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Pd-Catalyzed Efficient One-Pot Sequential Cross-Coupling Reactions of Aryl Dihalides

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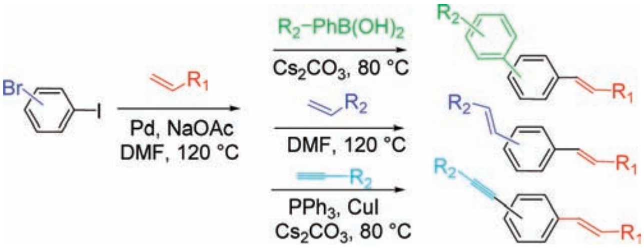
ABSTRACT



The palladium complex containing N-heterocyclic carbene ligands catalyzes one-pot sequential Heck/Suzuki, Heck/Heck, and Heck/Sonogashira coupling reactions of aryl dihalides to afford unsymmetrically substituted arenes in excellent yields.

Sequential double C−N/C−C couplings of aryl dihalides or equivalents leading to unsymmetrically substituted arenes are of practical importance for pharmaceutical, fungicide, and material industries.[1] Recently, one-pot sequential C−N/Heck couplings have been applied for the preparation of *N*,*N*-diarylaminostilbenes.[2] Unsymmetric terphenyls and disubstituted pyridines have been prepared through double Suzuki−Miyaura reactions by using different arylboronic acids.[3] Very recently, the sequential copper-mediated C−N and subsequent Pd-catalyzed C−C couplings of aryl dihalides were also known to give tris(hetero)aryl compounds.[4] To achieve high regioselectivity, double couplings of the dihaloarene equivalents have been explored. For example, unsymmetrical terphenyls can be obtained through separate Pd- and Ni-catalyzed coupling reactions of bromobenzenesulfonates with arylboronic acids and arylmagnesium bromides[5] and one-pot double coupling of bromoarenediazonium tetrafluoroborate.[6] Such a route has been applied for the synthesis of liquid crystal materials via sequencial Negishi/Still couplings.[7] However, some reported sequential coupling reactions suffer disadvantages such as requirement of two different catalysts, the intermediate products have to be separated prior to the second coupling, or using not easily available substrates.[3a,4,8] From the viewpoint of efficiency, one-pot sequential reactions of commercially available inexpensive aryl dihalides with a single catalyst are desirable, and so far only a few successful examples have been reported.[2,3b,9]

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10.1021/ol801589p CCC: $40.75

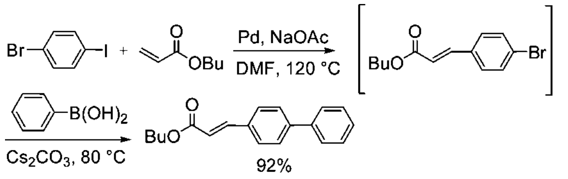
A successful one-pot coupling reaction requires that the catalyst is highly efficient and chemoselective toward the first coupling and maintains its catalytic activity in the subseqent coupling. Palladium complexes of N-heterocyclic carbenes (NHCs) would be potentially suitable for double coupling because of their wide applications in various coupling reactions.[10] Here we describe the facile and efficient one-pot sequential reactions of aryl dihalides to afford unsymmetrically substituted arenes.

We first chose 4-chloroiodobenzene as the substrate for the study of one-pot Heck/Suzuki couplings because of the ease of regiocontrol. The Pd/IPr•HCl (IPr = 1,3-bis(2,6-diisopropylphenylimidazolylidene)) system has proved to be one of the best catalysts for C−C couplings.[11] Actually, the coupling of 4-chloroiodobenzene and *n*-butyl acrylate could proceed in DMF at 120 °C with 0.5 mol % of $Pd_2(dba)_3$ and 2 mol % of IPr•HCl affording (*E*)-butyl 3-(4-chlorophenyl)acrylate in a quantitative yield within 30 min; however, palladium black was observed in this process. After cooling to room temperature, $PhB(OH)_2$ and Cs_2CO_3 were directly added to the reaction vessel without isolation and heated to 80 °C. Unfortunately, the Suzuki coupling could not proceed. Although palladium black can be avoided in the presence of a catalytic amount of pyridine or PPh_3, no double coupled product was observed. The combination of $Pd(OAc)_2$ and $PdCl_2$ with IPr•HCl or IMes•HCl (Imes = 1,3-bis(2,4,6-trimethylphenylimidazolylidene) was also not successful.

