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Efficient palladium-catalyzed N-arylation of a sulfoximine with aryl chlorides $\dagger \ddagger$

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The efficient N-arylation of a sulfoximine with aryl chlorides was developed by using $Pd_2(dba)_3$ as a catalyst and various ligands. The reactions using RuPhos as a ligand afforded the coupled products in fair to excellent yields.

The *N*-arylation of sulfoximines has been of interest over the past decade because the products of the process are important as chiral ligands¹ and heretofore unknown heterocycles.² From a more fundamental point of view, the study of such reactions affords the opportunity to learn more about the chemical behavior of the sulfoximine nitrogen atom, which is neither a typical amine or amide nitrogen.³

Our interest in the *N*-arylation of NH-sulfoximines began with a study demonstrating the *N*-arylation of 1 and *o*-bromobenzaldehyde to afford benzothiazine 3 (Scheme 1).⁴

The process represents a general method for accessing chiral, enantiomerically pure 2,1-benzothiazines. For that and other work,⁵ we made use of an *N*-arylation protocol introduced by Bolm,⁶ who showed that treatment of simple aryl bromides with sulfoximine **4** in the presence of a palladium source, racemic BINAP, and a base, afforded *N*-arylated sulfoximines in good to excellent yields.

The *N*-arylation of sulfoximines has been reported using aryl bromides, iodides and sulfonate esters under palladium, copper, nickel and iron catalysis.^{7,8} Aryl boronic acids have been used as arylating agents with copper as well.⁹ More recently, certain azoles and polyfluoroarenes have been used for *N*-arylation *via* C–H activation with catalysis by copper salts.¹⁰

While the arylation of sulfoximines with aryl chlorides would be economically and practically attractive, efforts in this direction have only been reported sparingly. We applied the Bolm catalyst system to the arylation of sulfoximine **4**

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[‡] Electronic supplementary information (ESI) available: Experimental procedures and analytical data for all new compounds. See DOI: 10.1039/c1cc12444g



Scheme 1 N-Arylation of a sulfoximine with 2-bromobenzaldehyde.

using microwave methodology and found that *N*-arylation could be achieved in yields ranging from 31–94%.¹¹ The lower yields in this approach were typically associated with aromatic chlorides bearing electron-donating groups.

Though yields could be improved by using chloroaromatics as solvents in the reaction, this solution left much to be desired. Further, our microwave apparatus was constrained to the preparation of relatively small batches of product.

We wondered if changes in the ligand used in the process could improve the *N*-arylation of aryl bromides and/or chlorides and if a procedure that could be run without excessive concern about air or moisture might be developed.

We began our work with an investigation of the *N*-arylation of **4** using bromobenzene. The experiments were conducted by combining reagents in an undried, but ultimately sealed tube, and heating for 12 h at 110 $^{\circ}$ C. The results are shown in Scheme 2. A sealed tube system was used in anticipation of our using aryl chlorides in the process, since this would mimic the reactions we had performed with aryl chlorides in the past using microwave irradiation.¹¹

As can be seen, bidentate ligands were preferred in this reaction, with some exceptions as represented by dppf and others.¹² Monodentate phosphine ligands were also poor performers. The three best monodentate ligands were tricyclohexylphosphine, *t*-Bu-XPhos and BippyPhos,¹³ while other simple phosphines were ineffective.¹²

Several palladium sources were examined in order to probe counterion/ligand effects in the process. RuPhos was chosen for most of these studies as the phosphine ligand. The results are summarized in Table 1.

In general, Pd^0 species afforded higher yields than Pd(II) species as can be seen from a comparison of entry 5 with entries 1–3 of Table 1. It is interesting to note that $Pd(PPh_3)_4$ was a viable Pd source (Table 1, Entry 4). In the absence

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of RuPhos, this metal complex did not lead to Buchwald–Hartwig coupling, suggesting dynamic ligand exchange enabling access to a catalytically active species containing RuPhos. Since BrettPhos has recently been established as a superior ligand in the Buchwald–Hartwig amination reaction,¹⁴ we tested it, but it was not superior to RuPhos (Table 1, entry 6). Carbene ligands, such as PEPPSI-I and II have also found extensive use in metal-catalyzed reactions.¹⁵ However, neither catalyst gave useful results in the synthesis of **6** (Table 1, entries 7–8).

