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pH-Dependent conjugate addition of arylboronic acids to α,β-unsaturated enones catalyzed by a reusable palladium(II)/cationic 2,2′-bipyridyl system in water under air

Shao-Hsien Huang, Tzu-Min Wu and Fu-Yu Tsai*

A reusable $Pd(NH_3)_2Cl_2$/cationic 2,2′-bipyridyl system for the catalysis of the conjugate addition of arylboronic acids to α,β-unsaturated enones in water under air was developed. Addition of arylboronic acids to both cyclic and acyclic enones progressed smoothly, providing the products in good to high yields, the best result being obtained when HBF_4 was used to adjust the pH value to 1.0. After the reaction, the residual aqueous solution could be reused several times, making the reaction greener and reducing wastage of precious metals. Copyright © 2010 John Wiley & Sons, Ltd.

Keywords: palladium(II)/cationic 2,2′-bipyridyl; reusable; pH-dependent; water; conjugate addition

Introduction

In recent years, with the development of environmentally benign synthesis methods and sustainable technologies, there has been an increasing number of attempts by chemists to perform transition-metal-catalyzed organic reactions in an aqueous phase.[1–3] In particular, the use of water, a nonconventional reaction medium, provides opportunities for facilitating the recovery and recycling of the catalyst, not only due to its low cost, high safety and the simple operational techniques involved, but also to the fact that the organic products are insoluble and therefore easily separated.[4–11] Hence, the development of water-compatible transition-metal catalysts is especially useful as it leaves the catalyst in the aqueous phase for reuse after separation from organic products.

Transition-metal-catalyzed conjugate addition of organometallic reagents to α,β-unsaturated enones is one of the most useful methods for the construction of C–C bonds.[12–15] Besides Rh(I) catalysts,[16,17] Pd is another excellent catalyst for facilitating the conjugate addition of organoboronic acids to α,β-unsaturated enones. These Pd-catalyzed conjugate addition reactions are usually performed in the presence of organophosphines as auxiliary ligands in organic[18–21] or organic–water mixed solvents,[22–28] or involve the employment of $SbCl_3$ as a co-catalyst under ligand-free conditions.[29] Recently, Lu's group reported that the combination of Pd(II) and a 2,2′-bipyridine ligand acts as a superior catalyst for conjugate addition, as the presence of bipyridine can inhibit β-hydride elimination and promote protonolysis of the carbon–palladium bond.[30–34] The catalytic reaction can be performed in water in the presence of a phase-transfer agent.[35] We recently developed a water-soluble cationic 2,2′-bipyridyl ligand (Scheme 1) that can be used in combination with $Pd(NH_3)_2Cl_2$ to catalyze C–C-bond-forming reactions in water under aerobic conditions and exhibits excellent reusability.[36–39] Herein, we report that this reusable catalytic system can also be employed in
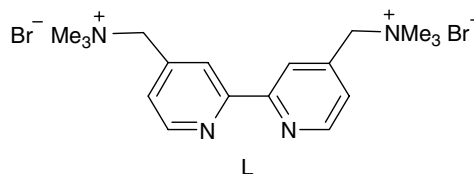
**Scheme 1.** Water-soluble cationic 2,2′-bipyridyl ligand.

the conjugate addition of arylboronic acids to α,β-unsaturated enones under acidic conditions.

Results and Discussion

Our initial goal was to optimize the reaction conditions in water under air. As shown in Table 1, 2-cyclohexenone **1a** (1 mmol), phenylboronic acid **2a** (2 mmol) and $Pd(NH_3)_2Cl_2$/L (2 mol%) were reacted in an open-air reactor at 80 °C using water as the solvent. Unfortunately, we found that this reaction gave only poor yields of **3a** when conducted under both basic and neutral conditions (entries 1–6). There have been reports that this conjugate addition can be performed under acidic conditions;[25,33] hence, we employed HBF_4 (50 wt% in H_2O) to adjust the pH of our catalytic system, and the product yields were drastically increased when the pH <3.0, and a 99% GC yield was obtained when the pH was adjusted to 1.0 before conducting the reaction at 80 °C (entries 7–11). Therefore, controlling the reaction mixture at pH = 1.0 before heating produced the best result (entry 11).

