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Nickel-Catalyzed Reductive Aryl Thiocarbonylation of Alkene via Thioester Group Transfer Strategy

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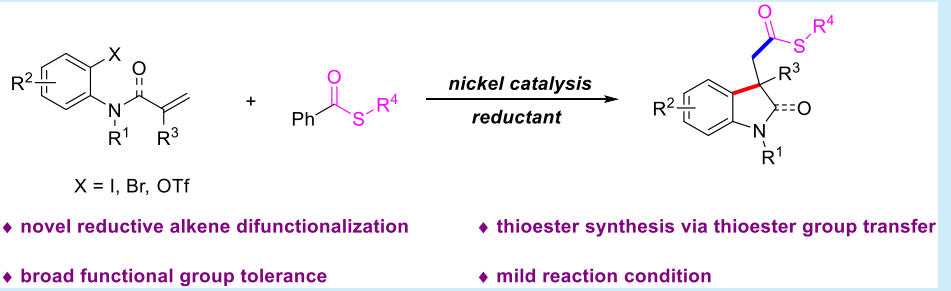
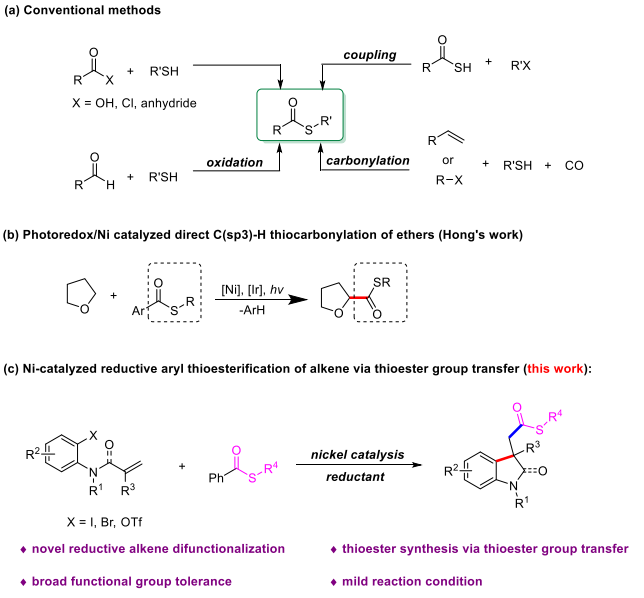


ABSTRACT: Herein reported is a nickel-catalyzed reductive aryl thiocarbonylation of alkene via thioester group transfer strategy by using simple and readily available thioesters. In contrast to traditional activation of weaker C(acyl)−S bond, the C(acyl)−C bond of thioester was selectively cleaved to enable this reaction under mild conditions. Furthermore, this approach features operational simplicity and broad substrate scope, providing a complementary and practical route for thioester synthesis without requiring toxic thiol or CO gas.

The incorporation of thioester moiety into an organic molecule is highly attractive, since this structural motif not only plays a critical role in biological processes such as metabolism[1] and cellular function regulation,[2] but also serves as valuable building blocks[3] and versatile intermediates in organic synthesis.[4] In this context, many efforts have been directed to the construction of thioester through different strategies. Among all these methods, the most straightforward methodology for thioester synthesis involves the reaction of a thiol with an activated carboxylic acid derivative,[5] or the coupling between a thioacid and an electrophile.[6] However, both approaches suffer from significant limitations, because of the harsh reaction conditions, high oxidation state carbon-based reactants, and sensitivity of thiols toward oxidation, thereby restricting the utilities of the reactions. Alternatively, several synthetically useful methods have been developed, including the oxidative coupling of aldehydes with thiols[7] and the transition-metal-catalyzed thiocarbonylation of alkenes or organic halides with carbon monoxide gas.[8] Most of these methodologies require either thiols with a repulsive odor or toxic CO gas, and a suitable coupling partner is often essential, bearing similar limitations to conventional syntheses (Scheme 1a). As an analogue of carboxylic acid, thioester has been intensively investigated as coupling partner in ketone synthesis via selective activation of a relatively weak C(O)−S bond.[9] Reports on the direct use of the thiocarbonyl group as a thioester source are scarce; only a single recent example using photoredox/metal

Scheme 1. Thioester Synthesis



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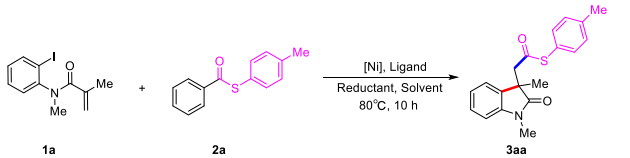
dual catalysis to achieve thioester group transfer via an unprecedented selective C(acyl)−C bond activation has been disclosed by Hong and co-workers, in which diverse aryl thioesters could be synthesized in high yields. However, the use of aliphatic thioester failed as coupling partner in this reaction (Scheme 1b).[10] Given the importance of thioester, the development of a novel and practical route for their synthesis is highly desirable.

