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Pd–Catalyzed Intermolecular Transthiolation of Ar–OTf using Methyl 3–(Methylthio) Propanoate as a Thiol Surrogate

Dandan Pan,[a] Shasha Xu,[a] Qingqiang Tian[a] and Yahui Li*[a]

[a] Dr. Dandan Pan, Miss. Shasha Xu, Mr. Qingqiang Tian and Prof. Dr. Yahui Li, Department Key Laboratory of Agri–Food Safety of Anhui Province, School of Resources and Environment, Anhui Agricultural University, Hefei 230036, China, E–mail: Yahui.Li@ahau.edu.cn

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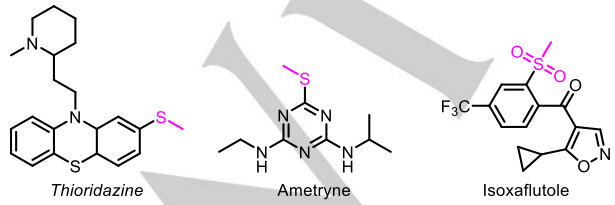
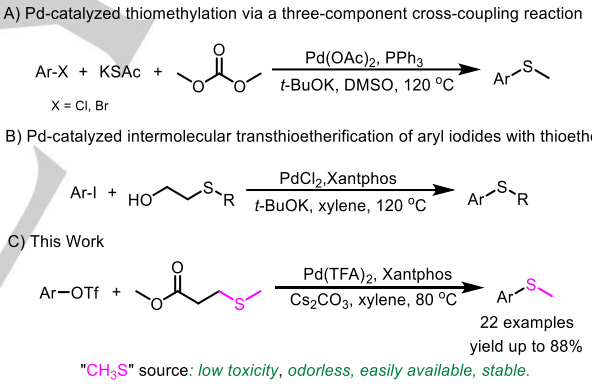
Abstract: A method for odorless synthesis of unsymmetrical sulfides via Csp2–O bond and Csp3–S activation is presented. Using methyl 3–(methylthio) propanoate as a MeSH surrogate, a series of substituted aryl methyl sulfides have been obtained in moderate to good yields. This catalytic protocol can also tolerate methyl 3–(methylthio)propionate derivatives to afford corresponding aryl sulfides.

Organosulfur compounds represent an important class of biological organic compounds that can be found in pharmaceuticals, natural products, and agrochemicals.[1] Aryl methyl sulfide, sulfoxide, and sulfone molecular are of great importance in modern pharmaceutical and agrochemical science(Scheme 1). Thioridazine, a classical neurological drug, is used for treating schizophrenia in adults and children.[2] Ametryn is a triazine herbicide with selective uptake and conduction.[3] Isoxaflutole, an isoxazole–containing compound, is a herbicide as inhibitor of *p*–hydroxy–phenylpyruvate dioxygenase (HPPD).[4] Considering the importance of these compounds, the development of a novel process for the preparation of aryl methyl sulfide is of great significance.[5] Transition–metal–catalyzed C–S bond cross–coupling reactions between aryl (pseudo)halide and mercaptans represent the most classical and important method for the synthesis of aryl methyl sulfides.[6] However, methyl mercaptan is a poisonous and fetid gas that not only cause intractable problems, such as unpleasant odor, catalysts poisoning, environmental pollution, and terrible risks during the manufacturing process. Alternative sodium methyl mercaptide is a concentration of 20% aqueous solution, which impedes its application.



Scheme 1. Methylsulfide–containing chemicals.

In order to overcome this problem, developing new kinds of sulfurating reagents is attractive(Scheme 2).[7] In 2018, Jiang and co–worker developed a Pd–catalyzed thiomethylation of aryl halides via a three–component cross–coupling strategy.[8] In 2020, Our group reported an intermolecular transthioetherification of aryl iodides with thioethers.[9] Although these methods provided alternative methods for the synthesis of aryl methyl sulfides, substrates mainly focused on aryl iodides or bromides. Phenols are one of the most common skeleton structures in natural products and bioactive compounds.[10] Using phenol derivatives in the formation of aryl methyl sulfide can provide an efficient and convenient way for the rapid late–stage modification approach.[11] Also, methyl 3–(methylthio) propanoate is an odorless, easily available, and stable substrate that has been used as a chemistry additive. The direct use of methyl 3–(methylthio) propanoate derivatives as a methylthio source are attractive from a practical and environmental point of view.



