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An Efficient Palladium-catalyzed Coupling Reaction for the Preparation of Biaryls and Polyaryls

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Abstract: In the case of $Pd(PPh_3)_4$ as catalyst and toluene as reaction solvent, the desired biaryls and polyaryls were synthesized in excellent yield and on a large scale.

Keywords: Palladium-catalyst, coupling reaction, preparation, biaryl, polyaryl.

Recently series attempts are being made to the formation of carbon-carbon bond between aryls or heteroaryls as these compounds form main bulk in several types of compounds including natural products[1,2], polymers[3], NLO materials[4], liquid crystals, ligands and molecules of drugs[5]. Numerous methods involving cross-coupling reaction with a variety of metal catalysts have been developed over last two decades[6]. In the later 1970´s, Stille reaction was carried out by treating aryl halides on triflates with arylstannanes to afford biaryl compounds[7]. This reaction proceeds under neutral conditions and can tolerate a wide range of substituents for coupling partners. The early 1980´s Suzuki reaction[8], like Stille reaction, proved to be extremely useful and has been extensively employed in natural product synthesis[9]. But it is very difficult to enhance the conversion at large scale. Among them one of the most efficient methods is palladium-catalyst system. Here, we report a novel coupling reaction which can enhance the yield of biaryl or polyaryls effectively.

Either $Pd(dba)_2$ or $Pd(OAc)_2/P(o\text{-}tolyl)_3$ was used as catalyst in our experiment,. Benzene, xylene, THF, DMF, and mixture of benzene and THF were tried to use as solvent, respectively. However, the yield of biaryls or polyaryls was low. After a series of tests, $Pd(PPh_3)_4$ was selected as catalyst under the same conditions, yielding the corresponding product in 30%.

This is one of the best results for this cross-coupling reaction. After optimized the catalyst, the effect of solvent was also investigated and the result showed that in the presence of $Pd(PPh_3)_4$ benzene or toluene could give improved result as shown in **Table 1**. Moreover, under this condition the reaction time was decreased from more than 10 hr to 4-6 hr whereas the scale of the preparation was increased to 10 grams. The optimized catalysis system for this coupling reaction was $Pd(PPh_3)_4$ in toluene without any base. At the same time we improved the synthesis of arylstannanes. The

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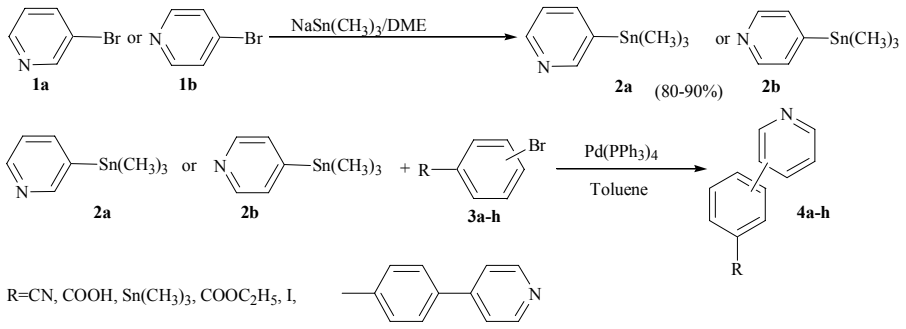
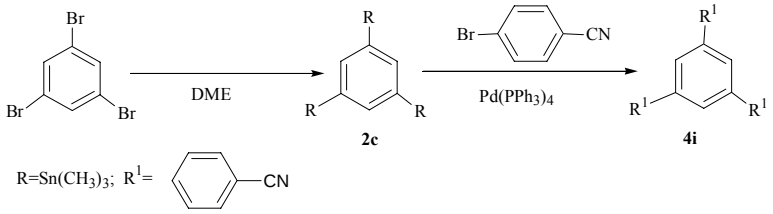
Scheme 1



