Palladium-Catalyzed *N*-Arylation of Sulfoximines with Aryl Bromides and Aryl Iodides

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Various *N*-arylated sulfoximines have been synthesized in high yield by a direct approach which is based on a palladium-catalyzed cross-coupling strategy. Aryl bromides of variable substitution pattern were found to be the most effective coupling partners, whereas aryl iodides showed a nonpredictable behavior requiring lithium or silver salts as additives to ensure product formation in acceptable yields. Coupling of (*S*)-2-(2′-bromophenyl)-4-*tert*-butyloxazoline with enantiomerically pure (−)-(*RS*)-*S*-methyl-*S*-phenylsulfoximine afforded the corresponding product in good yield as a single diastereomer, showing that the palladium-catalyzed arylation proceeds in a stereospecific manner. The reaction with dibromobenzenes yielded the monosulfonimidoyl arenes in all cases, suggesting that the introduction of the sulfonimidoyl moiety deactivates the arene, thus preventing a second coupling step.

Introduction

Since the discovery of the sulfonimidoyl moiety—contained in (2*S*,5*S*)-methionine sulfoximine (**1**, Figure 1)—in the 1940s,[1] sulfoximines have been widely used as versatile building blocks in organic synthesis.[2] Applications of the sulfonimidoyl group range from the use as chiral auxiliary[3] or chiral ligand[4] to its incorporation into peptidic structures.[5]

Representing nitrogen analogues of sulfones, sulfoximines show several characteristic features such as (i) the stereogenic sulfur atom, (ii) the acidified hydrogens at the α-carbon to sulfur, (iii) the decreased nucleophilicity of the sulfoximine-nitrogen compared to imines, and (iv) its structural and configurational stability toward thermal, reductive, basic, and acidic strain. These properties allow the use of this functional group even under drastic reaction conditions as well as the simple and efficient derivatization of sulfoximines at the imine-nitrogen and the α-carbon. Functionalization is usually accomplished by deprotonation followed by addition of an appropriate electrophile. The sulfoximine-nitrogen can easily be acylated, alkylated, or benzylated by this route.[2] In contrast, the synthesis of *N*-aryl sulfoximines is difficult: it is accomplished either by oxidation of *N*-aryl sulfimines with permanganate or peracid[6a,b] or by a multistep reaction sequence starting from *N*-aryl sulfonimidoyl chlorides, which are converted into the corresponding sulfoximines by treatment with an organometallic reagent such as alkyl- or aryllithium.[6c−f] The obvious disadvantages of these syntheses are insufficient functional group tolerance and the fastidious preparation of the sulfonimidoyl halide precursors from the corresponding sulfinamides, which includes the use of *tert*-butyl hypochlorite.

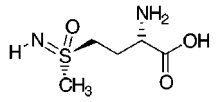

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Figure 1.

In recent years, the palladium-catalyzed amination of aryl halides and aryl triflates established independently by Buchwald and Hartwig has become a general method for the synthesis of arylamines.[7] It has also been successfully applied to the synthesis of arylated imines and azoles.[8,9] Despite their decreased nucleophilicity at the

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Scheme 1

sulfonimidoyl-nitrogen, we expected sulfoximines to resemble other nitrogen-based substrates in amination and imination reactions and hoped to develop a novel method for the direct introduction of an aryl group at the sulfoximine nitrogen by a palladium-catalyzed coupling strategy.[10] Using aryl bromides as coupling partners, *N*-arylated sulfoximines were obtained from simple and easily accessible precursors in high yield (Scheme 1).

In this article we disclose our results of a detailed study demonstrating the scope and the limitations of this arylation method. The coupling reaction is applicable to a large variety of substituted aryl bromides with different electronic and steric properties. However, aryl iodides proved problematic: substrates with electron-withdrawing substituents underwent imination only in the presence of lithium or silver salts, and 2-iodo anisole was even found to be unreactive.

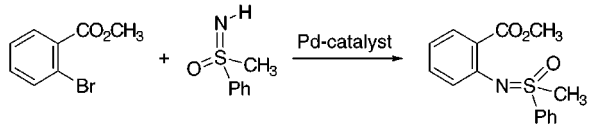
Results and Discussion

Synthesis of *N*-Aryl Sulfoximines from Aryl Bromides. Methyl 2-bromobenzoate (**2**) was considered as an appropriate substrate for the reaction with *S*-methyl-*S*-phenylsulfoximine (**3**) (Scheme 2),[10] and this combination was tested with various mono- and bidentate phosphines and different palladium sources in order to determine the optimal conditions for the catalytic *N*-arylation (Table 1).

Palladium catalysts bearing monodentate phosphine ligands were not effective in catalyzing the arylation of **3** (entries 1−4): while tetrakis(triphenylphosphine)-palladium(0) is known to be a poor catalyst in related intermolecular amination reactions,[7] the unsatisfying performance of more hindered tri-*ortho*-tolylphosphine in combination with both palladium(II) and palladium(0) precursors was suprising taking into account that this catalyst system represents the successful first-generation catalyst for palladium-catalyzed aminations.

However, the yields of coupling product could be greatly improved by changing to bidentate phosphine ligands (entries 5−15). Here, BINAP[11] and Tol-BINAP[12] gave the best results, affording *N*-[2-(methyl oxycarbonyl)phenyl]-*S*-methyl-*S*-phenylsulfoximine (**4**) in good to high yield, with Tol-BINAP being slightly more effective. Employing $PdCl_2$(DPPF)/DPPF[13] and $Pd(OAc)_2$/DPEphos[14] resulted in slightly lower yields. $Pd(OAc)_2$/DPPP (1,3-diphenylphosphinopropane) afforded the *N*-arylated product in excellent, 94% yield (entry 14), but the efficiency of this catalyst was substrate dependent, giving low yields with other aryl halides (vide infra). The use of cesium carbonate[15] as base gave the best results, and toluene was found to be superior to THF (entries 5−7, 9, 10).

