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Pd-Catalyzed Coupling of Thioamides with *N*-Tosylhydrazones/Trapping by Esters Cascade Reaction

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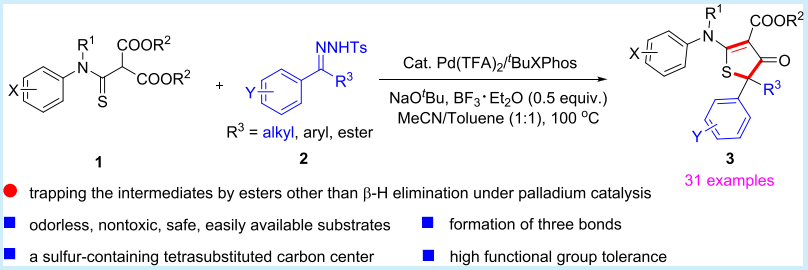

ABSTRACT: *N*,*N*-Disubstituted thioamides coupled with *N*-tosylhydrazones under $Pd(TFA)_2$/^{t}BuXPhos catalyst and NaO^{t}Bu, and the intermediates from palladium carbene migratory insertion containing *β*-hydrogen were trapped by intramolecular esters activated by BF_3·Et_2O instead of undergoing *β*-H elimination, providing polyfunctional thiophen-3(2*H*)-ones with sulfur-containing tetrasubstituted carbon centers in moderate to good yields. The reaction features the formation of three bonds in a single operation, odorless, safe, and easily available substrates, wide substrate scope, and excellent functional group tolerance.

Sulfur-containing heterocycles exist widely in natural products, drugs, biological compounds, and materials.[1] Odorless, nontoxic, and easily available starting materials for preparing sulfur-containing heterocycles are highly desirable. Recently, we reported the ready synthesis of *N*,*N*-disubstituted thioamides bearing *α*,*α*-diesters from malonate esters and thiocarbamoyl fluorides[2] in which the sulfur atom was derived from sulfur (S_8).[3] Thioamides, which are odorless and nontoxic/low toxic, have been widely used to synthesize sulfur-containing heterocycles via intramolecular coupling reactions including C−H functionalizations.[2,4] Metal-catalyzed intramolecular or intermolecular reactions of thioamides with hydrazones or *α*-diazocarbonyl compounds to transform C═S to C═C bonds have also been reported.[5] However, intermolecular reactions involving thioamides in a single operation for the construction of complex and diversified heterocycles with sulfur-containing tetrasubstituted carbon centers are underdeveloped. Sulfur heterocycles in this class exist in natural products such as thiolactomycin and thiotetroamide as well as in biological compounds demonstrating anticancer,[1d] weight loss,[1d] antibacterial,[6a−c] antimalarial,[6d,e] antituberculosis,[6f,g] and pesticidal activities.[6h]

The Hu group pioneered the development of a series of multicomponent reactions of trapping of ylides or zwitterionic intermediates derived from nucleophiles and diazocarbonyl compounds by electrophiles such as aldehydes, ketones, imines, or *α*,*β*-unsaturated compounds to form tetrasubstituted carbon centers.[7] The challenge of these methods lies in the 1,2-proton transfer in the active intermediates. Esters have never been documented to realize the trapping of active intermediates as above. Due to their low electrophilicity, competitive 1,2-proton transfer might be faster. Dual-metal-catalyzed carbene sp^2 C−H functionalization/Conia−ene cascade reactions have also been reported.[8] Diazo compounds bearing alkyls have never been used in the above reactions due to their instability and difficulty in separation and purification. *N*-Tosylhydrazones are safe and easily available precursors of diazo compounds and have attracted considerable attention.[9] Palladium-catalyzed cross-couplings involving *N*-tosylhydrazones bearing alkyl groups normally give alkenyl products via *β*-H elimination of the metal alkyl intermediates generated from palladium carbene migratory insertion.[9a,b] For example, Yamaguchi reported that thioesters reacted with *N*-tosylhyrazones under Pd-catalysis to furnish Z-alkenyl thioethers (Scheme 1, previous work, 1).[10] Reactions of heteroatom nucleophiles (X-H) with *N*-tosylhydrazones under transition-metal free conditions could lead to X-H insertion products. For example, thiophenols/mercaptans coupled with *N*-tosylhydrazones under basic conditions to give S-H insertion products (Scheme 1, previous work, 2).[11] Under photoredox conditions, thiophenols/mercaptans and *N*-tosylhydrazones have been

