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Efficient One-Pot Suzuki-Miyaura Double Cross-Coupling Reactions Using Very Low $Pd(PPh_3)_4$ Catalyst Loading

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Efficient One-Pot Suzuki–Miyaura Double Cross-Coupling Reactions Using Very Low $Pd(PPh_3)_4$ Catalyst Loading

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Abstract: Suzuki–Miyaura double cross-coupling to form teraryls of interest as Schiff-base precursors can be achieved efficiently in near-quantitative yields using a low mol% amount of $Pd(PPh_3)_4$ and easily accessible dibromoaryls.

Keywords: Dibromoaryls, palladium-catalyzed cross-coupling, Suzuki–Miyaura, teraryls

The Suzuki–Miyaura (SM) palladium-catalyzed cross-coupling reaction,[1] as numerous authors have pointed out,[2] is one of the most important and versatile synthetic transformations for the synthesis of biaryl systems developed in the 20th century. Since the original methodology was described, many modifications have been reported. These include, for example, the use of different catalyst/ligand systems[3] and solvents and the use by Molander and Ellis[2a] of trifluoroborates instead of the usual boronic acid or ester components of the SM reaction. The scope of the reaction has also been extended to the synthesis of bisaryl- and bisnaphthyl-methanes.[4]

Noniterative,[5] one-pot, double-SM coupling reactions[6] with dihalogenated arenes to form oligo- and polyaryl[5a] products, however,

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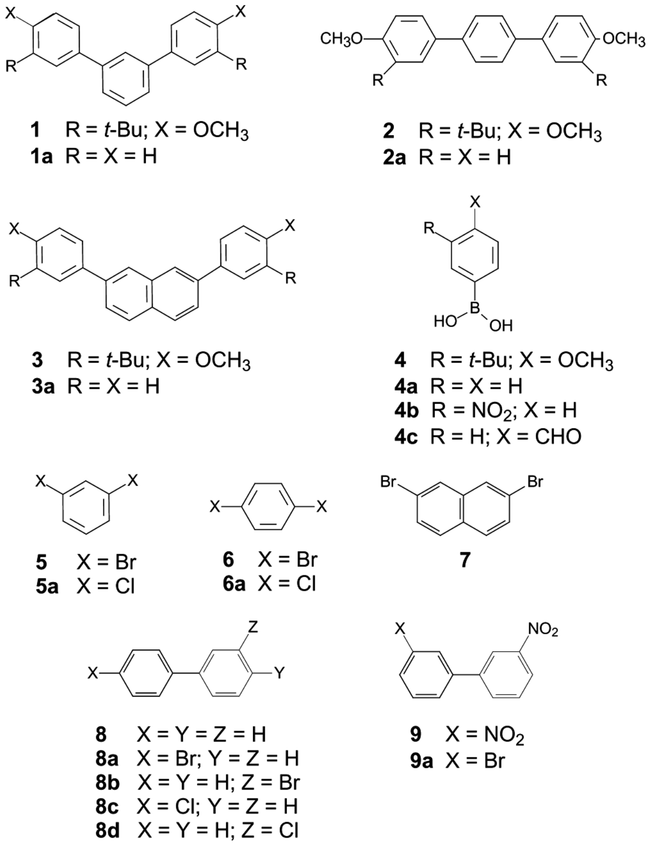
have received relatively less attention. The main challenge in such reactions is to achieve selectivity of single- over bis-coupling reactions. To achieve a desired Pd-catalyzed, double-SM cross-coupling reaction, the appropriate sequential steps of the oxidative addition–transmetalation and reductive elimination catalytic cycle are required.