[Pd(3-(2,4-dimethyl-1,8-naphthyrid-7-yl)-1- pycolylimidazolylidene)$_2$]-(PF$_6$)$_2$ (**1**) is a highly efficient catalyst for Heck coupling reactions of aryl iodides and bromides.[12] To our delight, complex **1** is suitable for the Heck/Suzuki coupling of 4-chloroiodobenzene, although the expected unsymmetric double coupling product was obtained in only 6% yield after 24 h. Variation of catalyst loadings, bases, and solvents did not improve the overall yields. When two equivalent of PPh_3 was added, a better yield (32%) was obtained but accompanied by 48% of the dechlorinated product. Apparently, the catalyst is not sufficiently active for Suzuki coupling of the resultant aryl chloride.

4-Bromoiodobenzene would be a more suitable substrate for this sequential coupling since Suzuki reaction of the resultant 4-bromocinnamate is easier, provided that the catalyst shows good chemoselectivity in the initial Heck coupling reaction. Fortunately, complex **1** exhibits sufficient regioselectivity for the Heck coupling of 4-bromoiodobenzene and *n*-butyl acrylate (1:1) and allows the coupling of aryl iodide to be completed before aryl bromide starts its reaction giving monocoupled product *n*-butyl 3-(4-bromophenyl)acrylate in 94% yield together with 3% double coupled product after 30 min (Scheme 1). To ensure the complete consumption of 4-bromoiodobenzene and avoid the difficulties in the isolation of the final product, 1.05 equiv of *n*-butyl acrylate was employed in the following reactions.

Scheme 1. Heck/Suzuki Coupling of 4-Bromoiodobenzene



Encouraged by the success of the chemoselective mono-Heck coupling, one-pot sequential Heck/Suzuki coupling reactions were studied in detail, and the conditions were optimized. As shown in Table 1, without isolation of *n*-butyl 4-bromocinnamate, the second coupling was started by direct addition of $PhB(OH)_2$ and Cs_2CO_3 after cooling to room temperature, and the Suzuki reaction was completed within 3 h at 80 °C with a quantitative yield detected by GC (Table 1, entry 5). NaOAc is the most suitable base for Heck coupling but a poor base for Suzuki reaction (Table 1, entry 1). Although Na_2CO_3 and K_2CO_3 are efficient for both Heck and Suzuki reactions, the reactions require a longer time (Table 1, entries 2 and 3). Cs_2CO_3 is known to be the best base for Pd-catalyzed Suzuki reaction; however, the Heck reaction of 4-bromoiodobenzene using Cs_2CO_3 afforded the

Table 1. Base Effect on the One-Pot Heck/Suzuki Reaction

entry	base[a]	time (min)	yield (%)[b]	base[c]	time (h)	yield (%)[d]
1	NaOAc	30	97/3	NaOAc	24	31
2	Na_2CO_3	45	95/3	Na_2CO_3	12	86
3	K_2CO_3	45	92/5	K_2CO_3	12	80
4	Cs_2CO_3	60	67/7			
5	NaOAc	30	97/3	Cs_2CO_3	3	92

[a] Aryl halide 1.0 mmol, *n*-butyl acrylate 1.05 mmol, base 1.2 mmol, Pd 1.0 mol %, DMF 5 mL, 120 °C. [b] GC yield of mono/double coupled product. [c] $PhB(OH)_2$ 1.5 mmol, base 1.2 mmol, 80 °C. [d] Isolated yield.

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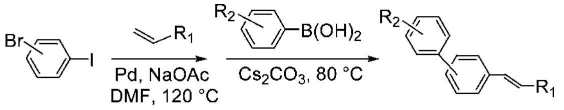
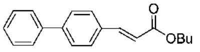
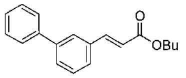
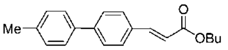
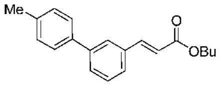
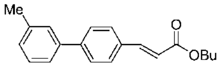
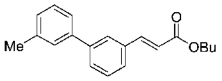
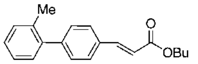
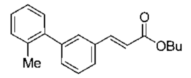
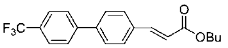
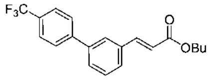
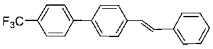
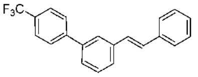
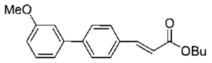
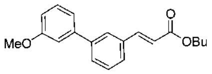
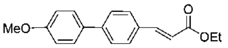
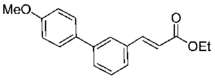
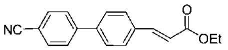
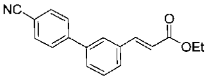
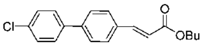
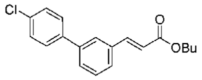
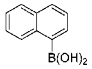
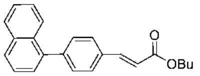
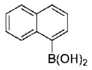
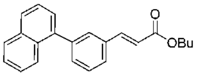
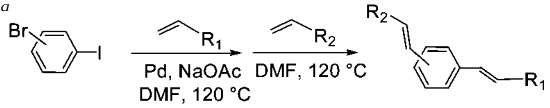
Table 2. One-Pot Double Heck/Suzuki Reactions with Various Arylboronic Acids[a]