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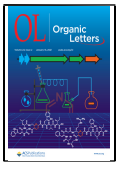

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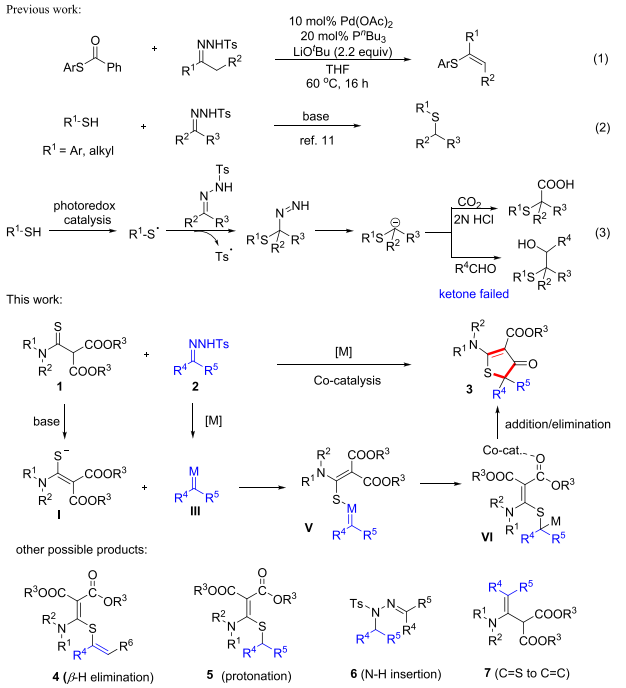
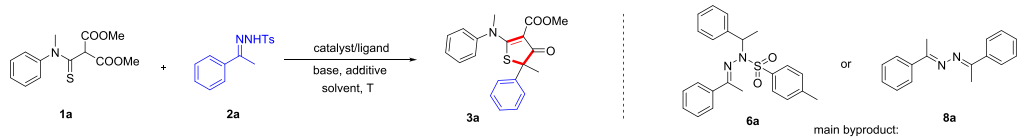
Scheme 1. Reactions of Sulfur Reagents with *N*-Tosylhydrazones



reported to form carbanion intermediates, which can then be trapped by CO_2 or aldehydes but cannot be trapped by ketones (Scheme 1, previous work, 3).[12] Our question was whether the palladium intermediates containing β-hydrogens, formed via palladium carbine migratory insertion, could be trapped by more challenging esters instead of undergoing β-hydride elimination. To the best of our knowledge, the formation of a second bond at the same carbon of the palladium carbene, which also contains β-hydrogens, via 1,2 addition or 1,2 addition/elimination with electrophiles such as esters has never been explored and accomplished.

We envision expanding the use of *N*,*N*-disubstituted thioamides bearing α,α-diesters **1** to intermolecular reactions with *N*-tosylhydrazones **2** (Scheme 1, this work). Under suitable catalytic systems, a base abstracts the α-H of thiocarbonyl of **1** to form thioenolate anion **I**, which coordinates with the metal of the carbene **III** derived from *N*-tosylhydrazone **2** to give the intermediate **V**, followed by carbene migratory insertion to give **VI**. The resulting intermediate **VI** or the anion derived from **VI** losing metal might then undergo cascade intramolecular 1,2-addition/elimination with an ester functionality activated by a co-catalyst, selectively delivering polyfunctional thiophen-3(*2H*)-one **3** (Scheme 1, this work). Various undesired pathways exist that could minimize or halt the formation of the desired products. For instance, β-H elimination or protonation of **VI** yields **4** or **5**. *N*-Tosylhydrazones **2** might also self-condense to form N−H insertion products **6**. Thioamides **1** might also react with **2** to transform the C═S bond into a C═C bond, furnishing enamines **7** (Scheme 1, this work, other possible products). Herein, we disclose that *N*,*N*-disubstituted thioamides **1** couple with *N*-tosylhydrazones **2** bearing alkyl substituents under Pd(II) catalysis, ^{t}BuXPhos as the ligand,

