Letter

Palladium-Catalyzed Carbothiolation via Trapping of the σ -Alkyl Palladium Intermediate with RSTIPS

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Supporting Information

ABSTRACT: A palladium-catalyzed carbothiolation via the reaction of a σ -alkyl palladium intermediate with a TIPS thioether is described. It was found that the use of Cs₂CO₃, (IPr)Pd(allyl)Cl, and a TIPS thioether was key to obtaining alkyl aryl and dialkyl sulfides in high yield through the reaction of a σ -alkyl palladium intermediate. The developed reaction is applicable to a wide range of substrates and thiols.



C ascade reactions, which are chemical processes that consist of more than two consecutive reactions, are important in organic synthesis, in terms of efficiency, because they enable the successive formation of new bonds, leading to the construction of complex structures while reducing waste output, as well as the time and labor required for the overall transformation. Catalytic reactions are also vital in reducing the use of energy and resources.

Palladium-catalyzed reactions are ideal reactions, because they feature a catalytic cycle of successive basic reactions. Moreover, the generated reactive species undergo sequential reactions in a cascade manner. For example, the Heck reaction has been a widely used palladium-catalyzed reaction, and the reaction of substrate, in which β -elimination does not occur, affords a σ -alkyl palladium intermediate that undergoes subsequent reaction. Thus, an aryl-Pd(II) intermediate, which is derived from the oxidative addition of Pd(0) to compound **A** (Scheme 1), undergoes alkene insertion to afford the σ -alkyl palladium intermediate **B** with an all-carbon quaternary center at the adjacent position. Intermediate **B** does not undergo β -elimination, because of the lack of a β hydrogen; however, **B** will react with a nucleophile to form a new bond to afford **C**.

It has been reported that the reaction of σ -alkyl palladium intermediate **B** with nucleophiles affords compound **C** with an all-carbon quaternary center (see Scheme 1a).¹ In addition to this type of palladium-catalyzed reaction, the reactions of intermediate **B** with bis(pinacolate) diboron (Scheme 1b),² hexamethyldisilane, and hexamethyldistannane (Scheme 1c)³ affording the corresponding alkyl pinacol borane, silane, and stannane, respectively, have recently been reported.⁴

Over the course of our synthetic studies on bioactive natural products, we have noticed that a benzylic all-carbon quaternary center appended with a functional group is included in many structures of bioactive natural products.⁵ Specifically, some bioactive compounds include an allylic or a benzylic all-carbon quaternary center with an arylthiomethyl group in their structures.⁶

Scheme 1. Palladium-Catalyzed Cascade Reactions



Sulfide is stable under both acidic and basic reaction conditions and can be converted to the corresponding carbonyl group, a useful synthetic intermediate for organic synthesis, via the Pummerer rearrangement of the corresponding sulfoxide. Moreover, the carbon–sulfur bond can be reductively cleaved,⁷ and when sulfide is oxidized to sulfone, its anion can act as a nucleophile to form a new bond, after which the new carbon–sulfur bond can be converted to a carbon–hydrogen bond by reduction.

The efficiency and power of palladium-catalyzed processes, as well as the reasoning described above, prompted us to develop a method to prepare compound D possessing a

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benzylic all-carbon quaternary center with an adjacent alkyl or arylthiomethyl group via σ -alkyl palladium intermediate **B**.

Palladium-catalyzed carbothiolations starting from organosulfur compounds⁸ and thiolation of the π -allyl palladium intermediates⁹ have been reported. However, to the best of our knowledge, the thiolation of σ -alkyl palladium intermediate **B** has never been reported.¹⁰ We have investigated the thiolation of σ -alkyl palladium intermediate **B** and found that the carbon–sulfur bond was successfully formed, affording alkyl aryl and dialkyl sulfides for the first time; this palladiumcatalyzed cascade reaction was applicable to a wide range of substrates. Herein, we report the observed findings and results.

We selected compound **1a** as a model compound for the optimization of reaction conditions for the carbothiolation reaction. Compound **1a** was readily prepared by the Mitsunobu reaction of 2-iodophenol with 3-methylbut-3-ene-1-ol.¹¹ The preliminary reaction of **1a** was performed using thiophenol and Cs_2CO_3 in the presence of a catalytic amount of Pd(PPh₃)₄ in toluene (see Table 1, entry 1), but no reaction was noted. The reactions using thiophenol under several reaction conditions also failed to afford the desired product.



