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Palladium-Catalyzed C–H Iodination of Arenes by Means of Sulfinyl Directing Groups

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Dedication

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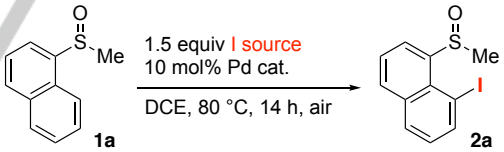
Abstract: C–H iodination of aromatic compounds has been accomplished with the aid of sulfinyl directing groups under palladium catalysis. The reaction proceeds selectively at the *peri*-position of polycyclic aryl sulfoxides or at the *ortho*-position of phenyl sulfoxides. The iodination products can be further converted via iterative catalytic cross-coupling at the expense of the C–I and C–S bonds. Computational studies suggest that *peri*-C–H palladation would proceed via a non-directed pathway, wherein neither of the sulfur nor oxygen atom of the sulfinyl group coordinates to the palladium before and at the transition state.

Catalytic methods for the direct functionalization of C–H bonds are significantly important to streamline the synthesis of complex organic molecules in atom- and step-economical manners. Directing-group-assisted C–H functionalizations are among the most powerful methods to execute regioselective C–H transformations.[1] Although most of such reactions focus on ortho-selective functionalizations, transformations of the *peri*-C–H bonds of polycyclic aromatic compounds should be an important method. For example, this approach allows for the synthesis of 1,8-difunctionalized naphthalenes that are difficult to synthesize via conventional strategies.[2] In light of these situations, peri-selective C–H functionalizations have been investigated with diverse directing groups including amide,[2c–g] hydroxy,[2h,3] cyano,[4] and silyl[2i,j] groups. Recently, *peri*-selective C–H functionalizations directed by sulfur substituents have gained increasing attention. For example, alkenylation[5] and arylation[6] have been accomplished with the aid of sulfanyl directing groups.[7] However, because sulfanyl groups are intrinsically sensitive to oxidation, they are not compatible with strongly oxidative transformations such as C–H halogenation and alkoxylation.[8] Although Roger and Hierso recently accomplished *ortho*-C–H halogenation and acetoxylation of aryl sulfides, a 2-pyridyl group should be attached onto the sulfur atom as a directing and electron-withdrawing group.[9]

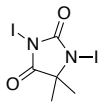
We recently developed *peri*-selective C–H alkoxylation by means of sulfinyl directing groups of high compatibility with oxidative conditions. In the presence of a palladium catalyst and a hypervalent iodine reagent as an oxidant, *peri*-selective C–H fluoroalkoxylation of aryl sulfoxides has been accomplished.[10] To further demonstrate the latent directing group ability of sulfinyl groups, we herein report palladium-catalyzed *peri*-C–H iodination of polycyclic aromatic compounds.[11,12] The iodo moiety as well as the remaining sulfinyl moiety were convertible, which allowed further decoration of the aromatic rings. Computational studies revealed that the C–H palladation step would proceed via a sulfinyl-assisted electrophilic aromatic substitution mechanism.

The iodination of methyl 1-naphthyl sulfoxide (**1a**) was chosen as a model reaction (Table 1). In the presence of 10 mol% of $Pd(OAc)_2$, **1a** was treated with 1.5 equiv of *N*-iodosuccinimide (NIS) in 1,2-dichloroethane (DCE) under air. As a result, desired iodination product **2a** was obtained in 78% yield (entry 1). Of note, only the *peri*-iodination product was obtained and the regioisomeric *ortho*-iodination product was not observed.

Table 1. Screening of Iodine Sources and Catalysts.



1a **2a**

entry	Pd cat.	I source	NMR yield (%)
1	$Pd(OAc)_2$	NIS	78
2	$Pd(OAc)_2$	NIS	74[a]
3	none	NIS	0
4	$Pd(OAc)_2$		77[b]
5	$Pd(OAc)_2$	I_2	12
6	$PdCl_2$	NIS	50
7	$Pd(OPiv)_2$	NIS	10
8	$Pd(OCOCF_3)_2$	NIS	81
9	$Pd(OCOCF_3)_2$	NIS	73[c]
10	$Pd(OCOCF_3)_2$	NIS	77[d]

[a] Under N_2. [b] With 0.75 equiv of 1,3-diiodo-5,5-dimethylhydantoin. [c] With 1.2 equiv of NIS. [d] With 5.0 mol% of $Pd(OCOCF_3)_2$.