Table 1. Optimization of the Reaction Conditions for 3[a]



entry	catalyst	ligand	base	additive	T (°C)	solvent	yield[b] (%)
1[c]	$Pd(TFA)_2$		NaO^{t}Bu[d]		90	MeCN	23
2[c]	$Rh_2(OAc)_4$		NaO^{t}Bu[d]		90	MeCN	<5%
3[c]	AgTFAtfa)		NaO^{t}Bu[d]		90	MeCN	9
4[c]	CuI		NaO^{t}Bu[d]		90	MeCN	12
5[c]	$Pd(TFA)_2$	BINAP	NaO^{t}Bu[d]		90	MeCN	14
6[c]	$Pd(TFA)_2$	X-Phos	NaO^{t}Bu[d]		90	MeCN	39
7[c]	$Pd(TFA)_2$	X-Phos	NaO^{t}Bu[d]		100	MeCN/toluene (1:1)	45
8[c]	$Pd(TFA)_2$	X-Phos	LiO^{t}Bu[d]		100	MeCN/toluene (1:1)	29
9[c]	$Pd(TFA)_2$	X-Phos	NaH[d]		100	MeCN/toluene (1:1)	28
10[c]	$Pd(TFA)_2$	X-Phos	$NaOSiMe_3$[d]		100	MeCN/toluene (1:1)	48
11	$Pd(TFA)_2$	X-Phos	NaO^{t}Bu		100	MeCN/toluene (1:1)	50
12	$Pd(TFA)_2$	X-Phos	NaO^{t}Bu	$FeCl_3$	100	MeCN/toluene (1:1)	62
13	$Pd(TFA)_2$	X-Phos	NaO^{t}Bu	$AlCl_3$	100	MeCN/toluene (1:1)	54
14	$Pd(TFA)_2$	X-Phos	NaO^{t}Bu	$BF_3{\cdot}Et_2O$	100	MeCN/toluene (1:1)	65
15	$Pd(TFA)_2$	^{t}BuXPhos	NaO^{t}Bu	$BF_3{\cdot}Et_2O$	100	MeCN/toluene (1:1)	70
16	$Pd(TFA)_2$	^{t}BuXPhos	$NaOSiMe_3$	$BF_3{\cdot}Et_2O$	100	MeCN/toluene (1:1)	0
17		^{t}BuXPhos	NaO^{t}Bu	$BF_3{\cdot}Et_2O$	100	MeCN/toluene (1:1)	6
18	$Pd(TFA)_2$	^{t}BuXPhos		$BF_3{\cdot}Et_2O$	100	MeCN/toluene (1:1)	0
19	$Pd(TFA)_2$		NaO^{t}Bu	$BF_3{\cdot}Et_2O$	100	MeCN/toluene (1:1)	41
20	$Pd(TFA)_2$	^{t}BuXPhos	NaO^{t}Bu		100	MeCN/toluene (1:1)	55

[a]Reaction conditions: **1a** (0.15 mmol), **2a** (0.375 mmol), 10 mol % of catalyst, 20 mol % of ligand, 50 mol % of additive, NaO^{t}Bu (0.6 mmol) reacted in 3 mL of anhydrous solvent for 12 h. [b]Isolated yield. [c]**2a** (0.3 mmol, 2.0 equiv). [d]NaO^{t}Bu (0.3 mmol, 2.0 equiv). X-Phos: 2-(dicyclohexylphosphino)-2′,4′,6′-tri(isopropyl)biphenyl; ^{t}BuXPhos: 2-di-*tert*-butylphosphino-2′,4′,6′-tri(isopropyl)biphenyl.

