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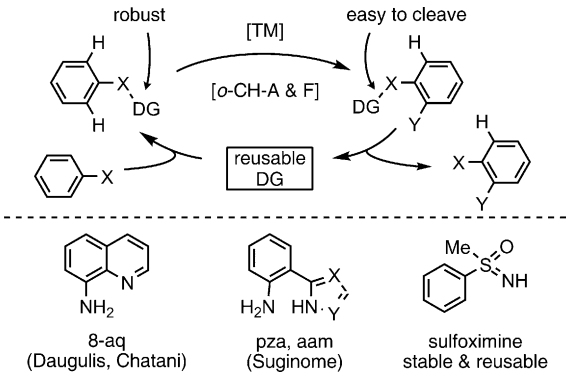
Sulfoximines: A Reusable Directing Group for Chemo- and Regioselective *ortho* C–H Oxidation of Arenes

M. Ramu Yadav, Raja K. Rit, and Akhila K. Sahoo*[a]

Dedicated to Professor Dr. Hans-Joachim Gais on the occasion of his 70th birthday

The directing-group-assisted, transition-metal-catalyzed C–H oxidation of arenes is recognized as an elegant and versatile approach for the synthesis of useful phenol derivatives.[1,2] The ability of the directing group (DG) to coordinate the transition metal triggers the activation of the remote C–H bond and facilitates the formation of the product with better regioselectivity.[3] The Sanford and Yu groups have explored the regioselectivity and the mechanism involved in the DG-assisted C–H oxidation of arenes.[4,5] Subsequently, a variety of DGs for *ortho* C–H oxidations have been extensively investigated.[6] In spite of these significant advances, the use of nonremovable and nonmodifiable DGs and the lack of generality limit the broad synthetic application of this transformation. In addition, highly chemoselective functionalization in the presence of a variety of C–H bonds remains elusive.[7] The incorporation of easily removable and robust DGs can overcome some of these limitations.[8] So far, the attachable and detachable directing groups 8-aq (8-amino quinoline),[9a,b] pza (2-pyrazole-5-ylaniline),[9c] and aam (anthranilamide)[9d] have been used in the C–H functionalization of arenes (Scheme 1). Recently, the easily modifiable DGs sulfur[10a] and Si-tethered pyridyl derivatives[10b,c,d] have been employed for the efficient C–H oxidation of arenes.

Inspired by the previous results and the concerns pertaining to this transformation, we envisioned the use of sulfoximines[11] as an easily attachable and detachable new DG for C–H functionalizations. A direct and elegant approach for the *ortho* hydroxylation of benzoic acid in the presence of O_2 has been demonstrated by Yu.[5b] The C(sp^2)–H acetoxylation of anilides, deriving from the corresponding anilines, has been performed with palladium catalysis.[1d] With the aid of bidentate systems, *ortho* acetoxylations of amides have been achieved under harsh reaction conditions.[1f] Herein, we report the initial results on the chemo- and regioselective

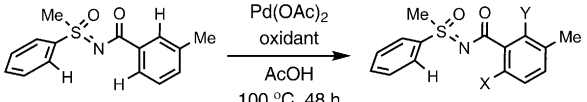


Scheme 1. Reusable directing groups in *ortho* C–H functionalizations. [*o*-CH-A & F] = *ortho* C–H activation and functionalization.

ortho C–H acetoxylation of *N*-benzoylated methylphenylsulfoximines; this directing group is easily detached from the C–H oxidation product and can be reused.

To test this hypothesis, compound **2a** was subjected to the known reaction conditions [$Pd(OAc)_2$ (10 mol%) and $PhI(OAc)_2$ in AcOH] at 100 °C for 48 h (Table 1, entry 1).[1b,4a] Interestingly, formation of the *ortho*-acetoxylation products

Table 1. Optimization of the reaction conditions.[a]



