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Palladium-Catalyzed α-Arylation of Sulfoximines

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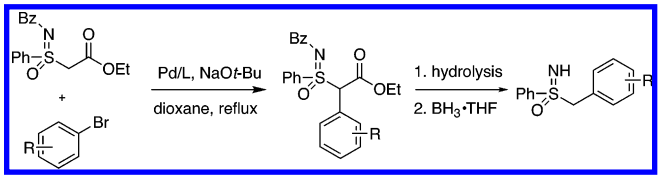
ABSTRACT



Palladium-catalyzed α-arylation of *N*-benzoyl sulfoximine ethyl ester with various aryl bromides leads to α-arylated products that can easily be hydrolyzed, giving the corresponding N-protected benzyl phenyl sulfoximines. In this manner, new sulfoximine derivatives are accessible that have so far been difficult to prepare in enantiopure form.

Since the first independent reports by Hartwig,[1] Buchwald,[2] and Miura[3] on palladium-catalyzed α-arylations of ketones in 1997, this method has found numerous synthetic applications.[4] Under similar conditions other substrates with acidic hydrogens such as nitriles[5] and sulfones[6] react also leading to the corresponding α-arylated products, which are often synthetically highly valuable intermediates. We wondered if this approach would also prove useful for the preparation of novel sulfoximines.[7] Recently, such sulfur-containing compounds attracted significant attention due to their applicability as building blocks for chiral ligands[8] and as structural units in pseudopeptides.[9] A number of approaches have been developed for their synthesis, and several of them allow the preparation of various enantiopure derivatives in a relatively straightforward manner. Most of them, however, rely on the use of a single starting material, *S*-methyl-*S*-phenylsulfoximine (**1a**; R = H, Ar = Ph), since this particular derivative can easily be prepared as a racemate in multigram quantities and resolved with camphorsulfonic acid (CSA) following well-established protocols introduced by Fusco[10a] and improved by Johnson[10b,c] and Gais.[10d] Other sulfoximine derivatives, in particular those bearing aryl groups in the α position, such as **2**, are either inaccessible by this route or

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(3) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 1740.
(4) For recent examples, see: (a) Muratake, H.; Natsume, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4646. (b) Muratake, H.; Natsume, M.; Nakai, H. *Tetrahedron* **2004**, *60*, 11783. (c) Chae, J.; Yun, J.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 4809. (d) Willis, M. C.; Brace, G. N.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 403.
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(7) Reviews on sulfoximines: (a) Johnson, C. R. *Acc. Chem. Res.* **1973**, *6*, 341. (b) Pyne, S. G. *Sulfur Rep.* **1999**, *21*, 281. (c) Reggelin, M.; Zur, C. *Synthesis* **2000**, 1. (d) Harmata, M. *Chemtracts* **2003**, *16*, 660. (e) Okamura, H.; Bolm, C. *Chem. Lett.* **2004**, *33*, 482.
(8) For recent examples, see: (a) Bolm, C.; Simic, O. *J. Am. Chem. Soc.* **2001**, *123*, 3830. (b) Harmata, M.; Ghosh, S. K. *Org. Lett.* **2001**, *3*, 3321. (c) Bolm, C.; Martin, M.; Simic, O.; Verrucci, M. *Org. Lett.* **2003**, *5*, 427. (d) Bolm, C.; Verrucci, M.; Simic, O.; Cozzi, P. G.; Raabe, G.; Okamura, H. *Chem. Commun.* **2003**, 2816. (e) Bolm, C.; Martin, M.; Gescheidt, G.; Palivan, C.; Neshchadin, D.; Bertagnolli, H.; Feth, M. P.; Schweiger, A.; Mitrikas, G.; Harmer, J. *J. Am. Chem. Soc.* **2003**, *125*, 6222. (f) Langner, M.; Bolm, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 5984.
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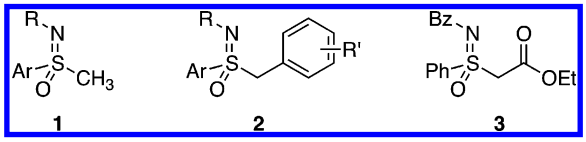
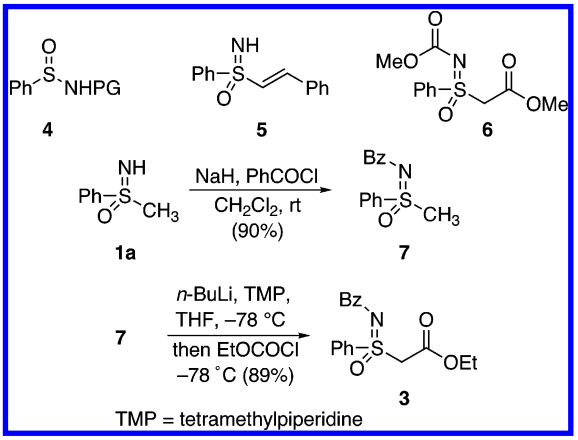


