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Integrated Suzuki Cross-Coupling/Reduction Cascade Reaction of *meta-/para*-Chloroacetophenones and Arylboronic Acids under Batch and Continuous Flow Conditions

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Abstract: Overcoming the incompatibility of a pair of conflicting catalysts via a flow methodology has great significance in the practical applications for multistep organic transformations. In this study, a multiple continuous-flow system is developed, which can boost the reactivity and selectivity in a sequential enantioselective cascade reaction. During this process, a periodic mesoporous organosilica-supported Pd/carbene species as a Suzuki cross-coupling catalyst is packed in the first column reactor, whereas another periodic mesoporous organosilica-supported Ru/diamine species as an asymmetric transfer hydrogenation catalyst is packed in the second column reactor. As we envisioned, the initially Pd-catalyzed cross-coupling reaction of *meta-/para*-chloroacetophenones and aryl boronic acids followed by the subsequentially Ru-catalyzed reduction provides chiral biarylols with enhanced yields and enantioselectivities. Furthermore, the advantages of the easy handling and the simple procedure make this system an attractive application in a scale-up preparation of optically pure organic molecules under environmentally-friendly conditions.

Introduction

An integrated Suzuki cross-coupling/asymmetric transfer hydrogenation (ATH) cascade reaction, Suzuki cross-coupling reaction of acetyl-substituted aryl halides and aryl boronic acids followed by an ATH transformation, is a simple and efficient method to prepare optically pure biarylols. Especially, the use of cheap aryl chlorides as starting materials has great value in industrial applications, as shown in Figure 1.[1] However, under batch systems, a one-pot Suzuki cross-coupling/ATH cascade reaction of acetyl-substituted aryl chlorides and aryl boronic acids to access chiral biarylols is quite difficult (Figure 1A).[2] Main limitations lie in that the common Pd/NHC-catalysts (NHC = N-heterocyclic carbene) used in the Suzuki cross-coupling reactions often import a negative effect on those chiral N-sulfonylated diamine-based chiral catalysts, owing to the cross-interaction between NHC and chiral diamine-based ligands.[3] As a result, this cascade reaction often leads to decreased yield and/or enantioselectivity relative to two corresponding single-step reactions. Interestingly, some reported hetero-bifunctional catalysis systems,[4] such as heterobimetallic complexes[4a] and dual active center fabricated silica network,[4b] have enabled a one-pot Suzuki cross-coupling/ATH cascade reaction. However, their applications in the scale-up preparation of chiral biarylols are still challenging. Therefore, the exploration of a multiple continuous-flow Suzuki cross-coupling/ATH cascade process to realize a highly efficient synthesis of biarylols from cheap aryl chlorides is highly desirable, which not only complements the methodological drawback but also broadens the applied scope in a potential industrial application.

Recently, the continuous-flow systems have grown into a practical methodology for the scale-up preparation of various pharmaceutical intermediates and/or commercial chemicals, which nicely leverage the balance between heterogeneous catalysis and industrial application.[5] Unlike traditional batch systems, the continuous-flow systems present some unique

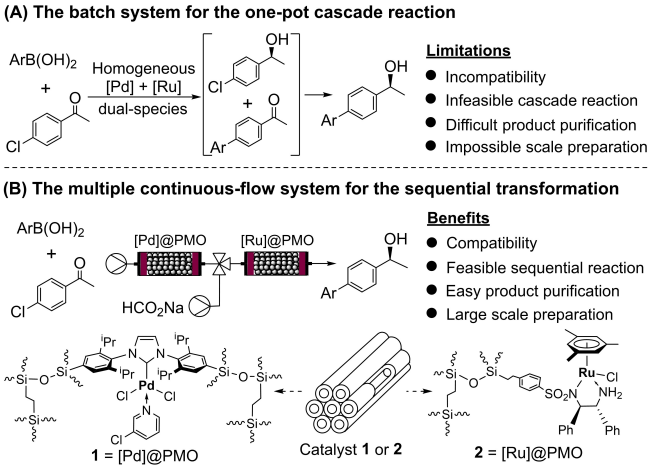

Figure 1. Preparation of chiral biarylols. (A) The batch system for the one-pot cascade reaction. (B) The multiple continuous-flow system for the sequential transformation.

