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A Reusable Palladium/Cationic 2,2′-Bipyridyl System-Catalyzed Double Mizoroki-Heck Reaction in Water

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Abstract: A reusable $PdCl_2(NH_3)_2$/cationic 2,2′-bipyridyl system was used to catalyze the double Mizoroki-Heck reaction of aryl iodides with electron-deficient alkenes in water in the absence of inert gas, giving β,β-diarylated carbonyl derivatives in good to excellent yields. The formation of unsymmetrical β,β-diarylated alkenes were also studied by coupling aryl iodides with the corresponding aryl-substituted α,β-unsaturated carbonyl compounds. This water-soluble catalyst can be swiftly separated from the organic layer using simple extraction for the further reuse, and, thus, makes it an operationally-simple and environmentally-benign procedure.

Keywords: double Mizoroki-Heck reaction; β,β-diarylation; water; reusable; cationic 2,2′-bipyridyl

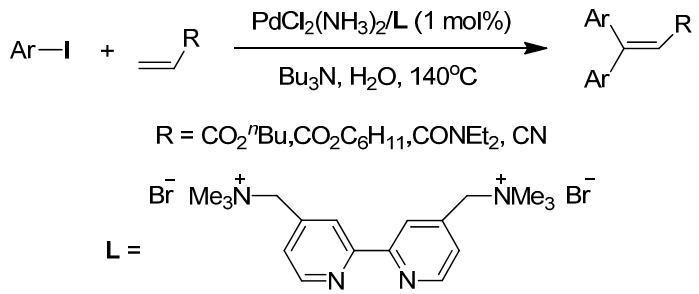
1. Introduction

β,β-diaryl substituted alkenes are valuable intermediates in organic synthesis. They show high activities against viruses [1–8] and can be used as anti-inflammatory and anticancer agents [9,10]. Transition-metal-catalyzed β,β-double arylation of α-olefins is one of the most straightforward and common routes, in modern organic synthesis, to synthesize β,β-diaryl substituted alkenes. Double Suzuki-Miyaura reaction of 1,1-dibromo-1-alkenes and arylboronic acids can afford β,β-diaryl substituted alkenes; however, the variety of available coupling partners is limited [11–14]. Palladium-catalyzed double Mizoroki-Heck coupling of aryl halides with olefins might be the most convenient method to fulfill the formation of β,β-diaryl substituted alkenes, due to the use of low catalyst loading and a large variety of reactants, which are commercial available. Palladium-phosphine [15–21], -carbene [22], and -arylurea [23,24] complexes, as well as $Pd(OAc)_2$ [25,26], have been applied in this reaction, using organic solvents as the reaction medium. Alternatively, supported Pd complexes have also been used as catalysts for β,β-double arylation of α-olefins. For example, montmorillonite-anchored methylsilyl diphenylphosphine Pd(II) chloride was employed to achieve β,β-diarylation of acrylonitrile [27]; polystyrene resin-supported palladium(0) nanocomposite was able to catalyze aromatic aldehydes, methylene compounds, and aryl iodides, yielding double arylated products in a one-pot reaction [28].

Recently, the development of green catalytic systems, using non-conventional solvents, has received a great deal of attention [29–32]. For instance, double Mizoroki-Heck reaction of haloarenes and alkenes can be accomplished, using ionic liquid [33] or glycerol [34] as the reaction medium. Additionally, the introduction of the greenest and most abundant solvent, water, as a reaction medium has several advantages, such as being cheap, safe, non-toxic, non-flammable, and making catalysts recyclable or reusable [35–47]. β,β-diarylation of aryl iodides with α,β-unsaturated carbonyl compounds can be achieved in water; however, only subsequent addition of 1-chloro-4-iodobenzene

and *tert*-butyl acrylate has been performed; no reuse or recycling study has been performed for this water-soluble oxime-derived palladacycle catalyst [48,49]. Thus, the development of a recyclable or reusable procedure for the double Mizoroki-Heck reaction, using water as the medium, is highly valuable to approach the goal of practical application.

