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Graphical Abstract

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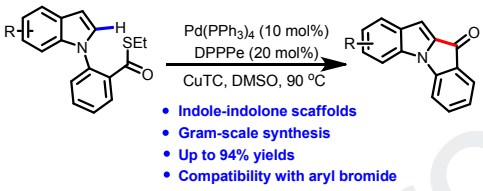

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Palladium-catalyzed Intramolecular C–H Acylation of Indoles with Thioester

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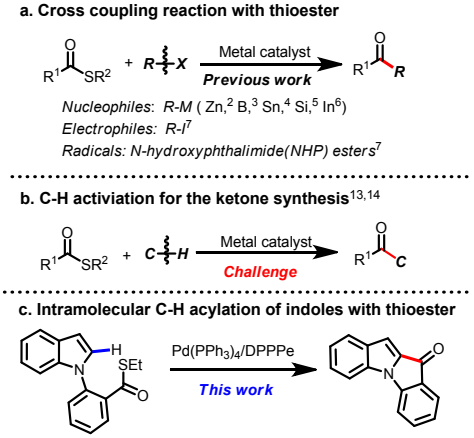
ABSTRACT

A palladium-catalyzed intramolecular C–H acylation of indole with thioester is described, providing a direct and effective approach for the synthesis of the biologically active indole-indolone scaffolds. The method obviates the need for the prefunctionalized starting materials including organometallic reagents, alkyl halides, and NHP esters in previous metal-catalyzed cross-coupling reaction with thioester. Substrates bearing sensitive halo groups are compatible in the reaction, leaving a functional handle for further structural elaborations.

Thioesters, as versatile building blocks in organic chemistry, has been successfully applied in the metal-catalyzed ketone synthesis due to their highly chemoselective activation of C(O)–S bond by oxidative addition to a low-valent transition metal.[1] In 1998, Fukuyama reported a novel ketone synthesis by the palladium-catalyzed coupling reaction of thioesters with nucleophilic organozinc reagent (Scheme 1a).[2] The reaction proceeded *via* a C–S bond activation/C–C bond formation sequence under the mild condition. Subsequently, by using air- and moisture-stable, relatively low toxic organoboron reagent as coupling partner, Liebeskind and Srogl reported a mechanistically unprecedented ketone synthesis with thioester under "baseless" conditions, which is known as Liebeskind-Srogl cross-coupling reaction.[3] Since then, organotin,[4] organosilicon,[5] and organoindium[6] were employed as the nucleophilic metallic reagent in the palladium-catalyzed ketone synthesis with thioester. Beside these nucleophilic organometallic reagents, Weix group developed novel ketone synthesis by Ni-catalyzed cross-electrophile coupling of thioester with alkyl halides or N-hydroxyphthalimide (NHP) esters as alkyl radical donors (Scheme 1a).[7] Despite significant progresses have been made, prefunctionalized starting materials are required in these protocols, which will add costly chemical steps to the ketone construction. Thus, the development of more efficient methodologies that utilizes the readily available starting material would be highly desirable.



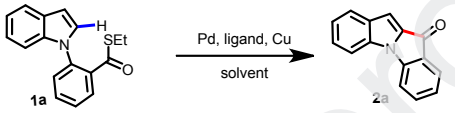
Scheme 1 Metal-catalyzed ketone synthesis with thioester

Recently, transition-metal-catalyzed C–H activation has drawn significant attentions due to the merit of obviation of the halogenation or stoichiometric metalation of starting materials.[8] Pd-catalyzed C–H acylation of arenes by using aldehyde,[9] α-oxocarboxylic acids[10], acyl

ion of arenes with thioester is still a challenge problem and rarely reported (Scheme 1b). In 2016, Gu reported a Pd/norbornene/Cu-catalyzed *ortho* C−H acylation and *ipso* thiolation reaction of aryl halides with thioesters.[13] Recently, by using dual catalyst system containing Ni catalyst and Ir photosensitizer, Doyle realized the direct *α*-C−H acylation of N-phenyl pyrrolidine with thioester.[14] To develop an alternative and improved avenue for the ketone synthesis, we questioned whether we could harness C–H as the starting material in lieu of organometallic reagents and alkyl halides to couple with thioester. Herein, we report the first example of palladium-catalyzed intramolecular C–H acylation of indole derivatives with thioester (Scheme 1c).

