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Palladium-Catalyzed Carbon-Nitrogen Bond Formation: A Novel, Catalytic Approach towards *N*-Arylated Sulfoximines#

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This article is dedicated to Prof. Dr. Gernot Boche on the occasion of his 60th birthday.

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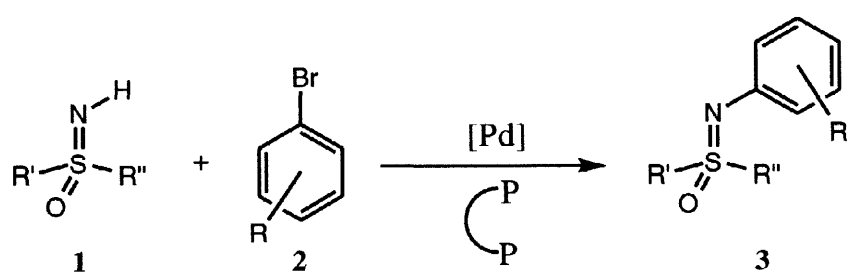
Abstract: The coupling of sulfoximines **1** with various aryl bromides of different substitution pattern in the presence of a catalytic amount of $Pd(OAc)_2$ and a chelating bisphosphine affords *N*-arylated products **3** with yields of up to 96%.

Over the last few years, the palladium catalyzed amination of aryl halides and triflates has emerged as a powerful tool in organic synthesis.[2] While the original procedure involved toxic aminostannanes,[3] recent investigations by Buchwald[4] and Hartwig[5] have shown that free amines can also be used as nucleophiles in this transformation, independent of the substitution pattern of the amine and the aryl halide/triflate.

Recently, Buchwald and co-workers reported the synthesis of *N*-aryl aniline derivatives using benzophenone imine as substrate.[6] Subsequently, Hartwig published his findings on the coupling of azoles and imines with aryl bromides.[7] The fact that even relatively weak nucleophiles such as azoles were suitable coupling partners led us to consider the use of other types of nitrogen based nucleophiles in this palladium catalyzed hetero cross-coupling reaction. Our interest in the application of the sulfonimidoyl moiety in chiral ligands for enantioselective metal catalysis[8] and in pseudopeptides[9] prompted us to investigate the potential of sulfoximines as coupling partners as shown in eq. 1.



eq. 1

We first examined the reaction of *S*-methyl-*S*-phenyl sulfoximine (**1a**) with methyl 2-bromobenzoate employing a set of different palladium sources and phosphine ligands (Table 1).

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Table 1. Coupling of *S*-methyl-*S*-phenyl sulfoximine (**1a**) with methyl 2-bromobenzoate (**2** with R = 2-CO_2CH_3) catalyzed by various Pd/phosphine complexes[a]

Entry	Precatalyst[b]	Time [h]	Base[c]	Yield of **3** [%][d]
1	$Pd(OAc)_2$/P(*o*-tol)$_3$	36	Cs_2CO_3	<4
2	$Pd_2(dba)_3$/P(*o*-tol)$_3$	36	Cs_2CO_3	<4
3	$Pd(OAc)_2$/BINAP	36	Cs_2CO_3	82
4	$Pd(OAc)_2$/BINAP	36	NaO^{t}Bu	76
5	$Pd(OAc)_2$/BINAP	48	Cs_2CO_3	92
6	$Pd(OAc)_2$/Tol-BINAP	48	Cs_2CO_3	96
7	$PdCl_2$(DPPF)/DPPF	48	Cs_2CO_3	87

[a] All reactions were performed in toluene at 110°C using 1 eq. of methyl 2-bromobenzoate and 1.2 eq. of *S*-methyl *S*-phenyl sulfoximine. [b] Entries 1-4: 4 mol% of Pd-source and 6 mol% of phosphine; entries 5, 6: 5 mol% of $Pd(OAc)_2$, 7.5 mol% of phosphine; entry 7: 5 mol% of $PdCl_2$(DPPF), 20 mol% of DPPF. [c] 1.4 eq. of base were used in each run. [d] Yields refer to isolated amounts of analytically pure material and are an average of at least two runs.