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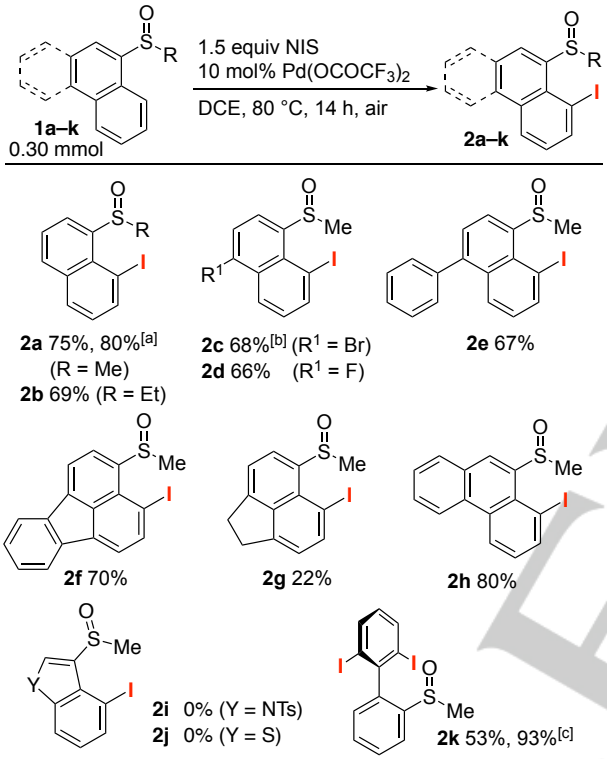
The reaction smoothly proceeded even under an atmosphere of N_2 (entry 2). Naturally, no iodination took place without the palladium catalyst (entry 3). Instead of NIS, 1,3-diiodo-5,5-dimethylhydantoin also promoted the reaction whereas only a 12% yield of **2a** was obtained with I_2 (entries 4 and 5).[13,14] We then investigated the effect of palladium catalysts. In place of $Pd(OAc)_2$, $PdCl_2$ also catalyzed the reaction to afford **2a** in 50% yield (entry 6). On the other hand, palladium pivalate ($Pd(OPiv)_2$) was found to be inappropriate probably because steric bulkiness of the pivaloxy ligand prevents coordination of the substrate to the palladium center (entry 7). Gratifyingly, the use of $Pd(OCOCF_3)_2$ improved the yield to 81% (entry 8). The employment of lower amounts of NIS and $Pd(OCOCF_3)_2$ slightly decreased the yield (entries 9 and 10).

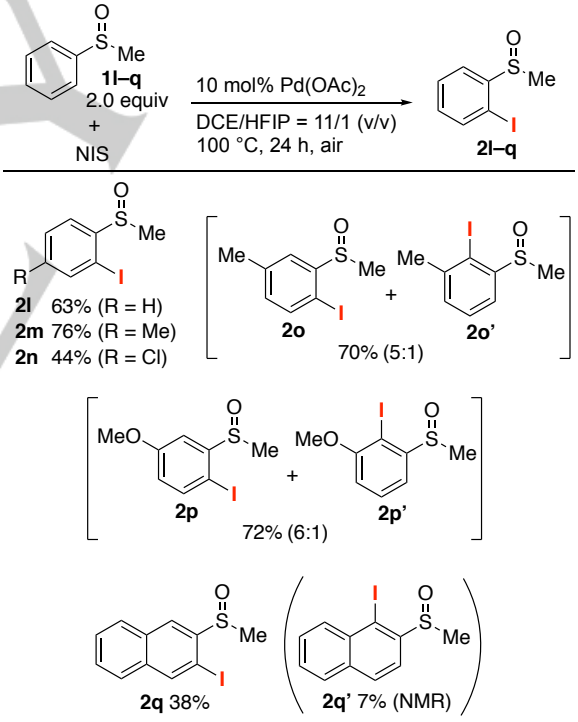


Scheme 1. Scope of *peri*-C–H Iodination. [a] 5.0 mmol scale. [b] With 2.0 equiv of NIS, for 24 h. [c] With 3.0 equiv of NIS.

