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Controlled Ni-catalyzed mono-and double-decarbonylations of α -ketothioesters

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A method for Ni-catalyzed controlled decarbonylation of α ketothioesters is described. Mono- and double-decarbonylations, which gave could thioesters and thioethers, respectively, were selectively achieved by changing the ligands. A fundamental study of Ni-catalyzed decarbonylation of α -ketothioesters is presented.

The formation of C-S bonds is of fundamental importance in organic chemistry because sulfur-containing motifs form part of various natural products and pharmaceutical agents.¹ Despite the robustness of classical protocols for the synthesis of C-S bonds,² the development of alternative methods, particularly catalytic synthetic routes, is still a formidable Intramolecular CO extrusion-recombination challenge. reactions provide a powerful methods for the formation of chemical bonds.³ In the past few decades, advances in decarbonylative bond formation, which can be used to create C-C,⁴ C-P,⁵ C-N,⁶ C-Cl,⁷ and C-O,⁸ bonds through transitionmetal catalysis, have been made (Scheme 1A). Recently, the groups led by Sanford,^{9a} Szostak,^{9b} and Yamaguchi^{9c} independently developed methods for the Ni-catalyzed intramolecular decarbonylative conversion of thioesters to thioethers. This provides a valuable alternative to traditional cross-couplings in the construction of C-S bonds (Scheme 1B). In view of the unique nature of thioester decarbonylation,¹⁰ we considered whether such an activation mode could be extended to α -ketothioesters. The challenges are two-fold. (1) Mono- and double-decarbonylations of 1,2-dicarbonyl compounds are competing reactions, therefore controlled activation of the α -ketothioesters must be achived catalytically. (2) Unlike thioesters, ketothioesters with two electrophilic carbon centers can undergo facile thiolate transfer¹¹ and cyclization,¹² therefore chemoselectivity is difficult to achieve. Derivatives of α -keto acids are valuable precursors and

intermediates in the production of various pharmaceuticals and bioactive molecules.¹³ Because of their vast potential, much attention has focused on the synthesis of these compounds in recent years. They can be prepared from methyl 2-phenylacetate,¹⁴ cyano keto phosphoranes,¹⁵ α -aryl halo derivatives,¹⁶ 1,3-diones,¹⁷ terminal alkynes,¹⁸ α -hydroxy esters,¹⁹ aldehydes,²⁰ and other compounds.²¹ In this report, we present a Ni-catalyzed, controlled decarbonylation of α ketothioesters. The use of different ligands enabled mono- and double-decarbonylations to be selectively achieved, to give thioesters and thioethers, respectively (Scheme 1C).

A Transition-metal-catalyzed decarbonylative C-X bond formation

Х:

B Decarbonylation of thioesters (Sanford, Szostak and Yamaguchi 2018)

$$Ar \xrightarrow{O} Ni catalyst \rightarrow Ar - SR$$

C Controlled Ni-catalyzed decarbonylation of α-ketothioesters (this work)

Scheme 1. Ni-catalyzed, controlled decarbonylation of α -ketothioesters

The reactivities of α -ketothioesters were investigated by using *S*-phenyl 2-oxo-2-phenylethanethioate (**1a**) as a model substrate. Initially, Ni(cod)₂/ligand combinations that have previously been successfully used in Ni-catalyzed direct decarbonylation of ketones^{4f} and thioesters^{9a} were used as catalysts (Table 1). As anticipated, the efficiency was strongly

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⁺ Electronic Supplementary Information (ESI) available: Experimental procedures, mechanistic details, spectroscopic data and copies of ¹H and ¹³C NMR spectra. See DOI: 10.1039/x0xx00000x