Scheme 2



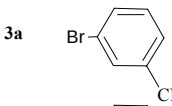
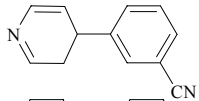
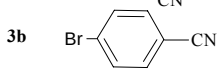
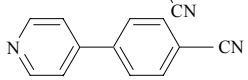
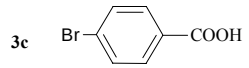
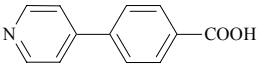
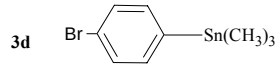
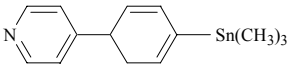
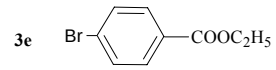
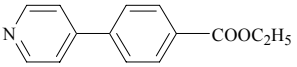
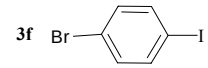
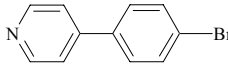
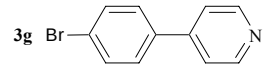
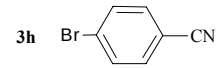
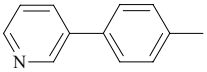
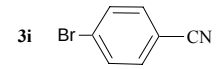
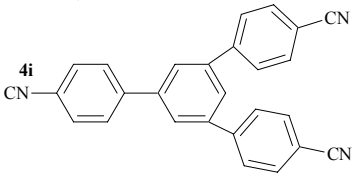
preparation of arylstannanes was carried out at temperature –10°C in the absence of light. After the addition of haloaryls the reaction was run in DME at room temperature for two hours and followed by refluxing for another one hour. In this way, the yield of arylstannanes was increased from 60%[10] to 88%.

The study of the mechanism for this novel coupling reaction is now in progress.

Experimental

The typical procedure To a three-neck flask 19.9 g (0.1 mol) of trimethyltin chloride was added dropwise to a suspension of 4.6 g (0.2 mol) of sodium in DME under nitrogen in dark at –10°C for 20 min and the reaction mixture was allowed to stir in ice-salt bath for 2 hr. Excess of sodium was filtered off and the filtrate was transferred to another flask under nitrogen, and 12.5 g (0.079 mol) of 4-bromopyridine was added dropwise over a period of 30 min. The reaction mixture was allowed to stir 1 hr at room temperature followed by refluxing for 1 hr. After cooling to room temperature, the reaction mixture was filtered,and then the filtrate was concentrated in vacuum. The residue was purified by vacuum distillation, 16.8 g of 4-trimethylstynnyl pyridine was obtained (88%).

Table 1 Isolated yield of coupling reactions with $Pd(PPh_3)_4$/toluene catalytic system

Substrates **3**	Product **4**	Time(h)	Yield(%)
3a 	**4a** 	5	95
3b 	**4b** 	5	98
3c 	**4c** 	6	85
3d 	**4d** 	5	90
3e 	**4e** 	5	89
3f 	**4f** 	4	94
3g 	**4g** 	5	94
3h 	**4h** 		96
3i 	**4i** 	5	75

To the solution of 1.01 g (6.40 mmol) of 3-bromobenzonitrile **3a** in 20 mL toluene 1.53 g (6.33 mmol) of 4-trimethyl stannyl pyridine and 5% mole of $Pd(PPh_3)_4$ was added. The reaction mixture was allowed to reflux for 5 hrs. After cooled to room temperature, the mixture was washed by saturated brine, and concentrated in vacuum. The residue was purified by silica gel column, (hexane: ethyl acetate = 1:1) and 0.97 g (6.3 mmol) of product **4a** was obtained (95%).

