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Modifiable Sulfur Tethers as Directing Groups for Aromatic C–H Acetoxylation Reactions

Heinrich Richter,[a] Stephan Beckendorf,[a] and Olga García Mancheño[a,*]

[a] Organisch-Chemisches Institut, Universität Münster, Corrensstrasse 40, 48149 Münster, Germany
Fax: (+49)-251-83-33202; phone: (+49)-251-83-33239; e-mail: olga.garcia@uni-muenster.de

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Abstract: A designed new class of modifiable sulfur tethers for aromatic C–H bond functionalizations is presented. As a model, the palladium-catalyzed directed acetoxylation reaction was studied. The more challenging sulfoxide tethers were the most effective in this transformation, showing a broad functionality tolerance, high S oxido-redox stability and no catalyst poisoning. Preliminary mechanistic studies indicate that the higher reactivity and selectivity shown by the sulfoxide tethers *vs.* the corresponding sulfones can be attributed to an extra coordination of the sulfoxide S atom to the catalyst. The utility of the presented methodology to generate structurally interesting aromatic derivatives by a subsequent modification of the S-tether is also exemplified.

Keywords: acetoxylation; arenes; C–H activation; sulfur; synthetic methods

In the past few years, the development of metal-catalyzed *ortho*-directed C–H bond functionalizations of arenes[1] has experienced particular attention towards more atom efficient transformations. Although great advances in this area have been made, there are still some intrinsic limitations in this approach: i) the structural scope of the substrate due to the presence of the directing group at the end of the transformation, and ii) the nature of the employed directing groups [mainly restricted to Ar–C_{group} (e.g., N-containing heterocycles, carboxylic acids, acyl groups, oxime ethers, etc) and Ar–N_{group} (e.g., anilines, anilides, diazoarenes, etc.)[1] or more recently Ar–O_{group} (e.g., phenol esters, phenoxypyridines)].[2]

To overcome the first issue a small number of examples of removable and modifiable Si-, B- and N-based directing groups have been recently reported,[3,4] however, the identification of new detachabale and/or modifiable directing agents would be very valuable for further synthetic applications. On the other hand, the introduction of S-containing directing groups is very desirable due to the importance of sulfur derivatives in nature (e.g., cysteine-cystine couple, etc.), organic synthesis (e.g., aryl thiols as key building blocks in the synthesis of sulfur-containing bioactive compounds and natural products) and catalysis (e.g., for the synthesis of useful sulfur-containing ligands).[5] Considering the well-known *ortho*-directing properties of several S-containing groups such as sulfones or sulfoxides (Figure 1),[6,7] it is surprising that the directing ability of these groups in C–H bond functionalizations has hardly been exploited.[8] However, there is a need for developing fancy technology since some important issues such as the poisoning of the transition metal (TM) catalysts by strong coordination[9] (e.g., thiols, sulfides and sulfoxides) and undesirable oxido-redox processes have to be tackled. Herein we report the use of 2-pyridyl sulfur tethers as a new class of modifiable *ortho*-directing groups for the acetoxylation reaction of arenes.

We based our design of the new modifiable/removable directing groups on the use of S-tethers with a further heterocyclic coordinating group Y (Figure 1). After the C–H bond functionalization reaction, the C–S bonds would be easier cleaved or further functionalized than the usual C–C or C–N bonds of previous standard directing groups. We also envisioned that a heterocyclic substitution such as electron-poor 2-pyridine and 2-quinoline or electron-rich 2-thiophene would bring additional advantages: i) it will guarantee a good coordination with the metal-catalyst facilitating the appropriate geometry for the C–H bond activation, and ii) it will make the method more versatile by allowing a later selective functionalization or cleavage of one of the C(sp^2)–S bonds *a* or *b* of the tether[6,10,11] to generate more valuable arene derivatives.

