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Advanced Synthesis & Catalysis

Palladium-Catalyzed Alkene Thioacylation: A C–S Bond Activation Approach for Accessing Indanone Derivatives

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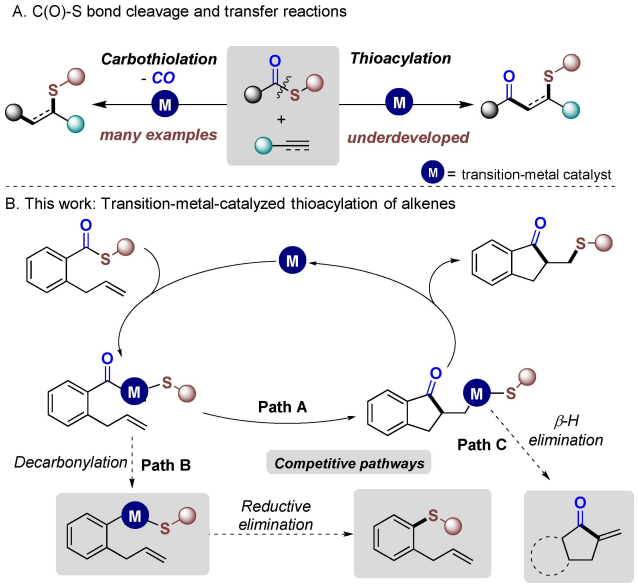
Abstract: A palladium-catalyzed intramolecular alkene thioacylation reaction initiated by the activation of thioester C(acyl)–S bonds is reported. This approach successfully suppressed decarbonylation and β-hydrogen elimination with related acyl and alkyl metal thiolate intermediates, providing an efficient and atom-economical method to access indanone scaffolds. Mechanistic studies provide support for C(acyl)–Pd bond insertion of olefins. The synthetic utility of this protocol is demonstrated by the further conversion of the newly formed methylene sulfide substituent.

Keywords: Thioacylation; Thioester; C–S Bond activation; Palladium catalysis; Indanone

The transition-metal-catalyzed "cut and sew" transformation has recently emerged as a useful strategy for preparing complex molecular structures.[1] This strategy provides efficient access to substituted molecules from readily available alkenes by installing functional groups across their carbon–carbon double bonds. Molecular complexity can be built by coupling olefins with a range of simple, readily available starting materials, such as aldehydes,[2] ketones,[3] esters,[4] and amides.[5]

Thioesters are more reactive than alcohol-derived esters because of the poorer orbital overlap between the sulfur atom and the carbonyl group. They have similar reactivity to acyl chloride, but they are bench stable and can be stored for a long time.[6] Thioesters can be synthesized using various methods based on acylation chemistry or metal-catalyzed transformations. The decarbonylative addition of thioesters to unsaturated bonds represents an attractive approach for the simultaneous introduction of carbon and sulfur functional groups,[7] demonstrated in the pioneering works of Pt-catalyzed carbothiolation of alkynes,[8a] as well as the recent work of Matsubara et al. on Ni-catalyzed reactions.[8b–d] In contrast, transition-metal-catalyzed thioacylation of unsaturated systems, especially for alkene, is relatively underdeveloped (Scheme 1A).[9–11] The hitherto known successful examples are limited to the use of activated olefins such as allenes[9c] and norbornenes.[9e]

Motivated by the pivotal role of C–S bond formation in organic synthesis and the pharmaceutical importance of sulfur-containing compounds,[12] we wanted to explore the feasibility of using a "cut and sew" approach by investigating thioesters. The intramolecular insertion of olefins into the C(acyl)–S bonds of thioesters, which proceed much faster than intermolecular reactions and are easier to control in transition-metal-catalyzed reaction, leads to an indanone framework, which is a key motif in a number of biologically important natural products (Figure 1).[13] However, achieving the desired C–S bond formation is not trivial (Scheme 1B, Path A) because decarbonylative products are generally dominant when olefin insertion is slow (Scheme 1B, Path B),[14] and alkyl metal thiolate intermediates tend to undergo β-hydride elimination rather than the desired C–S bond formation (Scheme 1B, Path C).[15] Herein, we describe the development of a palladium-catalyzed olefin thioacylation reaction of thioesters for rapid access to indanone.



