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for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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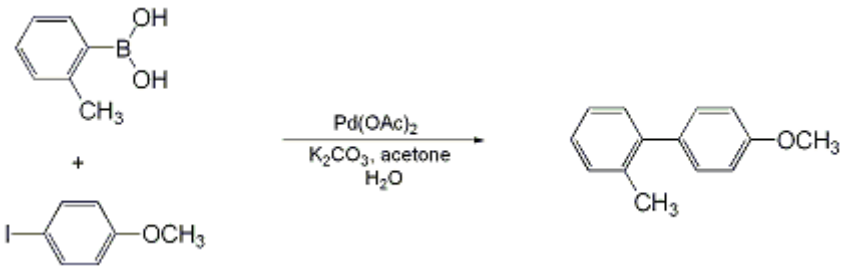
ACCELERATED SUZUKI COUPLING VIA A LIGANDLESS PALLADIUM CATALYST: 4-METHOXY-2'-METHYLBIPHENYL

[1,1'-Biphenyl, 4'-methoxy-2-methyl-]



Submitted by Felix E. Goodson, Thomas I. Wallow[1] , and Bruce M. Novak[2] .
Checked by Ingrid M. Fellows and Stephen F. Martin.

1. Procedure

4-Methoxy-2'-methylbiphenyl . o-Tolylboronic acid, 10.0 g (73.6 mmol) (Note 1), 16.8 g (71.8 mmol) of 4-iodoanisole (Note 2), and 200 mL of acetone (Note 3) are combined in a 1-L, three-necked flask equipped with an efficient stirbar, two stoppers, and a reflux condenser attached to a gas-flow adapter with a stopcock. Potassium carbonate, 25.0 g (0.180 mol), is dissolved in 200 mL of water (Note 4) in a separate 250-mL Schlenk flask. In a third flask (25-mL Schlenk flask) 3.30 mg (0.02 mmol, 0.2%) of palladium acetate (Note 5) is dissolved in 10 mL of acetone . All three flasks are then thoroughly degassed by four freeze-pump-thaw cycles. Under an argon back flow, one of the stoppers on the three-necked flask is replaced with a rubber septum, and the carbonate and catalyst solutions are added via cannula to form a biphasic mixture. The top layer turns brown upon addition of the catalyst. The septum is replaced with the glass stopper and three additional freeze-pump-thaw cycles are applied. The flask is then backfilled with argon, and the reaction is brought to reflux under a positive argon pressure. After 2 hr at reflux the heat source is removed and the reaction is allowed to cool. By this time the brown color has faded and the reaction is a triphasic mixture with copious amounts of palladium black floating between the layers. The reaction is transferred to a 1-L separatory funnel and extracted into diethyl ether (3 × 100 mL). The organic layers are combined, washed with water (1 × 100 mL) saturated with sodium chloride , and dried over magnesium sulfate . Solvent is removed with a rotary evaporator to yield a yellow oil which is distilled (125-130°C, 0.10 mm) to give 12.8 g of 4-methoxy-2'-methylbiphenyl as a colorless oil (90.3% yield) (Note 6).

2. Notes

1. o-Tolylboronic acid is used as received from Aldrich Chemical Company, Inc. The reagent is listed as 95% pure, but NMR analysis reveals that the predominant impurity is o-tolylboronic anhydride that reverts back to the acid in the presence of water. In one bottle there was a slight brownish impurity as well, but the presence of this impurity did not affect the reaction. The slight excess of this reagent is to ensure complete conversion of the 4-iodoanisole, which is difficult to separate from the final product.
2. Commercial 4-iodoanisole (Aldrich Chemical Company, Inc.) is sublimed immediately prior to use.
3. Commercial reagent grade acetone (Fisher Scientific Company) is used without further purification.
4. Commercial HPLC grade water (Sigma Chemical Company) is used without further purification.
5. Palladium acetate (99.99+%) is used as received from Aldrich Chemical Company, Inc.
6. The spectral properties are as follows: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.26 (s, 3 H), 3.80 (s, 3 H), 6.94 (d, 2 H, J = 8.7), 7.20-7.25 (m, 6 H) ; ^{13}C NMR (200 MHz, $CDCl_3$) δ: 20.5, 55.2, 113.5, 125.7, 126.9, 129.9, 130.2, 134.4, 135.4, 141.5, 158.5 ; mass spectrum (CI) m/z 199.1118 (M+1 requires 199.1122) .