Scheme 2



2 **3** **4**

Table 1. Catalytic Coupling of Methyl 2-Bromobenzoate (2) and *S*-Methyl *S*-Phenyl Sulfoximine (3) Using Different Palladium Complexes and Mono- and Bidentate Phosphine Ligands[a]

entry	precatalyst	base[f]	temp [°C]	time [h]	solvent	yield [%]
1[b]	$Pd(OAc)_2$/P(*o*-tolyl)$_3$	Cs_2CO_3	110	36	toluene	<4
2[b]	$Pd(OAc)_2$/P(*o*-tolyl)$_3$	NaO^{t}Bu	70	36	toluene	<4
3[b]	$Pd_2(dba)_3$/P(*o*-tolyl)$_3$	Cs_2CO_3	110	36	toluene	<4
4[c]	$Pd(PPh_3)_4$	Cs_2CO_3	100	36	toluene	18
5[b]	$Pd(OAc)_2$/BINAP	Cs_2CO_3	110	36	toluene	82
6[b]	$Pd(OAc)_2$/BINAP	NaO^{t}Bu	110	36	toluene	76
7[b]	$Pd(OAc)_2$/BINAP	Cs_2CO_3	110	36	THF	53
8[d]	$Pd_2(dba)_3$/BINAP	Cs_2CO_3	110	48	toluene	89
9[d]	$Pd(OAc)_2$/Tol-BINAP	Cs_2CO_3	110	48	toluene	96
10[d]	$Pd(OAc)_2$/Tol-BINAP	NaO^{t}Bu	110	48	toluene	72
12[d]	$Pd(OAc)_2$/BINAP	Cs_2CO_3	110	48	toluene	92
11[e]	$PdCl_2$(DPPF)/DPPF	Cs_2CO_3	110	48	toluene	87
13[d]	$Pd_2(dba)_3$/Tol-BINAP	Cs_2CO_3	110	48	toluene	90
14[d]	$Pd(OAc)_2$/DPPP	Cs_2CO_3	110	48	toluene	94
15[d]	$Pd(OAc)_2$/DPEphos	Cs_2CO_3	110	48	toluene	90

[a] Conditions: 1 equiv of methyl 2-bromobenzoate, 1.2 equiv of *S*-methyl-*S*-phenylsulfoximine as a 0.1 M solution. [b] 4 mol % $Pd(OAc)_2$ or $Pd_2(dba)_3$, 6 mol % phosphine ligand. [c] 10 mol % catalyst. [d] 5 mol % $Pd(OAc)_2$ or $Pd_2(dba)_3$, 7.5 mol % phosphine ligand. [e] 5 mol % $PdCl_2$(DPPF), 20 mol % DPPF. [f] 1.4 equiv of base was used.

The catalytic cycle of the *N*-arylation, which is most probably similar to related palladium-catalyzed amination reactions, is depicted in Scheme 3.

After initial reduction of the Pd(II) precursor to phosphine-ligated Pd(0), oxidative addition into the aryl−bromide bond takes place to generate an aryl−palladium(II)−bromide complex [L_2Pd(aryl)(Br)]. The sulfoximine then coordinates to palladium, and in the presence of base an aryl−palladium−sulfoximide intermediate is formed, which can undergo reductive elimination to the *N*-arylated product, regenerating the catalytically active Pd(0) species.

Sulfoximines exhibit lower nucleophilic character at the nitrogen than amines and imines, and they are more comparable in reactivity to azoles or imidazoles. This is also consistent with the higher catalyst loading and prolonged reaction times compared to similar reactions with amines or imines. Although oxidative addition of palladium into the aryl−bromide bond is assumed to be rate-determining in amination reactions with DPPF and

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(11) Racemic BINAP [2,2′-bis(diphenylphosphino)-1,1′-binaphthyl] was used in all runs.

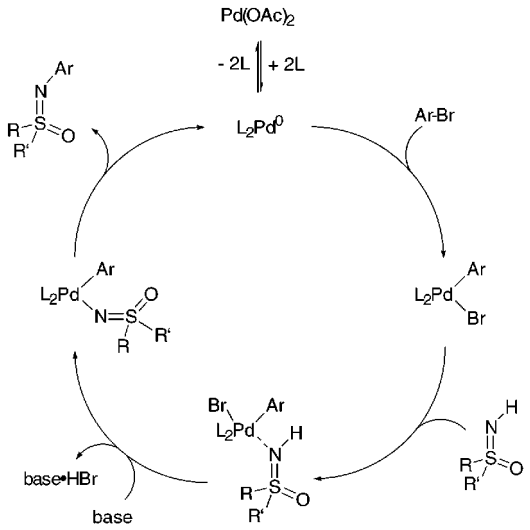
(12) Tol-BINAP [2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl] was used either as the (*S*)- or the (*R*)-enantiomer; both gave identical results in the arylation reactions.

(13) DPPF: 1,1′-(diphenylphosphino)ferrocene.

(14) DPEphos: 2,2′-bis(diphenylphosphino)-1,1′-diphenyl ether. (a) For the synthesis of DPEphos see: Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K., Fraanje, J. *Organometallics* **1995**, *14*, 3081. For its use in related amination reactions see: (b) Sadighi, J. P.; Harris, M. C.; Buchwald, S. L. *Tetrahedron Lett.* **1998**, *39*, 5327. (c) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 3694.

(15) The lower yields that were obtained with NaO-*t*-Bu could be due to partial ester hydrolysis. Cesium carbonate was suggested to be the base of choice owing to its greater functional group tolerance. For a short overview of the application of Cs_2CO_3 in organic synthesis see: Flessner, T.; Doye, S. *J. Prakt. Chem.* **1999**, *341*, 186.

Scheme 3



BINAP ligands, we think that in the present case the rate of arylation depends on the reductive elimination of the *N*-aryl sulfoximine from a palladium−sulfoximide aryl complex. In related couplings with azoles it was found that the reductive elimination of *N*-aryl azoles is less favorable than that of the corresponding arylamines and that the rates for reductive elimination of different types of sp^2-hybridized nitrogens from palladium differ markedly.[9] Alternatively, the low nucleophilicity of the sulfoximine could retard coordination to palladium and formation of the intermediary (BINAP)Pd[(sulfoximide)-(aryl)] complex.