Under the optimal reaction conditions (Table 1, entry 8), **2a** was isolated in 75% yield (Scheme 1). The iodination is applicable to a gram-scale synthesis; 80% (1.3 g, 4.0 mmol) yield of **2a** was obtained from 5.0 mmol of **1a**. The ethylsulfinyl group of ethyl 1-naphthyl sulfoxide (**1b**) also directed the reaction to provide **2b** in 69% yield. The reaction accommodates bromo, fluoro, and phenyl substituents; iodination products **2c–e** were uneventfully obtained. The bromo-substituted **2c** was obtained in 68% yield with 2.0 equiv of NIS and a prolonged reaction time. In place of naphthyl sulfoxides, fluoranthenyl, acenaphthenyl, and phenanthryl sulfoxides also underwent the reaction to yield **2f–h**, whereas the yield of **2g** was 22% probably due to oxidative decomposition of the substrate or product having the benzylic C–H bonds. Notably, the C–H bond at the 8 position of 9-phenanthryl sulfoxide was selectively converted to give **2h** as a sole product, while the C–H bond at the 10 position is generally regarded to be the most reactive. Although we attempted C4-selective iodination of 3-(methylsulfinyl)heterocycles **1i** and **1j**, complex product mixtures were obtained without formation of the desired iodination products.

The reaction of 2-methylsulfinylbiphenyl under the standard conditions afforded diiodination product **2k** in 53% yield accompanied by a 20% yield of the corresponding monoiodination product. Naturally, the use of 3 equivalents of NIS increased the yield of **2k** to 93%.

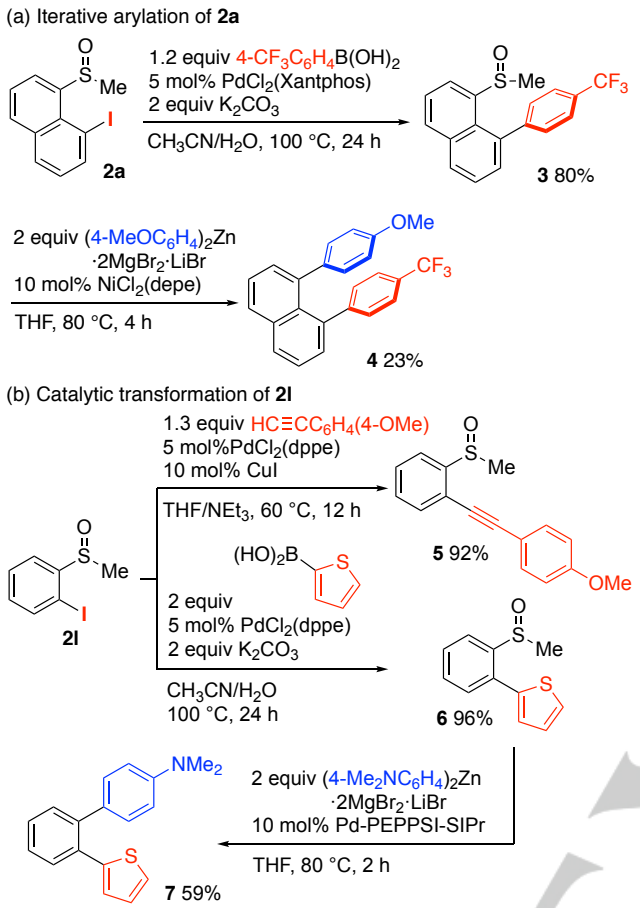
Instead of π-extended aryl sulfoxides, methyl phenyl sulfoxide (**1l**) underwent the iodination at the expense of the *ortho*-C–H bond (Scheme 2). Re-evaluation of the reaction conditions revealed that the use of 10 mol% of $Pd(OAc)_2$ under DCE/HFIP (1,1,1,3,3,3-hexafluoro-2-propanol) co-solvent system was found to be optimal for the *ortho*-iodination (See Table S1 for optimization studies).[15,16] In this case, the employment of an excess amount (2.0 equiv) of aryl sulfoxide was effective; a 63% yield (based on the molar amount of NIS) of iodination product **2l** was obtained. Similarly, the iodination proceeded with methyl 4-methylphenyl sulfoxide to afford **2m** in 76% yield. An electron-deficient chloro group slightly retarded the reaction; **2n** was obtained in 44% yield. The iodination of 3-methyl- and methoxyphenyl sulfoxides **1o** and **1p** occurred preferentially at the sterically less hindered 6 position whereas the regioselectivities were not high (**2o**:**2o'** = 5:1 and **2p**:**2p'** = 6:1). In a similar fashion, the reaction of methyl 2-naphthyl sulfoxide gave 3-iodinated product **2q** in 38% yield as the major product. Notably, in the *ortho*-C–H iodination reactions, no 2,6-diiodination product was observed.