Dong and Hu[7] reported highly selective double-SM coupling (up to 99:1 double vs. mono-coupling) of different dihalobenzenes using equimolar amounts of *o*- or *p*-tolylboronic acid, or *p*-methoxyphenylboronic acid and t-Bu_3P (10%) with 2.5% $Pd_2(dba)_3$. These authors proposed that the high selectivities were achieved via a preferential oxidative addition pathway. In their mechanism, the Pd(0) released from the first reductive elimination reacts preferentially in the oxidative addition reaction with the already-formed first coupling product rather than with unreacted dihalide starting material.

In general, however, relatively poor results for double-Suzuki coupling[5a,8,9] have been reported using the more readily accessible $Pd(PPh_3)_4$ catalyst. The results described in this article show that the teraryl systems **1**–**3** (Fig. 1, Scheme 1) can be synthesized in quantitative yields via one-pot double-SM coupling by using a low mol% of $Pd(PPh_3)_4$. Teraryl compounds **1** and **2**, which are of particular interest to us as Schiff base[8f] precursors in the synthesis of novel calixsalen targets,[10] were obtained by the coupling reactions of boronic acid **4**[8a] with *m*- or *p*-dibromobenzene **5** or **6** in the presence of $Pd(PPh_3)_4$ and $Ba(OH)_2$ as the base at 80°C for 48 h. However, to optimize the reaction conditions by examining the effect of changing the mol% of the Pd(0) catalyst employed, *m*-dibromobenzene (**5**) was used as a model compound.

The results are summarized in Table 1: Using 1,2-dimethoxyethane (DME)[11] as the solvent resulted in products **1** and **2** being formed in 45 and 76% yields from the reactions of **4** with **5** or **6**, respectively (Entries 1 and 2). In the case of **6**, the corresponding single-coupling product was also detected by ^1H NMR monitoring of the reaction. When dimethylacetamide (DMA)[8a,8e] was used as the solvent with all of the other conditions being the same, teraryl product **1** was obtained with **5** in only 50% yields; increasing the reaction times or raising the reaction temperature to 100°C did not improve the yields. However, when the mol% of the Pd catalyst was decreased to as low as only 0.025% and DMA again was used as the solvent at 80°C, with $Ba(OH)_2$ as the base, the yields of **1** were significantly improved from 50% to quantitative (Entries 3–8). Similar results were obtained when the same conditions, and only 0.025 mol% of the Pd catalyst was used in the reactions of **6** and **7** (Entries 7 and 8), forming **2** and **3** in 99 and 96% yields, respectively. The results summarized in Table 1 clearly show that decreasing the mol% of $Pd(PPh_3)_4$ to 0.025% in DMA as the solvent resulted in



1 R = *t*-Bu; X = OCH_3
1a R = X = H

2 R = *t*-Bu; X = OCH_3
2a R = X = H

3 R = *t*-Bu; X = OCH_3
3a R = X = H

4 R = *t*-Bu; X = OCH_3
4a R = X = H
4b R = NO_2; X = H
4c R = H; X = CHO

5 X = Br
5a X = Cl

6 X = Br
6a X = Cl

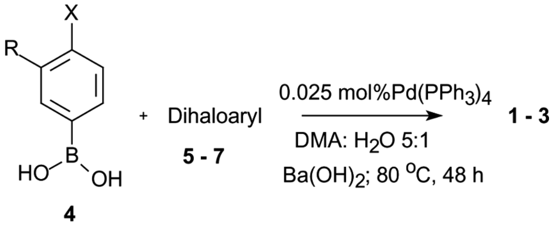
7

8 X = Y = Z = H
8a X = Br; Y = Z = H
8b X = Y = H; Z = Br
8c X = Cl; Y = Z = H
8d X = Y = H; Z = Cl

9 X = NO_2
9a X = Br

Figure 1. Structures of aryl- and naphthyl halides, and boronic acids employed in this study.

quantitative formation of the desired double-SM products, **1**–**3**. Compounds **1**–**3** all showed accurate mass measurements for their respective structural formulas.



Scheme 1. General scheme for the Suzuki–Miyaura double cross-coupling reactions.