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11. 11Charaterization of the products:
    3-(4´-pyridyl)benzonitrile (4a) ^{1}H NMR($CDCl_3$, δppm): 7.26 (d, 2H, J=6.2Hz), 7.33 (s, 1H), 7.33 - 7.35 (m, 3H), 8.47(d, 2H, J=6.2Hz). MS: *m/z* 180 (M^+). ^{13}C NMR: 113.60, 118.42, 121.60, 130.18, 130.73, 131.44, 132.48, 139.61, 146.12, 150.75.
    4-(4´-pyridyl)benzonitrile (4b) ^{1}H NMR($CDCl_3$, δppm): 7.51 (d, 2H, J=4.39Hz), 7.75 (d, 2H, J=8.30Hz), 7.79 (d, 2H, J=8.30Hz), 8.73 (d, 2H, J=4.39Hz). MS: *m/z* 180 (M^+). ^{13}C NMR: 112.90, 118.50, 121.73, 127.88, 133.01, 142.69, 146.44, 150.69.
    4-(4´-pyridyl)benzoic acid (4c) ^{1}H NMR(D_2O,δppm): 8.07 (d, 2H, J=8.40Hz), 8.25 (d, 2H, J=8.40Hz), 8.39 (d, 2H, J=6.90Hz) 8.85 (d, 2H, J=6.90Hz). MS: *m/z* 199 (M^+). ^{13}C NMR: 121.56, 126.83, 130.65, 131.12, 143.37, 148.12, 172.01.
    4-(4´-trimethylstannanyl-phenyl) pyridine (4d) ^{1}H NMR($CDCl_3$, δppm): 0.37 (s, 9H), 7.50 (d, 2H, J=5.48Hz), 7.61 (d, 2H, J=7.70Hz), 7.65 (d, 2H, J=7.70Hz), 8.67 (d, 2H, J=5.48Hz). MS: *m/z* 318 (M^+). ^{13}C NMR: 40.35, 67.20, 106.36, 110.40, 118.84, 133.94, 142.25, 142.24.
    ethyl 4-(4´-pyridyl)benzoate (4e) ^{1}H NMR($CDCl_3$, δppm): 1.42 (t, 3H, J=7.13Hz), 4.41 (q, 2H, J=7.13Hz), 7.53 (d, 2H, J=4.94Hz), 7.70 (d, 2H, J=8.30Hz), 8.15 (d, 2H, J=8.30Hz), 8.70 (d, 2H, J=4.94Hz). MS: *m/z* 227 (M^+). ^{13}C NMR: 14.50, 61.38, 121.88, 127.16, 130.49, 131.13, 142.52, 147.50, 150.59, 166.26.
    1-bromo-4-(4´-pyridyl)benzene (4f) ^{1}H NMR($CDCl_3$, δppm): 7.46 (d, 2H, J=5.49Hz), 7.49 (d, 2H, J=8.23Hz), 7.61 (d, 2H, J=8.23Hz), 8.66 (d, 2H, J=5.49Hz). MS: *m/z* 234 (M^+). ^{13}C NMR: 121.46, 123.69, 128.66, 132.42, 137.12, 147.21, 150.51.
    1,4-di(4´-pyridyl)benzene (4g) ^{1}H NMR($CDCl_3$, δppm): 7.44 (d, 4H, J=6.35Hz), 7.48 (d, 2H, J=8.60Hz), 7.59 (d, 2H, J=8.60Hz), 8.64 (d, 4H, J=6.35Hz). MS: *m/z* 232 (M^+). ^{13}C NMR: 121.35, 123.54, 128.54, 132.30, 137.03, 147.10, 150.38.
    4-(3´-pyridyl)benzonitrile (4h) ^{1}H NMR($CDCl_3$, δppm): 7.49 (d, 2H, J=5.44Hz), 7.63 (t, 1H, J=7.68Hz), 7.73 (d, 1H, J=7.68Hz), 7.87 (d, 1H, J=7.68Hz), 7.92 (s, 1H), 8.73 (d, 2H, J=5.44Hz). MS: *m/z* 180 (M^+). ^{13}C NMR: 112.56, 116.50, 120.82, 123.85, 127.70, 132.54, 133.48, 134.23, 148.81, 149.49.
    1,3,5-tri(4´-cynophenyl)benzene (4i) ^{1}H NMR($CDCl_3$,δppm): 7.24 (s, 3H), 7.66 (d, 6H, J=8.80Hz), 7.76 (d, 6H, J=8.80Hz). MS: *m/z* 381 (M^+). ^{13}C NMR: 111.47, 116.50, 125.23, 128.16, 132.55, 137.60, 141.93.

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