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Water Compatible Multicomponent Cascade Suzuki/Heck–Aldol, Suzuki–Aldol–Suzuki, and Aldol–Suzuki–Aldol Reactions: An Ecofriendly Paradigm for Multiple Carbon−Carbon Bond Formation in One Pot

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Water is the most precious and abundant liquid on earth and is the solvent of choice in nature for biochemical and chemical reactions. In this context, the pioneering research by Rideout and Breslow[1] in the early 1980s on Diels–Alder reactions in water triggered more widespread interest because of sustainable environmental and economic concerns over conventional reactions in organic solvents.

Among various organic transformations in water,[2] Suzuki–Miyaura (S–M) cross-coupling[3] and Aldol condensation (AC) reactions[4] occupy esteemed positions as both reactions tend to enrich molecular diversity by formation of C−C and C=C bonds, respectively. However, cascade reactions involving Suzuki–Miyaura cross-coupling and Aldol condensation reactions in one pot in an aqueous environment for the generation of biarylchalcones (C_6-C_6-C=C-CO-C_6) is an important but still challenging transformation because of oxidative scission of the double bond in the presence of palladium catalysts,[5] the dehydroboration of boronic acids with water at elevated temperatures,[6] and the formation of β-arylated ketones as a side product.[7]

Biarylchalcones have gained significance in the field of medicinal chemistry because of their anticancer activities[8] (Figure 1). However, their synthesis[8,9] either proceeds through one-pot two-step processes or in water–co-solvent mixtures as the reaction media. Recently, the synergy between multicomponent and cascade reactions has emerged as a tool for the generation of multifunctional molecules in an operationally simple manner with the fewest possible steps and high atom economy.[10] Therefore, it would be the icing on the cake if a multicomponent cascade synthesis of biarylchalcones was found that could be carried out solely in an aqueous medium by overcoming the existing issues,[5–9] including the incompatibility of the catalysts with different substrates and their insolubility in water.

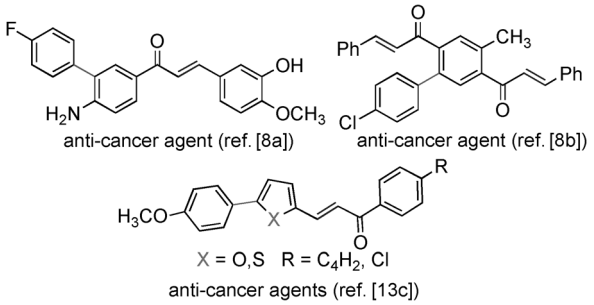

Figure 1. Biologically potent biaryl(hetero)chalcone scaffolds.

In continuation of our interest in the development of tandem/sequential cross-coupling methods,[11] we herein present a water-compatible, highly efficient multicomponent cascade Suzuki–Miyaura–Aldol (S–M–A) reaction of readily available precursors, to form biaryl(hetero)chalcones without the requirement for a ligand or an organic solvent (Scheme 1). This further enabled the construction of multiple carbon–carbon bonds in one pot through Suzuki–Miyaura–Aldol–Suzuki–Miyaura (S–M–A–S–M) and Aldol–Suzuki–Miyaura–Aldol (A–S–M–A) reactions in pure water.

After an initial survey of reaction conditions, a mixture of 4-bromobenzaldehyde (**1a**, 0.05 g), phenylboronic acid (**2a**, 1.2 equiv), and acetophenone (**3a**, 1.1 equiv) was heated at 90 °C for 6 h in water (4 mL) with $Pd(OAc)_2$ (4 mol %) as the catalyst, Na_2CO_3 (2 equiv) as the base and tetrabutylammonium bromide (TBAB; 1.0 equiv) as the phase-transfer catalyst (PTC). The crude reaction mixture was then analyzed by RP-HPLC (see the Supporting Information), which confirmed the formation of the desired (2*E*)-1-phenyl-3-(4-phenylphenyl)prop-2-en-1-one (**5a**) in 51 % yield along with the intermediate biphenyl-4-carboxaldehyde (**4a**) in 31 % yield (Table 1, entry 1). To further increase the yield of **5a**, different bases (Table 1, entries 2–8) were screened by using TBAB as the PTC, and a maximum yield of 56 % was obtained in 6 h when K_2CO_3 was used as the base (Table 1, entry 2).