Table 1. Effect of mol% of catalyst on yields using using boronic acid **4**

Entry	Starting material	Mol% of catalyst	Solvent	Product	Yield (%)[a]
1	**6**	13	DME	**2**	76
2	**5**	13	DME	**1**	45
3	**5**	13	DMA	**1**	50
4	**5**	1	DMA	**1**	70
5	**5**	0.05	DMA	**1**	82
6	**5**	0.025	DMA	**1**	100
7	**6**	0.025	DMA	**2**	99
8	**7**	0.025	DMA	**3**	96

[a] Yields reported are based upon isolated yields. Experimental details are included in the Experimental section.

A possible explanation to account for these results is to consider that when Pd(0) is present in the reaction solution in relatively high concentrations, inactive black Pd-Pd clusters[12] are preferentially formed. Dark-colored reaction mixtures indicative of the formation of such black Pd–Pd clusters could be observed in our reactions when the amount of Pd was used in the higher mol% quantities. As a consequence of such cluster formation, the presence or effectiveness of active Pd(0) intermediates involved in the catalytic cycle of the SM reaction decreased, resulting in the lesser yields of the double-SM coupling products. Conversely, when the concentrations of Pd(0) in the reaction solution are low, the potential of forming such inactive Pd–Pd clusters is minimized and the relative amounts of the active Pd(0) are greater, allowing the preferential oxidative pathway proposed by Dong and Hu to occur efficiently when low Pd(0) concentrations are used.

To determine whether the observed reaction conditions are also more generally applicable, reactions were conducted with the less-reactive chloro analogs, *o*- and *m*-dichlorides **5a** and **6a**. Because boronic acid **4** is expected to be relatively electron-rich and could therefore be more reactive under the conditions developed, some other representative less electron-rich boronic acids such as **4a**–**4c** were also tried. The results are summarized in Table 2. In the reactions of dichloro precursors **5a** and **6a** with phenylboronic acid **4a**, the yields of *m*- and *p*-terphenyls **1a** and **2a** were less (39 and 40%, respectively) than those obtained with the corresponding dibromides **5** and **6** (69 and 68%, respectively). With the less reactive phenylboronic acid, biphenyl **8** itself was the major by-product in each of the reactions studied, along with the mono-coupled products **8a**–**d** formed from the respective chloro- or bromo- precursors. With 3-nitrophenylboronic acid (**4b**), none of the corresponding terphenyls were obtained. Instead, unexpectedly, 3,3′-dinitrobiphenyl (**9**) in 62–74% yields

Table 2. Yields of coupling products obtained with phenylboronic acid (**4a**) and 3-nitrophenylboronic acid (**4b**)[a]

Entry	Starting material	Boronic acid	Product	Yield (%)
1	**5**	**4a**	**1a**	69
			8	25
			8b	4
2	**5a**	**4a**	**1a**	39
			8	30
			8d	Trace
3	**6**	**4a**	**2a**	68
			8	25
			8a	5
4	**6a**	**4a**	**2a**	40
			8	31
			8c	Trace
5	**7**	**4a**	**3a**	65
			8	21
6	**5**	**4b**	**9**	63
			9a	33
7	**6**	**4b**	**9**	68
8	**6a**	**4b**	**9**	62
9	**7**	**4b**	**9**	74

[a] Yields reported are based upon isolated yields. Compounds other than those reported in the Experimental section are based upon comparisons with those same compounds reported in the literature.

was obtained. In the case of the reaction of **4b** with *m*-dibromobenzene (**5**), the mono-coupled product **9a** was also obtained. With *p*-formylphenylboronic acid, no product formation with either dibromo- or dichlorobenzene was observed under the conditions examined.

Despite the longer reaction times required (which were not necessarily optimized) and some of the limitations noted herein, an advantage of the methodology reported herein (besides the reduction in the amounts of expensive Pd catalyst required) is that it is also applicable to the more easily accessible and less expensive dibrominated aryl precursors. Further investigation of the exact mechanism for the observations noted in this communication is warranted and is ongoing in our laboratory.

