In recent years, the transition metal-catalyzed C–H bond functionalization of arenes has been widely investigated as a powerful tool for the synthesis of pharmaceuticals, bioactive molecules, and functional materials. In particular, the construction of C–O bonds from C–H activation has attracted much attention due to the significant importance of this class of molecules in both academic research and industry. However, many of these transformations suffer from poor reactivity and regioselectivity. To overcome the uncontrolled site selectivity, a number of examples of C–O bond forming reactions have been reported in recent years through the introduction of a directing group. In 2004, Sanford and co-workers described a regio- and chemoselective Pd-catalyzed acetoxylation of C(sp²)–H bonds using pyridine or other N-containing heteroarenes as directing groups. A copper-catalyzed ortho-acetoxylation of aryl C–H bonds was developed by Yu and co-workers using dioxygen gas as the terminal oxidant. Since these pioneering reports, various directing groups, such as oximes, sulfoximines, pyrimidines, anilides, amides and organophosphates, have been successfully employed as the directing groups for the selective C(sp²)–H acetoxylation using Pd, Rh or Cu catalysts. In recent years, the more challenging oxygenation of C(sp³)–H bonds has been achieved employing various N-based directing groups by several research groups. A majority of these successful acetoxylation reactions were performed in acetic anhydride with 1,2-dichloroethane as a solvent. The palladium-catalyzed acetoxylation of aromatic C(sp²)–H bonds utilizing thioether as the directing group was developed. Both benzyl sulfides and phenethyl sulfides could react with PhI(OAc)₂ to afford the site-selectively acetoxylated products in good yields. The directing groups could be further transformed into synthetically useful functional groups or successfully removed.

Thioether-directed acetoxylation of C(sp²)–H bonds of arenes by palladium catalysis†

Binjie Wang, Cong Lin, Yue Liu, Zili Fan, Zhanxiang Liu and Yuhong Zhang

The palladium-catalyzed acetoxylation of aromatic C(sp²)–H bonds utilizing thioether as the directing group was developed. Both benzyl sulfides and phenethyl sulfides could react with PhI(OAc)₂ to afford the site-selectively acetoxylated products in good yields. The directing groups could be further transformed into synthetically useful functional groups or successfully removed.

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the product in 63% yield (entry 10). Further investigation into other additives such as LiOAc, AgOAc, LiF, and K2CO3 demonstrated that the best isolated yield was achieved when 1.0 equiv. of AgOAc was used as an additive (entries 11–14). Thus the optimal reaction condition was 10 mol% of Pd(OAc)2 with 1.5 equiv. of PhI(OAc)2 as the oxidant, AgOAc as the additive, and Ac2O/DCE (1:1) as the solvent at 110 °C.

With the optimized reaction conditions in hand, we examined the reactivity of various substrates of benzyl(p-tolyl)sulfane in Scheme 1. Replacement of p-tolyl thioether with 4-methoxyphenyl thioether led to a decreased yield and the benzyl(methyl)sulfane failed to react, which indicated that the electronic nature of sulfur played an important role during the C–H activation (Scheme 1, 2a–2b). Different substituents in an aryl ring played an important role on the efficiency of the acetoxylation reaction. For example, arenes with a methyl group at the ortho, meta and para positions afforded the product in good yields (Scheme 1, 2c–2e). The electron-donating group such as methoxyl could afford the corresponding product in 81% yield (Scheme 1, 2f). Substrates bearing halides on the arene such as bromo, chloro, and fluoro gave the desired products in moderate yields (Scheme 1, 2g–2i), which were consistent with an electrophilic palladation process. It should be noted that a wide range of functional groups such as CF3, OCF3, CN and COOMe were compatible with this protocol, showing a relatively broad functionality tolerance to the transformation (Scheme 1, 2j–2m).

Encouraged by the efficient acetoxylation reaction via a five-membered palladacycle, we further examined the substrates with a longer length tether between the sulfur and arene in Scheme 2. The phenethyl sulfides were found to be stable under these oxidative conditions and promoted the reaction in a selective fashion (Scheme 2, 2a–2i). The presence of electron-donating substituents on the aromatic ring has a positive effect on the reaction, leading to the corresponding acetoxylation products in good yields (Scheme 2, 2b–2d).

### Table 1 Optimization of the reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Oxidant</th>
<th>Additive</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)2</td>
<td>DCE/Ac2O (1:1)</td>
<td>PhI(OAc)2</td>
<td>—</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)2</td>
<td>DCE/Ac2O (1:1)</td>
<td>AgOAc</td>
<td>—</td>
<td>N.R.</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)2</td>
<td>DCE/Ac2O (1:1)</td>
<td>Cu(OAc)2</td>
<td>—</td>
<td>N.R.</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)2</td>
<td>DCE/Ac2O (1:1)</td>
<td>K2S2O8</td>
<td>—</td>
<td>N.R.</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)2</td>
<td>THF/Ac2O (1:1)</td>
<td>PhI(OAc)2</td>
<td>—</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)2</td>
<td>Toluene/Ac2O (1:1)</td>
<td>PhI(OAc)2</td>
<td>—</td>
<td>N.R.</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)2</td>
<td>DCE</td>
<td>PhI(OAc)2</td>
<td>—</td>
<td>22</td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)2</td>
<td>Ac2O</td>
<td>PhI(OAc)2</td>
<td>—</td>
<td>18</td>
</tr>
<tr>
<td>10</td>
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<td>DCE/Ac2O (1:1)</td>
<td>PhI(OAc)2</td>
<td>Li2CO3</td>
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<tr>
<td>11</td>
<td>Pd(OAc)2</td>
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<td>PhI(OAc)2</td>
<td>LiOAc</td>
<td>56</td>
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<tr>
<td>12</td>
<td>Pd(OAc)2</td>
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<td>PhI(OAc)2</td>
<td>AgOAc</td>
<td>70</td>
</tr>
<tr>
<td>13</td>
<td>Pd(OAc)2</td>
<td>DCE/Ac2O (1:1)</td>
<td>PhI(OAc)2</td>
<td>LiF</td>
<td>N.R.</td>
</tr>
<tr>
<td>14</td>
<td>Pd(OAc)2</td>
<td>DCE/Ac2O (1:1)</td>
<td>PhI(OAc)2</td>
<td>K2CO3</td>
<td>N.R.</td>
</tr>
</tbody>
</table>