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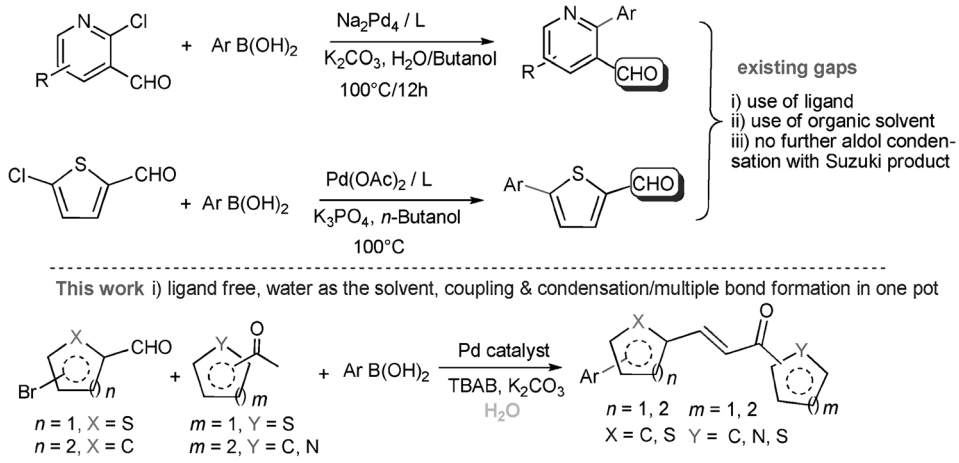
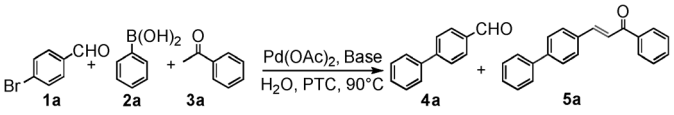


Scheme 1. Water compatible multicomponent cascade synthesis of biaryl(hetero)chalcones through a Suzuki–Miyaura–Aldol strategy. The top reaction is reported in Reference [15d] and the middle reaction is reported in Reference [15b]

Table 1. Screening of different bases and PTCs for the synthesis of biarylchalcones through the Suzuki–Miyaura–Aldol strategy in water.[a]



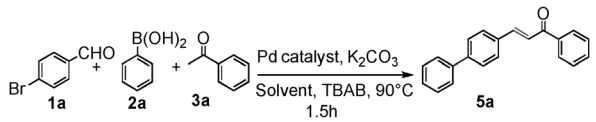
Entry	Base	PTC	Time [h]	Yield [%][b] 4a	5a
1	Na_2CO_3	TBAB	6	31	51 (45)[c]
2	K_2CO_3	TBAB	6	29	56 (50)[c]
3	$NaHCO_3$	TBAB	6	79	11
4	Cs_2CO_3	TBAB	6	30	27
5	NH_4OAc	TBAB	6	78	11
6	KOH	TBAB	6	65	25
7	NaOAc	TBAB	6	79	12
8	Na_2CO_3 + NaOAc	TBAB	6	70	3
9	K_2CO_3	TBAI	6	73	8
10	K_2CO_3	TBACl	6	83	7
11	K_2CO_3	TBAF	6	57	10
12	K_2CO_3	CTAB	6	36	27
13	K_2CO_3	BTMAB	6	85	2
14[d]	K_2CO_3	TBAB	5	25	60
15[e]	K_2CO_3	TBAB	3	18	65
16[e,f]	K_2CO_3	TBAB	1.5	10	70
17[e,g]	K_2CO_3	TBAB	1.5	5	77 (70)[c]
18[g]	K_2CO_3	–	6	39	3

[a] General conditions: **1a** (0.05 g), phenylboronic acid (1.2 equiv), acetophenone (1.1 equiv), $Pd(OAc)_2$ (4 mol%), base (2.0 equiv), PTC (1.0 equiv), H_2O (4 mL), 90°C; [b] yield on the basis of HPLC; [c] yield of the isolated product is given in parentheses; [d] 1.2 equiv of TBAB were used; [e] 1.3 equiv of TBAB were used; [f] 3 equiv of base were used; [g] 4 equiv of base were used.

