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Rhodium-catalyzed carbonylative coupling of alkyl halides with thiols: a radical process faster than easier nucleophilic substitution†‡

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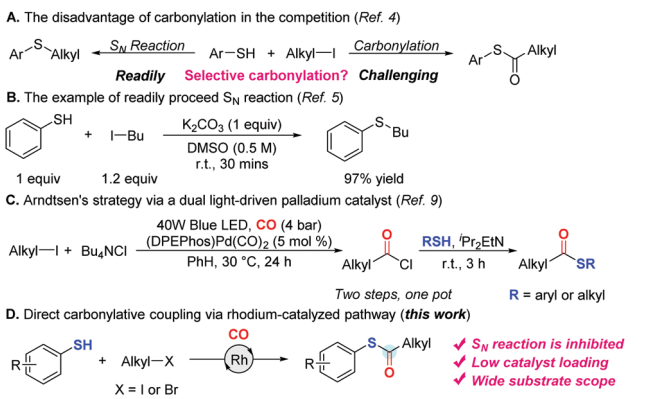
How to make a carbonylative coupling faster than the easier nucleophilic substitution? In this communication, a rhodium-catalyzed radical-based carbonylative coupling of alkyl halides with thiolphenols has been realized. Thioesters were isolated in good yields in general.

Transition metal-catalyzed carbonylative coupling reaction has emerged as one of the most common methods for the synthesis of carbonyl-containing compounds.[1] By manipulating the electrophiles, nucleophiles, and CO sources, researchers have developed numerous reactions over the past several decades. Alkyl halides, are considered as more challenging[2] but simple and useful electrophiles in carbonylation, have received increasing attention in recent years.[3] Unfortunately, alkylation with nucleophile, the annoying side reaction in carbonylation, is prone to proceed, thus restricts the use of many key substrates. Thiophenols are one of the most representative substrates owing to their high polarizability and strong nucleophilicity. Due to the high nucleophilicity of ArS^-, S_N reaction (nucleophilic substitution reaction) between alkyl halides and thiophenols is extremely prone to proceed (Scheme 1A).[4] For example, at room temperature under air, only for 30 minutes, phenyl butyl sulfide was formed in 97% yield from thiophenol and iodobutane (Scheme 1B).[5] In addition to this, thiols possess strong binding affinities to late-transition metals and could cause the loss of catalyst activity.[6] Consequently, makes the thiocarbonylation of alkyl halides a winner of the competition between carbonylation and S_N reaction is very challenge.

Thioesters are a class of useful intermediates that could serve as entry points to various classes of functionalities.[6,7] Directly thiocarbonylative coupling of aryl halides or alkyl halides thus provides a straightforward approach for their synthesis. However, although the carbonylative coupling reaction of thiols with aryl halides or alkenes have been established,[8] the successful example of alkyl halides as the coupling partner remain rare. The only case was given by Arndtsen and co-workers very recently. By utilizing a dual light-driven palladium catalyst, they developed an elegant carbonylation under ambient reaction conditions, which allowed alkyl halides to be converted into acid chlorides and which subsequently reacted with thiols to form the corresponding thioesters (Scheme 1C).[9] Although such a strategy expands the scope of products available *via* a two-step process, however, the key issue, strong competitive of S_N reaction to the carbonylation, has not been fundamentally solved.

With the idea that discovery of new carbonylative protocols in this field will lead to efficient synthetic routes toward advanced intermediates, and the known achievements of the rhodium catalyst in organic chemistry,[10,11] our approach to this challenge is focused on developing Rh-catalyzed method for thiocarbonylation of alkyl halides. After systematic studies, we herein report the first Rh-catalyzed direct carbonylative



Scheme 1 Challenges and strategies for carbonylative coupling of thiophenols and alkyl halides.

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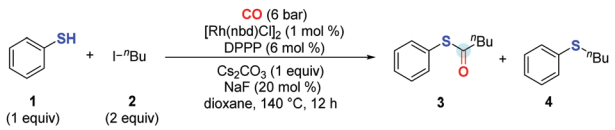
coupling of thiophenols with alkyl halides, leading to thioesters instead of thioethers as the main reaction products (Scheme 1D).

