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Palladium-Catalyzed Intermolecular Transthioetherification of Aryl Halides with Thioethers and Thioesters

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Abstract: Functional group transfer reaction is an important synthetic tool in modern organic synthesis. Herein, we developed a new palladium-catalyzed intermolecular transthioetherification of aryl halides with thioethers and thioesters. The synthetic utility and practicality of this catalytic protocol are demonstrated in a wide range of successful transformations (>70 examples). This catalytic protocol is applicable in carbonylative coupling process as well and the first example of carbonylative methylthioesterification of aryl halides has been achieved. Notably, this work also provides an approach to use nature products, such as methionine and selenomethionine, as the functional group sources.

Functional group transfer reactions have become an indispensable tool for organic synthesis.[1] Representative examples such as metathesis[2] and transfer hydrogenation[3-6] have had enormous applications on polymer materials and pharmaceuticals. Recently, the border of transfer hydrogenation has been extended successfully. Besides hydrogen, other small molecules (H_2/CO, RCOH) can also be applied in these processes.[7-12] In 2016, Morandi and co-workers reported an elegant Ni-catalyzed reversible transfer hydrocyanation between alkyl nitriles and alkenes under mild conditions.[13a] Later on, they reported their new achievement on palladium-catalyzed C-S bond metathesis (Fig. 1, B).[13b] In 2018, the research groups of Arndtsen and Morandi reported their achievements on palladium-catalyzed metathesis between aroyl chlorides and aryl iodides, respectively.[14] By using Pd_2dba_3/Xantphos as the catalyst system, new acid chlorides can be produced effectively. Among all the carbon-heteroatom bond transfer reactions, the formation of carbon-sulfur and carbon-selenium are attractive targets due to a broad range of pharmaceuticals, biological molecules, agrochemicals contain these bonds (Fig. 1, A).[15-16] However, several challenges need to be overcame in order to realize this hypothesis, because compared with C-C bond metathesis displacement of dative ligands by thiols and thiolates usually deactivate late transition metals by the formation of ionic thiolate complexes or bridging thiolate complexes that undergo slow reductive elimination.[17]