Thereafter, different PTCs (Table 1, entries 9–13) were screened in combination with K_2CO_3. The maximum yield of **5a** (77%; based on HPLC analysis, see the Supporting Information) was obtained with 1.3 equivalents of TBAB and 4 equivalents of K_2CO_3 in a shorter reaction time of 1.5 h (Table 1, entry 17). Product **5a** was obtained in only 3% yield in the absence of TBAB (Table 1, entry 18). This clearly emphasizes the crucial threefold role of TBAB to 1) increase solvation; 2) increase the rate of the coupling reaction by activating the boronic acid to form $[ArB(OH)_3]^-$-$[R_4N]^+$;[3i] and 3) efficiently facilitate the condensation reaction.

To further improve the yield of **5a**, different Pd catalysts (Table 2, entries 1–3) were screened, but unfortunately **5a** was obtained in inferior yields with all catalysts except $Pd(OAc)_2$ (Table 1, entry 17). Finally, the maximum yield of **5a** (79%, isolated) was obtained with 1 mol% $Pd(OAc)_2$ (Table 2, entry 6). Furthermore, the use of different co-solvents failed to have a positive influence on the yield of **5a** (Table 2 entries 8 and 9).

Table 2. Screening of different palladium catalysts and solvents for the synthesis of a biarylchalcone through the Suzuki–Miyaura–Aldol strategy.[a]



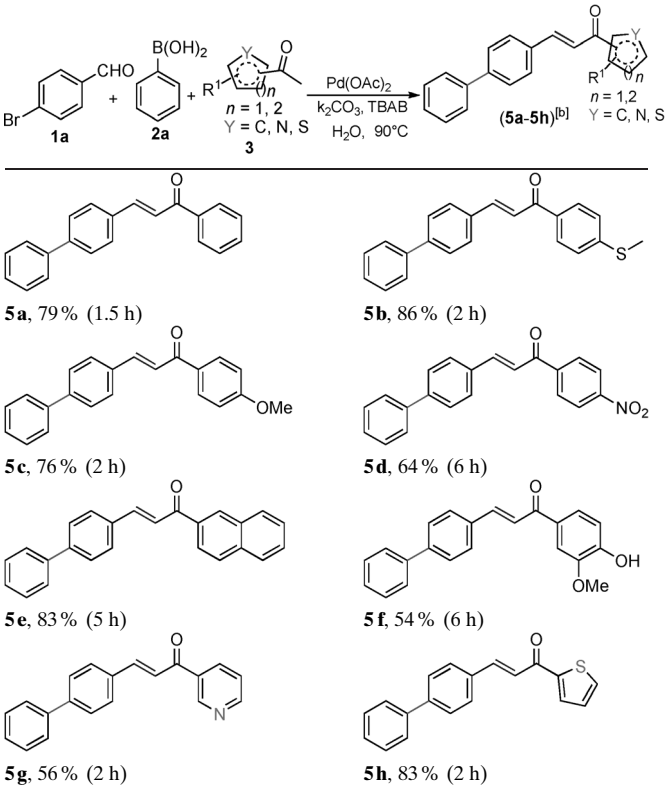
Entry	Pd catalyst	[mol%]	Solvent	Yield [%][b]
1	$PdCl_2$	4	H_2O	59
2	$[PdCl_2(PPh_3)_2]$	4	H_2O	62
3	Pd/C	4	H_2O	45
4	$Pd(OAc)_2$	3	H_2O	75
5	$Pd(OAc)_2$	2	H_2O	77
6	$Pd(OAc)_2$	1	H_2O	79
7	$Pd(OAc)_2$	0.5	H_2O	70
8	$Pd(OAc)_2$	1	H_2O + EtOH	68
9	$Pd(OAc)_2$	1	H_2O + THF	39

[a] General conditions: **1a** (0.05 g), phenylboronic acid (1.2 equiv), acetophenone (1.1 equiv), Pd catalyst, K_2CO_3 (4 equiv), TBAB (1.3 equiv), H_2O (4 mL), 90°C. [b] Yield of the isolated product.