Our studies began with the carbonylative coupling of thiophenol **1** and iodobutane **2** (Table 1). We determined that the catalytic system comprising 1 mol% $[Rh(nbd)Cl]_2$ and 6 mol% bidentate ligand 1,3-bis(diphenylphosphino)propane (DPPP) facilitates efficient thiocarbonylation of substrate **2**, provided the desired thioester **3** in high yield (80%; entry 1).[12] Other precatalysts, such as, $RhCl_3$, $[Rh(cod)Cl]_2$ and Rh(cod)acac, were inferior to $[Rh(nbd)Cl]_2$ (entries 2–4). Slightly decreased or increased the bite angle of the ligand,[13] the yield of **3** dropped significantly (entries 5 and 6). When 4,5-bis(diphenylphosphino)-9,9-dimethyl (Xantphos) was used, only undesired thioether **4** could be obtained (entry 7). These results imply that the right bite angel is crucial for the success. Monodentate ligand such as triphenylphosphine (PPh_3) gave only a 6% yield of **3** (entry 8). Without NaF or used NaCl instead of it, the yield was slightly reduced (entries 9 and 10). The reaction was sensitive to moisture, as shown in entry 11, no carbonylation product could be detected when 1 equivalent of H_2O was added. The use of Cs_2CO_3 was critical for the reaction, thioether **4** became the main product if it replaced with Na_2CO_3, Rb_2CO_3, or CsF, (entries 12–14). Finally, performing the reaction in toluene diminished the yield of **3** (entry 15).

With the optimal conditions in hand, we then turned our attention to investigate the scope of this reaction. As shown in Table 2, employing iodobutane **2** as the coupling partner, various thiols could be converted into the corresponding thioesters in moderate to good yields. Generally, carbonylation of thiophenols bearing electron-donating substituents proceeded well, such as substrates substituted with 4-alkyl

Table 1 Representative results for the optimization of the Rh-catalyzed carbonylative coupling of 1 and 2[a]

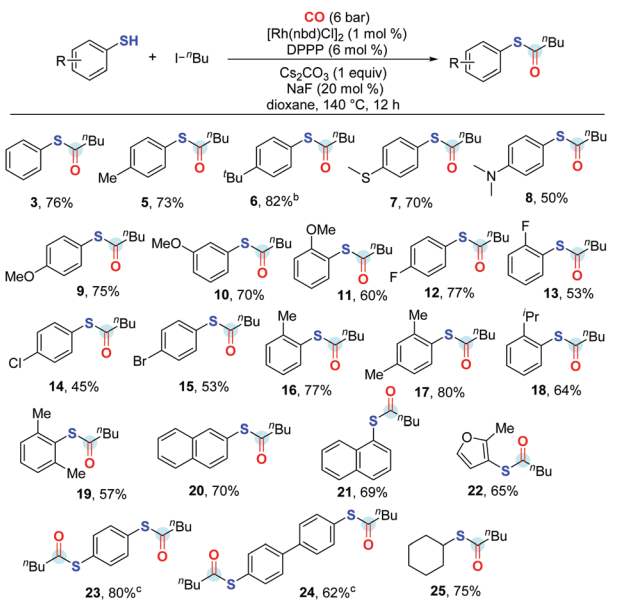


1 (1 equiv) 2 (2 equiv) 3 4

Entry	Variation from standard conditions	3[b] (%)	4[b] (%)
1	None	80	16
2	$RhCl_3$ instead of $[Rh(nbd)Cl]_2$	26	72
3	$[Rh(cod)Cl]_2$ instead of $[Rh(nbd)Cl]_2$	72	25
4	Rh(cod)acac instead of $[Rh(nbd)Cl]_2$	78	17
5	DPPE instead of DPPP	23	76
6	DPPB instead of DPPP	25	73
7	Xantphos instead of DPPP	0	99
8	12 mol% PPh_3 instead of DPPP	6	91
9	Without NaF	75	22
10	NaCl instead of NaF	78	21
11	With H_2O (1 equiv.)	0	98
12	Na_2CO_3 instead of Cs_2CO_3	18	80
13	Rb_2CO_3 instead of Cs_2CO_3	11	85
14	CsF instead of Cs_2CO_3	25	71
15	Toluene instead of dioxane	11	86