Whereas P(*o*-tol)$_3$ in combination with either $Pd(OAc)_2$ or $Pd_2(dba)_3$ did not promote the coupling (entries 1, 2), the corresponding *N*-arylated product was obtained in high yield when either BINAP or Tol-BINAP[10] were employed as ligand (entries 3-6).

$PdCl_2$(DPPF) also catalyzed the reaction efficiently, albeit affording slightly diminished yields of coupling product (entry 7). These results suggest that the use of chelating bisphosphines is essential in order to obtain the *N*-arylated sulfoximines in high yield,[11] (entries 3-7) while the palladium source does not seem to have a significant influence.[12] The relatively high catalyst loading compared to the amination protocol for aryl bromides is probably due to the decreased nucleophilicity of the sulfoximine nitrogen. It is reasonable that the electronic nature of the nitrogen nucleophile is also of major importance for the rate of reductive elimination to proceed from an intermediate palladium-sulfoximide aryl complex.[13] Cesium carbonate as base gave higher yields of coupling product than sodium *tert*-butoxide (entries 3, 4). Toluene was found to be the solvent of choice.[14]

We next treated various aryl bromides with sulfoximines **1a-c** to test the scope of this coupling reaction. The most significant results are summarized in Table 2. In order to compare the influence of electronic and steric factors in the substitution pattern of both the aryl bromide and the sulfoximines, all reactions were conducted under identical conditions:[15] BINAP or Tol-BINAP were employed together with $Pd(OAc)_2$ and cesium carbonate as base in refluxing toluene for 48 hours.

Aryl bromides bearing electron-withdrawing groups in *ortho*- or *para*-position coupled efficiently to provide the corresponding *N*-aryl sulfoximines in high yields (entries 1-6 and 9-14). In contrast, 4-*tert*-butyl bromobenzene performed less efficiently giving the coupled product with BINAP and Tol-BINAP as ligands in only 24% and 38% yield, respectively (entries 7, 8). These results reflect Hartwig's findings in the coupling of pyrrole with 4-*tert*-butyl bromobenzene which proceeded at lower rate compared to other hetero cross-coupling reactions of this kind and required higher temperature, longer reaction times, and higher catalyst loading.[7] In order to increase the yield in reactions with electron-rich substrates, an excess of aryl halide and base was required. Here, (4-*tert*-butyl phenyl)-*S*-methyl-*S*-phenyl sulfoximine could be obtained in 67% yield using

$Pd(OAc)_2$/BINAP as precatalyst and 1.5 equivalents relative to sulfoximine **1a** of both, 4-*tert* butyl bromobenzene and sodium *tert*-butoxide.

Table 2. Palladium-catalyzed *N*-arylation of sulfoximines **1a-c** with a representative set of aryl bromides according to eq. 1[a]

Entry	R	Sulfoximine	R'	R''	Bisphosphine	Yield of **3** [%][c]
1	H	**1a**	Me	Ph	BINAP	72
2	H	**1a**	Me	Ph	Tol-BINAP	83
3	2-CN	**1a**	Me	Ph	BINAP	94
4	2-CN	**1a**	Me	Ph	Tol-BINAP	91
5	4-CO_2CH_3	**1a**	Me	Ph	BINAP	89
6	4-CO_2CH_3	**1a**	Me	Ph	Tol-BINAP	90
7	4-*tert*-Bu	**1a**	Me	Ph	BINAP	38
8	4-*tert*-Bu	**1a**	Me	Ph	Tol-BINAP	24
9[b]	H	**1b**	Me	Me	BINAP	86
10[b]	H	**1b**	Me	Me	Tol-BINAP	95
11[b]	4-CO_2CH_3	**1b**	Me	Me	BINAP	94
12[b]	4-CO_2CH_3	**1b**	Me	Me	Tol-BINAP	90
13	4-CO_2CH_3	**1c**	Me	*p*-Tol	BINAP	88
14	4-CO_2CH_3	**1c**	Me	*p*-Tol	Tol-BINAP	93