With the optimized reaction conditions in hand, we set out to explore the substrate scope of this method (Table 3). For this, 4-bromobenzaldehyde (**1a**) and phenyl boronic acid (**2a**) were coupled in water and subsequently condensed in the same pot with various electronically different acetophenones (**3a–e**) and in the presence of a hydroxyl-containing reagent (**3f**), without relying on protection and deprotection strategies, to form biarylchalcones (**5a–f**) in varying yields (54–86%). Interestingly, acetyl derivatives of pyridine and thiophene (**3g** and **h**) also successfully afforded heterobiarylchalcones (**5g** and **h**) in 56 and 83% yields, respectively.

On reversing the halogen coupling partner of the Suzuki–Miyaura coupling, that is, replacing 4-bromobenzaldehyde (**1a**; Table 3) with 4-bromoacetophenone (**3aa**), a reduced

Table 3. Cascade Suzuki- Miyaura-Aldol reaction of 4-bromobenzaldehyde and aryl boronic acid with different acetophenones in water.[a]



[a] Reaction conditions: **1a** (0.05 g), aryl boronic acid (1.2 equiv), acetophenone (1.1 equiv), $Pd(OAc)_2$ (1 mol %), K_2CO_3 (4 equiv), TBAB (1.3 equiv), H_2O (4 mL), 90 °C. [b] Yield of the isolated product.

yield of **5i** and **5j** (69 and 72 %, respectively), containing C_6-C_6-CO-C=C-C_6 units, in comparison to **5a** and **5b** (79 and86 %, respectively), containing C_6-C_6-C=C-CO-C_6 units was observed (Scheme 2).

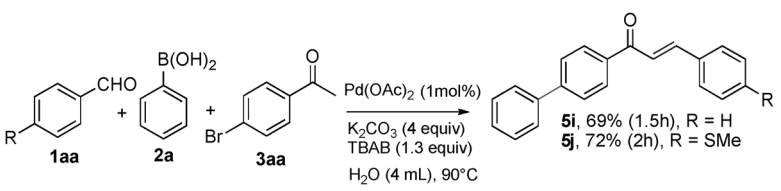
In consideration of the effect of choosing 4-bromobenzaldehyde (**1a**) instead of 4-bromoacetophenone (**3aa**), the generality of the optimized reaction conditions was tested with different substituted boronic acids (**2**) as the coupling partner with 4-bromobenzaldehyde (**1a**) and a selection of acetophenones (**3**) for the construction of biaryl-(hetero)chalcones (**6a–h**). The results are shown in Table 4.

While implementing the study into the substrate scope (Tables 3 and 4), we observed that thiophene-containing biarylchalcone **5h** (Table 3) was obtained in excellent yield (83 %). This scaffold has attracted the attention of synthetic and medicinal chemists because thiophene nuclei are found in many natural products that show promising biological activities,[12] including anticancer, antibacterial, and antifungal activities.[13] Specifically, a thiophene nucleus flanked by a phenyl ring on one side and a phenylpropenone on the other imparted significant anti-breast-cancer activity.[13d]