In recent years, nickel-catalyzed reductive difunctionalization of alkene, which allows the installation of two electrophiles across the C═C double bond, has emerged to be a powerful tool for the preparation of valuable polyfunctionalized compounds.[11] In comparison with classical alkene difunctionalization with an electrophile and a nucleophile, reductive alkene difunctionalization avoids the preparation of sensitive organometallics and allows the reaction to proceed under mild conditions.[12,13] Through this strategy, nickel-catalyzed three-component reductive dicarbofunctionalization of alkenes has been developed to achieve alkene alkylarylation, diarylation, and alkylacylation by the groups of Nevado,[12a,b] Diao,[12c,d] and Chu,[12e,f] respectively. Moreover, Diao,[12d] Wang,[13a−f] Peng,[13g−i] Kong,[13j−l] and Shu[13m] independently described reductive alkylarylation, dialkylation, diarylation, and arylalkenylation of organohalide-tethered alkenes. Despite the impressive success mentioned above, it is highly attractive to develop a novel nickel-catalyzed difunctionalization protocol to enrich scope of functional group introduced across the C═C bond. In continuation of our interest in alkene difunctionalization and to explore another reaction pattern of thioester, we herein describe a nickel-catalyzed reductive aryl thiocarbonylation of alkene via the thioester group transfer strategy by using simple and readily available thioester molecule as a thioester source (see Scheme 1c).

We commenced our study with acrylamide **1a** and S-(*p*-tolyl) benzothioate **2a** as standard substrates to identify the optimal conditions, and typical results are summarized in Table 1. Unfortunately, no desired product of **3aa** was observed under the conditions of $NiCl_2$ (10 mol %), **L1** (2,2′-bipyridine, 10 mol %), and zinc powder (0.6 mmol) in toluene at 80 °C for 10 h (Table 1, entry 1). Optimization of the conditions indicated that the solvent played an important role on this transformation: when using dimethyl formamide (DMF) as the solvent, the targeted product **3aa** was isolated in 50% yield (Table 1, entry 4), although full conversion was not reached. In the case of N-methyl-2-pyrrolidone (NMP), the isolated yield dramatically increased to 74% with all starting materials consumed; and other mediate polar solvents such as acetonitrile and 1,4-dioxane (Table 1, entries 2 and 3) failed to maintain the process of the coupling reaction. Further attempts made by using mixed solvents showed that a 1:1 mixture of NMP and dimethyl sulfoxide (DMSO) was found to be the optimal choice of solvent, affording **3aa** in 85% yield (Table 1, entries 6, 7 and 8). Conducting reactions with other nickel salts resulted in a slight decrease in yields (Table 1, entries 9−13), and the use of $Ni(NO_3)_2{\cdot}6H_2O$ completely shut down this transformation. The screening of ligands revealed that 2,2′-bipyridine was the best choice, and other substituted bipyridine or diazaphenanthrene ligands (Table 1, entries 14−17) promoted this reaction with low efficiency. Replacing Zn with Mn as the reductant led to diminished yield (Table 1, entry 18), but the reaction did not proceed when B_2Pin_2 was used (Table 1, entry 19). Finally, we defined the optimized criteria: $NiCl_2$ (10 mol %), L1 (10 mol %), and zinc powder (0.6 mmol) as the reductant, in a 1:1 mixed solvent of NMP (1 mL) and DMSO (1 mL) at 80 °C for 10 h under a N_2 atmosphere.