Since BINAP and Tol-BINAP afforded the highest yields with methyl 2-bromobenzoate (**2**), these two ligands were chosen for all couplings with other sulfoximines and aryl bromides (Table 2).

Reactions with aryl bromides bearing electron-withdrawing substituents proceeded smoothly, and the yields of the corresponding *N*-aryl sulfoximine were uniformly high regardless of the substitution pattern of either substrate (entries 1, 5, 6, 11−15, and 18−20). A comparison of the yields obtained with BINAP and Tol-BINAP shows that these ligands differ only slightly in their effectiveness. However, carrying out the arylation under standard conditions with (4-*tert*-butyl)bromobenzene (**7b**) afforded (4-*tert*-butylphenyl)-*S*-methyl-*S*-phenylsulfoximine (**9**) in only poor yield with either BINAP or Tol-BINAP (entries 2, 3). Interestingly, employing an excess of aryl bromide led to smooth reaction, and the desired product **9** was obtained in 67% yield (entry 4).[16] Similarly, 3-bromoanisole (**7d**), which gave only low yields under standard conditions with BINAP (entry 7), was formed in good yield by this modified protocol (entry 8).

***N*-Arylation of (*RS*)-*S*-Methyl-*S*-phenylsulfoximine Using a Chiral Aryl Bromide.** Since differently substituted sulfoximines are chiral at the central sulfur atom, we wondered if the palladium-catalyzed arylation of enantiomerically pure sulfoximines would occur in a stereospecific manner. Since partial racemization in palladium-catalyzed aminations is mainly due to β-hydrogen elimination to form an imine,[17] it was supposed that the reaction of an enantiopure sulfoximine would proceed with retention of configuration. We have been engaged in exploring optically active sulfoximines as ligands for asymmetric catalysis[4] in recent years, and thus we chose (*S*)-2-(2′-bromophenyl)-4-*tert*-butyl oxazoline[18] [(*S*)-**19**] and (*RS*)-**3** as suitable substrates which would directly produce compound (*RS*,*S*)-**20**, a potential ligand for asymmetric catalysis (Scheme 4).

The results for the palladium-catalyzed arylation of (*RS*)-*S*-methyl-*S*-phenylsulfoximine [(*RS*)-**3**] with (*S*)-**19** in the presence of various bisphosphines are depicted in Table 3.

Indeed, **20** was obtained in moderate yield when slightly modified conditions were used with an excess of (*RS*)-**3** or (*S*)-**19** (entries 1 and 2). We then discovered that couplings are best performed when equal amounts of both coupling partners are employed. Here, the yield of **20** was raised to 86% with $Pd(OAc)_2$/DPEphos as catalyst. Only one diastereomer was obtained, indicating that the coupling proceeded without racemization at the chiral sulfur atom. Although not rigorously proven, we assume that the coupling occurred with retention of configuration at sulfur, giving the (*RS*,*S*)-configured product.[19]

***N*-Arylation Reactions with Dibromobenzenes.** Since we have been involved in the development of C_2-symmetric bissulfoximines[20] in recent years, we decided to probe the arylation protocol for the synthesis of bissulfonimidoyl aryls. 1,2-Dibromobenzene (**21**) was considered as a suitable precursor and was reacted with 2.5 equiv of **3** in the presence of $Pd(OAc)_2$/BINAP (5 mol % and 7.5 mol %) under standard reaction conditions.

Surprisingly, only monosulfonimidoyl arene **22** was formed with the second bromide still attached to the aromatic moiety (Scheme 5). However, the isolated yield of monobrominated **22** was remarkable at 74%. Again, use of phosphines other than BINAP were not successful. For example, using DPPP afforded **22** in only 17% yield. The identical result was obtained when 1,3-dibromobenzene (**24**) was used as starting material, yielding **25** in 51% yield (Scheme 6). Apparently, a possible steric hindrance of the adjacent bulky sulfonimidoyl moiety, which is introduced in the first step, cannot be responsible for the failure of the second coupling.

Neither employing a higher catalyst loading of 10 mol % $Pd(OAc)_2$/15 mol % BINAP nor a larger excess of *S*-methyl-*S*-phenylsulfoximine (**3**) of up to 4 equiv resulted in the formation of the desired bissulfoximine. We also did not observe the corresponding hydrodehalogenated monocoupled product, so that we conclude that palladium probably does not insert into the second aryl−bromide bond after substitution with the first sulfonimidoyl group. Since several groups reported related bisamination reactions with the corresponding phenyl[21] and

(16) On the other hand, DPEphos, which was among the best ligands for methyl 2-bromobenzoate (**2**), afforded (4-*tert*-butylphenyl)-*S*-methyl-*S*-phenylsulfoximine (**9**) in a disappointing yield of 23% under these modified conditions.

(17) Partial racemization of optically active amines was observed by Buchwald and co-workers with P(*o*-tolyl)$_3$ as ligand in the synthesis of chiral arylamines. Racemization was avoided utilizing chelating ligands such as BINAP and DPPF: Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451.

(18) Zhou, Q.-L.; Pfaltz, A. *Tetrahedron* **1994**, *50*, 4467.

(19) ^{1}H NMR shift experiments with **18** obtained from racemic and enantiomerically pure **3** provide further evidence that the coupling proceeds without racemization (see Supporting Information).