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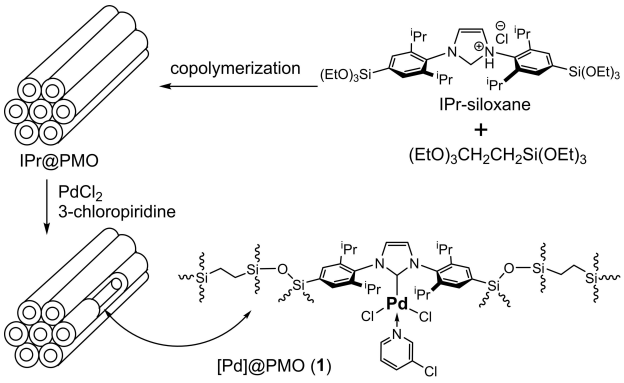
advantages used in catalysis, reflecting in the technical innovation and theoretical research. At the level of technical innovation, the biggest advantage is a scale-up preparation, which provides a practical technology in synthetic chemistry. A further advantage is selectable manipulations, such as adjustable flow rate going through the column reactor and controllable reagent introduction during the catalytic process, which benefits to enhance the reactivity and selectivity owing to the maximum elimination of the overreactions. The other advantage of the continuous-flow systems is wide-diversity in terms of in-line detection, isolation, and purification, which offers feasibility in industrial applications. At the level of theoretical research, a general benefit of a continuous-flow system allows a rapid mixture of starting materials to avoid heat transfer. This advantage ensures some impossible reactions containing highly reactive intermediates and short-lived intermediates under batch systems to proceed in a continuous-flow process. Another impressive benefit can control the catalysis sequence of a sequential reaction *via* a multiple continuous-flow process with a cascade repeat unit. This advantage can overcome the incompatibility of a pair of conflicting catalysts, making unfeasible multi-step transformations under batch systems possible. Based on these advantages of continuous-flow process,[6] especially the benefits of a multiple continuous-flow process,[7] it is reasonable to expect that a multiple continuous-flow process can overcome the drawbacks of the Suzuki cross-coupling/ATH cascade reaction under the batch conditions for the scale-up preparation of optically pure biarylols.

In this contribution based on our previous interest in the silica-supported catalysts,[8] we propose a rational design of a multiple continuous-flow system by using two periodic mesoporous organosilica (PMO)-supported catalysts as the cascade repeat units for the highly efficient preparation of chiral biarylols (Figure 1B). The feature lies in that the supported Pd/NHC catalyst in the first column reactor acts as a coupling catalyst for the Suzuki cross-coupling reaction, whereas the supported chiral Ru/diamine catalyst in the second column reactor works as an ATH catalyst for the sequential reduction of the *in-situ* generated coupling intermediates. As we envisioned, this multiple continuous-flow process with a Suzuki cross-coupling/ATH reaction sequence enables an efficient two-step sequential organic transformation of *meta-*/*para*-chloroacetophenones and arylboronic acids, providing chiral biarylols in high yields with up to 99% enantioselectivity.

Results and Discussion

Immobilization of the Pd/NHC species within the ethylene-bridged PMO for the construction of catalyst **1**, abbreviated as [Pd]@PMO and refers to IPrPdCl$_2$(3-chloropyridine)@PMO (Ipr[9] = 1,3-bis(2,6-diisopropylphenyl)-2,3-dihydro-1*H*-imidazolium chloride), was performed *via* a simple two-step procedure, as shown in Scheme 1. In the first step, the co-condensation of 1,2-bis(triethoxysilyl)ethylene and IPr-siloxane led to the ligand-functionalized IPr@PMO. In the second step, the coordination of IPr@PMO with PdCl$_2$ in the presence of 3-chloropyridine



Scheme 1. Preparation of the [Pd]@PMO (**1**).

produced catalyst **1** as a grayish-yellow powder (see Experimental and Figure S1–S5 of ESI). The solid-state ^{13}C cross-polarization (CP)/magic angle spinning (MAS) NMR spectrum disclosed the well-defined single-site Pd/NHC species incorporated within the PMO network (see Fig. S1 of ESI). Besides the general carbon signal at $\delta = 9.2$ for the ethyl carbon atoms in the ethane-bridged silica, catalyst **1** presented typically characteristic signals at $\delta = 153.9$ ppm corresponded to the carbon atom bonded to palladium in the Pd/NHC-complex. The other signals at $\delta = 27.5$ and 32.7 ppm due to the alkyl carbon atoms in the isopropyl phenyl group could also be observed. All these peaks were the same as that of its homogeneous counterpart,[10] demonstrating the formation of the single-site Pd/NHC species. Solid-state ^{29}Si MAS NMR spectrum also revealed that catalyst **1** had an organic silica network with the strongest T^3 species (R–Si(OSi)$_3$: R = ethylene-bridged groups and/or the linked Pd/NHC-complexes) as its main silica wall (see Figure S2 of ESI).[10] In addition, its small-angle X-ray diffraction pattern (see Figure S3 of ESI) exhibited a well-resolved peak at $2\theta = 0.8°$–$1.0°$, and its nitrogen adsorption-desorption isotherm showed an IV-type with an H_2 hysteresis loop (see Figure S4 of ESI), suggesting its ordered dimensional-hexagonal (*P6 mm*) mesoporous channels proven by its transmission electron microscopy image (see Figure S5 of ESI).