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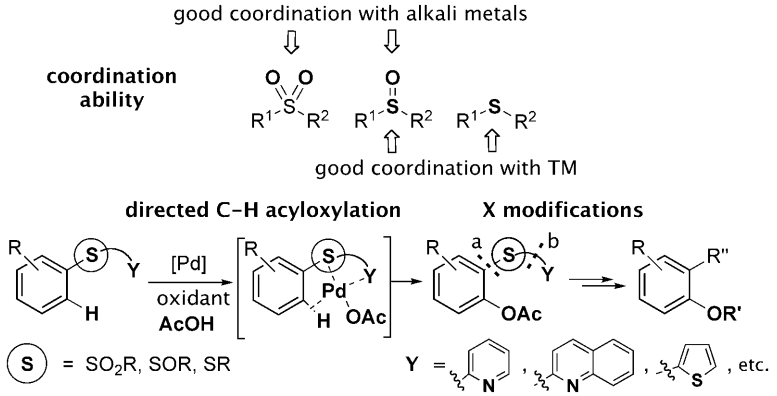
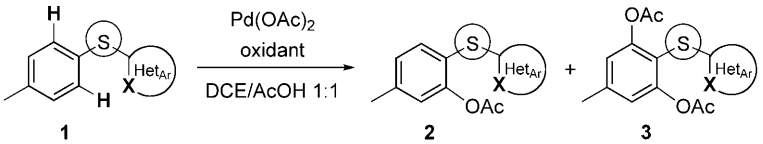


Figure 1. Coordination ability and design of modifiable sulfur tethers.

To prove our concept using S-tethers we selected the palladium-catalyzed directed acetoxylation of aromatic C–H bonds,[12] which has emerged as a powerful tool for the direct formation of structurally and synthetically important oxygenated arenes. Being aware of the possible poisoning of the transition metal catalysts by strong coordination to the S atom or their oxidation instability under the standard C–H activation reaction conditions, our initial studies were focused on the more robust sulfones (Table 1, entries 1–9). After screening a few oxidative systems such as PhI(OAc)$_2$, oxone or $K_2S_2O_8$ using 10 mol% Pd(OAc)$_2$ as catalyst, 2 equivalents of the oxidant and 2-pyridyl as coordinating group in DCE-AcOH at 100 °C,[13] we found that $K_2S_2O_8$ was the most suitable oxidant (entries 1–3). However, low mono-/diacetoxylation selec-

Table 1. Optimization of the acetoxylation reaction with S-tethers.[a]



Entry	S-Het$_{Ar}$, **1**	Pd (mol%)	Oxidant (equiv.)	T [°C]/t [h]	Yield of **2**/**3** [%][b]
1	SO_2-2-Py, **1a**	10	PhI(OAc)$_2$ (2)	100/24	30/–
2	SO_2-2-Py, **1a**	10	Oxone (2)	100/24	10/–
3	SO_2-2-Py, **1a**	10	$K_2S_2O_8$ (2)	100/16	29/42
4	SO_2-2-Py, **1a**	5	$K_2S_2O_8$ (1.2)	80/5	67/8
5	SO_2-2-Py, **1a**	5	$K_2S_2O_8$ (4)	80/18	–/71
6	SO_2-2-MePy, **1b**	5	$K_2S_2O_8$ (1.2)	80/16	66/14
7	SO_2-2-T, **1c**[c]	5	$K_2S_2O_8$ (1.2)	80/16	–[d]
8	SO_2-2-Q, **1d**[c]	5	$K_2S_2O_8$ (1.2)	80/16	–[e]
9	SO_2CH_2-2-Py, **1e**	5	$K_2S_2O_8$ (1.2)	80/16	–[e]
10	SO-2-Py, **1f**	5	$K_2S_2O_8$ (1.2)	80/12	56/–
11	SO-2-Py, **1f**	5	$K_2S_2O_8$ (2)	80/3	80/–
12	SO-2-Py, **1f**	2.5	$K_2S_2O_8$ (2)	80/18	55/–[f]
13	SO-2-Py, **1f**	5	$K_2S_2O_8$ (4)	80/18	48/22
14	SO-3-Py, **1g**	5	$K_2S_2O_8$ (2)	80/18	–[g]
15	S-2-Py, **1h**	5	$K_2S_2O_8$ (1.2)	80/3	(34)[h]
16	S-2-Py, **1h**	5	$K_2S_2O_8$ (2.5)	80/5	(27)/(14)[i]