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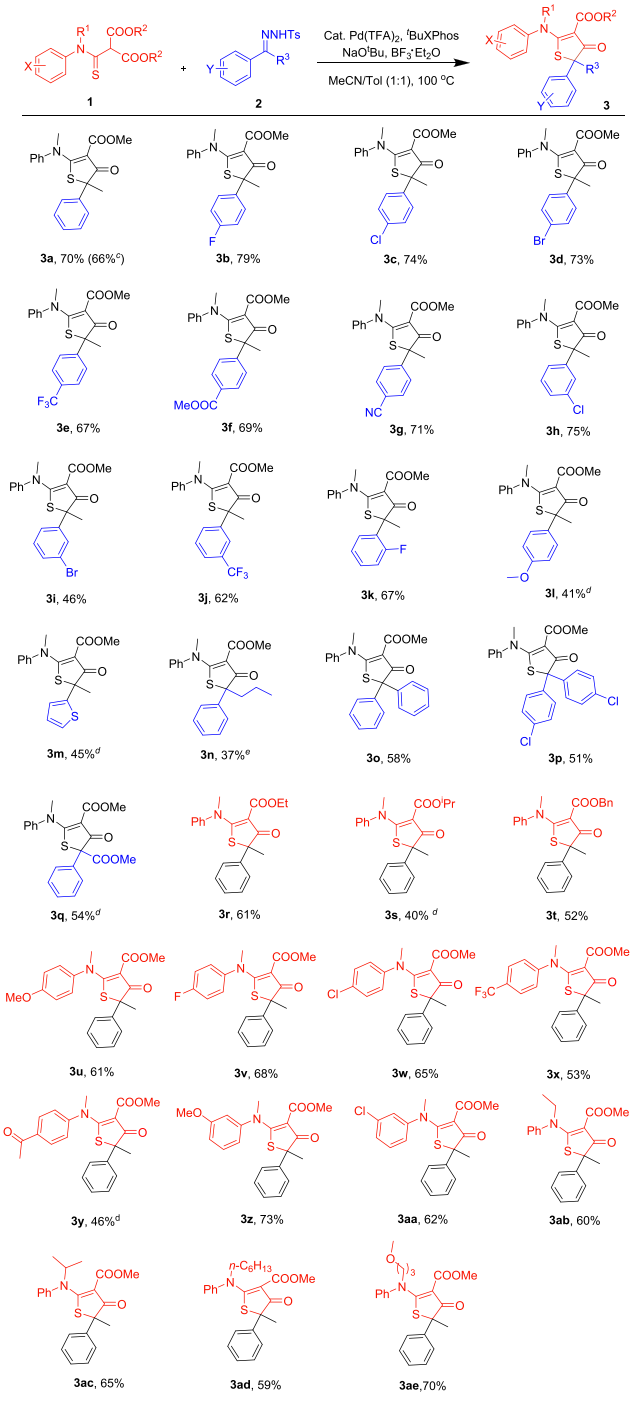
and with $BF_3{\cdot}Et_2O$ as the co-catalyst to selectively access polyfunctional thiophen-3(2*H*)-ones with sulfur-containing tetrasubstituted carbon centers in moderate to good yields.