Having obtained this well-established catalyst, we tested the **1**-catalyzed Suzuki cross-coupling reaction under the batch conditions. The aim determines whether catalyst **1** has a high catalytic efficiency in the reaction of low active aryl chloride and phenylboronic acids, which guarantees this coupling product as an intermediate in a multiple continuous-flow process to be fully converted. By summarizing those supported Pd/NHC catalysts used in a Suzuki cross-coupling reaction to date,[11] only a few examples were employed the low active aryl chlorides as a starting material for the coupling with aryl boronic acid.[12] Therefore, we compared the catalytic performance of catalyst **1** and its analogs by using the reaction of 1-(4-chlorophenyl)ethan-1-one (**3a**) and phenylboronic acid (**4a**) as a model, wherein the reaction was performed in ^{i}PrOH with 0.5% Pd-loading of [Pd]@PMO as a catalyst, 1.5 equivalent of potassium *tert*-butoxide as a base according to the reported reaction conditions.[12a,b] It was found that the **1**-catalyzed

Suzuki cross-coupling reaction could produce the targeting cross-coupling product, 1-(biphenyl-4-yl)ethanone (**5a**), in a 92% yield. Such a result was markedly faster than that of a supported $IPrPd(OAc)_2$ catalyst,[12a] and was comparable to that of a supported IPrPdCl(acetylacetonate) catalyst.[12b] This comparison suggested that catalyst **1** possessed the expected catalytic efficiency to meet the demands of a multiple continuous-flow process. In addition, because the inorganic base was not completely soluble in ^{i}PrOH, the co-solvents of water and ^{i}PrOH were further optimized. It was found that the **1**-catalyzed Suzuki cross-coupling reaction with 1.0% Pd-loading of [Pd]@PMO and cesium carbonate as a base in the $H_2O/^{i}PrOH$ (v/v = 1/1) could lead to a complete conversion within 2 h among those selected tested bases (see Table S1 of ESI). Interestingly, this co-solvents system was also compatible with the aqueous second-step ATH transformation,[13] which is beneficial to maintain a highly enantioselective performance.

In light of the above reaction conditions, we employed catalyst **1** to investigate its single-step continuous-flow Suzuki cross-coupling process during the reaction of **3a** and **4a** referred to those reported continuous-flow Suzuki cross-coupling processes in the literature.[14] In this case, catalyst **1** was filled into a packed bed reactor of an X-Cube (ThalesNano), and a diluted solution 1 containing **3a**, **4a**, and cesium carbonate was previously prepared. When the stabilizing reaction parameters were observed, the processing was then started with a blank diluted solution only containing cesium carbonate to wash this packed bed reactor. After that, the diluted reaction solution containing substrates was passed through this reactor to produce the coupling product **5a**. As shown in Figure 2, in 0.1 mL min^{-1} of flow rate (the residence time of 6 minutes), this process could steadily provide **5a** in a 97% yield with a sustaining 6.5 hours run, which was obviously better than those supported palladium catalysts.[14]

Through a similar two-step procedure, catalyst **2** (abbreviates as [Ru]@PMO and refers to MesityleneRuArDPEN@PMO (MesityleneRuArDPEN:[15] Mesitylene = 1,3,5-trimethylbenzene and ArDPEN-siloxane = (*S*,*S*)-4-((trimethoxysilyl) ethyl)phenylsulfonyl-1,2-diphenylethylene-diamine) could be steadily obtained according to our previous method[15a,b] (see Experimental of ESI). Similarly, the incorporation of the well-defined single-site MesityleneRuArDPEN species within the ordered dimensional-hexagonal (*P6 mm*) mesoporous channels of the PMO network was confirmed by the solid-state MAS NMR spectra and electron microscopy analyses (see Figures S1–S5 of ESI). For comparison, an SBA-15-supported Ru/diamine catalyst (abbreviates as [Ru]@ SBA-15 (**2′**) was also used as a catalyst since they have a similar dimensional-hexagonal pore structure. The difference is that [Ru]@PMO (**2**) has the organic ethylene-bridged silica network whereas [Ru]@SBA-15 (**2′**) possesses the inorganic SiO_2-bridged silica network.[16] The aim to choose two different types of supported Ru-catalysts attempts to determine the suitable type of catalysts used in a continuous-flow ATH process.

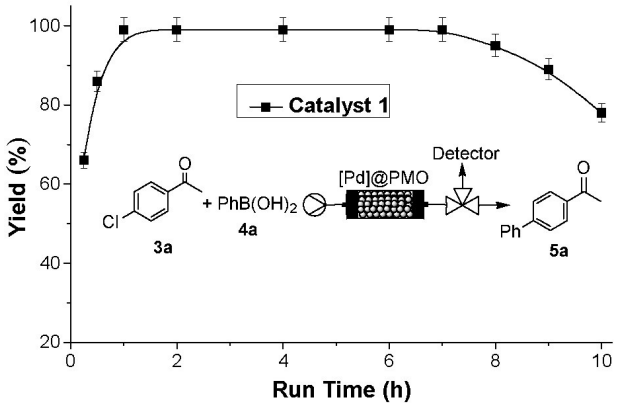


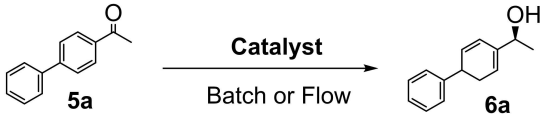
Figure 2. Conversion profile obtained for the continuous-flow Suzuki cross-coupling process with 230 mg of catalyst **1** (see Table S2 of ESI). The first ~22 min, in which no compound is observed for the dead volume of the reactor. Flow conditions: Solution 1: 0.10 M of substrates (1 equiv. of **3a**, 1.2 equiv. of **4a** and 0.5 equiv. of Cs_2CO_3) in $H_2O/^{i}PrOH$ (v/v = 1/1). Flow rate: 0.1 mL min^{-1} (residence time: 6 minutes at 80 °C).