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Table 1. pH value screening for the Pd-catalyzed conjugate addition of phenylboronic acid **2a** to 2-cyclohexenone **1a** in water[a]
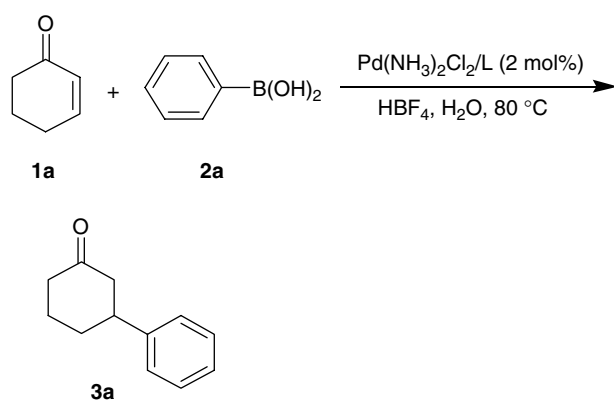
Entry	pH Value[b]	Yield (%)[c]
1	12.3	5
2	11.1	4
3	10.5	21
4	9.0	12
5	8.4	4
6	7.1	6
7	6.7	11
8	5.9	8
9	4.4	7
10	2.5	45 (38)
11	1.0	99 (93)
12[d]	1.0	4
13[e]	1.0	66 (58)
14[f]	1.0	21
15[g]	1.0	58 (50)

[a] Reaction conditions: 2-cyclohexenone (1 mmol), $C_6H_5B(OH)_2$ (2.0 mmol), Pd(NH$_3$)$_2$Cl$_2$/L (2 mol%), H$_2$O (2 ml), 80 °C for 24 h. [b] NaOH was used for adjustment of the pH value to achieve basic conditions, and HBF$_4$ (50 wt% in H$_2$O) was used for acidic conditions. [c] GC yields. Isolated yields are given in parentheses. [d] In the absence of ligand L. [e] 2,2'-Bipyridine was used as the ligand. [f] HCl was used to adjust the pH value. [g] H$_2$SO$_4$ was used to adjust the pH value.

with arylboronic acids in order to explore the scope of this green catalytic system. As shown in Table 2, various arylboronic acids, **2a–f**, were added to **1a** and **1b** efficiently, affording the corresponding products at yields between 83 and 91%, whether electron-withdrawing or electron-donating groups were present at the *para*-position of **2** (entries 1–5 and 7–12). Even when the sterically hindered arylboronic acid **2g** was used, only slightly lower yields were obtained (entries 6 and 13). When **1c** was employed under identical conditions, good yields of the addition products were isolated (entries 14–19). The lower product yields obtained using **1c** may be explained by the fact that the donation of electron density from the oxygen lone pair to β-carbon leads to weakening of the electrophilicity of the β-carbon. Hence, **1c** was recovered in yields between 10 and 25% in the reactions shown in entries 14–19. In addition, acyclic α,β-unsaturated enones such as **1d** and **1e** could also be employed in our catalytic system, and high isolated yields were obtained when they were reacted with phenyl and 4-substituted arylboronic acids (entries 20, 21, 23 and 24). Because **1d** and **1e** are *trans*-alkenes, in which the approach of palladium is obstructed by the substituents, the employment of sterically-hindered **2g** under optimized conditions furnished the corresponding addition products in slightly lower yields (entries 22 and 25).

Next, the reusability of the aqueous catalytic system was examined. We chose **1a** and **2a** as representative reactants for this experiment. Under conditions identical to those described in Table 1, entry 11, after reaction at 80 °C for 24 h, the reaction mixture was extracted with hexane (3 ml ×3) and the product was purified by column chromatography. The remaining aqueous solution was then charged with **1a** and **2a** and the pH adjusted to 1.0 for the second-run reaction. As shown in Table 3, this catalytic system could be reused many times, and at the ninth run still gave an isolated yield of 90% (entry 9). However, the activity was drastically decreased at the tenth run, resulting in only a 38% yield of **3a** (entry 10). Although the by-product, B(OH)$_3$, remained in the aqueous phase after extraction, its increased accumulation with each reuse run did not harm the catalyst. The successful application of the residual aqueous solution in subsequent experiments indicates that our catalytic system is stable and acts macrobiotically in the conjugate addition of arylboronic acids to α,β-unsaturated enones in water under air.
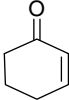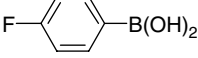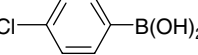
For comparison, experiments in which the water-soluble ligand was not employed and in which 2,2'-bipyridine was used as the ligand were performed under the same conditions, resulting in a 4 and 66% GC yield, respectively (entries 12 and 13). These results indicate the significance of the use of the water-soluble ligand to take the Pd complex into the aqueous phase, facilitating conjugate addition. Although the addition of a phase-transfer agent to the aqueous solution has been found to lead to a high yield of **3a** when 2,2'-bipyridine is used as the ligand,[35] such an additive was not needed in our catalytic system, perhaps owing to a surfactant role of the quaternary ammonium salts on the ligand, making the reaction more homogeneous. When HCl and H$_2$SO$_4$ were used to adjust the pH value, GC yields of 21 and 58% was observed, respectively (entries 14 and 15). These yields were lower than that observed with the employment of HBF$_4$, presumably due to the presence of large amounts of coordinatable chloride and sulfate anions in the aqueous phase.

