

Unprecedented Palladium-Catalyzed Cross-Coupling Reaction of α -Bromo Sulfoxides with Boronic Acids

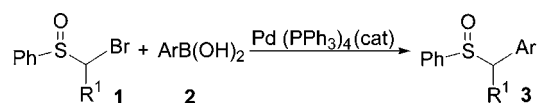
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ABSTRACT



$R^1 = \text{H, CH}_3$

Ar = Ph, *p*-CH₃OC₆H₄, *o*-CH₃C₆H₄, *o*-CH₃OC₆H₄, *p*-BrC₆H₄,
m-NO₂C₆H₄, 2-thienyl, 3-thienyl

A new Suzuki-type palladium-catalyzed reaction of boronic acids with α -bromo sulfoxides has been developed using a protocol similar to the well-documented reaction of boronic acids with aryl halides. Both cross-coupling and homocoupling processes were observed. The best yields in cross-coupling products were obtained when the presence of oxygen was carefully excluded using degassed solvents. The oxidative addition palladium complex intermediate could be isolated and characterized by X-ray single-crystal diffraction.

Palladium-catalyzed cross coupling reactions have been used widely to connect two sp^2 carbon centers.¹ The formation of sp^2 – sp^3 C–C bonds is comparatively less common and in general comes from the reaction of aryl halides with enolates.² The direct arylation of carbonyl CH-acids (in situ generated enolates) has received attention in recent years,³ but in contrast, the reaction with sulfonyl or sulfinyl CH-acids has been scarcely explored. Recently, a procedure for direct palladium-catalyzed monoarylation of several functionalized sulfones has been described, but it occurs only in the presence of an additional electron-withdrawing α -substituent, and for this reason, the scope of the method is limited to the arylation of strongly CH-acidic sulfones.⁴ On the other hand, the lack of reactivity of lithium anions derived

from sulfones and sulfoxides in cross-coupling palladium-catalyzed reactions was reported by Negishi years ago.⁵ Thus, the palladium-catalyzed arylation of simple sulfones or sulfoxides remains a challenge. Sulfones are important synthons widely used in the synthesis of useful organic compounds.⁶ Sulfoxides possess similar features with the added value of their chirality, which makes of these compounds valuable auxiliaries in asymmetric synthesis.⁷ Owing to the versatility and popularity of sulfoxide chemistry in synthesis, we decided to explore the palladium-catalyzed reactions of methyl sulfoxides as a suitable route to the arylation of these compounds.

In a preliminary series of experiments, we attempted unsuccessfully the direct arylation of sulfoxides with haloarenes under similar conditions as described for the arylation

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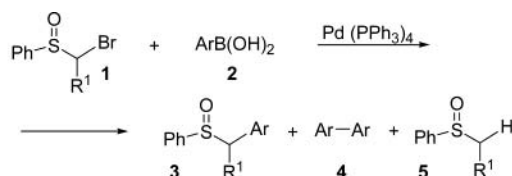
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of ketones.⁸ For instance, a mixture of 3-bromoanisole and methyl phenyl sulfoxide was heated at reflux in the presence of NaO-t-Bu and 2% Pd₂(dba)₃/BINAP, but the reactants were recovered unchanged. The failure of the method could be attributed, at first, to an inefficient generation of the sodium α -sulfinyl anion due to the weaker C α -H acidity of sulfoxides if was compared with the acidity of carbonyl compounds. Since the base-mediated direct arylation seemed unattainable, we then evaluated the possibility of arylation of the sulfinyl anion. However, attempts at arylating lithium α -sulfinyl anions were reported to be unsuccessful by Negishi.⁵ In addition, methylsulfinyl anions react with haloarenes without a catalyst to give mixtures of several compounds as reported by Corey and co-workers in their pioneering work on the reactivity of methylsulfinyl carbanions.⁹

