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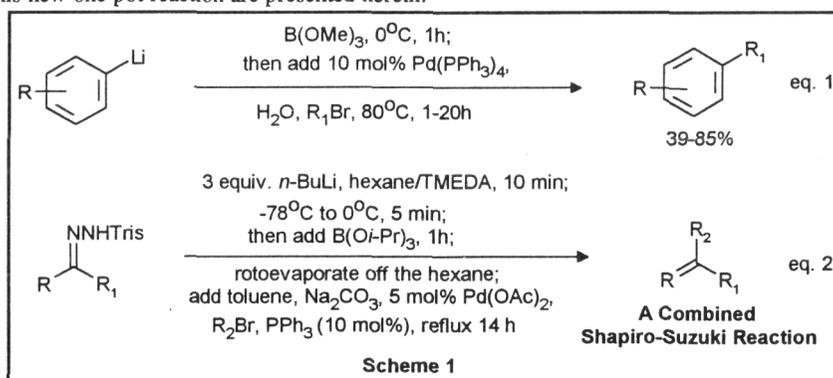
A One Pot *In Situ* Combined Shapiro-Suzuki Reaction

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Abstract: The Shapiro and Suzuki reactions have been combined *in situ* to provide aryl-alkenes in moderate to good yields without the isolation of boron containing intermediates.

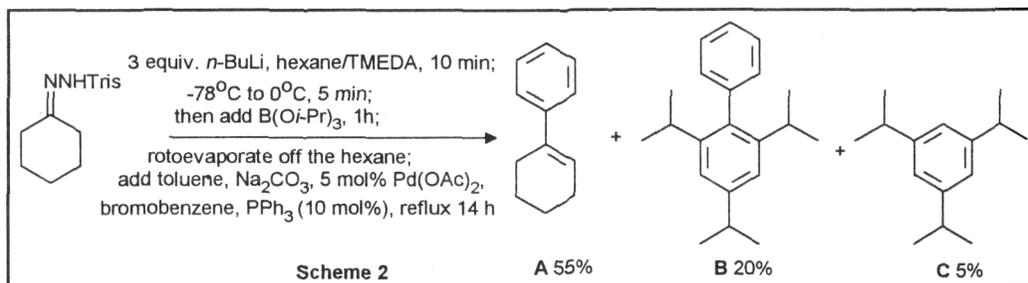
We have previously reported an *in situ* variation of the Suzuki reaction which does not require the isolation of the boronic acid (eq. 1, Scheme 1).¹ Various anions (aryl, vinyl, and alkyl) were treated with trimethylborate, followed by the addition of an aryl- or vinyl-halide, a palladium catalyst (10 mol%), and water. The mixture was refluxed to provide cross-coupled products in yields that were comparable to the Suzuki reaction which had been performed with isolated boronic acids.² We have taken this reaction one step further and designed reaction conditions which combine the Shapiro³ and Suzuki reactions (eq. 2, Scheme 1). The result is a reaction which can be performed in one pot without isolation of the vinyl boronic acid. Previous two step methods that resulted in similar products have involved: (1) the formation and isolation of an enol triflate followed by a Stille coupling with vinyl- and aryl-stannanes;⁴ and (2) trapping a Shapiro generated vinyl anion with tri-*n*-butylstannane and treating the isolated vinylstannane with aryl halides via a Stille reaction.⁵ The details of this new one pot reaction are presented herein.



After a large number of experiments, optimized reaction conditions were found to provide a variety of products in yields ranging from 48-65% (Table 1). Although the yields are moderate to good, they are similar to the average yield reported for the Shapiro reaction alone³ and represent the isolated yield after two steps. The optimized reaction conditions are listed in equation 2 of Scheme 1. Thus, a 2,4,6-triisopropylsulfonyl (Tris)

hydrazone is treated with 3 equivalents of *n*-BuLi in a hexane/TMEDA (1:1) mixture at -78°C . The mixture is allowed to warm to 0°C . After the evolution of N_2 has ceased, triisopropylborate is added and the reaction stirred for 1h at 0°C . The hexane is removed on a rotoevaporator, and toluene, sodium carbonate, $\text{Pd}(\text{OAc})_2$, PPh_3 and an aryl halide are added and the mixture is refluxed for 14 hours. A normal workup and purification provided the product expected from a two step Shapiro-Suzuki reaction. Conducting the reaction in a variety of solvents (THF, neat TMEDA, ether, or hexane), palladium catalysts (both Pd(0) and Pd(II)), boron reagents ($\text{B}(\text{OMe})_3$ and *B*-chlorocatecholborane), for different times and at different temperatures did not result in higher yields. The combined Shapiro-Suzuki reaction can be used with a variety of trisylhydrazones (aryl, cycloalkyl and alkyl) and aryl halides (bromides and iodides).