$\begin{array}{c c} PhSTIPS (1.5 equiv) \\ Pd(PPh_3)_4 (10 mol \%) \\ \end{array}$									
1a (X = I), 1b (X = SPh) $conditions$ $2a (R1 = SPh), 2b (R1 = I)$									
				Yield (%)					
entry	base ^a	solvent	temperature (°C)	time (h)	2a	2b			
1 ^c	Cs_2CO_3	toluene	100	12	0^d	0 ^{<i>d</i>}			
2 ^e	Cs_2CO_3	toluene	80	10	43	0			
3	Cs_2CO_3	DMF	80	10	0^d	0^d			
4	Et ₃ N	toluene	80	10	13	9			
5	Cs_2CO_3	toluene	100	10	65	0			
6	K ₂ CO ₃	toluene	100	10	48	25			
7 ^e	Na_2CO_3	toluene	100	10	7	21			
8	K ₃ PO ₄	toluene	100	10	81	6			
9 ^f	Ag ₂ CO ₃	toluene	100	10	14	0			
10	CsF	toluene	100	10	50	16			
11	Cs ₂ CO ₃	toluene	100	24	77	0			
^{<i>a</i>} 1.5 equiv. ^{<i>b</i>} Isolated yields. ^{<i>c</i>} PhSH was used. ^{<i>d</i>} No reaction. ^{<i>e</i>} 1a remained f_{1} b (56%) was formed									

It has been reported that sulfur compounds can poison palladium catalysts, because of their strong affinity.¹² Therefore, we next examined the reaction using a thiophenol derivative bearing a bulky group, which would not coordinate with a palladium catalyst. Triisopropylsilyl ether of thiophenol (PhSTIPS)¹³ was selected for the reaction, because of the bulkiness of the TIPS group and its stability. To our delight, the reaction of 1a with PhSTIPS and Cs₂CO₃ in the presence of a catalytic amount of $Pd(PPh_3)_4$ in toluene at 80 °C afforded 2a in a 43% yield (Table 1, entry 2). Toluene was found to be a suitable solvent for this reaction, whereas the use of other solvents resulted in low yields or no reaction (e.g., DMF; see Table 1, entry 3). The use of other bases, except K₃PO₄, resulted in lower yields (Table 1, entries 4, 6, 7, 9, and 10) and, in the case of K_3PO_4 (Table 1, entry 8), the formation of iodide 2b was noted, while the yield was 81%.¹⁴ The reaction at 100 °C (Table 1, entry 5) and a prolonged reaction time increased the yield (Table 1, entry 11). The results in

Table 1 indicated that the use of Cs_2CO_3 accelerated the reaction rate to afford the desired product, **2a**.

We next screened various palladium catalysts to further optimize the conditions determined from Table 1. Cs_2CO_3 was used to investigate the conditions, because 2a was not formed in the reaction of 1a using Cs_2CO_3 . The reaction using Pd_2dba_3 and PPh_3 at 100 °C resulted in a decreased yield (15%) of 2a and the formation of 2b (19%) was observed (Table 2, entry 1). The use of $PdCl_2dppf_2$ - CH_2Cl_2 increased

Table 2. Palladium-Catalyzed Carbothiolation of 1a



			Yield ^a (%)	
entry	catalyst	time (h)	2a	2b
1	Pd ₂ dba ₃ , PPh ₃ (20 mol %)	21	15	19
2	PdCl ₂ (dppf) ₂ -CH ₂ Cl ₂	21	54	0
3 ^b	Pd ₂ dba ₃ , dppf (10 mol %)	22	74	0
4	Pd ₂ dba ₃ , Xantphos (10 mol %)	8	0	82
5	Pd ₂ dba ₃ , QPhos (20 mol %)	24	0	54
6	Pd ₂ dba ₃ , AmPhos (20 mol %)	24	12	65
7 ^b	(IPr)Pd(cinnamyl)Cl	24	76	0
8 ^{<i>b</i>,<i>c</i>}	(IPr)Pd(cinnamyl)Cl	23	85	0
9 ^c	(IPr)Pd(allyl)Cl	36	91 $(90)^d$	0
10 ^e	(IPr)Pd(allyl)Cl	36	14	0
11 ^{c,f}	(IPr)Pd(allyl)Cl	36	79	0
	-			