These disappointing results in the palladium-catalyzed reaction of aryl halides with sulfoxides prompted us to change our strategy and to attempt the palladium-catalyzed arylation of sulfoxide derivatives using arylboronic acids. Recently, the α -arylation of carbonyl compounds by a Suzuki type reaction of the corresponding α -halo carbonyl derivatives with arylboronic acids has been achieved.¹⁰ Competitive cross-coupling and homocoupling processes occur, and the control of the selectivity depends on the nature of the phosphine ligand on palladium.^{10a} However, despite this precedent, we have found that Pd(PPh₃)₄ catalyzes the cross coupling reaction of α -bromo sulfoxides **1**¹¹ with boronic acids **2** under mild conditions in the presence of aqueous Na₂CO₃ to give the corresponding α -monoarylated sulfoxides **3** with high to moderate yields (Scheme 1, Table 1).¹² This

Scheme 1



1	R ¹	2	Ar	3	R ¹	Ar	4	Ar	5	R ¹
a	H	a	C ₆ H ₅	a	H	C ₆ H ₅	a	C ₆ H ₅	a	H
b	CH ₃	b	<i>p</i> -MeOC ₆ H ₄	b	H	<i>p</i> -MeOC ₆ H ₄	b	<i>p</i> -MeOC ₆ H ₄	b	CH ₃
		c	<i>o</i> -MeC ₆ H ₄	c	H	<i>o</i> -MeC ₆ H ₄	c	<i>o</i> -MeC ₆ H ₄	c	=CH ₂
		d	<i>o</i> -MeOC ₆ H ₄	d	H	<i>o</i> -MeOC ₆ H ₄	d	<i>o</i> -MeOC ₆ H ₄		
		e	<i>p</i> -BrC ₆ H ₄	e	H	<i>p</i> -BrC ₆ H ₄	e	<i>p</i> -BrC ₆ H ₄		
		f	3-thienyl	f	H	3-thienyl	f	3-thienyl		
		g	2-thienyl	g	H	2-thienyl	g	2-thienyl		
		h	<i>m</i> -NO ₂ C ₆ H ₄	h	H	<i>m</i> -NO ₂ C ₆ H ₄	h	<i>m</i> -NO ₂ C ₆ H ₄		
		i		i	CH ₃	C ₆ H ₅				
		j		j	CH ₃	<i>p</i> -BrC ₆ H ₄				

reaction is unprecedented and represents to the best of our knowledge the first example of participation of a methyl sulfoxide derivative in a palladium catalyzed C(sp³)-C(sp²) bond formation reaction.

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Table 1. Reaction of α -Bromo Sulfoxides **1** with Boronic Acids **2**

run	1	2	method ^a	convn ^b (%)	3 (%)	5 (%)	ratio 3/4
1	a	a	A	100	a (80)	a (20)	2:1
2	a	b	A	100	b (87)	a (13)	2.5:1
3	a	c	A	90	c (76)	a (13)	1.7:1
4	a	d	A	74	d (53)	a (21)	1:1
5	a	d	B	89	d (56)	a (34)	1.1
6	a	e	A	100	e (60)	a (40)	2.3:1
7	a	f	A ^c	26	f (7)	a (19)	1:2.4
8	a	f	A ^d	62	f (25)	a (37)	1:2.2
9	a	f	B	13	f (0)	a (13)	0
10	a	g	A ^{c,d}	22	g (0)	a (22)	0
11	a	h	A	38	h (11)	a (27)	1:3
12	a	h	B	22	h (0)	a (22)	0
13	b	a	A	85	i (43)	b ^e (23)	2.6:1
14	b	e	A	72	j (43)	b (29)	3.0:1
15	b	e	B	60	j (0)	b ^f (19)	0
16	a	d	C	90	d (81)	a (9)	2.8:1
17	a	h	C	100	h (70)	a (30)	2:1
18	a	f	C	76	f (39)	a (37)	1:1.5
19	a	g	C ^c	25	g (0)	a (25)	0

^a Method A: MeOH, Na₂CO₃ 2 M, 10% catalyst, 16 h. Method B: DME, Na₂CO₃ 2 M, 10% catalyst, 16 h. Method C: Conditions A using degassed solvents. ^b Conversion of **1** determined by NMR. ^c Reaction time 32 h. ^d 20% catalyst. ^e Compound **5c** (19%) was also obtained. ^f Compound **5c** (41%) was also obtained.

