Highly Efficient Suzuki Coupling of Aryl Chlorides in a Continuous Flow Capillary Microreactor

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Abstract: The Suzuki reactions of aryl chlorides containing both electron-donating and electron-withdrawing groups with aryl boronic acid, catalyzed by a simple non-phosphine ligand catalyst system, $Pd(OAc)_2/DABCO$, were performed in a continuous capillary microreactor at 50 °C. In the microreactor, the coupling product was obtained mostly in near quantitative yield within a four hour residence time. In contrast, the conversions were only 12–69% in batch reactions.

Key words: Suzuki, coupling, aryl chlorides, capillary, microreactor

There is an increasing demand for research and development of new technologies that enable rapid and efficient performance enhancement of difficult reactions, especially in the construction of biologically interesting small molecules.¹ The application of automated methods to the synthesis of focused libraries² in order to populate screening collections is an important field of research, particularly for the biopharmaceutical sectors and increasingly for the academic community.³ In recent years, the use of microreactors as an alternative to round-bottom flask chemistry for organic synthesis has attracted considerable interest, particularly within the biochemical and fine chemicals industries.⁴ The use of microreactors represent a promising way to reduce reaction time and the costs of chemical processes. They provide great benefits that cannot be achieved in traditional reactors, such as increased surface-to-volume ratios, excellent mass- and heat-transfer capabilities, process safety, significantly higher yields, greater product selectivity, facility for scaling up and diminishing the quantity of waste (e.g. solvent), all of which would be expected to promote highly effective chemical reactions. Thus, microreactors have been widely applied to high temperature and long reaction time processes, which do not proceed well through conventional large scale synthesis.⁵

The Suzuki reaction, a cross-coupling reaction between aryl halides and arylboronic acids, is a well-known general and versatile method employed for the construction of C–C bonds.⁶ In particular, the method can be used for the formation of unsymmetrical biaryls in a single step, which represent important intermediate materials in the pharma-

SYNLETT 2009, No. 15, pp 2534–2538 Advanced online publication: 27.08.2009 DOI: 10.1055/s-0029-1217730; Art ID: W06909ST © Georg Thieme Verlag Stuttgart · New York ceutical industries.⁷ As an intriguingly flexible reaction, it offers considerable potential in the syntheses of bioactive natural products, pharmaceuticals and polymers. The traditional Suzuki reaction is usually conducted with palladium catalysts, and phosphine ligands are most frequently used.⁸ However, many phosphines are sensitive to air and moisture and are often not environmentally friendly. Due to the instability of most phosphine ligands, the coupling reactions are usually carried out under anhydrous conditions. However, water or aqueous solutions represent very attractive mediums for organic reactions, and considerable effort has been directed toward the application of these solvents in coupling reactions.⁹ To date, significant advances have been made including the use of palladium nanoparticles,10 water-soluble amines as ligands,11 and microwave technologies.^{9a} Aryl iodides and aryl bromides are the most frequently used reactants for the coupling. However, their higher price has limited their industrial application. In order to use cheaper and more readily available aryl chlorides, due to their poor reactivity, there are general requirements for special catalysts and complex ligands.¹² Furthermore, reaction times are usually longer, the temperatures required are generally higher (100-120 °C), and the yields are not ideal.¹³

In our efforts directed toward developing reasonable reaction conditions for C–C bond formation that are environmentally benign and efficient, a methodology study on palladium-catalyzed Suzuki reactions using a microreactor was performed. Here, we report a highly efficient Suzuki coupling of aryl chlorides catalyzed by a simple catalyst system, Pd(OAc)₂/DABCO, using a continuous flow capillary microreactor, which gave satisfactory residence times and excellent conversions. The results obtained using the microreactor were also compared with those obtained using a round-bottom glass flask (batch reaction).