2a

X = OAc, Y = H; **3a**
X, Y = OAc; **4a**

Entry	Catalyst (10 mol%)	Oxidant	Cosolvent	Yield [%][b] (**3a**/**4a**/[c])
1	$Pd(OAc)_2$	$PhI(OAc)_2$	–	57 (10:1:3)
2	$Pd(OAc)_2$	Oxone	–	19 (**3a**)
3	$Pd(OAc)_2$	$K_2S_2O_8$	–	70 (1:1:8)
4	$Pd(OAc)_2$	TBHP	–	0
5	$Pd(OAc)_2$	$K_2S_2O_8$	DCE	90 (13:1:1)
6	**$Pd(OAc)_2$**	**$K_2S_2O_8$**	**$CHCl_3$**	**95 (14:1:1)**[d]
7	$Pd(OAc)_2$	$K_2S_2O_8$	Ac_2O	57 (18:1:2)
8	$Pd(OAc)_2$	$K_2S_2O_8$	toluene	78 (20:1:4)
9	$PdCl_2$	$K_2S_2O_8$	$CHCl_3$	90 (4:1:2)
10	$Pd(TFA)_2$	$K_2S_2O_8$	$CHCl_3$	91 (2:1:0.6)

[a] Reaction conditions: **2a** (50 mg, 0.18 mmol), oxidant (0.36 mmol), and AcOH/cosolvent (1:1, 1.0 mL). [b] Conversion based on crude ^1H NMR spectroscopy. [c] Mono-deacylated product. [d] AcOH/$CHCl_3$ (2:3, 1.5 mL) was used. TBHP = *tert*-butyl hydroperoxide.

[a] M. R. Yadav, R. K. Rit, Prof. Dr. A. K. Sahoo
School of Chemistry, University of Hyderabad
Hyderabad-500046 (India)
Fax: (+91) 40-23134822
E-mail: akssc@uohyd.ernet.in

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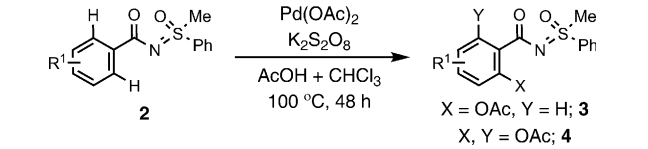
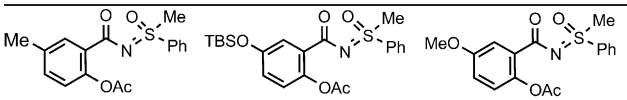
3a and **4a**, along with a small amount of the mono-deacylated compound, was observed in 57% yield by NMR spectroscopy. It is highly intriguing that the *ortho* C–H bonds of the *N*-benzoylated aryl ring have been exclusively functionalized among the two different arenes of compound **2a**. Even though the *ortho* hydrogen atoms of both aromatic rings are present at the same proximity to the metal-coordinating nitrogen atom, the factors responsible for this chemoselective $C(sp^2)$–H oxidation are unclear. The acidic sp^3 S-methyl-hydrogen atom did not participate in the oxidation reaction. No traces of the monoacetoxylation product from selective replacement of the more-hindered *ortho* C–H bond were detected in the crude NMR spectrum. These results clearly demonstrate the chemo- and regioselective C–H oxidation of arenes. From various oxidants screened (entries 2–4), $K_2S_2O_8$ turned out to be superior (entry 3), forming the analogues phenol as major product, whereas benzoquinone, $Cu(OAc)_2$, and H_2O_2 were completely ineffective.[12] To reduce the formation of deacylated product, various combinations of solvents with AcOH were tested. Chlorinated solvents appeared effective (entries 5 and 6) and chloroform was found to be the best cosolvent (entry 6). Among the amounts of solvent screened, a 2:3 mixture of AcOH:$CHCl_3$ (1.5 mL for 0.2 mmol of substrate) resulted optimum (entry 6). The exploration of other solvents, such as Ac_2O and toluene, produced moderate amounts of **3a** (entries 7 and 8), whereas DMF and DMSO gave **3a** in poor yield.[12] Other Pd catalysts were found to be similarly efficient (entries 9 and 10). As expected, no product was detected in the absence of either the Pd catalyst or the oxidant. Gratifyingly, the presence of air/moisture did not affect the reaction efficiency.