There are a handful of reports for the synthesis of thiophene-centered biarylchalcones[14] through Suzuki-coupling–Wittig-olefination reactions,[14a] direct arylation of thiophene-containing alkenes,[14b] and arylation of thiophene carboxaldehyde followed by Aldol condensation;[13d] however, these methods are plagued by several limitations, such as the requirement for one-pot two-step reactions, low selectivity for the product, and longer reaction times. Moreover, heterobiarylcarboxaldehyde,[15] a key intermediate for the synthesis of thiophene-centered biarylchalcones, is usually formed in the presence of expensive ligand, such as dialkylbiphenylphosphinyl,[15a,b] with a metal catalyst in an organic solvent. Keeping in mind the importance of the thiophene scaffold, we were also intrigued to investigate whether our catalytic system could efficiently result in the synthesis of thiophene-centered biarylchalcone **7a** by overcoming the existing gaps in reported protocols.[14,15]

Pleasingly, 5-bromo-2-thiophene carboxaldehyde (**1aaa**) successfully coupled with arylboronic acid (**2a**) and subsequently condensed with 4-(methylthio)acetophenone (**3b**) in a cascade manner, providing **7a** in 84 % yield. Thereafter, different substituted boronic acids (**2**) were coupled with **1aaa** and subsequently condensed with different acetophenones, to afford thiophene-centered biarylchalcones (Table 5, **7b–e**) in good to excellent yields. To the best of our knowledge, there are no reports available in which S–M cross-coupling and AC reactions were carried out in a cascade manner employing water as the sole reaction medium for the synthesis of **7a–e**. Furthermore, the significance of the method was demonstrated through the successful coupling and condensation of two thiophene moieties to form bisthiophene-substituted enone derivatives (Table 5, **7f–h**) in moderate to good yields.

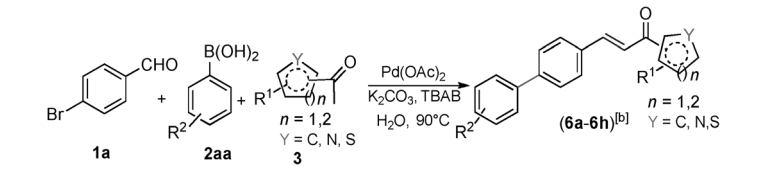
Under the optimized conditions, a double Suzuki–Miyaura–Aldol reaction is also possible, allowing the formation of interesting bisbiarylated chalcone **8a** (Scheme 3) in 76 % yield, with facile generation of multiple carbon–carbon bonds (i.e., one C=C and two C–C bonds) in one pot through a Suzuki–Miyaura–Aldol–Suzuki–Miyaura (S–M–A–S–M) reaction.

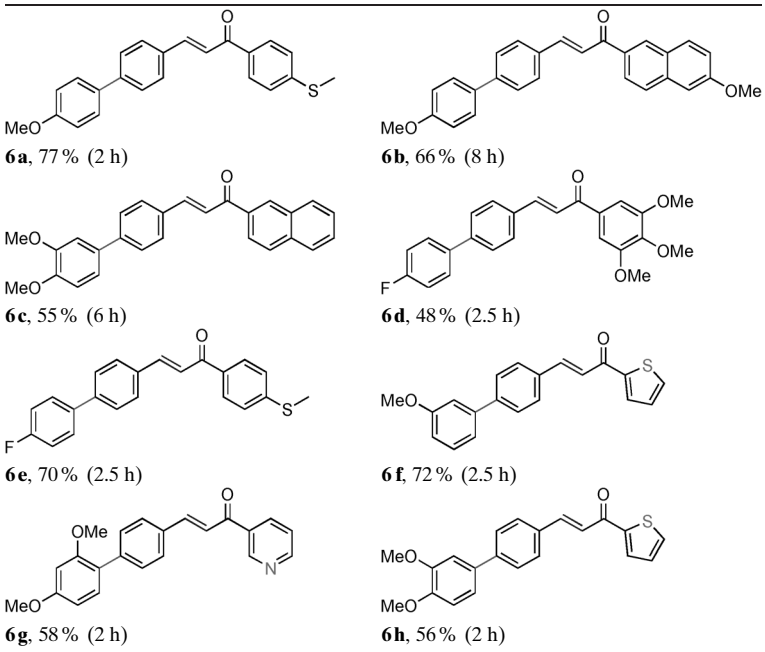


Scheme 2. Cascade Suzuki–Miyaura–Aldol reaction between 4-bromoacetophenone, aryl boronic acid, and benzaldehyde.