Scheme 2. Scope of *ortho*-C–H Iodination.

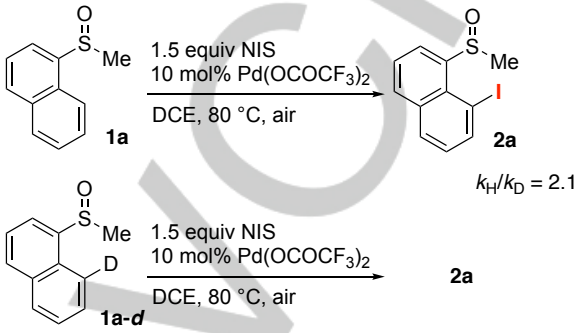
The iodo moieties installed onto the products were convertible to other carbon substituents via catalytic cross-coupling reactions. In the presence of 5 mol% of $PdCl_2$(Xantphos), arylation with 4-(trifluoromethyl)phenylboronic acid afforded 8-aryl-1-naphthyl sulfoxide **3** (Scheme 3a). The C(aryl)–S bond of **3** was then converted via nickel-catalyzed Negishi-type arylation.[17] Although the yield is not satisfactory, 1,8-diarylnaphthalene **4** that shows nonlinear optical property[18] could be synthesized. 2-Iodophenyl sulfoxide **2l** also participated in palladium-catalyzed Sonogashira alkynylation and Suzuki-Miyaura thienylation to provide **5** and **6** in high yields (Scheme 3b). The thienylation product **6** was further

transformed to teraryl **7** in good yield via palladium–NHC-catalyzed arylation with arylzinc reagent.[17]



Scheme 3. Further Transformations of Iodination Products **2**.

To gain insight into the reaction mechanism, particularly for the C–H-cleaving step, we measured kinetic isotope effects (KIE) of the present iodination. The initial reaction rates of the iodinations of **1a** and **1a-*d*** (k_H and k_D) were independently measured. As shown in Scheme 4, the k_H/k_D value of 2.1 was observed (See Figure S1 in the Supporting Information for details). We also conducted the reaction in the presence of acetic acid-d_4, and no deuterium incorporation into the recovered substrate was observed. These results are consistent that the C–H-cleaving step is the turnover limiting step of the present iodination.



Scheme 4. Measurement of KIE with **1a** and **1a-*d***.

To further investigate the C–H-cleaving step and to reveal the roles of the sulfinyl group in this iodination reaction, we explored reaction pathways of the C–H palladation of naphthyl sulfoxide **1a** by employing artificial force induced reaction method (AFIR) in GRRM17 program[19,20] associated with Gaussian16 program.[21] In these calculations,[22] $Pd(OAc)_2$ was employed as a palladium catalyst to reduce calculation costs, which was comparable to $Pd(OCOCF_3)_2$ for the present iodination reaction (See Table 1). Since sulfoxide **1a** has a chiral center, all reaction "modes" based on their coordinating atoms (*vide infra*) should have two diastereomeric reaction "pathways" respectively. The favorable pathway for each reaction mode is shown in Figure 1. All reaction pathways we obtained are described in Supporting Information.