We also studied the effect of a base on the reaction and the results are summarized in the supporting information.[‡]

The first aryl chloride examined was chlorobenzene (under reaction conditions described in Table 1, entry 5, at 135 °C for 6 h), which afforded only trace amounts of sulfoximine **6**. We increased the amount of catalyst to 5% and ligand to 10%, but the yield of the product was still low (3%) compared directly to the bromobenzene experiment (Table 1).

The low reactivity of the aryl chloride was not surprising. We nevertheless performed a competition experiment between p-bromotoluene and 4-ethylchlorobenzene with 4. This afforded sulfoximines 9 and 10 in 83% and 5% yields, respectively, the

Table 1 Effect of Pd sources on coupling reaction

1	Fu(OAC) ₂	Kurnos	55
2	PdCl ₂	RuPhos	71
3	PdCl ₂	RuPhos	56 ^a
4	$Pd(PPh_3)_4$	RuPhos	61
5	$Pd_2(dba)_3$	RuPhos	92^{b}
6	$Pd_2(dba)_3$	BrettPhos	57^{b}
7^c	PEPPSI-I	_	6
8 ^c	PEPPSI-II	_	28

^{*a*} 10 mol% AgSbF₆ added. ^{*b*} 2.5 mol% catalyst added. ^{*c*} 5 mol% catalyst, 1.6 equiv Cs₂CO₃, toluene, 115 $^{\circ}$ C, 12 h.



latter species being derived from an impurity in **8**. No products derived from 7 were found (Scheme 3).



Scheme 3 Competition experiment.

Table 2 N-arylation of sulfoximine 4 with aryl chlorides



^{*a*} A: 1.2 equiv **4**, 2.5% Pd₂(dba)₃, 7.5% RuPhos, 1.4 equiv Cs₂CO₃; B: 1.2 equiv **4**, 5% Pd₂(dba)₃, 10% RuPhos, 1.4 equiv Cs₂CO₃; C: 2.2 equiv **4**, 10% Pd₂(dba)₃, 10% RuPhos, 3.2 equiv Cs₂CO₃; D: 2.2 equiv **4**, 5% Pd₂(dba)₃, 10% RuPhos, 3.2 equiv Cs₂CO₃. ^{*b*} 5 mol% RuPhos was used. ^{*c*} (*R*)-**4** was used.

However, we were aware that the coupling process we had discovered was qualitatively faster than that which used BINAP. We therefore wondered if the coupling reaction with aryl chlorides might work under conditions that were more demanding. This turned out to be the case (Table 2).

Variations in procedures generally involved changing amounts of catalyst and ligand, as well as occasional increases in the amount of **4** used for coupling. Entries 1 and 2 illustrate that chloride coupling is possible and can result in near quantitative yields to afford an *N*-arylated sulfoximine, provided sufficient amounts of palladium and ligand are present.¹⁶ Chloride **12** presented some difficulties but once again with only a slight increase in catalyst loading, good yields of coupling product **13** could be obtained.

Interestingly, *o*-dichlorobenzene (14) afforded the bis-coupling product 15 in 60% yield (Table 2, entry 8). This ligand was first reported by Bolm as a product of the corresponding dibromide¹⁷ and it has been used in a number of interesting catalytic, asymmetric processes, with variable results.¹⁸ Its accessibility from 14 should broaden interest in its further application or modification.

We expected that aryl chlorides bearing additional electronwithdrawing groups would couple with greater facility than those without and this was apparently the case. Both 16 and 18 gave good yields of the corresponding coupling products 17 and 19 (Table 2, entries 9–10). We expected and found that *o*-chlorobenzophenone (20) successfully reacted with 4 to afford benzothiazine 21 in 77% yield (Table 2, entry 11). We thought that fluorine substitution would be a problem with aldehyde 22, but even in the presence of excess 4 the fluorinated benzothiazine 23 was obtained in excellent yield with no evidence of fluoride displacement under the reaction conditions (Table 2, entries 12–13). Finally, the dapsone analogue 25 was produced from the dichloride 24.

In conclusion, we have found a catalyst system that facilitates the *N*-arylation of sulfoximine **4** with aryl chlorides. These results suggest that this methodology will be useful for the generation of *N*-aryl sulfoximines from both aryl bromides and chlorides. Further studies of this chemistry are in progress and results will be reported in due course.

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