[a] **1** (0.15 mmol), Pd(OAc)$_2$ and oxidant in 1:1 DCE:AcOH (1 mL).
[b] Isolated yield.
[c] T = 2-thiophene Q = 2-quinoline.
[d] Partial decomposition of **1** occurred (only 56% of **1c** was reisolated).
[e] Pyridine or quinoline *N*-oxide was formed.
[f] Traces of pyridine *N*-oxide were detected by MS analysis.
[g] **1g** was re-isolated in 91% yield.
[h] Yield of sulfoxide **1f** in brackets.
[i] **2f** and **3f** were obtained in 27% and 14% yield, respectively.

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tivity was observed (29% **2a** and 42% **3a**, entry 3). By reducing the amount of catalyst (5 mol%), oxidant (1.2 equiv.) and temperature (from 100 to 80 °C) a better selectivity in the formation of **2** was obtained (67% **2a** *vs.* 8% **3a**, entry 4). Different heterocyclic substituents at sulfur showed the superiority of the 2-pyridyl pattern to promote this transformation (entries 3–6).[1j] Thus, whereas 2-thiophene (T), 2-quinoline (Q) and 2-pyridylmethylene groups led to decomposition or the formation of the corresponding *N*-oxide, 2-pyridyl sulfoxide **1a** and its 3-methyl derivative **1b** provided the acetoxylated products **2** and **3** in good overall yields (80 and 75%, entries 4 and 6, respectively). On the other hand, the use of a larger excess of oxidant and longer reaction times provided exclusively the di-OAc product **3a** in 71% yield (entry 5).

Next, the reaction with the corresponding 2-pyridyl sulfoxide **1f** was investigated (Table 1, entries 10–13). We were pleased to observe that the less oxido-redox stable sulfoxide moiety was stable to these oxidative conditions and promoted the reaction in a more selective fashion. Thus, only monoacetoxylated product **2f** was formed in a moderate 56% yield. However, when 2 equivalents of the oxidant were employed, the desired product was selectively obtained in a good 80% isolated yield after 3 h reaction time (entry 11). The use of 2.5 mol% of catalyst showed a less effective transformation, leading to a moderate 55% yield after 18 h (entry 12). Additionally, the higher monoacetoxylation selectivity of sulfoxides *vs.* sulfones was also probed by conducting the reaction with 4 equivalents of the oxidant. Then, no full conversion into the di-OAc product **3f** was observed even after prolonged reaction times (entry 13). Considering a possible coordination of the S atom of sulfoxide **1f** with Pd and to be able to evaluate the involvement of the pyridyl group in this case, 3-pyridylsulfoxide **1g** was tested. Compound **1g** did not participate in the reaction, confirming the necessity of the 2-pyridine group to pre-coordinate and direct the Pd catalyst to promote this transformation.

Lastly, the reaction with sulfide **1h** was also conducted. Unfortunately, sulfide **1h** turned out not to be stable under these reaction conditions, leading mainly to decomposition along with small amounts of sulfoxide **1f** or sulfoxide-acetoxylation products **2f/3f** (entries 15 and 16).