Figure 1.

at least difficult to prepare in enantiomerically pure form.[11] Motivated by our previous work on *intra*molecular α-arylations of sulfoximines affording heterocycles,[12] we wondered if palladium-catalyzed *inter*molecular α-arylations would offer a solution. If **1** (or an appropriate masked derivative of it) could be efficiently arylated at the *S*-methyl group with an appropriate aryl halide, structurally diverse aryl benzyl sulfoximines **2**, which we intend to apply as key elements in chiral ligands and pseudopeptides, would result in a highly flexible manner. Here, we report the successful implementation of this strategy by palladium-catalyzed α-arylation of *N*-benzoyl sulfoximine ethyl ester **3** with aryl bromides, followed by sequential hydrolytic decarboxylation and deprotection.

Initial experiments revealed that the coupling reaction required carefully selected starting materials and strictly optimized reaction conditions. For example, simple N-protected derivatives of **1** (with Ar = Ph) having Boc, CF_3-CO, TBDMS, or tosyl groups at the sulfoximine nitrogen did not undergo palladium-catalyzed α-arylations at all. Either no reaction occurred or undesired products such as sulfinamides **4** or olefinic NH-sulfoximine **5** were formed.[13] Assuming that the pK_a values of the *S*-methyl protons were relevant for the coupling and that the acidity at this position needed to be increased, further experiments were conducted with N-protected sulfoximine esters. Supporting this hypothesis, *N*-methoxylcarbonyl sulfoximine methyl ester (**6**), which can be prepared from NH-free phenyl methyl sulfoximine (**1a**) with NaHMDS and dimethyl carbonate in a single step, provided the first α-arylated product using phenyl bromide as aryl source and $Pd_2(dba)_3$/PCy_3 (in combination with NaO*t*-Bu in dioxane at 70 °C) as catalyst in 27% yield. Aiming to increase the efficiency of the catalysis and taking into account the stability profile of N-aroylated sulfoximines,[14] we next focused our attention on the synthesis and use of *N*-benzoyl sulfoximine ethyl ester (**3**). The reaction sequence, which led from **1a** to **3** in high overall yield, is depicted in Scheme 1.

Scheme 1



Gratifyingly, protected sulfoximine ester **3** proved to be a very suitable substrate for the α-arylation, and after an intensive optimization of the reaction conditions using phenyl bromide as coupling partner, a high yield (79%) of the corresponding arylated product **8a** was obtained (Table 1, entry 1).[15] In general, combinations of $Pd_2(dba)_3$ and BINAP or $Pd(OAc)_2$ and PCy_3 gave the most active catalysts.[16] The catalyst loading could be as low as 1 mol %. Increasing it to 9 mol % affected the reaction rate but had only a minor influence on the yield of **8a** (74% versus 79%, respectively). Subsequently, most α-arylations of **3** were performed with a catalyst consisting of 3 mol % of $Pd(OAc)_2$ and 9 mol % of PCy_3. Several bases such as NaH, KHMDS, NaHMDS, Cs_2CO_3, KO*t*-Bu, NaOMe, and Na_2CO_3 were examined, but none of them were as effective as sodium *tert*-butoxide. To achieve full conversion, at least 2 equiv of base was required, with 3 equiv of NaO*t*-Bu being optimal. As solvent, dioxane was superior to others such as THF, toluene, or DMF. An excess of aryl halide was not essential for good yields, and in most cases the reaction was complete within 1 h under reflux.

To investigate the substrate scope, several other aryl bromides were applied under the conditions optimized for the coupling with phenyl bromide. The results are summarized in Table 1.

(11) In principle, enantiopure aryl benzyl sulfoximines **2** should also be accessible by sterospecific iminations of the corresponding sulfoxides, which can be obtained by methods developed by Naso et al. (see Capozzi, M. A. M.; Cardellicchio, C.; Naso, F.; Rosito, V. *J. Org. Chem.* **2002**, *67*, 7289). Then, however, each substrate would have to be prepared individually starting from the corresponding sulfide, which would significantly limit the flexibility and synthetic value of the overall approach towards **2**.

(12) (a) Bolm, C.; Martin, M.; Gibson, L. *Synlett* **2002**, 832. (b) Bolm, C.; Okamura, H.; Verrucci, M. *J. Organomet. Chem.* **2003**, *687*, 444.