To probe the effect of the (*S*)-methyl-(*S*)-phenylsulfoximine (MPS) directing group on the chemo- and regioselective *ortho* C–H acetoxylation of arenes, the optimized reaction conditions (Table 1, entry 6) were surveyed to various *N*-benzoylated MPSs (Table 2). At first, the regioselective *ortho* acetoxylation of *meta*-substituted *N*-benozylated sulfoximines was investigated. The reaction of *N*-(*meta*-methylbenzoyl)-MPS (**2a**) gave **3a** as a single regioisomer in 65% yield; the *ortho*-diacetoxylated product **4a** and the mono-deacylated product were also isolated in small amounts. We believe that the compound **4a** is obtained from **3a**. To verify this observation, **3a** was subjected to the optimized conditions and **4a** was isolated, albeit in poor yield. Interestingly, the TBS (*tert*-butyldimethylsilyl) group was tolerated under these reaction conditions and the product **3b** was obtained in 47% yield. A *meta*-methoxy group did not exhibit the secondary directing effect and produced **3c** exclusively;[4c] the bulky methoxy group inhibits the formation of diacetoxylated product **4c**. However, a poor level of regioselectivity was observed in the case of *N*-(*meta*-fluorobenzoyl)-MPS (**3d**).[4c] Unfortunately, the bromo-substituted **3e** was obtained in poor yield, even though the reaction was run for 96 h; the precursor **2e** was recovered in 42% yield. The corresponding debromination product was observed in negligible amounts (<5%) by crude NMR spectroscopy. The reaction of β-naphthyl derivative **2f** under the catalytic conditions gave **3f** and **4f** in 56 and 15% yield, respectively. These results suggest that the selectivity is governed by the steric, as well as the electronic effect of the *meta* substituent.[4c] The electronically neutral compound **2g** and the *para*-substituted *N*-benzoylated MPSs **2h–k** gave the desired mono- and diacetoxylated products in moderate to good overall yields. However, the reaction of *N*-[*para*-chlorobenzoyl]-MPS (**2j**) gave the mono-deacylated compound as a major product. The halogen substituents in **3e** and **3j′** can be amenable to further synthetic transformations. Acetoxylation products **3l–m** were isolated in excellent yields from electron-rich *ortho*-substituted *N*-benzoylated MPSs **2l–m**.[1f,5b] Similarly, the less-hindered *ortho* C–H bond was replaced with an acetoxy group in **3n**. Gratifyingly, a moderate yield of the diacetoxylated product **4g** was isolated from the reaction of **3g**. This reaction cleanly delivers two new molecules of mono- and diacetoxylated products. In case of moderate yields of products, the mass-balance can be justified with the recovery of the precursors.

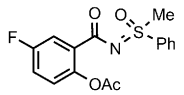
Table 2. *ortho* Acetoxylation of *N*-benzoylated sulfoximines.[a,b]

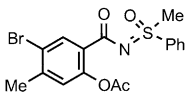


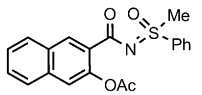

3a, 65%; **4a**, 13%; 4%[c]; 5%[d]

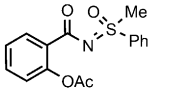
3b, 47%

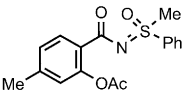
3c, 53%;[e] 20%[d]

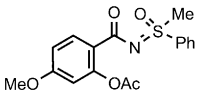

3d, 48% (3:1);[f] 5%[d]

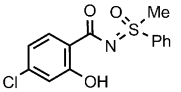

3e, 27%;[g] 42%[d]

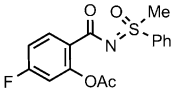

3f, 56%; **4f**, 15%; 9%[d]

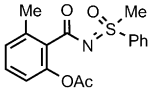

3g, 54%; **4g**, 12%; 30%[d]

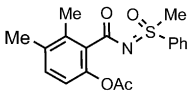

3h, 57%; **4h**, 32%; 10%[d]

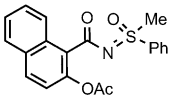

3i, 43%; **4i**, 31%; 8%;[c] 10%[d]

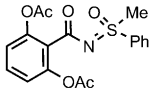

3j′, 40%;[c] 25%[d]


