved in H_2O (3 mL), and the mixture was stirred at 80 °C for 1 h (until complete conversion of **1a**). Then aromatic ketone **3c**, **3f**, or **3g** (0.30 mmol) was added, and the mixture was stirred at 80 °C for 5 h. The progress of reaction was monitored by TLC and GC–MS. When the reaction was complete, the same work-up procedure described above was adopted to give pure **5bc**–**5bg**.

Synthesis of Compounds 5cc and 5ch: 4-Bromobenzaldehyde (**1a**; 0.27 mmol), [4-(trifluoromethyl)phenyl]boronic acid (**2c**; 0.32 mmol), $Pd(OAc)_2$ (3 mol-%), KOH (6.5 equiv.), and C18-OPC (0.5 equiv.) were dissolved in H_2O (3 mL), and the mixture was stirred at 80 °C for 2 h (until complete conversion of **1a**). Then aromatic ketone **3c** or

3h (0.30 mmol) was added, and the mixture was stirred at 80 °C for 5 h. The progress of reaction was monitored by TLC and GC–MS. After the reaction was complete, the same work-up procedure described above was adopted to give pure **5cc** and **5ch**.

Synthesis of Compounds 6ab–6ag: 4-Bromoacetophenone (**3e**; 0.25 mmol), phenylboronic acid (**2a**; 0.30 mmol), $Pd(OAc)_2$ (3 mol-%), KOH (6.5 equiv.), and C18-OPC (0.5 equiv.) were dissolved in H_2O (3 mL), and the mixture was stirred at 80 °C for 1 h (until complete conversion of **3e**). Then aromatic aldehyde **1b**–**1g** (0.28 mmol) was added, and the mixture was stirred at 80 °C for 5 h. The progress of reaction was monitored by TLC and GC–MS. When the reaction was complete, the same work-up procedure described above was adopted to give pure **6ab**–**6ag**.

Synthesis of Compounds 7ac–7bg: 5-Bromothiophene-2-carbaldehyde (**1h**; 0.26 mmol), arylboronic acid **2a** or **2b** (0.31 mmol), $Pd(OAc)_2$ (3 mol-%), and KOH (6 equiv.) were dissolved in H_2O (3 mL), and the mixture was stirred at 80 °C for 1 h (until complete conversion of **1h**). Then aromatic ketone **3c**, **3f**, or **3g** (0.29 mmol) was added, and the mixture was stirred at 80 °C for 5 h. The progress of reaction was monitored by TLC and GC–MS. When the reaction was complete, the same work-up procedure described above was adopted to give pure **7ac**–**7bg**.

Synthesis of Compound 8g: 4-Bromobenzaldehyde (**1a**; 0.27 mmol), (4-formylphenyl)boronic acid (**2d**; 0.32 mmol), $Pd(OAc)_2$ (3 mol-%), KOH (10.75 equiv.), and C18-OPC (0.75 equiv.) was dissolved in H_2O (4 mL), and the mixture was stirred at 80 °C for 2 h (until complete conversion of **1a**). Then 2-acetylthiophene (**3g**; 0.59 mmol) was added, and the mixture was stirred at 80 °C for 5 h. The progress of reaction was monitored by TLC and GC–MS. When the reaction was complete, the mixture was cooled to room temp., diluted with water (2 mL), and extracted with ethyl acetate (3 × 6 mL). The combined organic phases were washed with brine, and dried with Na_2SO_4. The solvent was removed under reduced pressure, and the solid residue was purified by recrystallization from methanol to give pure **8g**.

Synthesis of Compound 9b: 4-Bromobenzaldehyde (**1a**; 0.27 mmol), 4-bromoacetophenone (**3e**; 0.30 mmol), KOH (8.75 equiv.), and C18-OPC (0.75 equiv.) were dissolved in H_2O (5 mL), and the mixture was stirred at 80 °C for 2 h (until complete conversion of **1a**). Then (4-methoxyphenyl)boronic acid (**2b**; 0.65 mmol) and $Pd(OAc)_2$ (6 mol-%) were added, and the mixture was stirred at 80 °C for 2 h. The progress of reaction was monitored by TLC and GC–MS. When the reaction was complete, the mixture was cooled to room temp., diluted with water (2 mL), and extracted with ethyl acetate (3 × 7 mL). The combined organic phases were washed with brine, and dried with Na_2SO_4. The solvent was removed under reduced pressure, and the solid residue was purified by recrystallization from methanol to give pure **9b**.

