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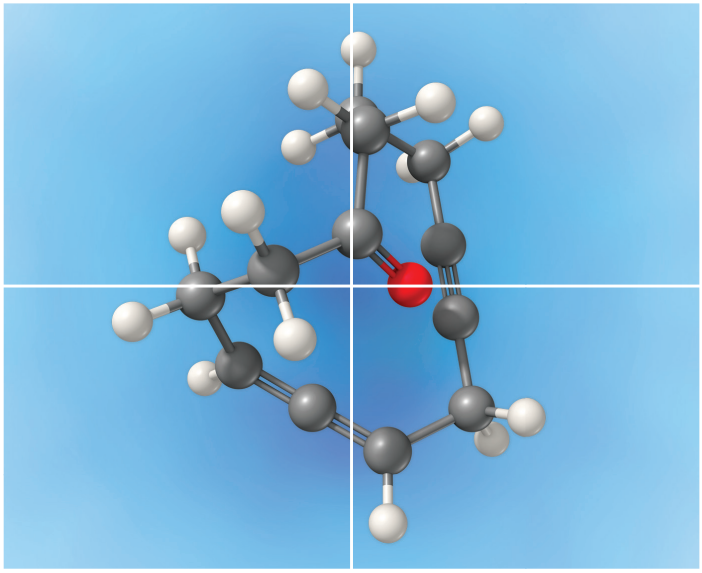

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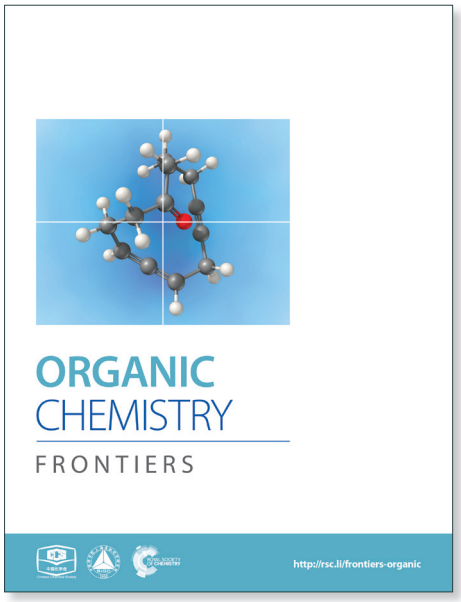

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Journal Name

ARTICLE

Thioether-directed acetoxylation of C(sp^2)–H bond of arenes by palladium catalysis

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The palladium-catalyzed acetoxylation of aromatic C(sp^2)–H bonds utilizing thioether as the directing group was developed. Both of 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.

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.[1] In particular, the construction of C–O bond from C–H activation has attracted much attention due to the significant importance of this class of molecules in both academic research and industry.[2] However, many of these transformations suffer from the poor reactivity and regioselectivity. To overcome the uncontrolled site selectivity, a number of examples of C–O bond forming reactions have been reported through introduction of a directing group in recent years.[3-9] In 2004, Sanford and co-workers described a regio- and chemoselective Pd-catalyzed acetoxylation of C(sp^2)–H bonds using pyridine or other *N*-containing heteroarene as directing groups.[3a] A copper-catalyzed *ortho*-acetoxylation of aryl C–H bonds was developed by Yu and coworkers using dioxygen gas as the terminal oxidant.[4a] Since these pioneering reports, various directing groups, such as oxime,[5] sulfoximine,[6] pyrimidine,[7] anilide,[8] amide[9] and organophosphates[10] have been successfully employed as the directing groups for the selective C(sp^2)–H acetoxylation using Pd, Rh or Cu catalysts. In recent years, the more challenging oxygenation of C(sp^3)–H bonds has been achieved employing various N-based directing groups by several groups.[11] The majority of these successful acetoxylation reactions were limited to the efficient coordination between the nitrogen and/or oxygen with the transition metals, thus expanding the scope of the directing group remains a critical challenge.