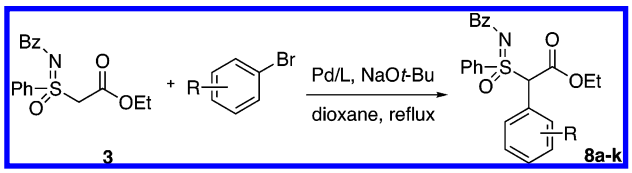
(13) The formation of **5** in up to 80% yield starting from *N*-trifluoroacetyl phenyl methyl sulfoximine in the presence of $Pd(dba)_2$, dppf, and potassium bis(trimethylsilyl)amide (KHMDS) in dioxane at room temperature was rather surprising and will be the subject of further investigations.

(14) N-Aroylated sulfoximines are rather stable compounds with a peculiar reactivity pattern (see Bolm, C.; Hackenberger, C. P. R.; Simic, O.; Verrucci, M.; Müller, D.; Bienewald, F. *Synthesis* **2002**, 879). Their treatment with boran-based reducing agents does not lead to the expected *N*-benzyl derivatives but results in either no conversion or the formation of free NH-sulfoximines. This particular aspect was expected to be benefical in the program described here, since it allowed a selective deprotecting of the α-arylated products under reductive conditions.

(15) In this study mostly racemic sulfoximines were used, and generally, the α-arylated products were isolated as a ca. 1:1 mixture of diastereomers (for **8k** = 2:1). Based on previous results, we expect that a "chiral switch" should simply lead to idential compounds in enantiomerically pure form.

(16) In this initial catalyst screening the following yields of **8a** were obtained with sulfoximine ethyl ester **3** (1.0 equiv), phenyl bromide (1.8 equiv), and sodium *tert*-butoxide (3 equiv) in dioxane (0.1 M with respect to compound **3**) under reflux. (a) $Pd(OAc)_2$ (3 mol %) + PCy_3 (9 mol %): 79%. (b) $Pd(OAc)_2$ (3 mol %) + BINAP (5 mol %): 76%. (c) $Pd_2(dba)_3$ (3 mol %) + PCy_3 (9 mol %): 68%. (d) $Pd_2(dba)_3$ (3 mol %) + BINAP (5 mol %): 76%. (e) $Pd_2(dba)_3$ (3 mol %) + BINAP (5 mol %). Use of only 1.1 equiv of PhBr: 79%.

Table 1. Optimized Protocol for the Palladium-Catalyzed α-Arylation of Sulfoximine Ethyl Ester **3** with Aryl Bromides[a]



entry	R	product	yield (%)
1	H	**8a**	79
2	4-OCH_3	**8b**	87
3	4-CN	**8c**	90[b]
4	4-NO_2	**8d**	73
5	4-Cl	**8e**	71[b,c]
6	4-SCH_3	**8f**	85
7	4-Ph	**8g**	86
8	3-OCH_3	**8h**	79
9	3-NO_2	**8i**	50[b]
10	3-Br	**8j**	82[d]
11	2-CH_3	**8k**	73

[a] Reagents and reaction conditions: *N*-benzoyl sulfoximine ethyl ester **3** (1 equiv), Ar-Br (1.2 equiv), $Pd(OAc)_2$ (3 mol %), PCy_3 (9 mol %), NaO*t*-Bu (3 equiv), dioxane, reflux. [b] $Pd_2(dba)_3$ (3 mol %) was used instead of $Pd(OAc)_2$. [c] Only the 4-chlorobenzene derivative was formed. [d] Combined yield of mono- (**8j-A**) and dicoupled (**8j-B**) products (in a ratio of 1:1).

As revealed by the data presented in Table 1, a large variety of aryl bromides could be efficiently coupled with *N*-benzoyl sulfoximine ethylester (**3**). Interestingly, in most cases PCy_3 proved more effective as a ligand than BINAP (data not shown), and better yields were obtained in reactions with the former. For some substrates the use of PCy_3 was even crucial for obtaining any of the desired arylated product. For example, the coupling reaction of **3** with 4- or 3-nitrophenyl bromide did not give any of the corresponding products with BINAP, whereas moderate to good yields of **8d** and **8i** were achieved using PCy_3 as ligand (Table 1, entries 4 and 9). This behavior was in contrast to that observed during reaction with phenyl bromide, where both phosphines worked equally well.