After obtaining the optimized reaction conditions (Table 1, entry 11), a variety of α,β-unsaturated enones **1** were reacted

Conclusion

In conclusion, we successfully employed an environmentally benign Pd(II)/cationic 2,2'-bipyridyl system to catalyze the conjugate addition of arylboronic acids to α,β-unsaturated enones using water as the reaction medium under air. Both cyclic and acyclic enones could be used as reactants, and good to high yields were afforded when HBF$_4$ was employed to adjust the pH value to 1.0. The residual aqueous solution could be reused several times, making the reaction greener and reducing the wastage of precious metals. Further studies on the applicability of this catalytic system to other organic syntheses are in progress.

Experimental

General

Chemicals were purchased from commercial suppliers and were used without further purification. With the exception

Table 2. Pd-catalyzed conjugate addition of arylboronic acids to α,β-unsaturated enones in water[a]

$$R^1\!\!-\!\!CH\!\!=\!\!CH\!\!-\!\!C(=O)R^2 \;(\mathbf{1}) + ArB(OH)_2\;(\mathbf{2}) \xrightarrow[\text{HBF}_4,\ H_2O,\ pH=1,\ 80\ ^\circ C]{\text{Pd(NH}_3)_2\text{Cl}_2/\text{L (2 mol\%)}} R^1\!\!-\!\!CH(Ar)\!\!-\!\!CH_2\!\!-\!\!C(=O)R^2\;(\mathbf{3})$$

Entry	α,β-Unsaturated enone	ArB(OH)₂		Product	Yield (%)[b]
1	1a (cyclohex-2-enone)	1a	2b (F–C₆H₄–B(OH)₂)	2b → 3b	91
2		1a	2c (Cl–C₆H₄–B(OH)₂)	2c → 3c	88
3		1a	2d (4-acetyl–C₆H₄–B(OH)₂)	2d → 3d	90
4		1a	2e (Me–C₆H₄–B(OH)₂)	2e → 3e	88
5		1a	2f (MeO–C₆H₄–B(OH)₂)	2f → 3f	84
6		1a	2g (2-OMe–C₆H₄–B(OH)₂)	2g → 3g	77
7	1b (cyclopent-2-enone)	1b	2a (C₆H₅–B(OH)₂)	2a → 3h	88
8		1b		2b → 3i	89
9		1b		2c → 3j	91
10		1b		2d → 3k	90
11		1b		2e → 3l	84
12		1b		2f → 3m	83
13		1b		2g → 3n	80
14	1c (chromone / 4H-chromen-4-one)	1c		2a → 3o	80
15		1c		2b → 3p	75
16		1c		2c → 3q	68
17		1c		2e → 3r	66
18		1c		2f → 3s	66
19		1c		2g → 3t	64
20	1d (Ph–CH=CH–C(=O)Me)	1d		2a → 3u	88
21		1d		2f → 3v	88
22		1d		2g → 3w	67
23	1e (Ph–CH=CH–CHO)	1e		2a → 3x	82
24		1e		2f → 3y	80
25		1e		2g → 3z	66

[a] Reaction conditions: enone (1 mmol), ArB(OH)₂ (2.0 mmol), Pd(NH₃)₂Cl₂/L (2 mol%), H₂O (2 ml), HBF₄ (50 wt% in H₂O to adjust the reaction mixture to pH = 1.0), 80 °C for 24 h. [b] Isolated yields.

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Table 3. Reuse studies of Pd-catalyzed conjugate addition of phenylboronic acid **2a** to 2-cyclohexenone **1a** in water[a]

Cycle	Yield (%)[b]	Cycle	Yield (%)[b]
1	93	6	92
2	93	7	91
3	92	8	90
4	93	9	90
5	93	10	38

[a] Reaction conditions: 2-cyclohexenone (1 mmol), $C_6H_5B(OH)_2$ (2.0 mmol), $Pd(NH_3)_2Cl_2/L$ (2 mol%), H_2O (2 ml), HBF_4 (50 wt% in H_2O, to adjust the reaction mixture to pH = 1.0), 80 °C for 24 h. [b] Isolated yields.

of 4-acetylphenylboronic acid, **2d**, other arylboronic acids[40] and the cationic 2,2'-bipyridyl ligand[36,37] were prepared according to published procedures. GC analysis was performed on a Shimadzu GC-14B machine equipped with a fused silica capillary column, and all ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 25 °C on a Varian 200 NMR spectrometer. Elemental analyses were performed at the Instrument Center Service, National Science Council of Taiwan.