[a] All reactions were performed in toluene at 110°C using 1 eq. of aryl bromide, 1.2 eq. of sulfoximine, and 1.4 eq. of Cs_2CO_3 in the presence of 5 mol% $Pd(OAc)_2$ and 7.5 mol% bisphosphine. [b] *S,S*-dimethyl sulfoximine was added as a 0.2 M solution in THF *via* cannula. [c] Yields refer to isolated amounts of analytically pure material and are an average of at least two runs.

In summary, we have presented a novel, catalytic method for the direct *N*-arylation of sulfoximines. High yields are obtained with electron deficient aryl bromides, whereas the use of 4-*tert*-butyl bromobenzene requires a modified procedure to provide the corresponding *N*-aryl sulfoximine in acceptable yield.
Currently, we are focussing our efforts on the application of this coupling protocol towards the synthesis of new sulfoximine based ligands for asymmetric catalysis.[16]

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10. BINAP [2,2'-bis(diphenylphosphino)-1,1'-binaphthyl] was used as a racemate; both enantiomers of Tol-BINAP [2,2'-bis(di-*p*-tolyl-phosphino)-1,1'-binaphthyl] gave identical results and can be used interchangeably.
11. $Pd(PPh_3)_4$ catalyzed this reaction to give the *N*-aryl sulfoximine in 18% yield.
12. The use of $Pd_2(dba)_3$ instead of $Pd(OAc)_2$ in the reaction of **1a** with methyl 2-bromobenzoate gave comparable results.
13. Similar observations were made by Hartwig *et al.* in the coupling reactions of azoles which also exhibit low nucleophilic character.
14. Conducting the reaction in THF for 36 hours in the presence of $Pd(OAc)_2$ (4 mol%), BINAP (6 mol%) and 1.4 eq. of cesium carbonate afforded *N*-[2-(methyl oxycarbonyl)phenyl] *S*-methyl-*S*-phenyl sulfoximine in 53% yield.
15. Representative Procedure: A dry 25 ml two-neck flask equipped with a magnetic stirring bar, a septum inlet and a reflux condenser was charged with $Pd(OAc)_2$ (5 mol%, 0.05 mmol) and BINAP (7.5 mol%, 0.08 mmol) under an atmosphere of argon. Then, toluene (10 mL) was added, followed by methyl 2-bromobenzoate (1.0 eq., 1.10 mmol), *S*-methyl-*S*-phenyl sulfoximine **1a** (1.25 eq., 1.37 mmol) and Cs_2CO_3 (1.4 eq., 1.54 mmol), and the resulting mixture was heated at 110°C for 48 hours. After the mixture was allowed to cool to room temperature it was diluted with methyl *tert*-butyl ether, filtered through a pad of Celite, and the Celite was rinsed with methyl *tert*-butyl ether. The solvents were removed *in vacuo*, and purification by flash column chromatography (silica gel, methyl *tert*-butyl ether/hexanes) afforded the product in 92% yield (1.0 mmol). Analytical data for *N*-[2-(methyl oxycarbonyl)-phenyl]-*S*-methyl-*S*-phenyl sulfoximine: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.23 (s, 3H); 3.94 (s, 3H); 6.88-6.96 (m, 1H); 7.20-7.24 (m, 2H); 7.50-7.62 (m, 4H); 8.15 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.18, 51.87; 120.48; 123.25; 124.98; 127.74; 128.39; 129.53; 131.15; 132.30; 138.33; 143.97; 166.96. Anal. Calcd. for $C_{15}H_{15}NO_3S$: C, 62.26; H, 5.22; N, 4.84. Found: C, 62.09; H, 5.21; N, 4.74.
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