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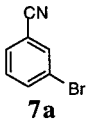
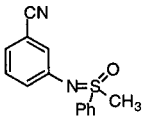
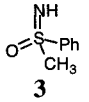
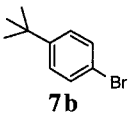
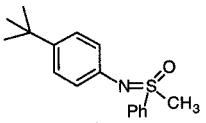
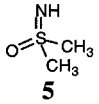
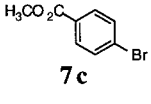
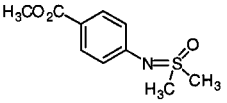
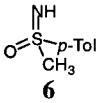
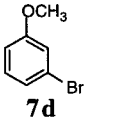
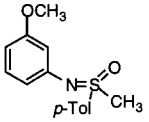
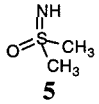
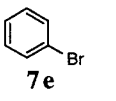
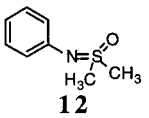
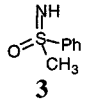
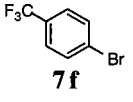
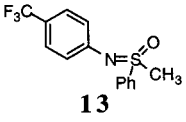
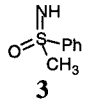
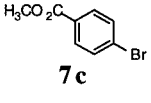
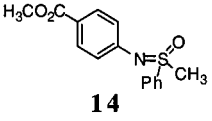
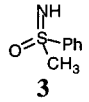
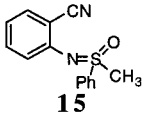
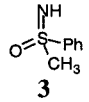
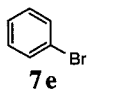
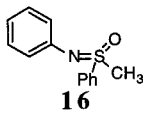
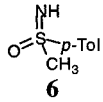
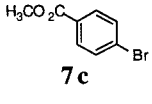
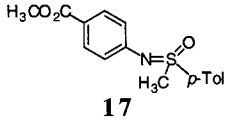
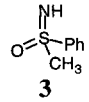
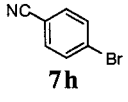
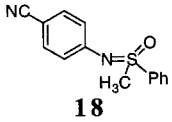
Table 2. Palladium-Catalyzed Coupling of Aryl Bromides with Sulfoximines[a]

Entry	Sulfoximine	Aryl Bromide	Product	Method[b]	Yield (%)[d]
1	 **3**	 **7a**	 **8**	A1	78
2	 **3**	 **7b**	 **9**	A1	38
3				A2	24
4				B	67
5[c]	 **5**	 **7c**	 **10**	A1	94
6[c]				A2	90
7	 **6**	 **7d**	 **11**	A1	29
8				B	74
9[c]	 **5**	 **7e**	 **12**	A1	86
10[c]				A2	95
11	 **3**	 **7f**	 **13**	A1	82
12	 **3**	 **7c**	 **14**	A1	89
13				A2	90
14	 **3**	 **7g**	 **15**	A1	94
15				A2	91
16	 **3**	 **7e**	 **16**	A1	72
17				A2	83
18	 **6**	 **7c**	 **17**	A1	88
19				A2	93
20	 **3**	 **7h**	 **18**	A1	93

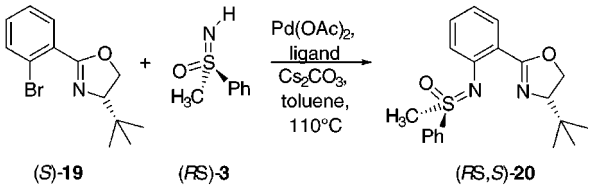
[a] All reactions were carried out under an atmosphere of argon in toluene at 110 °C with 1.4 equiv of Cs_2CO_3, 5 mol % $Pd(OAc)_2$, and 7.5 mol % of bisphosphine ligand. [b] Method A1: 1.2 equiv of sulfoximine and 1 equiv of aryl bromide were used with BINAP as ligand. Method A2: 1.2 equiv of sulfoximine and 1 equiv of aryl bromide were employed with Tol-BINAP as ligand. Method B: 1 equiv of sulfoximine and 1.2 equiv of aryl bromide were used with BINAP as ligand. [c] *S,S*-Dimethylsulfoximine (**5**) was added as a 2.0 M solution in THF. [d] Yields refer to isolated and pure material and are an average of at least two runs. Yields are relative to the limiting starting material.

pyridine[22] derivatives as well as bisiminations with benzophenone imine,[8] we assume that the sulfonimidoyl moiety deactivates the second bromide on the aryl group toward oxidative addition.[23] This is further supported by the observation that other palladium-catalyzed processes with **22** as substrate such as Suzuki couplings with phenylboronic acid or aminations with (−)-α-methyl benzylamine also failed.[24]

***N*-Arylation with Aryl Iodides.** To determine the scope of the sulfoximine arylation, we turned our attention to aryl iodides as potential coupling partners. Aryl iodides are more susceptible toward oxidative addition of palladium than the corresponding bromides; therefore, we expected our protocol to be applicable to them, too.

(22) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240.

Scheme 4



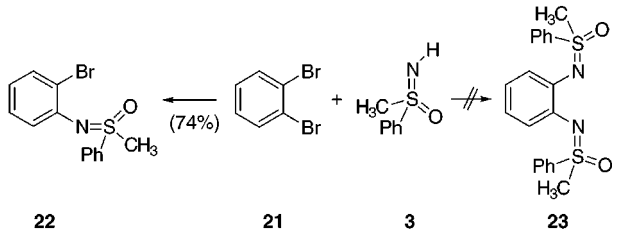
(*S*)-**19** (*RS*)-**3** (*RS*,*S*)-**20**

Table 3. Coupling of (*RS*)-3 with (*S*)-19 To Give (*RS*,*S*)-20 Using Various Palladium Catalysts

entry	Pd-source/ligand	ratio of (*RS*)-**3**:(*S*)-**19**	yield of (*RS*,*S*)-**20** (%)
1	$Pd(OAc)_2$/BINAP	1:2	54
2	$Pd(OAc)_2$/BINAP	2:1	61
3	$Pd(OAc)_2$/BINAP	1:1	82
4	$PdCl_2$(DPPF)/DPPF	1:1	75
5	$Pd(OAc)_2$/DPEphos	1:1	86