It is known that bischalcones possess wide-ranging medicinal profiles including antimicrobial, cytotoxic, and anti-inflammatory activities.[16] Thus, bischalcone **9a** (Scheme 4) was also synthesized by using an Aldol–Suzuki–Miyaura–Aldol (A–S–M–A) approach in a one-pot process, whereas an

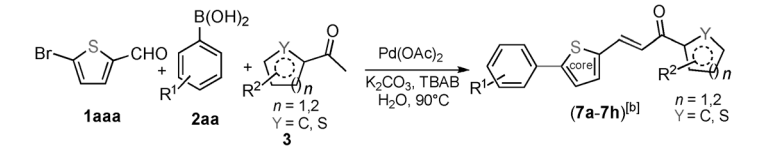
Table 4. Cascade Suzuki–Miyaura–Aldol reaction of different aryl boronic acids with 4-bromobenzaldehyde and various acetophenones in water.[a]

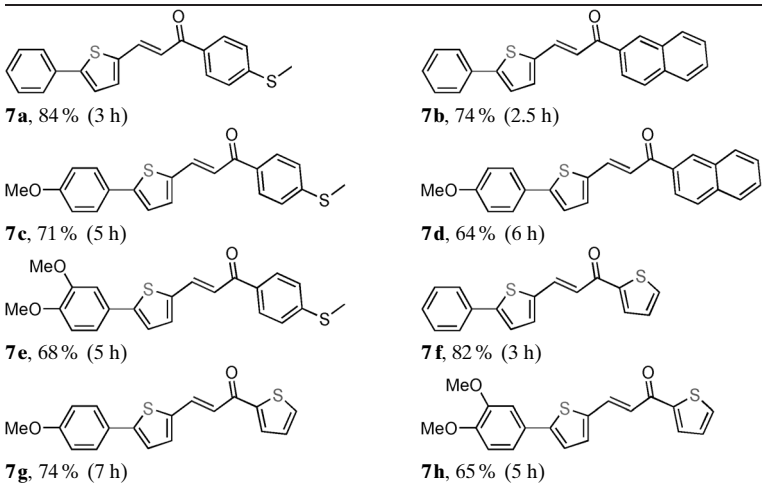




[a] Reaction conditions: **1a** (0.05 g), aryl boronic acid (1.2 equiv), acetophenone (1.1 equiv), $Pd(OAc)_2$ (1 mol%), K_2CO_3 (4 equiv), TBAB (1.3 equiv), H_2O (4 mL), 90°C. [b] Yield of the isolated product.

Table 5. Cascade synthesis of thiophene-centered biarylchalcones in water through the Suzuki–Miyaura–Aldol reaction.[a]





[a] Reaction conditions: **1a** (0.05 g), aryl boronic acid (1.2 equiv), acetophenone (1.1 equiv), $Pd(OAc)_2$ (1 mol%), K_2CO_3 (4 equiv), TBAB (1.3 equiv), H_2O (4 mL), 90°C. [b] Yield of the isolated product.

analogue of **9a** was previously synthesized by a six-step route,[16c] demonstrating the generality and robustness of our protocol.

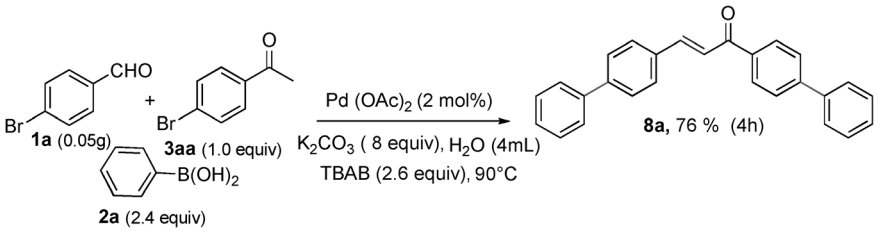
Finally, the methodology was successfully extended to the synthesis of a hybrid molecule, stilbenechalcone **10a** (Scheme 5), in 53% yield by using a cascade Mizoroki–Heck–Aldol (M–H–A) strategy. It is worth mentioning that similar hybrid molecules are known to possess potent biological profiles against malaria.[11d]