Having identified the optimum reaction conditions: use of 2-pyridyl sulfoxides, $Pd(OAc)_2$ (5 mol%) and $K_2S_2O_8$ (2 equiv.) in a 1:1 mixture of DCE:AcOH at 80 °C, the generality of the reaction was studied (Table 2). Initially, phenyl and tolyl derivatives were examined. Substitution at *para*-, *meta*- and *ortho*-positions was tolerated, leading to the corresponding acetoxylation products in good yields (entries 1–4), even for the more sterically hindered *ortho*-tolyl substrate **1k** (69%, entry 4). Other electron-rich arenes (entries 5–10) with methoxy or phenyl groups and the 2-naphthyl derivative **1o** were successfully employed (yields ranging from 62 to 80%), with the exception of 2-methoxyphenyl **1n** which did not react under these conditions (entry 7, see discussion below). We observed that electron-rich arenes were easier acyloxylated than electron-deficient ones (entries 11–17). Although the 4-nitro derivative **1r** did not participate in the reaction (entry 11), halogenated substrates such as 4-chloro- **1s**, 4-fluoro- **1t** and 2-trifluoromethanephenyl sulfoxides **1u** were able to undergo the C–H bond activation/acetoxylation reaction in moderate to good yields (59, 66 and 77%, entries 11–13). Moreover, other arenes presenting groups such as an ester **1v**, an acetyl group **1w** and an alkyl sulfoxide **1x** were also acetoxylated (entries 14–16), showing the relatively broad functionality tolerance of the transformation.

Our initial mechanistic studies indicated that sulfoxides are not only more selective but also more reactive than the corresponding sulfones. Thus, a competitive experiment using equimolecular amounts of **1a** and **1f** in the presence of only 1.2 equivalents of oxidant revealed that the sulfoxide **1f** exclusively reacted, whereas sulfone **1a** was not altered [Scheme 1, Eq. (1)].

On the other hand and as shown in Table 2 (entry 7), arenes with coordinating groups in *ortho* positions such as OMe were not suitable substrates for aryl sulfoxides but were able to deliver the desired acyloxylation product with the less reactive sulfone derivatives [Scheme 1, Eq. (2)].[14] In addition, no reaction was observed when a mixture of equimolecular amounts of *ortho*-methoxy sulfoxide **1n** and sulfone **1y** were submitted to the Pd-catalyzed acetoxylation conditions [Scheme 1, Eq. (3)]. These observations could be explained by a chelation effect preventing the catalyst from undergoing the C–H bond activation reaction. Thus, in the case of the sulfone the coordination sphere of the S atom is saturated whereas in the sulfoxides the S can actively participate.[15] Moreover, this fact is in good accordance with the higher monoselectivity observed for the sulfoxide derivatives since the new acetyloxy group introduced in the *ortho* position can also contribute to chelation.

The present Pd-catalyzed acyloxylation reaction is believed to follow the typical C–H activation pathway as shown in Figure 2 (see Supporting Information for additional mechanistic experiments), in which after the reductive elimination to form the new C–O bond a chelation with the formed product might occur, hampering the second *ortho* C–H bond activation process (Figure 2, *above*). In addition, the k_H/k_D value (4.0) observed in the intramolecular kinetic isotope effect studies of the acyloxylation reaction of **1f-D**

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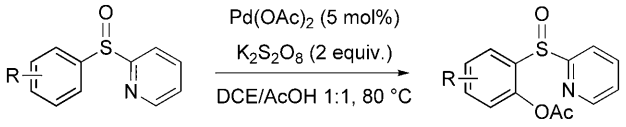
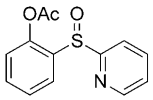
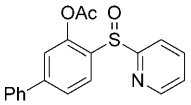
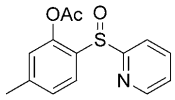
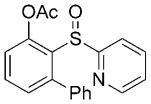
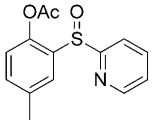
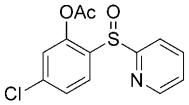
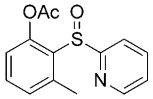
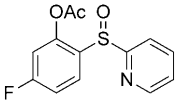
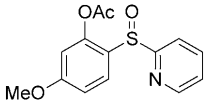
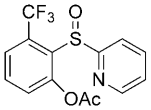
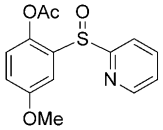
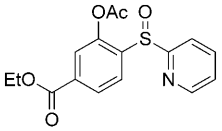
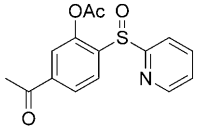
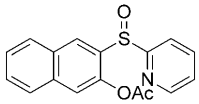
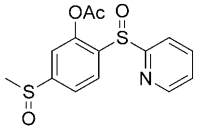
Table 2. Scope of the C–H activation/acetoxylation reaction.[a]