Table 1. Optimization of Reaction Conditions[a]



entry	Ni catalyst	ligand	solvent	yield (%)[b]
1	$NiCl_2$	L1	toluene	NR
2	$NiCl_2$	L1	CH_3CN	0
3	$NiCl_2$	L1	dioxane	NR
4	$NiCl_2$	L1	DMF	50
5	$NiCl_2$	L1	NMP	74
6	$NiCl_2$	L1	NMP/DMSO = 1:1	85
7	$NiCl_2$	L1	NMP/CH_3CN = 1:1	45
8	$NiCl_2$	L1	NMP/dioxane = 1:1	47
9	$NiCl_2{\cdot}6H_2O$	L1	NMP/DMSO = 1:1	74
10	$Ni(acac)_2$	L1	NMP/DMSO = 1:1	67
11	$NiCl_2{\cdot}DME$	L1	NMP/DMSO = 1:1	75
12	$Ni(NO_3)_2{\cdot}6H_2O$	L1	NMP/DMSO = 1:1	0
13	$Ni(COD)_2$	L1	NMP/DMSO = 1:1	74
14	$NiCl_2$	L2	NMP/DMSO = 1:1	81
15	$NiCl_2$	L3	NMP/DMSO = 1:1	78
16	$NiCl_2$	L4	NMP/DMSO = 1:1	77
17	$NiCl_2$	L5	NMP/DMSO = 1:1	72
18	$NiCl_2$	L1	NMP/DMSO = 1:1	56[c]
19	$NiCl_2$	L1	NMP/DMSO = 1:1	0[d]

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), Ni catalyst (10 mol %), ligand (10 mol %), Zn (0.6 mmol), solvent (2.0 mL), sealed Schleck tube, N_2 atmosphere, 80 °C, 10 h. [b]Isolated yields. NR = No Reaction. [c]Mn was used. [d]B_2Pin_2 was used.

With the optimized conditions in hand, we then focused on exploring the substrate scope of this nickel-catalyzed aryl thiocarbonylation, with respect to an array of thioesters (Scheme 2). Generally, diverse aryl thioesters were applied for this reaction with synthetically useful yields for corresponding products. Aryl thioesters with different alkyl groups including methyl (**3aa**, **3ab**, **3ai**) and *t*-butyl (**3ae**) at the *ortho*-, *meta*-, and *para*-positions were proven to be competent coupling partners, affording the desired products in decent to moderate yields. Methoxyl-substituted aryl thioesters (**3af**−**3ah**) reacted smoothly to give yields of 78%−81%, regardless of the positions on the aromatic rings. Interestingly, reactions with substrates bearing halogens (**3ac**−**3ad**) at the ring of arylthiols were accomplished readily and delivered products in valuable yields, which provided functional handles for further modification via classic coupling reactions. In comparison with unsubstituted aryl thioester, which afforded alkene difunctionalization product in 83% yield (**3aj**), the use of 2-naphthyl thioester (**3ak**) led to an obvious decrease in yield, presumably because of the electronic difference between naphthyl and phenyl. However, replacing the phenyl ring to the 2-thiophenyl group resulted in a moderate yield of product obtained (**3al**). Notably, aliphatic thioesters (**3am**−**3ao**), which exhibited no reactivity under photoredox/nickel dual catalysis in previous Hong's work,[10] were found to be effective substrates and furnished the corresponding products in

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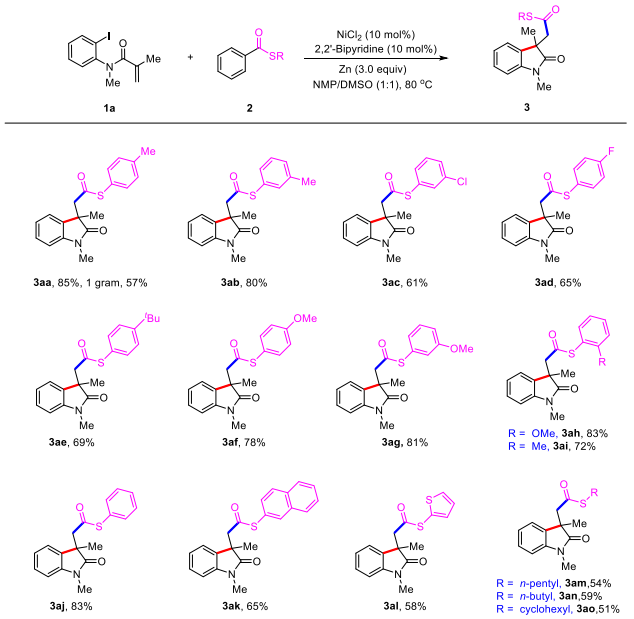
Scheme 2. Substrates Scope of Thioesters[a,b]