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dependent on the nature of the ligand. Reactions using phosphine ligands afforded thioesters in high yields (Table 1, entries 1 - 3); the best ligand was PPh₃, which provided the mono-decarbonylated product in 85% yield (Table 1, entry 2). Further optimization focused on using different solvents; switching the solvent from toluene to dioxane or chlorobenzene did not provide a better yield (Table 1, entries 4 and 5). We then evaluated a series of N-heterocyclic carbene (NHC) ligands with the expectation that their strong σ -donor facilitate properties would the required double decarbonylation. Among the NHCs examined, IPr^{Me} was the most effective; the desired doubly decarbonylated product 3a was isolated in 40% yield (Table 1, entry 9). Changing the solvent to dioxane and prolonging the reaction time to 22 h gave further improvements and 3a was isolated in 77% yield (Table 1, entry 10). Reactions performed in the presence of $Pd[P(o-tol)_3]_2/dppf$ (Table 1, entry 11)^{9b} or $Pd(PPh_3)_4$ (Table 1, entry 12),^{10b} both of which have been reported to catalyze decarbonylation of thioesters, did not produce any 3a or gave 3a in a low yield. Molecular sieves have been reported to greatly enhance Pd-catalyzed decarbonylation of aldehydes because of their ability to remove trace amounts of water,²² but in our reaction the addition of molecular sieves was not necessary.

Table 1 Optimization of reaction conditions.^a

	S S	Ni(cod) ₂ (10 r Ligand (20 m	nol%) ool%) O	Ph + Ph
	Pn Pi O 1a	Solvent, 150 °(✓ Ph´ `S´ C, 15 h 2a	3a
entry	ligand	solvent	2a , yield ^b (%)	3a , yield ^b (%)
1	РСуз	toluene	81	<5
2	PPh_3	toluene	85	<5
3	dppe	toluene	52	31
4	PPh_3	dioxane	74	18
5	PPh_3	chlorobenzene	79	12
6 ^c	IMes.HCl	toluene	52	25
7 ^c	IMes ^{Me} .HCl	toluene	53	20
8 ^c	IPr.HCl	toluene	50	36
9 ^c	IPr ^{Me} .HCl	toluene	48	40
10 ^c	IPr ^{Me} .HCl	dioxane	<5	77
11 ^d	dppf	toluene	84	<5
12 ^e	-	toluene	16	0
		$\begin{array}{c} \text{Me} & \text{Me} \\ \searrow = \swarrow \\ \text{R}^{-N} \searrow^{N} \gamma \text{R} \\ \vdots \end{array}$	Ph ₂ P PPh ₂	Ph ₂ P
$\begin{array}{ll} \text{IMes} \ (\text{R} = 2,4,6\text{-Me}_3C_6H_2) & \text{IMes}^{\text{Me}} \ (\text{R} = 2,4,6\text{-Me}_3C_6H_2) & \text{dppe} & \\ \text{IPr} & (\text{R} = 2,6\text{-}Pr_2C_6H_3) & \text{IPr}^{\text{Me}} & (\text{R} = 2,6\text{-}Pr_2C_6H_3) & \\ \end{array}$				

^{*a*}Reaction conditions: **1a** (0.2 mmol), Ni(cod)₂ (10 mol%), ligand (20 mol%), solvent (2 mL), 150 °C, 15 h. ^{*b*}Isolated yields. ^{*c*}Cs₂CO₃ (20 mol%), 22 h. ^{*d*}Pd[P(otol)₃]₂ in place of Ni(cod)₂. ^{*e*} Pd (PPh₃) ₄ in place of Ni(cod)₂.

Having established the optimum conditions, we then investigated the scope of the mono-decarbonylation. A range of functional groups were found to be compatible, including methyl ether (2d), fluoride (2e), chloride (2f), bromide (2g), and ester (2j) groups. Notable examples include the halides (2e–g), which provide handles for further functionalization via

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conventional cross-coupling reactions. Finally, this ARRETORN was extended to the polyaromatic composited **2009**/the desired product was obtained in good yield.

Table 2 Scope of mono-decarbonylation of α -ketothioesters. ${}_{a,b,c}$



^aStandard conditions: **1** (0.2 mmol), Ni(cod)₂ (10 mol%), PPh₃ (20 mol%), toluene (2 mL), 150 °C, 15 h. ^bIsolated yields. ^cMono-decarbonylation:double -decarbonylation selectivities are given in parentheses.