We have recently reported that the $PdCl_2(NH_3)_2$/cationic 2,2′-bipyridyl catalytic system can very efficiently catalyze monoarylation of activated olefins using water as a solvent [50]. Based on these results, we slightly modified the reaction conditions in order to study the double Mizoroki-Heck reaction using the same catalytic system. This water-soluble catalyst can be swiftly separated from organic products and reactants, by simple extraction, for further reuse runs (Scheme 1).



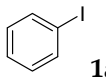
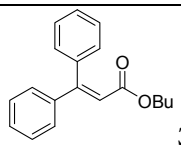
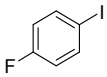
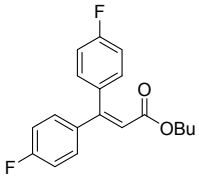
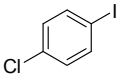
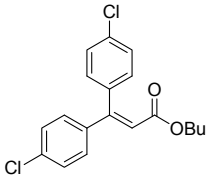
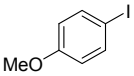
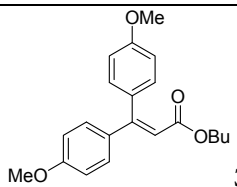
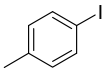
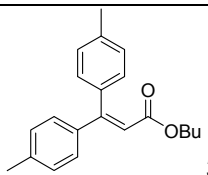
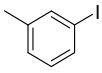
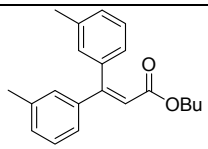
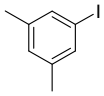
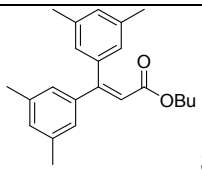
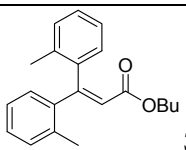
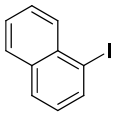
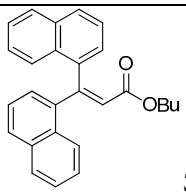
Scheme 1. Reusable Pd(II)/cationic 2,2′-bipyridyl-catalyzed double Mizoroki-Heck reaction in water.

2. Results and Discussion

As shown in Entry 1 of Table 1, with the treatment of iodobenzene **1a** (2.5 mmol) with *n*-butyl acrylate **2a** (1.0 mmol), in the presence of $PdCl_2(NH_3)_2$/cationic 2,2′-bipyridyl (1 mol %) and Bu_3N (2.5 mmol) in H_2O (2 mL), at 140 °C for 24 h, the double Mizoroki-Heck product, **3a**, was isolated in a 95% yield after extracting the reaction mixture with hexane/EtOAc (1/1, 3 × 3 mL) and purifying using column chromatography. The reuse of the residual aqueous solution provided a 90% yield of **3a** when the same reactants and base were recharged, and the process was conducted under identical conditions. Moreover, an 84% yield could still be obtained in the second reuse run (Entry 1). These reuse studies indicated that this catalytic system is stable in an aqueous solution under air, and can be separated from the organic phase using simple extraction. Although the leaching of Pd into the organic layer was not found by ICP-MASS (inductively coupled plasma mass spectrometry) analysis, the gradual loss of catalyst activity due to consecutive extractions, or the formation of a small portion of Pd black in the aqueous phase, which was invisible to the naked eye, cannot be excluded. Under identical conditions, aryl iodides, containing electron-withdrawing groups at the 4-position, such as **1b** and **1c**, gave slightly lower yields of β,β-diarylated products (Entries 2 and 3). It was previously reported that 4-substituted aryl iodides, with strong electron-withdrawing groups, such as NO_2– and CF_3–, make the second Mizoroki-Heck reaction inert [25,33]. As a result, the employment of such functional groups in our catalytic system only delivered mono-arylated products in near quantitative yields. Electron-donating aryl iodides, **1d** and **1e**, β,β-diarylated to **2a** smoothly, which furnish **3d** and **3e** in excellent yields in the initial runs; over 70% yields can be reached in the second reuse runs (Entries 4 and 5). 3-substituted aryl iodides, **1f** and **1g**, possessed no electronic and steric effects on arylation; therefore, similar results to **1a** were observed (Entries 6 and 7). A dramatic decrease in the yield of the double Mizoroki-Heck reaction was found with the use of sterically-congested **1h** and **1i**, which afforded **3h** and **3i** in only 60% and 68% yields, respectively, in the initial run. However, the residual aqueous solution was still active; thus, further reuse studies provided the corresponding products in good yields (Entries 8 and 9).

