Organic LETTERS

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Rhodium(III)-Catalyzed *Ortho* Halogenations of *N*-Acylsulfoximines and Synthetic Applications toward Functionalized Sulfoximine Derivatives

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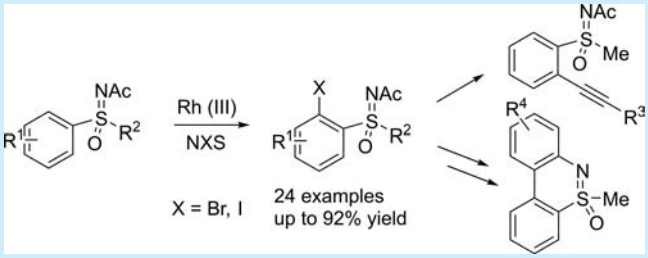
Supporting Information

ABSTRACT: Rhodium(III)-catalyzed *ortho* brominations and iodinations of *N*-acylsulfoximines by C−H bond activations have been developed. Subsequent product functionalizations involving cross-coupling reactions provide alkynylated sulfoximine derivatives and benzothiazines with wide potential for further synthetic applications.



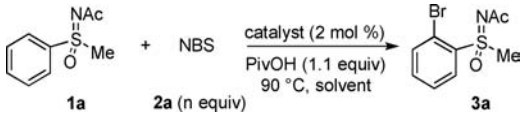
Sulfoximines offer versatile properties for applications in asymmetric synthesis,[1] crop protection,[2] and medicinal chemistry.[3] Sulfoximines have gained considerable attention from a wide range of chemists, as finding efficient and practical functionalizations of such compounds has become highly desirable.

In recent years, transition-metal-catalyzed C−H bond functionalization for the construction of C−C and C−heteroatom bonds has attracted much attention.[4] Along these lines, organic halides became prime targets[5] because of their high synthetic relevance as coupling partners in preparative organic chemistry.[6] Initial C−H bond halogenations were reported by Sanford,[7] Yu,[8] Shi,[9] and others,[10] who applied palladium catalysts and electrophilic halogenating reagents. Soon after, Glorius achieved high-yielding C−Br and C−I bond formations of arenes by rhodium catalysis.[11] More recently, also other metals such as ruthenium, copper, and cobalt were found to catalyze *ortho* C−H halogenations.[12]

Following our interest in sulfoximine chemistry with reports on rhodium-catalyzed C−H bond activations for annulations,[13] olefinations,[14] and hydroarylations,[15] we felt challenged to develop a catalytic process for *ortho* halogenations of such compounds.[16] Here, we describe brominations and iodinations of sulfoximines leading to products, which can subsequently be functionalized to give alkynylated derivatives and sulfoximidoyl-based heterocycles with potential for further synthetic applications.[17]

The study was initiated by a catalyst screening with *N*-acylsulfoximine **1a** and *N*-bromosuccinimide (NBS, **2a**, 1.1 equiv) as starting materials (0.2 mmol scale), pivalic acid as an additive (1.1 equiv), and 2 mol % of the metal complex in 1,2-dichloroethane (1,2-DCE, 2 mL) at 90 °C for 21 h (Table 1). To our surprise, $[RhCp^*Cl_2]_2$ was inactive under these conditions (Table 1, entry 1). With $[Cp^*Rh(MeCN)_3][BF_4]_2$ as the catalyst, the desired product **3a** was obtained in 55% yield (Table 1, entry 2). Noteworthy was the excellent selectivity toward the monosubstituted product. The yield of **3a** increased to 68% when $[Cp^*Rh(MeCN)_3][SbF_6]_2$ was applied (Table 1, entry 3). With the latter catalyst, a solvent screening was performed. Disappointingly, catalyses in MeCN, toluene, and 1,4-dioxane remained unsuccessful (Table 1, entries 4−6). A positive effect on the product yield was observed when the amount of NBS was increased from the previously used 1.1 equiv to 1.5 equiv affording **3a** in 85% yield (Table 1, entry 7). With 2.0 equiv of NBS the yield of **3a** dropped to 74% presumably due to side reactions becoming more dominant (Table 1, entry 8). A control experiment confirmed that the presence of the rhodium catalyst was essential for this bromination to occur (Table 1, entry 9).