With the catalysts **2** and **2′** in hand, we firstly compared their catalytic performances under the batch conditions using the ATH of **5a** as a model based on the optimization of reaction conditions (see Table S3 of ESI). The ATH reaction catalyzed by **2** or **2′** was carried out with 1.0 mol% of Ru-loading (with respect to substrate) and the HCOONa as a hydrogen resource in the optimal co-solvents system ($H_2O/^{i}PrOH$ = 3:1) at 45 °C. As shown in Table 1, it was found that two reactions were able to produce the chiral products, (*S*)-1-(biphenyl-4-yl)ethanol (**6a**), with nearly the same *ee* values. But their reaction rates were different. Reaction with Ru@PMO (**2**) was able to reach the complete conversation within 1 h (entry 1 versus entry 2, Table 1), whereas that with [Ru]@SBA-15 (**2′**) needed 3.5 hours to complete this organic transformation (entry 3 versus entry 4, Table 1). This comparison suggested that the Ru@PMO (**2**) was suitable for the continuous-flow process because catalyst **2** had a more than threefold faster reaction rate than catalyst **2′**.

Due to the highly enantioselective demand for the two-step sequential organic transformation, a systemic optimization of the continuous-flow ATH of 1-(biphenyl-4-yl)ethanone packed with Ru@PMO (**2**) was then investigated in detail. During this process, it was found that the optimal co-solvent system ($H_2O/^{i}PrOH$ = 3:1) under the batch conditions was suitable for this continuous-flow ATH process because the nearly same result, a 99% yield with 95% *ee*, could be obtained (entries 6 versus entries 5 and 7, Table 1). Also, we found that the column reactor temperature with 0.1 mL/min of flow rate (6 minutes residence time) 45 °C could produce the highest yield and *ee* value relative to those at 50 °C and at 40 °C (entries 6 versus entries 8–9, Table 1). In addition, the flow rate had a significant effect on their catalytic performances, where the 0.1 mL/min of flow rate (6 minutes residence time) was better than 0.2 mL/min of flow rate (3 minutes residence time) in this continuous-flow process (entries 6 versus entry 10, Table 1). As a result, the optimal flow conditions was the 0.1 mL/min of a flow rate of the $H_2O/^{i}PrOH$ (v/v = 2/1) at 45 °C.

Based on the optimal optimizations, two continuous-flow ATH of 1-(biphenyl-4-yl)ethanone packed with Ru@PMO (**2**)

Table 1. Optimizations of the ATH of 1-(biphenyl-4-yl)ethanone under the batch and continuous-flow conditions.[a]



Entry	Catalyst (Condition)	Solvent	Time/°C	Yield/ee (%)[b]
1	**2** (Batch)	H_2O/^{i}PrOH (3/1)	0.5 h/45 °C	97/95
2	**2** (Batch)	H_2O/^{i}PrOH (3/1)	1.0 h/45 °C	99/95
3	**2′** (Batch)	H_2O/^{i}PrOH (3/1)	1.0 h/45 °C	53/95
4	**2′** (Batch)	H_2O/^{i}PrOH (3/1)	3.5 h/45 °C	98/95
5	**2** (Flow)	H_2O/^{i}PrOH (2/1)	11 h/45 °C	91/95
6	**2** (Flow)	H_2O/^{i}PrOH (3/1)	11 h/45 °C	99/95
7	**2** (Flow)	H_2O/^{i}PrOH (4/1)	11 h/45 °C	88/95
8	**2** (Flow)	H_2O/^{i}PrOH (3/1)	11 h/40 °C	97/95
9	**2** (Flow)	H_2O/^{i}PrOH (3/1)	11 h/50 °C	99/92
10[c]	**2** (Flow)	H_2O/^{i}PrOH (3/1)	2.5 h/45 °C	81/95

[a] Experimental procedure. Batch conditions: catalyst (1.0 mol% of Ru based on ICP analysis), Cs_2CO_3 (0.12 mmol), HCO_2Na (1.0 mmol), 1-(biphenyl-4-yl) ethanone (0.10 mmol), and 2.0 mL of H_2O/^{i}PrOH (v/v = 3/1), reaction temperature (45 °C). Flow conditions: Solution 2: 0.05 M of substrates and reagent (1 equiv. of **5a** and 10 equiv. of HCO_2Na) in the co-solvents of H_2O/^{i}PrOH. Flow rate: 0.1 mL min^{-1} (residence time: 6 minutes at 45 °C). [b] Yields were determined by ^{1}H NMR analysis and *ee* values were determined by chiral HPLC analysis. [c] Flow rate: 0.2 mL min^{-1} (residence time: 3 minutes).