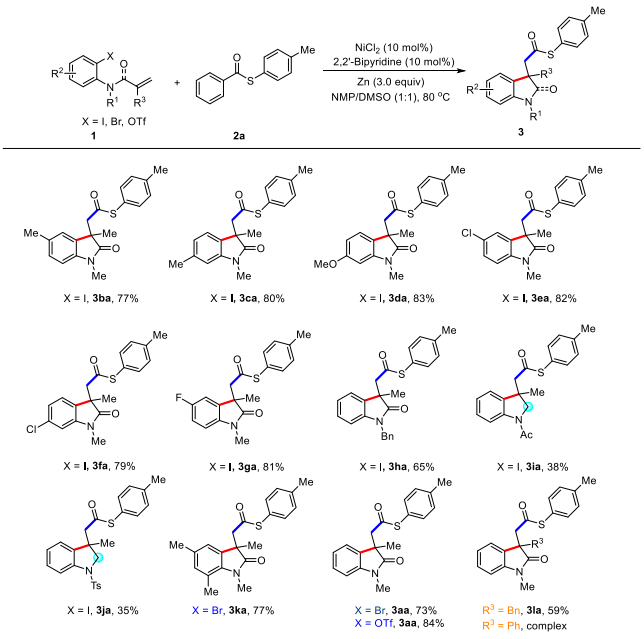


[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), $NiCl_2$ (10 mol %), 2,2′-bipyridine (10 mol %), zinc powder (3.0 equiv), 80 °C, 10 h. [b]Isolated yields.

moderate yield. In addition, this transformation could be scaled up to 1-g quantities (**1a**, 1.0 g, 3.3 mmol), and targeted compound **3aa** was isolated in 57% yield.

Next, the substrate scope of aryl halides compatible with this approach was investigated by coupling with (*p*-tolyl) benzothioate **2a** (Scheme 3). A wide range of aryl iodides with substituents at different positions were found to be amenable to this nickel-catalyzed reductive alkene difunctionalization

Scheme 3. Scope with Respect to Aryl Halides[a,b]

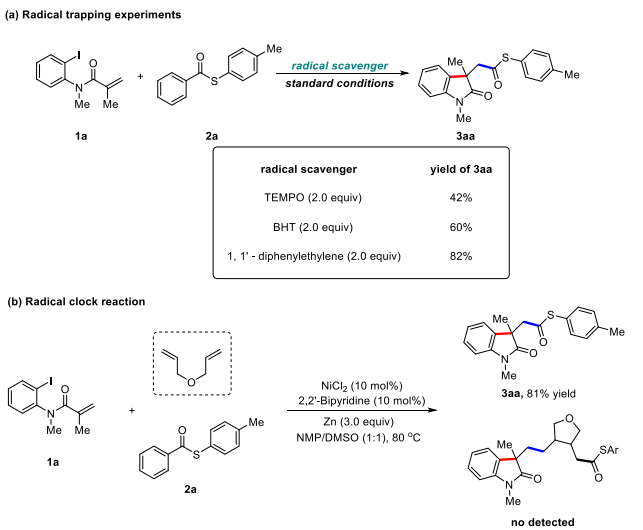


[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), $NiCl_2$ (10 mol %), 2,2′-bipyridine (10 mol %), zinc powder (3.0 equiv), 80 °C, 10 h. [b]Isolated yields.

process, and the desired thioesters **3ba**−**3ga** were obtained in moderate to good yields. This approach also exhibited good functional group compatibility: various groups in targeted products, including methyl (**3ba**, **3ca**), methoxy (**3da**), chlorine (**3ea**, **3fa**), and fluorine (**3ga**), were tolerated. In addition, the effect of substituent at nitrogen on this transformation was also studied. When replacing *N*-methyl with *N*-benzyl (**3ha**), the reaction could still proceed smoothly, albeit 65% isolated yield of product observed, which could be further converted to N−H oxindole by removal of the benzyl group. Inspired by these results, we considered functionalizing unactivated alkenes. However, substrates bearing the *N*-(2-methylallyl) moiety, such as **1i** and **1j**, proved to be challenging coupling partners with low efficiency, only resulting in a low amount of thioester products. Subsequently, we investigated the effects of the electrophile, and we found that aryl bromide was slightly less reactive than aryl iodide, delivering corresponding product **3aa** in 73% yield. Another aryl bromine substrate containing two methyl groups was also tested to provide desired **3ka** in 77% yield. Aryl triflate was also a competent substrate, exhibiting efficiency similar to that of aryl iodide. Other substituted acrylamides were then examined under standard conditions. Among them, only the benzyl-substituted substrate was smoothly converted to the corresponding product in 59% yield (**3la**). However, only a complex mixture was formed when 2-phenylacrylamide was used, with all substrates consumed.