Scheme 2. Development of transfer catalysis

In all these backgrounds, we wish to report that the Pd–catalyzed intermolecular transthiolation of aryl triflates using methyl 3–(methylthio) propanoate and its derivatives as the sulfurating reagent to afford a wide range of aryl sulfides. To begin the study, we selected naphthalen–1–yl trifluoromethane–sulfonate (**1a**) and methyl 3–(methylthio) propanoate (**2a**) as the model substrate in the presence of $PdCl_2$, xantphos, and Cs_2CO_3 at 100 °C for 17h, the desired product **3a** was obtained in 20% yield (Table 1, entry 1). Then different bases were tested and Cs_2CO_3 shown the best result. Moreover, more mild or strong bases, such as K_3PO_4 and KO^{t}Bu, were ineffective for this transformation (Table 1, entries 2 and 3). Different Pd salts was also screened, such as $Pd(OAc)_2$, $Pd_2(dba)_2$, $Pd(ally)Cl_2$, $Pd(CH_3CN)_2Cl_2$ and $Pd(TFA)_2$. $Pd(TFA)_2$ was proved to be a better choice affording the desired product in 47% yield (Table 1, entry 8). After that, other ligands were tested and which, however, did not exhibit any superior performance than xantphos (Table 1, entries 9, 10, and 11). In addition, $Pd(TFA)_2$ is ineffective for this

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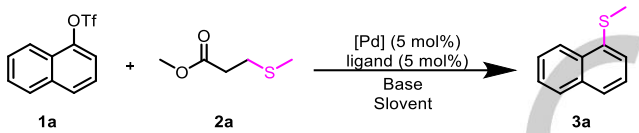
reaction in the absence of the ligand (Table 1, entry 12). Interestingly, when the reaction temperature decreased to 80 °C, the yield of desired **3a** increased to 68% yield (Table 1, entry 13). A further study showed that argon atmosphere is more beneficial for this transformation, and 83% yield could be achieved, although this catalytic protocol was adapted to air atmosphere (Table 1, entry 15). Finally, the optimal condition was established as 5 mol% $Pd(TFA)_2$/Xantohos Cs_2CO_3 (3 equiv.), xylene (2 mL), 80 °C, and 17 h.

Table 1. Optimization of Pd–catalyzed C–S bond formation[a]



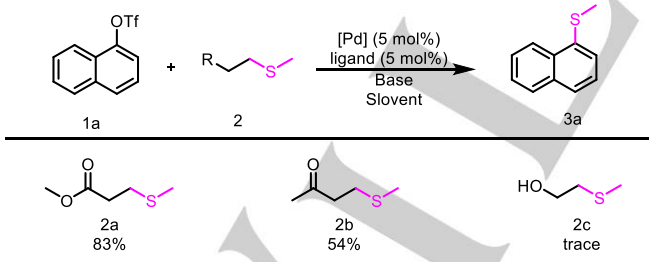
1a 2a 3a

entry	catalyst	ligand	base	T(°C)	yield[b](%)
1	$PdCl_2$	Xantphos	Cs_2CO_3	100	20
2	$PdCl_2$	Xantphos	K^{t}OBu	100	–
3	$PdCl_2$	Xantphos	K_3PO_4	100	–
4	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	100	35
5	$Pd_2(dba)_2$	Xantphos	Cs_2CO_3	100	–
6	$Pd(ally)Cl_2$	Xantphos	Cs_2CO_3	100	45
7	$Pd(CH_3CN)_2Cl_2$	Xantphos	Cs_2CO_3	100	27
8	$Pd(TFA)_2$	Xantphos	Cs_2CO_3	100	47
9	$Pd(TFA)_2$	dppe	Cs_2CO_3	100	–
10	$Pd(TFA)_2$	PPh_3	Cs_2CO_3	100	–
11	$Pd(TFA)_2$	Brettphos	Cs_2CO_3	100	–
12	$Pd(TFA)_2$	–	Cs_2CO_3	100	–
13	$Pd(TFA)_2$	Xantphos	Cs_2CO_3	80	68
14	$Pd(TFA)_2$	Xantphos	Cs_2CO_3	60	37
15	$Pd(TFA)_2$	Xantphos	Cs_2CO_3	80	83[c]