Waste Disposal Information

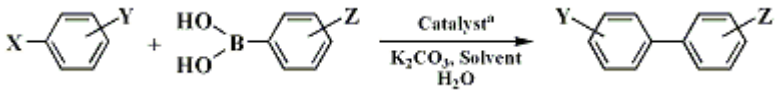
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The palladium-mediated cross-coupling reaction of an aryl halide with an aryl-boronic acid, (Suzuki coupling), is a versatile method for synthesizing unsymmetrical biaryls.[3] [4] [5] Traditionally, these reactions have been carried out using phosphine-based palladium catalysts. The primary advantage of the ligandless[6] [7] methodology presented here is that it eliminates two phosphine related side reactions, aryl-aryl exchange,[8] [9] and phosphonium salt formation,[10] that plague the traditional phosphine-based systems. The first of these side reactions equilibrates the aryl group bound to the palladium in the $ArPdL_2I$ catalyst intermediate with the aryl groups bound to the phosphorus atoms, allowing the ligand-bound phenyl groups to enter the cross-coupling cycle in lieu of the aryl-halide derived aryl moieties. This, in turn, can sometimes introduce substantial amounts of phenylated by-products into the product mixture.[11] [12] The second side reaction is the palladium-catalyzed formation of tetraarylphosphonium iodides from iodoarenes and triarylphosphines.[10] To the degree that this occurs during cross-coupling, it represents a nonproductive consumption of aryl halides. A second key advantage of the ligandless methodology is a marked improvement in reaction efficiency, allowing for shorter reaction times, milder conditions and greater catalytic turnovers. Indeed, on small scale reactions, as little as 0.02% catalyst is required for complete conversion.[13] Electron-rich, sterically hindered aryl boronates and heteroaromatic boronates in particular are known to be troublesome substrates for Suzuki couplings under standard conditions because of their enhanced susceptibility toward base-catalyzed protodeboronation.[14] Increased catalytic efficiency represents one of the few tools available for minimizing this side reaction.

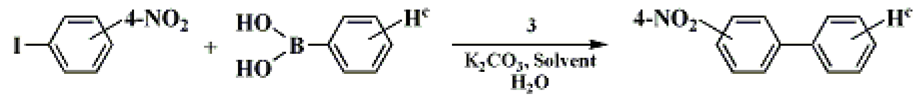
To investigate the scope and limitations of this procedure, small-scale couplings were carried out on a variety of substrates using different catalysts and solvents (1 mmol halide, 1.05 equiv of boronic acid precursor, 2.5 mL of solvents). The results are summarized in Table I. (Some of these results were presented in the submitters' earlier publication.[13]) Electron withdrawing and electron donating substituents on either the aryl halide or boronic acid have no effect on the ability of the ligandless catalyst to promote this reaction to completion. Aryl bromides undergo coupling as well as aryl iodides, but the required reaction times are longer (2-4 hr). When aryl iodides are used, increased steric hindrance on either substrate also has no detrimental effect on conversion. On aryl bromides, however, increased steric hindrance does hinder quantitative product formation. Palladium acetate **(1)**, tris (dibenzilideneacetone)dipalladium $[Pd_2(dba)_3]$ **(2)**, and allylpalladium chloride **(3)** all serve as satisfactory ligandless catalyst precursors. However, as the first is the most air, light, and heat stable, it is the most convenient to use. Although the ligandless methodology is relatively insensitive to the above parameters, the choice of solvent is critical. Of the solvents screened, only acetone and tetramethylurea promote quantitative conversion to the biphenyl, even after prolonged reaction times. In general, the reaction is facilitated by more polar solvents, but the failure of dimethyl sulfoxide to produce quantitative product formation suggests that this generalization is not universal. If a Suzuki coupling reaction must be carried out in a less polar solvent because of solubility, substrate compatibility, etc., the submitters suggest the addition of two catalyst equivalents of the bulky tri(o-tolyl)phosphine ligand. This phosphine is known to suppress the formation of by-products derived from aryl-aryl transfer in palladium-mediated couplings.[15] [16] [17] Furthermore, palladium complexes of tri(o-tolyl)phosphine have also found use in the formation of aryl amines from aryl halides and tin amides[18] [19] [20] or secondary amines.[21] [22]

