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An Optimized Palladium Catalyzed Cross-Coupling of Nonracemic Trifluoromethylsulfonyl and Fluorosulfonyl Enol Ethers to Arylboronic Acids

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Abstract: Several trifluoromethylsulfonyl and fluorosulfonyl nonracemic (> 99% e.e.) enol ethers were cross-coupled to arylboronic acid under palladium [PdCl₂(dppf)] catalysis to provide in high yield (>98%) selected 1,3-diaryl nonracemic indenes. © 1998 Elsevier Science Ltd. All rights reserved.

SmithKline Beecham has reported the discovery of two endothelin (ET-1) receptor antagonists, SB 209670 (1a) and SB 217242 (1b) which have been clinically evaluated for systemic hypertension, pulmonary hypertension, renal and myocardial ischemia, stroke, subarachnoid hemorrhage, restenosis, congestive heart failure, and chronic renal failure.¹ Both structures were recognized as being a considerable synthetic challenge because they possessed three contiguous stereogenic centers in an indane nucleus.² Two approaches undertaken revolved around a Suzuki coupling reaction between the nonracemic trifluoromethylsulfonyl and fluorosulfonyl enol ethers 2 (Table I) with arylboronic acid 3. These approaches differed only in their method of preparation of the nonracemic keto precursor. This laboratory has just recently reported the synthesis of the prerequisite fluorosulfonyl enol ether 2 (R = OMe) in high enantiomeric purity (>99% e.e.).³

The palladium catalyzed cross-coupling of aryl-, vinyl-, and alkylboronic acids with aryl- and vinyl halides,^{4,5} diazonium salts,⁶ and triflates⁴ is a powerful and popular method for the formation of carbon-carbon bonds. Although the reaction with halides proceeds readily, organotriflates have been recognized as especially valuable partners in the cross-coupling reaction,^{4b,7,8} in part, due to their easy access from phenols or carbonyl precursors.^{4f,4g} However, the less expensive fluorosulfonates have not been utilized extensively,⁹ even though they appear to react similarly. The success of Roth^{9a} in the use of fluorosulphonates in palladium catalyzed cross-coupling reactions spurred us to explore their use in the coupling of nonracemic 2 with 3 to form 4, which we intended to utilize in a synthesize of 1a and 1b. The required aryl boronic acid was prepared in up to 89% yield by exposing the corresponding Grignard or lithium reagent to trimethyl borate at – 60 °C followed by quenching in 10% HCl.

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 Table I. Palladium Catalyzed Cross-Coupling of Arylboronic Acids 3 to Nonracemic

 Fluorosulfonyl-and Trifluoromethylsulfonyl Enol Ethers 2

SM	R	R ¹	R ²	Catalyst	mol% (Cat)	Yield ^d
2a	CF ₃	Xc ^c	3b	Pd(PPh ₃) ₄	10	55%
2 b	F	Xc	3b	Pd(PPh3)4	10	56%
2a	CF3	Xc	3b	PdCl ₂ (PhCN) ₂ Ph ₃ As ^b	5	<50%
2a	CF ₃	Xc	3b	PdCl2dppf	5	95%
2 b	F	Xc	3b	PdCl2dppf	0.5	97%°
2a	CF ₃	Xc	3b	NiCl ₂ dppf	5	NR
2a	CF ₃	Xc	3b	PdCl ₂ dppe	5	SM decom
2a	CF ₃	Xc	3b	PdCl ₂ dppb	5	74%
2a	CF ₃	Xc	3b	PdCl ₂ [P(o-tolyl) ₃] ₂	5	72%
2a	CF ₃	Xc	3b	PdCl ₂ [P(o-	5	87%
	Ŧ			MeOPh)3]2		
2a	CF ₃	Xc	e	Pd(PPh ₃) ₄	10	81%
2a	CF ₃	Xc	3c	PdCl2dppf	0.3	98.6%
2 c	F	OMe	3a	PdCl2dppf	5	94%
2 c	F	OMe	3a	PdCl2dppf	0.1	86%
2 d	CF ₃	OMe	3a	PdCl ₂ /dppf ^b	5	85%
2 c	F	OMe	3a	Pd(OAc) ₂ /	2.5	95%
				PPh ₂ (m-SO ₃ Ph)		

^aXc is (4*S*)-4-Phenyl-2-oxazolidinone. ^bGenerated *in-situ*. ^cChromatographed yield. ^dCrude product yields determined by HPLC solution assay. All optical purities were determined by chiral phase HPLC (Diacel Chiralpak AD, 7% IPA / hexanes). ^e3 is phenylboronic acid.