Typical Procedure for the Conjugate Addition Reaction

A 20 ml reactor was charged with enone (1 mmol), arylboronic acid (2 mmol) and catalyst (2 mol%, 0.02 mmol in 2 ml H_2O). The pH value of the reaction mixture was adjusted to 1.0 by adding HBF_4 (50 wt% in H_2O), following which the mixture was stirred at 80 °C under air for 24 h. After cooling of the reaction mixture to room temperature, the aqueous solution was extracted with hexane. The organic phase was dried over $MgSO_4$ and the solvent was then removed under vacuum. Column chromatography on silica gel afforded the desired product.

*3-Phenylcyclohexanone (**3a**)*

Light brown oil. Spectral data were in agreement with the published literature.[20]

*3-(4-Fluorophenyl)cyclohexanone (**3b**)*

Light brown oil. Spectral data were in agreement with the published literature.[41]

*3-(4-Chlorophenyl)cyclohexanone (**3c**)*

Pale yellow oil. Spectral data were in agreement with the published literature.[29]

*3-(4-Acetylphenyl)cyclohexanone (**3d**)*

Light brown solid. Spectral data were in agreement with the published literature.[42]

*3-(4-Tolyl)cyclohexanone (**3e**)*

Light brown oil. Spectral data were in agreement with the published literature.[43]

*3-(4-Methoxyphenyl)cyclohexanone (**3f**)*

Light brown oil. Spectral data were in agreement with the published literature.[20]

*3-(2-Methoxyphenyl)cyclohexanone (**3g**)*

Light brown oil. Spectral data were in agreement with the published literature.[44]

*3-Phenylcyclopentanone (**3h**)*

Pale yellow oil. Spectral data were in agreement with the published literature.[29]

*3-(4-Fluorophenyl)cyclopentanone (**3i**)*

Yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.89–2.06 (m, 1H), 2.21–2.54 (m, 4H), 2.61–2.74 (m, 1H), 3.31–3.44 (m, 1H), 6.98–7.07 (m, 2H), 7.18–7.22 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 31.0, 38.6, 41.3, 45.6, 115.1 (d, J_{C-F} = 20.6 Hz, 2C), 127.9 (d, J_{C-F} = 8.4 Hz, 2C), 138.6 (d, J_{C-F} = 3.1 Hz), 161.3 (d, J_{C-F} = 242.7 Hz), 217.6. Anal. calcd for $C_{11}H_{11}FO$: C, 74.14; H, 6.22; found C, 74.41; H, 6.46.

*3-(4-Chlorophenyl)cyclopentanone (**3j**)*

Light brown oil. Spectral data were in agreement with the published literature.[45]

*3-(4-Acetylphenyl)cyclopentanone (**3k**)*

Light brown oil. Spectral data were in agreement with the published literature.[46]

*3-(4-Methylphenyl)cyclopentanone (**3l**)*

Pale yellow oil. Spectral data were in agreement with the published literature.[29]

*3-(4-Methoxyphenyl)cyclopentanone (**3m**)*

Light brown oil. Spectral data were in agreement with the published literature.[47]

*3-(2-Methoxyphenyl)cyclopentanone (**3n**)*

Light brown oil. Spectral data were in agreement with the published literature.[48]

*Flavanone (**3o**)*

Yellow solid. Spectral data were in agreement with the published literature.[49]

*4'-Fluoroflavanone (**3p**)*

Light brown solid. Spectral data were in agreement with the published literature.[50]

*4'-Chloroflavanone (**3q**)*

Light brown solid. Spectral data were in agreement with the published literature.[51]

4′-Methylflavanone (3r)

Yellow solid. Spectral data were in agreement with the published literature.[52]

4′-Methoxyflavanone (3s)

Yellow solid. Spectral data were in agreement with the published literature.[49]

2′-Methoxyflavanone (3t)

Light brown oil. Spectral data were in agreement with the published literature.[53]

4,4-Diphenylbutan-2-one (3u)

Yellow oil. Spectral data were in agreement with the published literature.[54]

4-(4-Methoxyphenyl)-4-phenylbutan-2-one (3v)

Light brown oil. Spectral data were in agreement with the published literature.[54]

4-(2-Methoxyphenyl)-4-phenylbutan-2-one (3 w)

Pale yellow solid. Spectral data were in agreement with the published literature.[55]

3,3-Diphenylpropanal (3x)

Yellow oil. Spectral data were in agreement with the published literature.[56]

3-(4-Methoxyphenyl)-3-phenylpropanal (3y)

Pale yellow oil. Spectral data were in agreement with the published literature.[56]

3-(2-Methoxyphenyl)-3-phenylpropanal (3z)

Yellow oil. Spectral data were in agreement with the published literature.[57]

Typical Procedure for the Reuse of the Residual Aqueous Solution

The reaction was conducted following the previously described procedure. After reaction, the aqueous reaction mixture was washed three times with hexane (3 ml) under vigorous stirring, and the organic product was isolated from the combined organic phase according to the previously described procedure. The residual aqueous solution was then charged with **1a** and **2a**, and the pH value adjusted to 1.0 for the next run.

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