Generally, catalysts prepared from $Pd(OAc)_2$ gave yields better than those obtained from $Pd_2(dba)_3$. In reactions of 4-bromobenzonitrile, 4-bromochlorobenzene and 3-nitrophenyl bromide, however, the latter palladium source proved more effective (Table 1, entries 3, 5, and 9). The conversion of 4-bromochlorobenzene afforded the corresponding 4-chloro derivative exclusively, which revealed a high degree of chemoselectivity of the coupling. Although the reaction with 2-bromotoluene provided α-arylated **8k** in good yield (Table 1, entry 11), ortho-substituted aryl bromides were generally unsuitable substrates. Thus, 2-bromoanisole gave the coupled product in only 25% yield, and *N*,*N*-dimethyl-2-bromoaniline, 2-bromobenzonitrile, and 2-bromobenzaldehyde did not afford the expected products at all. The use of heterocyclic aryl halides such as 2-bromopyridine, 2-bromothiophene, and 3-bromopyridine was also investigated, but none of the reactions gave satisfying results.

Of particular interest is entry 10 in Table 1, which describes the α-arylation of **3** with 1,3-dibromobenzene. Here, a 1:1 mixture of mono- and dicoupled products (**8j-A** and **8j-B**, respectively) was obtained. Accordingly, use of enantiopure **1a** should afford the corresponding C_2-symmetric bissulfoximine **8j-B**,[15] which we then plan to apply in analogy to Pincer-type ligands such as **9** (Figure 2).[17]

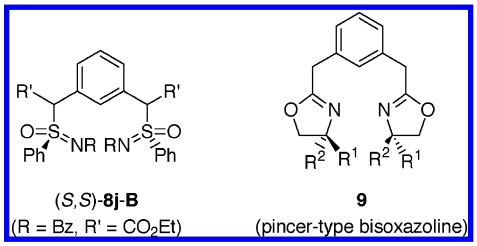
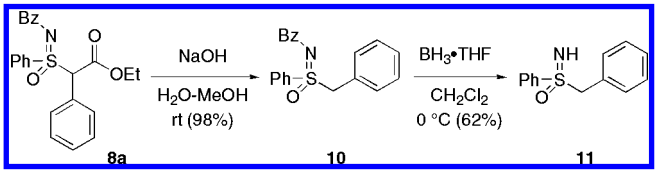


Figure 2.

In order for the developed α-arylation process to be truly valuable in synthesis, a selective deprotection strategy had to be established. For this purpose, we first demonstrated that arylated compound **8a** could easily be hydrolyzed by brief treatment with an aqueous methanolic solution of NaOH, affording N-protected phenyl benzyl sulfoximine **10** in quantitative yield (Scheme 2).[18]

Scheme 2



Since in most ligand and pseudopeptide syntheses the "free" NH-sulfoximines are employed, the possibility of cleaving the N-protective group had also to be realized. Much to our surprise, *N*-benzoyl sulfoximine **10** proved rather stable under basic conditions (K_2CO_3, NaOH, NaOMe, and NH_3−ethanol),[19] and even after extended reaction times no conversion was observed. Acidic conditions (1.2 N HCl, reflux) led to decomposition of the starting material. Attempts to reductively cleave the N-protective group by treatment of **10** with DIBAL-H were also unsuccessful. Finally, we utilized the BH_3·THF complex for the reductive *N*-benzoyl cleavage, which afforded the desired "free" NH-phenyl benzyl sulfoximine (**11**) in good yield (Scheme 2).

(17) Gerisch, M.; Krumper, J. R.; Bergman, R. G.; Tilley, T. D. *J. Am. Chem. Soc.* **2001**, *123*, 5818.

(18) Rapid decarboxylations have also been observed in reaction sequences involving other α-sulfoximidoyl carboxylates. Since some ammonium salts proved rather stable at ambient temperature, they could be applied in coupling reactions providing sulfoximine-containing pesudopeptides. For details, see refs 9c and 9d.

(19) For a detailed investigation of the nature of the N−C(O)-bond in acylated sulfoximines, see: Hackenberger, C. P. R.; Raabe, G.; Bolm, C. *Chem. Eur. J.* **2004**, *10*, 2942.

In summary, various phenyl benzyl sulfoximines can be readily prepared using palladium-catalyzed α-arylation. For a successful coupling, the appropriate combination of palladium source, ligand, and base is crucial. *N*-Benzoyl-protected sulfoximine ethyl ester (**3**) proved to be a particularly suitable starting material for both the coupling and the subsequent deprotection steps leading to the desired final products. In further studies we plan to prepare and utilize enantiopure derivatives of these products in the preparation of new chiral ligands for asymmetric catalysis and building blocks for pseudopeptides.

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Supporting Information Available: Experimental procedures and full characterization (^{1}H and ^{13}C NMR data and spectra, MS, IR, and CHN analyses) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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