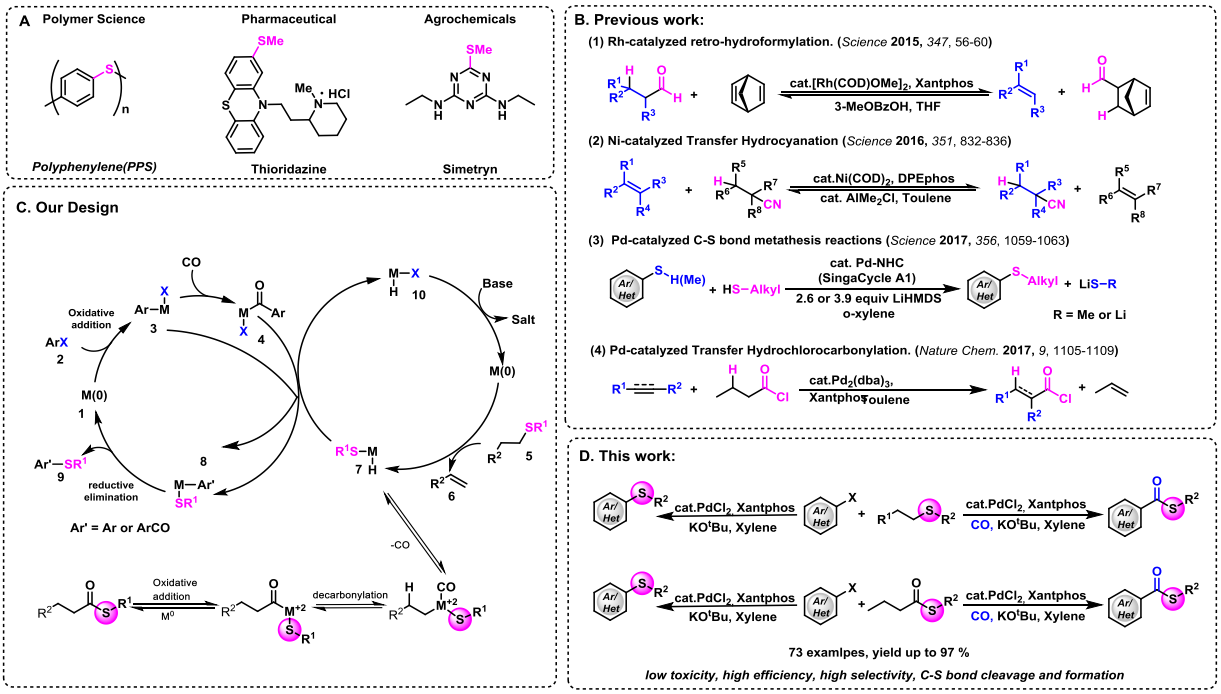

Fig. 1 | Development of catalysts and design of thiomethylation and carbonylative thiomethylation of aryl halide. A. Selected examples of compound containing C-S bond. B. Development of transfer catalysis. C. Our transfer strategy. D. This work.

On the other hand, existing examples on transfer reaction usually occurred between two components. Therefore development of multicomponent transfer reaction remains an interesting area for exploration. Transition metal-catalyzed carbonylation reactions are one of the most potent tool for the synthesis of carbonyl-containing chemicals.[18-21] In these transformations, carbon monoxide (CO) can be used as one of the cheapest and abundant C_1 building blocks,

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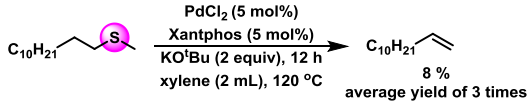
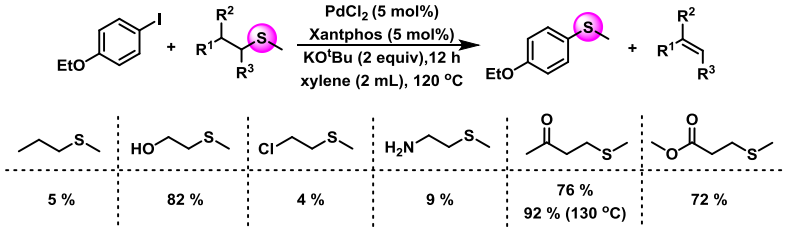
meanwhile the carbon chain of the parent molecules can also be increased. However, most of the known procedures need ready-made chemicals as the nucleophile. More specifically, amines and alcohols are more frequently explored nucleophiles. Thio-related reagents are much less explored, due to their odor and/or gas properties. Consequently, the development of new process to transfer more challenging nucleophiles remains an important goal. For example, methyl thioesters are important intermediates and building blocks in nature and organic synthesis.[22-23] However, to the best of our knowledge, there is no example that uses carbonylation reaction in the synthesis of aryl methylthioesters exist. This may due to the fact that methyl mercaptan is a flammable and highly toxic gas and can explode after mixed with air.

Under all these backgrounds, we wish to report here the first example on palladium-catalyzed thiomethylation and carbonylative thiomethylation of aryl halide by using alkyl sulfide or methyl thioester as a convenient methylthio reagent (Fig. 1, D). Inspired by the previous works[13], we hypothesized that simple alkyl sulfide bearing *β*-H hydrogens could possibly be employed as methylthio reagent (Fig. 1, C). We envisaged that a challenging sequence of C-SMe bond oxidative addition followed by *β*-H elimination could be mediated by a metal catalyst and give the important intermediate H-M-SMe specie **7**. Subsequently, the organometallic nucleophile (H-M-SMe) undergoes transmetallation with ArCO-M-X **4** or Ar-M-X **3** to form the desired thioester or aryl methyl sulfides after reductive elimination. And the active M^0 species **10** could be regenerated after the reaction between H-M-I and a base.