1 2

Entry	R	*t* [h]	Product	Yield of **2** [%][b]	Entry	R	*t* [h]	Product	Yield of **2** [%][b]
1	H	5		**2i**, 71	9	4-Ph	5		**2p**, 80
2	4-Me	3		**2f**, 80[c] (73)[d]	10	2-Ph	4		**2q**, 73
					11	4-NO_2	18	–	**2r**, –[f]
3	3-Me	4		**2j**, 75[c,e]	12	4-Cl	3		**2s**, 59[c,f]
4	2-Me	5		**2k**, 69	13	4-F	3		**2t**, 66[c,f]
5	4-MeO	3		**2l**, 73	14	2-CF_3	5		**2u**, 77[f]
6	3-MeO	2		**2m**, 62	15	4-CO_2Et	5		**2v**, 78[f]
7	2-MeO	18	–	**2n**, –[f]	16	4-Ac	6		**2w**, 45[c,h]
8	2-naphthyl	3		**2o**, 75[f,g]	17	4-SOMe	6		**2x**, 48[f,i]

[a] **1** (0.15 mmol), 5 mol% $Pd(OAc_2$ and $K_2S_2O_8$ (2 equiv.) in 1:1 DCE:AcOH at 80 °C.
[b] Isolated yield.
[c] Reaction on a 0.3 mmol scale.
[d] Reaction on a 1.5 mmol scale.
[e] Obtained as a 2:9 mixture of regioisomers.
[f] Use of 10 mol% $Pd(OAc)_2$.
[g] Obtained as a 1:6 mixture of regioisomers.
[h] The same result was obtained with both 5 and 10 mol% Pd.
[i] Obtained as a 1:1 mixture of diastereoisomers.

further supports the C–H activation mechanism (Figure 2, **below**).[16]

After developing the directed C–H acyloxylation reaction, we explored further transformations of the S-tether with the model product **2f** (Scheme 2). Firstly, the cleavage of the S-tether was achieved under reductive conditions using Raney Ni in alkali media, affording the corresponding phenol **4a** in 73% yield (Scheme 2, *top left*). Furthermore, the reaction of **2f** with Grignard reagents led predominately to the self-coupling product **5**.[17] Taking advance on the higher activation towards organometallic insertion of the

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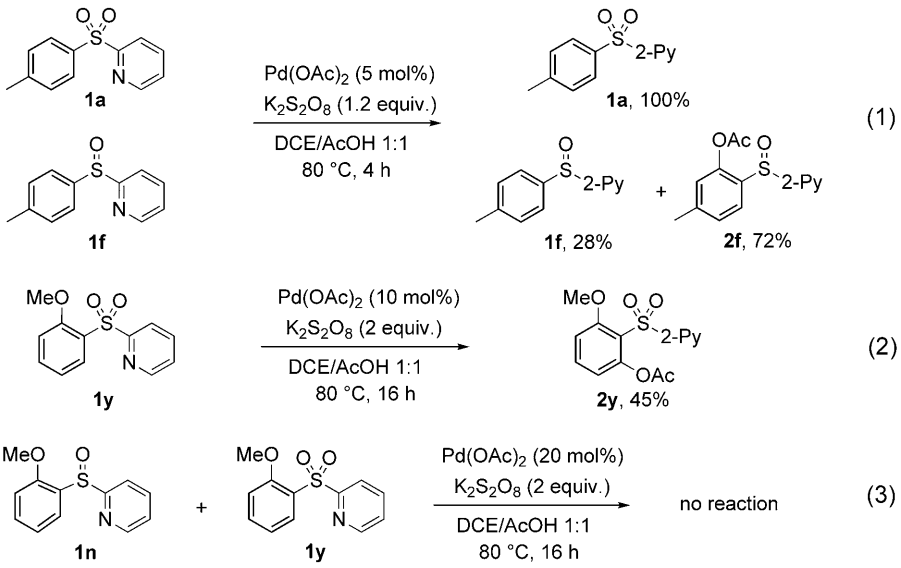

Scheme 1. Competition experiments of sulfone *vs.* sulfoxide.