Mechanistically, it is presumed that there are two plausible pathways for the synthesis of biaryl chalcone **5a**, that is, an Aldol–Suzuki–Miyaura reaction (path A) or a Suzuki–Miyaura–Aldol reaction (path B; Scheme 6). In path A, 4-bromobenzaldehyde (**1a**) and acetophenone (**3a**) condense first, leading to the formation of an aldol intermediate (i.e., a bromochalcone), which is then coupled with phenylboronic acid (**2a**) in the presence of the Pd catalyst to afford the desired product **5a**. In path B, in situ generated biaryl benzaldehyde **4a**, formed through cross-coupling of 4-bromobenzaldehyde (**1a**) with phenylboronic acid (**2a**), subsequently condenses with acetophenone (**3a**) to provide **5a**. Therefore, to prove the exact pathway, we performed HPLC analysis of the reaction mixture at different time intervals, which revealed the formation of product **5a** via intermediate **4a** (see the Supporting Information), thus revealing that the Suzuki–Miyaura–Aldol reaction (path B) is the predominant path for the synthesis of **5a**.

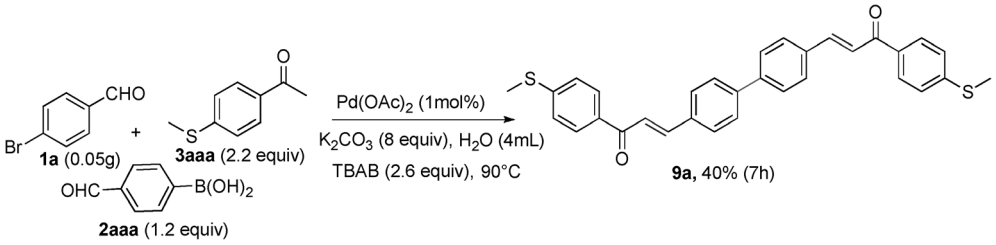
In summary, we have developed a highly efficient, water compatible catalytic system for multicomponent cascade Suzuki–Miyaura–Aldol reactions for the generation of biaryl-(hetero)chalcones. In addition, we have uncovered the threefold role of TBAB, which governs the efficiency of the cross-coupling and condensation reactions in one pot. Moreover, the method was expanded for the cascade Suzuki–Miyaura–Aldol–Suzuki–Miyaura, Aldol–Suzuki–Miyaura–Aldol, and Mizoroki–Heck–Aldol reactions to form multiple carbon–carbon bonds in one pot, adding benefits to its practical utility. Overall, the developed method is carbon economic, ligand-free, environmentally friendly, devoid of the use of toxic reagents/solvents, and has wide substrate scope. We anticipate that this catalytic system will find applications in academia and industry.

Experimental Section

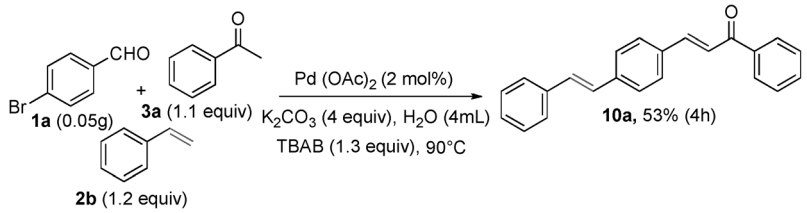
Representative procedure: A mixture of 4-bromobenzaldehyde (**1a**, 0.05 g), boronic acid **2a** (1.2 equiv), acetophenone (**3a**, 1.1 equiv), $Pd(OAc)_2$ (1 mol%), K_2CO_3 (4 equiv), tetra-



