

Communications

Palladium-Catalyzed Synthesis of Aryl Sulfides from Aryl Triflates

Nan Zheng,* J. Christopher McWilliams, Fred J. Fleitz, Joseph D. Armstrong III, and R. P. Volante

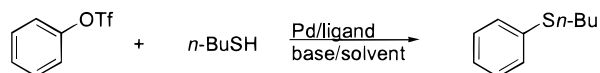
Department of Process Research, Merck Research Laboratories, P.O. Box 2000, Mail Drop R80Y-360, Rahway, New Jersey 07065

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Aryl sulfides are useful chemical intermediates in organic synthesis.¹ A number of synthetic methods have been developed to prepare them from aryl halides.² Since the number of commercially available phenols is greater than that of aryl halides, a mild and efficient conversion of phenols into aryl sulfides would have significant synthetic value. However, the palladium-catalyzed formation of aryl sulfides from phenols has been elusive.^{2e,3} Buchwald^{4a} and Hartwig^{4b} have had recent success in the palladium-catalyzed amination of aryl triflates based on chelating bis(phosphine) ligands, such as BINAP, Tol-BINAP, and DPPF, and we felt that this type of coupling reaction could be extended to the conversion of aryl triflates to aryl sulfides. Herein we report that a combination of Pd(OAc)₂ and Tol-BINAP is an effective catalyst for the coupling of aryl triflates with sodium alkanethiolates to give alkyl aryl sulfides.

Our initial studies were conducted with phenyl triflate and 1-butanethiol (Scheme 1) in toluene.⁵ The effectiveness of different palladium catalyst systems for the coupling reaction of phenyl triflate with this thiol to give *n*-butyl phenyl sulfide is detailed in Table 1. As expected, in the absence of Pd catalyst and ligands no *n*-butyl phenyl sulfide was detected by HPLC (entry 1). Other attempts to promote the coupling that were also unsuccessful included the use of Pd(dba)₂ or Pd(OAc)₂ without additional ligands or employment of a combination of Pd(dba)₂ and monodentate phosphine ligands such as P(*o*-tol)₃ and P(2-furyl)₃ (entries 2–5). In contrast, a combination of Pd(dba)₂ and BINAP gave *n*-butyl phenyl sulfide in 69% yield (entry 8). Surprisingly, preformed Pd(dba)BINAP⁶ resulted in a much lower yield of the coupled product (23%) (entry 9), although its origin

Scheme 1



was not clear. Other chelating ligands, such as DPPF and PHANEPHOS,⁷ were significantly less effective for the coupling (entries 6 and 7). An improved yield for the coupling reaction was observed when Pd(dba)₂ was replaced by Pd(OAc)₂, presumably due to inhibition of the oxidative addition to phenyl triflate by the dba ligand⁸ (entry 14). The yield for the coupling reaction was further improved when employing Tol-BINAP as ligand and Pd(OAc)₂ as precatalyst (entry 18). These results indicated that the specific structures of BINAP and Tol-BINAP might be the key to the success of this catalyst system.⁹

We have also surveyed a variety of bases and additives for this coupling reaction. The use of bases weaker than NaOt-Bu, such as K₂CO₃, NaHCO₃, and TEA, afforded lower yields of the coupled product (entries 10–12). CuI has been used as cocatalyst with Pd₂(dba)₃ to promote the coupling of 2-naphthyl triflate and *N*-acetyl-L-cysteine.^{2e} We found that the use of 10 mol % of CuI improved the yield for the coupling when employing Pd(dba)₂ and BINAP with TEA as base (entry 13). Added LiCl is often necessary for the successful coupling of aryl triflates and organostannanes (Stille coupling),¹⁰ although this effect is poorly understood and strongly depends on the solvent and the ligand of the palladium.¹¹ Buchwald and Hartwig found that added halides either had no effect on the amination of aryl triflates or were detrimental to the coupling.^{4a,b} In the case of our studies for the coupling of aryl triflates and thiols, addition of LiCl or LiBr improved the yield of the reaction when using Pd(OAc)₂ as precatalyst and BINAP as ligand (entries 15 and 16). Surprisingly, the presence of CuI completely shut down the catalyst activity under the condition of Pd(OAc)₂ and BINAP (entry 17).