[a] Reaction conditions: thiophenol (0.5 mmol), iodobutane (1 mmol), catalyst (2 mol% Rh), ligand (0.03 mmol, 6 mol%), Cs_2CO_3 (0.5 mmol), NaF (0.1 mmol, 20 mol%), dioxane (1.5 mL). [b] GC yields were determined relative to hexadecane internal standard. nbd = 2,5-norbornadiene; cod = 1,5-cyclooctadiene; acac = acetylacetone.

Table 2 Scope of the thiols[a]



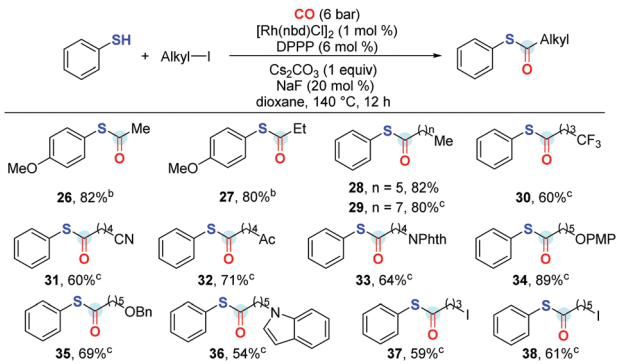
[a] Thiophenols (0.5 mmol), iodobutane (1 mmol), $[Rh(nbd)Cl]_2$ (1 mol%), DPPP (6 mol%), Cs_2CO_3 (0.5 mmol), NaF (0.1 mmol, 20 mol%), dioxane (1.5 mL), isolated yields. [b] The reaction was performed on a 0.2 mmol scale. [c] 0.25 mmol of the thiol was used.

(**5**, **6**), 4-methylthio (**7**), 4-*N*,*N*-dimethylamino (**8**), 4-methoxy (**9**). Meanwhile, electron-withdrawing substituents, including fluoro (**12**, **13**), chloro (**14**), and bromo (**15**) groups, were tolerated as well. It is worth mentioning that methylthio group could be successfully retained (**7**), implying that the reaction did not go through a thioether intermediate. Furthermore, as shown for **16**–**19**, the reaction was not seriously hampered by the presence of *ortho*-substituent. Likewise, naphthylthiols could provide similar yields of **20** and **21**, respectively. The presence of oxygen-containing heterocycles did not interfere the carbonylative coupling (**22**). Subsequently, dithiophenols were successfully converted into the corresponding dithioesters **23**–**24** in good yields. As expected, alkyl mercaptan can be converted into the desired thioester in good yield as well (**25**).

Encouraged by the findings in Table 2, we then evaluated the scope with different alkyl iodides (Table 3). By decreasing or increasing the carbon chain of the alkyl iodides, good yields of the desired products could be obtained without exception (**26**–**29**). Likewise, excellent functional group compatibility was observed including trifluoromethyl (**30**), cyanide (**31**), ketone (**32**), imide (**33**), ethers (**34**, **35**), and indole (**36**). In addition, diiodoalkanes were successfully converted into iodide-substituted thioesters (**37**, **38**), offering potential opportunities for further structure modifications.

As we expected, alkyl bromides could also be successfully converted to the corresponding thioesters with NaI as the additive, although the yields were slightly decreased (Table 4). Here, NaI is needed for the *in situ* alkyl iodides formation *via* Finkelstein reaction[14] and then ready for the designed carbonylation reaction. Without NaI, only a 9% yield of **3** was obtained.