The scope of the double-decarbonylation reaction was also explored (Table 3). Various substituents, including some with electron-donating (**3b** and **3c**), or electron-withdrawing (**3e** and **3g**) properties, on the thiol-derived fragment were well tolerated; the desired adducts were obtained in moderate to good yields (57%–77%). Finally, the scope of the reaction with different carboxylic acid-derived portions was briefly examined. A selection of sterically-hindered (**3h**), electrondeficient (**3j**), and electron-rich (**3k** and **3l**) substrates were converted into the desired thioethers in good yields. Recently, Yamaguchi and Itami reported a Ni-catalyzed decarbonylative etherification of aromatic esters.⁷ We were intrigued to find that these Ni-catalyzed decarbonylations proceeded in the presence of the sensitive aryl ester linkage; this shows the high chemoselectivity of the present method.





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3m 77% (>20:1)

^a Standard conditions: **1** (0.2 mmol), Ni(cod)₂ (10 mol%), IPr^{Me}.HCl (20 mol%), Cs₂CO₃ (20 mol%), toluene (2 mL), 150 °C, 22 h. ^b Isolated yields. ^c Double-decarbonylation:mono-decarbonylation selectivities are given in parentheses.

Preliminary studies showed that mono-decarbonylation of aryl–alkyl ketothioesters was also feasible (Scheme 2). The reaction gave a low yield (34%) under mono-decarbonylative conditions, but the product **2n** was obtained in 74% yield with Ni(PCy₃)₂Cl₂ as the catalyst.^{9b} However, under the standard double-decarbonylative conditions, the aryl–alkyl ketothioester **1n** only gave the mono-decarbonylated product **2n**.



Scheme 2. Ni-catalyzed decarbonylation of aryl-alkyl ketothioester.

A series of control experiments were performed to investigate the reaction pathway. The reaction of **1a** was initially conducted under double-decarbonylative conditions but with a shorter reaction time; **3a** (35%) and **2a** (55%) were obtained (Scheme 3a). As shown in Scheme 3b, the reaction of **1a** afforded **3a** (22%) and **2a** (60%) under mono-decarbonylative conditions with a longer reaction time. This suggests that **2a** could be an intermediate in the double decarbonylation. Thioester **2a** was also used as the substrate under both sets of conditions. The results show that thioester **2a** was converted to the desired product **3a** in 86% yield under doubledecarbonylative conditions and in 52% yield under monodecarbonylative conditions (Scheme 3c).



Scheme 3. Control experiments

Based on these observations and literature reports,⁹ we propose the possible mechanism shown in Scheme 4. The first step is oxidative cleavage of the C(acyl)–S bond to form the corresponding Ni(II) intermediate **INT1**. Subsequent decarbonylation generates the corresponding intermediate **INT2**. Reductive elimination from **INT2** affords thioester **2a**. Under double-decarbonylative conditions, thioester **2a** undergoes C(acyl)–S activation to give intermediate **INT3**. Subsequent decarbonylation and reductive elimination give thioether **3a**.



Scheme 4. Possible mechanism

Finally, to highlight the utility of this decarbonylation reactions, sequential cross-couplings were investigated (Scheme 5). The bromide moiety in **5** can serve as the first reactive center in a Suzuki coupling to give biaryl **40**, and the ketone can then provide a functional handle for the synthesis of thioethers and thioesters.





Scheme 5. Site-selective cross-coupling/decarbonylations.

In summary, an unusual reactivity of α -ketothioesters is described. The use of different ligands enabled Ni-catalyzed mono- and double-decarbonylative C–S bond formation to be achieved in a controlled fashion. Compared with traditional methods for C–S bond formation, the new protocols have the

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advantages of high atom efficiency, synthetic flexibility, and use of inexpensive Ni catalysts. This decarbonylative strategy therefore provides a viable alternative for the synthesis of thioesters and thioethers.

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Conflicts of interest

There are no conflicts to declare.

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A method for Ni-catalyzed controlled decarbonylation of $\alpha\mbox{-}ketothioesters$ via changing the ligands was achieved