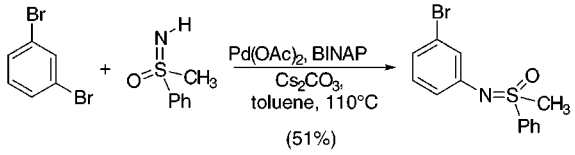
Hartwig and Driver reported that anilines can be coupled with aryl iodides in high yields by using (DPPF)$PdCl_2$/DPPF in THF,[25] whereas Buchwald and Wolfe found that aryl iodides are competent substrates in amination reactions with BINAP when dioxane was used as solvent and that the amination could be carried out at room temperature in the presence of crown ethers. They reported that aryl iodides display a significantly different reactivity than aryl bromides in related aminations,[26] and examples of palladium-catalyzed arylation reactions of sp^2-hybridized nitrogen nucleophiles with aryl iodides are still very rare.[27] Indeed, attempts to apply our general reaction conditions for aryl bromides to aryl iodides with both electron-withdrawing and electron-releasing substituents were uniformly unsuccessful. Carrying out the reaction of **3** with 2-methyl iodobenzoate (**26a**) in 1,4-dioxane or using NaO-*t*-Bu as base together with 18-crown-6 in THF met with failure. Changing to (DPPF)-$PdCl_2$/DPPF afforded *N*-[2-(methyloxycarbonyl)phenyl]-*S*-methyl-*S*-phenylsulfoximine (**4**), albeit in poor yield (17%). Finally, *N*-arylated sulfoximines could be obtained from aryl iodides in acceptable yield when more "conventional" additives were added to the reaction mixture (Table 4). Thus, employing lithium bromide as additive in the reaction of **3** with 2-methyl iodobenzoate (**26a**) catalyzed by $Pd(OAc)_2$/BINAP, **4** was formed in 56% yield (entry 1).[28] Probing another electron-deficient aryl iodide, 4-(nitrophenyl) iodide (**26c**) in the reaction with *S*-methyl-*S*-(*p*-tolyl)sulfoximine (**6**), gave the corresponding *N*-arylated product **28** in moderate yield (31%) (entry 7). When lithium chloride was used in these couplings, inferior yields resulted in all cases (entries 2, 8), and employing the corresponding sodium salts (i.e., NaCl, NaBr) gave even lower yields.

Scheme 5



22 **21** **3** **23**

Scheme 6



24 **3** **25**

In contrast, *N*-(4-nitrophenyl)-*S*-methyl-*S*-(*p*-tolyl)sulfoximine (**28**) was obtained in 79% yield in the presence of 2 equiv of silver triflate (entry 9). In independent studies we found that 4-(nitrophenyl) triflate reacts with *S*-methyl *S*-(*p*-tolyl)sulfoximine (**6**) under otherwise identical reaction conditions to give **28** in 86% isolated yield. These results could indicate that after oxidative addition of Pd into the aryl−iodide bond and efficient exchange of iodide for triflate both reactions proceed via the same intermediates. Methyl 2-iodobenzoate (**26a**) yielded **4** in a surprising yield (7%) under these conditions (entry 3).[29] Electron-rich and ortho-substituted 2-iodoanisole (**26b**) did not react in the presence of any of the employed additives (entries 4−6).[30]

Conclusion. We have developed a novel protocol for the direct arylation of sulfoximines which is based on palladium-catalyzed cross-coupling methodology. This approach is general and high yielding for aryl bromides; however, dibromo aryls react exclusively at one bromide to produce the corresponding (bromophenyl) sulfoximines, which are inert toward a second palladium-catalyzed substitution. Furthermore, it was demonstrated that enantiomerically pure sulfoximines can be arylated in a stereospecific manner to directly produce potential ligands for asymmetric catalysis. Aryl iodides require lithium or silver salts to undergo the coupling. However, the effectiveness of the additives is not uniform and they have to be optimized for individual substrates.

Experimental Section

General Procedures. Unless otherwise specified, all reagents were purchased from commercial suppliers and used without further purification. Bromobenzene was distilled before use. 1,4-Dioxane, toluene, and THF were distilled from sodium benzophenone ketyl radical under argon. All other

(23) The separate reaction of isolated **22** with **3** did not result in the formation of bissulfoximine **23**. While this article was under review, Harmata published a paper on the synthesis of chiral benzothiazines derived from 1,3- and 1,4-dibromobenzenes bearing additional formyl groups (see: Harmata, M.; Pavri, N. *Angew. Chem.* **1999**, *111*, 2577; *Angew. Chem., Int. Ed.* **1999**, *38*, 2419). Applying our protocol, they succeeded in substituting both bromines. However, the corresponding bissulfoximines were formed in only moderate yield.

(24) Bolm, C.; Hildebrand, J. P. Unpublished results.

(25) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217.

(26) (a) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133. (b) Room-temperature arylation of amines with aryl iodides using crown ethers as additives: Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 6066. (c) For room-temperature arylations of amines with aryl iodides using a highly reactive Pd catalyst see: Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369. (d) Intramolecular amination with aryl iodides: Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525.(e) For a high-yielding palladium-catalyzed reaction of an aryl iodide with diphenylhydrazone see: Hartwig, J. F. *Angew. Chem.* **1998**, *110*, 2249; *Angew. Chem., Int. Ed.* **1998**, *37*, 2090.

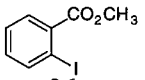
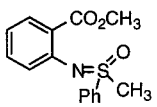
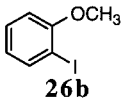
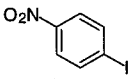
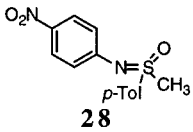
(27) For an example of a copper(I)-catalyzed high-yielding arylation protocol of imidazoles see: Kiyomori, A.; Marcoux, J.-F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657.

(28) The analogous reaction with $PdCl_2$(DPPF)/DPPF and 2 equiv of LiBr in THF afforded only 34% of coupled product.

(29) No product derived from hydrodehalogenation (methyl benzoate) was observed as side product as determined by GC/MS.

(30) This result is in contrast to Buchwald's protocol, which gives good to high yields with both electron-poor and electron-rich aryl iodides (ref 26b), and Hartwig reported that aniline can be coupled with 2-iodoanisole in 96% yield (ref 25).