Scheme 1. Transition-metal-catalyzed C(O)–S bond cleavage and transfer reactions.

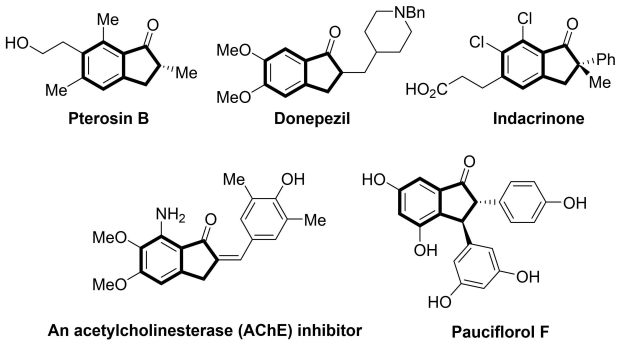
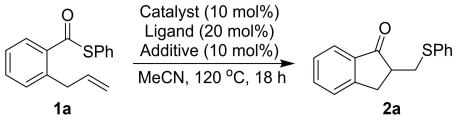


Figure 1. Representative biologically active molecules derived from indanone derivatives.

For optimization of the reaction conditions, we utilized thioester **1a**, which incorporates a terminal olefin, as a standard substrate. Initially, various types of Pd, Ni, and Rh catalysts, which have previously been successfully used in the activation of C(acyl)–S bonds,[12] were tested (Table 1, entries 1–7). As anticipated, these catalysts afforded the desired product **2a**, as confirmed by X-ray crystallography,[16] and a promising result was achieved using $PdCl_2$ as the catalyst (Table 1, entry 6). Although the reactions with $Ni(cod)_2$, $Ni(acac)_2$ and $Pd(OAc)_2$ gave the products in comparable yields, a complex mixture with decomposition of the starting material was observed (Table 1, entries 1, 2 and 5). Next, other ligands were tested to improve the reaction efficiency, and dppb was determined to be the best (Table 1, entries 8–11). Attempts with additives succeeded in improving the reaction performance, and KF displayed the best result,[17]

Table 1. Optimization of reaction conditions.[a]



entry	catalyst	ligand	additive	yield (%)[b]
1	$Ni(cod)_2$	dppb	–	54
2	$Ni(acac)_2$	dppb	–	52
3	$Ni(PPh_3)_2Cl_2$	dppb	–	22
4	$Pd(PPh_3)_4$	dppb	–	49
5	$Pd(OAc)_2$	dppb	–	55
6	$PdCl_2$	dppb	–	57
7	$[Rh(OH)(cod)]_2$	dppb	–	8
8	$PdCl_2$	dppp	–	< 5
9	$PdCl_2$	PPh_3	–	48
10	$PdCl_2$	IMes·HCl	–	n.r.
11	$PdCl_2$	2,2'-bipyridine	–	n.r.
12	$PdCl_2$	dppb	NaF	67
13	$PdCl_2$	dppb	KF	79
14	$PdCl_2$	dppb	K_2CO_3	63
15[c]	$PdCl_2$	dppb	KF	51