Considering the high importance of the indole and indolone derivatives in pharmaceuticals and agrochemicals, the development of new methodologies is an important objective in organic chemistry.[15] In this manuscript, we commenced our studies by treating indole-contained thioester **1a** with 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, and 0.3 mmol CuTc at 90 °C, To our delight, C-2 acylated indole-indolone scaffolds were obtained exclusively in 26% yields (entry 1, Table 1). Other palladium catalyst were also examined, and $Pd(PPh_3)_4$ could give the desired product in 30% yields (entry 2-4). Phosphine ligands play an important role in palladium-catalyzed C–H activation. So we screened various phosphine ligands, and found DPPPe gave the desired product in 58% yields (entry 5-10). The influence of solvent was also examined, and DMSO shown the best results (entry 11-14). Furthermore, we could improve the yield to 77% by increase the concentration of **1a** to 0.1 M (entry 15). No desired product **2a** was observed in the absence of $Pd(PPh_3)_4$ or CuTC (entry 16, 17). In Liebeskind-Srogl cross-coupling reaction, Cu salts were required to facilitate the transmetalation by forming a stronger Cu–S bond, or acting as a reactive transmetalation center.[3] So we screened some Cu salts, and found that CuOAc and $Cu(OAc)_2$ could also gave the desired products in 38% and 46% yields, respectively (entry 18-21). Finally, the optimal conditions involved the following parameters: 10 mol% $Pd(PPh_3)_4$, 20 mol% DPPPe, 3 equivalents of CuTc in 0.5 mL DMSO at 90 °C.

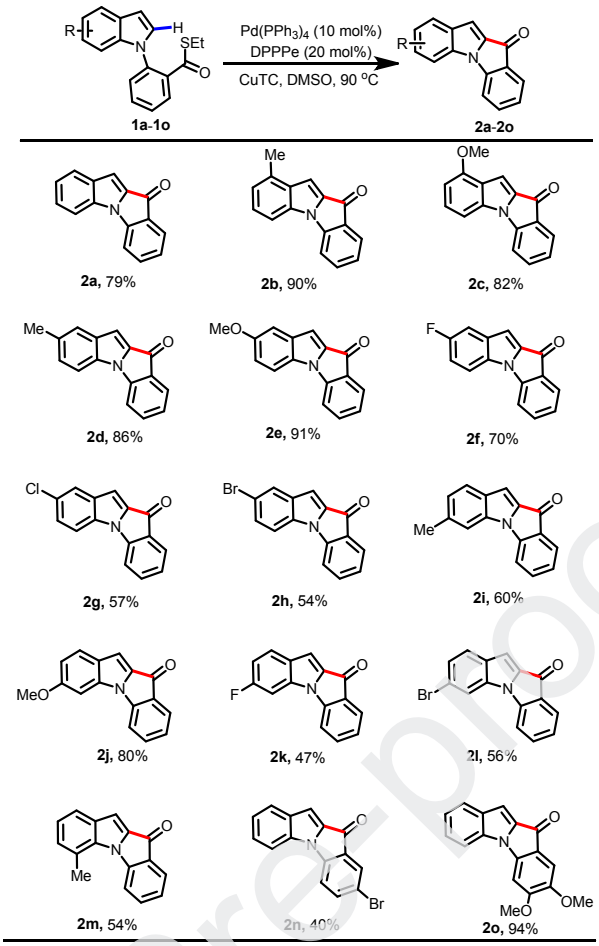
Table 1 Optimization of the reaction conditions[a]



Entry	Pd catalyst	Copper salt	Ligand	Solvent	Yield (%)
1	$Pd(OAc)_2$	CuTC	PPh_3	CH_3CN	26
2	Pd_2dba_3	CuTC	PPh_3	CH_3CN	7
3	$PdCl_2$	CuTC	PPh_3	CH_3CN	15
4	$Pd(PPh_3)_4$	CuTC	-	CH_3CN	30
5	$Pd(PPh_3)_4$	CuTC	PCy_3	CH_3CN	22
6	$Pd(PPh_3)_4$	CuTC	P^tBu_3	CH_3CN	16
7	$Pd(PPh_3)_4$	CuTC	DPPE	CH_3CN	40
8	$Pd(PPh_3)_4$	CuTC	DPPP	CH_3CN	8
9	$Pd(PPh_3)_4$	CuTC	DPPB	CH_3CN	35
10	$Pd(PPh_3)_4$	CuTC	DPPPe	CH_3CN	58
11	$Pd(PPh_3)_4$	CuTC	DPPPe	DMF	54
12	$Pd(PPh_3)_4$	CuTC	DPPPe	THF	30
13	$Pd(PPh_3)_4$	CuTC	DPPPe	Cyclohexane	17
14	$Pd(PPh_3)_4$	CuTC	DPPPe	DMSO	65
15[b]	$Pd(PPh_3)_4$	CuTC	DPPPe	DMSO	77
16[b]	-	CuTC	DPPPe	DMSO	0
17[b]	$Pd(PPh_3)_4$	-	DPPPe	DMSO	0
18[b]	$Pd(PPh_3)_4$	CuCl	DPPPe	DMSO	0
19[b]	$Pd(PPh_3)_4$	CuI	DPPPe	DMSO	0
20[b]	$Pd(PPh_3)_4$	CuOAc	DPPPe	DMSO	38
21[b]	$Pd(PPh_3)_4$	$Cu(OAc)_2$	DPPPe	DMSO	46