[a]Reaction conditions: 1a (0.2 mmol, 1.0 equiv.), 2 (0.6 mmol, 3.0 equiv.), [Pd] (5 mol%), ligand (5 mol%), base (0.6 mmol, 3.0 equiv.), xylene (2 mL), 80 °C , 17 h. [b]Yield was determined by GC using n–dodecane as internal standard.[c]Under N_2

The reactivity of other thioether reagents, such as 2–(methylmercapto) ethanol and 4–(methylthio)–buta–2–one, also been tested in the reaction with aryl triflates. But no better yield was obtained (Table 2).

Table 2. Reactivity of differernt thiol donors[a]



[a]Reaction conditions: 1a (0.2 mmol, 1.0 equiv.), 2 (0.6 mmol, 3.0 equiv.), [Pd] (5 mol%), ligand (5 mol%), base (0.6 mmol, 3.0 equiv.), xylene (2 mL), 80 °C , 17 h. [b]Yield was determined by GC using n–dodecane as internal standard. [c]Under N_2

With the optimized reaction conditions in hand, we investigated the substrate scope of this Pd–catalyzed transthiolation of alkyl trifluoromethanesulfonate with thioether, and the results summarized in Table 3. Alkyl trifluoromethanesulfonate containing electron–donating groups, such as CH_3O– or C_4H_9O–, reacted smoothly and the led to corresponding products in 67% (**3b**), 81% (**3c**), and 76% (**3d**) respectively. Halogen atom Cl can also be tolerated and led to desired sulfide in 88% (**3f**) and 68% (**3l**) yield, respectively, which provides the possibility for further transformation. In addition, aryl triflates containing Ac and CN group can also be converted into aryl sulfide smoothly, such as 1–(3–(methylthio)phenyl)ethan–1–one and 3–(methylthio)benzonitrile, and give the desired products **3j** and **3k** in 57% and 67% yield. It is worth mentioning that medicinally relevant CF_3S group can also be tolerated and gave the desired product in 65% yield (**3m**).

To further make sure the synthetic value of this catalytic protocol, we turned to test the scope of 4–methylthio–propionic acid methyl ester derivatives. Substrates containing alkylthio- instead of methylthio- could react smoothly and gave the desired products in the range between 59–76% yield. Also, when the reaction was performed benzylthio and phenylethylthio derivatives, the sulfide product of benzyl(naphthalen–1–yl)–sulfane and naphthalen–1–yl(phenethyl)sulfane could also be obtained in 73% and 83% yield, respectively. It is noteworthy that heterocycle thiophene was compatible in standard conditions and furnish target product **3t** in 67% yield. Methyl 3-(arylthio)propanoate can also be applied in this reaction. We have performed the reaction of Ar-OTf with methyl 3-(p-tolylthio)propanoate, and the desired product could be obtained in 70% yield (**3u**). We also compared the reactivity of 1-iodonaphthalene, 1-bromonaphthalene and 1-naphthyl triflate.1-Iodonaphthalene shown the best result (88% yield), and 1-bromonaphthalene has the similar reactivity with 1-naphthyl triflate.