^{*a*}Isolated yields. ^{*b*}**1b** (trace) was formed. ^{*c*}Cs₂CO₃ (3.0 equiv) was used. ^{*d*}The yield using the corresponding bromide is given in parentheses. ^{*e*}The reaction in the absence of Cs₂CO₃. ^{*f*}PhSTBS was used.

the yield to 54% (Table 2, entry 2), while the reaction with Pd_2dba_3 and dppf afforded 2a in a yield of 74%, with the formation of a trace amount of 1b (Table 2, entry 3).

Interestingly, when Pd_2dba_3 and Xantphos (Table 2, entry 4) or Pd_2dba_3 and QPhos (Table 2, entry 5) were used, **2a** was not formed; instead, **2b** was formed in yields of 82% and 54%, respectively.¹⁴ The reaction with Pd_2dba_3 and AmPhos also preferentially afforded **2b** (see Table 2, entry 6).

The reactions employing catalysts with NHC ligands showed different results, compared to those with phosphine ligands; the reaction using (IPr)Pd(cinnamyl)Cl¹⁵ (Table 2, entry 7) proceeded faster than that with dppf (Table 2, entry 3) to afford 2a in a comparable yield (76%) without forming 2b, giving a trace amount of 1b as a side product. When the reaction with (IPr)Pd(cinnamyl)Cl was performed with 3.0 equiv of Cs₂CO₃ (Table 2, entry 8), the yield was increased to 85%, but a trace amount of 1b was still obtained.

Pleasingly, the reaction in the presence of a catalytic amount of (IPr)Pd(allyl)Cl¹⁶ in toluene at 100 °C afforded **2a** in a 91% yield (Table 2, entry 9). Under these conditions, the reaction required 36 h to reach completion; however, **1b** and **2b** were not formed. The reaction of the analogous bromide of **1a** also proceeded under the same reaction conditions to afford **2a** in 90% yield, while the reaction of the corresponding chloride did not proceed under the same conditions. The reaction using (IPr)Pd(allyl)Cl in the absence of Cs₂CO₃ afforded **2a** in a yield of only 14% (see Table 2, entry 10), indicating that the reaction was accelerated by the presence of Cs₂CO₃. The reaction with PhSTBS resulted in an inferior yield (79%) (Table 2, entry 11).

Under the optimized reaction conditions, reactions of 1a with a variety of TIPS thioethers were examined (see Scheme 2). The reaction of TIPS thioethers of *p*-substituted

Scheme 2. Palladium-Catalyzed Carbothiolation of 1a with Various TIPS Thioethers



thiophenols afforded 2c-2f with yields of 74%–96%. The reaction of *p*-fluorothiophenol was sluggish and required 82 h to come to completion, likely because of the electronic effect of the fluorine substituent.¹⁷ The reaction of TIPS thioethers of *m*- and *o*-substituted thiophenols proceeded without problem (affording 2g and 2h-2k, respectively). The reaction of *o*-dimethyl thiophenol slowly afforded 2l in a yield of 25%, while the yield was increased to 48% after 82 h. However, the reaction of *o*-dichloro thiophenol did not afford 2m. The results of 2l and 2m indicate that the yield of this reaction could be dependent on the steric and electronic effect of the substituents.¹⁷ The reaction of TIPS thioethers of alkanethiols also afforded the desired products 2n-2p, while these reactions were sluggish, except the reaction with TIPS thioether of benzylthiol.

Note that the yield is strongly dependent on the purity of TIPS thioether, because the crude TIPS thioether contains thiol, which could coordinate with a catalyst to retard the reaction. Indeed, the reaction of **1a** in the presence of benzenethiol was found to be sluggish (see Scheme 3).

We next explored the reaction of compound 3 using a variety of TIPS thioethers under the optimized reaction conditions (see Scheme 4). The yields of products 4a-4j were 67%-99%, and most yields were better than the corresponding reactions of 1a (Scheme 2), which forms the six-membered ring, indicating that this palladium-catalyzed reaction would be more effective for the formation of five-membered rings. The reactions with TIPS thioethers of benzylthiol, dodecanethiol, and propane-2-thiol resulted in low yields.