Table 1. Optimization of the Reaction Conditions



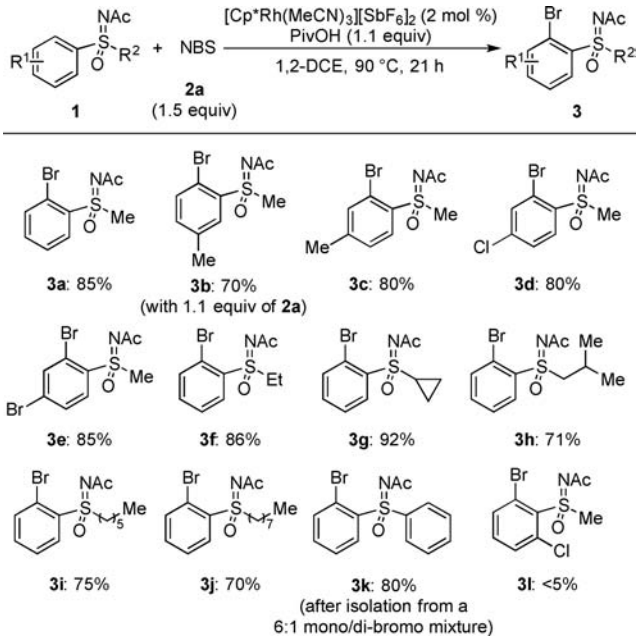
entry	catalyst	*n* (equiv)	solvent	yield (%)
1	$[Cp^*RhCl_2]_2$	1.1	1,2-DCE	0
2	$[Cp^*Rh(MeCN)_3][BF_4]_2$	1.1	1,2-DCE	55
3	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	1.1	1,2-DCE	68
4	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	1.1	MeCN	0
5	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	1.1	toluene	0
6	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	1.1	1,4-dioxane	0
7	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	1.5	1,2-DCE	85
8	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	2.0	1,2-DCE	74
9	–	1.5	1,2-DCE	0

Received: January 6, 2017
Published: January 20, 2017

DOI: 10.1021/acs.orglett.7b00043
Org. Lett. 2017, 19, 726−729

With the optimized reaction conditions in hand the reaction scope was explored. First, various diversely substituted sulfoximines **1** were reacted with NBS (Scheme 1). In general,

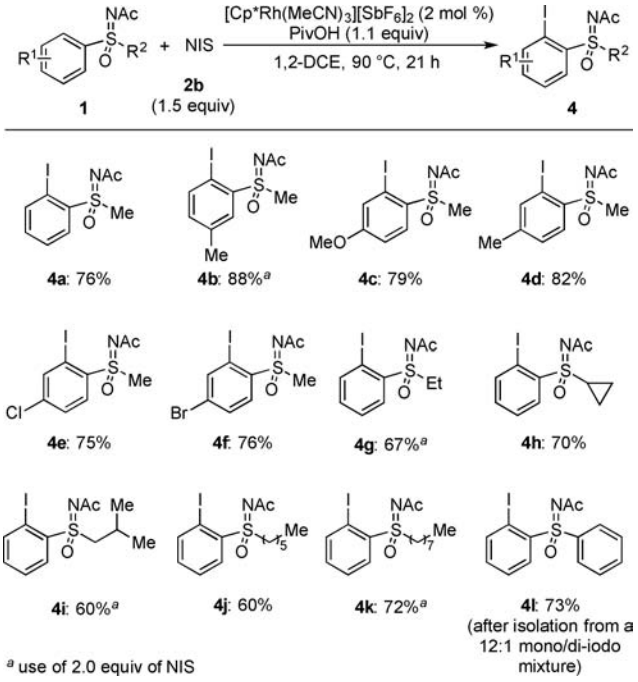
Scheme 1. Brominations of Sulfoximines with NBS



the functional group tolerance was good, and the respective products (**3a**–**3k**) were obtained in yields ranging from 70% to 92%. The reaction of the *meta*-methyl substituted sulfoximine **1b** showed exclusive regioselectivity toward **3b** affording the product in 70% yield (with 1.1 equiv of **2a**). Alternation of the *para* substituent (methyl, chloro, and bromo) had no significant effect on the yields (of **3c**–**e**). Also varying the *S*-alkyl substituent of *S*-phenyl sulfoximines was possible allowing isolation of the corresponding brominated products **3f**–**j** in yields ranging from 70% to 92%. In none of the cases, C(sp^3)–H bond halogenation was observed.[18] Applying *S*,*S*-diphenyl sulfoximine (**1k**) in the catalytic bromination gave an easy to separate 6:1 mixture of mono- and dibromonated products (as determined by ^{1}H NMR). After column chromatography, monohalogenated **3k** was obtained in 80% yield. Probably due to steric factors induced by the *ortho* chloro substituent of **1l**, the yield of **3l** was poor (<5%).

Next, rhodium-catalyzed iodinations of sulfoximines were attempted (Scheme 2). Replacement of NBS (**2a**) by NIS (**2b**, 1.5 equiv) in the reaction with **1a** led to a smooth halogenation affording the corresponding *ortho* iodinated product **4a** in 76% yield. Thus, compared to the analogous bromination reaction the iodination yield was slightly lower (76% for **4a** versus 85% for **3a**) presumably due to the increased steric requirement of the iodine atom. The applicability of other *N*-acylsulfoximines was investigated next. In general, the iodinations went well, providing monosubstituted products in good yields (60–88%). Even with 2.0 equiv of NIS (instead of the commonly used 1.5 equiv) only monoiodinated products (**4b**, **4g**, **4i**, and **4k**) were observed. Sulfoximine **1b** with a *meta*-methyl substituent gave **4b** in 88% yield. Reactions of *para*-substituted phenyl-sulfoximines with **2b** led to the *ortho*-iodinated products **3c**–**f** in yields ranging from 75% to 82%. *S*-Phenylsulfoximines with