[a]Reaction conditions: 1 (0.05 mmol), Pd catalyst (10 mol%), ligand (20 mol%), CuTC (0.15 mmol), sovent (1 mL). The yield was determined by GC-MS analysis of crude product using $C_{16}H_{34}$ as internal standard. DPPE = 1,2-Bis(diphenylphosphino)ethane, DPPP = 1,3-Bis(diphenyl phosphino)propane, DPPB = 1,4-Bis(diphenylphosphino)butane, DPPPe = 1,5-Bis(diphenylphosphino)pentane. CuTC = Copper(I) thiophene-2-carboxylate; [b]0.5 mL DMSO.

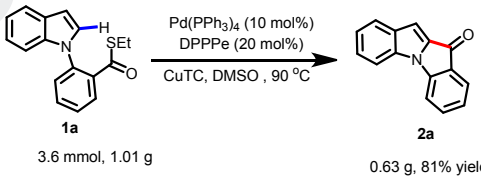
With the optimized reaction conditions in hand, we examined the substrates scope for this reaction. As shown in Scheme 2, substrates bearing electron-donating and electron-withdrawing substituents (-Me, -OMe, -F, -Cl, and -Br) at the 4-, 5-, 6- and 7- position of the indole fragment were compatible in the reaction, giving the corresponding C-2 selective acylated products in moderate to good yields (**2a-2m**). Notably, the bromo-contained substrates could be well tolerant in the present of Pd(0), leaving a functional handle for further structural elaborations. Substrates bearing bromo and methoxyl substituents on the thioester fragment could be acylated smoothly, giving the corresponding product **2n** and **2o** in 40% and 94% respectively.



[a]Reaction conditions:1 (0.1 mmol), $Pd(PPh_3)_4$ (10 mol%), DPPPe (20 mol%), CuTC (0.3 mmol), DMSO (1 mL), 90 °C, N_2, 13 h.

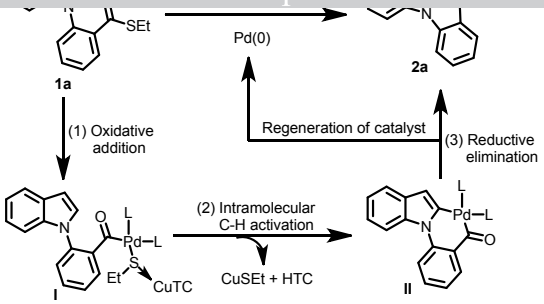
Finally, we investigated the feasibility of this transformation for gram-scale reaction under the standard condition, and the desired product could be isolated in 81% yields (Scheme 3).

Scheme 3 Gram-scale synthesis



Based on the previous reports[3], a plausible mechanism for the reaction is proposed in scheme 4. First, oxidative addition of Pd(0) into C(O)–S bond of thiolester generate the Pd(II) complex **I**. Due to the poor electrophilic ability of the organopalladium intermediate, the copper salt was needed as an activator to enhance the electrophilicity by forming a stronger Cu-S bond. Subsequently, intramolecular C–H activation of indoles at the C2-position forms the stable six-membered cyclopalladium species **II**. Finally, reductive elimination of complex **II** give the desired product **2a** with the regeneration of Pd(0).

Scheme 4 Proposed mechanism



In summary, we have developed a palladium-catalyzed intramolecular C-2 selective acylation of indoles with thioester. A range of functional groups are tolerated in this reaction. It provides a direct and effective method for the synthesis of indole fused indolone scaffolds, which play an important role in bioactive molecules.

Acknowledgments

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