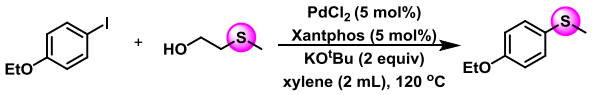
A. Control experiment



B. Thiomethylation: Formation of relative thermodynamic stability of the alkene can enhance the efficiency of the reaction



C. Screening of Reaction Conditions.[a]



Entry	Variations from the standard conditions	Yield
1	-	82 %
2	$Pd(OAc)_2$	75 %
3	$Pd(TFA)_2$	73 %
4	Without KOtBu	-
5	1 equiv. KOtBu	37 %
6	K_2CO_3 instead of KOtBu	16 %
7	NaOtBu instead of KOtBu	43 %
8	NaOMe instead of KOtBu	28 %
9	PPh_3 instead of Xantphos	trace
10	DPPE instead of Xantphos	25 %
11	Without Catalyst or Ligand	-

Fig. 2 | Control experiments and Condition Selection. A. Control experiment**.** B. Reagent optimization for thiomethylation. C. Condition Selection: [a]Reaction conditions: 1a (0.2 mmol), 2 (0.6 mmol), [Pd] (5 mol%), ligand (5 mol%), base (0.4 mmol), xylene (2 mL), 120 °C, 12 h. [b]Yield was determined by GC using n-dodecane as internal standard.

To prove the hypothesis is valuable, control experiments have been done. And palladium catalyst was chosen as the metal catalyst because Pd(0) complexes are very active species in the formation and cleavage of C-S bonds. As shown in Fig 2. A, with 5 mol% of $PdCl_2$ and Xantphos, 8 % yield of 1-dodecene could be obtained. The result shows the catalytic cycle can be achieved by using palladium salt as the catalyst.

Subsequently, a range of alkyl sulfides were tested as potential methylthiolating reagents (Fig 2. B). And experiments results shown that 5%, 82%, 9%, 76%, 72% yields of the desired product were obtained, when methyl(propyl)-sulfane, 2-(methylmercapto)ethanol, 2-(methylthio)ethylamine, 4-(methylthio)butan-2-one and methyl 3-(methylthio)-propanoate were used in the reaction independently. Here, the existing of a suitable coordinatable atom in the reagent, such as oxygen, might be able to favor the target reaction. Additionally, the possibility on further

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transforming the eliminated alkene can promote the desired reaction in addition. For example, when 2-(methylmercapto)ethanol was used as the methylthio reagent, eliminated product ethenol could be transferred into acetaldehyde, which could drive the reaction toward right.

After that we selected 1-ethoxy-4-iodobenzene and 2-(methylmercapto)ethanol as the model substrates to establish this thiomethylation procedure. Upon the variation of reaction conditions, different yields could be obtained (Fig 2. C). Among the different metal catalyst precursors, $PdCl_2$ showed the best result (82% GC yield; 80% isolated yield). Notably, no significant decrease of the yield was obtained when we used $Pd(OAc)_2$ and $Pd(TFA)_2$ instead of $PdCl_2$. Moreover, without catalyst or ligand, no desired product could be detected. The amount of KO^{t}Bu plays an important role in this reaction. Only 37% yield of the desired product was obtained if we decreased the loading of KO^{t}Bu from 2 equivalents to 1 equivalent. The property of base seems have strong influence on this transformation, when NaO^{t}Bu, NaOMe, or K_2CO_3 were used instead of KO^{t}Bu, the yield of the target product decreased significantly. Next, the effects of different ligands were studied. The reaction with PPh_3 or DPPE resulted in decreased yields. Extensive evaluation revealed that a reaction in the presence of 5 mol% of $PdCl_2$ and Xantphos together with 2 equiv. of KO^{t}Bu under 120 ^{o}C, can gave the desired product in 82% yield.