and [Ru]@SBA-15 (**2′**) were further compared. Figure 3 presented their conversion profiles, where the 0.10 M of the diluted reaction solution containing substrates and reagents was passed through the respective column reactor with Ru@PMO (**2**) or [Ru]@SBA-15 (**2′**) in 0.1 mL min^{-1} of flow rate 45 °C. The results showed that the continuous-flow process with Ru@PMO (**2**) was markedly better than that with Ru@SBA-15 (**2′**) because the former has a rapid response in the full conversation. Furthermore, this process was able to sustain a continuous 11.0 hours run, still affording the chiral product of (*S*)-1-(biphenyl-4-yl)ethanol (**6a**) in a 97% yield with 94% *ee*, indicating that the 0.95 mol% of the Ru-loading in **2** enabled a sustainable transformation in a multiple continuous-flow process.

Before the incorporation of two single continuous-flow processes into a multiple continuous-flow process, we initially

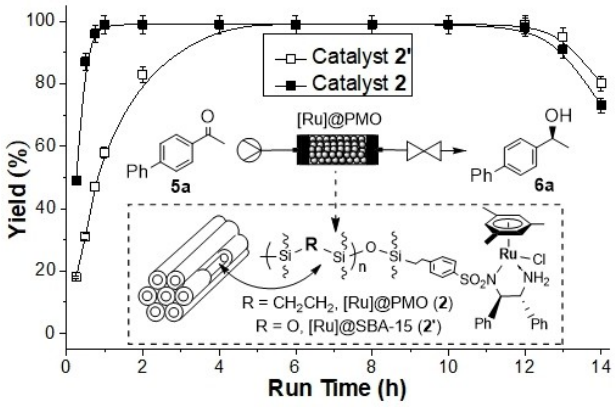
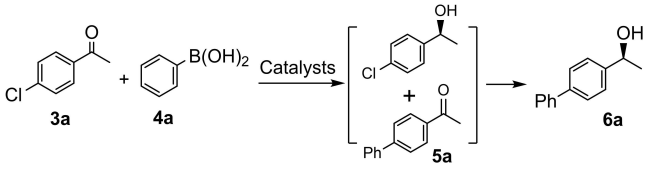


Figure 3. Conversion profiles obtained for the continuous-flow ATH process with Ru@PMO (**2**) and [Ru]@SBA-15 (**2′**) (see SI in Table S4). The first ~22 min, in which no compound is observed for the dead volume of the reactor. Flow conditions: Solution 2: 0.05 M of substrates and reagent (1 equiv. of **5a** and 10 equiv. of HCO_2Na) in H_2O/^{i}PrOH (v/v = 3/1). Flow rate: 0.1 mL min^{-1} (residence time: 6 minutes at 45 °C).

investigated three different types of integrated models under the batch systems to understand the necessity of a multiple continuous-flow process. Taking the model reaction of **3a** and **4a** as an example, the reactions were carried out according to the optimal reaction conditions (see Table S1 and S3 of ESI), as shown in Table 2. In the first case by using the physically mixed homogeneous dual-species as a homogeneous integrated model, we found that the one-pot cascade reaction catalyzed by the mixed homogeneous Pd/NHC and Ru/diamine complexes as dual-catalysts either at 80 °C or 45 °C was able to produce the chiral product **6a**, but both yields and *ee* values were poor (entries 1–2, Table 2). This finding revealed that there were the negative cross-interactions between the Ru/diamine species and Pd/carbene species under the batch conditions, which led to the obviously decreased yields and slightly diminished *ee* values relative to two single-step catalysis reactions. In the second case by using the physically mixed heterogeneous dual-species as a heterogeneous integrated model, a similar phenomenon was also observed. Although a one-pot cascade reaction catalyzed by two PMO-supported **1** plus **2** as dual-catalysts either at 80 °C or 45 °C could lead to the enhanced yields (entries 3–4 versus entries 1–2, Table 2), their *ee* values were still lower than that of the single-step enantioselective reaction. This comparison demonstrated that a heterogeneous integrated model relative to a homogeneous integrated model was able to overcome the negative cross-interactions to a certain extent, but it is impossible to eliminate this negative effect completely, suggesting the necessity of a multiple continuous-flow process.

In the third case, we still used two heterogeneous integrated models, but their reaction temperature was manipulated owing to the unique reaction sequences of this cascade reaction; the specificity is that it might have two completely opposite reaction sequences. The reaction either *via* an initial Suzuki cross-coupling of **3a** and **4a** followed by an ATH transformation (Suzuki coupling/ATH sequence) or *via* an initial

Table 2. Optimizations of integrated models in the cascade reaction of *para*-chloroacetophenone and phenylboronic acid under the batch condition.[a]



Entry	Catalysts	Temp. (°C)	Time/h	Yield/ee (%)[b]
1	[Ru] + [Pd][c]	45 °C	3	73/92
2	[Ru] + [Pd][c]	80 °C	3	64/86
3	**1** + **2**	45 °C	3	85/93
4	**1** + **2**	80 °C	3	93/90
5	**1** + **2**	80 °C for 2 h then 45 °C for 1 h		96/92
6	**1** + **2**	45 °C for 2 h then 80 °C for 1 h		97/89