We started our studies with **1a** and **2a** as model substrates. Selected results are shown in Table 1 (details are provided in the Supporting Information (SI)). Initially, palladium catalysts including $Pd(TFA)_2$, $Pd(OAc)_2$, $Pd_2(dba)_3$, and $Pd(PPh_3)_4$ were investigated in the reaction of 0.15 mmol of **1a**, 2.0 equiv of **2a**, and 2.0 equiv of NaO^{t}Bu in the presence of 10 mol % of palladium catalyst in MeCN at 90 °C under N_2 (Table 1, entry 1, and SI). $Pd(TFA)_2$ was optimal and afforded the desired product **3a** in 23% yield (Table 1, entry 1, and SI). Catalysts based on other metals such as Rh, Ag, and Cu were tried but led to inferior results compared to $Pd(TFA)_2$ (Table 1, entries 2−4, and SI). Then we attempted to investigate the effect of the ligands under $Pd(TFA)_2$ during this transformation. 20 mol % of ligand including BINAP, dppp, dppb, Xantphos, PCy_3, PPh_3, or X-Phos was added to the entry 1 conditions (Table 1, entries 5, 6, and SI). It was found that X-Phos was optimal (Table 1, entry 6). Next, different solvents and temperatures were screened. It was found that mixed solvents of MeCN and toluene (1:1) at 100 °C (oil bath temperature) improved the yield of **3a** to 45% (Table 1, entry 7) and N−H insertion product **6a** (21% yield) was the main byproduct. Evaluation of other bases revealed that only $NaOSiMe_3$ gave a slightly higher yield of **3a** than NaO^{t}Bu (Table 1, entries 8−10, and SI), but further study demonstrated that $NaOSiMe_3$ was not compatible with Lewis acid additives (SI). We improved NaO^{t}Bu to 4.0 equiv and **2a** to 2.5 equiv, leading to **3a** in 50% yield with **8a** (main byproduct) in 25% yield (Table 1, entry 11). We found that introducing an additive such as $FeCl_3$, $AlCl_3$, or $BF_3{\cdot}Et_2O$ to activate the ester functionality (Table 1, entries 12−14) under NaO^{t}Bu to facilitate the desired pathway and $BF_3{\cdot}Et_2O$ was superior (Table 1, entries 12−14). Finally, ligands including Xantphos, DPEphos, DavePhos, ^{t}BuXPhos, S-Phos, and RuPhos were screened (Table 1, entry 15, and SI). ^{t}BuXPhos furnished the desired **3a** in 70% yield (Table 1, entry 15), which was identified as the optimized conditions for **3a**. The use of sealing tube under the otherwise same conditions afforded **3a** in 71% yield (SI). Decreasing the amounts of catalyst or ligand both led to a decrease in the yield of **3a** (SI). Deletion experiments demonstrated that $Pd(TFA)_2$ and NaO^{t}Bu were crucial for this cascade reaction (entries 17 and 18), and ^{t}BuXPhos and $BF_3{\cdot}Et_2O$ improved the reactivity and selectivity for **3a** (Table 1, entries 19 and 20).

With the optimized conditions in hand, we investigated the substrate scope of the novel cascade reactions of *N*,*N*-disubstituted thioamides **1** and *N*-tosylhydrazones **2** (Scheme 2). *N*-Tosylhydrazones **2** were first investigated. *N*-Tosylhydrazones **2** bearing *para* (**2b**−**2g**)-, *meta* (**2h**−**2j**)-, or *ortho* (**2k**)-electron-withdrawing substituted aryls proceeded smoothly to afford the corresponding products **3b**−**3k** in moderate to good yields. It is important to note that fluoro (**2b**, **2k**), chloro (**2c**, **2h**), bromo (**2d**, **2i**), trifluoromethyl (**2e**, **2j**), ester (**2f**), and even cyano (**2g**) were all well tolerated. Fluoro, chloro, and bromo could serve as handles for further elaboration, and trifluoromethyl is a privileged group in medicinal chemistry. The reactivity of **2l** bearing electron-donating *p*-methoxy-substituted aryl with **1a** was sluggish, but still moderate yields of the desired product **3l** could be obtained via slightly improved amounts of the catalyst and the ligand. *N*-Tosylhydrazone **2m** bearing heterocycle 2-thienyl was also tolerated. *N*-Tosylhydrazone **2n** bearing a longer alkyl

Scheme 2. Substrate Scope of the Cascade Reactions[a]



[a]Reaction conditions: **1** (0.15 mmol), **2** (0.375 mmol), 10 mol % of $Pd(TFA)_2$, 20 mol % of ^{t}BuXPhos, 50 mol % of $BF_3{\cdot}Et_2O$, NaO^{t}Bu (0.6 mmol) reacted in 3 mL of MeCN and toluene (1:1) for 12 h. [b]Isolated yield. [c]1 mmol. [d]15 mol % of $Pd(TFA)_2$, 30 mol % of ^{t}BuXPhos. [e]15 mol % of $Pd(OAc)_2$, 30 mol % of P(2-furyl)$_3$, **2** (4.0 equiv), NaO^{t}Bu (5.5 equiv).