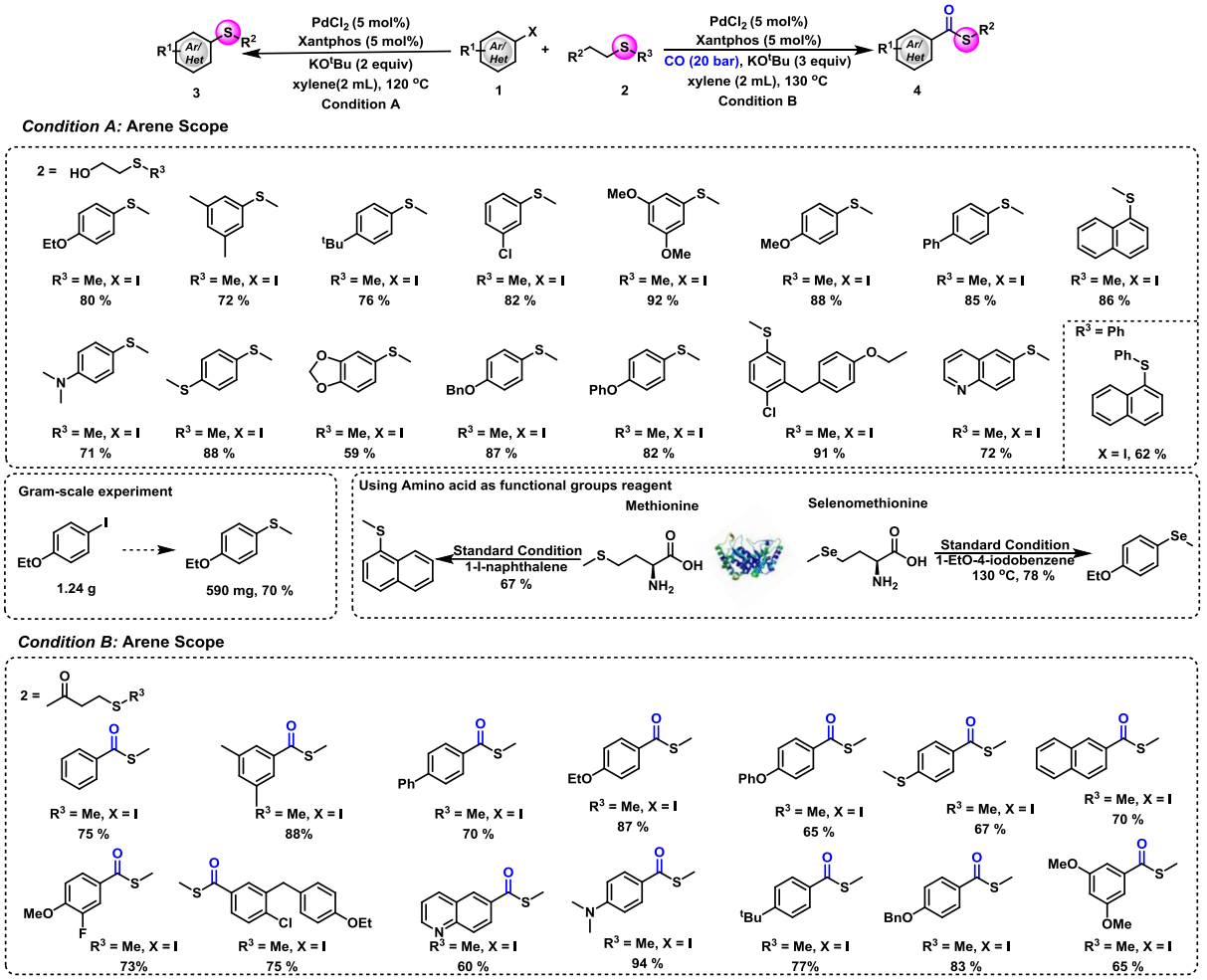

Fig. 3 | Substrate scope. (A) Thiomethylation of aryl halide and 2-(methylmercapto)ethanol. (B) Carbonylative thiomethylation of aryl halide and 4-(methylthio)butan-2-one. Condition A: 1 (0.2 mmol), 2 (0.6 mmol), $PdCl_2$ (5 mol%), Xantphos (5 mol%), KO^{t}Bu (0.4 mmol), xylene (2 mL), 120 ^{o}C, 12 h, isolated yield. Condition B: 1 (0.2 mmol), 2 (0.6 mmol), $PdCl_2$ (5 mol%), Xantphos (5 mol%), KO^{t}Bu (0.6 mmol), xylene (2 mL), 20 bar CO, 130 ^{o}C, 16 h.