3k, 45%; **4k**, 8%; 42%[d]


3l, 95%


3m, 83%

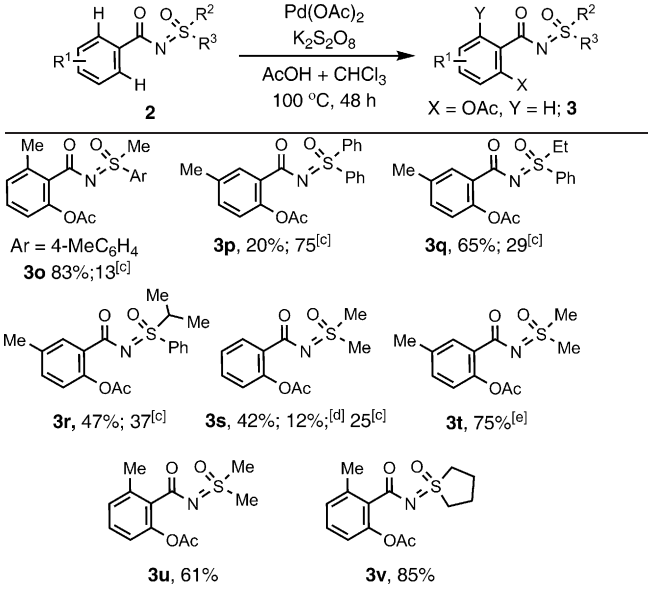

3n, 65%; 25%[d]


4g, 43%;[h] 42%[d]

[a] Reaction conditions: **2** (1.0 mmol), $Pd(OAc)_2$ (10 mol%), $K_2S_2O_8$ (2.0 mmol), and AcOH/$CHCl_3$ (3:5, 8.0 mL). [b] Isolated yields. [c] Formation of mono-deacetylated product. [d] Starting material recovered. [e] 72 h. [f] Regioisomeric mixture. [g] **2e** (0.57 mmol) at 120 °C for 96 h. [h] 96 h.

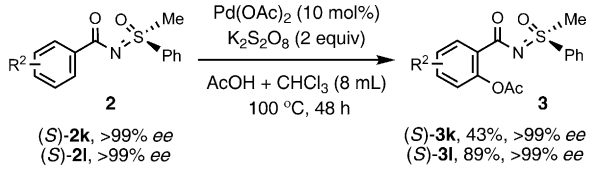
We next investigated the steric and electronic effects of sulfoximine derivatives on the *ortho* acetoxylation of arenes (Table 3). The electron-rich (*S*)-methyl-(*S*)-(4-methylphenyl)sulfoximine imparts slightly lower efficiency, resulting in **3o** in 83% yield compared to **3l** (95% yield, Table 2). Poor reactivity was noticed in the case of (*S,S*)-diphenyl-substituted sulfoximine **2p**. The bulkiness on the sulfur atom retards the reaction efficiency: the (*S*)-ethyl-substituted sulfoximine **2q** shows identical reactivity in comparison to **3a** and delivered **3q** in 65% yield, whereas the (*S*)-isopropyl-substituted sulfoximine gave **3r** in poor yield. Moreover, a similar trend of selectivity and reactivity was observed for the *ortho*-acetoxylation products of *N*-benzoylated (*S,S*)-dimethylsulfoximines **3s–u** compared to **3g**, **3a**, and **3l**, respectively. The cyclic (*S,S*)-tetramethylenesulfoximine showed analogous reactivity with respect to the (*S*)-methyl-(*S*)-phenylsulfoximine and gave **3v** in 85% yield. Based on these experimental results, (*S*)-methyl-(*S*)-phenylsulfoximine is conceived as a potential directing group for the *ortho* acetoxylation of arenes.

