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Stille coupling for the synthesis of isoflavones by a reusable palladium catalyst in water

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Abstract

Isoflavones were synthesized from the reaction of 3-bromochromone derivatives and aryltributylstannanes via Stille coupling catalyzed by a water-soluble and reusable $PdCl_2(NH_3)_2$/2,2′-cationic bipyridyl system in aqueous solution. For prototype 3-bromochromone, the coupling reaction was performed at 80°C for 24 hr with 2.5 mol% catalyst in water in the presence of tetrabutylammonium fluoride. After the reaction, the aqueous solution could be reused for several runs, indicating that its activity was only slightly decreased. For substituted 3-bromochromones, the addition of $NaHCO_3$ and a higher reaction temperature (120°C) were required to gain satisfactory outcomes. In addition, naturally occurring products, such as daidzein, could be obtained by this protocol via a one-pot reaction.

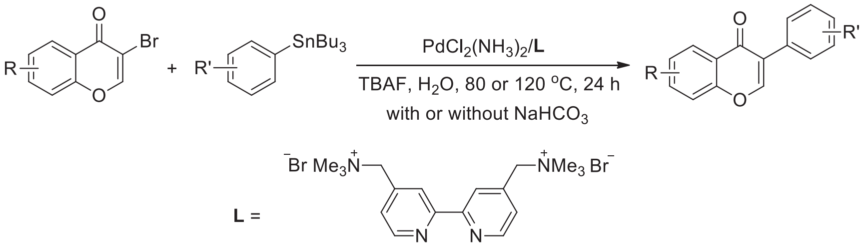
KEYWORDS

isoflavone, natural product, reusable catalyst, Stille coupling, water

1 | INTRODUCTION

Isoflavones are a type of naturally occurring products, which have been found in the Leguminosae family.[1] Biological studies of these compounds reveal that isoflavones have anti-inflammatory,[2] antifungal,[3] antiviral,[4] antioxidant,[5] and anticancer[6] properties. Conventional synthetic methods for the preparation of isoflavones include deoxybenzoin cyclization of 2-hydroxyphenylbenzylketones,[7–16] oxidative rearrangement,[17–22] or epoxidation[23] of a chalcone to form isoflavones, *N*-heterocyclic carbene-catalyzed reactions,[24,25] intramolecular [2+2] ketene cycloadditions,[26] reduction and cyclization of isoxazole derivatives,[27] and oxidation of flavanones.[20,28–31] Recently, coupling of 3-iodochromones with heteroaromatics by a photochemical process,[32] and K10 montmorillonite-catalyzed one-pot reactions of 1-(2-hydroxyphenyl)butane-1,3-diones and 2,5-dimethoxy-2,5-dihydrofuran[33] to produce 3-heteroarylchromones were also reported.

Transition-metal-catalyzed reactions toward the formation of isoflavones afford a more convenient protocol to fulfill this purpose. Rh(I)-catalyzed oxidative-coupling of salicylaldehyde with phenylacetylene[34] and Cu(I)-catalyzed cyclization of 3-(2-bromophenyl)-3-oxopropanals[35] gave isoflavones. Transition-metal-catalyzed C—C bond cross-coupling, such as Negishi coupling by Pd[36] or Ni[37,38] and Suzuki-Miyaura reactions,[39–55] were widely applied for the synthesis of isoflavones in recent years. In addition, triarylbismuths were also employed as a coupling partner of 3-iodo or 3-trifloxychromones for Pd-catalyzed cross-coupling.[56,57] The Stille coupling is one of the most powerful palladium-catalyzed reactions to build a new C—C bond.[58–60] Organostannanes are moisture and O_2 stable and have tolerance toward a great variety of functional groups. Hence, they can be handled under air and harsh reaction conditions. In several large-scale pharmaceutical purposes, especially for the synthesis of complex heterocyclic systems, Stille cross-coupling reactions are superior



SCHEME 1 Pd-catalyzed Stille coupling for the formation of isoflavones in water

TABLE 1 Optimal condition studies for the Stille coupling of 3-bromo-4*H*-chromen-4-one (**1a**) and $PhSnBu_3$ (**2a**) in water