Scheme 3. Palladium-Catalyzed Carbothiolation of 1a with PhSTIPS in the Presence of PhSH







Scheme 5 shows products 5–13, which were prepared by the optimized palladium-catalyzed reaction. Compounds 5 and 6 were formed in yields of 89% and 87%, respectively, by the reaction of aryl-substituted derivatives of 1a. Compound 7, which is a derivative of compound 3, was also formed in a yield of 89%. Derivatives of indoline and indolin-2-one, 8–10, which possess an important scaffold seen in bioactive compounds,⁵ were also prepared in yields of 74%–99%. The developed reaction was applicable to the formation of 11, which contains a six-membered carbocyclic ring, and 12, which is a 2,3,4,5tetrahydrobenzo[b]oxepine derivative. This reaction also produced 13 bearing an electron-withdrawing ester group in a yield of 79%.

The data shown in Schemes 2, 4, and 5 indicate that the optimized reaction is applicable to a wide range of substrates when a TIPS ether of the necessary thiol is used.

It has been reported that the oxidative addition of Pd(0) to alkyl iodide affords σ -alkyl palladium.¹⁸ Hence, alkyl iodide **2b**, which was formed as a side product during the development of our optimized reaction conditions, could be converted to the corresponding σ -alkyl palladium intermediate and thus undergo reaction with PhSTIPS to afford **2a**. Indeed, when alkyl iodide **2b** was subjected to the optimized reaction conditions shown in Scheme 6, **2a** was formed in a yield of 64%. Since compound **2a** was formed in 91% yield by the reaction of **1a** under the same reaction conditions (Table 2, entry 9) and the

Scheme 5. Palladium-Catalyzed Carbothiolation with PhSTIPS



Scheme 6. Reactions of 2b with PhSTIPS



formation of **2b** was not observed via TLC during the course of the reaction, the transformation from **2b** to **2a** is not indicated as a major pathway in the reaction of **1a**, although it could not be ruled out. We also tested the reaction of **2b** in the absence of palladium catalyst; no reaction occurred, indicating that the reaction of **2b** with PhSTIPS and Cs_2CO_3 does not afford **2a**.

Based on the results of this study and earlier reports, the proposed catalytic cycle of the developed reaction is given in Scheme 7. It was rationalized that the palladium-catalyzed reaction involves the formation of σ -alkyl palladium intermediates 15-17. The oxidative addition of Pd(0) to 1a affords σ -aryl palladium intermediate 14, followed by insertion to the alkene to afford 15. The use of a monodentate ligand, such as (IPr)Pd(cinnamyl)Cl or (IPr)Pd(allyl)Cl, facilitates the reaction of 15 with Cs_2CO_3 to give 16, which undergoes transmetalation with R^2 STIPS (R^2 = alkyl or aryl) to afford 17, because of the high affinity of the O and Si atoms. Finally, reductive elimination of 17 delivers product 2a and also regenerates Pd(0). σ -Aryl palladium intermediate 14 could also undergo transmetalation with R^2STIPS (where R^2 = alkyl or aryl), but this pathway is dependent on the ligand used. When a bulky phosphine ligand is employed,¹⁴ it could prevent the reaction of 15 with Cs₂CO₃; thus, the reductive elimination affording alkyl iodide 2b preferentially occurs. The iodide 2b was confirmed to be reconverted to 15 via reaction with Pd(0).

In summary, we have developed a palladium-catalyzed carbothiolation reaction via the interaction of a σ -alkyl palladium intermediate with a TIPS ether derivative of alkane or arylthiol. It was found that the use of Cs₂CO₃, (IPr)Pd-

Scheme 7. Plausible Mechanism for the Pd-Catalyzed Carbothiolation



(allyl)Cl, and a TIPS ether derivative of thiol in toluene was key to obtain the desired product in high yield. This is the first example of the formation of alkyl aryl and dialkyl sulfides through the trapping of the σ -alkyl palladium intermediate with a TIPS thioether. The developed reaction is applicable to a wide range of substrates and thiols. Further studies on the reaction using a variety of substrates and TIPS thioethers are currently underway.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.9b03046.

Experiment procedure and the characterizations of the substrates and products (PDF)

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The authors declare no competing financial interest.

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