Table 3 Scope of the alkyl iodides[a]

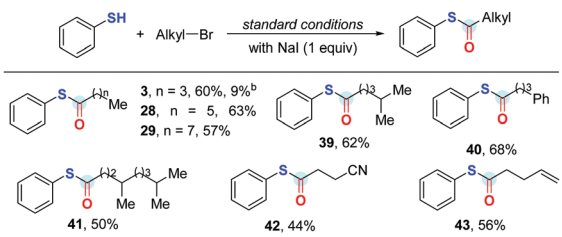


[a] Thiophenol (0.5 mmol), alkyl iodides (1 mmol), $[Rh(nbd)Cl]_2$ (1 mol%), DPPP (6 mol%), Cs_2CO_3 (0.5 mmol), NaF (0.1 mmol, 20 mol%), dioxane (1.5 mL), isolated yields. [b] *p*-Methoxythiophenol was used. [c] The reaction was performed on a 0.2 mmol scale. NPhth = phthalimide group; PMP = *p*-methoxyphenyl; Bn = benzyl.

This is due to the lower activity of alkyl bromides compared to alkyl iodides in carbonylation reactions.[15] In analogy with the results in Table 3, the length of the carbon chain of the alkyl bromides hardly affects the reaction outcomes (**3**, **28**, **29**). Similarly, different alkyl chains (**39**, **40**, **41**) and functional groups such as cyano (**44**), olefin (**43**) could also be equally accommodated in moderate to good yields. Under these conditions, no thioester products could be formed from alkyl tosylates (OTs) or alkyl chlorides.

To gain some mechanistic insight into the reaction pathway, several control experiments were conducted (See ESI‡). Under the standard conditions, the thioether **4** could not be converted to the thioester **3**, which was consistent with the previous result, indicating the carbonylative coupling did not undergo a carbonylation-after-coupling process. Subsequently, to explore whether a radical process was involved, radical trapping, inhibition, and clock experiments were performed. When TEMPO was added into the reaction, the thioester **3** was hardly formed and the radical trapping product **44** was detected by GC–MS. However, **3** could still be obtained in 51% yield even in the presence of 3 equivalent of radical scavenger butylated hydroxytoluene (**BHT**). Furthermore, the radical clock experiment, by the reaction of **1** and iodomethyl-cyclopropane **45** under the standard

Table 4 Scope of the alkyl bromides[a]



[a] Thiophenol (0.5 mmol), alkyl bromides (1 mmol), $[Rh(nbd)Cl]_2$ (1 mol%), DPPP (6 mol%), Cs_2CO_3 (0.5 mmol), NaF (0.1 mmol, 20 mol%), dioxane (1.5 mL), NaI (1 equiv.), isolated yields. [b] Without NaI.

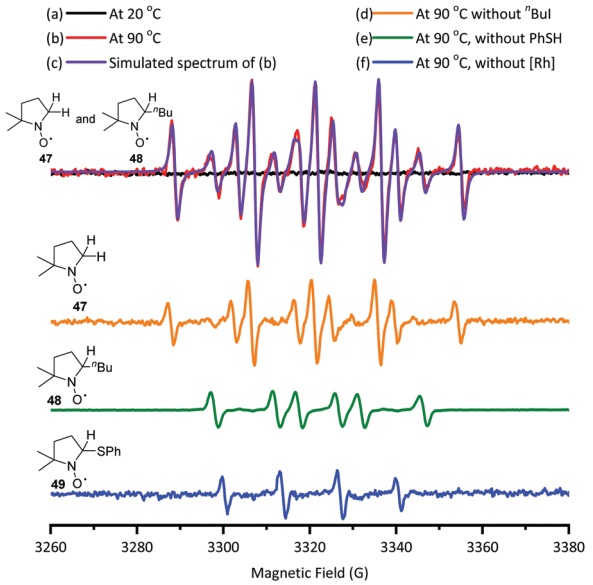
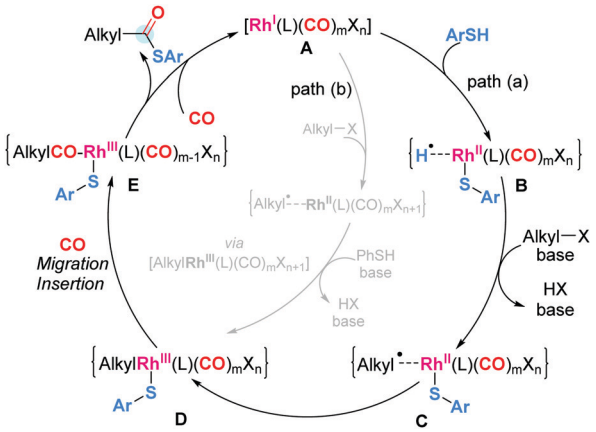