Entry	1a (mmol)	2a (mmol)	TBAF (mmol)	Base (mmol)	Temp. (°C)	Yield (%)[a]
1	0.5	1.0	—	—	80	12
2	0.5	1.0	1.0	—	80	24
3	1.0	0.5	—	—	80	38
4	1.0	0.5	0.5	—	80	89
5	0.75	0.5	0.5	—	80	74
6[b]	1.0	0.5	0.5	—	80	78
7[c]	1.0	0.5	0.5	—	80	88
8[d]	1.0	0.5	0.5	—	80	0
9	1.0	0.5	0.5	—	120	80
10	1.0	0.5	0.5	$NaHCO_3$ (0.5)	80	76
11	1.0	0.5	0.5	KOAc (0.5)	80	66
12	1.0	0.5	0.5	K_2CO_3 (0.5)	80	40
13	1.0	0.5	0.5	K_3PO_4 (0.5)	80	45
14	1.0	0.5	0.5	$NaHCO_3$ (0.5)	120	85

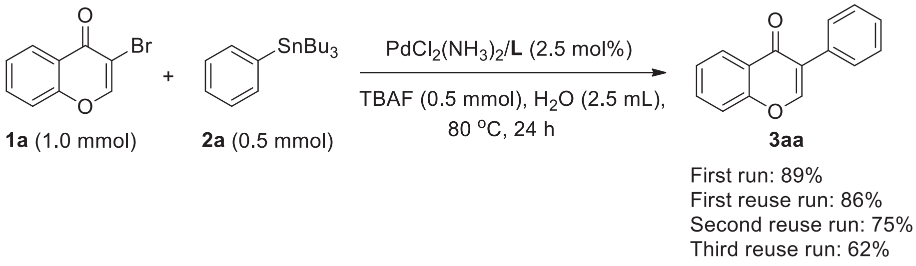
Note: Reaction conditions: **1a**, **2a**, TBAF, base, $PdCl_2(NH_3)_2$/**L** (2.5 mol%), H_2O (2.5 ml) at 80 or 120°C for 24 hr.

[a] Isolated yields of **3aa**.

[b] Reaction time was 12 hr.

[c] 5 mol% of catalyst was used.

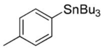
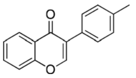
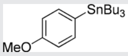
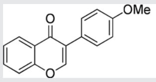
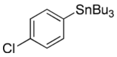
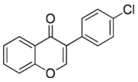
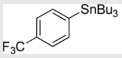
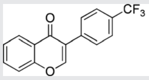
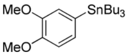
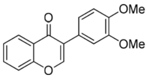
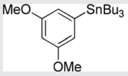
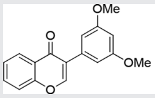
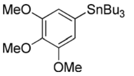
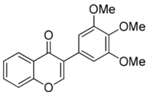
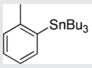
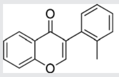
[d] In the absence of **L**.



SCHEME 2 The reuse studies of residual aqueous solution in Stille coupling of **1a** and **2a**

to Suzuki-Miyaura and Negishi couplings.[61,62] Therefore, the Stille reaction is still a promising process in modern organic synthesis. In comparison with other name reactions, such as Suzuki-Miyaura reactions, their study for the synthesis of isoflavones is still limited. Known procedures include coupling of 3-(trimethylstannyl)-4*H*-1-benzopyran-4-ones with 4-iodonitrobenzene in *N*-Methyl-2-pyrrolidone[63] and tetrathiophentins with substituted 3-iodochromones in refluxing EtOH.[64] However, both the reactions use organic solvents as the reaction medium, and the reuse of the expensive catalyst has not been reported. Although the coupling of 3-iodo-7-isopropoxychromone with tetraphenyltin has been performed under LiCl-promoted conditions to give ipriflavone, harmful *N*,*N*-Dimethylformamide was used as the solvent.[65] Hence, from the viewpoints of sustainable and green chemistry,

TABLE 2 Stille coupling of **1a** and **2** under in water

Entry	$ArSnBu_3$		Product		Yield (%)[a]
1		**2b**		**3ab**	73
2		**2c**		**3ac**	83
3		**2d**		**3ad**	62
4		**2e**		**3ae**	31
5		**2f**		**3af**	75
6		**2g**		**3ag**	64
7		**2h**		**3ah**	83
8		**2i**		**3ai**	0

Note: Reaction conditions: **1a** (1.0 mmol), **2** (0.5 mmol), TBAF (0.5 mmol), $PdCl_2(NH_3)_2$/**L** (2.5 mol%), and H_2O (2.5 ml) at 80°C for 24 hr.
[a]Isolated yields.

the development of a reusable catalytic system, which is compatible with a green solvent, water, is highly valuable.