A second unexpected product has been detected from some of the reactions listed in Table 1. For example, the trisylhydrazone of cyclohexanone when coupled with bromobenzene provided the expected Shapiro-Suzuki product 1-phenyl-1-cyclohexene (**A**) plus 2,4,6-triisopropyl-1-phenylbenzene (**B**) in 55 and 20% yields respectively, along with triisopropylbenzene (**C**, 5%) (Scheme 2). The formation of compound **B** was investigated further. Aryl sulfonic acids have been reported to form biphenyl in the presence of Na_2PdCl_4 through the loss of SO_2 .⁶ However, an alternative mechanism must be occurring in this reaction since the byproduct is formed from the triisopropylbenzene and aryl halide components of the reaction. Treatment of sodium benzenesulfinate with bromobenzene in the presence of $\text{Pd}(\text{OAc})_2$ did not result in the formation of biphenyl, thus we feel the lithium 2,4,6-triisopropylbenzenesulfinate formed after decomposition of the trisylhydrazone must be losing SO_2 to form an aryl anion which is trapped by the triisopropylborate. A Suzuki coupling then occurs when the arylhalide and palladium catalyst are added resulting in the formation of compound **B**. Compound **C** forms by either the aryl anion reacting with the solvent to pick up a proton or by hydrodeboration of the boron intermediate at the elevated temperatures during the Suzuki coupling.^{7,8}



Thus, we have developed a one pot reaction which combines the Shapiro and Suzuki reactions to provide vinyl arenes in moderate to good yields. Application of this method to the synthesis of natural products is currently underway.

Table 1: Results From The *in situ* Combined Shapiro-Suzuki Reaction

Entry	Starting Hydrazone	Aryl Halide	Product (Compound A)	% Yield of A ^a
1				55 ^b
2				55 ^b
3				55
4				48
5				65
6				58
7				50
8				47 ^b
9				48 ^b
10				49
11				55

a) Isolated yields. b) Some of the corresponding 1-substituted-2,4,6-triisopropylbenzene was detected by GC/MS. The substituent is the aryl component of the halide listed in column 3 of the table (see text and Scheme 2).

Typical Experimental: To a suspension of 2-methylcyclohexanone (2,4,6-triisopropylphenyl)sulphonylhydrazone (400 mg, 1.02 mmol) in hexanes (1 mL) at -78°C was added TMEDA (1 mL) and the solution stirred for 10 minutes. *n*-BuLi (1.22 mL of 2.5 M in hexanes, 3.06 mmol) was added and after 10 minutes warmed to 0°C at which time N_2 was evolved. When the evolution of N_2 gas stopped (~ 15 min), the mixture was cooled to -78°C and trimethylborate (450 μL , 2.0 mmol) was added and the solution stirred at 0°C for one hour. The hexanes were removed *in vacuo* and toluene (5 mL), Na_2CO_3 (2 mL of 2 M), palladium acetate (9 mg, 0.04 mmol), triphenylphosphine (16 mg, 0.08 mmol) and 1-bromonaphthalene (210 mg, 1.01 mmol) were added. The mixture was refluxed under N_2 for 14 hours, during which time the mixture turned light yellow and a black precipitate formed. The organic phase was washed with water (2 x 10 mL), CuSO_4 (10 mL of 10%), and saturated NaCl (10 mL), dried (Na_2SO_4) and removed *in vacuo* to yield a brown oil (270 mg). Flash chromatography on silica gel (hexanes) and distillation provided 6-methyl-1-(1-naphthyl)cyclohex-1-ene as a clear colourless oil (124 mg, 55%).

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References and Notes

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8. Changing the hydrazone to a tosylhydrazone³ resulted in a much cleaner reaction, since the corresponding compound **B** was not detected; however, the yield of compound **A** was reduced to 20%.

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