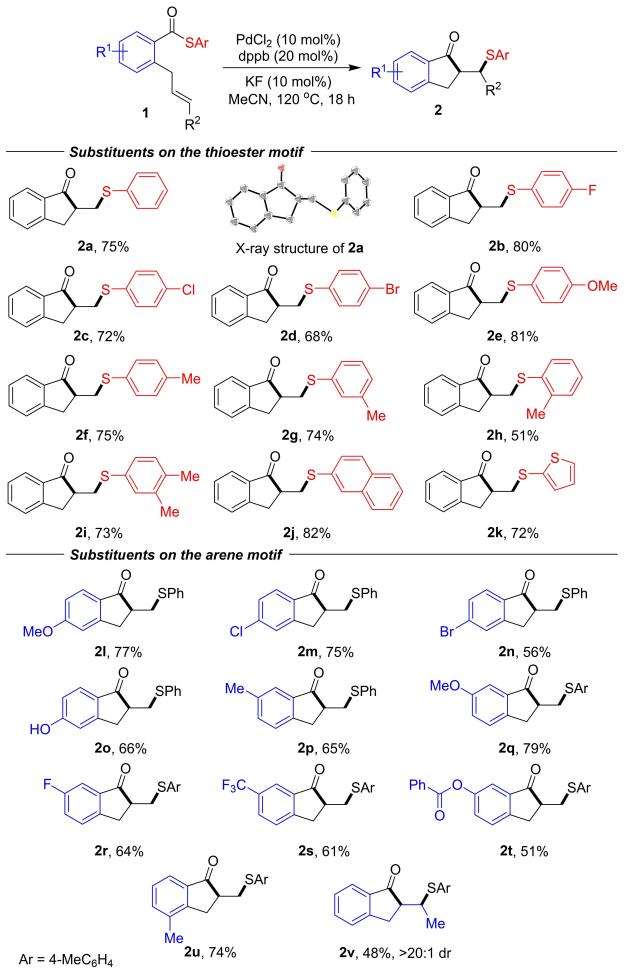
[a] Reaction conditions: **1a** (0.1 mmol), catalyst (10 mol%), ligand (20 mol%), additive (10 mol%) in MeCN at 120 °C for 18 h.
[b] The yield was determined by ^1H NMR using CH_2Br_2 as an internal standard.
[c] $PdCl_2$ (5 mol%) and dppb (10 mol%) were used.

improving the yield to 79%. Finally, reducing the catalyst loading resulted in diminished yields, with the formation of **2a** with 51% yield.

With the optimized reaction conditions determined, the substrate scope with regard to the thioester was examined. As shown in Table 2, a range of thioesters smoothly underwent the olefin thioacylation reaction to deliver an indanone in moderate to high yields (Table 2, **2a**–**2k**). Indanone **2a** was isolated in 75% yield, and other thioesters with electron-withdrawing (**2b**–**2d**) and electron-donating (**2e**–**2g**) substituents, at either the *para* or *meta* position, were similarly efficient. Disubstituted phenyl (**2i**) and 2-naphthyl (**2j**) substituents could also be readily incorporated. Furthermore, heterocyclic thioesters (**2k**) can readily participate in this reaction. It is notable that the sterically hindered thioester provided indanone **2h** in a moderate yield of 51%, accompanied by the recovery of **1h** in 38% yield. Alkyl thioesters with benzyl and ethyl substituents were also investigated, but no product was observed.[18]

After examining the influence of the thioester on the reactivity, the effect of substitution on the arene moiety was evaluated. A broad range of functional groups can readily generate indanone products (**2l**–**2v**). Methyl and electron-rich methoxy groups at the 3-, 4-, or 5-positions of arene all gave the thioacylation

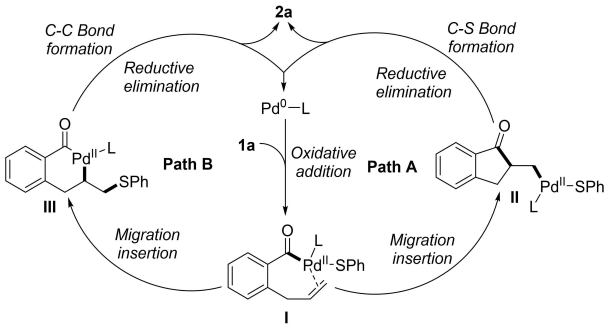
Table 2. Substrate scope of Pd-catalyzed olefin thioacylation reaction of thioesters.[a,b]



[a] Reaction conditions: **1** (0.1 mmol), $PdCl_2$ (10 mol%), dppb (20 mol%), KF (10 mol%) in MeCN at 120 °C for 18 h.
[b] Isolated yield.

products in moderate to good yields (**2u**, **2l** and **2p**, **2q**). Halide-functionalized substrates, such as chloro- (**2m**) and bromo- (**2n**) thioesters, which are generally reactive moieties in transition metal catalysis, are well tolerated. The use of substrates containing a fluoride (**2r**) or trifluoromethyl group (**2s**), both of which are critical in medicinal chemistry, gave rise to products smoothly. As demonstrated by the synthesis of **2o**, substrates bearing free phenol could also be utilized. It is important that full selectivity for C(acyl)–S activation was observed in the reaction of ester- and thioester-containing substrates (**1t**), attesting to the high chemoselectivity of this protocol. Finally, arene containing a substituted allyl unit was also evaluated, forming the desired product in moderate yield (**2v**).