Table 4. Pd-Catalyzed *N*-Arylation of 3 and 6 with Aryl Iodides in the Presence of Various Additives

Entry	Sulfoximine	Aryl Iodide	Product	Additive	Yield (%)
1	**3**	 **26a**	 **4**	LiBr	56
2	**3**			LiCl	22
3	**3**			AgOTf	7
4	**3**	 **26b**	 **27**	LiBr	<2
5	**3**			LiCl	<2
6	**3**			AgOTf	<2
7	**6**	 **26c**	 **28**	LiBr	31
8	**6**			LiCl	17
9	**6**			AgOTf	79

solvents were reagent grade and used as received. *S*,*S*-Dimethyl sulfoximine (**5**), *S*-methyl *S*-phenyl sulfoximine (**3**), and *S*-methyl-*S*-(*p*-tolyl)sulfoximine (**6**) were prepared according to reported methods.[1,2] Racemic **3** was resolved into its enantiomers using the method of Brandt and Gais.[31] Unless otherwise noted all reactions were carried out under argon using standard Schlenk and vacuum line techniques. Yields refer to average yields of pure material of at least two runs of coupling reactions. ^{1}H NMR and ^{13}C NMR spectra were recorded relative to TMS as internal standard. All microanalyses were conducted at the Institut für Organische Chemie der RWTH Aachen. The synthesis of *N*-phenyl-*S*-methyl-*S*-phenylsulfoximine (**16**),[6] *N*-phenyl-*S*,*S*-dimethyl sulfoximine (**12**),[32] and *N*-[4-(methyloxycarbonyl)phenyl]-*S*,*S*-dimethylsulfoximine (**10**)[6b] has been reported previously.

Representative Procedures (A1/A2) for the Coupling of Sulfoximines with Aryl Bromides. A dry 25 mL two-neck flask equipped with a magnetic stirbar, a septum inlet, and a reflux condenser was charged with $Pd(OAc)_2$ (5 mol %) and diphosphine (7.5 mol %; A1, BINAP; A2, Tol-BINAP) under an argon atmosphere. Then, toluene was added (10 mL), followed by the aryl bromide (1 mmol), the sulfoximine (1.25 mmol), and cesium carbonate (1.4 mmol). After heating the mixture to reflux for 48 h, it was allowed to cool to room temperature, diluted with methyl *tert*-butyl ether, and filtered through a plug of Celite, and the Celite was rinsed with methyl *tert*-butyl ether. The solvents were removed in vacuo, and the resulting oily residue was purified by flash column chromatography.

Representative Procedure (B) for the Reaction of Sulfoximines with 4-*tert*-Butylbromobenzene (7b) and 3-Bromoanisole (7d) with Cesium Carbonate As Base. A dry Schlenk tube, equipped with a magnetic stirbar, was charged with $Pd(OAc)_2$ (5 mol %), BINAP (7.5 mol %), and toluene (10 mL). Then, the aryl bromide (1.2 mmol) was added, followed by the sulfoximine (1 mmol) and base (1.4 mmol). The tube was then sealed, and the mixture was heated at 110 °C for 48 h. Workup and purification were carried out in accordance with the general procedure A.

Representative Procedure (C) for the Reaction of Sulfoximines with Aryl Iodides in the Presence of Additives. A dry Schlenk tube, equipped with a magnetic stirbar, was charged with $Pd(OAc)_2$ (5 mol %), BINAP (7.5 mol %), and toluene (10 mL). Then, the aryl bromide (1.2 mmol) was added, followed by the sulfoximine (1 mmol), the additive (2 mmol), and cesium carbonate (1.4 mmol). The tube was then sealed, and the mixture was heated at 110 °C for 48 h. Workup and purification were then performed as noted in general procedure A.

***N*-[2-(Methyloxycarbonyl)phenyl]-*S*-methyl-*S*-phenylsulfoximine (4)** was obtained from methyl 2-bromobenzoate (**2**) in 96% yield as a yellow oil using Tol-BINAP (method A2). ^{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, 51.8, 120.48, 123.25, 124.98, 127.74, 128.39, 129.53, 131.15, 132.30, 138.33, 143.97, 166.96. MS (EI, 70 eV): 289 (M, 100), 194 (64). IR (cap. film): 3022, 2929, 1723, 1482, 1301, 1204. 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.

***N*-[3-(Cyano)phenyl]-*S*-methyl-*S*-phenylsulfoximine (8)** was obtained from 3-bromobenzonitrile (**7a**) following the general method A1 in 78% yield as a yellow oil using BINAP. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.27 (s, 3H), 7.09−7.25 (m, 4H), 7.53−7.64 (m, 3H), 7.93−7.96 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.46, 112.91, 119.24, 125.15, 126.34, 127.89, 128.67, 130.02, 133.96, 138.68, 146.47. MS (EI, 70 eV): 256 (86), 193 (100). IR (cap. film): 3022, 2925, 2228, 1588, 1472, 1279. Anal. Calcd for $C_{14}H_{12}N_2O_3S$: C, 65.60; H, 4.71; N, 10.92. Found: C, 65.58; H, 4.91; N, 10.98.

***N*-(4-(*tert*-Butyl)phenyl)-*S*-methyl-*S*-phenylsulfoximine (9)** was obtained from 4 *tert*-butylbromobenzene (**7b**) following the general procedure B in 67% yield as a yellow oil using BINAP. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (s, 9H), 3.22 (s, 3H), 6.90−6.96 (m, 2H), 7.11−7.17 (m, 2H), 7.50−7.62 (m, 3H), 7.98−8.01 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.39, 45.91, 122.699, 125.84, 128.60, 129.51, 133.14, 139.77, 141.85, 144.35. MS (EI, 70 eV): 287 (M), 272 (100%). IR (cap. film): 3029, 2961, 1605, 1505, 1446, 1291. Anal. Calcd for $C_{17}H_{21}NOS$: C, 71.04; H, 7.36; N, 4.87. Found: C, 71.01; H, 7.61; N, 5.18.

***N*-[3-(Methoxy)phenyl]-*S*-methyl *S*-(*p*-tolyl)sulfoximine (11)** was obtained from 3-bromoanisole (**7d**) following the general procedure B in 74% yield as a pale yellow oil using BINAP. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.40 (s, 3H), 3.22 (s, 3H), 3.70 (s, 3H), 6.41−6.45 (m, 1H), 6.58−6.62 (m, 2H), 6.97−7.02 (m, 1H), 7.29−7.32 (m, 2H), 7.82−7.86 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.52, 46.17, 55.08, 107.66, 108.93, 115.64, 128.62, 129.46, 130.20, 136.29, 144.16, 146.36, 160.21. MS (EI, 70 eV): 275 (M, 100). IR (cap. film): 3004, 2928, 1597, 1481, 1297. Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.60; H, 6.22; N, 5.08. Found: C, 65.24; H, 6.46; N, 5.36.

