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Pd-Catalyzed C−S Activation/Isocyanide Insertion/Hydrogenation Enables a Selective Aerobic Oxidation/Cyclization

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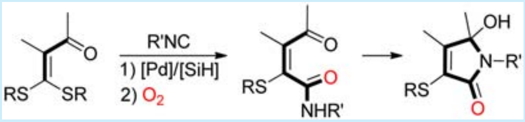
Supporting Information

ABSTRACT: Unique imidoylation of thioorganics with isocyanides endows an unprecedented aerobic oxidation process. Catalyzed by $Pd(Ph_3P)_2Cl_2$ in the presence of Ph_3SiH under N_2 then upon exposure to air, a wide range of α-acyl ketene dithioacetals react with isocyanides to afford 5-hydroxy-α,β-unsaturated γ-lactams via a C−S bond activation, isocyanide migratory insertion, hydrogenation, selective aerobic oxidation, and intramolecular nucleophilic addition sequence.

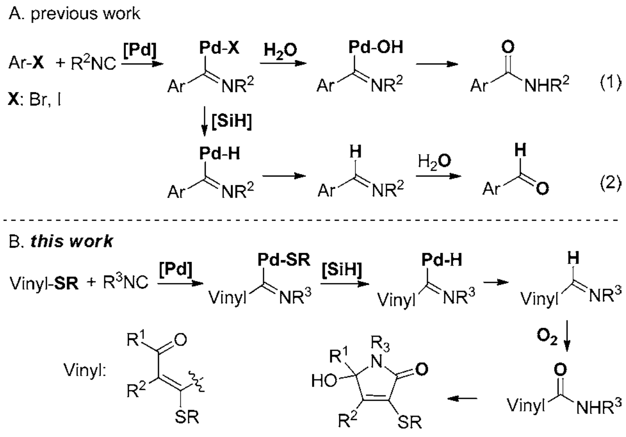


Palladium-catalyzed imidoylation of organohalides or pseudo halides with isocyanides and sequential coupling with a nucleophile provide an intriguing strategy for the synthesis of various *N*-containing compounds.[1−6] Thioorganics have found broad utilizations in cross-coupling chemistry[7,8] by taking advantage of their accessibility, stability, and structural diversity.[9] However, the work on the metal-catalyzed desulfurative imidoylation of organosulfur compounds with isocyanides is rare.[10]

Recently, we developed a set of synthetic strategies based on transition-metal-catalyzed C−S cleavage for C−C formations.[11] Readily available functionalized ketene dithioacetals[12] have been developed to be new coupling partners[11,13] and presented alternative reactivity and high selectivity under Pd catalysis. By considering both the important applications of isocyanides[1−6] and new reaction pattern that arose from ketene dithioacetals[11] in cross-coupling chemistry, we combined two chemistries and envisioned a migratory insertion of isocyanides based on C−S activation by using hydrosilanes as reductants. To our delight with a slight surprise, the Pd-catalyzed reaction of ketene dithioacetals with isocyanides included a highly selective aerobic oxidation (Scheme 1B), instead of either C−O cross-coupling of imidoyl-Pd with H_2O (Scheme 1A-(1))[2f] or reduction followed by a hydrolysis of the imine intermediate (Scheme 1A-(2))[2g] even in the presence of water. Additionally, this oxidation process evolved to a cyclization to furnish 5-hydroxy-α,β-unsaturated γ-lactams, a class of important *N*-heterocycles.[14]