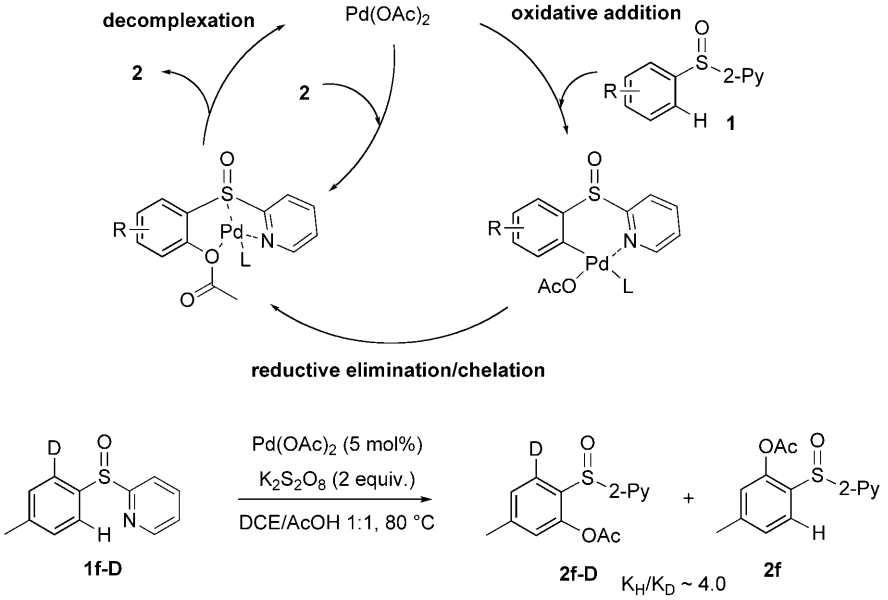

Figure 2. Proposed mechanism and kinetic isotope effect study.

more electron deficient character of the $C_{Py}(sp^2)$–S bond *vs.* $C_{Ar}(sp^2)$–S bond, the transformation of **2** into the corresponding thiols was next studied. As a result, thiols **6** could be selectively obtained after treatment of **2** with activated Zn[18] in AcOH at 80 °C followed by deacetylation with HCl in methanol (Scheme 2, *top right*). Although the crude reaction mixture showed the formation of relatively pure mercapto-phenols **6**, they underwent rapid oxidation to the corresponding disulfides during chromatographic purification, providing **7** in moderate to good yields (52–84%). It was also possible to carry out the acetoxylation/reduction of **2f** in a one-pot reaction sequence, however, the yield dropped down significantly from 84% to 48%. Additionally, diacetylated sulfone **3a** was transformed into an aryl 1,3-diol, motif which is present in a large number of natural and bioactive compounds, by reductive cleavage with Raney Ni (81%, Scheme 2, *left bottom*). Moreover, sulfone **3a** also reacted under our standard thiol-disulfide formation conditions (Zn, AcOH, 80 °C), allowing access to the corresponding 2,6-diphenolic disulfide **8** in a good 65% yield (Scheme 2, *right bottom*).

In conclusion, a new class of modifiable S-tethers has been designed for aromatic C–H functionalization reactions. The model Pd-catalyzed directed acetoxylation reaction was efficiently achieved for a variety of arenes with 2-pyridyl sulfone and sulfoxide tethers.