Concerning the mechanism of the arylation reaction, we were able to prove that the arylation occurs through the conventional catalytic cycle (oxidative addition, transmetalation and reductive elimination). The α -sulfinylpalladium(II) complex **Ia** (R¹ = H; Hal = Br) (Figure 1) derived

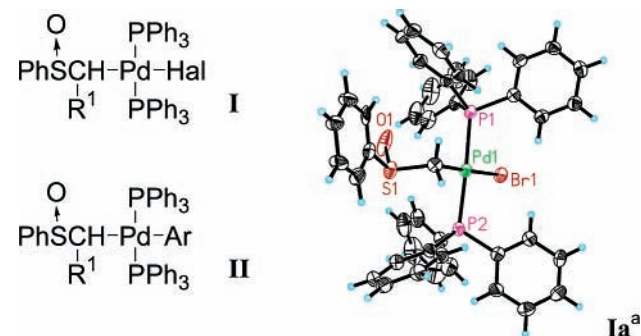


Figure 1. Oxidative addition (I) and transmetalation (II) of palladium intermediates in the arylation of α -bromo sulfoxides **1**. ^a Thermal ellipsoid plot (50%) probability of compound **Ia** (R¹ = H; Hal = Br).

from the oxidative addition of **1a** to Pd(PPh₃)₄ was stable enough to be isolated and characterized by X-ray single-

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crystal diffraction.¹³ The crystal structure shows a slightly distorted square planar palladium complex with the sulfinyl ligand trans to bromine (Figure 1). A similar complex **I** ($R^1 = H$; Hal = Cl) was characterized by Floriani¹⁴ by reaction of *cis*-[PdCl₂(PPh₃)₂] with potassium α -sulfinyl anion. To ensure that **1a** is an intermediate in the arylation of **1a**, it was allowed to react with **2a** leading, as expected, to the formation of the cross-coupling product **3a**.

In the palladium-catalyzed reaction of **1a** with **2a** the cross-coupling derivative **3a** was the main product, but formation of the homocoupling compound **4a** was also detected. The **3a/4a** ratio was 2:1, thus showing a remarkable chemoselectivity for the cross-coupling process. The homocoupling derivative **4a** was formed along with debrominated sulfoxide **5a** generated by reduction of starting bromo sulfoxide **1a**. A similar reductive side reaction also happens when α -bromo carbonyl compounds are reacted with boronic acids.^{10b}

The generality of the C(sp³)-C(sp²) cross-coupling reaction was investigated using a number of arylboronic acids **2a-h** and the secondary bromo sulfoxide **1b** (Scheme 1, Table 1). The reaction of **1a** with electron-rich substituted boronic acids **2b** and **2c** using the same conditions as in the case of the parent compound **2a** gave **3b** and **3c**, respectively, with similar chemoselectivity and conversion. The presence of the *o*-methoxy group in acid **2d** resulted in a lower chemoselectivity with only partial conversion of the starting bromo sulfoxide **1a**. Although the chemoselectivity was only moderate in this case, the cross-coupling reaction was also the main process. The use of dimethoxyethane as solvent (conditions B) allowed an increased reaction temperature and complete solubilization of the catalyst Pd(PPh₃)₄, but these modifications did not lead to significant changes in the chemoselectivity or the degree of conversion of the starting bromosulfoxide **1a**. The effect of the presence of electron-withdrawing groups in the boronic acid moiety was also studied. Bromo-substituted boronic acid **2e** reacted with **1a** to completion. The cross-coupling was the main process with a chemoselectivity similar to the case of the *o*-methoxy substituted acid **2d**. With the nitro-substituted acid **2h**, the homocoupling was the main reaction observed giving rise to the formation of biaryl **4h** and only 11% yield in the cross-coupling product **3h** (see Table 1). Thiophene boronic acids **2f** and **2g** led only to partial conversion of the starting bromo

sulfoxide **1a** under our standard conditions with predominance of the homocoupling reaction.