According to our previous work,[11c] the reaction of **1a** with biphenyl isocyanide was initially carried out in DMSO by using 10 mol % of $Pd(PPh_3)_2Cl_2$ in the presence of 2 equiv of Ph_3SiH at 90 °C. A cyclic product, 5-hydroxy-α,β-unsaturated γ-lactam **2a**, was isolated in 43% yield after 7 h (Scheme 2A-(1)). Based on the literature (Scheme 1A-(1)),[2f] the formation of **2a** seemed to result from a C−O coupling of imidoyl-Pd with trace H_2O in the solvent followed by an intramolecular nucleophilic addition. However, additional water made the reaction sluggish due to the significant decomposition of $4\text{-}PhC_6H_4NC$ in DMSO−H_2O mixed solvent (Scheme 2A-(2)). Other isocyanides, including $PhCH_2NC$, EtO_2CCH_2NC, *t*BuNC, and $TsCH_2NC$, were then subject to this catalytic system in the presence of H_2O. It was found that EtO_2CCH_2NC was the compatible substrate to afford **3a**[15] in good yield (Scheme 2B-(1)). By comparison, *t*BuNC only furnished an acyclic amide **4a** as the final product (Scheme 2C). In the case of $TsCH_2NC$ (Scheme 2D), **1a** was recovered in 90% yield along with the consumption of isocyanide by itself change. Further investigation showed that water indeed played an important role for the transformations. When **1a** reacted with EtO_2CCH_2NC in dried DMSO in the presence of 4 Å MS, only a trace amount of **3a** was detected (Scheme 2B-(2); see also Supporting Information (SI)).

Scheme 1. Pd-Catalyzed Isocyanide Insertion and Transformations



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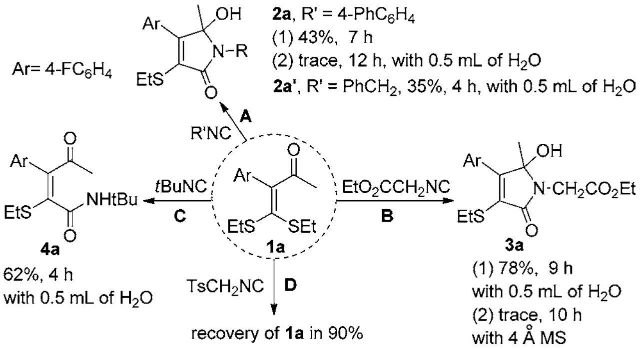
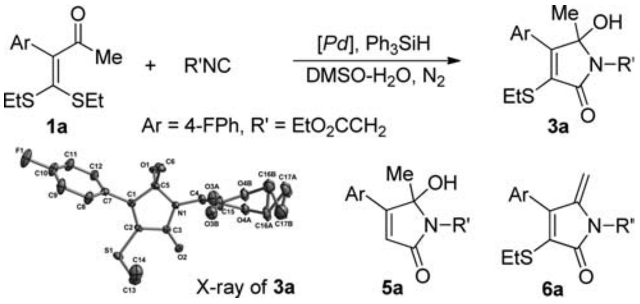
Scheme 2. Couplings of 1a with Isocyanides[a]



[a]Reaction conditions: **1a** (0.5 mmol), R′NC (3 equiv), Pd(PPh$_3$)$_2$Cl$_2$ (10 mol %), Ph$_3$SiH (2 equiv), DMSO (5 mL), N$_2$, 90 °C. Isolated yield.

Thus, we chose EtO$_2$CCH$_2$NC for screening the reaction conditions. It was found that 5 mol % of Pd(PPh$_3$)$_2$Cl$_2$ was enough (Table 1, entry 2) for the catalytic cycle, while 2.5 mol % of Pd catalyst resulted in an incomplete transformation (entry 3). The desulfurative reduction product **5a** and the dehydration product **6a** were often detected to accompany **3a**, but could be avoided with a shorter reaction time and at lower temperature (entries 1−4). Furthermore, the reaction could complete in 4 h to afford **3a** in 86% yield at 70 °C even by using 1.2 equiv of Ph$_3$SiH (entry 5). Prolonging the reaction time led to more **5a** (entry 6), and decreasing the amount of EtO$_2$CCH$_2$NC made the conversion incomplete (entry 7). Other Pd-catalysts and solvents were also investigated for the reactions but proved not to be comparable to the reaction system of Pd(PPh$_3$)$_2$Cl$_2$ in DMSO (entries 8−14).