***N*-[4-(Trifluoromethyl)phenyl]-*S*-methyl *S*-phenylsulfoximine (13)** was obtained from 4-(trifluoromethyl)bromobenzene (**7f**) following the general procedure A1 in 82% yield as a yellow oil using BINAP. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.26 (s, 3H), 7.06 (d, 2H, J = 8.3 Hz), 7.33 (d, 2H,

(31) Brandt, J.; Gais, H.-J. *Tetrahedron: Asymmetry* **1997**, *8*, 909.

(32) Furukawa, N.; Takahashi, F.; Yoshimura, T.; Oae, S. *Tetrahedron* **1979**, *35*, 317.

J = 7.8 Hz), 7.50−7.63 (m, 3H), 7.94 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 46.38, 122.88, 126.15, 126.48, 128.56, 129.82, 133.69, 138.85, 148.81. MS (EI, 70 eV): 299 (M, 100). IR (KBr): 3029, 2928, 1613, 1514, 1326, 1269. Anal. Calcd for $C_{14}H_{12}F_3NOS$: C, 56.17; H, 4.04; N, 4.67. Found: C, 56.44; H, 4.02; N, 4.68.

***N*-[4-(Methyloxycarbonyl)phenyl]-*S*-methyl-*S*-phenylsulfoximine (14)** was obtained from 4-bromo methylbenzoate (**7c**) following the general procedure A1/A2 as a yellow oil in 89% (BINAP) and 90% (Tol-BINAP) yield, respectively. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.30 (s, 3H); 3.82 (s, 3H); 7.00 (d, J = 8.8 Hz, 2H), 7.54−7.60 (m, 3H), 7.78 (d, J = 6.8 Hz, 2H), 7.95 (d, J = 7.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 46.28, 51.73, 122.47, 123.18, 128.54, 129.77, 130.87, 133.71, 138.57, 149.82, 167.08. MS (EI, 70 eV): 289 (M, 100), 166 (51). IR (cap. film): 3001, 1716, 1505, 1263, 1178. Anal. Calcd for $C_{15}H_{15}NO_3S$: C, 62.26; H, 5.22; N, 4.84. Found: C, 62.09; H, 5.28; N, 4.75.

***N*-[2-(Cyano)phenyl]-*S*-methyl-*S*-phenylsulfoximine (15)** was obtained from 2-bromobenzonitrile (**7g**) following the general procedure A2 in 94% yield using Tol-BINAP as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.31 (s, 3H), 6.87−6.91 (d, J = 7.7 Hz, 1H), 7.12−7.15 (d, J = 7.7 Hz, 1H), 7.21−7.27 (m, 1H), 7.48−7.50 (d, J = 7.7 Hz, 1H), 7.54−7.66 (m, 3H), 8.03−8.07 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 46.03, 118.53, 121.50, 122.04, 128.24, 129.78, 133.27, 133.36, 133.78, 138.62, 148.96. MS (EI, 70 eV): 256 (M, 100). IR (cap. film): 3069, 2220, 1591, 1479, 1284. Anal. Calcd for $C_{14}H_{12}N_2O_3S$: C, 65.60; H, 4.71; N, 10.92. Found: C, 65.34; H, 4.68; N, 10.85.

***N*-[4-(Methyloxycarbonyl)phenyl]-*S*-methyl-*S*-(*p*-tolyl)sulfoximine (17)** was obtained from 4-bromo methylbenzoate (**7c**) following the general method A1/A2 as an off-white solid in 88% (BINAP) and 93% (Tol-BINAP) yield, respectively. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.39 (s, 3H), 3.26 (s, 3H), 3.81 (s, 3H), 6.98−7.02 (d, J = 8.4 Hz, 2H), 7.29−2.32 (d, J = 7.9 Hz, 2H), 7.77−7.83 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.11, 47.08, 52.26, 122.99, 123.33, 129.10, 130.94, 131.36, 136.14, 145.20, 151.04, 167.69. Mp: 102 °C. MS (EI, 70 eV): 303 (m, 100). IR (cap. film): 3021, 2950, 1711, 1601, 1269. Anal. Calcd for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.64; N, 4.61. Found: C, 63.23; H, 5.62; N, 4.54.

***N*-[4-(Cyano)phenyl]-*S*-methyl-*S*-phenylsulfoximine (18)** was obtained from 4-bromobenzonitrile (**7h**) following the general method A1 in 93% yield as a yellow oil using BINAP. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.29 (s, 3H), 6.99−7.03 (d, J = 7.8 Hz, 2H), 7.36−7.39 (d, J = 8.8 Hz, 2H), 7.54−7.66 (m, 3H), 7.92−7.95 (d, J = 7.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 46.48, 104.07, 119.63, 123.16, 128.38, 129.85, 133.17, 133.84, 138.41, 150.15. MS (EI, 70 eV): 256 (M, 100). IR (cap. film): 3022, 2928, 2220, 1601, 1499, 1298. Anal. Calcd for $C_{14}H_{12}N_2O_3S$: C, 65.60; H, 4.71; N, 10.92. Found: C, 65.59; H, 4.57; N, 10.90.