Palladium complexes are excellent catalysts for various coupling reactions.¹⁴ As a cheap and green catalyst system, Pd(OAc)₂/DABCO has been used in the Suzuki reactions in order to avoid the use of phosphine ligands, and good results have been obtained for the coupling of aryl iodides and aryl bromides with phenylboronic acid.¹⁵ However, the yields for aryl chlorides, especially with electron-donating substituents, were only 24–64% using this catalyst system.^{11,15} In order to obtain appropriate reaction conditions, an optimization of the reaction system was conducted using a batch reaction (Table 1). We tested

OH OH OH OH CH CI OH CI CI CI CI CI CI CI CI CI CI CI CI CI							
Entry	Base	Solvent (1:1, v/v)	T (°C)	Conversion (%) ^b			
1	K ₂ CO ₃	H ₂ O-PEG200	80	27			
2	K ₂ CO ₃	H ₂ O–DMF	80	61			
3	K ₂ CO ₃	H ₂ O–THF	80	trace			
4	K ₂ CO ₃	H ₂ O-MeCN	80	trace			
5	K ₂ CO ₃	H ₂ O–Acetone	80	12			
6	K ₂ CO ₃	PEG200–DMF	80	69			
7	K ₂ CO ₃	PEG200-THF	80	57			
8	K ₂ CO ₃	PEG200-MeCN	80	39			
9	K ₂ CO ₃	PEG200–Acetone	80	38			
10	K_3PO_4 ·3 H_2O	H ₂ O–THF	80	59			
11	$K_3PO_4 \cdot 3H_2O$	H ₂ O–Acetone	80	93			
12	$K_3PO_4 \cdot 3H_2O$	H ₂ O–Dioxane	80	trace			
13	K ₃ PO ₄ ·3H ₂ O	PEG200–DMF	80	14			
14	$K_3PO_4 \cdot 3H_2O$	PEG200–Acetone	80	60			
15	K_3PO_4 ·3 H_2O	H ₂ O–DMF	80	98			
16	K ₃ PO ₄ ·3H ₂ O	H ₂ O–DMF	50	98			

 Table 1
 Suzuki Coupling of 4-Chlorotoluene with Phenylboronic Acid^a

^a Reaction conditions: 4-chlorotoluene (1.0 equiv), phenylboronic acid (1.5 equiv).

^b Determined by ¹H NMR.

the reaction with respect to three key variables: solvent composition, nature of the base and reaction temperature. ¹H NMR analysis of the product mixture was used to determine the extent of product conversions.¹⁶ Due to the modest solubility of the palladium complexes in water and in order to increase the solubility of all the reactants, cosolvents including H₂O or PEG200 were incorporated with organic solvents. The coupling reactions were performed in the presence of K_2CO_3 and $K_3PO_4 \cdot 3H_2O$. In agreement with previously reported results, the co-solvents with K_2CO_3 did not provide satisfactory yields. However, when the base was changed to $K_3PO_4 \cdot 3H_2O$ in a H₂O–DMF co-solvent system, the target coupling product 4-methylbiphenyl was afforded with 98% conversion after 24 hours, while the reported yields were 24-61% using the same Pd(OAc)₂/DABCO catalyst system.^{11,15} Furthermore, the reaction temperature could be lowered to 50 °C under this reaction system with the same high yield, compared to the conventional reaction temperature of about 120 °C.^{11,15} The results revealed that the use of an appropriate co-solvent system and base were critical for the successful coupling; not only did they significantly increase the reactants conversion, but they also reduced the required reaction temperature. In all reactions, 0.1 equivalents of TBAB was added in order to prevent the generation of palladium black and make the catalytic system more stable. $^{15\mathrm{b}}$

Based on the results presented above (Table 1), a continuous flow capillary microreactor was employed under the same conditions as the batch reaction. The microreactor made use of a TS2-60 syringe pump and two SGE gastight syringes, one containing aryl chloride, Pd(OAc)₂, DABCO and TBAB in DMF, the other containing $K_3PO_4\cdot 3H_2O$ and phenylboronic acid in H_2O (50 µL DMF was added in order to dissolve phenylboronic acid well). The two reactant streams were mixed in a 1:1 ratio through a micro static mixing Tee, and then delivered into a 200 cm capillary coil with an inner diameter of 530 µm. Different flow rates were used in order to adjust reaction times (Figure 1).