[a] Reaction conditions: catalysts (1.0 mol% of Pd and 1.0 mol% of Ru, based on ICP analysis), *para*-chloroacetophenone (1.0 mmol), phenylboronic acid (1.20 mmol), Cs_2CO_3 (0.50 mmol), HCO_2Na (10.0 mmol) in 20.0 mL of H_2O/^{i}PrOH (v/v = 3/1). [b] Yields were determined by ^{1}H NMR analysis and *ee* values were determined by chiral HPLC analysis. [c] [Ru] = MesityleneRuTsDPEN, [Pd] = $IPrPdCl_2$(3-chloropyridine).

ATH of **3a** followed by a Suzuki cross-coupling process (ATH/Suzuki coupling sequence) could provide the desirable targeting chiral products. It was found that this cascade reaction catalyzed by two PMO-supported catalysts firstly at 80 °C for 2 h followed by at 45 °C for 1 h (or firstly at 45 °C for 1 h followed by at 80 °C for 2 h) could produce **6a** with the further enhanced yields (entries 5–6, Table 2). However, their *ee* values were still low as expected. This comparison explains the cascade reaction *via* an adjustment of the reaction temperature is still difficult to meet the demand of the high enantioselectivity under the batch conditions. This behavior is possibly attributed to the part racemizations of chiral products or intermediates in relatively high 80 °C reaction temperature (the part racemization either during the enantioselective reduction of 1-(biphenyl-4-yl) ethanone (**5a**) in a Suzuki coupling/ATH sequence or during the enantioselective reduction of **3a** in ATH/Suzuki coupling sequence). This finding indicates the necessity of a multiple continuous-flow process, which might bypass this defect *via* a selectable temperature manipulation in two isolated column reactors to boost the enantioselectivity.

Subsequently, we transferred them into a multiple continuous-flow system to examine the ability in the enhancement of the enantioselectivity. Considering the match of two sustainable times in the optimal single continuous-flow processes (Figures 2–3), 460 mg of catalyst **1** was filled into the first packed bed reactor and 260 mg of catalyst **2** was filled into the second packed bed reactor of an X-Cube. Two diluted solutions (solution 1 containing **3a**, **4a**, and cesium carbonate in the H_2O/^{i}PrOH (v/v = 1/1) and solution 3 containing sodium formate in the H_2O) were previously prepared, where the molar concentration with respect to **3a** in the first stage for Suzuki cross-coupling process is 0.10 M, and that in the second stage for the ATH process was 0.05 M. The processing was then started after the reaction parameters stabilized and the blank diluted solution wash the packed bed reactors. As shown in Figure 4, a time course of the multiple continuous-flow process in this Suzuki coupling/ATH reaction of **3a** and **4a** was also performed. The initial Suzuki cross-coupling reaction of **3a** and

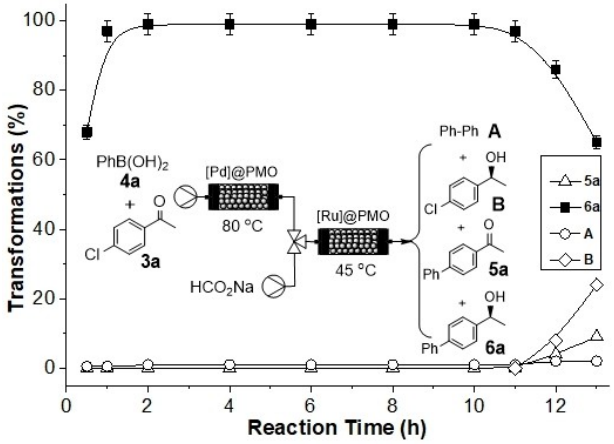


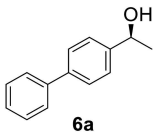
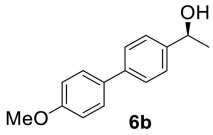
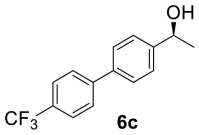
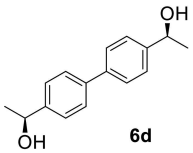
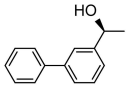
Figure 4. Time course for a multiple continuous-flow process in the reaction of *para*-chloroacetophenone and phenylboronic acid with 460 mg of catalyst **1** and 260 mg of catalyst **2** (see Table S5 and Figures S6 of ESI). The first ~40 min, in which no compound is observed for the dead volume of the reactor. Flow conditions: Two solutions were prepared. Solution 1: 0.10 M of substrates (1.2 equiv. of **3a**, 1.2 equiv. of **4a** and 0.5 equiv. of Cs_2CO_3) in H_2O/^{i}PrOH (v/v = 1/1); Solution 3: 0.10 M of HCO_2Na in H_2O. Flow rate: 0.1 mL min^{-1} (residence time: 6 minutes at 80 °C for the first reactor and 6 minutes at 45 °C for the second reactor).