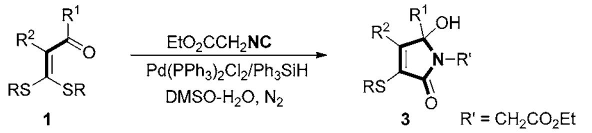
Table 1. Optimization of Reaction Conditions[a]



entry	[Pd]/ligand (mol %)	Ph$_3$SiH (equiv)	solvent/temp (°C)/time (h)	yield (%)[b]
1	Pd(PPh$_3$)$_2$Cl$_2$ (10)	2	DMSO/90/9	78[c]
2	Pd(PPh$_3$)$_2$Cl$_2$ (5)	2	DMSO/90/7	85[c]
3	Pd(PPh$_3$)$_2$Cl$_2$ (2.5)	2	DMSO/90/18	38[c,d]
4	Pd(PPh$_3$)$_2$Cl$_2$ (5)	1.5	DMSO/70/4	85
5	Pd(PPh$_3$)$_2$Cl$_2$ (5)	1.2	DMSO/70/4	86
6	Pd(PPh$_3$)$_2$Cl$_2$ (5)	1.2	DMSO/70/18	71[e]
7	Pd(PPh$_3$)$_2$Cl$_2$ (5)	1.2	DMSO/70/18	40[f]
8	Pd(OAc)$_2$ (5)/PPh$_3$ (15)	1.2	DMSO/70/20	38
9	Pd(CF$_3$CO$_2$)$_2$ (5)/ PPh$_3$ (15)	1.2	DMSO/70/7	70
10	PdCl$_2$ (5)/PPh$_3$ (15)	1.2	DMSO/70/7	77
11	Pd$_2$(dba)$_3$ (5)	1.2	DMSO/70/20	28
12	Pd(PPh$_3$)$_2$Cl$_2$ (5)	1.2	MeCN/70/12	32
13	Pd(PPh$_3$)$_2$Cl$_2$ (5)	1.2	DMF/70/18	46
14	Pd(PPh$_3$)$_2$Cl$_2$ (5)	1.2	1,4-dioxane/70/20	trace

[a]Reaction condition: **1a** (0.5 mmol), EtO$_2$CCH$_2$NC (3 equiv), solvent (5 mL), H$_2$O (0.5 mL). [b]Isolated yield. [c]**5a** and **6a** were detected in trace amounts. [d]50% of **1a** was recovered. [e]Approximately 10% of **5a** and 5% of **6a** were isolated. [f]EtO$_2$CCH$_2$NC (1.5 equiv). 51% of **1a** was recovered.

Table 2. Scope of Ketene Dithioacetals 1[a,b]



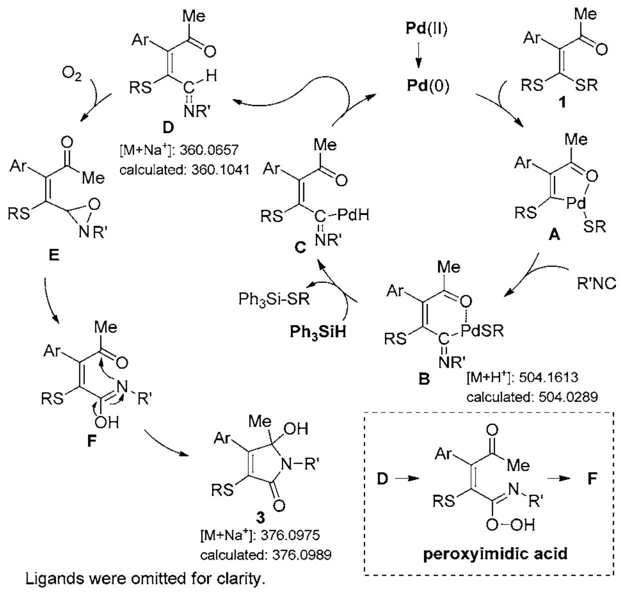
entry	R^1	R^2	R	time (h)	3	yield (%)[b]
1	Me	4-FC$_6$H$_4$	Et	4	**3a**	86
2	Me	4-ClC$_6$H$_4$	Et	3	**3b**	87
3	Me	4-MeOC$_6$H$_4$	Et	3	**3c**	80
4	Me	3-MeO-4-MeOC$_6$H$_3$	Et	7	**3d**	81
5	Me	2-MeOC$_6$H$_4$	Et	4	**3e**	82
6	Me	2-FC$_6$H$_4$	Et	5	**3f**	87
7	Me	4-FC$_6$H$_4$	Bn	6	**3g**	72
8	Me	4-FC$_6$H$_4$	Me	3	**3h**	81
9	Me	4-ClC$_6$H$_4$	Me	3	**3i**	79
10	Me	Me	Me	5	**3j**	83
11	Me	H	Et	5	**3k**	58
12	Me	PhCO	Et	4	**3l**	92[c]
13	Me	MeCO	Et	3	**3m**	60[c]
14	Me	EtO$_2$C	Et	4	**3n**	65[c]
15	Et	Ph	Et	3	**3o**	77
16	Ph	Ph	Et	16	**3p**	65
17	Ph	PhCO	Et	5	**3q**	83[c]
18	H	4-MeOC$_6$H$_4$	Et	6	**3r**	complex