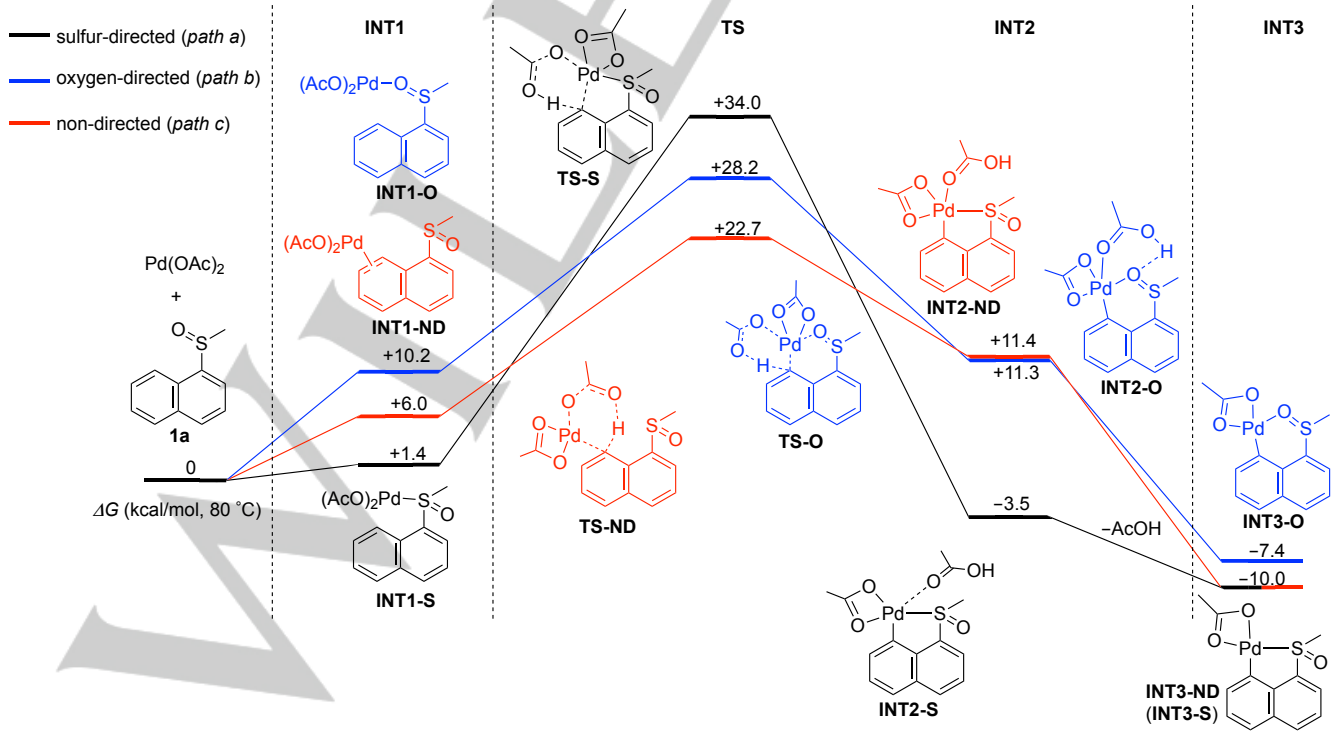
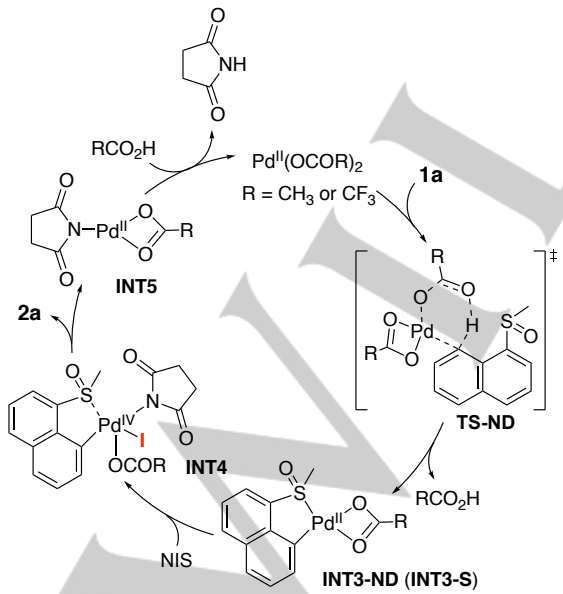


Figure 1. Energy Profile of the *peri*-C–H Palladation of **1a**.