***N*-[2-(Bromo)phenyl]-*S*-methyl-*S*-phenylsulfoximine (22).** To a dry Schlenk tube equipped with a magnetic stirbar was added $Pd(OAc)_2$ (11 mg, 5 mol %) and BINAP (47 mg, 7.5 mol %) followed by toluene (10 mL). Then, 1,2-dibromobenzene (**21**) (234 mg, 1 mmol) and *S*-methyl *S*-phenyl sulfoximine (**3**) (465 mg, 2.5 equiv) were added and finally cesium carbonate (918 mg, 2.8 equiv). The tube was sealed, and the mixture was heated at 110 °C for 48 h. It was then allowed to cool to room temperature, and finally, methyl *tert*-butyl ether was added. The mixture was filtered through a pad of Celite, and the Celite washed with methyl *tert*-butyl ether followed by evaporation of the solvent. The resulting residue was subjected to column chromatography (hexanes/methyl *tert*-butyl ether, 1:1.5) to afford 224 mg of *N*-[2-(bromo)phenyl]-*S*-methyl-*S*-phenylsulfoximine (**22**) (74%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.22 (s, 3H); 6.72−6.80 (m, 1H); 6.96−7.08 (m, 1H); 7.18−7.24 (d, 7.8 Hz, 1H); 7.48−7.65 (m, 4H); 8.05−8.12 (d, 7.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 45.35, 119.77, 123.57, 123.89, 127.46, 128.14, 129.37, 133.31, 133.90, 138.44, 143.27. MS (EI, 70 eV): 310 (M, 50), 167 (100). IR (cap. film): 3060, 1581, 1470, 1321, 1206. Anal. Calcd for $C_{13}H_{12}NOSBr$: C, 50.33; H, 3.89; N, 4.51. Found: C, 50.70; H, 4.00; N, 4.83.

***N*-[3-(Bromo)phenyl]-*S*-methyl-*S*-phenylsulfoximine (25).** To a dry Schlenk tube equipped with a magnetic stirbar was added $Pd(OAc)_2$ (11 mg, 5 mol %) and BINAP (46 mg, 7.5 mol %) followed by toluene (10 mL). Then, 1,3-dibromobenzene (**24**) (234 mg, 1 mmol) and *S*-methyl *S*-phenyl sulfoximine (**3**) (465 mg, 2.5 equiv) were added and finally cesium carbonate (918 mg, 2.8 equiv). The tube was sealed, and the mixture was heated at 110 °C for 48 h. It was then allowed to cool to room temperature, and then methyl *tert* butyl ether was added. The mixture was filtered through a pad of Celite, and the Celite was washed with methyl *tert*-butyl ether followed by evaporation of the solvent. The resulting residue was subjected to column chromatography (hexanes/methyl *tert*-butyl ether, 1:1.5) to afford 158 mg of *N*-[3-(bromo)phenyl]-*S*-methyl-*S*-phenylsulfoximine (**25**) in 51% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.24 (s, 3H), 6.92−7.03 (m, 3H), 7.12−7.15 (m, 1H), 7.52−7.64 (m, 3H), 7.94−7.96 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 46.14, 121.81, 122.60, 124.67, 126.30, 128.59, 129.74, 130.22, 133.58, 139.07, 146.81. MS (EI, 70 eV): 310 (M, 50), 167 (100). IR (KBr): 3022, 2925, 1588, 1473, 1312, 1189. Anal. Calcd for $C_{13}H_{12}NOSBr$: C, 50.33; H, 3.89; N, 4.51. Found: C, 50.66; H, 3.84; N, 4.41.

(*RS*,*S*)-2-[*S*-Methyl-*S*-phenylsulfonimidoyl]phenyl-4-*tert*-butyloxazoline (20). A dry Schlenk flask equipped with a magnetic stirbar was charged with $Pd(OAc)_2$ (11 mg, 5 mol %) and DPEphos (40 mg, 7.5 mol %) against a positive argon flow, followed by toluene (10 mL). Then, (*RS*)-*S*-methyl-*S*-phenylsulfoximine (1 equiv, 155 mg, 1 mmol), (*S*)-2-(2′-bromophenyl)-4-*tert*-butyloxazoline [(*S*)-**19**] (1 equiv, 282 mg, 1 mmol), and cesium carbonate (1.4 equiv, 459 mg, 1.4 mmol) were added, and the Schlenk flask was sealed. The mixture was heated to 110 °C for 48 h, allowed to cool to room temperature, and diluted with methyl *tert*-butyl ether. The crude reaction mixture was filtered through a pad of Celite, the Celite was rinsed with methyl *tert* butyl ether, and the combined ethereal solutions were removed in vacuo. The resulting oily residue was purified by column chromatography (hexanes/methyl *tert* butyl ether, 1:1) to yield the title compound in 86% (306 mg). $[\alpha]_D = -92.2$ (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 (s, 9H), 3.20 (s, 3H), 4.14−4.24 (m, 2H), 4.33−4.40 (m, 1H), 6.89−6.95 (m, 1H), 7.13−7.23 (m, 2H), 7.49−7.62 (m, 4H), 8.22−8.26 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.93, 34.07, 46.23, 68.73, 76.21, 127.72, 127.97, 128.05, 128.16, 128.27, 128.30, 129.29, 131.52, 133.07, 143.64, 163.25. MS (EI, 70 eV): 356 (M, 15), 159 (100). IR ($CHCl_3$): 3062, 2958, 1651, 1487, 1298. HRMS calcd for $C_{20}H_{24}N_2O_2S$: 356.155851. Found: 356.155617.

***N*-[4-(Nitro)phenyl]-*S*-methyl-*S*-(*p*-tolyl)sulfoximine (28)** was obtained from 4-(nitrophenyl) iodide (**26c**) following the general procedure C with 2 equiv of AgOTf as additive in 79% yield as a yellow solid. Mp: 122 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.42 (s, 3H), 3.30 (s, 3H), 6.98−7.01 (d, J = 8.8 Hz, 2H), 7.33−7.36 (d, J = 8.0 Hz, 2H), 7.80−7.82 (d, J = 8.3 Hz, 2H), 7.96−7.98 (d, J = 8.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.58, 46.70, 122.35, 125.11, 128.38, 130.55, 135.01, 141.52, 145.12, 152.90. MS (EI, 70 eV): 290 (M, 52), 59 (100). IR (cap. film): 3017, 2932, 1585, 1490, 1275. Anal. Calcd for $C_{14}H_{14}N_2O_2S$: C, 57.92; H, 4.86; N, 9.65. Found: C, 57.91; H, 4.80; N, 9.58.

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Supporting Information Available: Spectral characterization (^{1}H NMR, ^{13}C NMR) of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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