Two different pathways to achieve the desired products are proposed in Scheme 2. Initially, the active Pd(0) catalyst can oxidatively add to the thioester



Scheme 2. Proposed mechanism.

C(acyl)–S bond to form aroyl palladium(II) intermediate **I**. At this stage, two pathways are possible: one is the migration insertion of the C(acyl)–Pd bond into the olefin (Scheme 2, Path A), which undergoes reductive elimination to form the product. An alternative path is the olefin insertion into the Pd–S bond (Scheme 2, Path B), and the subsequent reductive elimination via intermediate **III** to form the product.

To gain mechanistic insights, a preliminary DFT study was conducted. Two possible mechanistic pathways are shown in Figure 2. The catalytic cycle starts with coordination between the Pd(0) complex and substrate **1a**, giving catalyst-substrate complex **INT0**. **INT0** undergoes oxidative addition via **TS1**, requiring an activation free energy of 6.3 kcal mol^{-1}. This step is exoergic by 0.2 kcal mol^{-1} and generates **INT1**. In Path A, olefin migration insertion into the C(acyl)–Pd bond converts **INT1** to **INT2-A** (via **TS2-A**), followed by C–S reductive elimination (via **TS3-A**) to give the product. An alternative path is olefin insertion into the Pd–S bond (Scheme 2, Path B), which generates **INT2-B** (via TS2-B) for the C(acyl)–C reductive elimination (via **TS3-B**) to form the product. The reductive elimination processes (**TS3-A** and **TS3-B**) have the highest energy barriers in these two pathways. **TS3-A** is more stable than **TS3-B** by 8.3 kcal/mol, which indicates that the C–S reductive elimination (Path A) is preferred.

To demonstrate the significance of the developed protocol further, we performed a gram-scale reaction, and the reaction proceeded smoothly to afford the corresponding product **2f** in comparable yield (Scheme 3). In addition, considering the potential of this methodology for the construction of indanone for diverse applications, a reduction of **2f** followed by a Friedel-Crafts-type cyclization was performed, producing polycycle product **3a** (Scheme 3, eq A).[19] Selective oxidation of **2f** and further functionalization can be achieved by transferring the C–S bond to a C–C bond (Scheme 3, eq B).[20] The thioether group can also be removed under mild conditions, and further cyclization giving polycycle product **3c** with the presence of P(*p*-tolyl)$_3$ and PBu_3 (Scheme 3, eq C).[21]