In order to prove the synthetic potential of this methodology, the testing of different aryl iodides was also conducted under our standard conditions. Good yields of the desired aryl methyl sulfides can be produced by reacting 1-iodo-3,5-dimethylbenzene and 1-(*tert*-butyl)-4-iodobenzene with 2-(methylmercapto)ethanol (72% and 76% yield respectively). Substrates bearing electron-donating or electron-withdrawing groups reacted well and gave the desired product in good to excellent yields. Also good to excellent yields of the desired aryl methyl sulfides can be obtained from the corresponding *ortho*-, *meta*-, and *para*-substituted aryl iodides. The substrates bearing different functional group with oxygen, nitrogen and sulfur atom such as 4-iodo-*N*,*N*-dimethylaniline, (4-iodophenyl)(methyl)sulfane, and 1-iodo-4-phenoxy-benzene were well tolerated and the corresponding products were obtained in 71%, 88%, and 82% yields, respectively. Additionally, heteroaromatic ring can also proceed in this reaction and yield 6-(methylthio) quinoline in 72% yield. Furthermore, in order to further demonstrate the synthetic utility of this strategy, we also performed an experiment

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that use 2-(phenylthio) ethanol to replace 2-(methylmercapto)ethanol under our standard conditions. The arylthio group can also be transferred to aryl iodide, and gave the corresponding thioether in 62% yield. To clearly illustrate the synthetic power of the reaction, gram-scale experiment has also been done and 70% of the desired product was obtained. Methionine is an essential amino acid in humans, which plays a critical role in the metabolism and health.[24-25] Additionally, it is the main source of active methyl, sulfur and methylthio in the body. Herein, we implement a synthetic version that features the transfer of a methylthio group from methionine to aryl iodides. As shown in Fig. 3, good yield of the desired aryl methyl sulfide can be produced by reacting 1-iodonaphthalene with methionine. Another important element, selenium, can also participate in this reaction; the methyl selenization of 1-ethoxy-4-iodobenzene gave the corresponding product in good yield. We next aimed to evaluate the universality of our process on carbonylative thiomethylation of aryl halides. We found that the tested aryl halides can be effectively transformed in general. Good to excellent yields of the desired aryl methylthioesters can be obtained. The reaction also showed good functional group tolerances.

Having successfully developed a method for transferring a methylthio group from methyl sulfide to aryl halides, we next aimed to extend the scope of methylthio source. Despite the fact that methylthioesters provide meaningful chemoselectivity in the synthesis of biomolecules and Fukuyama coupling, they have rarely been used as methylthio source. Hence, we turned our attention to methylthioesters. We envisaged a mechanism that involves oxidative addition, decarbonylation and β-hydride elimination (Fig.1,C).