With respect to aryl bromides, we found that only strongly-activated aryl bromides could be utilized for the mono Mizoroki-Heck reaction in the presence of tetrabutylammonium bromide [50]. Unfortunately, double Mizoroki-Heck coupling failed when these aryl bromides were used [25,33]. Similar results to aryl bromides were observed when aryl triflates were employed as the aryl halide partner in this catalytic system.

Table 1. Palladium-catalyzed β,β-diarylation of butyl acrylate (**2a**) in water [a].

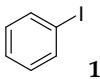
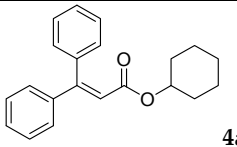
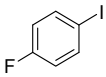
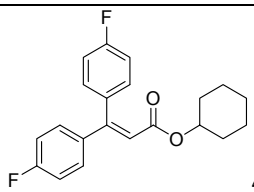
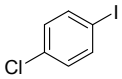
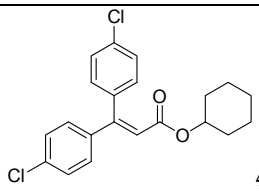
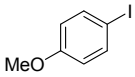
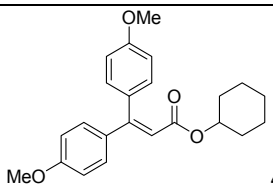
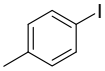
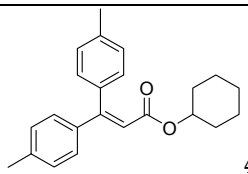
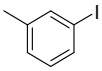
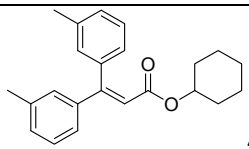
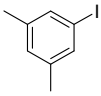
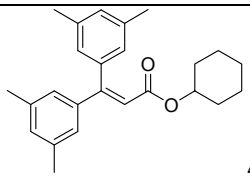
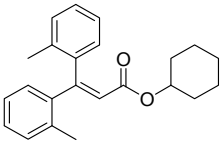
Entry	Aryl Iodide	Product	Yield (%) [b]
1	 **1a**	 **3a**	95 [c] 90 [d] 84 [e]
2	 **1b**	 **3b**	86 [c] 79 [d] 72 [e]
3	 **1c**	 **3c**	68 [c] 62 [d] 57 [e]
4	 **1d**	 **3d**	97 [c] 92 [d] 78 [e]
5	 **1e**	 **3e**	95 [c] 85 [d] 73 [e]
6	 **1f**	 **3f**	93 [c] 91 [d] 81 [e]
7	 **1g**	 **3g**	92 [c] 91 [d] 90 [e]
8	 **1h**	 **3h**	60 [c] 59 [d] 52 [e]
9	 **1i**	 **3i**	68 [c] 66 [d] 65 [e]

[a] Reaction conditions: **1** (2.5 mmol), **2a** (1 mmol), $PdCl_2(NH_3)_2$/**L** (1 mol %), Bu_3N (2.5 mmol), water (2 mL) at 140 °C for 24 h. [b] Isolated yields. [c] The initial run. [d] The first reuse run. [e] The second reuse run.