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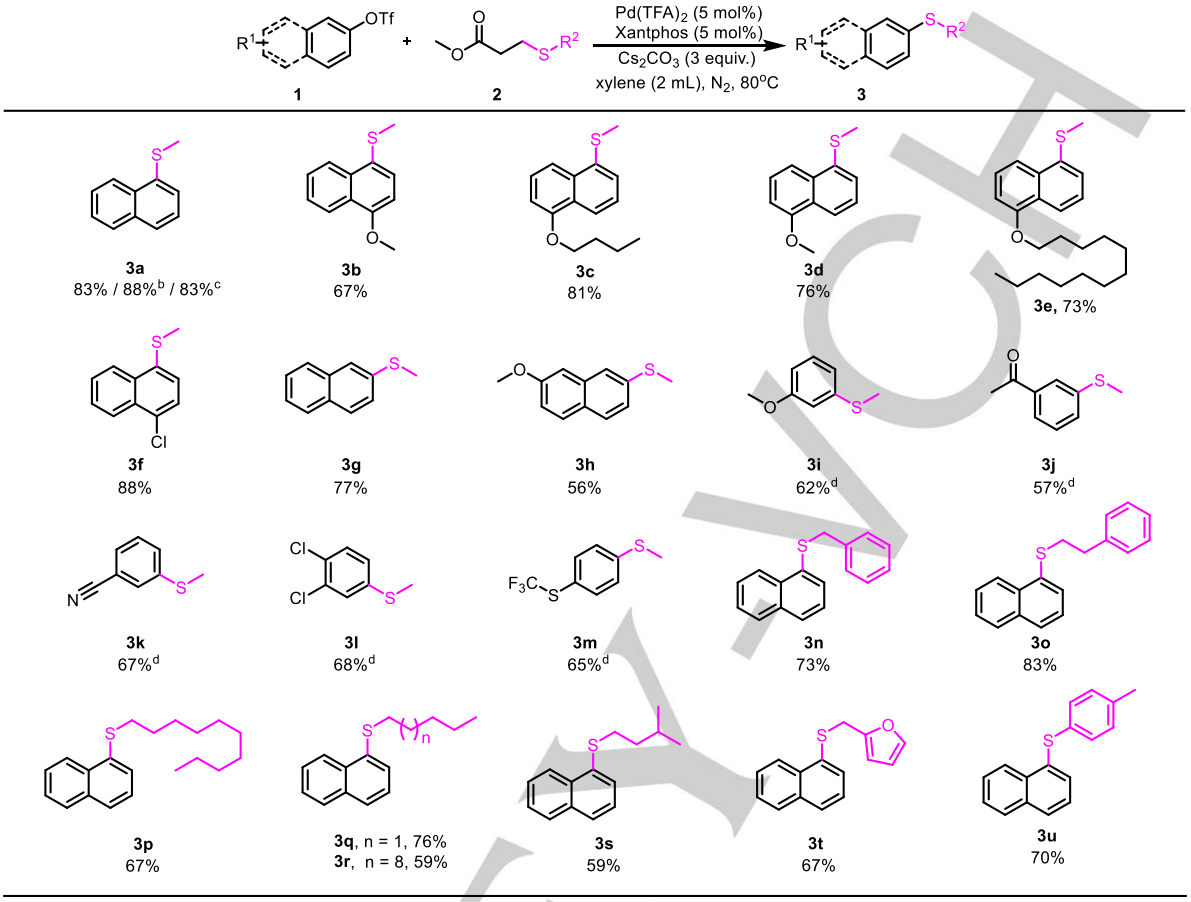
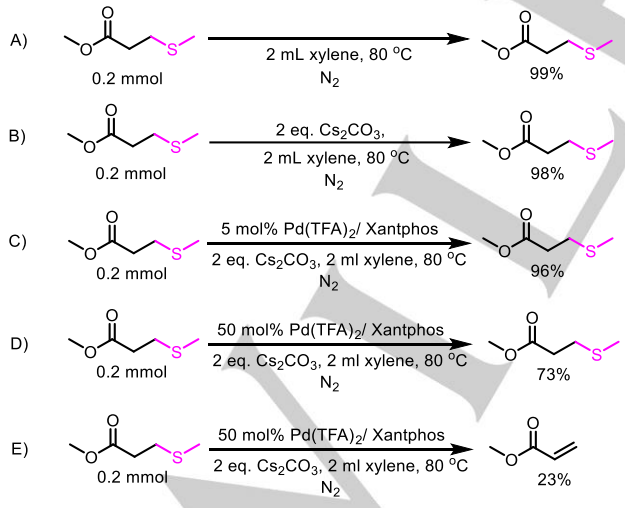
Table 3. Pd–catalyzed thioetherification of aryl trifluoromethanesulfonate[a]