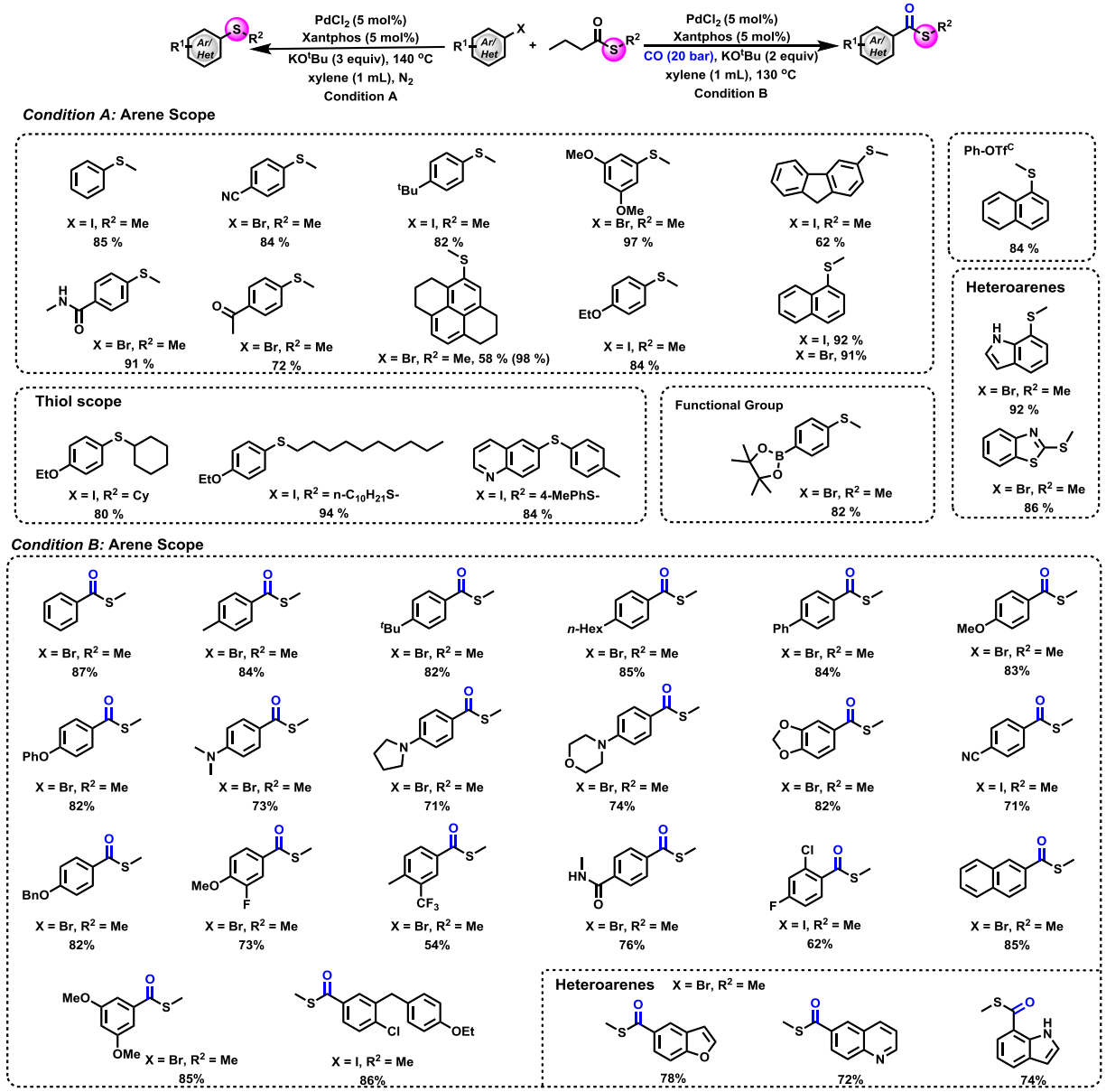

Fig. 4 |Substrate scope. (A) Thiomethylation of aryl halide and S-methyl butanethioate. (B) Carbonylative thiomethylation of aryl halide and S-methyl butanethioate. Condition A: 1 (0.2 mmol), 2 (0.6 mmol), $PdCl_2$ (5 mol%), Xantphos (5 mol%), KO^tBu (0.6 mmol), xylene (1 mL), 140 ^oC, N_2, 12 h, isolated yield. Condition B: 1 (0.2 mmol), 2 (0.6 mmol), $PdCl_2$ (5 mol%), Xantphos (5 mol%), KO^tBu (0.6 mmol), xylene (1 mL), 20 bar CO, 130 ^oC, 16 h. C: using NaOMe as the base

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After a small modification of the reaction condition, several aryl halides and phenyl triflate were selectively thiomethylated and gave the corresponding products in good to excellent yields. As shown in Fig. 4, good to excellent yields of the desired aryl methyl sulfides can be obtained from the corresponding substrates bearing either electron-deficient or electron-donating groups. *ortho*-Substituted aryl halides reacted well under our reaction conditions. Heterocycles such as unprotected indole, benzothiazole and quinoline were well tolerated under our conditions. Notably, 4-bromophenylboronic acid, pinacol ester also reacted well in our reaction, which provides useful handles for further synthetic transformations. Also the scope of thioesters, as shown in Fig 4, cyclohexanethio-, 1-decanethio- and arylthio- can also be tolerated in our process and gave the desired products in good to excellent yields. After proving the compatibility of aryl halides and thioesters of this methodology, we become interested in carbonylative thiomethylation. Different aryl halides were tested under our standard conditions successively. The corresponding carbonylation products were produced in good to excellent yields with excellent selectivity.

In conclusion, a novel palladium-catalyzed intermolecular transthioetherification reaction of aryl halides has been developed. With alkyl sulfides, thioester and even nature products as a convenient functional reagent, different aryl sulfides and thioester were obtained. Overall, the broad scope, excellent functional group compatibility, and high efficiency allow for efficient and safe synthesis of related chemicals in pharmaceuticals and laboratory.

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Competing financial interests

The authors declare no competing financial interests.

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