The utility of this reaction protocol for cyclohexyl acrylate, **2b**, was then evaluated (Table 2). β,β-diarylation of **1a** onto **2b** took place to afford excellent yields in the initial and reuse runs (Entry 1). However, **1b** and **1c** furnished yields of **4b** and **4c** between 61% and 78% (Entries 2 and 3). As

expected, **1d–1g** reacted very efficiently with **2b** to provide high yields in the initial, as well as the reuse, runs (Entries 4–7); **4h** was obtained in yields between 34% and 47%, in the initial and reuse runs, when **1h** was employed (Entry 8). Unfortunately, a β,β-diarylated product was unable to be obtained when *tert*-butyl acrylate was employed. In this case, only a quantitative yield of monoarylated product was observed. This result was in contrast with a report from Nájera's group [48,49]. They achieved a β,β-diarylated reaction in water with only *tert*-butyl acrylate for acrylate substrates in order to avoid the hydrolysis of primary and secondary alkyl acrylates; in our system, β,β-diarylation was active for both *n*-butyl and cyclohexyl acrylates, without any hydrolysis of ester functions, but was inert for *tert*-butyl acrylate.

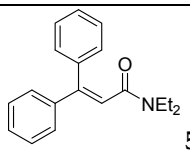
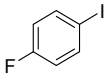
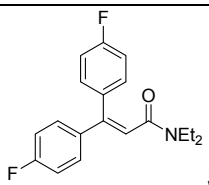
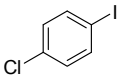
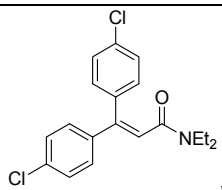
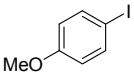
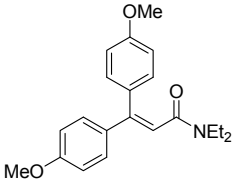
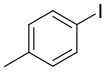
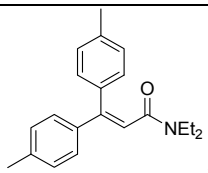
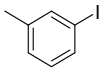
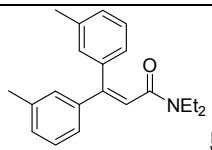
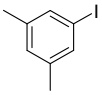
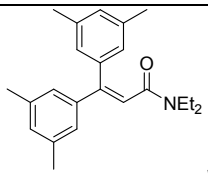
Table 2. Palladium-catalyzed β,β-diarylation of cyclohexyl acrylate (**2b**) in water [a].

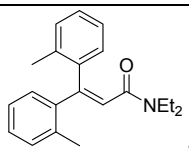
Entry	Aryl Iodide	Product	Yield (%) [b]
1	 **1a**	 **4a**	98 [c] 95 [d] 91 [e]
2	 **1b**	 **4b**	78 [c] 77 [d] 66 [e]
3	 **1c**	 **4c**	72 [c] 61 [d] 61 [e]
4	 **1d**	 **4d**	99 [c] 97 [d] 95 [e]
5	 **1e**	 **4e**	96 [c] 91 [d] 90 [e]
6	 **1f**	 **4f**	90 [c] 83 [d] 76 [e]
7	 **1g**	 **4g**	99 [c] 93 [d] 87 [e]
8	 **1h**	 **4h**	47 [c] 40 [d] 34 [e]

[a] Reaction conditions: **1** (2.5 mmol), **2a** (1 mmol), $PdCl_2(NH_3)_2$/**L** (1 mol %), Bu_3N (2.5 mmol), water (2 mL) at 140 °C for 24 h. [b] Isolated yields. [c] The initial run. [d] The first reuse run. [e] The second reuse run.

With *N*,*N*-diethylacrylamide, **2c**, β,β-diarylacrylamides, **5**, could also be obtained using the double Mizoroki-Heck reaction. As illustrated in Table 3, **1a** coupled with **2c** at 140 °C gave yields of **5a** at 50% and 60% when the reaction times were 24 h and 36 h, respectively (Entries 1 and 2). Further prolonging the reaction time to 48 h furnished **5a** in a 79% yield, and, thus, 69% and 63% yields were achieved in the subsequent reuse runs (Entry 3). Hence, by extending the reaction time to 48 h, β,β-diarylation of **1** onto **2c** provided an efficient method to furnish the desired products in high yields (Entries 3 and 4, and 6–9), with the exception of the electron-poor **1c** and the sterically-congested **1h** (Entries 5 and 10).

Table 3. Palladium-catalyzed β,β-diarylation of *N*,*N*-diethylacrylamide (**2c**) in water [a].