[a]Reaction condition: **1** (0.5 mmol), EtO$_2$CCH$_2$NC (3 equiv), Pd(PPh$_3$)$_2$Cl$_2$ (5 mol %), Ph$_3$SiH (1.2 equiv), DMSO (5 mL), H$_2$O (0.5 mL), 70 °C. [b]Isolated yield. [c]Ph$_3$SiH (2 equiv), 90 °C.

With an optimized set of reaction conditions (Table 1, entry 5) in hand, we examined the scope of this C−S activation-based isocyanide insertion and cyclization sequence. As described in Table 2, a variety of α-acyl ketene dithioacetals **1** were prepared as substrates for the Pd-catalyzed imidoylation reaction. On one hand, aromatic R^2 substituents at the α-position of **1**, bearing either an electron-donating or -withdrawing group at the different positions of the phenyl ring, were compatible with the reaction to produce **3a−f** in high yields. In the case of **1g−i** with dibenzylthio or dimethylthio functional groups, the corresponding **3g−i** were obtained in 72−81% yields, respectively. The reaction also proved to tolerate those substrates, including **1j** with aliphatic α-Me, **1k** without an α-substituent, and **1l−n** with an α-carbonyl. On the other hand, the reactions of **1o−q** bearing different R^1 were carried out under the identical conditions to afford **3o−q** as the desired products. Finally, it was found that α-formyl ketene dithioacetal **1r** (R^1 = H) led to a complex mixture. In this case, the desired **3r** could not be obtained even by further optimization of the reaction conditions.

To gain information on the role of water for the transformation (for details, see SI), an additional reaction in DMSO and H$_2{}^{18}$O (10:1) was first carried out under N$_2$. However, no ^{18}O-labeled **3a** was observed in its HRMS analysis. Another reaction which was quenched by H$_2{}^{18}$O did not afford ^{18}O-labeled **3a** either. The results ruled out a coupling process with water as proposed in literature.[2f] Interestingly, the formation of **3a** was observed just during workup. More importantly, exposing the reaction mixture to air during workup was proven to be the key for furnishing **3a**. A further control experiment was performed by stirring the resulting mixture under $^{18}O_2$ after **1a** was consumed in the [Pd]/[SiH] catalytic system under N_2. ^{18}O-Labeled **3a** was detected by HRMS.

Scheme 3. Proposed Mechanism



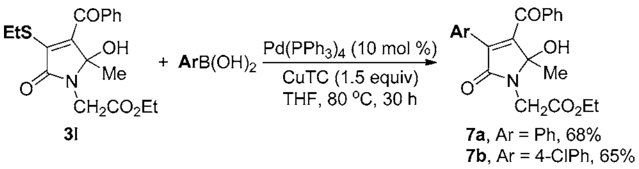
Ligands were omitted for clarity.