Despite the success of the catalyst system consisting of Pd(OAc)₂ and BINAP with LiCl (entry 15, Table 1), we decided to choose the combination of Pd(OAc)₂ and Tol-BINAP (entry 18, Table 1) as the optimal catalyst system for the coupling of aryl triflates and sodium alkanethiolates mainly due to its simplicity and convenience. A wide range of aryl triflates was examined. As can be seen in Table 2, this chemistry appears to be general for alkyl aryl sulfides. Good to excellent yields of coupled products were obtained with electronically neutral or deficient aryl triflates such as phenyl triflate, 4-*tert*-butylphenyl triflate, 2-methylphenyl triflate, 4-cyanophenyl triflate, 4-benzoylphenyl triflate and 2-naphthyl triflate (entries 1, 3–8). In contrast, 4-nitrophenyl triflate gave a significantly lower yield (entry 9). The coupling reaction was very sluggish with electron-rich aryl triflates such as 4-methoxyphenyl triflate (entry 5). This

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(5) In control experiments without Pd catalyst and ligands, phenyl triflate decomposed faster in THF, DMF, and *p*-dioxane than in toluene under the condition of preformed sodium butanethiolate. The major byproduct was phenol. Thus, toluene was chosen as the solvent in our studies.

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(9) The mechanism for this reaction presumably follows a similar pathway to the one proposed by Buchwald^{4a} for the palladium-catalyzed amination of aryl triflates, although no intermediates in the catalytic cycle have yet been identified or isolated.

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Table 1. Evaluation of Different Catalyst Systems for Cross-Coupling of *n*-BuSH and PhOTf^a

entry	Pd	ligand	base	additive	yield (%)
1	none	none	NaO <i>t</i> -Bu	none	0
2	Pd(dba) ₂	none	NaO <i>t</i> -Bu	none	0
3	Pd(OAc) ₂	none	NaO <i>t</i> -Bu	none	0
4	Pd(dba) ₂	P(<i>o</i> -tol) ₃ ^b	NaO <i>t</i> -Bu	none	0
5	Pd(dba) ₂	P(2-furyl) ₃ ^c	NaO <i>t</i> -Bu	none	0
6	Pd(dba) ₂	DPPF	NaO <i>t</i> -Bu	none	44
7	Pd(dba) ₂	(±)-PHANEPHOS	NaO <i>t</i> -Bu	none	28
8	Pd(dba) ₂	(<i>R</i>)-(+)-BINAP	NaO <i>t</i> -Bu	none	69
9	Pd(dba)(BINAP) ^d	none	NaO <i>t</i> -Bu	none	23
10	Pd(dba) ₂	(<i>R</i>)-(+)-BINAP	K ₂ CO ₃	none	57
11	Pd(dba) ₂	(<i>R</i>)-(+)-BINAP	NaHCO ₃	none	27
12	Pd(dba) ₂	(<i>R</i>)-(+)-BINAP	TEA	none	65
13	Pd(dba) ₂	(<i>R</i>)-(+)-BINAP	TEA	CuI ^e	74
14	Pd(OAc) ₂	(<i>R</i>)-(+)-BINAP	NaO <i>t</i> -Bu	none	80
15	Pd(OAc) ₂	(<i>R</i>)-(+)-BINAP	NaO <i>t</i> -Bu	LiCl ^f	93
16	Pd(OAc) ₂	(<i>R</i>)-(+)-BINAP	NaO <i>t</i> -Bu	LiBr ^g	88
17	Pd(OAc) ₂	(<i>R</i>)-(+)-BINAP	NaO <i>t</i> -Bu	CuI ^e	0
18	Pd(OAc)₂	(<i>R</i>)-(+)-Tol-BINAP	NaO<i>t</i>-Bu	none	94(93)^h