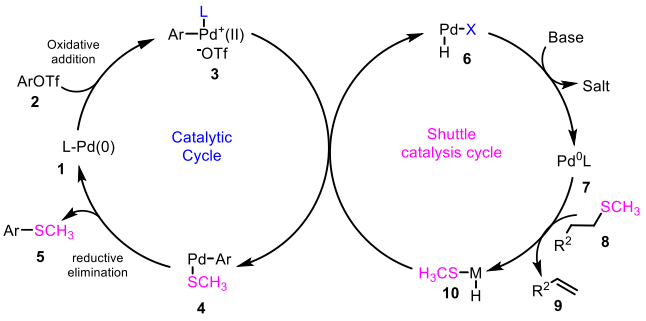


[a]Reaction condition: 1a (0.2 mmol, 1.0 equiv.), 2 (0.6 mmol, 3.0 equiv.), $Pd(TFA)_2$ (5 mol%), Xantphos (5 mol%), Cs_2CO_3 (0.6 mmol, 3.0 equiv.), xylene (2 mL), 80 °C,17h, isolated yield. [b]using1-iodonaphthalene instead of 1-naphthyl triflate. [c]using 1-bromonaphthalene instead of 1-naphthyl triflate. [d]24h



Scheme 3. Control experiments

To gain insight into the reaction mechanism, several control experiments were conducted (see the Supporting Information). The results implied that methyl 3–(methylthio)propanoate would not depose at 80 °C without catalyst and base (Scheme 3, A and B), but when we performed the reaction with 5 mol% of catalyst and 2 equiv. Cs_2CO_3, 5% of methyl 3–(methylthio)propanoate was consumed(Scheme 3, C). Furthermore, increasing the loading of $Pd(OAc)_2$ to 50 mol%, 27% of methyl 3–(methylthio)propanoate was deposed(Scheme 3, D), and 23% of methyl acrylate was detected. The results indicated that the palladium salt and base play important roles in this C–S bond cleavage process.



Scheme 4. Proposed Catalytic Cycle

We hypothesized that precatalyst activation generates a Pd0 active species 1 (Scheme 4), which undergoes oxidative addition with an Ar–OTf to form an organometallic Pd II halide complex 3. Subsequently, a challenging sequence of C–SMe bond oxidative addition followed by *β*–H elimination could be mediate by Pd–

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catalyst and give the important intermediate H–Pd–SMe species 10. The organometallic nucleophile (H–Pd–SMe) undergoes transmetalation with Ar–M–L 3 to form the intermediate 4 that is followed by reductive elimination to give the desired aryl methyl sulfides. And the active Pd0 species 6 could be regenerated after the reaction between H–Pd–X and a base.

In conclusion, we have described grenral and functional–group–tolerant Pd–catalyzed transthiolation system to coupling of aryl triflates with methyl 3–(methylthio) propanoate and its derivatives. With methyl 3–(methylthio) propanoate as the low toxicity, odorless, easily available, and stable methyl mercaptan surrogates, the desired sulfide was produced in moderate to good yields. The method exhibits a broad scope and a high tolerance for functionality.

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Keywords: Cleavage reactions • Cross-coupling • Csp3-S activation • Elimination • MeSH Surrogate

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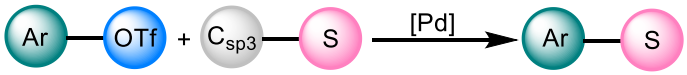

Intermolecular Transthiolation, Thiol Surrogate

23 examples
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Developing efficient strategies for the synthesis of organosulfur compounds is scientifically interesting and of high value, due to their broad application in pharmaceuticals, nature products and agrochemicals. The work describes an intermolecular transthiolation of Ar–OTf using methyl 3–(alkyllthio) propanoate as an odourless thiol surrogate.

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