Table 3. Steric and electronic effects of sulfoximine derivatives on the *ortho* acetoxylation of arenes.[a,b]



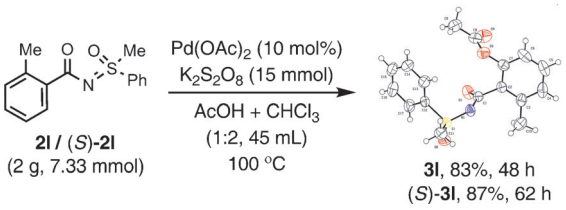
[a] Reaction conditions: **2** (1.0 mmol), $Pd(OAc)_2$ (10 mol%), $K_2S_2O_8$ (2.0 mmol), and $AcOH/CHCl_3$ (3:5, 8.0 mL). [b] Isolated yields. [c] Starting material recovered. [d] Formation of mono-deacetylated product. [e] **2v** (100 mg, 0.47 mmol) was used.

Sulfoximines serve as potential chiral ligands for asymmetric synthesis.[11d,13] Therefore, we examined the effect of catalytic conditions to the acetoxylation of chiral *N*-benzoylated sulfoximines. Gratifyingly, the acetoxylation of (*S*)-**2k** and (*S*)-**2l** gave (*S*)-**3k**[14] and (*S*)-**3l** with >99% *ee* in 43 and 89% yield, respectively (Scheme 2). This observation reveals that the stereointegrity of the sulfoximine moiety is preserved in this transformation. We believe that this strategy would create a wide array of new optically active sulfoximines bearing complex molecules in an efficient manner.[13]



Scheme 2. Acetoxylation of chiral *N*-benzoylated sulfoximines.

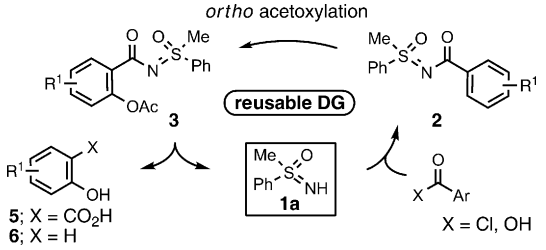
Finally, the robustness of this reaction was demonstrated through gram-scale *ortho* acetoxylations of arenes. Thus, the reactions of **2l** and (*S*)-**2l** were independently performed under the optimized catalytic conditions and the products **3l**[14] and (*S*)-**3l** were obtained in 83 and 87% yield, respectively [Eq. (1)].



(1)

To show the practical utility of this strategy, we examined the reusability of the directing group. Thus, hydrolysis of the *N*-benzoyl moiety of **3** was investigated (Table 4). Unfortunately, the *N*-benzoyl moiety of **3a** was not cleaved under base-induced hydrolysis.[15,16a] However, hydrolysis of **3a** with HCl (12 N) at 80°C was found successful and the desired 2-hydroxy-5-methyl benzoic acid (**5a**) was extracted in 79% yield (entry 1). Neutralization of the acidic mother liquor, followed by standard work-up, delivered the (*S*)-methyl-(*S*)-phenylsulfoximine (**1a**) in good yield. The reaction of crude **1a** afforded **2a** efficiently. Similarly, the corre-

Table 4. Reusability of the sulfoximine directing group.[a]

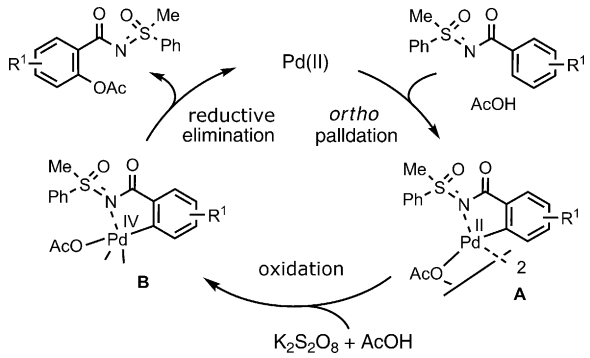


Entry	3	Yield of 5 [%][b]	Yield of 1a [%][c]	Yield of 2 [%][d]
1	**3a**	79	71	87
2	**3g**[e]	87	74	84
3	**3k**	75	61	73
4	**3m**	89[f]	73	68
5	(*S*)-**3l**	82[f]	85	92

[a] Reaction conditions: **3** (100 mg), HCl (12 N, 5.0 mL), 80°C, 48 h. [b] Extracted from the crude reaction mixture. [c] Isolated yields of **1a**. [d] Isolated yields of the corresponding product **2** from **1a**. [e] **3g** (1.0 mmol) was used. [f] Yield of the corresponding decarboxylated product **6**.