General Procedure for Recycling Test of the Pd/H_2O Catalytic System: 4-Bromobenzaldehyde (**1a**; 0.27 mmol), phenylboronic acid (**2a**; 0.32 mmol), $Pd(OAc)_2$ (3 mol-%), and KOH (6 equiv.) were dissolved in H_2O (3 mL), and the mixture was stirred at 80 °C for 1 h (until complete conversion of **1a**). Then acetophenone (**3a**; 0.30 mmol) was added, and the mixture was stirred at 80 °C for 5 h. The progress of reaction was monitored by TLC and GC–MS. When the reaction was complete, the mixture was cooled to room temp., diluted with water (2 mL), and extracted with ethyl acetate (3 × 5 mL). The combined organic phases were washed with brine, and dried with Na_2SO_4. The solvent was removed under reduced pressure, and the solid residue containing the product (i.e., **5aa**) was stored. After the first cycle, the aqueous phase containing the Pd catalyst and the base was subjected to the next run by adding 4-bromobenzaldehyde (**1a**; 0.27 mmol), phenylboronic acid (**2a**; 0.30 mmol), KOH (2 equiv.), and acetophenone (**3a**; 0.30 mmol) under the same reaction conditions. At the end of each of the later runs, the same work-up procedure described above was adopted. The solid residues obtained at the end of the three runs, each containing the product (i.e., **5aa**), were stored separately for subsequent determination of the amount of Pd catalyst lost during the work-up procedure.

General Procedure for Recycling Test of the Pd/C18-OPC/H_2O Catalytic System: 4-Bromoacetophenone (**3e**; 0.25 mmol), phenylboronic acid (**2a**; 0.30 mmol), $Pd(OAc)_2$ (3 mol-%), KOH (6.5 equiv.), and C18-OPC (0.5 equiv.) were dissolved in H_2O (3 mL), and the mixture was stirred at 80 °C for 1 h (until complete conversion of **3e**). Then 4-chlorobenzaldehyde (**1f**; 0.28 mmol) was added, and the mixture was stirred at 80 °C for 5 h. The progress of reaction was monitored by TLC and GC–MS. When the reaction was complete, the mixture was cooled to room temp., diluted with water (2 mL), and extracted with ethyl acetate (3 × 5 mL). The combined organic phases were washed with brine, and dried with Na_2SO_4. The solvent was removed under reduced pressure, and the solid residue containing the product (i.e., **6af**) was stored. After the first cycle, the aqueous phase containing the Pd catalyst, C18-OPC, and the base was subjected to the next run by adding 4-bromoacetophenone (**3e**; 0.25 mmol), phenylboronic acid (**2a**; 0.30 mmol), KOH (2 equiv.), and 4-chlorobenzaldehyde (**1f**; 0.28 mmol) under the same reaction conditions. At the end of each of the later runs, the same work-up procedure described above was adopted. H_2O (0.5 mL) was added to the catalytic system in the third run. The solid residues obtained at the end of the five runs, each containing the product (i.e., **6af**), were stored separately for subsequent determination of the amount of Pd catalyst lost during the work-up procedure.

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[28] For compound **5ab**, the cold reaction mixture was slightly acidified with an aqueous hydrochloric acid solution, and subsequently extracted with ethyl acetate (3 × 5 mL).

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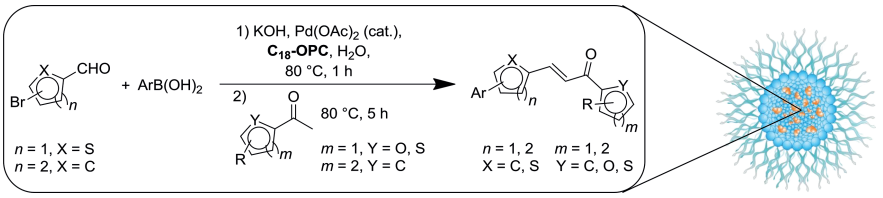
Multicomponent Reactions



The multicomponent cascade synthesis of biaryl-based chalcones was carried out in pure water and in an aqueous micellar system. The first step of the protocol was a simple Pd-catalysed, ligand-free, and aerobic Suzuki–Miyaura reaction in aqueous medium. The resulting intermediates then underwent an in-situ aldol condensation reaction to give biaryl(hetero)chalcones in good to excellent yields.

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