According to the above experimental results, an alternative mechanism was thus proposed as described in Scheme 3. First, C–S bond activation of **1** by Pd(0) under N_2 afforded Pd-SR **A**, which was converted into imidoyl Pd-SR **B** by the insertion of isocyanide. Then, reduction of **B** in the presence of Ph_3SiH produced imidoyl-Pd–H **C** along with the release of Ph_3Si–SR.[16] Next, reductive elimination of **C** led to imine **D** with the regeneration of Pd(0) for the next catalytic cycle. After **1** was consumed, the resulting mixture was exposed to air and quenched with H_2O. **3** were formed by a tandem aerobic oxidation of **D** leading to oxaziridine **E**,[17] isomerization of **E** to give **F**,[18] and an intramolecular nucleophilic addition of **F**. In the case of *t*BuNC, the reaction stopped at **F** to furnish acyclic amide **4a** (Scheme 2C) likely due to the steric hindrance of *tert*-butyl group. Further ESI-HRMS studies of the model reaction showed that, after 4 h, the reaction mixture includes a peak at m/z = 504.1613 regarded as **B** and a peak at m/z = 360.0657 assigned to **D**. No **3a** was detected by TLC at this stage. In contrast, **3a** was observed by TLC in accordance with the peak at m/z = 376.0975 in MS after exposing the reaction mixture to air and stirring at room temperature. The role of water in the reaction is not yet clear, while another control experiment showed that the reaction of **1a** without Ph_3SiH could afford **3a** but in less than 30% yield under standard conditions. In this case, a protodepalladation of **B** with water may be involved for yielding imine **D**. But there is no efficient reduction of the released Pd(II) to reactive Pd(0) for a smooth catalytic cycle in the absence of hydrosilanes. This process could not be excluded in the presence of silanes at this stage.

Oxidation of imines to oxaziridines usually required a strong oxidant, or a combination of an oxidant with a metal catalyst or with an additive.[17] On the other hand, the rearrangement of oxaziridines to amides generally occurred in the presence of the metal catalysts, or via a photochemical process, or under solvent-free conditions.[18] By comparison, the oxidation of imine **D** delivering amide **F** in our work took place spontaneously during workup. In fact, an example of direct autoxidation of imines to amides is rare. In 1984, Boyd and co-workers reported an unusual autoxidation of neat liquid imines.[19] A peroxyimidic acid intermediate, resulted from the autoxidation of imines, oxidized a further molecule of imines to provide amides and oxaziridines in equal amounts. Although the yields of oxidation product **3** were isolated in more than 50% yields in our work, the mechanism for the conversion of **D** into **F** via a peroxide species (Scheme 3) could not be ruled out at the present time.

To highlight the potential transformations of the method, Pd-catalyzed cross-couplings of **3l** with aryl boronic acids were carried out by the assistance of copper(I)-thiophene-2-carboxylate (Scheme 4, CuTC).[8a,d,11a,d] Thus, 4-aryl-α,β-unsaturated γ-lactams **7** were isolated in good yields.

Scheme 4. Cross-Coupling of 3l with Boronic Acids



In summary, we described a unique imidoylation of α-acyl ketene dithioacetals with isocyanides, which evolves to a hydrogenation, selective aerobic oxidation, and intramolecular nucleophilic addition. The reaction was applied for the synthesis of 5-hydroxy α,β-unsaturated γ-lactams. As the key step, unprecedented oxidation of imine species by O_2 leading to amides may take advantage of the reactivity of imine intermediates bearing the structural features of ketene dithioacetals. The synthetic potential of the method was presented in the cross-coupling of SR-substituted γ-lactams with boronic acids.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01780.

Experimental procedures, analytical data for new compounds (PDF)

Crystallographic data for **3a** (CIF)

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Notes

The authors declare no competing financial interest.

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(15) CCDC 1042264 contains the supplementary crystallographic data for **3a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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