Organosulfur compounds are commonly served as important intermediates in organic synthesis and crucial precursors to the functionalized molecules. Many of the sulfur containing molecules present the unique properties and thus have found wide applications in pharmaceuticals and functional materials.[12,13] Accordingly, the direct functionalization of the *S*-containing compounds via C–H bond activation is highly desirable. However, the relevant examples using sulfur species as the directing groups for C-H bond activation are still under developed.[14] Recently, our group reported the example employing thioether as a directing group for the palladium-catalyzed alkenylation and arylation of arenes.[14a,14b] The alkenylation of benzyl thioethers and phenylsulfoxides via Rh-catalyzed aryl C–H activation was described by Shi[14d] and Miura[14f] groups. In connection with our interest in C–H functionalization of arenes, we herein describe the palladium-catalyzed oxidative acetoxylation of C(sp^2)–H bond of arene applying thioether as a removable directing group. Site-selectively acetoxylated products could be afforded in moderate to good yields with tolerance of a wide variety of functional groups.

We initiated the investigation by the reaction of 1.0 equiv of benzyl sulfide **1a** with 10 mol % of $Pd(OAc)_2$ and $PhI(OAc)_2$ (1.5 equiv) in DCE/Ac_2O (1:1) at 110 °C for 24 h. The expected mono-acetoxylated product was isolated in 31% yield. With this promising result, we were encouraged to optimize the reaction conditions (Table 1). No desired product was generated in the absence of palladium catalyst. The effect of the oxidants was examined in details, and $PhI(OAc)_2$ showed the best reactivity. Other oxidants, such as AgOAc, $Cu(OAc)_2$, and $K_2S_2O_8$ failed to generate the product (entries 2-4). The reaction displayed a tremendous solvent dependence characteristic and was performed in acetic anhydride with 1,2-dichloroethane as cosolvent. Other cosolvents, such as acetonitrile, tetrahydrofuran, and toluene were also screened, which brought decreased yields (entries 5-7). The transformation performed in pure Ac_2O or DCE gave the yield of 22% or 18%, respectively (entries 8-9). Moreover, the reaction efficiency could be further improved by the use of different additives.[4b] The employment of a stoichiometric amount of Li_2CO_3 gave the product in 63% yield (entry 10). Further investigation on other additives such as LiOAc, AgOAc, LiF, K_2CO_3 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

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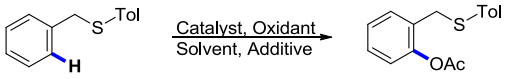
10 mol % of $Pd(OAc)_2$ with 1.5 equiv of $PhI(OAc)_2$ as the oxidant, AgOAc as the additive, and Ac_2O/DCE 1:1 as the solvent at 110 °C.

Table 1. Optimization of the Reaction Conditions[a]