A series of control experiments was performed to gain insights into the mechanism of this nickel-catalyzed reductive alkene arylthiocarbonylation. When radical scavenger TEMPO was added to the standard conditions, the reaction still reacted smoothly with product **3aa** being afforded only in 42% isolated yield. Considering the toxic effect of TEMPO on Ni catalyst, this finding was not adequate to serve as proper evidence in favor of a radical-involved process. In contrast, the reactions proceeded cleanly in the presence of other radical scavengers, such as BHT and 1,1′-diphenylethylene, and targeted product **3aa** was produced in the yields of 60% and 82%, respectively (Scheme 4a). Moreover, a radical ring closing experiment was performed by subjecting diallyl ether to the reaction system, and only alkene difunctionalized product was observed, whereas ring-closing product was not obtained (Scheme 4b). Taking these above results into consideration, we could exclude the possibility

Scheme 4. Mechanistic Investigations



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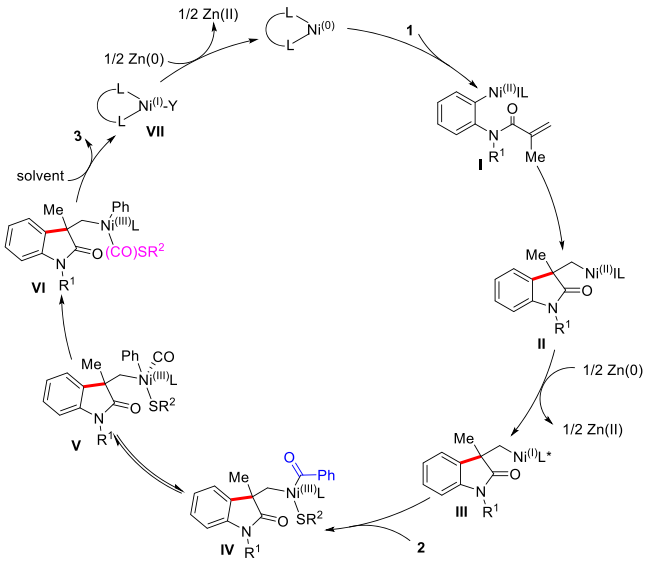
of existence of the C-center radical generated by homolytic Ni-alkyl bond cleavage after the migratory insertion process.

On the basis of the above-mentioned experimental results as well as previous literature reports from Kong,[13i] Nevado,[12a,b] and Hong,[10] a plausible catalytic cycle for this transformation is proposed as depicted in Scheme 5. Initially, catalytically active

Scheme 5. Plausible Catalytic Cycle



Ni(0), formed in situ under reductive conditions, undergoes oxidative addition with aryl iodide **1** to produce Ni(II) species **I**. Next, migratory insertion of intermediate **I** into double bond affords a σ-alkyl-Ni(II) complex **II**. Upon reduction with stoichiometric Zn(0), a more nucleophilic σ-alkyl-Ni(I) complex **III** is furnished, and then the relatively weak C(acyl)-S bond of thioester **2** preferably oxidative adds to complex **III** to give acyl-Ni(III) species **IV**, which goes through decarbonylation with the formation of intermediate **V**. Subsequently, CO migratory insertion into Ni(III)-S bond generates complex **VI**. Finally, reductive elimination of complex **VI** furnishes the desired product **3**, together with a Ni(I) species, which could undergo hydrogen abstraction from solvent following by reduction by Zn(0) to regenerate catalytically active Ni(0).

In summary, we developed the first nickel-catalyzed reductive aryl thiocarbonylation of alkene via the thioester group transfer strategy by using bench-stable and readily available thioester molecule as thioester source without the requirements of toxic thiol or CO gas. This approach demonstrated broad substrate scopes: aryl, heteroaryl, and even aliphatic thioesters are compatible. Furthermore, this approach features operational simplicity and mild conditions, providing complementary and novel routes for thioester synthesis. The further detail of mechanism is still under exploration in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02091.

Experimental details, characterization data, and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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