4a proceeds smoothly to convert into **5a** as described in the single continuous-flow process. After that, the ATH reduction of **5a** begins and chiral product (**6a**) is detected after 40 minutes due to the dead volume of the reactor, which reaches the 99% yield after 1.0 hours. Next, this conversion sustains 10 hours in a maintainable *ee* value concomitant with the tiny self-coupling byproduct (**A**). Finally, after this continuous run, the yield of **6a** gradually decreases with the appearance of intermediates (*S*)-1-(4-chlorophenyl)ethan-1-ol (**B**) and **5a**, where the yield of **6a** is down to 65% after 13 h run concomitant with the 24% yield of **B** and 9% yield of **5a**. This kinetic investigation discloses a continuously available transformation from **3a** and **4a** with 1.23 mmol% of Pd-loading and 0.95 mmol% of Ru-loadings, providing the targeting product 1.19 mg of **6a**. Moreover, the detailed analysis of the Pd- and Ru-leaching were further

investigated once per two hours, finding that the amounts of Pd- and Ru-leaching in the collected product solutions were low, where the maximum of Pd- and Ru-leaching in the collected product solutions were 19 μg and 25 μg after 12 h, respectively (see Table S5 of ESI). This observation indicated that the decreased activity after 12 h was attributed to the factor that the leaching Pd- and Ru-centers precipitated on catalyst's supports detected by ICP-OES analysis.

Finally, based on this investigation of the multiple continuous-flow system, the representative reactions were further examined in this multiple continuous-flow process under similar conditions to consolidate its general practicability. As shown in Table 3, it was found that the tested four representatives continuous-flow processes could steadily provide the corresponding chiral products with high yields and enantioselectivities. It was worth mentioning that all the obtained chiral products in the multiple continuous-flow process presented markedly higher yields and *ee* values than those attained with their corresponding homogeneous models (the combined homogeneous $IPrPdCl_2$(3-chloropyridine) plus MesityleneRuTsDPEN as dual catalysts) under the batch systems that were indicated at data in the bracket of Table 3. Interestingly, a more challenging chiral biaryldiols could also be obtained with the enhanced yields with excellent *ee* and *dr* (95/5 under a continuous-flow system versus 94/6 under a batch system) (Entry 4, Table 3). All these achievements demonstrate the practicability of a multiple continuous-flow process in the preparation of chiral biarylols

Table 3. Extension of the multiple continuous-flow process for the preparation of chiral biarylols.[a]

Entry	Product	Duration (h)	Yield (%)[b]	ee (%)[c]
1	 **6a**	8.5	98 (64)[d]	95 (90)[d]
2	 **6b**	7.5	96 (67)	93 (91)
3	 **6c**	6.5	98 (55)	94 (90)
4	 **6d**	5.0	95 (51)	99 (99)
5	 **6e**	6.0	91 (60)	96 (94)

[a] Experimental conditions: all reactions in the multiple continuous-flow systems with 460 mg of catalyst **1** and 260 mg of catalyst **2** (see Figures S7–S8 of ESI). The first ~40 min, in which no compound is observed for the dead volume of the reactor. Flow conditions: Two solutions were prepared. Solution 1: 0.10 M of substrates (1.2 equiv. of **3a**, 1.2 equiv. of **4** and 0.5 equiv. of Cs_2CO_3) in H_2O/^{i}PrOH (v/v = 1/1); Solution 3: 0.10 M of HCO_2Na in H_2O. Flow rate: 0.1 mL min^{-1} (residence time: 6 minutes at 80 °C for the first reactor and 6 minutes at 45 °C for the second reactor). [b] Yields were determined by ^{1}H NMR analysis. [c] *ee* values were determined by chiral HPLC analysis. [d] Data in the bracket were obtained by using the corresponding MesityleneRuTsDPEN and $IPrPdCl_2$(3-chloropyridine as dual catalysts under the batch conditions.

Conclusion

In conclusion, a multiple continuous-flow strategy was developed through the integration of two single continuous-flow processes. As presented in this study, this process performs an efficient two-step organic transformation from the sequential Pd-catalyzed Suzuki cross-coupling reaction of *meta-*/*para*-chloroacetophenones and aryl boronic acids to the Ru-catalyzed asymmetric transfer hydrogenation, providing the corresponding chiral biarylols with high yields and up to 99% enantioselectivity. This study also highlights a multiple continuous-flow process not only overcomes the restriction of homogeneous co-catalysis systems in multi-step organic transformation but also bridges the gap between heterogeneous catalysis and potential application in the scale preparation of optically pure biarylols under environmentally friendly conditions.