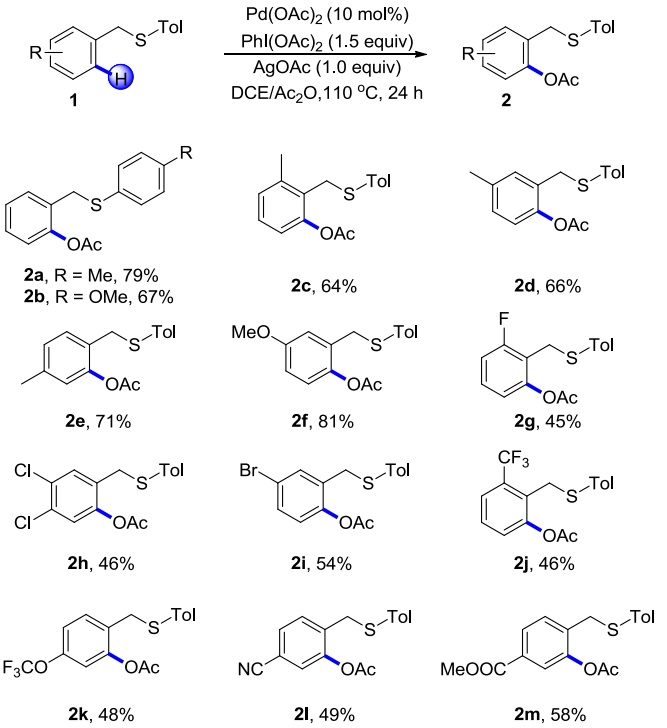


1a **2a**

Entry	Catalyst	Solvent	Oxidant	Additive	Yield (%)[b]
1	$Pd(OAc)_2$	DCE/Ac_2O (1:1)	$PhI(OAc)_2$	—	31
2	$Pd(OAc)_2$	DCE/Ac_2O (1:1)	AgOAc	—	N.R.
3	$Pd(OAc)_2$	DCE/Ac_2O (1:1)	$Cu(OAc)_2$	—	N.R.
4	$Pd(OAc)_2$	DCE/Ac_2O (1:1)	$K_2S_2O_8$	—	N.R.
5	$Pd(OAc)_2$	CH_3CN/Ac_2O (1:1)	$PhI(OAc)_2$	—	15
6	$Pd(OAc)_2$	THF/Ac_2O (1:1)	$PhI(OAc)_2$	—	14
7	$Pd(OAc)_2$	Toluene/Ac_2O (1:1)	$PhI(OAc)_2$	—	N.R.
8	$Pd(OAc)_2$	DCE	$PhI(OAc)_2$	—	22
9	$Pd(OAc)_2$	Ac_2O	$PhI(OAc)_2$	—	18
10	$Pd(OAc)_2$	DCE/Ac_2O (1:1)	$PhI(OAc)_2$	Li_2CO_3	63
11	$Pd(OAc)_2$	DCE/Ac_2O (1:1)	$PhI(OAc)_2$	LiOAc	56
12	**$Pd(OAc)_2$**	**DCE/Ac_2O (1:1)**	**$PhI(OAc)_2$**	**AgOAc**	**79**
13	$Pd(OAc)_2$	DCE/Ac_2O (1:1)	$PhI(OAc)_2$	LiF	N.R.
14	$Pd(OAc)_2$	DCE/Ac_2O (1:1)	$PhI(OAc)_2$	K_2CO_3	N.R.

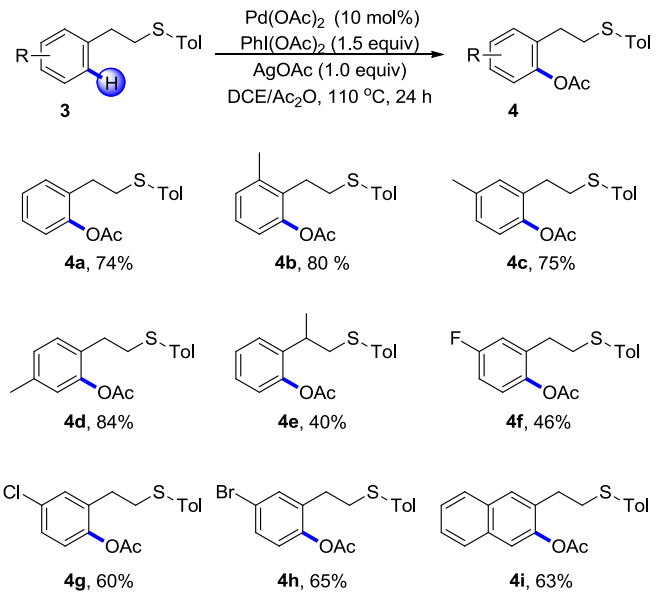
[a] Reaction conditions: **1a** (0.2 mmol), catalyst (10 mol%, 0.02 mmol), oxidant (1.5 eq, 0.3 mmol), additive (1.0 eq, 0.2 mmol), solvent (2 mL), 110 °C, 24 h, in a sealed tube. [b] isolated yields.

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 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, 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 CF_3, OCF_3, CN and COOMe were compatible with this protocol, showing the relatively broad functionality tolerance of the transformation (Scheme 1, **2j-2m**).



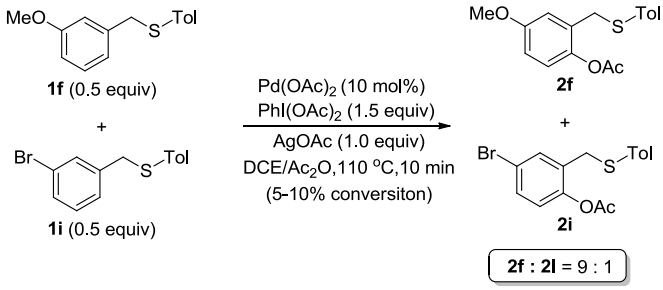
Scheme 1. Thioether-directed acetoxylation of C(sp^2)–H bond of benzyl (*p*-tolyl)sulfane.[a] [a] Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (10 mol%, 0.02 mmol), $PhI(OAc)_2$ (1.5 eq, 0.3 mmol), AgOAc (1.0 eq, 0.2 mmol), DCE/Ac_2O (2 mL), 110 °C, 24 h, in a sealed tube.