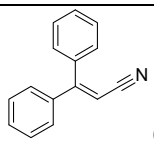
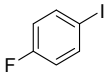
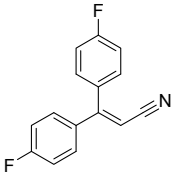
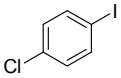
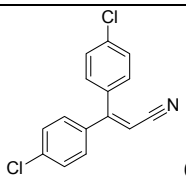
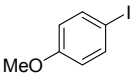
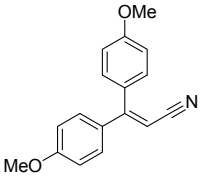
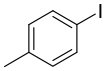
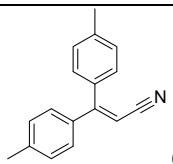
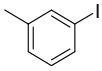
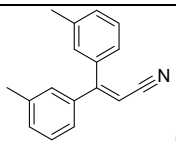
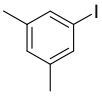
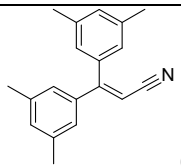
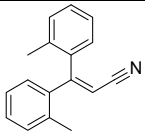
Entry	Aryl Iodide	Product	Yield (%) [b]
1 [c]	 **1a**	 **5a**	50 [e]
2 [d]	**1a**	**5a**	60 [e]
3	**1a**	**5a**	79 [e] 69 [f] 63 [g]
4	 **1b**	 **5b**	71 [e] 66 [f] 57 [g]
5	 **1c**	 **5c**	43 [e] 38 [f] 32 [g]
6	 **1d**	 **5d**	80 [e] 79 [f] 72 [g]
7	 **1e**	 **5e**	91 [e] 90 [f] 82 [g]
8	 **1f**	 **5f**	80 [e] 76 [f] 68 [g]
9	 **1g**	 **5g**	90 [e] 83 [f] 77 [g]

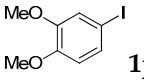
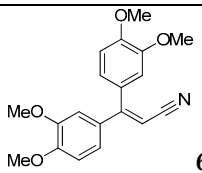
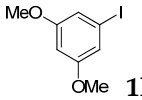
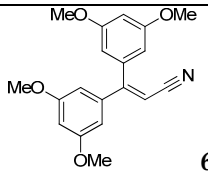
10	 **1h**	 **5h**	68 [e] 54 [f] 47 [g]

[a] Reaction conditions: **1** (2.5 mmol), **2c** (1 mmol), $PdCl_2(NH_3)_2$/**L** (1 mol %), Bu_3N (2.5 mmol), water (2 mL) at 140 °C for 48 h. [b] Isolated yields. [c] Reaction time was 24 h. [d] Reaction time was 36 h. [e] The initial run. [f] The first reuse run. [g] The second reuse run.

Aryl iodides were also able to be double arylated onto low-boiling-point acrylonitrile, **2d**, and the results are shown in Table 4. All of the double Mizoroki-Heck reactions efficiently provided the corresponding β,β-diarylated products, with reuses of the catalytic system showing only slight decreases to activities (Entries 1–10).

Table 4. Palladium-catalyzed β,β-diarylation of acrylonitrile (**2d**) in water [a].

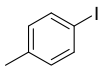
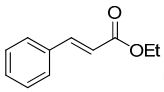
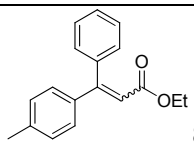
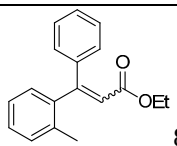
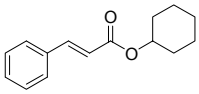
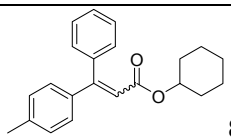
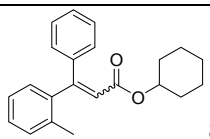
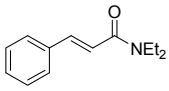
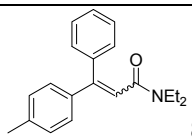
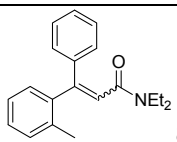
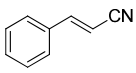
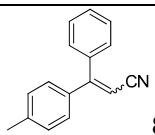
Entry	Aryl Iodide	Product	Yield (%) [b]
1	 **1a**	 **6a**	97 [c] 92 [d] 83 [e]
2	 **1b**	 **6b**	74 [c] 72 [d] 64 [e]
3	 **1c**	 **6c**	58 [c] 52 [d] 47 [e]
4	 **1d**	 **6d**	93 [c] 92 [d] 88 [e]
5	 **1e**	 **6e**	98 [c] 97 [d] 94 [e]
6	 **1f**	 **6f**	96 [c] 95 [d] 93 [e]
7	 **1g**	 **6g**	96 [c] 93 [d] 83 [e]
8	 **1h**	 **6h**	89 [c] 86 [d] 81 [e]