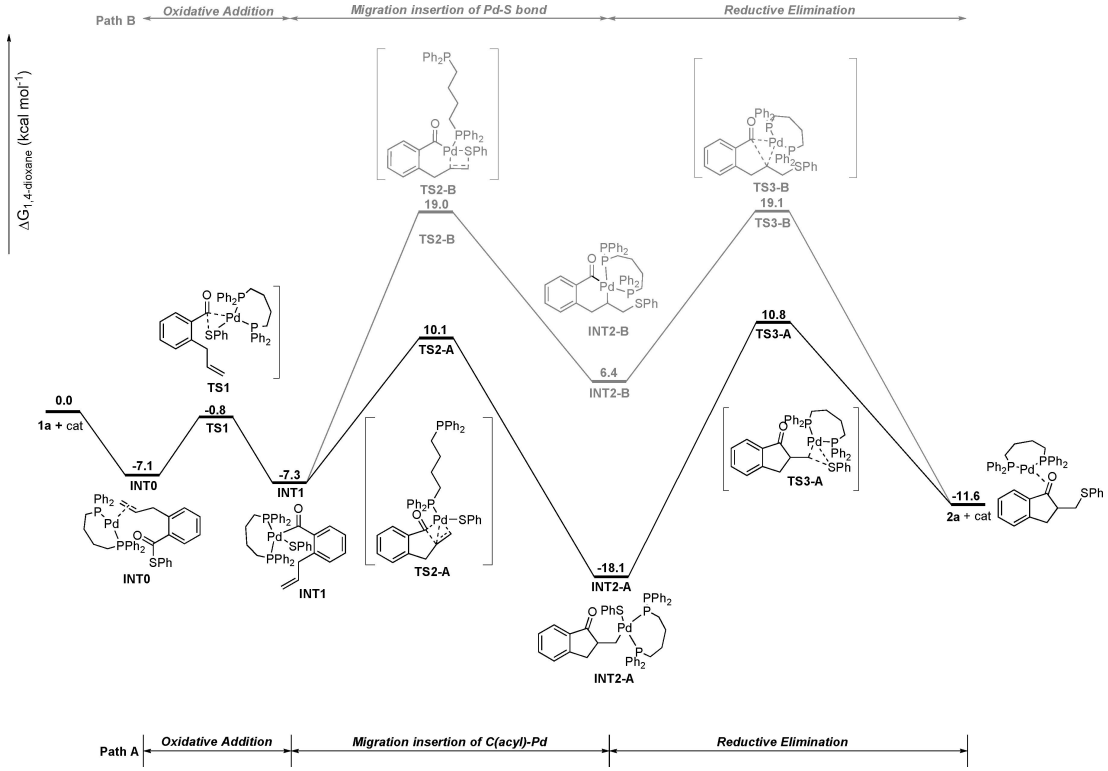
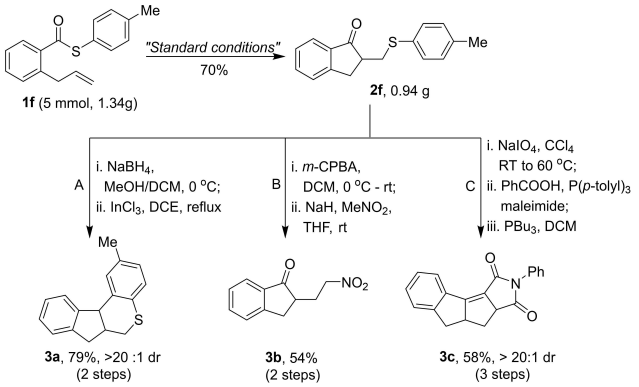


Figure 2. DFT-calculated reaction energy profile of Pd-catalyzed alkene thioacylation.



Scheme 3. Derivatization of products.

In conclusion, we developed a Pd-catalyzed intramolecular alkene thioacylation reaction initiated by the activation of thioester C(acyl)–S bonds. This process tolerated variation on both the alkene and aryl moieties, providing an efficient and atom-economical method to access indanone scaffolds. Most importantly, this approach successfully suppressed decarbonylation and β-hydrogen elimination with the related acyl and alkyl metal thiolate intermediates, furthering the utility of thioesters as powerful building blocks in organic synthesis. DFT studies demonstrated that the likely mechanism involves C(acyl)–Pd bond insertion of olefins. Further studies aimed at expanding the scope of thioester-based coupling are ongoing in our group and will be reported in due course.

Experimental Section

General experimental procedures of intramolecular coupling. In a nitrogen filled glove box, a 2.0 mL vial was charged with the thioester substrates (**1**, 0.1 mmol), $PdCl_2$ (1.8 mg, 0.01 mmol), dppb (8.5 mg, 0.02 mmol) and potassium fluoride (0.6 mg, 0.01 mmol). After adding 0.5 mL CH_3CN, the vial was capped and the solution was maintained at 120 °C for 18 h. Upon completion, it was cooled to room temperature and the solvent was removed by rotary evaporator under reduced pressure. The crude product was directly purified by silica gel flash chromatography to yield **2**.

Acknowledgements

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[16] CCDC-2059279 (**2 a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam. ac.uk/data-request/cif.

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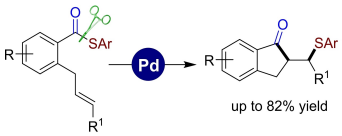

- Unique reactivity of thioesters
- High functional group tolerance
- Valuable indanone derivatives
- Completely atom-economical protocol