Encouraged by the efficient acetoxylation reaction via five-membered palladacycle, we further examined the substrates with longer length tether between sulfur and arene in Scheme 2. The phenethyl sulfides were found to be stable to these oxidative conditions and promoted the reaction in a selective fashion (Scheme 2, **4a**-**4i**). 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, **4b-4d**). 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 regionisomer.



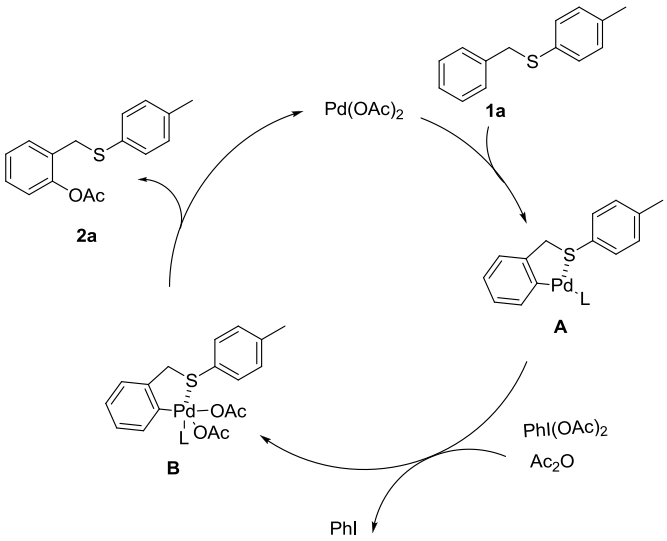
Scheme 2. Thioether-directed acetoxylation of C(sp^2)–H bond of phenethyl sulfides.[a] [a] Reaction conditions: **3** (0.2 mmol), $Pd(OAc)_2$ (10 mol%, 0.02 mmol), $PhI(OAc)_2$ (1.5 eq, 0.3 mmol), AgOAc (1.0 eq, 0.2 mmol), DCE/Ac_2O (2 mL), 110 °C, 24 h, in a sealed tube.

To gain insight into the mechanism, a competition 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**) proceeded the acetoxylation faster, which was consistent with an electrophilic palladation pathway.



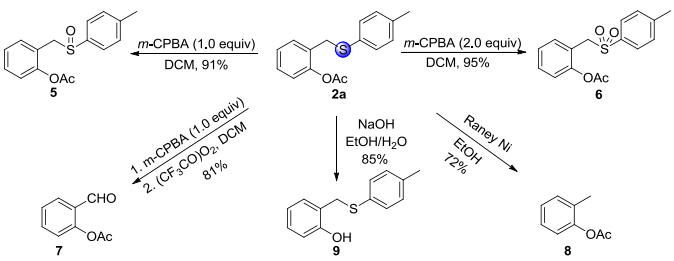
Scheme 3. Competitive Experiment

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 five- or six-membered palladacycle **A**, which is oxidated by $PhI(OAc)_2$ in the presence of Ac_2O and DCE to generate the 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.



Scheme 4. Reaction mechanism.

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** in the presence of acetic anhydride through Pummerer rearrangement. The cleavage of the S-tether was achieved under reductive conditions using Raney Ni, affording the corresponding *o*-tolyl acetate **8** in a 72% yield. Finally, the 2-((*p*-tolylthio)methyl)phenyl acetate **2a** was successfully hydrolyzed by NaOH in EtOH/H_2O to afford the product **9** in 86% yield.



Scheme 5. Transformation of Thioethers

Conclusions

In conclusion, a palladium(II)-catalyzed thioether-directed regioselective acetoxylation of C(sp^2)–H bond 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. ^{1}H NMR spectra were recorded at 400 MHz using TMS as internal standard. ^{13}C NMR spectra were recorded at 100 MHz using TMS as 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(II)-catalyzed thioether-directed acetoxylation of C(sp^2)–H bond of arenes.

A mixture of benzyl sulfide derivative (0.2 mmol), $PhI(OAc)_2$ (76 mg, 0.3 mmol), $Pd(OAc)_2$ (4 mg, 10 mol%), AgOAc (33 mg, 0.2 mmol) in 2 mL DCE/Ac_2O (1:1) was stirred at 110 ^{o}C for 24 h. Afterward, 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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