^a Reactions were conducted with 10 mol % catalyst, 11 mol % ligand, 1.4 equiv of 1-butanethiol, and 1.4 equiv of NaO*t*-Bu in toluene at 80 °C for 24 h on a 2.21 mmol scale of phenyl triflate. Yields are HPLC assay yields based on standards purchased from Sigma Aldrich. ^b 22 mol % P(*o*-tol)₃. ^c 22 mol % P(2-furyl)₃. ^d Pd(dba)BINAP was prepared by heating 0.1 equiv of Pd(dba)₂ and 0.11 equiv of (*R*)-(+)-BINAP in toluene at 50 °C for 0.5 h. ^e 0.1 equiv of CuI. ^f 3 equiv of LiCl. ^g 3 equiv of LiBr. ^h Isolated yield in parentheses.

Table 2. Coupling of Sodium Alkanethiolate with Various Aryl Triflates Catalyzed by 10 Mol % Pd(OAc)₂ and 11 Mol % Tol-BINAP^a

entry	aryl triflates	thiols	products	time (h)	yield (%)
1	PhOTf	<i>n</i> -BuSH	PhS <i>n</i> -Bu	24	93
2	PhOTf	<i>t</i> -BuSH	PhS <i>t</i> -Bu	24	66 ^b
3	2-Naphthyl Triflate	<i>n</i> -BuSH	2-naphthyls <i>n</i> -Bu	12	95
4	4- <i>t</i> -BuPhOTf	<i>n</i> -BuSH	4- <i>t</i> BuPhS <i>n</i> -Bu	24	92
5	4-MeOPhOTf	<i>n</i> -BuSH	4-MeOPhS <i>n</i> -Bu	108	54(73) ^c
6	2-MePhOTf	<i>n</i> -BuSH	2-MePhS <i>n</i> -Bu	24	79
7	4-CNPhOTf	<i>n</i> -BuSH	4-CNPhS <i>n</i> -Bu	12	82
8	4-PhC(O)PhOTf	<i>n</i> -BuSH	4-PhC(O)PhS <i>n</i> -Bu	14	91
9	4-NO ₂ PhOTf	<i>n</i> -BuSH	4-NO ₂ PhS <i>n</i> -Bu	14	60

^a Reactions were conducted with 10 mol % catalyst, 11 mol % ligand, 1.4 equiv of thiol, 1.4 equiv of NaO*t*-Bu, and 2.21 mmol of aryl triflates in toluene at 80 °C. Yields referred to isolated yields after silica gel chromatography. ^b The product was isolated as a mixture of PhS*t*-Bu and 4-MePhS*t*-Bu. The yield was based on proton ratios determined by ¹H NMR. ^c The yield in parentheses was based on recovered starting material. The reduced product, anisole, was the major byproduct in this reaction.

observation was consistent with the oxidative addition of aryl triflates being slower when the aryl triflates were substituted by an electron-donating group.¹¹ Also notable were the formation of di(*n*-butyl) disulfide and the cleavage of aryl triflates to phenols as the major competing side-reactions in these processes. Besides 1-butanethiol, sterically hindered 2-methyl-2-propanethiol also participated in the coupling reaction, and a moderate yield was obtained when coupled with phenyl triflate (entry 2). The major byproduct in this reaction was *tert*-butyl 4-methylphenyl sulfide, presumably due to an interchange between phosphorus-bound toluene moieties in Tol-BINAP and palladium-bound phenyl groups.¹² Other thiol nucleophiles such as PhSH and KSAc did not afford the desired coupled products under these conditions.

In conclusion, we have exploited a palladium catalyst system capable of catalyzing the cross-coupling between aryl

triflates and sodium alkanethiolates and demonstrated the importance of the bidentate phosphine ligands such as Tol-BINAP. This protocol further expands the scope of palladium-catalyzed formation of carbon-heteroatom bonds and provides mild conditions for the conversion of phenols to alkyl aryl sulfides via aryl triflates. Further studies on the scope and mechanism of this transformation are in progress.

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Supporting Information Available: Details of experiments and characterization data (17 pages).

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