was relatively inert, furnishing the desired product in low yield (10%). However, a moderate yield of 37% of **3n** could be obtained by the use of $Pd(OAc)_2$/P(2-furyl)$_3$ catalytic system with improving amounts of **2n** and the base. It is worth noting that *N*-tosylhydrazones (**2o** and **2p**) bearing two aryls were also compatible in the cascade reaction (**3o** and **3p**). In addition, *N*-tosylhydrazone **2q** bearing a phenyl and an ester as

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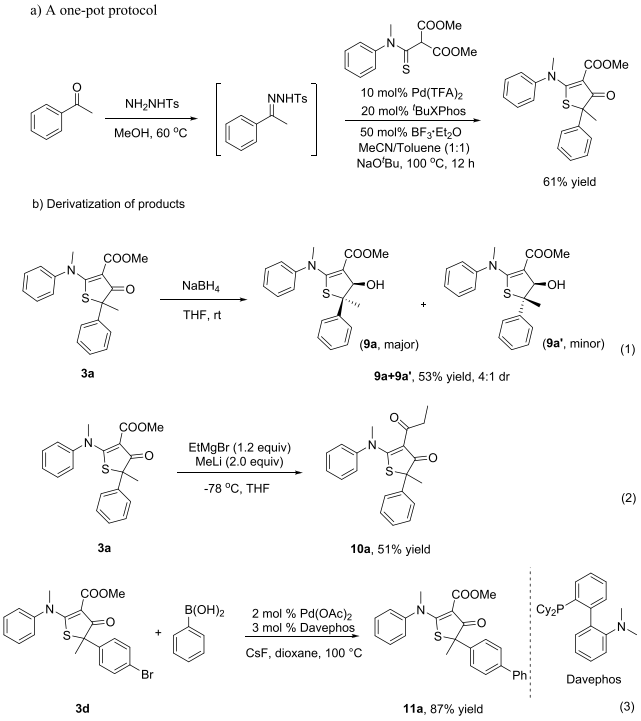
the safe precursor of methyl phenyldiazoacetate afforded the desired product **3q** in 54% yield.

Then we turned our attention to the scope of the substrate **1**. As illustrated in Scheme 2, an array of *N*,*N*-disubstituted thioamides bearing *α*,*α*-diesters **1** could bifunctionalize a single carbon of *N*-tosylhydrazones **2** smoothly. Thioamides **1** bearing other esters, including ethyl esters (**1r**), isopropyl esters (**1s**), and benzyl esters (**1t**), were compatible (**3r**−**3t**). Thioamides **1** with *para*- or *meta*-electron-donating and electron-withdrawing substituted aryls on nitrogen both afforded the desired product **3u**−**3aa** in moderate to good yields. Methoxy (**1u, 1z**), fluoro (**1v**), chloro (**1w, 1aa**), trifluoromethyl (**1x**), and keto (**1y**) in aryls on nitrogen of **1** were all tolerated. In addition, Thioamides **1** containing other alkyl substitutions on nitrogen, including ethyl (**3ab**), isopropyl (**3ac**), *n*-hexyl (**3ad**), and 3-methoxypropyl (**3ae**), were all well tolerated, smoothly delivering the corresponding products **3ab**−**3ae** in moderate to good yields.

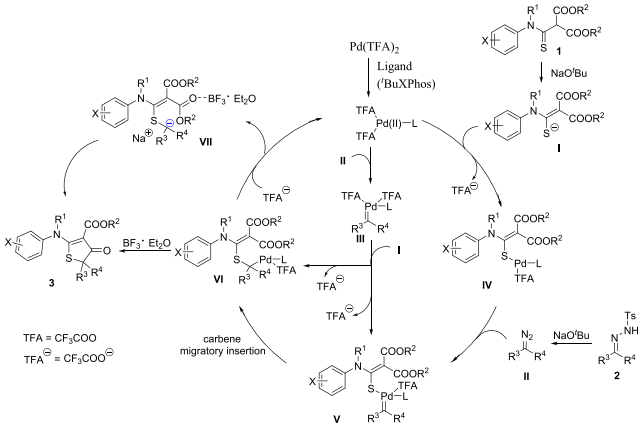
A one-pot reaction from 2.5 equiv of acetophenone, 2,5 equiv of 4-methylbenzenesulfonohydrazide (which form **2a** followed by the removal of solvent), and 1.0 equiv of **1a** worked to afford **3a** in 61% yield (Scheme 3, a). Derivatization