Scheme 2. Iodinations of Sulfoximines with NIS



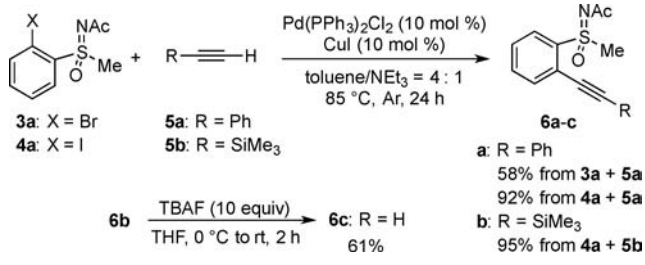
various *S*-alkyl substituents reacted smoothly giving **4g**–**k** in yields of 60–82%.

As in the bromination, *S*,*S*-diphenyl sulfoximine (**1k**) overreacted providing a mixture of mono- and diiodinated products (in a 12:1 ratio as determined by ^{1}H NMR spectroscopy of the crude mixture). Purification by column chromatography allowed isolation of **4l** as a single component in 73% yield.

Attempts to chlorinate under analogous conditions remained unsuccessful.[19]

Finally, a few transformations of the products were explored. As shown by Harmata et al., *N*-unprotected *ortho* halo-substituted sulfoximines can undergo cross-coupling reactions, but commonly, product mixtures were obtained rendering the yields of the individual products only moderate to good.[17,20] In contrast, applying the *N*-acetyl-protected derivatives obtained by the aforementioned rhodium catalysis (Schemes 1 and 2) in analogous transformations led to defined target structures in very good yields. For example, Sonogashira-type cross-couplings of *ortho*-bromo and *ortho*-iodo sulfoximines **3a** and **4a** with terminal alkynes **5a** and **5b** gave the corresponding alkynylated products **6a** and **6b** in up to 95% yield (Scheme 3).[21] The latter product could further be derivatized by silyl group cleavage to give **6c** (as a surprisingly sensitive compound) in 61% yield.

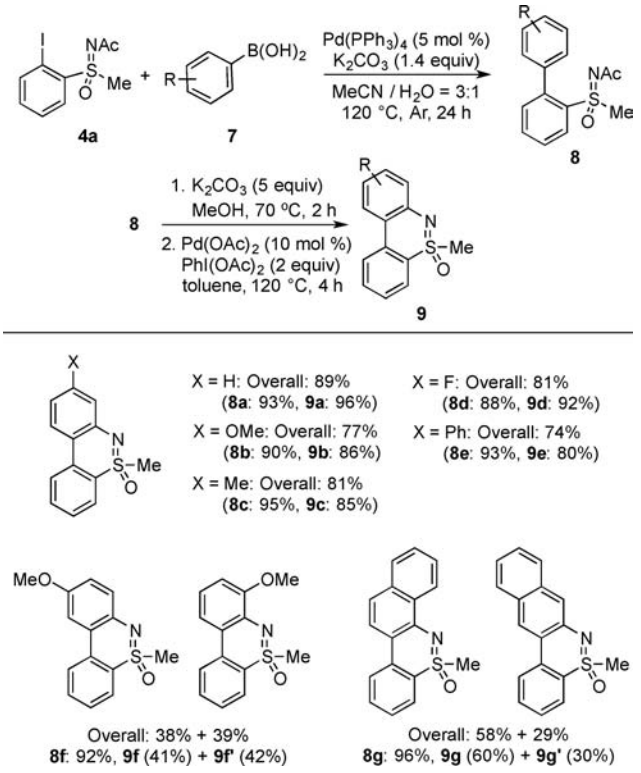
Scheme 3. Sonogashira Couplings of 3a and 4a



DOI: 10.1021/acs.orglett.7b00043
Org. Lett. 2017, 19, 726–729

Palladium-catalyzed Suzuki coupling reactions of **4a** with boronic acids **7** under basic conditions in $MeCN/H_2O$[22] afforded arylated products **8**, which could be *N*-deacetylated and oxidatively cyclized[16d,23] to give benzothiazines **9** in good overall yields (Scheme 4). Although few such heterocycles have been reported before,[16d,17,24] the approach reported here is attractive because it allows access to a wide range of derivatives from a single readily available key intermediate (**4a**).

Scheme 4. Synthesis of Benzothiazines Starting from 4a



In conclusion, we have developed rhodium-catalyzed halogenations of *N*-acylsulfoximines with NBS and NIS providing *ortho*-brominated and *ortho*-iodinated sulfoximines, respectively, in good yields. Subsequent product functionalizations open access to alkynylated derivatives and benzothiazines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00043.

Experimental procedures and full characterization for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Y.C. and W.D. thank the China Scholarship Council for predoctoral stipends. K.P. acknowledges support by the Alexander von Humboldt Foundation.

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