On the basis of our recent investigation on the Stille coupling in water,[66] we report herein an efficient Stille cross-coupling reaction of 3-bromochromone derivatives and aryltributylstannanes for the synthesis of isoflavones by a reusable $PdCl_2(NH_3)_2$/2,2′-cationic bipyridyl catalytic system hiring neat water as the reaction medium (Scheme 1). Moreover, the combination of this coupling reaction with demethylation, a natural product, daidzein, could be achieved through a one-pot synthesis.

2 | RESULTS AND DISCUSSION

As described in Table 1, treatment of 3-bromo-4*H*-chromen-4-one, **1a** (0.5 mmol), with $PhSnBu_3$, **2a** (1.0 mmol), in the presence of 2.5 mol% catalyst at 80°C for 24 hr resulted in the formation of 3-phenyl-4*H*-chromen-4-one, **3aa**, in 12% yield along with 85% chromone, which is formed via debromination of **1a** (Entry 1). When tetrabutylammonium floride (TBAF) was added for accelerating the transmetallation step,[67] the product yield of **3aa** was doubled; however, a significant amount of chromone was still found (Entry 2). Thus, the limiting reagent was changed from **1a** to **2a** for seeking the optimal conditions. It was found that the conditions of Entry 4 affording the best result (Entries 3–5). Reducing the reaction time to 12 hr gave 78% yield (Entry 6). An 88% yield of **3aa** was delivered when 5 mol % of catalyst was employed (Entry 7). Removing the water-soluble 2,2′-cationic bipyridyl, **L**, from the catalytic system did not afford **3aa**, owing to the poor solubility of $PdCl_2(NH_3)_2$ in water, supporting the necessity of this ligand when water was applied as a solvent (Entry 8). Elevating the reaction temperature to 120°C furnished **3aa** in 80% yield (Entry 9). In our former report, the addition of a weak inorganic base may help the Stille coupling reaction in aqueous solution.[66] Several inorganic bases were, therefore, added to obtain the best reaction conditions (Entries 10–13). Among them, $NaHCO_3$ was found to be the best base (Entry 10). However, the yield for the added base was still lower than that in Entry 4. Then, we further increased the reaction temperature to 120°C, which gave a comparable yield of **3aa** to Entry 4 (Entry 14). For the pharmaceutical synthesis through metal-catalyzed reactions, the metal contamination in the organic products is an issue of critical concern. Both Pd and Sn contents in **3aa** after silica gel chromatography was estimated to be less than 1 ppb by ICP-MS analysis.

The catalyst reuse study was conducted under the conditions of Table 1, Entry 4 and the results were shown in Scheme 2. After completion of the Stille coupling in the first run, the organic portion was extracted with EtOAc (3 ml × 3), and the product was purified by a typical work-up procedure, which provided an 89% yield of **3aa** in the first run. The residual aqueous phase was then recharged with **1a**, **2a**, and TBAF for the first reuse run. Only a slight decrease in its activity was found for each reuse run, revealing this catalyst is stable upon heating in aqueous solution, and could be separated easily from the organic phase by a simple extraction procedure.

The coupling reactions of **1a** with various aryltributylstannanes, **2**, were evaluated and the results were summarized in Table 2. Aryltributylstannanes with electron-rich or slightly electron-deficient groups at 4-position, **2b–2d**, coupled with **1a** smoothly gave **3ab–3ad** in high yields (Entries 1–3). A strongly electron-withdrawing group, —CF_3, at *para*-position caused C–Sn bond more covalent, and thus slowed the transmetallation rate resulting in a low yield of **3ae** (Entry 4). When the multi-methoxy substituted aryltributylstannanes, **2f–2h**, were utilized, the high product