Scheme 3. One-Pot Protocol and Product Derivatization



of the products was investigated. Product **3a** was reduced by $NaBH_4$ to furnish **9a** and **9a′** in 53% total yield with 4:1 diastereoselectivity, and the stereochemistry was assigned using 1D NOESY spectra of **9a** and **9a′** (Scheme 3 (b, 1) and SI). Product **3a** reacted with 1.2 equiv of EtMgBr and 2.0 equiv of MeLi under −78 °C, and only the ester group in **3a** was transformed into ketone to furnish **10a** in moderate yield (Scheme 3 (b, 2)). As mentioned above, the reaction is compatible with halogen atoms which can be used as handles for functionalization. Product **3d** reacted with phenylboronic acid under the reaction conditions reported by Buchwald[13] to afford **11a** in 87% yield (Scheme 3 (b, 3)). In addition, some chiral ligands instead of ^{t}BuXPhos were investigated, but none of the enantioselective product **3a** was obtained (see the details in the SI). Thus, the anions **VII** (Scheme 4) are more likely to be the trapped intermediates in this cascade process.

Scheme 4. Proposed Mechanism



A plausible mechanism for this novel reaction is proposed in Scheme 4. NaO^{t}Bu abstracts the *α*-H of thiocarbonyl of **1** to form the thioenolate anion **I**, which might coordinate with the palladium catalyst to give the palladium complex **IV**. The complex **IV** and the diazo compound **II** derived from *N*-tosylhydrazone **2** under NaO^{t}Bu might form the palladium carbene **V**, which undergoes carbene migratory insertion to give the intermediate **VI**. The organopalladium moiety in **VI** attacks the intramolecular ester activated by BF_3·Et_2O to afford product **3**. Also, intermediate **VI** might produce the anion **VII** along with recovery of $Pd(TFA)_2$/^{t}BuXPhos, and then the anion **VII** attacks the intramolecular ester activated by BF_3·Et_2O to afford the product **3** via addition/elimination. Alternatively, $Pd(TFA)_2$/^{t}BuXPhos reacts with the diazo compound **II** derived from *N*-tosylhydrazone **2** to give the metal carbene intermediate **III**. Then the thioenolate anion **I** derived from **1** might undergo ligand exchange with **III** to give the intermediate **V**, which forms **VI** via carbene migratory insertion followed by the similar intramolecular cyclization as above to afford **3**. In addition, the thioenolate anion **I** directly attacks the carbene carbon of **III** also might form the intermediate **VI**, and then the intermediate **VI** directly or the anion **VII** derived from **VI** undergoes cyclization to furnish **3**.

In conclusion, *N*,*N*-disubstituted thioamides bearing *α*,*α*-diesters coupled with *N*-tosylhydrazones bearing alkyls with $Pd(TFA)_2$ as the catalyst, ^{t}BuXPhos as the ligand, and NaO^{t}Bu as the base at 100 °C and the formed intermediates were unprecedentedly trapped by intramolecular ester functionalities activated by co-catalyst BF_3·Et_2O, affording polyfunctional thiophen-3(2*H*)-ones with sulfur-containing tetrasubstituted carbon centers in moderate to good yields. This represents the first time that the formed organopalladium intermediates containing *β*-hydrogen from palladium carbene migratory insertion selectively form the second bond at the same carbon via 1,2-addition/elimination with esters instead of undergoing *β*-hydrogen eliminations. The novel cascade reaction utilizes odorless, nontoxic, safe, and easily available starting materials. Wide substrate scope and a broad range of functional groups are tolerated. Products possess rich and valuable structures in medicinal chemistry and materials. Developing other novel reactions to selectively construct

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multiple bonds in a single process with odorless and nontoxic sulfur reagents as well as evaluation of the biological activities of novel thiophen-3(2*H*)-ones are currently being investigated in our laboratory and in our cooperative laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03796.

Experimental procedures and spectroscopic characterization data, ^{1}H and ^{13}C NMR spectra of the new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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