Experimental Section

Catalyst 1 preparation: In a typical synthesis, 2.0 g of a structure-directing agent, pluronic P123 $(CH_2CH_2O)_{20}(CH_2(CH_3)CH_2O)_{70}(CH_2CH_2O)_{20}$), was completely dissolved in a mixture of 80 mL of hydrochloric acid (0.2 N) and 6.0 g of KCl. The mixture was stirred at room temperature for 1.0 h. Subsequently, 3.51 g (9.90 mmol) of the silica precursor 1,2-bis(triethoxysilyl)ethane was added at 40 °C. After a pre-hydrolysis period of 40 minutes, 0.72 g (0.96 mmol) of the IPr-siloxane (1,3-bis(2,6-diisopropyl-4-(triethoxysilyl)phenyl)-2,3-dihydro-1H-imidazol-1-ium chloride) was added. The reaction mixture was stirred at 40 °C for 24 h and then aged at 100 °C for 24 h. The resulting solid was filtered, rinsed with excess ethanol, and then dried overnight on a filter. The surfactant template was removed by refluxing in acidic ethanol (400 mL per gram) for 24 h. The solid was filtered, rinsed with ethanol again, and then dried at 60 °C under reduced pressure overnight to afford ethylene-bridged IPr-functionalized periodic mesoporous organosilica (2.28 g) in the form of a white powder. The collected IPr-functionalized periodic mesoporous organosilica (1.0 g) was suspended in 4.0 mL of 3-chloropyridine, and 70.8 mg (0.40 mmol) of $PdCl_2$ and 276.0 mg (2.0 mmol) of K_2CO_3 were added to the solution at ambient temperature. The resulting mixture was stirred at 80 °C for 16 h. After cooling to room temperature, the mixture was filtered through filter paper and then rinsed with excess CH_2Cl_2. After Soxhlet extraction for 24 h in CH_2Cl_2 to remove homogeneous and unreacted starting materials, the solid was dried at ambient temperature under vacuum overnight to afford catalyst 1 (0.51 g) as a grayish-yellow powder. ICP-OES analysis showed that the Pd-loading was 16.94 mg (0.16 mmol) per gram of catalyst. ^{13}C CP/MAS

NMR (161.9 MHz): 153.9 (*C* of carbene), 151.8–120.5 (*C* of Ph, Ar and -CH=CH- groups), 69.8 (*C* of -OCH_2- in P123 molecule), 33.3 (*C*H of -$CH(CH_3)_2$, 27.5 (CH_3 of -$CH(CH_3)_2$, 9.2 (CH_2 of -CH_2Si) ppm. ^{29}Si MAS/NMR (79.4 MHz): T^2 ($\delta = -58.3$ ppm), T^3 ($\delta = -65.3$ ppm), Q^4 ($\delta = -101.4$ ppm).

General procedure for the Suzuki cross-coupling/asymmetric transfer hydrogenation under multiple continuous-flow conditions. A typical continuous-flow procedure was as follows. Catalyst 1 (460 mg of catalyst, 1.20 mL volume, 70 mm×4 mm) was filled into the first packed bed reactor and catalyst 2 (260 mg of catalyst, 0.6 mL volume, 70 mm×4 mm) was filled into the second packed bed reactor of an X-Cube, and two solutions were prepared (Solution 1: 0.10 M of substrates and reagent (1.2 equiv. of 3a, 1.2 equiv. of 4a and 0.5 equiv. of Cs_2CO_3) in H_2O/^{i}PrOH (v/v = 1/1); Solution 3: 0.10 M of HCO_2Na in H_2O). When the stabilizing reaction parameters (reaction temperature = 80 °C for the first reaction and 45 °C for the second reaction, and flow rate = 0.1 mL/min) was observed, the processing was then started with a blank diluted solution without the substrates to achieve desired reaction parameters. Finally, the prepared diluted reaction solution containing substrates was pumped. During this process, the product was collected constantly. The collected aqueous solution was extracted with ethyl ether (3×3.0 mL). The combined ethyl ether extracts were washed with brine twice and then dehydrated with Na_2SO_4. After the evaporation of ethyl ether, the residue was purified by silica gel flash column chromatography to afford the desired products.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Cascade reaction · Continuous-flow system · Mesoporous organosilica · asymmetric transfer hydrogenation · Suzuki cross-coupling

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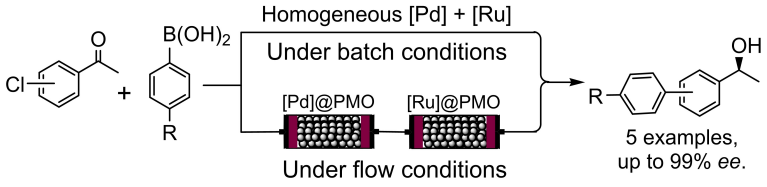

An integrated Suzuki cross-coupling/asymmetric transfer hydrogenation in a multiple continuous-flow process enables an efficient transformation of *meta*-/*para*-chloroacetophenones and aryl boronic acids to the optically pure biarylols.

Y. Li, C. Wang, Q. Chen, H. Li, Y. Su, Prof. Dr. T. Cheng, Prof. Dr. G. Liu, Dr. C. Tan**

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Integrated Suzuki Cross-Coupling/Reduction Cascade Reaction of *meta*-/*para*-Chloroacetophenones and Arylboronic Acids under Batch and Continuous Flow Conditions