TABLE 3 Stille coupling of **1** and **2** under aqueous medium

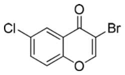
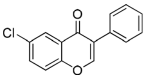
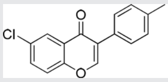
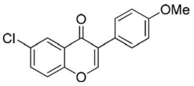
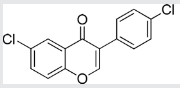
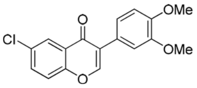
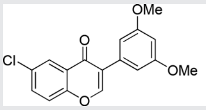
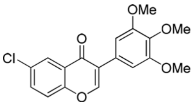
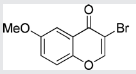
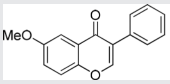
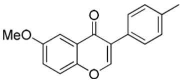
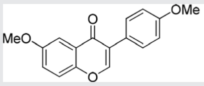
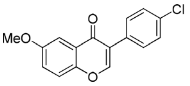
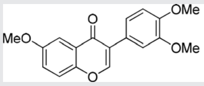
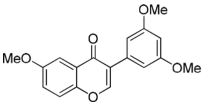
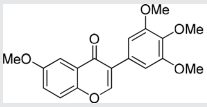
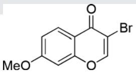
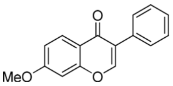
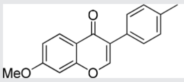
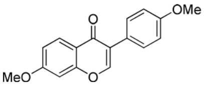
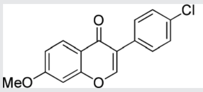
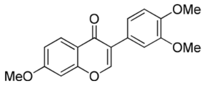
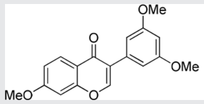
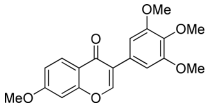
Entry	3-Bromochromone	$ArSnBu_3$	Product	Yield (%)[a]
1	 **1b**	**2a**	 **3ba**	0[b] 40[c] 76
2	**1b**	**2b**	 **3bb**	61
3	**1b**	**2c**	 **3bc**	88
4	**1b**	**2d**	 **3bd**	60
5	**1b**	**2f**	 **3bf**	59
6	**1b**	**2 g**	 **3bg**	55
7	**1b**	**2 h**	 **3bh**	66
8	 **1c**	**2a**	 **3ca**	91
9	**1c**	**2b**	 **3cb**	64
10	**1c**	**2c**	 **3cc**	80
11	**1c**	**2d**	 **3cd**	61
12	**1c**	**2f**	 **3cf**	92
13	**1c**	**2 g**	 **3cg**	78
14	**1c**	**2 h**	 **3ch**	81
15	 **1d** **1d**	**2a**	 **3da**	71
16	**1d**	**2b**	 **3db**	55
17	**1d**	**2c**	 **3dc**	68

TABLE 3 (Continued)

Entry	3-Bromochromone	$ArSnBu_3$	Product	Yield (%)[a]
18	**1d**	**2d**	 **3dd**	52
19	**1d**	**2f**	 **3df**	72
20	**1d**	**2 g**	 **3dg**	56
21	**1d**	**2 h**	 **3dh**	64

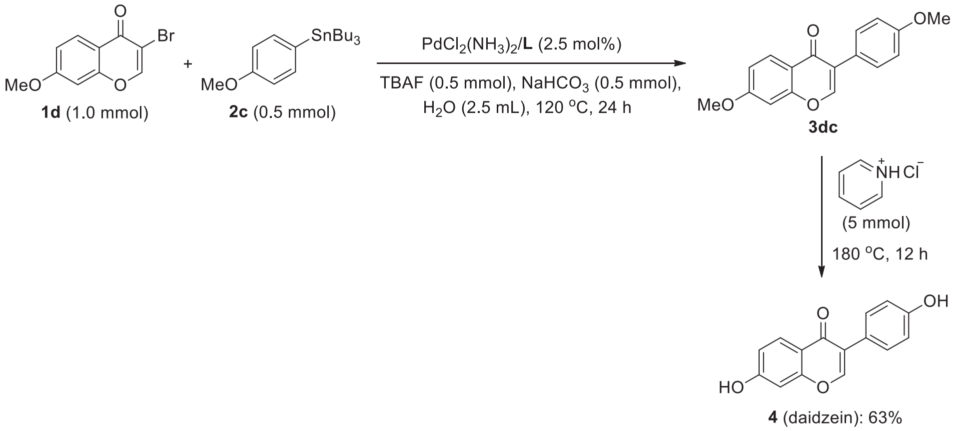
Note: Reaction conditions: **1** (1.0 mmol), **2** (0.5 mmol), TBAF (0.5 mmol), $NaHCO_3$ (0.5 mmol), $PdCl_2(NH_3)_2$/**L** (2.5 mol%), and H_2O (2.5 ml) at 120°C for 24 hr.

[a]Isolated yields.

[b]At 80°C in the absence of $NaHCO_3$.

[c]At 120°C in the absence of $NaHCO_3$.

SCHEME 3 One-pot reaction for the synthesis of daidzein



yields of **3af–3ah** could be achieved (Entries 5–7). However, the use of **2i** did not provide the corresponding coupling product, presumably because the transmetallation was retarded by sterically hindered organotin (Entry 8).