Fig. 1 EPR spectra of the control experiments in the presence of DMPO (0.13 mM) under Ar.

conditions,[16] afforded the ring-opening expansion product **43** in 28% yield along with 35% ring-retaining product **46**. These preliminary studies suggest that the alkyl radical was likely involved, however, instead of free radical, the formation of metal-involved tightly associated or caged radical intermediates more likely.[17]

To further determine the radical pathway[18] and further verify our speculation, *in situ* electron paramagnetic resonance (EPR) experiments were designed utilizing 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) as the spin trap to detect and identify the free radical intermediates (Fig. 1). Under the standard conditions at room temperature, no signal could be detected from the model reaction[19] (Fig. 1a). Two multiple-line EPR signals at g = 2.007 were detected during heating the reaction mixture at 90 °C, due to the formation of DMPO-H (**47**) [A_N = 14.58 G and A_H (2*H*) = 18.59 G] and DMPO-^{n}Bu (**48**) [A_N = 14.68 G and A_H = 18.92 G] spin adducts (Fig. 1b).[20] These spin adducts were nicely fitted by the simulation of the experimental spectrum (Fig. 1c).[21] In the absence of ^{n}BuI, the signal of **47** was still detected (Fig. 1d). On the other hand, without PhSH, the spin adduct of **48** could be detected (Fig. 1e). However, only the DMPO-SPh (**49**) spin adduct was detected in the absence of the rhodium catalyst (Fig. 1f). These results suggest that the H$^\bullet$ and ^{n}Bu$^\bullet$ are involved in the process, and the rhodium catalyst plays a vital role in the formation of them.

To figure out the beginning of the catalytic cycle, we designed additional EPR experiments. At 20 °C under Ar, when PhSH was added to the mixture of the dioxane, $[Rh(nbd)Cl]_2$, DPPP, and Cs_2CO_3, a signal of $[Rh^{II}]$ at g = 2.094 with A_L = 102 G was detected in addition to sharp signal at g =2.006 due to the formation of radical (Fig. S1, a, ESI‡).[22] Meanwhile, the signal decayed very fest with time. Using ^{n}BuI instead of PhSH, the $[Rh^{II}]$ could also be detected, however, the signal was very weak (Fig. S1, b, ESI‡).



Scheme 2 Plausible mechanism.

Based on the above studies and previous reports,[17,23] although a more detailed mechanism requires additional studies, we tentatively propose a plausible scenario as shown in Scheme 2. The rhodium(I) complex **A** irreversibly reacts with the thiol to generate the rhodium(II) tightly associated radical complex **B**. In the presence of base, the carbon-centered radical intermediate **C** is then formed by the radical transfer process. This step is followed by combination of the carbon-centered radical and the rhodium(II) complex. The resulting alkylrhodium(III) species **D** then provide the acylrhodium complex **E** through CO migratory insertion. The overall catalytic conversion is then completed by reductive elimination to produce the final thioester product and meanwhile releases Rh(I) complex for the next catalytic cycle. It is important to note that the possibility, the catalytic cycle begin with the rhodium(I) catalyst abstracts a halogen atom to form the rhodium(II) species, cannot be fully excluded (path b).

In summary, we have discovered a rhodium-catalyzed carbonylative coupling of thiophenols with alkyl halides. This study suggests that rhodium catalyst might lead to the foundation of discoveries within the field of carbonylative coupling of alkyl halides and strong nucleophiles. The wide substrates scope of the method suggests this protocol can be a powerful alternative to known methodologies for thioesters synthesis. The mechanism studies support a proposed organometallic-radical pathway.

Conflicts of interest

There are no conflicts to declare.

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