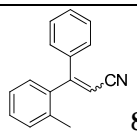
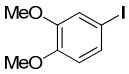
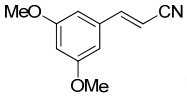
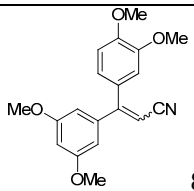
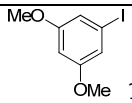
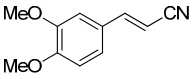
9 [f]	 **1j**	 **6j**	88 [c] 76 [d] 68 [e]
10 [f]	 **1k**	 **6k**	92 [c] 82 [d] 70 [e]

[a] Reaction conditions: **1** (2.5 mmol), **2d** (1 mmol), $PdCl_2(NH_3)_2$/**L** (1 mol %), Bu_3N (2.5 mmol), water (2 mL) at 140 °C for 24 h. [b] Isolated yields. [c] The initial run. [d] The first reuse run. [e] The second reuse run. [f] 3.0 mmol of **1** was employed.

Next, we moved on to the synthesis of unsymmetrical β,β-diarylated alkenes using the Mizoroki-Heck coupling of aryl iodides with aryl-substituted alkenes (Table 5). The coupling of **1e** or **1h** with **7**, giving a mixture of *E*/*Z* isomers, in high to excellent yields, with only a slight steric effect, was observed (Entries 1–8). It is interesting to note that the anticancer drug **8ej**, known as CC-5079 [10], could also be synthesized in excellent yields using this simple protocol (Entries 9 and 10). The stereochemistry of **8ej** can be controlled by the introduction of different aryl iodides, thus that, when **1j** was employed as the aryl iodide source, *Z* isomer was obtained as the major product; in contrast, *E* isomer predominated over the *Z* form, as **1k** was the aryl halide partner.

Table 5. Palladium-catalyzed monoarylation of α,β-unsaturated carbonyl compound in water [a].

Entry	Aryl Iodide	Alkene	Product	Yield (%) [b]	*E*/*Z* [c]
1	 **1e**	 **7a**	 **8ae**	94	2.3/1
2	 **1h**	**7a**	 **8ah**	74	1.0/1
3	**1e**	 **7b**	 **8be**	88	2.4/1
4	**1h**	**7b**	 **8bh**	80	1.0/1
5 [d]	**1e**	 **7c**	 **8ce**	98	12.4/1
6 [d]	**1h**	**7c**	 **8ch**	91	11.1/1
7	**1e**	 **7d**	 **8de**	97	6.5/1

8	**1h**	**7d**	 **8dh**	91	4.7/1
9	 **1j**	 **7e**	 **8ej**	90	1/5.2
10	 **1k**	 **7f**	**8ej**	97	4.3/1

[a] Reaction conditions: **1** (1.5 mmol), alkene (1 mmol), $PdCl_2(NH_3)_2$/**L** (1 mol %), Bu_3N (1.5 mmol), water (2 mL) at 140 °C for 24 h. [b] Isolated yields. [c] Determined by ^{1}H NMR. [d] Reaction time was 48 h.