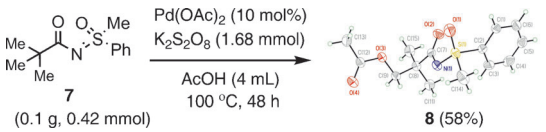
sponding *ortho*-hydroxybenzoic acids **5g** and **5k** were obtained from **3g** and **3k**, respectively, and **1a** was successfully recovered and reused (entries 2 and 3). Surprisingly, the *ortho*-substituted *ortho'*-acetoxylated compounds **3m** and (*S*)-**3l** underwent decarboxylation during hydrolysis and the corresponding 3,4-dimethylphenol (**6m**) and 3-methylphenol (**6l**) were isolated in 89 and 82% yield, respectively (entries 4 and 5). Following this method, the so far difficult *meta*-substituted phenols can be synthesized.[16b] Interestingly, the configuration of the chiral sulfoximine **1a** was retained in the acid-mediated hydrolysis of (*S*)-**3l**; (*S*)-**1a** was obtained in 85% yield with >99% *ee* (entry 5). Looking into the effective cleavability and reusability of the sulfoximine directing group, we hope that this strategy would be useful in fabricating complex phenol derivatives of pharmaceutical interest.

Based on the previous findings on Pd-catalyzed oxidative C–H functionalizations of arenes with $K_2S_2O_8$ as oxidant, the proposed catalytic cycle is likely to proceed involving a $Pd^{II/IV}$ species, as shown in Scheme 3. Interestingly, heteroatoms, such as S, S=O, C=O, and S=N, in *N*-benzoylated sulfoximines have the ability to coordinate the Pd species. Owing to the oxidation state of the S atom (+VI) and the polarization of the S=O bond in sulfoximines, the coordination of S to Pd^{II} can be excluded. Similarly, the chelation of the O atom of the polarized S=O bond is also believed unlikely, because it involves a seven-membered transition state. The spectroscopic and theoretical studies revealed that the conjugate delocalization of the nitrogen lone pair is prohibited, owing to its orthogonal orientation to the N–C(O) bond.[17] Among the nitrogen and carbonyl-oxygen atom, we presume that the chelation of N to Pd^{II} is more susceptible due to the localized electron density.[18] However, the coordination of the carbonyl-oxygen atom cannot be completely ruled out. Thus, the first step in the catalytic cycle involves the chelation of N to Pd^{II}, followed by palladation of the *ortho* C–H bond of the arene to produce the crucial five-membered cyclopalladated intermediate **A**. Next, oxidation of the Pd^{II} species of **A** with $K_2S_2O_8$ in the presence of AcOH gives the Pd^{IV} species **B**.[19] Finally, reductive elimination of **B** generates the desired *ortho*-acetoxylated product and the active Pd^{II} species for the next catalytic cycle.



Scheme 3. Proposed catalytic cycle.

The direct oxidative functionalization of unactivated C-(sp^3)–H bonds remains challenging.[20] Having succeeded in the selective *ortho* C–H acetoxylation of arenes, we explored the present catalytic conditions for the C–H acetoxylation of a methyl group. To our surprise, the desired acetoxylation product **8**[14] was obtained from **7**, albeit in moderate yield [Eq. (2)].



(2)

In conclusion, we have shown that the use of sulfoximines as a directing group exemplifies a novel approach to the chemo- and regioselective *ortho* acetoxylation of arenes. Even though our initial results are not comparable with the approach reported by Yu for the C–H oxidation of aromatic carboxylic acids, we hope that the sulfoximine directing group would contribute to the development of new and useful C–H functionalizations. Notably, the stereointegrity of chiral sulfoximines is preserved. The facile attachment and detachment of the robust sulfoximine moiety makes it highly reusable. Realization of milder reaction conditions for sp^2 and sp^3 C–H functionalizations, unraveling of mechanistic details, generation of axial chirality through asymmetric C–H activation, and exploration of novel synthetic applications are being actively pursued in our laboratory.

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