As shown in Table 3, several substituted 3-bromochromones, **1b–1d**, were examined in combination with **2a–2d** and **2f–2h**. In contrast to **1a**, substituted 3-bromochromone, **1b**, could not be coupled with **2a** under the conditions of Entry 4 in Table 1, leading to the recovery of **1b**. Elevating the reaction temperature to 120°C provided **3ba** in only 40% yield. To our delight, 76% of **3ba** was obtained when the reaction was conducted under the conditions of Table 1, Entry 14 (Entry 1). Therefore, a variety of isoflavones, **3bb–3dh**, can be readily synthesized in good to high yields by the coupling of substituted 3-bromochromones with aryltributylstannanes (Entries 2–21).

As an application of this protocol, we synthesized the naturally occurring isoflavone, daidzein (**4**), starting from the coupling reaction of **1d** and **2c** in one pot. After performing the Stille coupling based on the conditions of Entry 17 in Table 3, the aqueous phase was evaporated to dryness under vacuum. The residual mixture was then treated with an excess amount of pyridine hydrochloride and heated at 180°C under inert atmosphere for demethylation.[68] After cooling the reaction to room temperature, precipitation of the crude product and purification by column chromatography provided daidzein **4** in 63% yield (Scheme 3).

3 | EXPERIMENTAL

3.1 | General

Chemicals were utilized as received from the commercial source. The water-soluble cationic 2,2′-bipyridyl ligand, **L**,[69] **1**,[70] and **2**[71] were prepared according to published procedures. ^{1}H- and ^{13}C-NMR spectra were acquired at 25°C in $CDCl_3$ or DMSO-*d*$_6$ solution on a Bruker Biospin AG 300 NMR spectrometer (Bruker Co., Faellanden, Switzerland), where the chemical shifts (δ in ppm) were established with respect to $CHCl_3$ and the non-deuterated DMSO, which was employed as a reference (^{1}H-NMR: $CHCl_3$ at 7.24 and non-deuterated DMSO at 2.49 ppm; ^{13}C-NMR: $CDCl_3$ at 77.0 and DMSO-*d*$_6$ at 39.5 ppm). High-resolution mass spectra (HRMS) for new compounds were acquired on a Waters Synapt High Definition Mass Spectrometry (HDMS) G2 instrument with a LockSpray ESI source (see Supporting information for the spectral data of all Stille coupling products).

3.2 | Typical procedure for the Stille coupling reaction

A $PdCl_2(NH_3)_2$/**L** aqueous solution (0.0125 mmol, 2.5 mol%, in 2.5 ml H_2O) in a 25 ml sealable tube was charged with **1** (1.0 mmol), **2** (0.5 mmol), and TBAF (0.5 mmol). After stirring the mixture at room temperature for 30 min, the reaction tube was sealed and stirred at 80°C for 24 hr (In the cases of Table 3 and Scheme 3, addition of 0.5 mmol $NaHCO_3$ and stirred at 120°C are required). After cooling the mixture to room temperature, the organic portion was obtained by extracting the aqueous phase with EtOAc (3 × 3 ml). The collected organic layer was then dried over $MgSO_4$, evaporated the solvent under reduced pressure, and purified by column chromatography to provide isoflavones **3**.

3.3 | Procedure for the reuse studies of catalytic aqueous solution

The procedure was conducted following the previous description and under the conditions shown in Table 1, Entry 4. After the initial run was extracted with EtOAc (3 × 3 ml), **3aa** was isolated from the organic phase by the general work-up procedure. **1a**, **2a**, and TBAF were then added into the residual aqueous solution for the next reuse reaction.

3.4 | Procedure for the one-pot synthesis of daidzein

After the Stille coupling of **1d** (1.0 mmol) and **2c** (0.5 mmol) under the conditions in Table 3, Entry 17, this reaction tube was evaporated under vacuum to dryness. Pyridine hydrochloride (5.0 mmol) was added and the mixture was then heated at 180°C for 12 hr under N_2. After cooling to room temperature, 1N HCl aqueous solution was added to produce deep brown precipitates. The crude was purified by column chromatography (SiO_2, hexane/THF = 1/1, vol/vol) to afford daidzein **4** in 63% yield.

4 | CONCLUSIONS

In conclusion, we have successfully applied the $PdCl_2(NH_3)_2$/cationic 2,2′-bipyridyl system for the Stille coupling to prepare isoflavones in water. This water-soluble catalyst enables the reaction to be operationally-simple and easy separation of the catalyst from the organic layer for further reuse. Moreover, a naturally occurring isoflavone, daidzein, could be readily obtained by this simple protocol via a one-pot reaction.

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