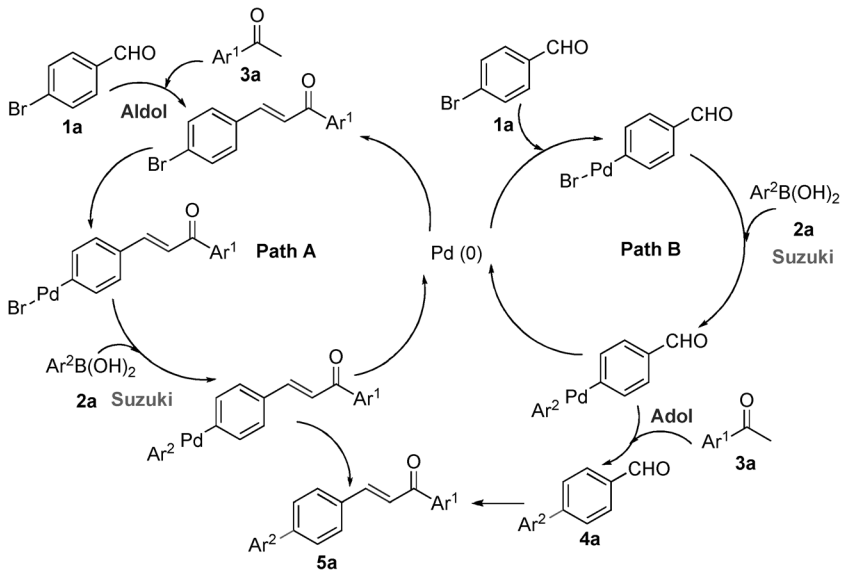
Scheme 3. Cascade Suzuki–Miyaura–Aldol–Suzuki–Miyaura reaction in water.



Scheme 4. Cascade Aldol–Suzuki–Miyaura–Aldol reaction in water.



Scheme 5. Cascade Mizoroki–Heck–Aldol reaction in water.



Scheme 6. Proposed mechanism for the cascade Suzuki–Miyaura–Aldol reaction.

butylammonium bromide (TBAB; 1.3 equiv), and water (4 mL) was heated at 90 °C for 1.5 h. Thereafter, the reaction mixture was acidified with dilute HCl and extracted with dichloromethane (2×20 mL). The combined organic layers were washed with water (2×10 mL), dried over Na_2SO_4, and concentrated under vacuum. The obtained residue was subsequently purified by column chromatography on silica gel (60–120 mesh size) using ethyl acetate (10%) in hexane to give a yellow solid, which was then recrystallized from methanol to provide pure **5a** in 79% yield.

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Keywords: chalcones · condensation · cross-coupling · domino reactions · water chemistry

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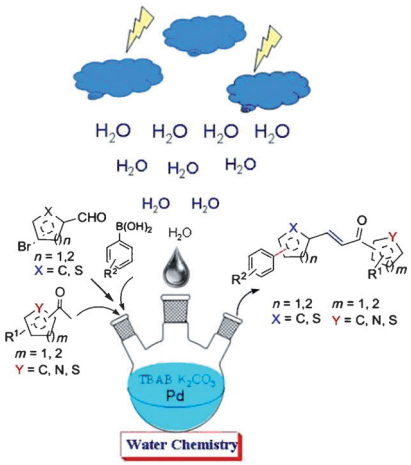
Aryls in hot water: A versatile strategy has been devised for the synthesis of biologically active biaryl-(hetero)chalcones from readily available precursors (see scheme). The method is step, pot, and carbon economic, ligand-free, devoid of toxic reagents/solvents, and has wide substrate scope.



Water Chemistry

*R. Kumar, Richa, N. H. Andhare, A. Shard, A. K. Sinha** ..... ▮▮▮▮–▮▮▮▮

Water Compatible Multicomponent Cascade Suzuki/Heck–Aldol, Suzuki–Aldol–Suzuki, and Aldol–Suzuki–Aldol Reactions: An Ecofriendly Paradigm for Multiple Carbon–Carbon Bond Formation in One Pot