In order to understand the coupling reaction process within the microreactor, a detailed reaction time course was performed. As shown in Figure 2, the microreactor greatly enhanced the reaction speed. Within four hours, the conversion of the coupling of 4-chlorotoluene with phenylboronic acid reached 98%, while it was just 60% in the batch reaction. To obtain the same yield, the reaction time using

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Figure 1 Continuous flow capillary microreactor

the batch system required 24 hours. Because the capillary microreactor has a higher surface-area-to-volume ratio, heat-transfer coefficient and mass transportation, the reactions in many cases were much more efficient and gave better yields than those obtained using a conventional system.¹⁷ In agreement with previous reported results,¹⁷ the present capillary microreactor possesses much higher reaction efficiency than the batch system.



Figure 2 Profile of the Suzuki coupling of 4-chlorotoluene with phenylboronic acid

As mentioned above, aryl chlorides are less reactive than the corresponding aryl iodides and bromides. However, electron-donating groups, such as methyl or methoxy groups could further lower the reactivity of the aryl halides and make the coupling reaction more difficult. In order to address this problem, the coupling reactions of various aryl chlorides containing mainly electron-donating groups were examined using the capillary microreactor. Keeping the flow rate constant for the residence time of four hours, the same microfluidic sequence also proved applicable to various aryl chlorides.¹⁸ As shown in Table 2, phenylboronic acid coupled to deactivated chlorotoluene derivatives to afford the corresponding biphenyls in the near quantitative conversions regardless of the substitution pattern in the chlorides (entries 1-4). Anisole derivatives (entries 6-7) also provided the same excellent yields. However, the conversion of an ortho-substituted substrate (entry 5) was lowered to 81% due to the steric hindrance; increasing of the amount of catalyst to 5 mol% did not improve the yield. The activated chloroacetophenone derivatives (entries 8-10) provided 99% conversions regardless of the substitution position. In order to further examine the suitability of the microreactor, the reactions of 4-methylphenylboronic acid with aryl chlorides (entries 11-13) were also conducted. Again, excellent yields were obtained. These results revealed that, in our microreactor system, aryl chlorides with both electron-donating and electron-withdrawing groups delivered the products in high conversions. As a comparison, the batch reactions under the same conditions for four hours were also performed.¹⁹ As can been seen from Table 2, the batch reactions of deactivated reactants gave only 10-60% conversions; this was particularly evident using ortho and para-methoxy substituted substrates (entries 5 and 7), where only 12% and 35% conversions were obtained, respectively. For activated reactants (entries 8-10 and 13), the product yields of the batch system after four hours were no more than 70%.

 Table 2
 Suzuki Coupling of Aryl Chloride and Arylboronic Acid in Water/DMF Using Pd(OAc)2^a

$R^{1} \xrightarrow{OH} H + CI \xrightarrow{R^{2}} R^{2} \xrightarrow{Pd(OAc)_{2} (3 \text{ mol}\%) \\ DABCO (6 \text{ mol}\%)}_{BABCO (3 \text{ equiv}) \\ TBAB (0.1 \text{ equiv}) \\ H_{2}O-DMF (1:1), 50 \text{ °C}} R^{1} \xrightarrow{R^{2}} R^{2}$								
Entry	ArB(OH) ₂	ArCl	Product	Conversion (%) ^b				
				Microreactor (4 h)	Batch (4 h)	Batch (24 h)		
1	ОН ОН ОН	CI	Me	99	52	86 (83)		
2	ОН ОН ОН	CI	Me	99	56	99 (94)		
3	ОН ОН	CI	Me	98	61	98 (95)		
4	ОН ОН	CI	Me Me	99	45	86 (85)		

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 Table 2
 Suzuki Coupling of Aryl Chloride and Arylboronic Acid in Water/DMF Using Pd(OAc)2^a (continued)

$R^{1} \xrightarrow{OH} OH + CI \xrightarrow{R^{2}} R^{2} \xrightarrow{Pd(OAc)_{2} (3 \text{ mol}\%) \\ DABCO (6 \text{ mol}\%)}_{K_{3}PO_{4} \cdot 3H_{2}O (3 \text{ equiv}) \\ TBAB (0.1 \text{ equiv}) \\ H_{2}O-DMF (1:1), 50 \text{ °C}} R^{1} \xrightarrow{R^{2}} R^{2}$							
Entry	ArB(OH) ₂	ArCl	Product	Conversion (%) ^b			
				Microreactor (4 h)	Batch (4 h)	Batch (24 h)	
5	ОН ОН	MeQ CI	MeO	81	12	37 (31)	
6	ОН ОН	CI	OMe	98	61	94 (91)	
7	ОН ОН	CI-OMe	ОМе	99	35	57 (54)	
8	ОН			99	66	99 (96)	
9	ОН	CI		99	64	99 (97)	
10	ОН ОН	CI		99	68	99 (98)	
11	Me B OH	CI	MeMe	99	65	99 (97)	
12	Ме	CI	Me	97	54	95 (89)	
13	Me B OH	CI	Me Me	99	69	99 (98)	