EXPERIMENTAL

Boronic acids **4a–c** and dihaloaryl compounds **5**, **5a**, **6**, and **6a** were purchased from Sigma-Aldrich. Boronic acid **4** was prepared as described in Ref. 8a, and 2,7-dibromonaphthalene (**7**) was prepared as described in Ref. 13.

Suzuki Coupling Reactions: General Procedure

A mixture of the respective dibromoaryl compound (3.21 mmol), boronic acid (6.7 mmol), barium hydroxide monohydrate (2.42 g, 12.8 mmol), *N,N*-dimethylacetamide (25 mL), and H_2O (5 mL) was thoroughly degassed by a nitrogen stream before the addition of $Pd(PPh_3)_4$ (2 mg, 0.0016 mmol). The mixture was heated at 80°C for 48 h under nitrogen. The resultant mixture was cooled, and dichloromethane (25 mL) was added. The organic phase was separated, washed with 10% hydrochloric acid (25 mL × 4), dried over $MgSO_4$, and filtered, and the solution was concentrated by a rotary evaporator. The product was purified using silica-gel chromatography and eluted with 5% dichloromethane–hexane.

Synthesis of 1,3-Bis(3-*tert*-butyl-4-methoxyphenyl)benzene (**1**)

The product **1** was collected as colorless crystals in quantitative yield: mp 106–108°C; ^{1}H NMR (C_6D_6) δ 1.69 (s, 18H), 3.36 (s, 6H), 6.82 (d, $J = 8.0$ Hz, 2H) 7.39 (t, 1H), 7.48 (dd, $J = 3.0$, 8.0 Hz, 2H), 7.60 (dd, $J = 2.0$, 8.0 Hz, 2H), 7.81 (d, $J = 2.0$ Hz, 2H), 8.07 (t, $J = 1.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 30.36, 35.57, 55.69, 112.43, 125.78, 126.22, 126.25, 126.41, 129.54, 133.99, 139.06, 142.63, 158.77; MS (APCI) *m/z* 403.1 (M + H), calcd. for $C_{28}H_{34}O_2$ 402.3.

Synthesis of 1,4-Bis(3-*tert*-butyl-4-methoxyphenyl)benzene (**2**)

The product **2** was collected as colorless crystals in 99% yield: mp 218–220°C; ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 18H), 3.90 (s, 6H), 6.98 (d, $J = 8.0$ Hz, 2H), 7.46 (dd, $J = 2.0$, 8.0 Hz, 2H), 7.56 (d, $J = 2.0$ Hz, 2H), 7.62 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 30.25, 35.46, 55.61, 112.34, 125.86, 126.05, 127.58, 133.35, 138.95, 140.289, 158.60; MS (APCI) *m/z* 403.3 (M + H), calcd. for $C_{28}H_{34}O_2$ 402.3.

Synthesis of 2,7-Bis(3-*tert*-butyl-4-methoxyphenyl)naphthalene (**3**)

The product **3** was collected as colorless crystals in 96% yield: mp 210–212°C; ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 18H), 3.93 (s, 6H), 7.03 (d, $J = 8.5$ Hz, 2H), 7.59 (dd, $J = 2.5$, 8.5 Hz, 2H), 7.70 (d, $J = 2.5$ Hz, 2H), 7.73 (dd, $J = 1.5$, 8.5 Hz, 2H), 7.91 (d, $J = 8.5$ Hz, 2H), 8.05 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 30.03, 35.26, 55.42, 112.17, 125.42, 125.63, 126.06, 126.12, 128.19, 131.30, 133.35, 134.34, 138.84, 139.44, 158.50; MS (APCI) m/z [M + H] 453.4, calcd. for $C_{32}H_{36}O_2$ 452.3.

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