The palladium-catalyzed arylation was also tested with the α -bromoethyl sulfoxide **1b**. Reaction with boronic acids **2a** and **2e** gave mainly the corresponding α arylated derivatives **3i** and **3j** although vinyl sulfoxide **5c** was also formed by β -elimination from the intermediate complexes **I** ($R^1 = CH_3$; Hal = Br) and **II** ($R^1 = CH_3$; Ar = C₆H₅, *p*-BrC₆H₄). Although β -elimination is a highly favored process in palladium chemistry, cross-coupling products predominate under mild conditions (method A). The use of higher reaction temperatures (method B) favors the formation of the elimination product **5c**.

The poor results obtained in the cross-coupling reaction with some of the boronic acids tried prompted us to run the reaction of **1** with **2** with the complete absence of oxygen using degasified solvents (runs 16–19, Table 1), and in some cases, with longer reaction times (run 16, Table 1). The yield in **3** increased significantly under these conditions. For instance, in the case of the *o*-methoxy-substituted acid **2d** the yield increased from 56% to 81% (runs 5 and 16, Table 1), and, more strikingly, the *p*-nitroboronic acid **2h** gave the cross-coupled sulfoxide **3h** in 70% yield (runs 11 and 17, Table 1). By contrast, the results obtained with thiopheneboronic acids **2f** and **2g** were roughly the same in the presence or absence of oxygen.

Self-coupling of aryl boronic acids in regular Suzuki reactions¹⁵ occurs when the cross-coupling is very slow. Moreno-Mañas and co-workers¹⁶ showed that self-coupling reactions are accelerated in atmosphere of oxygen and also by the presence of an electron donor substituent at the boronic acid moiety. In the same way, under standard Suzuki conditions large amounts of biaryls are formed in the reaction of arylboronic acids and α -bromo esters,^{10b} a reaction inhibited by the use of bulky, not too electron rich phosphines.^{10a} In the case of the reaction of α -bromo sulfoxides with boronic acids reported herein, several alternative and simultaneous reaction paths are envisaged to account for the formation of homocoupling products. At first, Pd(PPh₃)₂ species present in the medium would promote by oxidative addition (transmetalation) the direct self-coupling of boronic acids.^{16,17} A second mechanism would involve an oxidative homocoupling through the formation of a palladium(II) peroxide by reaction of oxygen with a Pd(PPh₃)₂ complex.¹⁸ These two mechanisms do not involve at all the participation of bromo sulfoxides **1** in the process leading to the formation of homocoupling products **4**. Alternatively, the homocoupling reaction might take place by a double transmetalation through the oxidative addition complex **I** in a similar way as proposed by Zhang for the homocoupling reaction observed in the reaction of α -halo carbonyl com-

(12) **Representative Procedure.** A mixture of α -bromo sulfoxide **1a** (0.4 mmol), boronic acid **2** (0.8 mmol), and Pd(PPh₃)₄ (0.04 mmol) in aqueous 2 M Na₂CO₃ (0.8 mL, 1.6 mmol) and methanol (8 mL) was heated at reflux for 16 h. The reaction mixture was then cooled to room temperature, quenched with water (10 mL), and extracted with diethyl ether (2 \times 15 mL) and dichloromethane (2 \times 15 mL). The combined organic extracts were dried with Na₂SO₄ and evaporated under reduced pressure.