3. Materials and Methods

3.1. General Methods

Chemicals were used as received from commercial suppliers. The cationic 2,2′-bipyridyl ligand [51,52], **7a–c** [50], **7e** [53] and **7f** [54] were synthesized according to known procedures. ^{1}H- and ^{13}C-NMR spectra were acquired for the $CDCl_3$ solution at 25 °C on a Bruker Biospin AG 300 NMR spectrometer (Bruker Co., Faellanden, Switzerland), in which the chemical shifts (δ in ppm) were determined with respect to the non-deuterated chloroform, which was used as a reference (^{1}H-NMR: $CHCl_3$ at 7.24; ^{13}C-NMR: $CDCl_3$ at 77.0 ppm). The melting points for the solid products were measured using an automated melting point apparatus. High-resolution mass spectra (HRMS) of the new compounds were recorded at the Instrument Center Service of National Central University, the Ministry of Science and Technology of Taiwan. The known double Mizoroki-Heck coupling products, and their physical data, are consistent with those reported in published papers (see Supplementary Materials for the spectral data of all double Mizoroki-Heck products, and copies of ^{1}H- and ^{13}C-NMR spectra, for unknown and unsymmetrical β,β-diarylated products).

3.2. Typical Procedure for the Double Mizoroki-Heck Reaction

Aryl iodide (2.5 mmol), alkene (1.0 mmol), Bu_3N (2.5 mmol), and H_2O (1 mL) was added to a 25-mL, sealable tube, equipped with a stirring bar. After the addition of $PdCl_2(NH_3)_2$/cationic 2,2′-bipyridyl aqueous solution (1 mL, 0.01 mmol in 1 mL H_2O), the tube was sealed using a Teflon-coated screw cap under air, and this tube was then stirred in an oil bath at 140 °C for 24 h (in the case of Table 3, the reaction time was 48 h). After cooling the reaction to room temperature, the resultant solution was extracted with hexane/EtOAc (1/1, 3 × 3 mL), the combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was then evaporated under reduced pressure. Flash chromatography on silica gel provided the double Mizoroki-Heck product.

3.3. Typical Procedure for the Reuse of Catalytic Aqueous Solution for the Double Mizoroki-Heck Reaction

The reaction was performed following the procedure in Section 3.2 After the initial reaction was extracted with hexane/EtOAc (1/1, 3 × 3 mL), the double Mizoroki-Heck product was purified from the combined organic layers, according to the previously-described method (Section 3.2). The residual aqueous layer was then recharged with aryl iodide, alkene, and Bu_3N for the reuse run.

3.4. Typical Procedure for the Synthesis of Unsymmetrical β,β-diarylated Alkenes

Aryl iodide (1.5 mmol), aryl substituted alkene (1.0 mmol), Bu_3N (1.5 mmol), and H_2O (1 mL) was added to a 25 mL sealable tube, equipped with a stirring bar. After the addition of $PdCl_2(NH_3)_2$/cationic 2,2′-bipyridyl solution (1 mL, 0.01 mmol in 1 mL H_2O), the tube was sealed

using a Teflon-coated screw cap under air, and stirred in an oil bath at 140 °C for 24 h (in the cases of Entries 5 and 6 of Table 5, the reaction time was 48 h). After cooling to room temperature, the aqueous reaction mixture was extracted with hexane/EtOAc (1/1, 3 × 3 mL), the combined organic phase was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography on silica gel gave the desired product.

4. Conclusions

In conclusion, we have proven that water-soluble $PdCl_2(NH_3)_2$/cationic 2,2′-bipyridyl is an efficient catalytic system to catalyze the double Mizoroki-Heck reaction of aryl iodides onto activated alkenes, using water as the reaction medium. After being separated from the organic phase by extracting with hexane/EtOAc, the residual aqueous layer is able to be reused for the next run, which makes this procedure greener and reduces the waste of precious metals. Polyarylation of aryl halides onto other alkenes is presently under investigation.

Supplementary Materials: The following are available online at www.mdpi.com/2073-4344/7/6/177/s1, ^{1}H- and ^{13}C-NMR data for all β,β-diarylated products, HRMS data for unknown products, and copies of ^{1}H- and ^{13}C-NMR spectra for unknown and unsymmetrical β,β-diarylated products.

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