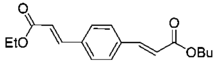
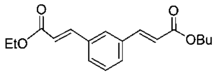
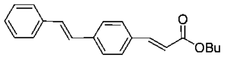
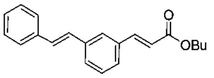


entry	R$_1$	R$_2$	product	yield (%)[b]
1	^{n}BuOCO	H		92
2	^{n}BuOCO	H		89
3	^{n}BuOCO	4-Me		93
4	^{n}BuOCO	4-Me		93
5	^{n}BuOCO	3-Me		88
6	^{n}BuOCO	3-Me		87
7	^{n}BuOCO	2-Me		87
8	^{n}BuOCO	2-Me		85
9	^{n}BuOCO	4-CF$_3$		91
10	^{n}BuOCO	4-CF$_3$		88
11[c]	Ph	4-CF$_3$		71
12[c]	Ph	4-CF$_3$		75
13	^{n}BuOCO	3-MeO		90
14	^{n}BuOCO	3-MeO		92
15	EtOCO	4-MeO		91
16	EtOCO	4-MeO		90
17	EtOCO	4-CN		88
18	EtOCO	4-CN		81
19	^{n}BuOCO	4-Cl		81
20	^{n}BuOCO	4-Cl		77
21	^{n}BuOCO			84
22	^{n}BuOCO			82

[a] Ary halide 1.0 mmol, olefin 1.05 mmol, NaOAc 1.2 mmol, Pd 1.0 mol %, DMF 5 mL. After 30 min, arylboronic acid 1.5 mmol and Cs$_2$CO$_3$ 1.2 mmol were added. [b] Isolated yield. [c] The (*Z*)-isomer was not isolated.

Table 3. Unsymmetric Double Heck Couplings of Aryl Dihalides[a]



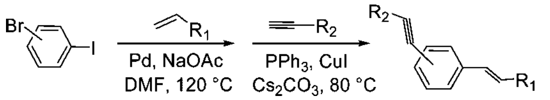
entry	R$_1$	R$_2$	product	yield (%)[b]
1	^{n}BuOCO	EtOCO		94
2	EtOCO	^{n}BuOCO		91
3	^{n}BuOCO	Ph		79/10[c]
4	Ph	^{n}BuOCO		69/7[c]

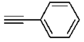
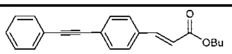
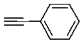
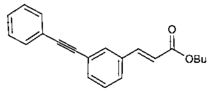
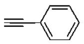
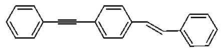
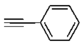
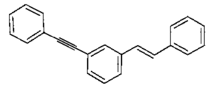
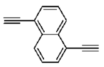
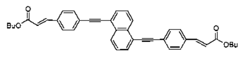
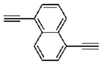
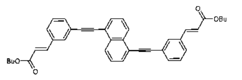
[a] Aryl halide 1.0 mmol, olefin 1.05 mmol, NaOAc 2.4 mmol, Pd 1.0 mol %, DMF 5 mL. After 30 min, the second olefin (1.1 mmol) was added directly to the vessel. [b] Isolated yield. [c] The molar ratio of (*E*)-butyl 3-(4-(*E*)-styrylphenyl)acrylate/(*E*)-butyl 3-(4-(*Z*)-styrylphenyl)acrylate.

intermediate product in only 67% yield together with 7% of the double Heck coupling product. NaOAc/Cs$_2$CO$_3$ was found to be the best base couple. 3-Bromoiodobenzene behaves similarly to 4-bromoiodobenzene, and the desired double coupled product could be obtained in good yield. Unfortunately, 2-bromoiodobenzene gave a mixture of mono and double Heck coupling products (the molar ratio is 23/28) under the same conditions, and thus it is not suitable for further reaction.