(13) X-ray crystal structure of **1a**: pale yellow prism of 0.40 \times 0.20 \times 0.20 mm size, triclinic, *P*-1, *a* = 12.171(2) Å, *b* = 12.483(3) Å, *c* = 15.933(3) Å, α = 93.98(3)°, β = 101.23(3)°, γ = 118.61(3)°, *V* = 2046.9(7) Å³, *Z* = 2, *D*_c = 1.520 g cm⁻³, $2\theta_{\max}$ = 53°, diffractometer Kappa CCD, Mo K α (λ = 0.710 73 Å), ω -scan, *T* = 173(2) K, 16 376 reflections collected of which 8357 were independent (*R*_{int} = 0.066), direct primary solution and refinement on *F*² (SHELXL-97, G. M. Sheldrick, University of Göttingen, 1997), 508 refined parameters, riding hydrogen atoms, The PhSO group is disordered over two sites, *R*₁[*I* > 2 σ (*I*)] = 0.0490, *wR*₂ (all data) = 0.1033.

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pounds with boronic acids^{10b} or in the Pd(OAc)₂-promoted homocoupling of aryl boronic acids.¹⁶ Indeed, biaryl **4h** was obtained by treatment of complex **I** (R¹ = H; Hal = Br) with boronic acid **2h** in the presence of oxygen, but we can argue that **I** decomposes prior to that to give a Pd(PPh₃)_n species which reacts with **2h** according to the reaction paths described above. In fact, we did not find a correlation between the amount of biaryls **4** and sulfoxides **5** obtained in the coupling processes collected in Table 1 as would be expected if biaryls **4** would arise exclusively through the double transmetalation mechanism. In general, the formation of dehalogenation products is uncommon in typical Suzuki coupling reactions.¹⁹

Although details of the reaction pathway remain unclear at present, the results of the palladium-catalyzed reaction of compounds **1** and **2** show that the relative extent of the cross-coupling and homocoupling processes depends on the electron-donating or -withdrawing character of the substituents in **2** and the presence or absence of oxygen in the reaction medium. This behavior could be related to the ability of **2** to undergo the transmetalation reaction with the intermediate complex **I** produced in the oxidative addition step and also to the stability of the complex **II** (Figure 1). If the transmetalation step is slow (electron-poor substituted Ar groups in **2**¹⁶), the formation of complex **I** would be unproductive leading by disproportion and/or hydrolysis to dehalogenation products **5**. In addition, partial phosphine oxidation occurs when reactions are carried out without careful exclusion of oxygen. Then, direct Pd⁰- and Pd^{II}-catalyzed homocoupling of **2** accounts for the formation of biaryls **4**. Alternatively, boronic acids **2** carrying groups with ability to coordinate palladium (**2f** and **2g**) or with strong electron-withdrawing character (**2h**) could afford adducts **II**^{15,20} stable enough to undergo a second transmetalation leading to the homocoupling products.

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Our data show that α -bromo sulfoxides are better substrates than α -bromo carbonyl compounds in Suzuki-type cross-coupling reactions since the parent triphenylphosphine is a suitable ligand in the case of sulfoxides while bulky phosphines are required for carbonyl derivatives. The high reactivity of the α -sulfinylpalladium(II) complexes shown in the cross-coupling is noteworthy if compared to the rather low reactivity exhibited by these complexes in insertion reactions.¹⁴

In conclusion, this new reaction allows the C α -arylation of alkyl sulfoxides with high yields under mild conditions. The palladium catalyzed process allows the substitution of bromine in α -bromo sulfoxides for nucleophiles opening new perspectives in sulfoxide chemistry. Work is in progress to amplify the synthetic value of this method with the conversion of the sulfoxide group in other functions and to clarify the detailed mechanism of the undesired competitive homocoupling reaction.

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Supporting Information Available: Experimental details for the synthesis and characterization of compounds **3** and **4** and X-ray crystallographic data in CIF format for compound **1a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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