Initial experiments explored tetrakistriphenylphospine palladium (0) $[(Ph_3)_4Pd]$ with bases such as thallium, sodium, cesium, or potassium carbonate as bases. However, yields in these experiments were generally moderate (~60%), regardless of the base or solvent conditions employed. Using triethylamine as base led to decomposition products. Strong bases such as sodium ethylate, potassium *t*-butoxide, and potassium phosphate were avoided since they formed an inden-2-one side-product.¹⁰ Generation of this impurity proved to be our most troublesome side-reaction. Triphenylphosphine was found to be sufficiently basic to generate

this impurity. Surprisingly, sodium bicarbonate was effective in this reaction, but reacted at a slower rate than sodium carbonate and resulted in a poorer reaction impurity profile. The mechanism of the Pd-catalyzed Suzuki reaction is thought to involve oxidative addition into aryl triflates, fluorosulfonates, or halides followed by transmetalation of the Ar-Pd-X with the boronate Ar B(OH), M⁺. The cycle is completed with reductive elimination of the cross-coupled product.^{3,11} Novak recently reported that reactions carried out in the presence of a bicarbonate : carbonic acid buffer (pH = 7-8.5) are retarded relative to cross-couplings buffered with a carbonate : bicarbonate buffer (pH = 9.5-11).¹² Changes in solvent and catalyst did not alter this effect. It was suggested that the higher pH was needed to enhance the concentration of a hydroxyboronate anion that appears to be the more reactive species. A slow reaction, as in our bicarbonate example, would allow the deprotonation pathway to favorably compete for starting material. To circumvent this problem, we continued to limit ourselves to carbonate bases but began to explore the effectiveness of some less basic ligands of phosphorus as well as other metals. The more readily available and inexpensive 1,1'-bis(diphenylphosphinoferrocene)NiCl., which has been found to be effective in other aryl boronic cross-coupling cases, ^{13,16a} was found to be ineffective with our system. (Diphenylphosphinoethane)PdCl, and (diphenylphosphinobutane)PdCl, both produced mainly the inden-2-one impurity. Palladium acetate without phosphine ligands yielded primarily decomposition materials. It was shortly discovered that 1,1'-bis(diphenylphosphinoferrocene)PdCl, catalyzed the cross-coupling of 2 to 3 much more efficiently than $(Ph_1)_4Pd$ (Table I). Presumably, the lower basicity of $PdCl_2(dppf)$ does not facilitate deprotonation of 2. It was also found that this catalyst could be employed using loadings as low as 0.1% mol. However, more consistent results were generally obtained with loadings within the 0.3-0.5 mol% range.

Generally, it was found that using THF, DME, and toluene with or without water provided yields of cross-coupled product in the 60-70% range along with substantial quantities of the inden-2-one. In optimization studies of the PdCl₂(dppf) catalyzed reaction, which was initially run in toluene/H₂O (4.5/0.25, v/v, several mixed solvents systems were explored. Recent reports suggested increased efficiency employing the three solvent system, toluene/H₂O/EtOH (7/1/1, ν/ν).^{5c,14} Adding ethanol to our solvent system dramatically increased the yield from ~70% to within the 92-98% range. After a thorough HPLC analysis of the mother liquors from one run using the toluene/H₂O/EtOH solvent system, it was determined that ethanol acted as a nucleophile by displacing the fluorosulfonate to form the ethyl enol ether in small quantities (3-5%). Replacement of ethanol with acetone or acetonitrile now provided the cross-coupled product in >98% vield. PdCl₂(dppf) generated *in-situ* generally resulted in ~ 5% less isolated yields than using the pre-formed catalyst. Other catalysts, tris-(o-methoxyphenyl)phoshinopalladium(II) chloride, tris-(o-tolyl)phoshinopalladium(II) chloride, and the water soluble diphenylphosphino $(m-NaO_3S-phenyl)PdCl_3^{15}$ were found to be as effective as PdCl₂(dppf), however their relatively high expense and/or lack of availability negated their use. The acetoxy and carbonate analogs of 2 did not allow palladium oxidative insertion and thus did not participate in this catalytic cycle.^{16c} Lithium chloride as an additive (3 equiv) completely shut down the reaction.^{16a,b}

In summary, we have reported a very efficient palladium catalyzed cross-coupling of the fluorosulfonyl and trifluoromethylsulfonyl enol ethers **2a-d** to aryl- and phenylboronic acids to provide in high yields (>98%) the nonracemic indene **4** while avoiding racemization. Catalyst turnovers as high as 1000 were observed. This reaction was found to be applicable to a variety of substituted aryl- and phenylboronic acids. Finally, a synthesis of **1a** and **1b** has been reported which incorporates the results reported herein.³

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