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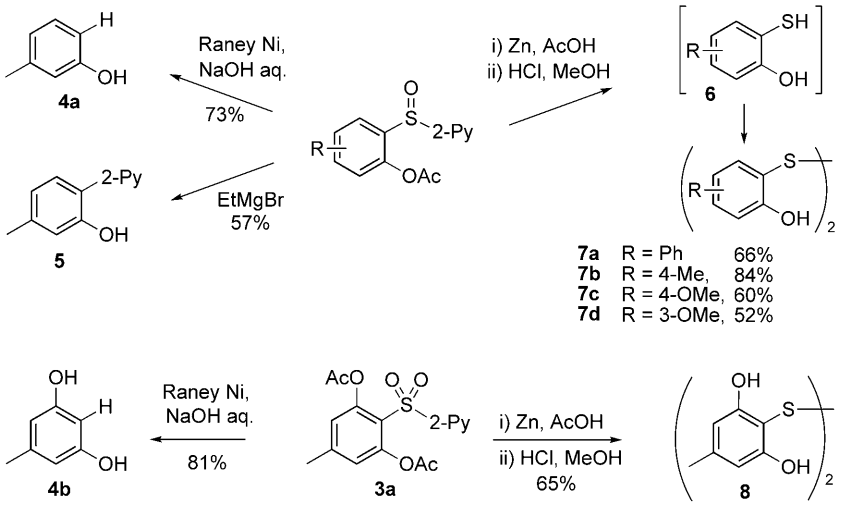

Scheme 2. Further transformations of the S-tether.

The less redox stable sulfoxide tethers proved to be the best choice for this transformation, showing high monoacetoxylation selectivity, functionality tolerance, oxido-redox stability and no catalyst poisoning. The activation of the C(sp^2)–S bond by the 2-pyridyl group attached to the S-tether was used for further modifications to generate structurally interesting phenolic derivatives such as thiols and disulfides. Preliminary mechanistic studies indicate that the higher and more selective reactivity shown by the sulfoxides *vs.* the corresponding sulfones can be explained by a participation in the coordination of the S atom to the metal. Further studies towards the development of iterative functionalizations using this observed differential reactivity are currently ongoing in our laboratory.

Experimental Section

General Procedure for the Acetoxylation Reaction

Sulfoxide or sulfone **1** (1 equiv.), $Pd(OAc)_2$ (5–10 mol%) and $K_2S_2O_8$ (2.0 equiv. for sulfoxides/1.2 equiv. for sulfones) were mixed together in a pressure Schlenk tube. The tube was evacuated and backfilled with argon three times, then a 1:1 mixture of DCE and AcOH (0.15 M) was added. The reaction mixture was stirred at 80 °C and monitored by TLC (pentane/EtOAc = 1:1). After full conversion the crude reaction mixture was purified by chromatography on silica gel eluting with pentane/EtOAc (2:1) to afford the desired compounds **2** and/or **3**.

General Procedure for the Reductive Cleavage with Raney Ni

To a pressure tube containing **2** or **3** (0.2 mmol) and Raney Ni (100 mg), 3 mL NaOH (4 M) were slowly added at room temperature (exothermic reaction!). The reaction mixture was then heated at 50 °C until consumption of the starting material. The mixture was neutralized with HCl (1 M) and filtered. The filtrate was extracted with DCM (2×) and AcOEt (2×), the solvent evaporated under reduced pressure and the crude mixture was purified by chromatography on silica gel to afford the desired compound **4**.

General Procedure for the Synthesis of Thiols and Disulfides

Sulfoxide or sulfone **2** (1 equiv.) and activated Zn (15–20 equiv.) were placed in a pressure Schlenk tube. AcOH (0.15 M) was added and the reaction mixture was stirred at 80 °C. After full conversion (monitored by TLC) the crude reaction mixture was filtered, washed with EtOAc and the solvent was evaporated. The residue was dissolved in MeOH (0.1 M), concentrated HCl (0.5–1.0 mL) was added and the mixture was stirred at room temperature until full conversion. The mixture was neutralized with NaOH (1 M) and the aqueous phase was extracted with DCM to give aryl thiols **6**. After purification by chromatography on silica gel, the corresponding disulfides **7** were obtained.

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$Cu(OAc)_2$ in combination with $PhI(OAc)_2$] provided only traces of the desired acetyloxilated products.
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