In general, sulfinyl-directed C–H metalation has been considered to proceed via an intermediate wherein the sulfur atom of the sulfinyl group coordinates to a metal catalyst.[23] Indeed, we found a reaction mode via transition state **TS-S** in which the sulfur atom coordinates to the palladium. However, the activation barrier was estimated to be 34.0 kcal mol^{-1} (Figure 1, *path a*), which is too high to allow the reaction to proceed at 80 °C. Instead, an oxygen-coordinating pathway (Figure 1, *path b*) can be considered.[24] However, the pathway in this mode also suffers from high activation energy at **TS-O** (28.2 kcal mol^{-1}).

Interestingly, we also found another reaction mode via an η^2-π-complex without coordination of the sulfinyl unit (Figure 1, *path c*). Moreover, this mode was found to undergo C–H palladation via **TS-ND** with the lowest activation barrier of 22.7 kcal mol^{-1}. Although there is no interaction between the sulfinyl unit and the palladium center before **TS-ND**, the palladium becomes coordinated after **TS-ND** to afford **INT2-ND**. The eventual liberation of AcOH provides naphthylpalladium **INT3-ND** which is identical to **INT3-S** in *path a*. Naphthylpalladium **INT3-ND** (**INT3-S**) thus generated would be stabilized by coordination of the sulfinyl unit. Other conceivable naphthylpalladium species such as an C7-palladation intermediate do not have the stabilization effect and would be thermodynamically unfavorable compared to **INT3-ND**. This thermodynamic stabilization effect would invoke the C8-selective palladation.

A plausible overall reaction mechanism elucidated by our mechanistic investigations and the literature[2g,12d–h] is shown in Scheme 5. Naphthylpalladium **INT3-ND** (**INT3-S**) would be generated through **TS-ND**. Subsequent oxidative addition of NIS would generate Pd(IV) intermediate **INT4**, which undergoes C–I-forming reductive elimination to afford **2a**. Finally, liberation of succinimide from **INT5** via protonation with RCO_2H would regenerate palladium carboxylate. As another possibility of a mechanism for the C–I bond formation, a direct electrophilic attack of NIS on the C8-position of **INT3-ND** (**INT3-S**) or its NIS complex without formation a Pd^{IV} species like **INT4** could also be considered.[25]



Scheme 5. A Plausible Reaction Mechanism.

In conclusion, we have developed *peri*- or *ortho*-C–H iodination of aromatic compounds with the aid of sulfinyl directing groups. By means of the installed iodo and remaining sulfinyl groups, the iodination products were further transformed via coupling reactions. Computational studies revealed an interesting non-directed *peri*-C–H palladation pathway wherein neither of the sulfur nor oxygen atom of the sulfinyl group coordinates to the palladium before and at the transition state and the palladium becomes coordinated after the transition state.

Acknowledgements

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Keywords: C–H activation • iodination • palladium catalysis • computational study • AFIR method

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[13] The combined use of I_2 with $PhI(OAc)_2$ as an external oxidant did not afford the product **2a** despite full consumption of **1a**.

[14] Instead of NIS, the employment of NBS for C–H bromination resulted in the formation of a complex product mixture whereas **1a** was fully consumed. Electrophilic bromination of the naphthalene ring might occur without recourse to the catalyst.

[15] Hydrogen bonding between HFIP and the acetate ligands on the palladium might render the palladium center more cationic. This promotes binding of the weakly coordinating sulfinyl group to the palladium center, resulting in acceleration of the *ortho*-C–H iodination. See also Ref 10.

[16] The addition of HFIP for the *peri*-C–H iodination of **1a** slightly decreased the yield of **2a** down to 70%.

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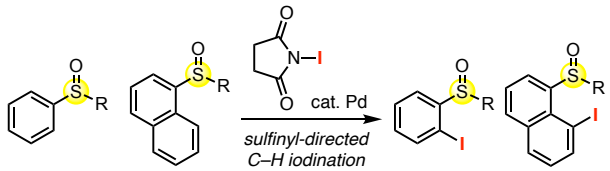

Pd-catalyzed C–H iodination of aromatic compounds has been accomplished with the aid of sulfinyl directing groups. The reaction proceeds selectively at the *peri*-position of polycyclic aryl sulfoxides or at the *ortho*-position of phenyl sulfoxides. Computational studies suggest that *peri*-C–H palladation would proceed via a non-directed pathway, wherein neither of the sulfur nor oxygen atom of the sulfinyl group coordinates to the palladium before and at the transition state.

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