TABLE
SYNTHESIS OF BIPHENYLS VIA SUZUKI COUPLING REACTIO



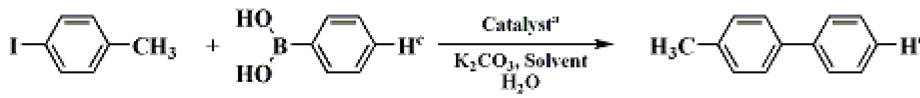
X	*Y*	*Z*	*Cat*
I	4-CH_3	H[c]	1
I	4-NO_2	H[c]	1
I	4-OCH_3	4-CF_3[e]	1
I	4-CF_3	4-OCH_3[e]	1
I	2-CH_3	4-OCH_3[e]	1
I	4-OCH_3	2-CH_3[e]	1
I	4-OCH_3	4-CF_3[e]	1
Br	4-OCH_3	4-CF_3[e]	1
Br	2-CH_3	4-OCH_3[e]	1
I	4-NO_2	H[c]	2
I	4-	H[c]	

NO_2



H^c

I 4- CH_3



H^c

I 4- CH_3

H^c

I 4- CH_3

H^c

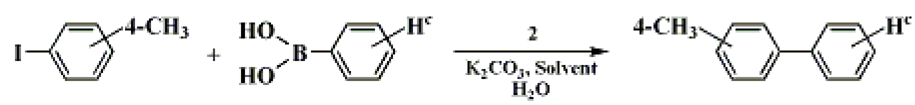
I 4- CH_3

H^c

I 4- CH_3

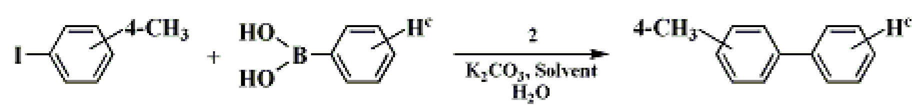
H^c

I 4- CH_3



H^c

I 4- CH_3

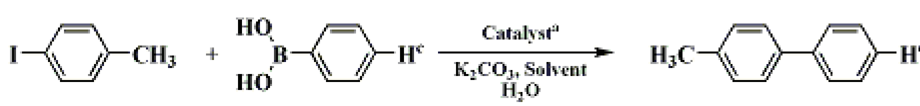


H^c

I 4- CH_3

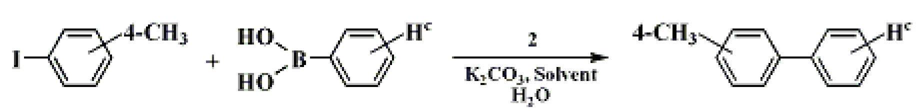
H^c

I 4- CH_3



H^c

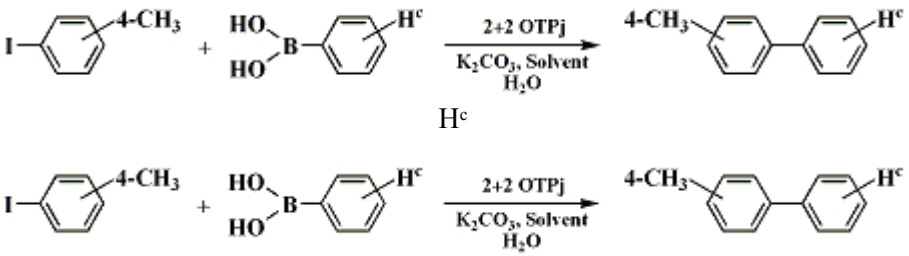
I 4- CH_3



I 4- CH_3

2
O

H^c



I 4-CH3 2 O

[a] **1**, Palladium acetate; **2**, tris(dibenzilidene acetone) dipalladium [$Pd_2(dba)_3$]; **3**, alllylpalladium chl NMR and/or thin layer chromatography. [c] Phenylboronic anhydride was used as the boronic acid p of reaction completion was not determined. [e]The ethylene glycol boronic ester was used as the bor catalyst was added at the beginning of the reaction, and again 12 hr into the reaction. [g] Dimethoxy Tetramethylurea. [j] Tri(o-tolyl)phosphine.

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

4-Methoxy-2'-methylbiphenyl:

1,1'-Biphenyl, 4'-methoxy-2-methyl- (11); (92495-54-0)

o-Tolylboronic acid:
o-Toluneboronic acid (8,9); (16419-60-6)

4-Iodoanisole:
Anisole, p-iodo- (8);
Benzene, 1-iodo-4-methoxy- (9); (696-62-8)

Palladium acetate:
Acetic acid, palladium (2+) salt (8,9); (3375-31-3)