^a Reaction conditions: aryl chloride (1.0 equiv), aryl boronic acid (1.5 equiv).

^b Determined by ¹H NMR. The isolated yield is shown in parentheses.

Because the reactant 4-chlorotoluene in the batch reaction gave a 98% conversion after 24 hours, the same set of reactions were also conducted in a round-bottomed flask for 24 hours. As shown in Table 2, the conversions of the activated reactants (entries 8–10 and 13) all reached 99%. For the deactivated reactants (entries 2, 3, 6, 11 and 12) good yields were obtained. However, the yields for entries 1 and 4 were lower, and those for entries 5 and 7 were extremely poor. Hence, the results revealed that our reaction conditions could provide relatively good yields even in the batch reactions compared with reported data.¹⁵

In conclusion, we have described an efficient and rapid synthesis using the Suzuki reaction in a continuous capillary microreactor. Our microreactor was assembled simply from syringes, a conventional capillary, a mixing unit, and one syringe pump. In this way, the coupling reactions of aryl chlorides, especially those containing electron-donating groups, showed a dramatic rate enhancement and increased conversion compared to the corresponding conventional flask reaction. Our results show for the first time the excellent conversions that can be achieved from coupling reactions of deactivated aryl chlorides under a conventional Pd(OAc)₂/DABCO catalyst system. The system has the potential to deliver grams of product if desired.²⁰ Continuous flow library preparation using this method is in progress.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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- (18) Microreactor Reaction; Typical Procedure. A stock solution of the aryl chloride (0.1 mmol), Pd(OAc)₂ (3 mol%), DABCO (6 mol%) and TBAB (0.1 equiv), in DMF (1 mL) was prepared and taken up in a SGE gas-tight syringe. A second stock solution containing K₃PO₄·3H₂O (3 equiv), and phenylboronic acid (1.5 equiv) in H_2O (1 mL), containing DMF (50 µL) as an added to dissolve phenylboronic acid, was also prepared and taken up in a second SGE gas-tight syringe. The syringes were placed on a TS2-60 syringe pump that was set to deliver 0.9 µL/min and the oil bath was set at 50 °C. The output from the reactor was quenched with Et₂O immediately. The resulting mixture was extracted with $Et_2O(3 \times 5 mL)$ and the combined organic phase was washed with brine, and dried with anhydrous Na₂SO₄, then concentrated and the desired product was submitted for NMR analysis. In optimization experiments, the ¹H NMR spectrum of the product mixture was recorded and the product conversion was determined by integration of the peaks arising from CH3 or OCH3 groups of both the aryl chloride and the product. The conversion was calculated using the formula: [Int.(prod)/Int.(prod + aryl chloride)] \times 100.
- (19) **Batch Reaction; Typical Procedure.** A mixture of aryl chloride (0.5 mmol), phenylboronic acid (1.5 equiv), $Pd(OAc)_2$ (3 mol%), DABCO (6 mol%), TBAB (0.1 equiv), $K_3PO_4 \cdot 3H_2O$ (3 equiv), H_2O (5 mL) and DMF (5 mL), was added to a 25 mL round-bottomed flask, and stirred at 50 °C or 80 °C for either 4 h or 24 h. After the reaction, the solution was cooled to room temperature and extracted with Et_2O (3 × 15 mL). The combined organic phase was washed with brine, and dried with anhydrous Na₂SO₄, then concentrated and the product was analyzed by ¹H NMR in order to judge the conversion of aryl chloride. All of the final compounds in this study were isolated by silica gel chromatography (petroleum ether) for the purpose of spectroscopic identification.
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