With these optimized conditions in hand, we continued our investigation of Heck/Szuki couplings of different olefins and arylboronic acids. The results were summarized in Table 2. Since the Heck reactions of dihaloarenes with acrylate and styrene proceeded to a complete conversion at 120 °C, the total yields of the Heck/Suzuki reactions depend on Suzuki coupling. At 1 mol % catalyst loading, both 3- and 4-bromoiodobenzene were converted to the desired products in 71−93% yields. In general, 3-bromoiodobenzene gave slightly lower yields. In all these cases, no homocoupling product of substituted arylboronic acid and dehalogenation product were detected. As illustrated in Table 2, the one-pot sequential coupling reaction was tolerant toward a variety of functional groups. Both electron-rich and electron-deficient arylboronic acids gave high yields within 3 h under the mild conditions (Table 2, entries 3−6, 9, 10, and 13−18). Steric hindered substrates, 2-tolylboronic acid and 1-naphthylboronic acid, gave a bit lower yields (Table 2, entries 7, 8, 21, and 22). Among these reactants, 4-chlorophenylboronic acid is more interesting (Table 2, entries 19 and 20) because the resultant products bear additional halides offering opportunity for the construction of more complex compounds. In the cases of styrene, the reaction time of Heck coupling has to be prolonged to 2 h to get a complete conversion. The overall yields are relatively lower because two intermediates (*E*/*Z* isomers) are formed (Table 2, entries 11 and 12). Aryl bromides were rather reactive in the Suzuki coupling

Table 4. Sequential Heck/Sonogashira Coupling of Aryl Dihalides[a]



entry	R_1	alkyne	product	yield (%)[b]
1	^{n}BuOCO			88
2	^{n}BuOCO			81
3[c]	Ph			64
4[c]	Ph			72
5[d]	^{n}BuOCO			60
6[d]	^{n}BuOCO			72

[a] Aryl dihalide 1.0 mmol, olefin 1.05 mmol, NaOAc 1.2 mmol, Pd 1.0 mol %, DMF 5 mL. After 30 min, alkyne 1.5 mmol, Cs_2CO_3 1.2 mmol, CuI 2.0 mol %, and PPh_3 1.0 mol %. [b] Isolated yield. [c] The (*Z*)-isomer was not isolated. [d] Alkyne 0.5 mmol.

reaction, thus the Heck/Suzuki sequence cannot be reversed. Suzuki/Heck reaction of bromoiodobenzene leads to double Suzuki coupling products, and the total yields were much lower.

The double coupling reaction can also be conducted in a stepwise way by using the isolated intermediate for the second coupling. Unexpectedly, the Suzuki couplings of the isolated (*E*)-butyl 3-(4-bromophenyl)acrylate and (*E*)-butyl 3-(3-bromophenyl)acrylate with $PhB(OH)_2$ afforded much lower yields than those of the one-pot reactions. The coupled products were obtained in only 56% and 24% yields after 6 h. The reason is not yet clear. The addition of NaI (1.0 mmol, 1 equiv) can significantly improve the overall yields of biphenylacrylate (see Table S1, Supporting Information).

In a similar manner, one-pot sequential Heck/Heck coupling reactions could also be realized, which were applied to the synthesis of unsymmetric di(alkenyl)arenes. The reactions could be easily performed by simply adding two different olefins in a stepwise way. As shown in Table 3, we were able to obtain the coupling products in nearly quantitative yields (Table 3, entries 1 and 2). Styrene often gave a relatively lower yield when used as the first coupling substrate rather than as the second coupling substrate. The final products usually are *E*/*Z* mixtures with a molar ratio of ca. 8/1 (Table 3, entries 3 and 4). The overall yields are also good.

This methodology has also been extended to sequential Heck/Sonogashira reactions for the preparation of enynes. After completion of the Heck reaction under the standard conditions and temperature was lowered to room temperature, alkyne, Cs_2CO_3, PPh_3, and CuI were subsequently added to the mixture and heated to 80 °C for another 3 h. This procedure successfully affords (alkynyl)(alkenyl)arenes (Table 4). The coupling products could be obtained in up to 80% yields (Table 4, entries 1 and 2). The yields of (*E*)-1-(phenylethynyl)-3- and 4-styrylbenzene are relatively low because the intermediates, 1-bromo-3- and 4-styrylbenzene, are less active. Sonogashira reaction of 1,5-diethynylnaphthalene also proceeded smoothly to produce enynes in moderate yields involving formation of four C−C bonds in a single pot.

In summary, we have demonstrated that the Pd−NHC complex allowed the sequential coupling of aryl dihalides, and various difunctionalized arenes have thus been obtained in excellent yields by combination of two different C−C couplings. The procedure uses a single catalyst for regioselctive formation of two or more C−C bonds in one pot. The use of the multifunctional catalyst for one-pot reactions generates less waste and also obviates the tedious separation and purification of the intermediate products. This approach opens up an easy access to unsymmetrically substituted arenes.

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Supporting Information Available: Experimental details and spectroscopic data for the coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

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