*Reaction conditions: 1a (0.2 mmol), catalyst (10 mol%, 0.02 mmol), oxidant (1.5 eq., 0.3 mmol), additive (1.0 eq., 0.2 mmol), solvent (2 mL), 110 °C, 24 h, in a sealed tube. a Isolated yields.*
When (2-phenylpropyl)(p-tolyl)sulfane 3e was used, the acetoxylated product was isolated in a low yield of 40%, in which the steric effect might be the major reason (Scheme 2, 4e). Substrates bearing halogen substituents such as fluoro, chloro and bromo were able to undergo the C–H bond acetoxylation reaction in moderate yields, providing a useful routine for further cross-coupling reactions (Scheme 2, 4f–4h). Moreover, 2-naphthalene derivative occurred smoothly, furnishing the desired product 4i as the single regioisomer.

To gain insight into the mechanism, a competitive experiment using both electron-rich (1f) and electron-deficient (1i) thioether was carried out (Scheme 3). It was revealed that the electron-rich substrate (1f) made the acetoxylation proceed faster, which was consistent with an electrophilic palladation pathway.

On the basis of the above results, the catalytic cycle for the chelation-controlled position-selective acetoxylation is proposed via the typical C–H activation pathway as shown in Scheme 4. The initial sulfur assisted ortho-palladation leads to the formation of a five- or six-membered palladacycle A, which is oxidized by Phl(OAc)2 in the presence of Ac2O and DCE to generate Pd(IV) intermediate B. The final reductive elimination of intermediate B could afford the ortho-acetoxylated product 2a and regenerate the active Pd(II) species. The rate-determining step might be the electrophilic palladation of the arene, which is consistent with the observed poor reactivity of arenes containing electron-withdrawing groups.

After developing the directed C–H acetoxylation reaction, we explored further transformations of the model product 2a (Scheme 5). For example, the oxidation of sulfide 2a by m-CPBA at 0 °C produced the corresponding synthetically useful sulfoxide 5 and sulfone 6 in high yields. The resulting sulfoxide moiety can be almost quantitatively transformed into aldehyde 7 through the Pummerer rearrangement. The cleavage of the S-tether was achieved under reductive conditions using RANEY® Ni, affording the corresponding o-tolyl acetate 8 in 72% yield. Finally, 2-[(p-tolylthio)methyl]phenyl acetate 2a was successfully hydrolyzed by NaOH in EtOH/H2O to afford the product 9 in 86% yield.

Conclusions

In conclusion, a palladium(II)-catalyzed thioether-directed regioselective acetoxylation of C(sp2)–H bonds of arenes is described. The ability of sulfur to direct the ortho C–H bond activation with different tether lengths is an important feature of this process. The directing group can be easily removed or converted into a myriad of functionalities, providing new synthetic methods for phenol derivatives. Further exploration of the substrate scope and synthetic utility of these transformations are in progress in our laboratory.

Experimental section

General methods

The materials and solvents were purchased from common commercial sources and used without additional purification, if not otherwise noted. 1H NMR spectra were recorded at 400 MHz using TMS as the internal standard. 13C NMR spectra were recorded at 100 MHz using TMS as the internal standard. The multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), multiplet (m), and broad resonances (br). Mass spectroscopy data were collected on an HRMS-EI and HRMS-ESI instrument.
General procedure for the Pd(n)-catalyzed thioether-directed acetoxylation of C(sp²)-H bonds of arenes

A mixture of benzyl sulfide derivative (0.2 mmol), Pd(OAc)$_2$ (76 mg, 0.3 mmol), and AgOAc (33 mg, 0.2 mmol) in 2 mL DCE/Ac$_2$O (1:1) was stirred at 110 °C for 24 h. Afterwards, the reaction mixture was allowed to cool to room temperature and filtered through a pad of Celite. The solvent was evaporated under reduced pressure and the residue was subjected to flash column chromatography (silica gel, ethyl acetate/petroleum ether = 1:10, v/v) to obtain the desired products.

Acknowledgements

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Notes and references


2 For selected reviews of C-O formation, see: (a) E. M. Beccalli, G. Broggiini, M. Martinelli and S. Sottocornola, Chem. Rev., 2007, 107, 5318; (b) T. W. Lyons and M. S. Sanford, Chem. Rev., 2010, 110, 1147.


